

COMPREHENSIVE ORGANIC FUNCTIONAL GROUP TRANSFORMATIONS II

Editors-in-Chief

Alan R. Katritzky, Richard L.E. Taylor

Volume

2

Carbon with One Heteroatom Attached by a Single Bond

Volume Editor

Janine Cossy



ÔUT ÚÜÒPÒÈÙÒÀÚÜÕÖÐÔÁ
 ÔMPÔNÖPÔŠÖÛUWÁ
 VÜÖÈÙÖUÛT ÖNÖPÙÁÖ



9X]hcf!]b! 7\]YZ`
 5"F ""? Uhf]m_ni` I b]j Yfg]hmcZ: `cf]XUž`
 ; U]bYgj]`Yž! G5
 F">"? "HUmcfž`8YdUfha YbhicZ7\Ya]ghfnž`
 I b]j Yfg]hmcZMcf_ž! ?

J c`i a Yg`d+!`+!J c`i a Y`GYh
 <UfXVci bXž`G6B. `!\$, !\$ ((&) *! \$ž`* +, , `dU[Ygž
 `di V`jVh]cb`XUHY. ` &\$\$(
 =a df]bh `9@G9J =9F

8YgV]dh]cb`
 7ca dFY\Ybg]j Y`Cf[Ub]W: i bV]cbU` ; fci d`HfUbgžcfa Uh]cbg`=f7C: ; H!
 =k`j`dfcj]XY`hY`Z]fghdc]bhicZYbhfmihc`hY`j]hYfUhi fY`žcf`U`gVYb]ghg`
]bhYfghYX`]b`VX`Ya]W`HfUbgžcfa Uh]cbg`DfYgYbh]b[`hY`j Ughgi V`YVh`cZ
 cf[Ub]Wgnb`hYg]g]b`hYfa g`cZ`hY`]bhfcXi V]cb`UbX`]bhYfVb] Yfg]cb`cZ
 U`_bck b`ž bV]cbU`[fci dgž`7C: ; H!=k`j`dfcj]XY`U`i b]ei Y`
]bžcfa Uh]cb`gci fV`XcW`a Ybh]b[`U`a Yh`cXg`cZYZZVYb]midYfžcfa]b[`U`dUfh]W`Uf`HfUbgžcfa Uh]cb`Cf[Ub]gYX`Vmi`hY`ž bV]cbU`[fci d`
 žcfa YXž`7C: ; H!=k`j`Vb]g]ghicZ%(`gdYV]U`]ghfYj]Yk gž`k f]hYb`Vmi
 `YUX]b[`gVYb]ghg`k`c`k`j`Yj U`i UhY`UbX`gi a`a Uf]gY`hY`a Yh`cXg`
 Uj`Uj`UV`Y`žcf`YUVX`ž bV]cbU`[fci d`HfUbgžcfa Uh]cb`

J c`i a Yg`

J c`i a Y`%` 7UfVcb`k]h`Bc`5HhUW`YX`<YhYfcUhca`g`

J c`i a Y`&` 7UfVcb`k]h`CbY`<YhYfcUhca`5HhUW`YX`VmiU`G]b[`Y`
 6cbX`

J c`i a Y`"`. 7UfVcb`k]h`CbY`<YhYfcUhca`5HhUW`YX`VmiU`A`i`h]d`Y`
 6cbX`

J c`i a Y`(. 7UfVcb`k]h`Hk`c`<YhYfcUhca`gž`9UW`5HhUW`YX`VmiU`
 G]b[`Y`6cbX`

J c`i a Y`). 7UfVcb`k]h`Hk`c`5HhUW`YX`<YhYfcUhca`g`k`]h`Uh`
 @YUgh`CbY`7UfVcb`!hc!<YhYfcUhca`A`i`h]d`Y`@]b_`

J c`i a Y`*. 7UfVcb`k]h`H`fYY`cf` : ci f`5HhUW`YX`<YhYfcUhca`g`

J c`i a Y`+. 5i`h`cf`=bXYI`UbX`7i`a`i`Uh]j`Y`Gi`V`YVh`=bXYI`

Editors-in-Chief

Professor Alan R. Katritzky, FRS

University of Florida, Gainesville, FL, USA

Professor Richard J. K. Taylor

University of York, York, UK

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, Mammecoumarins, 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 2

I could play this without the music – but why waste memory when I have the music
Victor Borge (Caught in the Act)

The modern chemist needs rapid recall but the subject is now too large to rely on memory alone. I cannot remember how many times I have forgotten a useful reaction. The interconversion of functional groups is at the heart of synthetic chemistry and, with an ever-growing literature, access to a systematic and comprehensive tabulation of functional group chemistry is an essential resource. A good memorized core knowledge is still important, but the difference between success and failure often lies in the detail. The introduction of *Comprehensive Organic Functional Group Transformations* (COFGT) in both electronic and printed format means that organic chemists' "music" is now instantly available wherever and whenever it is required.

Since the publication of COFGT (1995) progress in (i) further defining the scope and limitations of known transformations and (ii) the discovery of new ones has continued at a remorseless pace. Volume 2 of this second edition of COFGT systematically covers developments since 1995 in the preparation of functional groups containing one heteroatom attached to carbon by a single bond. Some significant contributions that were overlooked in COFGT (1995) have also been included in this volume: for full coverage of the literature both editions must be consulted. To aid cross-referencing the original main headings and, wherever possible, subheadings of chapters have been retained.

Volume 2, by definition, contains many of the fundamental organic functional groups, such as alcohols and amines, and this is reflected in the size of the volume for both editions. Chapters 2.1–2.11 cover functional groups in which a heteroatom is attached by a single bond to an alkyl carbon. Thus, Chapter 2.1 covers the alkyl halides and Chapters 2.2–2.4 cover the alkyl chalcogenides commencing with alcohols. Subsequent chapters move across the Periodic Table in a westerly direction, concluding with Chapter 2.11 describing alkylmetals. Chapters 2.12–2.19 cover the same functional groups attached to a vinyl or aryl carbon. Chapter 2.20 deals with carbon-centered ions and radicals bonded to one heteroatom. The volume concludes with the corresponding alkyne functional groups. Thus, Chapter 2.21 covers alkynyl halides and chalcogenides, Chapter 2.22 covers nitrogen and phosphorus groups, and Chapter 2.23 covers the remaining elements.

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

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

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 _N 1	first-order nucleophilic substitution
S _N 2	second-order nucleophilic substitution
S _N i	internal nucleophilic substitution
STM	scanning tunneling microscopy
TLC	thin-layer chromatography
UV	ultraviolet
vol.	volume
wt.	weight

REAGENTS, SOLVENTS, ETC.

Ac	acetyl CH ₃ CO-
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- <i>t</i> -butyl-4-methylphenol (butyrated hydroxytoluene)
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bipy	2,2'-bipyridyl
Bn	benzyl C ₆ H ₅ CH ₂ - (NB avoid confusion with Bz)
<i>t</i> -BOC	<i>t</i> -butoxycarbonyl
bpy	2,2'-bipyridyl
BSA	<i>N,O</i> -bis(trimethylsilyl)acetamide
BSTFA	<i>N,O</i> -bis(trimethylsilyl)trifluoroacetamide
Bt	benzotriazole
BTAF	benzyltrimethylammonium fluoride
Bz	benzoyl C ₆ H ₅ CO- (NB avoid confusion with Bn)
Bzac	benzoylacetone
CAN	ceric ammonium nitrate
Cbz	carbobenzoxyl
chalcogens	oxygen, sulfur, selenium, tellurium
CH ₂ Cl 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- <i>O</i> -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	<i>N,N'</i> -dimethylimidazolidinone
DMN	diaminomaleonitrile
DMSO	dimethyl sulfoxide
DMTSP	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	<i>N</i> -ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
Et	ethyl
Et ₂ O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
EWG	electron-withdrawing group
HMPA	hexamethyl phosphoramide
HMPT	hexamethylphosphoric triamide
IpcBH ₂	isopinocampheylborane
Ipc ₂ BH	diisopinocampheylborane
KAPA	potassium 3-aminopropylamide
K-selectride	potassium tri- <i>s</i> -butylborohydride
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LICA	lithium isopropyl cyclohexylamide
LITMP	lithium tetramethyl piperidide
L-selectride	lithium tri- <i>s</i> -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	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMP	<i>N</i> -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 <i>p</i> -toluenesulfonate
Pr	propyl
Pyr	pyridine
Red-Al	sodium bis(methoxyethoxy)aluminum dihydride
SDS	sodium dodecyl sulfate
SEM	trimethylsilylethoxymethyl
Sia ₂ BH	disiamylborane
SM	starting material
TAS	tris(diethylamino)sulfonium
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDMS	<i>t</i> -butyldimethylsilyl
TBDMS-Cl	<i>t</i> -butyldimethylsilyl chloride
TBDPS	<i>t</i> -butyldiphenylsilyl
TBHP	<i>t</i> -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 ₆ H ₄ (CH ₃)–
TosMIC	tosylmethyl isocyanide
TPP	meso-tetraphenylporphyrin
Tr	trityl (triphenylmethyl)
Tris	tris(hydroxymethyl)aminomethane
Ts	4-toluenesulfonyl (tosyl)
TTFA	thallium trifluoroacetate
TTMSS	tris(trimethylsilyl)silane
TTN	thallium(III) nitrate
X	halogen or leaving group

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2.01

Alkyl Halides

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2.01.1 GENERAL METHODS FOR ALKYL HALIDES

The synthetic approaches to alkyl halides have been reviewed thoroughly in COFGT (1995) <1995COFGT(2)1>. Since then the use of alkyl halides as intermediates in organic synthesis has continued to develop. Thus, several papers dealing with their synthesis have appeared in the literature. Some of these syntheses include methods which are already known, whereas there are others that involve new reagents and transformations. In this chapter emphasis is given to the coverage of the methods that are synthetically useful, whereas some less well-used methods are briefly mentioned. Mechanistic details are discussed only when it appears to be necessary and mainly to explain the regio-, stereo-, or chemoselectivity.

Due to the different reactivities of fluorides, chlorides, bromides, and iodides, the transformations which lead to their synthesis are presented in separate sections. However, there are a few methods of synthesis applicable to all four halogens and these are discussed in this general section.

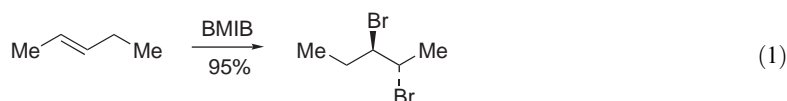
2.01.1.1 Alkyl Halides from Alkanes

Radical halogenations are probably the simplest way to functionalize hydrocarbons because they only require a radical chain initiator, light or high temperatures <B-1995MI001>. However, they often result in a mixture of alkyl halides and are not synthetically useful. The procedures that have appeared in the literature since 1995 are discussed in Sections 2.01.2.1, 2.01.3.1, 2.01.4.1, and 2.01.5.1.

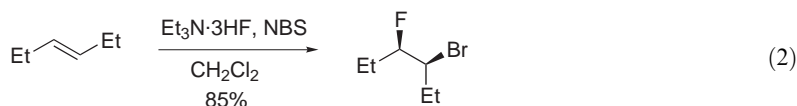
2.01.1.2 Alkyl Halides from Alkenes

The reactions of 1-octene, 1-hexene, and 1-methylcyclohexene with atomic hydrogen carried out in the presence of several transfer agents (CCl_4 , CCl_3Br , CCl_2Br_2) initiate a radical chain addition of $\text{CCl}_2\text{Hal}^\cdot$ and yield alkyl chlorides and bromides along with several other products <1996JOC6818>.

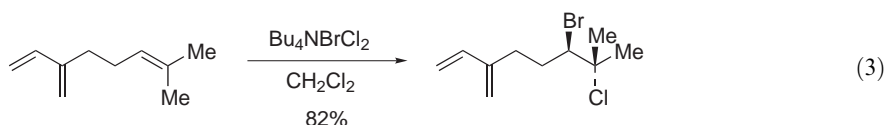
Room temperature ionic liquids [1-butyl-3-methylimidazolium hexafluorophosphate, 1-butyl-3-methylimidazolium tetrafluoroborate, 1-butyl-3-methylimidazolium bromide (BMIB), and 1-butyl-3-methylimidazolium chloride] can be used as “green” recyclable alternatives to chlorinated solvents for the stereoselective halogenation of alkenes and alkynes <2001OL1061>. A characteristic bromination is shown in Equation (1).



Interhalogen monofluorides which are generated *in situ* by reaction of triethylamine trihydrofluoride ($\text{Et}_3\text{N} \cdot 3\text{HF}$) or XeF_2 with alkyl hypochlorites, hypobromite, or *N*-halosuccinimides are used for fluorohalogen addition to electron-rich or neutral alkenes. A representative example is given in Equation (2) <1999JOC1094>.



Tetraalkylammonium dichlorobromate in methylene chloride halogenates one double bond in compounds having two or more double bonds (Equation (3)) <2001JAP064218>.

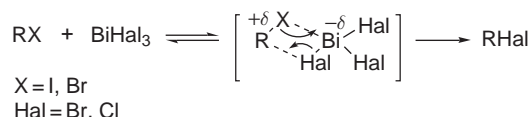


2.01.1.3 Alkyl Halides from Alkyl Halides

Boron halides (BHal_3) in hexane or methylene chloride are very reactive transforming at 0°C (5 min) primary alkyl fluorides into a mixture of alkyl halides (bromides and iodides) <1995JFC89>.

Tetraalkylammonium salts containing the relevant halogen anion transform alkyl iodides to alkyl halides. The enthalpies of this nucleophilic substitution of ethyl iodide have been determined in acetonitrile <1997JCS(P2)1765>.

Bismuth halides are efficient and selective reagents in halogen exchange reactions carried out under mild conditions in anhydrous 1,2-dichloroethane (DCE). This rapid high-yielding reaction (up to 93%) proceeds mainly with retention of configuration. The mechanism has been suggested to involve a 4-center transition state rather than formation of an ion-pair $\text{R}^+/\text{XBiHal}_3^-$ because of the low polarity of the solvent (Scheme 1) <1999T1971>.



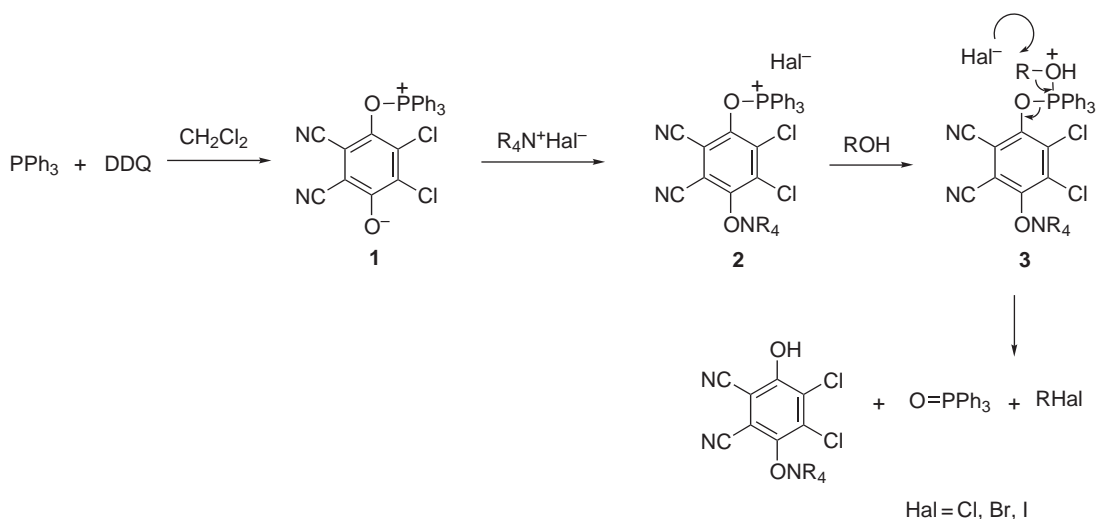
Scheme 1

2.01.1.4 Alkyl Halides from Alcohols and Their Derivatives

The transformations of alcohols into the corresponding halides represent an important functional group interconversion in organic synthesis. Various methods have been reported and require either one or two reaction steps <1995COFGT(2)1>. The simplest methods involve hydrogen halide, thionyl halide, or phosphorus halide reagents, though these methods tolerate a rather limited range of substrate functionalization. The majority of alcohol-to-halide transformations are based on the use of triphenylphosphine. Despite the great number of available methods for alcohol-to-halide conversion, there is still a need for improved mild and selective methodologies <1998JOC9565, 2001OL3727>.

It is well known that treatment of alcohols with aqueous HCl or HBr leads to the formation of the corresponding alkyl halide <1998JOC7707>.

A mixture of triphenylphosphine and 2,3-dichloro-5,6-dicyano-benzoquinone in dichloromethane in the presence of R_4NHal converts alcohols, thiols, and selenols into alkyl halides in high yields at room temperature. The method is highly selective for the conversion of primary alcohols in the presence of secondary ones, as well as for the conversion of primary and secondary alcohols in the presence of *t*-alcohols, thiols, epoxides, trimethylsilyl- and tetrahydropyranyl ethers, 1,3-dithianes, disulfides, and amides <2002T8689>. On the basis of the known reactions of Ph_3P and DDQ, the formation of the intermediate complex **2** has been suggested. Subsequently, an $\text{S}_\text{N}2$ displacement on the intermediate **3** by halide anion leads to alkyl halide (Scheme 2).

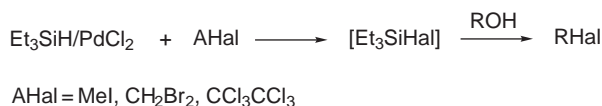


Scheme 2

The use of a combination of iodine and imidazole on polymer-supported triphenylphosphine provides a high-yielding iodination method applicable to allylic, benzylic, and other primary alcohols <2002OPRD190>. The methodology is extendable to bromination and chlorination of alcohols by replacing I_2/ImH with Br_2/ImH and NCS , respectively <2002OPRD190>.

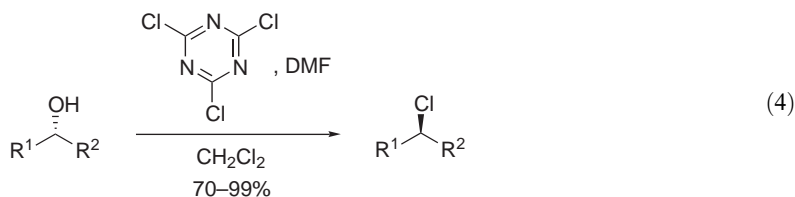
Alcohols are efficiently converted to alkyl halides using 1-*n*-butyl-3-methylimidazolium halides in the presence of Brønsted acids (usually H_2SO_4 or MeSO_3H) at room temperature <2001OL3727>.

Alcohols can be converted to the corresponding halides by adding $\text{PdCl}_2/\text{Et}_3\text{SiH}$ to an appropriate mixture of halogenating agents (i.e., MeI , CH_2Br_2 , or CCl_3CCl_3). Iodination, bromination, and chlorination are efficient for benzyl, allyl, and tertiary alcohols (Scheme 3) <1998JOM135>.

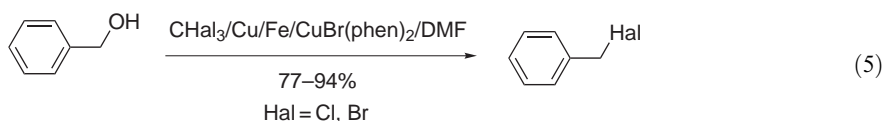


Scheme 3

Efficient conversion of alcohols into the corresponding alkyl chlorides can be carried out at room temperature in methylene chloride, using 2,4,6-trichloro[1,3,5]triazine (TCT) and *N,N*-dimethylformamide (DMF). The reaction of optically active alcohols was found to proceed with inversion of configuration at the chiral center (Equation (4)) <2002OL553>. Furthermore, alkyl bromides can be obtained by addition of sodium bromide and the alcohol to the TCT/DMF mixture in CH_2Cl_2 . However, in this case, a noticeable amount of the alkyl chloride may be recovered as by-product.

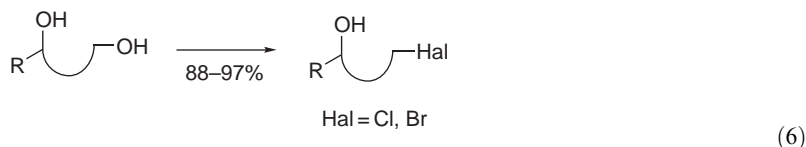


A simple and efficient method for the transformation of primary alcohols into primary alkyl halides in very good yields involves use of polyhalomethanes in the presence of a redox system. Thus, CCl_4 or CBr_4 in combination with $\text{Cu}/\text{Fe}/\text{CuBr}(\text{phen})_2/\text{DMF}$ is used for chlorination or bromination, respectively (Equation (5)) <1997JOC7061>.



In the presence of a catalytic amount of BiHal_3 ($\text{Hal} = \text{Cl}, \text{Br}, \text{I}$), halomethylsilanes can be used as halogenating agents for alcohols. The chlorination of (*R*)-(-)-octan-2-ol by TMSCl gives predominantly the (*S*)-(+)-2-chlorooctane with inversion of configuration at the secondary carbon <1995BSF522>.

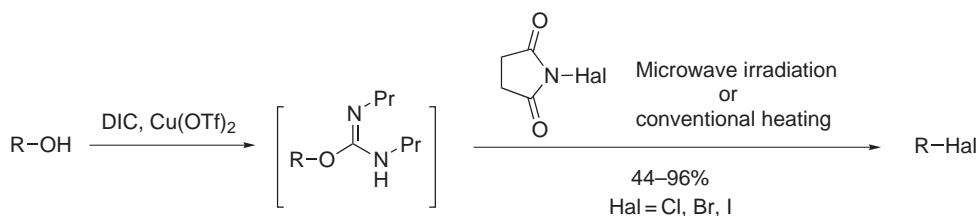
(Chlorophenylthiomethylene)dimethylammonium chloride (CPMA) reacts smoothly with a variety of alcohols to afford the corresponding alkyl chloride in good yields. In the presence of tetrabutylammonium bromide, the corresponding bromide is obtained. CPMA is selective for the chlorination or bromination of primary hydroxyl groups. The mild conditions involved are compatible with major alcohol-protecting groups as well as with acid-sensitive functions like epoxides (Equation (6)) <2000TL6049>.



Reagents for chlorination: CPMA, CH_2Cl_2 or CPMA, NEt_3 , CH_2Cl_2

Reagents for bromination: CPMA, $n\text{-Bu}_4\text{N}^+\text{Br}^-$, CH_2Cl_2 , or CPMA, $n\text{-Bu}_4\text{N}^+\text{Br}^-$, NEt_3 , CH_2Cl_2

Primary and secondary alcohols can be converted into the corresponding alkyl chlorides, bromides, and iodides in one step. The alcohol is treated with diisopropylcarbodiimide (DIC) to give the corresponding *O*-alkyl isourea which subsequently reacts with *N*-halosuccinimide in THF under either microwave irradiation at 150–160 °C or thermal heating at 80–100 °C to afford alkyl chlorides and bromides in high yields (60–96%) and alkyl iodides in moderate yields (44–73%) (Scheme 4). However, the reaction time when carried in a microwave oven is much shorter (5–10 min instead of 2–4.5 h). The reaction product from secondary alcohols is typically contaminated with a small amount of elimination product. A wide variety of functional groups including nitrile, alkyl bromide, TBDPS- ether, nitro, ester, and imide were tolerated under the reaction conditions. When enantiopure 4-phenyl-2-butanol is used, partial racemization occurs presumably through a Finkelstein reaction <2003TL8143>.

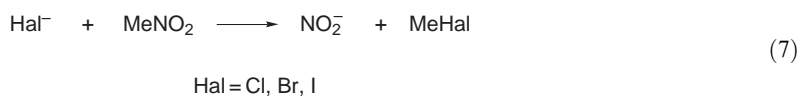


Scheme 4

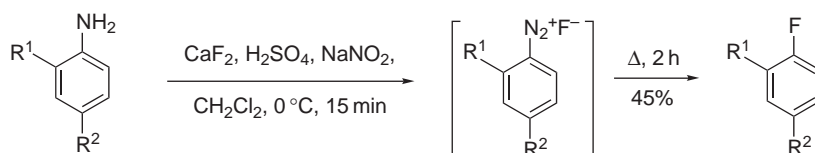
Finally, it has been reported that carbonylation of alcohols with CO/Pd(2-OCOC₅H₄N) (PPh₃)OTs/LiX gives alkyl chlorides and iodides as by-products in only 2–8% yields <2000OL203>.

2.01.1.5 Alkyl Halides from Amines and Their Derivatives

Since 1995, there have been no reports about general transformations of amines or their derivatives into alkyl halides. However, the successful photoinitiation of the gas-phase S_N2 reactions shown in Equation (7), through the Evans–Polanyi excited state surface, have been described. Reaction intermediates of the type Hal[−]·MeNO₂ were generated in a tandem time-of-flight mass spectrometer in a free jet expansion by association onto Hal[−] ions created by secondary electron attachment to CCl₄, CH₂Br₂, or MeI₂ (for Cl[−], Br[−], and I[−], respectively) <1997JA5067>.



Furthermore, there are some specific preparations of alkyl halides from amines. Thus, aniline is converted into fluorobenzene via diazotization followed by fluoro de-diazotization in the presence of calcium fluoride (Scheme 5) <1999JCS(P1)1491>, whereas phenyl hydrazine has been used as a precursor to fluorobenzene by treatment with IF₅ in Et₃N·3HF (Equation (8)) <2001CL222>. Aryl and vinyl halides are systematically covered in Chapter 2.12.

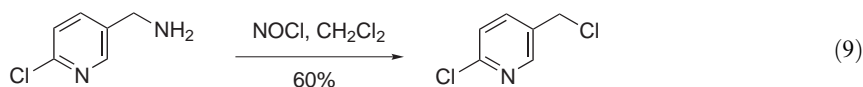


Scheme 5

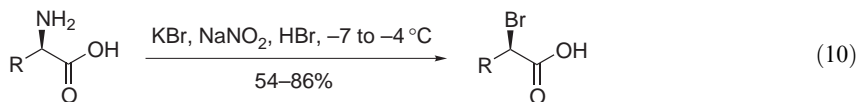


(Aminomethyl)pyridines are converted into (chloromethyl)pyridines via nitrosation (e.g., diazotization) in the presence of a thinning agent and, optionally, in the presence of HCl at −20 °C

to 5 °C. Thus, 5-(aminomethyl)-2-chloropyridine reacts with NOCl in CH₂Cl₂ to afford 2-chloro-5-(chloromethyl)pyridine in 60% yield (Equation (9)) <1995EUP632021>.



α -Amino acids with diverse, protected side chain functionality are transformed to the corresponding α -bromo acids in good yield and with high enantiopurity by treatment with KBr/NaNO₂/HBr (Equation (10)) <1999S583>.

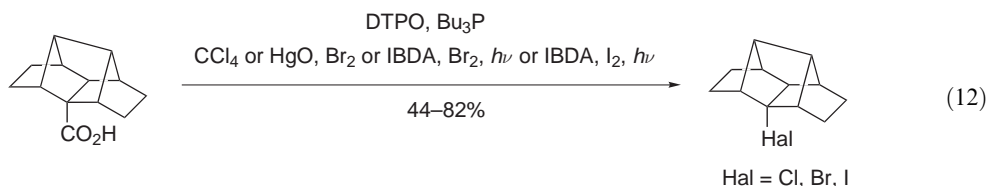


Finally, iodomethyltriethylammonium iodide is converted into ethyl iodide upon heating at 101 °C in CD₃CN (Equation (11)) <1999JCS(P2)1187>.



2.01.1.6 Alkyl Halides by Halodecarboxylation of Carboxylic Acids and Their Derivatives

8-Chloro-, 8-bromo-, and 8-iodo-pentacyclo[6.4.0.0^{2,8}.0^{3,7}.0^{4,9}]dodecane are prepared by halodecarboxylation of the corresponding acid (Equation (12)) <1999S854>.



The reagents which are used for the transformation of a carboxyl group to the halogen are first 2,2'-dithiobis-(pyridine-1-oxide) (DTBPO)/Bu₃P and, subsequently, CCl₄ for chlorides, HgO/Br₂/CH₂Br₂ or iodosobenzene diacetate (IBDA)/Br₂/CH₂Br₂/h ν for bromides, and iodosobenzene diacetate (IBDA)/I₂/benzene/h ν for iodides.

2.01.1.7 Alkyl Halides by Haloalkylation of Arenes

No significant developments have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)1>.

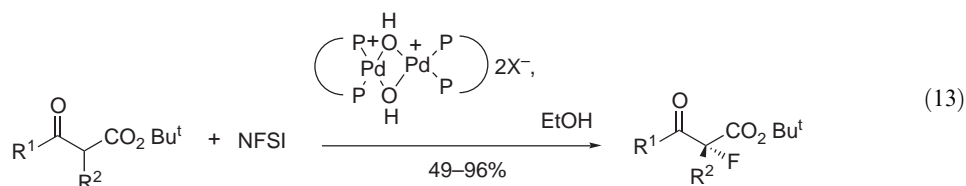
2.01.2 ALKYL FLUORIDES: RF

Fluorine-containing organic molecules find extensive use in biochemistry and medicinal chemistry as well as in material science. Therefore, selective fluorination (C—F bond formation) is regarded as one of the new frontiers in organic synthesis and there is also a continuing search for convenient and safe fluorinating agents <B-1995MI002, B-1999MI001, B-1999MI002, B-1999MI003>.

2.01.2.1 Alkyl Fluorides from Alkanes

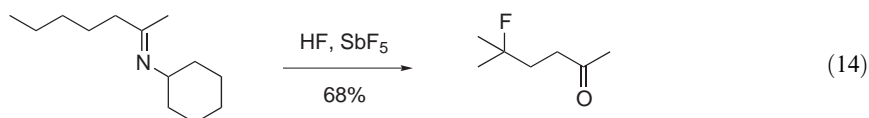
Selective fluorination of a range of hydrocarbons is achieved by reaction of elemental fluorine via an electrophilic mechanism <2002JCS(P1)2190>. However, it is well known that this is an exception since fluorination of unactivated alkanes with fluorine usually leads to either polyfluorination or fragmentation <1995COFGT(2)1>.

Using chiral palladium complexes, various β -ketoesters, including cyclic and acyclic substrates, are fluorinated by *N*-fluorobenzenesulfonimide with excellent enantioselectivity (Equation (13)).



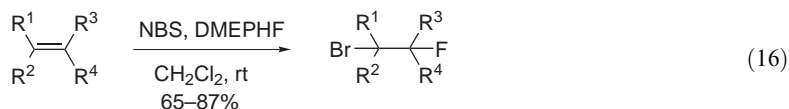
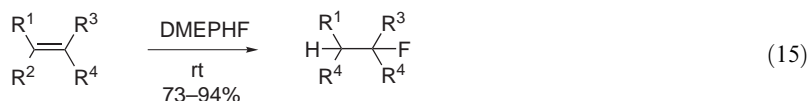
It is environmentally advantageous as this reaction proceeds well in solvents such as EtOH, rather than the usual organic solvents <2002JA14530>.

The reaction of cyclic imines in HF/SbF₅ in the presence of CCl₄ yields fluoro derivatives in good yields. A representative example is shown in Equation (14) <2002T6643>.

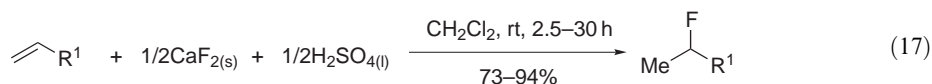


2.01.2.2 Alkyl Fluorides from Alkenes

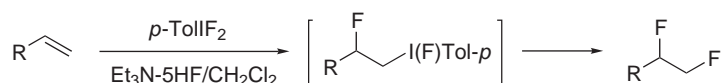
It is well known that the most widely used fluorinating reagents, namely anhydrous hydrogen fluoride (HF) and amine-stabilized HF, have some difficulties in handling and with regard to stability mainly because of HF volatility, high reactivity, corrosiveness, and toxic nature <1995COFGT(2)1>. Recently, the stable dimethyl ether/poly(hydrogen fluoride) (DMEPHF) was found to be a convenient and effective agent for hydrofluorination as well as for bromo-fluorination of alkenes <2002JA7728>. The monofluoro products were obtained in good-to-excellent yields (73–94%) with high selectivity (Equation (15)). Bromofluorination of alkenes can also be carried out with DMEPHF in good yields (65–87%) (Equation (16)).



The *in situ* generation of anhydrous HF by reaction of solid CaF₂ with H₂SO₄ in an inert organic solvent at ambient temperatures and pressures has been reported as an effective reagent for the hydrofluorination of alkenes in good yields (66–86%) (Equation (17)) <1999JCS(P1)1491>. When oct-1-yne was used as substrate 2-fluorooctene was easily isolated in 55% yield <1999JCS(P1)1491>.



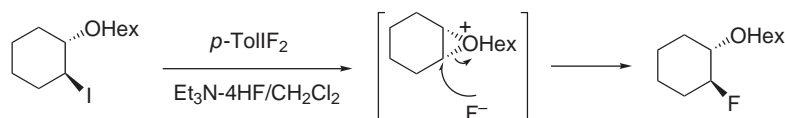
It has also been reported that *p*-iodotoluene difluoride (*p*-TolIF₂) reacts with 1-alkenes in the presence of an amine-HF complex to give *vic*-difluoroalkanes selectively. The reaction can be explained by presuming the formation of hypervalent alkyl iodine intermediates (Scheme 6) <2001T3315>.



Scheme 6

2.01.2.3 Alkyl Fluorides from Alkyl Halides

1-Chlorododecane has been converted to 1-fluorododecane in 35% yield under treatment with potassium fluoride in DMF at 170 °C <1997LA1333>, whereas 1-bromobutane led to the formation of 1-fluorobutane in 69% yield by treatment with KF in tetrahydrothiophene 1,1-dioxide for 5 h at 180–200 °C <2000MI3018>. A semimolten mixture of tetrabutylammonium fluoride (TBAF) and an alkali metal fluoride (KF or CsF) has been reported to be an efficient reagent system for the fluoride-ion displacement reaction on organohalides in very good yields (69–91%) <1995JFC185>. Hydrated TBAF, in particular the pentahydrate, has also been used to successfully displace chlorides, bromides, and iodides <1998JOC9587>. Reaction of alkyl bromides with polymer-bound tetraalkylammonium fluorides resulted in the formation of alkyl fluorides <2001SL547>. Tetrabutylammonium hydrogen difluoride in the presence of pyridine, in dioxane or THF, has been proved to be an effective reagent for nucleophilic fluorination <1998TL7305>. The oxidative fluorination of alkyl iodides with *p*-iodotoluene difluoride and Et₃N·4HF is an interesting process for the conversion of primary alkyl iodides to the corresponding alkyl fluorides <2001T3315>. Under the same conditions, *trans*-2-alkoxyiodocyclohexane gives *trans*-2-alkoxyfluorocyclohexane in moderate yield. As the *trans*-stereochemistry was completely retained, the reaction may take place through an oxonium intermediate (Scheme 7) <2001T3315>.



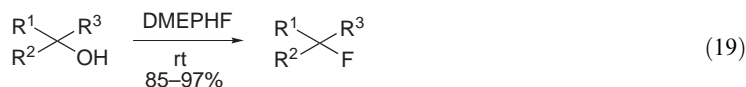
Scheme 7

Alkyl bromides were smoothly transformed to the corresponding alkyl fluorides by reacting with the fluoro complex [RuF(dppp)₂]PF₆ (dppp = propane-1,3-diylbis-[diphenylphosphine]) (Equation (18)) <1999HCA2448>.

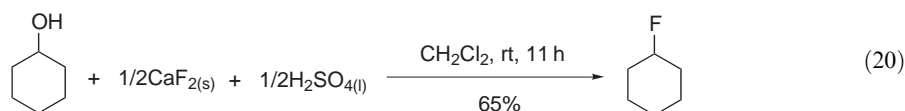


2.01.2.4 Alkyl Fluorides from Alcohols and Their Derivatives

The fluorination of tertiary and secondary alcohols via treatment with DMEPHF takes place in good-to-excellent yields (85–95%) (Equation (19)) <2002JA7728>. Secondary alcohols react sluggishly with DMEPHF at room temperature.

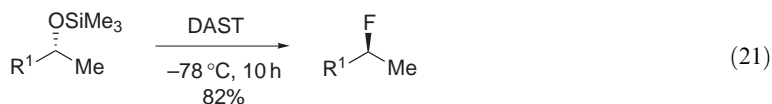


The substitution of hydroxy groups has been reported to proceed successively via addition of HF generated *in situ*. Cyclohexanol was converted to fluorocyclohexane in 65% yield (Equation (20)) <1999JCS(P1)1491>.



2,2-Difluoro-1,3-dimethylimidazolidine (DFI) is a new deoxo-fluorinating agent that is useful for the conversion of primary, secondary, and tertiary alcohols to alkyl fluorides in good yield <2002CC1618>.

Fluorination of (*R*)-2-octanol with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 resulted in poor selectivity, whereas modified fluorination of the corresponding silyl ether was found to give products with high selectivity (Equation (21)) <1995T8771>.



Ammonium or phosphonium perfluorocyclobutane ylides have been used for the replacement of hydroxyl groups by fluorine in alcohols. The reaction with primary or secondary alcohols proceeds in high or moderate yields with little side reaction, such as alkene formation <1996T2977>. Alcohols are transformed to alkyl fluorides on treatment with $\text{Ph}_2\text{S}(\text{O})\text{F}_2$ <2000JFC279>.

1,1,2,2-Tetrafluoroethyl-*N,N*-diethylamine (TFEDA) is found to be an effective reagent for the conversion of alcohols into alkyl fluorides. Reaction of TFEDA with primary alcohols proceeds with the formation of the corresponding alkyl fluorides in high yields at elevated temperatures. However, the reaction of secondary and tertiary alcohols rapidly takes place at 0–10 °C, producing corresponding alkyl fluorides as major products along with some alkenes <2001JFC25>.

Finally, transformation of alcohols to alkyl fluorides has also been achieved by reacting with IF_5 in $\text{Et}_3\text{N}\cdot 3\text{HF}$ <2001CL222>, whereas the hydroxy groups of phenols can be replaced with fluorine by DFI <2002CC1618>.

2.01.2.5 Alkyl Fluorides from Amines and Their Derivatives

These methods are discussed in Section 2.01.1.5.

2.01.2.6 Alkyl Fluorides by Fluorodecarboxylation of Carboxylic Acids and Their Derivatives

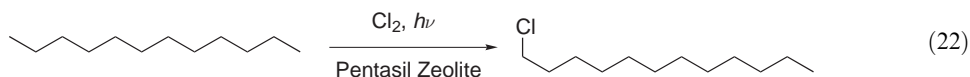
These methods are discussed in Section 2.01.1.6.

2.01.3 ALKYL CHLORIDES: RCl

Alkyl chlorides are commonly used as both very useful synthetic intermediates and valuable end products. Therefore, there is a continuous search for new reagents and improved preparative procedures for alkyl chlorides.

2.01.3.1 Alkyl Chlorides from Alkanes

The photoinduced chlorination of *n*-dodecane adsorbed on pentasil zeolites has been found to proceed, under a variety of conditions, with a high selectivity to produce 1-chlorododecane (Equation (22)) <1995JA4881>. In contrast, photochlorination of *n*-dodecane in solution afforded all the monochlorododecanes in comparable yields.

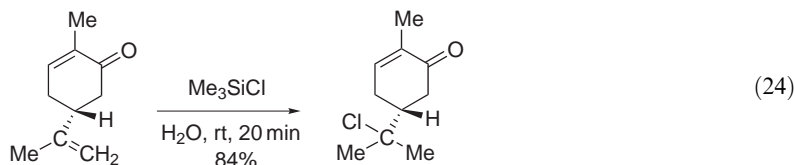
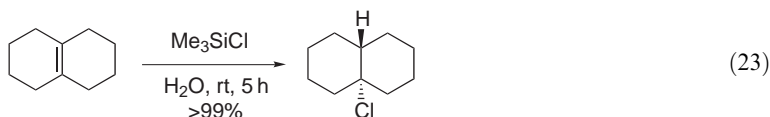


Supercritical carbon dioxide (SC-CO_2) has been found to be an excellent solvent for radical reactions such as photochlorination of alkanes <1998JA11839>.

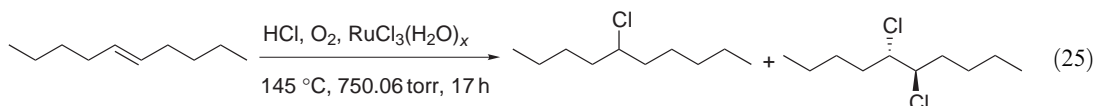
Heating of hexane at 120 °C in carbon tetrachloride and acetonitrile in the presence of catalyst $\text{PdBr}_2(\text{PPh}_3)_2$ gave a mixture of 1-, 2-, and 3-chlorohexane <1998ZOR862>. Reaction of 2-methylpropane with chromoyl chloride (CrO_2Cl_2) in cyclohexane gave 2-chloro-2-methylpropane along with a variety of other products <1995JA7139>. Similarly, treatment of propane with Cl_2 and O_2 at 10 torr led to many products in addition to 2-chloropropane <1996JPC18870>.

2.01.3.2 Alkyl Chlorides from Alkenes

Treatment of a 1:1:1 mixture of phenol, hex-1-ene and HCl in CHCl_3 at room temperature afforded 2-chlorohexane in 65% yield [<1997JCS\(P1\)257>](#). Similarly, reaction of 2-methyl-but-1-ene in acetic acid with hydrochloric acid gave 2-chloro-2-methyl-butane as one of the products [<2002JCS\(P2\)810>](#). Hydrochlorination of simple, as well as functionalized, alkenes in high yields was readily accomplished using a mixture of trimethylchlorosilane and water (Equation (23)). This reaction has been proved to be chemoselective and regioselective (Equation (24)) [<1996SC3479>](#).



Reaction of 2-methylpropene with $\text{Bu}_3(\text{PhCH}_2)\text{NCl}\cdot\text{Cl}_2$ in CCl_4 at room temperature gave all possible monochlorinated products along with 1,2-dichloro and 1,2,3-trichloro-2-methyl-propane [<1998IZV1584>](#), whereas treatment of dec-5-ene with concentrated HCl and O_2 in the presence of $\text{RuCl}_3(\text{H}_2\text{O})_x$ for 17 h at 145°C and 750.06 torr led to the formation of both mono- and dichlorinated decane (Equation (25)) [<2001MI447>](#).

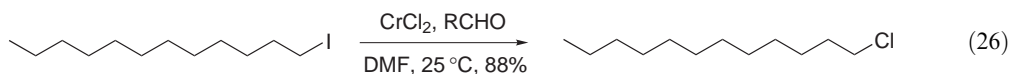


2.01.3.3 Alkyl Chlorides from Alkyl Halides

The rate constants for the reaction of chloride ion with methyl bromide under various buffer gas pressures and temperatures have been studied [<1995JA1828, 1997JPC\(A\)1501, 1997JPC\(A\)5543, 1997JCP1021>](#). The mechanism and the rate constant of the reaction of methyl bromide with chloride ion in H_2O at -32.1°C , which leads to methyl chloride, have been investigated [<1997JA577>](#).

Primary alkyl bromides can be quantitatively converted into the corresponding chlorides by treatment with trimethylsilyl chloride (TMSCl) in DMF at 90°C for 1 h in the presence of 2 equiv. of imidazole [<1996SC4563>](#).

Primary alkyl iodides are quantitatively transformed into the corresponding chlorides by their reaction with aldehydes and CrCl_2 in DMF (Equation (26)). In this case the rate of substitution by the chloride ion is faster than that of one-electron reduction with a chromium(II) ion. In contrast, secondary or tertiary alkyl iodides undergo reduction under the same conditions [<1998AG\(E\)152>](#).

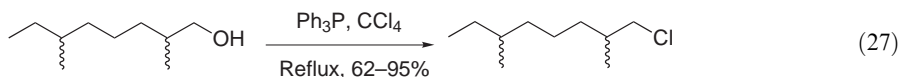


Finally, the rate constant of the reaction of iodoethane with chloride ion to form chloroethane has been studied [<1998JA6785>](#). The kinetics of the transformation of iodomethane into chloromethane under treatment with $\text{ICl}/\text{AgOTf}/\text{CD}_3\text{CN}$ or KCl have also been reported [<1995JA1828, 1998ZOR502, 1998ZOR670, 1998ZOR1293, 2002JOC7407>](#).

2.01.3.4 Alkyl Chlorides from Alcohols and Their Derivatives

A variety of reagents can be used to convert alcohols into alkyl chlorides [<B-1999MI002>](#). Substitution of alcohols with chloride ion is a widely used method for alkyl chloride preparation. Fuming [<2002JCS\(P1\)402>](#) or concentrated hydrochloric acid has been used for conversion of

tertiary alcohols into the corresponding chlorides in good yields <1996AG830, 1999JPO564>. Various highly crowded tertiary alkyl chlorides having a neopentyl or a (1-adamantyl)methyl substituent on the reaction center have been prepared via treatment of the corresponding alcohols with dry HCl gas in pentane at 0 °C or –40 °C (2–10 min) <2000JA7351, 2001JPO229>. Alcohols are easily transformed into alkyl chlorides upon heating with PPh₃/CCl₄ (Equation (27)) <1999ACS620, 1999JOC5581, 2001EJO353>.



Use of chlorotriphenylphosphonium dichlorophosphate, alkyltriphenylphosphonium chloride, or PCl₃ gives good yields of alkyl chlorides from primary alcohols <1995JOC2638, 2001IJ(B)842, 2001ZOB1307>. TMSCl/DMSO has been applied to alkyl chloride synthesis from primary and tertiary alcohols <1996JPC9671>. Silica chloride in CCl₄ easily transforms secondary alcohols into alkyl chlorides <1996OPP492>, whereas phenyltrichlorosilane converts primary alcohols into the corresponding alkyl halides <1999ZPK493>.

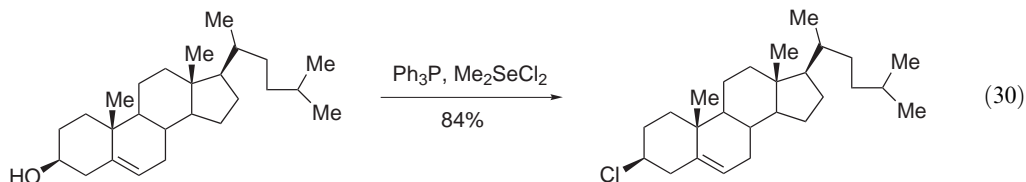
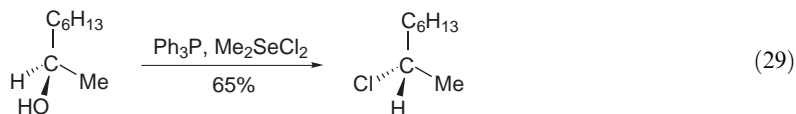
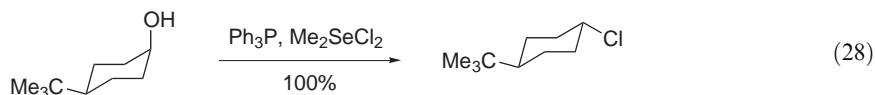
Cyclic, secondary, and tertiary alcohols are easily chlorinated with BiCl₃ in CCl₄ or without any solvent. The reaction is heterogenous since BiCl₃ is not soluble in CCl₄. Primary alcohols did not react under the same conditions <1995BSF522, 1998SC1737, 2001T1909>.

Classical methods using hydrochloric acid usually work well on tertiary systems <1998JOC7707> where an S_N1 mechanism is favored.

Thionyl chloride (SOCl₂) gives primary and tertiary alkyl chlorides from alcohols <1995MI783, 1999SL1763, 2002JOC1490>, sometimes with inversion of configuration <2000JCS(P2)2232>.

Trichloroisocyanuric acid with triphenylphosphine in anhydrous acetonitrile can convert primary alcohols into alkyl chlorides <2002SC2691>. Analogous results are obtained by using PPh₃/CCl₄ <2002TA835> or other reagents such as PCl₅, 1-*n*-butyl-3-methylimidazolium chloride/MeSO₃H or 2-chloro-1,3-dimethylimidazolium chloride/Et₃N/CH₂Cl₂ <1999JOC5832, 1999SC1415, 2001OL3727>.

Triphenylphosphine/dichloroselenurane has been reported to rapidly convert alcohols into alkyl chlorides <1998JOC9565>. It was found that the reaction proceeds either with inversion of configuration (cyclic, acyclic chiral alcohols) (Equations (28) and (29)) or with retention of configuration (cholesterol) (Equation (30)) <1998JOC9565>. Thus, the stereochemistry of this reaction is similar to that observed with other reagents due to the S_N1 mechanism involving the participation of a homoallylic carbonium ion.

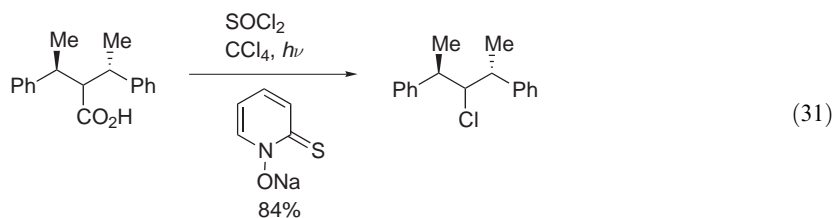


2.01.3.5 Alkyl Chlorides from Amines and Their Derivatives

Methodologies for these transformations are discussed in Section 2.01.1.5.

2.01.3.6 Alkyl Chlorides by Chlorodecarboxylation of Carboxylic Acids and Their Derivatives

(*S*)-3-Phenyl-2[(*S*)-phenylethyl]butanoic acid was converted to the corresponding chloride by refluxing with thionyl chloride and by subsequent irradiation in CCl₄ in the presence of sodium salt of 2-mercaptopyridine-*N*-oxide (Equation (31)) <1999JOC5581>.



2.01.4 ALKYL BROMIDES: RBr

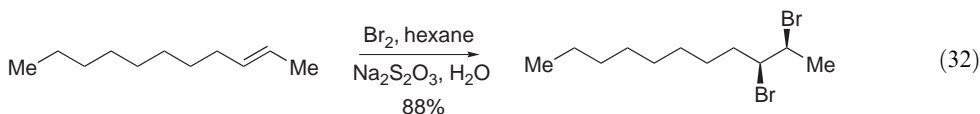
Alkyl bromides are important and versatile intermediates for use in a variety of reactions. There are numerous methods for accessing bromides <1995COFGT(2)1>. Although these compounds have similarities with alkyl chlorides, they have the benefit that they can be prepared and used under mild and neutral conditions.

2.01.4.1 Alkyl Bromides from Alkanes

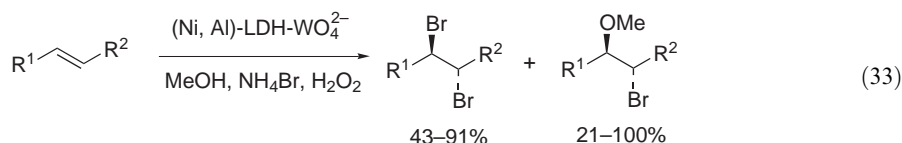
The aprotic organic superacid polybromomethane·2AlBr₃ (CBr₄·2AlBr₃) was shown to effectively catalyze low-temperature ionic bromination of alkanes and cycloalkanes <1995TL9365, 1996IZV1208>. Thus, ethane readily reacts with Br₂ at 55–65 °C, affording mainly 1,2-dibromoethane. Propane, butane, and C₅–C₆ cycloalkanes react at –40 to –20 °C, resulting in the formation of monobromides in high yield and good selectivity <1995TL9365, 1996IZV1208>.

2.01.4.2 Alkyl Bromides from Alkenes

Reactions using a fluorosolvent, such as perfluorohexanes, along with a second solvent less dense than the fluorosolvent, such as hexane or dichloromethane, containing the alkene are used for the stereoselective bromination of alkenes to give dibromides in 68–97% yield <2002JA12946>. A characteristic example is shown in Equation (32).

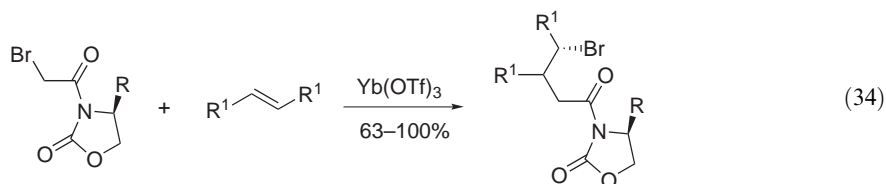


Tungstate (WO₄²⁻), exchanged on an (Ni, Al)-layered double hydroxide (LDH or hydrotalcite-type structure), is applied as a heterogeneous catalyst in the electrophilic bromination of alkenes. The high halogenation activity of the catalyst in essentially neutral conditions mimics the activity of bromoperoxidase enzymes. In methanol, alkenes are converted to methoxybromides and dibromides. These reactions show high chemo-, regio-, and stereoselectivities (Equation (33)) <2001JA8350>.

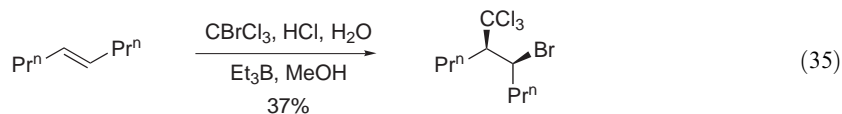


Bromoacetyl-2-oxazolidone amides undergo clean atom-transfer addition to 1-hexene as well as *cis*- or *trans*-3-hexene in the presence of Lewis acids to give the corresponding adduct products (Equation (34)). The best Lewis acids for this conversion are Sc(OTf)₃ and Yb(OTf)₃ <1999JA5155>. Secondary bromides react in the same way with 1-hexene but fail to react with

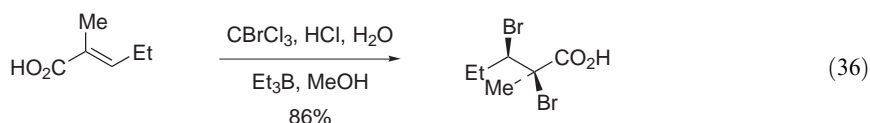
internal alkenes. Tertiary bromides do not react with alkenes. Use of chiral auxiliary oxazolidinones gives excellent control of configuration at the new stereogenic center generated in the final adduct product.



Treatment of alkenes with CBrCl_3 in the presence of a catalytic amount of triethylborane provides the corresponding adduct in good yield via an intermolecular radical addition reaction (Equation (35)) <1998SL1351>.



Trans-2-methyl-2-pentenoic acid is easily brominated with bromine. The reaction is stereoselective (Equation (36)) <1998SC729>.



2.01.4.3 Alkyl Bromides from Alkyl Halides

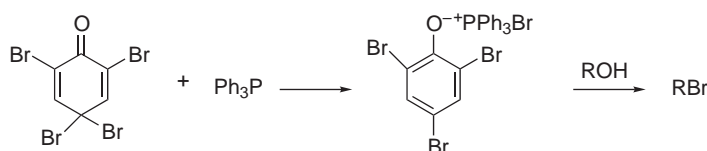
Lithium bromide (LiBr) in acetone or tetramethylammonium bromide (Me_4NBr) in acetonitrile easily transforms iodoethane to bromoethane <1996BCJ2619, 1997JCS(P2)1765, 2002JCS(P2)1449>. Furthermore, bismuth tribromide (BiBr_3) in 1,2-dichloroethane or methylene chloride converts primary, secondary, and tertiary alkyl iodides to the corresponding alkyl bromides in very good yields <1999T1971>.

2.01.4.4 Alkyl Bromides from Alcohols and Their Derivatives

$\text{Ph}_3\text{P}/\text{Br}_2$ in CH_2Cl_2 is a classical reagent for the transformation of primary alcohols into the corresponding bromides in good yields (49–73%) <2000MI2737>. Analogously, PBr_3 as well as $\text{Ph}_3\text{P}/\text{CBr}_4/\text{CH}_2\text{Cl}_2$ convert alcohols into alkyl bromides <1995LS2021, 1996BMC375, 1998JOM157>.

Bromotriphenylphosphonium salts, generated by adding 2,4,4,6-tetrabromo-2,5-cyclohexadienone to triphenylphosphine in methylene chloride or acetonitrile, convert alcohols to the corresponding bromides in high yields (Scheme 8) <1997TL1955>.

Primary alcohols are easily converted into alkyl halides in very good yields, often almost quantitatively, under treatment with several reagents such as: (i) allyltriphenoxyphosphonium bromide <2001IJC(B)842>; (ii) concentrated H_2SO_4 and HBr or KBr <1996IZV204,



Scheme 8

1998RRC215, 1999JIC246, 1999JMC593, 2000TL7499, 2001JOC3709, 2001SC2817>; (iii) BrCN/Ph₃P <1995MI253>; (iv) Ph₃P/CBr₄ <1996BMC375, 1997CPB1767, 1999MI21, 2000CPB272, 2000T5493, 2001S451, 2002H403>; (v) Ph₃P/Br₂ <1995TL8315, 1997MI1119, 2000MI1135, 2000MI2737, 2000S1863, 2001EJO3175, 2001JA6253, 2002JCS(P1)1810>; (vi) PBr₃ and heating <1995LS2021, 1998JOM157, 1999JIC246, 2000BMC665>; (vii) red phosphorous and Br₂ <2002TA835>; and (viii) NBS/Ph₃P <2001OL3253, 2002S479>.

It is well known that heating of alcohols with HBr in the presence of tetraalkylammonium bromides leads to the formation of alkyl bromides <2000TL7107>. Tertiary alcohols are also converted to tertiary halides under reflux with aqueous HBr <2001CEJ4790>. Furthermore, fatty alcohols are transformed into alkyl bromides via treatment with aqueous HBr in the presence of catalytic amounts of long chain quaternary ammonium salts (e.g., *n*-C₁₈H₃₇NMe₃Br) and microwave irradiation <1996MI847>.

2,4,4,6-Tetrabromo-cyclohexa-2,5-dienone in the presence of triphenylphosphine at room temperature transforms primary alcohols into the corresponding alkyl bromides in quantitative yield <1997TL1955>.

Bromine in the presence of catalytic amounts of 1,2-bis-(diphenylphosphino)ethane in CH₂Cl₂ easily transforms secondary alcohols into the corresponding bromides with inversion of configuration <1998ACS778>.

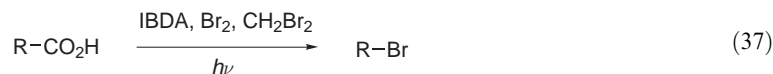
Finally, secondary alcohols are also transformed in the corresponding halides by PPh₃/Br₂ <1995MI2027, 1996MI103, 1999JPC(B)9690>.

2.01.4.5 Alkyl Bromides from Amines and Their Derivatives

These transformations are discussed in [Section 2.01.1.5](#).

2.01.4.6 Alkyl Bromides by Bromodecarboxylation of Carboxylic Acids and Their Derivatives

Carboxylic acids are bromodecarboxylated in moderate-to-good yield on reaction with iodoso-benzene diacetate (IBDA) and bromine under irradiation with a tungsten lamp. The reaction works very well with carboxylic acids having a primary, secondary, or tertiary α-carbon atom, although diphenyl acetic acid gives benzophenone ([Equation \(37\)](#)) <2000T2703>.

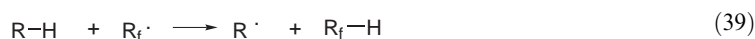


2.01.5 ALKYL IODIDES: RI

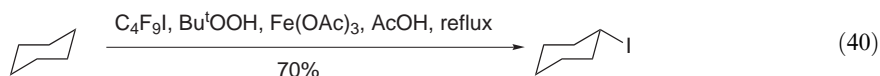
Alkyl iodides are the most reactive of the alkyl halides and in some cases iodides show unique reactivity. Their chemistry is very similar to that of the bromides. Both bromides and iodides are often used for carbon-carbon bond formation via radical or substitution reactions. In addition, they serve as intermediates in a wide variety of reactions and rearrangements.

2.01.5.1 Alkyl Iodides from Alkanes

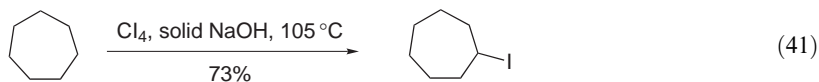
The direct free-radical iodination of alkanes by iodine, unlike the other halogens, is not feasible owing to the large positive enthalpy of hydrogen abstraction ([Equation \(38\)](#)). The rates of hydrogen abstraction from C-H bonds ([Equation \(39\)](#)) by perfluoroalkyl radicals (R_f·) are >10³ times larger than those of the analogous hydrocarbon radicals <1996CRV1557>.



Perfluoroiodides convert alkanes, in the presence of catalytic amounts of Bu^tOOH and $\text{Fe}(\text{OAc})_3$, to a mixture of alkyl iodides <1997CC1501>. A representative example is given in Equation (40).



A few direct and efficient iodinations of unactivated aliphatic or cyclic hydrocarbons have recently appeared in the literature. One of these involves treatment of alkanes with Cl_4 in the presence of powdered NaOH (Equation (41)) <1999AG(E)2786>.



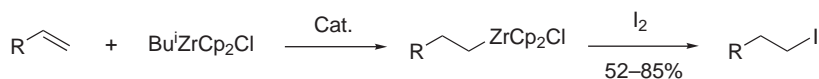
Direct iodination of alkanes can also be achieved by reaction with I_2 in the presence of $\text{CCl}_4 \cdot 2\text{AlI}_3$ in CH_2Br_2 (Equation (42)) <2002TL1333>.



2.01.5.2 Alkyl Iodides from Alkenes

Terminal alkenes are transformed into the corresponding alkyl iodides in two steps by treatment first with $\text{Bu}^t_3\text{Al}/\text{Cl}_2\text{Pd}(\text{PPh}_3)_2/\text{CH}_2\text{Cl}_2$ and subsequently with $\text{I}_2/\text{CH}_2\text{Cl}_2$ <2001TL785>.

Monosubstituted alkenes react with $\text{Bu}^t\text{ZrCp}_2\text{Cl}$ in the presence of catalytic amounts of various Lewis acidic metal compounds, most notably AlCl_3 , Me_3SiI , and Pd complexes such as Li_2PdCl_4 and $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$, and form products which are converted into alkyl iodides by treatment with iodine (Scheme 9) <1999EJO969>.



Scheme 9

$\text{AlCl}_3/\text{CH}_2\text{Cl}_2/\text{I}_2$ and $\text{HI}/\text{H}_2\text{O}/\text{AcOH}$ are reagents that convert alkenes into the corresponding alkyl iodides <2001OL3253, 2002JCS(P2)810>.

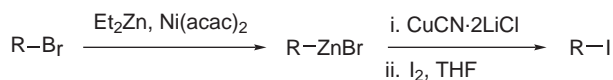
2.01.5.3 Alkyl Iodides from Alkyl Halides

Primary alkyl chlorides are easily converted into the corresponding iodides via treatment with sodium iodide <1998AQ56> or iodine <1995IZV1090>.

Poly(ethyleneglycol)-supported quaternary ammonium salt $\text{PhCH}_2\text{N}^+\text{Bu}_3\text{Br}^-$ efficiently catalyzes the reaction of primary alkyl bromides with potassium iodide to the corresponding alkyl iodides when the reaction is carried out under phase-transfer catalysis conditions <2000OL1737>. Potassium iodide in acetone <1997T13149>, sodium iodide in acetone <2001S451>, or hexakis-[N-(2-ethoxy)bis-(3,6,9,12,15-pentaoxaheptacosyl)amine]cyclophosphazene in chlorobenzene convert primary alkyl bromides to alkyl iodides almost quantitatively <1995G491>.

Primary alkyl bromides are converted into the corresponding alkyl iodides via a multistep process which is shown in Scheme 10. Primary alkyl bromides react with diethylzinc (Et_2Zn) in the presence of $\text{Ni}(\text{acac})_2$ to form the corresponding alkylzinc bromides via a Br-Zn exchange reaction. Transmetalation of zinc organometallics with $\text{CuCN} \cdot 2\text{LiCN}$ and subsequent treatment with iodine in THF leads to the formation of the corresponding alkyl iodides <1996JOC7473>.

The thermodynamic data for the transformation of bromoethane to iodoethane under treatment with LiI/MeCOCN , as well as for bromomethane to iodomethane under treatment with $\text{Me}_4\text{N}^+\text{I}^-/\text{MeCOCN}$, have been reported <1996BCJ2619, 2002JCS(P2)1449>.

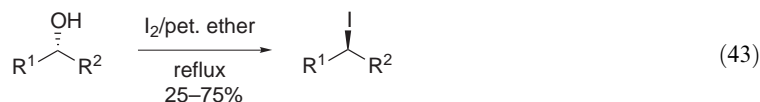


Scheme 10

2.01.5.4 Alkyl Iodides from Alcohols

Some of the methods for the transformation of alcohols to iodides have already been discussed in Section 2.01.1.4.1.

The adduct of triphenylphosphine with elemental iodine (Ph_3PI_2) is a classic reagent used to convert alcohols cleanly and with inversion to iodides <1996TL949>. Addition of imidazole is well known to promote this conversion with high yields <1996TL1913, 1997JOC784, 2000JA11799, 2000JA4984, 2000S1930, 2001MI18, 2001MI40, 2001MI463, 2000MI2723, 2002OL1447>. Furthermore, treatment of alcohols with triphenylphosphine and cyanogen iodide affords the corresponding iodides in good yields <1996MI217>. The reagent $\text{KI}/\text{BF}_3\cdot\text{Et}_2\text{O}$ in dioxane is highly selective and effective for the transformation of allylic and benzylic alcohols to iodides <2001TL951>. A mild and effective procedure for directly converting secondary, tertiary, and benzylic alcohols into the corresponding iodides involves treatment with iodine in refluxing petroleum ether. The reaction proceeds with inversion of configuration (Equation (43)) <1995TL609>. The reaction is selective for iodinating secondary alcohols in the presence of primary alcohols. Alkyl iodides can also be prepared in a single step from the corresponding alcohols upon treatment with the standard reagent P-I_2 <1998JA376, 2000JAP273057>. A less well used reagent, 1,2-bis-(diphenylphosphino)ethane, can be used to prepare iodides from primary alcohols in the presence of iodide <1996T12509>.



Cerium(III) chloride, a Lewis acid imparting high regio- and chemoselectivity in various chemical transformations, can be used in combination with sodium iodide in refluxing acetonitrile to replace a hydroxy by an iodo group (Equation (44)) <2000JOC2830>. This method cannot be applied to tertiary alcohols. In this case an alkene is derived by dehydration of the alcohol.



Finally, a classical method for the transformation of alcohols to halides is the well-known two-step procedure via a sulfonate ester, commonly tosylate (*p*-toluenesulfonate) <1995JCS(P1)1513, 1999EJO981, 2000MI973, 2000MI1713, 2000T8083, 2000TL4247, 2001MI1, 2001MI305, 2002MI233, 2002MI582, 2002MI1032, 2002TL3467> or mesylate (methanesulfonate) <1995OM5178, 1995TL687, 1996JOC7438, 2001SC827>. Treatment of the sulfonate esters with NaI or LiI gives iodides in good yields. The mechanism and the stereochemistry of the reaction has been extensively discussed in COFGT (1995) <1995COFGT(2)1>.

2.01.5.5 Alkyl Iodides from Amines and Their Derivatives

These methods have been discussed in Section 2.01.1.5.

2.01.5.6 Alkyl Iodides by Iododecarboxylation of Carboxylic Acids and Their Derivatives

These methods have been discussed in Section 2.01.1.6.

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2.02

Alkyl Chalcogenides: Oxygen-based Functional Groups

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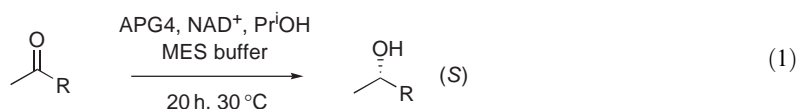
2.02.1 ALCOHOLS

The alcohol functional group is widespread in natural and unnatural products and has, therefore, long been the target of synthetic organic chemists. Hence, there is a wealth of literature concerning its synthesis and the reader is directed toward primary reviews in this area for a more detailed summary on the scope of the preparative routes available for obtaining this functional group <1995COFGT(2)37, 1996COS(3)65, 1997COS(4)435, 2000JCS(P1)2529>. This chapter focuses on developments in the area since the publication of COFGT (1995) <1995COFGT(2)37>, which have been dominated by novel asymmetric reactions, or “asymmetrized” versions of traditional processes.

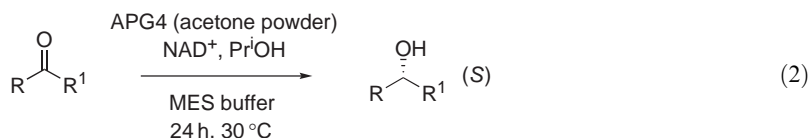
2.02.1.1 From Biotransformations

As described in COFGT (1995) <1995COFGT(2)37>, the utility and efficiency of obtaining alcohols via biotransformations, such as microbial oxidations of hydrocarbons, is extensively exploited in industry and since the 1990s the scope of enzymatic synthesis of alcohols has been expanded further. A particular reaction class that has attracted much attention is asymmetric reduction of carbonyls, which is an area of research that has recently been reviewed <2003TA2659>.

Thus, a wide range of ketones (the methods reported seem to focus especially upon methyl ketones) can be reduced with high levels of enantioselectivity to the corresponding (*S*)-alcohols using the well-known asymmetric reducing capabilities of *Geotrichum candidum* <2002MI703>. One study has reported upon the reduction of (mainly) aromatic ketones although β -ketoesters and certain aliphatic ketones are also reduced in good yield and with excellent enantioselectivity (Equation (1)) <1998JOC8957>.



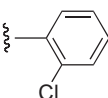
In an alternative process, ketoesters, aryl, alkyl, and dialkyl ketones are reduced enantioselectively using the acetone powder of *G. candidum* <1996TL1629> to afford (*S*)-configured secondary alcohols in good yields and again with excellent enantiocontrol. It is noteworthy that the enantioselectivity of the reduction is vastly superior using the acetone powder rather than the resting cell (>99% ee compared with 39% ee) (Equation (2) and Table 1).

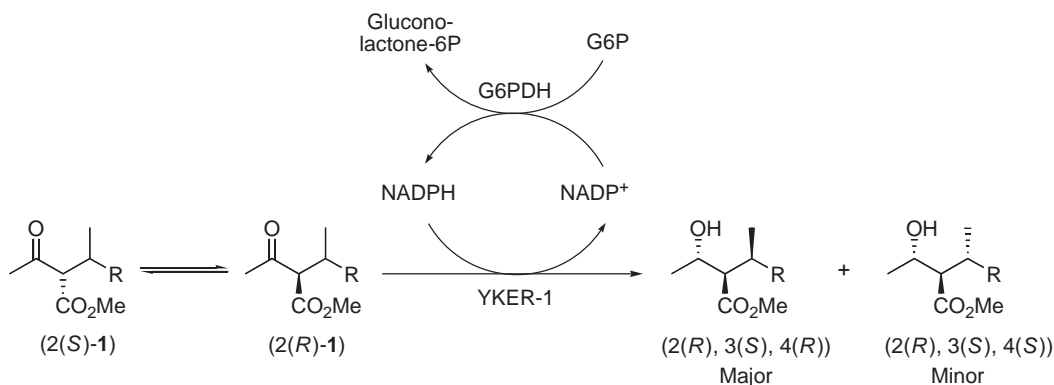


The microbial reduction of prochiral ketones utilizing *Yarrowia lipolytica* to give (*R*)-alcohols in variable yield and with poor-to-excellent enantiomeric excess has also been reported <1996T3547>.

4-Substituted 3-alkoxycarbonyl-2-pentanol of high diastereo- and enantiomeric purity may be obtained via bioreduction of 2-substituted ketoesters <1998TL9219>. The reaction involves a dynamic kinetic resolution, whereby only (2(*R*))-1 undergoes reduction by a reductase from bakers' yeast (YKER-1) (Scheme 1).

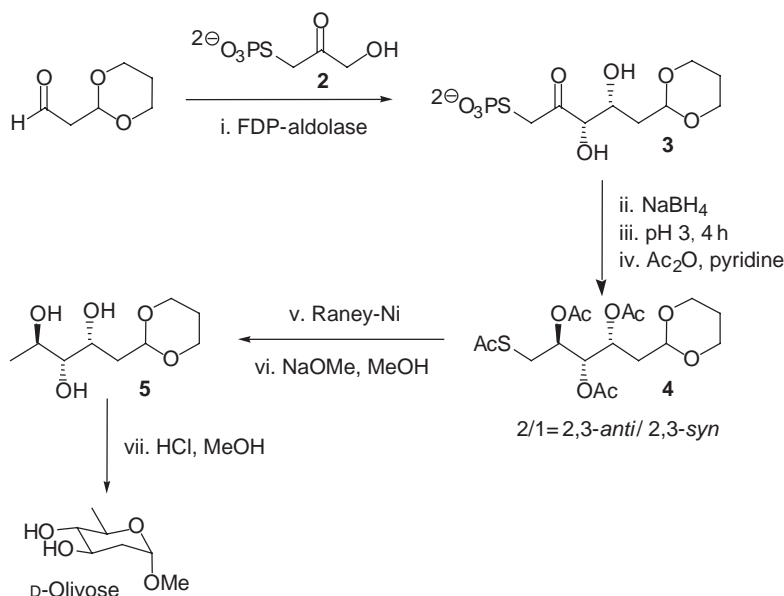
Table 1 Enantioselective reduction of ketones to (*S*)-alcohols using *G. candidum*

<i>R</i>	<i>R</i> ¹	<i>ee</i> (%)
Et	CO ₂ Me	>99
Et	CO ₂ Et	>99
Me	Ph	99
Me		>99

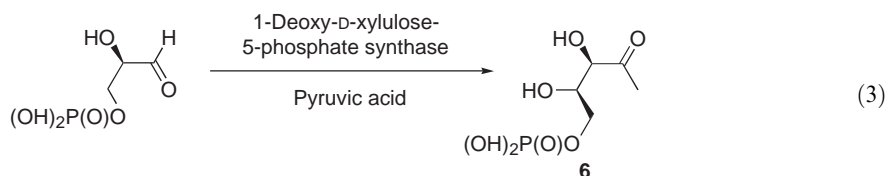
**Scheme 1**

2-Chloro-3-ketoesters are reduced with high diastereo- and enantioselectivity by a reductase from *Mucor plumbeus* <1995TA2199>, with the *anti*-2-chloro-3-hydroxyesters the favored products of the reaction.

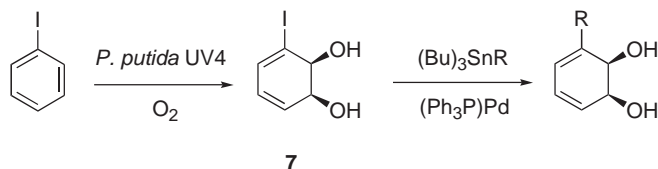
Deoxysugars may conveniently be prepared by aldolase-catalyzed reaction of 2-phosphatylthioalkyl ketones <1996JOC438>. Thus, reaction of 2-(formylmethyl)-1,3-dioxane with thiophosphate **2** in the presence of FDP-aldolase gave (it was inferred) the 3,4-*syn* diol aldol product **3**, which was not isolated but was reduced, dephosphorylated, and acetylated to give thiosugar **4**. Upon desulfurization and ketal hydrolysis, the triol **5** was converted into D-olivose (Scheme 2).

**Scheme 2**

The biosynthesis of 1-deoxy-D-xylulose-5-phosphate **6**, an intermediate in three major biosynthetic pathways, has been successfully obtained through the aldol condensation reaction of glyceraldehyde-3-phosphate with pyruvate in the presence of *E. coli* 1-deoxy-D-xylulose-5-phosphate synthase (Equation (3)) <1998JOC2375>. The synthesis of the phosphate **6** may also be effected by treating fructose-1,6-diphosphate and pyruvate with rabbit-muscle aldolase, triosephosphate isomerase, and partially purified synthase. Under this protocol **6** was obtained as its barium salt in 47% yield.

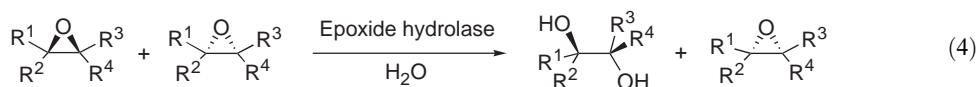


A chemoenzymatic route to a range of enantiomerically pure dihydrobenzene diols, which are difficult to obtain directly, have been prepared by utilizing *cis*-(1(*S*), 2(*S*))-1,2-dihydroxy-3-iodocyclohexa-3,5-diene **7** in Stille-like couplings (Scheme 3) <1998JCS(P1)1935>.

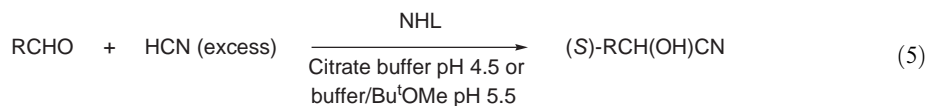


Scheme 3

Alcohols, in particular vicinal diols, can be acquired from the asymmetric hydrolysis of epoxides using epoxide hydrolases <1997MI491, 1999MI159, 1999MI199, 2001MI552>. These biocatalysts, isolated from a wide range of sources, are capable of forming a single enantiomeric diol from a racemic epoxide. In the majority of cases the reaction comprises a kinetic resolution in which one enantiomer is preferentially hydrolyzed over the other enantiomer <1995TA1911>. It has been found that both bacteria and filamentous fungi are excellent biocatalysts for achieving the resolution of several racemic epoxides. For example, bacterial epoxide hydrolases are highly enantioselective in the hydrolysis of 2,2- and 2,3-disubstituted epoxides (Equation (4)) <1999COCB16>. Alternatively, yeast epoxide hydrolase, from *Rhodotorula glutinis*, has been demonstrated to enantioselectively hydrolyze numerous aryl, alicyclic, and aliphatic epoxides.



(*S*)-Cyanohydrins of high enantiomeric purity can be obtained biosynthetically from the reaction of a range of aldehydes with HCN, catalyzed by the hydroxynitrile lyase (HNL) from *H. brasiliensis* (Equation (5)) <1998T14477>. Methyl ketones also undergo the reaction but with inferior levels of enantiocontrol (75–89% ee). The yields and enantioselectivity of the reaction are affected by the buffer system used.



2.02.1.2 By Addition to Alkenes

The addition of oxygen-containing species to alkenes is one of the most frequently employed synthetically efficient routes to alcohols: the acid-catalyzed hydration of alkenes is the simplest of all processes. Other well-used addition reactions include oxymercuration and the ubiquitous hydroboration reaction (previously discussed in detail in COFGT (1995) <1995COFGT(2)37>).

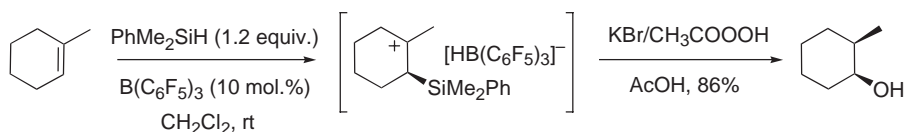
A recent report has described the oxymercuration–demercuration of 4,6-dimethyl-*s*-triazin-2-yl-substituted alkenes which give the unexpected *anti*-Markovnikoff product <2002JOC3202>. The regioselectivity was rationalized as an effect due to the presence of an adjacent, conjugated electron-withdrawing triazinyl substituent, which destabilized any positively charged intermediate on the adjacent α -carbon.

Allylic and homoallylic alkoxy functionality have been shown to exhibit powerful directing effects on the regioselectivity of hydroboration–oxidation processes <1999TL7907>. Thus, the usual *anti*-Markovnikoff regioselectivity was inverted: homoallylic oxygen functionality was found to have the greatest influence on the regiochemistry of hydration, while allylic oxygen functionality was observed to be the key stereocontrol element.

Since the publication of COFGT (1995), there have been more reports of the synthetic utility of main-group and transition metal-catalyzed hydroborations. Metals such as Li, Ni, La, Ru, Ir <2000OL981>, Ti <1996JA1696>, and Zr <1995CC979> have all been utilized, but Rh(I) has remained the metal of choice for such catalyzed hydroborations <1997T4957, 2000OL981>. The hydroboration of *trans*-4-octene using pinacolborane and RhCl(PPh₃)₃ has been reported to give only 1-octanol <1996JA809>. That the mechanism of Rh-catalyzed hydroborations is considerably more complicated than meets the eye was demonstrated when either 1-octene, *trans*-2-octene, or *trans*-4-octene were treated with RhCl₃·*n*H₂O and borane: in all cases, 1-octanol was the minor product and 4-octanol was the major product <2002JOC2481>. The observed regioselectivity of hydroboration was accounted for by considering the solubility of the catalyst, the oxidation state (Rh(III)), and the nature of the ligands surrounding the metal.

Alkenes undergo reactions with NO₂-diphenyl diselenide to afford products arising from the addition of O₂NO–SePh to the alkene <1996JCS(CC)475>. The reaction is highly regioselective, with the selanyl moiety of the product becoming attached to the least-hindered carbon of the alkene. The resulting nitrate esters can be hydrolyzed on silica gel to give the corresponding 2-hydroxy-1-phenylselanylalkanes in moderate-to-good overall yield.

Hydrosilanes undergo addition to C=C double bonds under catalysis by transition metal complexes to form alcohols, after subsequent oxidative cleavage of the C–Si bond. These asymmetric hydrosilylations have become a useful method for the preparation of optically active alcohols from alkenes. For asymmetric hydrosilylation of alkenes catalyzed by palladium complexes coordinated to axial chiral monophosphine the reader is recommended to the review by Hayashi <1999MI127>. Recently a convenient method for the Lewis acid-catalyzed, *anti*-selective hydrosilylation of alkenes has been developed <2002JOC1936>. The mechanism involves the direct addition of silylium-type species across the double bond followed by trapping of the resulting carbenium ion with a catalytic amount of boron-bound hydride (Scheme 4).



Scheme 4

Norbornene undergoes an asymmetric hydrosilylation reaction with trichlorosilane, catalyzed by chiral pyrazolyl ferrocenyl ligands **8** <1998TA3903>. The enantioselectivity of the reaction is improved by judicious choice of ligand substituents (Equation (6) and Table 2).

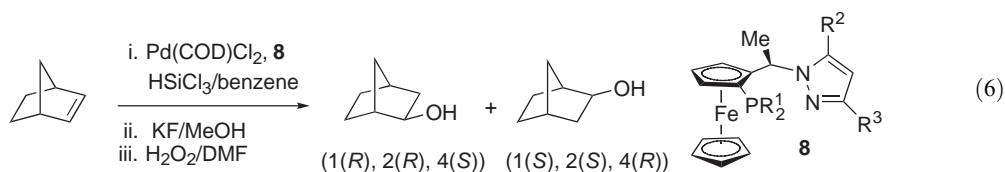
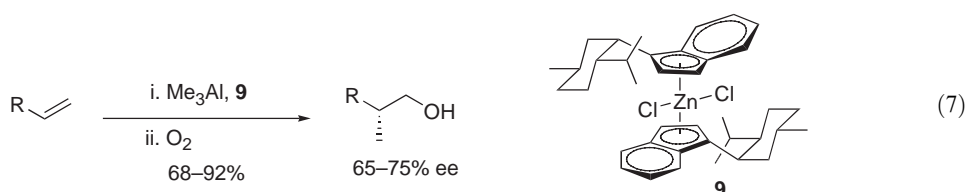


Table 2 Effect of ligand substituents on the asymmetric hydrosilylation of norbornene

R^1	R^2	R^3	Temp (°C)	ee (%)	Yield (%)
Ph	Me	Me	70	10	54
Ph	Me	Ph	50	39	47
Ph	H	9-Anthracenyl	25	81	54
Ph	H	2,4,6-(OMe) ₃ C ₆ H ₂	0	82	30
Ph	H	2,4,6-(Me) ₃ C ₆ H ₂	0	91	56
3,5-(F ₃ C) ₂ C ₆ H ₃	H	2,4,6-(Me) ₃ C ₆ H ₂	0	> 99.5	59

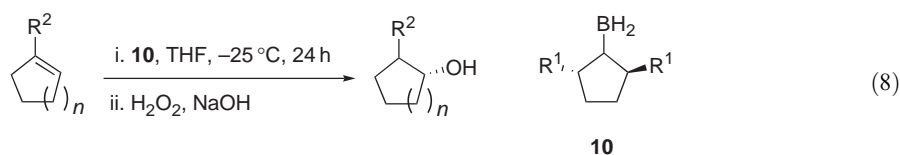
Dichlorobis(1-neomenthylindenyl)zirconium **9** mediates the asymmetric carboalumination of terminal alkenes (Equation (7)) <1995JA10771>. Reaction of alkyldimethylalane with oxygen gives the alkylative primary hydroxylation product in good yield with moderate enantiomeric excess.



2.02.1.2.1 Stereo- and enantiocontrol in hydroboration

Hydroboration is a *syn*-addition process, with addition occurring at the least-hindered alkenic face, and the overall sequence is an *anti*-Markovikoff hydration. A wide variety of alkylboranes <1995JOM1> and haloboranes <1996OM3504, 1996JOC5140, 1996TL1763> are commercially available and are especially useful in asymmetric hydroboration reactions <B-2001MI2025>. Camphor-derived chiral allenes undergo diastereoselective hydroboration reactions <2002JOC1308>. Thus, treatment of the allene with 9-BBN in THF followed by the usual oxidative work-up produces allylic alcohols with good diastereoselectivity (72–89% de).

Knochel and co-workers <1998AG(E)3014> have introduced a new class of *pseudo*-C₂-symmetric ligands to the asymmetric hydroboration of cyclic alkenes using chiral monoalkylboranes **10** (Equation (8)) <1999T8801>. The key feature of these cyclopentane ligands is the presence of a nonstereogenic center (chirotopic center).



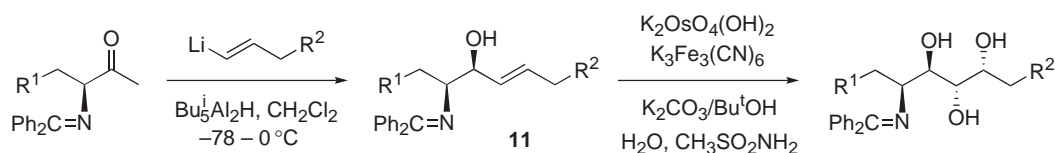
Hydroboration of enantioenriched *cis*-vinylepoxides or *syn*-chlorohydrins with 9-BBN or dicyclohexyborane provides access to chiral *cis*-3,4-epoxy alcohols <1998TL8059>.

2.02.1.2.2 Substrate control in osmylation

The use of osmium tetroxide (OsO₄) to transform an alkene into a stereochemically defined diol has been shown to be influenced by the hydroxy group on an allylic alcohol via facial selectivity <1995CRV1761>. However, the synthesis of chiral alcohols employing osmylation of alkenes via substrate control has received very little attention in recent years, due to the emergence of the more powerful technique by Sharpless involving 'reagent' control using chiral ligands. Nevertheless, several new examples have arisen which are discussed below.

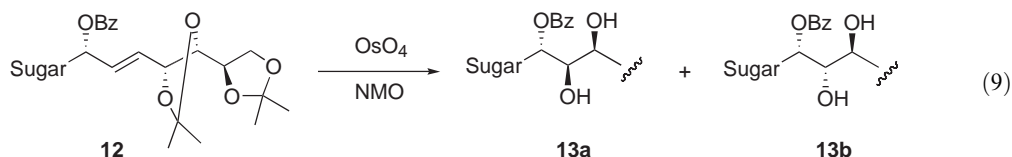
Brovetto and co-workers <1999NJC549> have described the osmylation of a series of chiral *cis*-cyclohexadienediols. Dihydroxylation occurs preferentially on the more electron-rich double bond. In the case of the osmylation of 3-methylcyclohexa-3,5-diene-1,2-diol, the presence of protecting groups on the diol functionality is crucial in determining the degree of regio- and stereoselectivity of the reaction. In addition, the regioselectivity of the reaction was found to depend on the osmylation method used; stoichiometric procedures were more selective than a catalytic one.

The substrate-controlled delivery of OsO_4 to an allylic system, consisting of a benzophenone Schiff base-protected unsaturated β -amino alcohol **11**, has been utilized to allow the stereoselective introduction of hydroxyl groups, thereby enabling the synthesis of glycosidase inhibitors (Scheme 5) <1999JOC6147>. In this particular protocol, both OsO_4 and $\text{K}_2\text{OsO}_2(\text{OH})_2$ were used as catalysts to give identical aminotriols (43–60% yield): both of these reactions did not reach completion without the addition of methanesulfonamide ($\text{CH}_3\text{SO}_2\text{NH}_2$). The addition of pyridine to the reaction had a negative effect on the rate, as did the substitution of potassium glycolate with MeSO_2NH_2 .

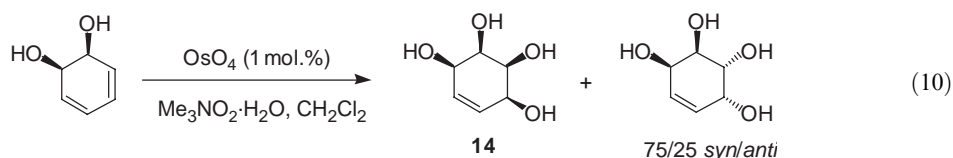


Scheme 5

A high yielding, selective methodology for the preparation of high carbon sugars via *syn*-hydroxylation has been reported <1998JCS(P1)3943>. Thus, osmylation of the benzyl ether protected allylic alcohol **12** gave diol **13** with very high selectivity (ratio **13a**:**13b** = 96:4) (Equation (9)). The high selectivity observed is rationalized as due to the attack of the osmylating agent occurring *anti* to the pre-existing adjacent oxygenated groups.

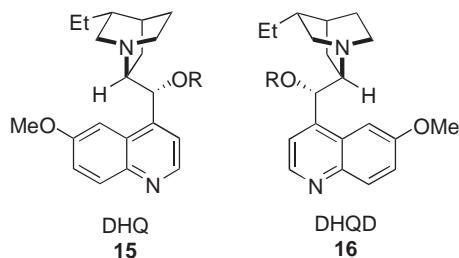


Donohoe and co-workers have reported a highly efficient synthesis of conduritol D **14** by using a hydroxyl-directing osmylation <1996TL3407, 1997JCS(P1)43>. Thus, *cis*-1,2-cyclohexadiene-diol was subjected to dihydroxylation under catalytic conditions in dichloromethane using trimethylamine *N*-oxide as stoichiometric reoxidant, giving *syn*-tetraol as the major product (*syn:anti* = 75:25) (Equation (10)). Through the use of an aprotic solvent (CH_2Cl_2) the inherent *anti*-distereofacial selectivity normally observed <1995AG(E)2031> was, it was postulated, inverted because of hydrogen bonding between OsO_4 and the allylic hydroxyl group. This contrasted with dihydroxylation of the same substrate in acetone–water, whereupon precisely the opposite stereoselectivity was demonstrated (*syn:anti* = 25:75).



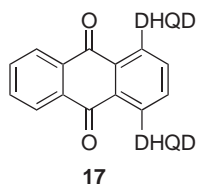
Syn-tri- and -tetraols have also been obtained selectively by directed oxidation of a range of five- and six-membered cyclic allylic alcohols, using OsO_4 /TMEDA <2002JOC7946, 2002SL1223>. The selectivity observed is again rationalized as being due to hydrogen bonding between OsO_4 and, in this case, the diamine additive.

practical and general asymmetric osmylation, the Sharpless AD of alkenes using cinchona alkaloid derived ligands (**15** and **16**), has become well known for the breadth of its scope and the range of its reliability across nearly the entire range of alkenes and substitution patterns on both laboratory and industrial scale <1995AG(E)1059, B-1998MI2022, 2000MI575>.

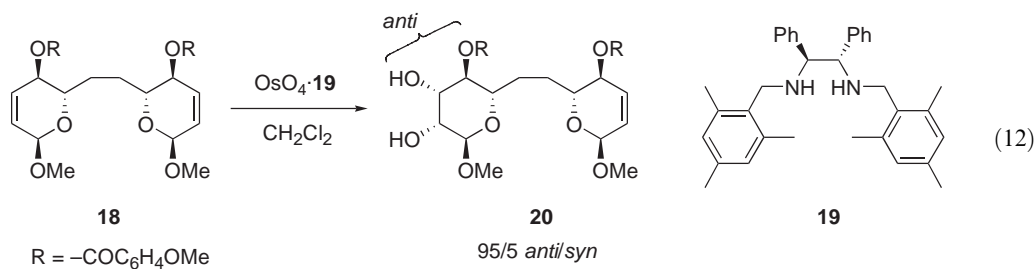


There are two general reaction systems for the Sharpless AD reaction. The first employs a mixture of chiral ligand, a sub-stoichiometric amount of K_2OsO_4 , *t*-butanol, and water with potassium hexacyanoferrate (K_3FeCN_6) as the stoichiometric oxidizing agent. The other system uses ligand, similar loadings of K_2OsO_4 , in an acetone–water media with *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric oxidizing compound. Though the utility of the process is indubitable, the exact mechanism of the osmylation, [2 + 2] versus [2 + 3], the role of the ligands, and the origin of the observed diastereofacial differentiation have been debated extensively <1996AG(E)2817, 1997CEN23>.

In the first of back-to-back papers, Becker and Sharpless have described another class of ligand, based upon 1,4-dihydroxyanthraquinone **17**, for the AD reaction <1996AG(E)448>. These new ligands have properties complementary to those of known ligands, and offer improvement in AD reactions of terminal alkenes, including halogenated compounds in poor-to-excellent enantiomeric excess.

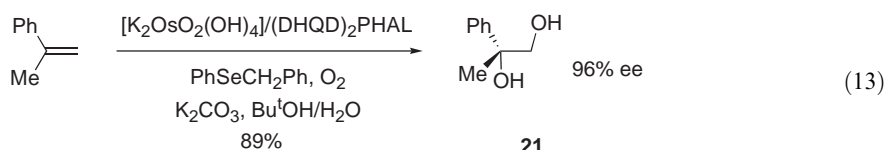


Alcohols can be prepared through enantioselective desymmetrization of *meso* compounds by AD. The strategy uses a chiral reagent to differentiate between enantiotopic functional groups in the starting material <2001CC2076>: the process was highlighted in a review discussing the desymmetrization of cyclic dienes <2002COC1369>. A promising ligand for the dihydroxylation of *meso*-bis(allylic-*p*-methoxybenzoate) **18** was the C_2 -symmetric diamine **19**, which was first introduced by Corey <2002JCS(P1)1631>. A typical example of the utility of this process is the reaction of ligand **18** with OsO_4 ·**19**, giving the desymmetrized *anti*-diol **20** as a single diastereoisomer in 75% yield with 50% ee (Equation (12)). By performing the reaction at $-20^\circ C$ an improved yield and stereoselectivity (84% and 60% ee, respectively) were observed. The stereochemical outcome of the reaction depends critically on the relative stereochemistry and substitution of the substrate or is directed by an allylic alcohol or *p*-methoxybenzoyloxy functional group.



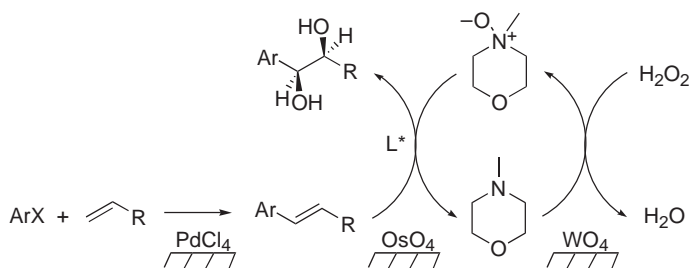
Other reports of enantioselective osmylation include the reaction of α,β -unsaturated sulfones affording enantioenriched α -hydroxy aldehydes <2003T7973>, the utilization of proline-based catalysts for highly enantioselective catalytic dihydroxylations of alkenes <2003OL3455>, and the AD of thiophene acrylates <2002TL3813>. A photoinduced catalytic vicinal dihydroxylation of benzene and arenes has been performed leading to a variety of usefully functionalized inositol and conduritol derivatives <1995AG(E)2031>. Studies investigating the AD procedure under controlled pH conditions have also been carried out <2000TL8083>. It was found that the maintenance of a constant pH of 12.0 led to improved reaction rates for nonterminal alkenes, while a pH of 10.0 was more suitable for terminal alkenes. In addition, using these conditions, hydrolysis aids like methanesulfonamide could be omitted.

Several co-oxidants have been investigated in osmium-catalyzed dihydroxylations to replace the ubiquitous ferricyanide in the reoxidation of Os(VI) to Os(VIII) <1996JOC3055> and until recently the use of molecular oxygen as a co-oxidant was neglected <2000AG(E)334>. Krief and co-workers have used selenoxide as an oxygen carrier to oxidize Os(VI) <1999TL4189, 2001SL501, 2002TL6255> to afford diol **21** in a similar selectivity and yield to that originally described by Sharpless using the AD-mix- β (Equation (13)). Remarkably, even air can be used in the reaction, instead of oxygen, with almost equal efficiency.



A more direct approach is that from Beller and co-workers <1999AG(E)3026, 2001JOM70>, where oxygen was used directly as the co-oxidant, and at optimum dihydroxylation conditions (pH 10.4, 50°C) high conversions of alkene to diol were observed (albeit with slightly lower selectivities than the procedures of Sharpless and Krief). The same group has also employed bleach, as an alternative selection to oxygen, as the oxidant <2003S295>.

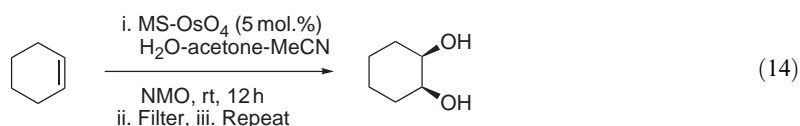
It goes without saying that AD procedures rely upon the ready availability of both substrate prochiral alkene and an appropriate stoichiometric oxidant. In a novel attempt to simplify and streamline the operation, a report has appeared detailing a single-pot, biomimetic synthesis of chiral 1,2-disubstituted 1,2-diols from terminal alkenes, mediated by a trifunctional solid catalyst consisting of active palladium, tungsten, and osmium species embedded in a single layered double-hydroxide matrix <2001AG(E)4620, 2003JOC1736>. The matrix provides the desired prochiral alkenes and NMO *in situ*, in an economical way, by an *in situ* Heck coupling and *N*-oxidation of *N*-methylmorpholine (NMM), respectively, for the AD reaction (Scheme 7). The methodology therefore uses NMM only in sub-stoichiometric amounts relying upon H₂O₂ as a cheap stoichiometric oxidant to provide a steady and continuous supply of NMO for the dihydroxylation reaction.



Scheme 7

The same group has also designed reusable, heterogeneous exchanger OsO₄ catalysts, prepared by ion-exchange, to mediate the AD reaction in the presence of a range of co-oxidants <2002JA5341>. An alternative procedure by Bäckvall and co-workers uses flavine to oxidize NMM to NMO <1999JA10424, 2001JA1365>. However, unlike the trifunctional catalyst system mentioned above, the homogeneous flavine-based process suffers from the drawback that catalyst recovery is difficult.

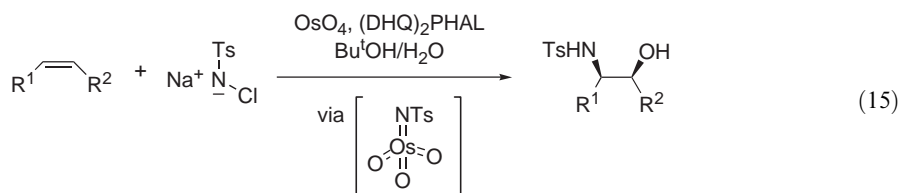
One drawback to the AD methodology is the complicated separation of the catalysts and the ligands at the end of the reaction. A modern paradigm to circumvent this hindrance is to attach either the ligand or the catalyst (<2003CC1716>) to a heterogeneous carrier (for instance silica or a resin <2000TA4039, 2002OL4685> or a soluble polymer <1998EJOC21, 1999CC1917, 2002MI2116>), thus, facilitating separation and recycling of the ligand. For instance, Han and Janda have applied Tentagel- and PEG-supported hydroquinidine cinchona alkaloids and *trans*-cinnamic acids ligands in the AD process and found the yields and ee values compared favorably to reactions mediated by solution-bound ligands <1996JA7632, 1997AG(E)1731>. In a different approach, the microencapsulation (MC) technique has been adopted by Kobayashi and co-workers <1999JA11229, 2001OL2649>: this involves the enveloping of OsO₄ in polymer capsules for the dihydroxylation of cyclic and acyclic alkenes. Thus, polymer immobilization of OsO₄ using a documented MC technique <1998JA2985> gave so-called “MC-OsO₄,” which neatly circumvents the infamous volatility problems of the free reagent. Furthermore, the reagent is reoxidized by NMO under typical reaction conditions (enabling sub-stoichiometricity in MC-OsO₄) and can be recovered from dihydroxylation reactions and reused <1998JOC6094>. The recovered MC-OsO₄ possesses very similar, if not identical, reactivity to the fresh reagent (Equation (14)). OsO₄ has also been microcapsulated in a polyurea matrix using an *in situ* interfacial polymerization approach <2003OL185>.



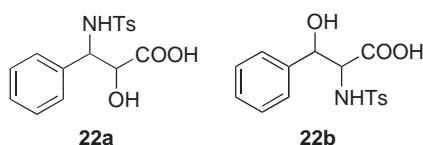
(ii) Asymmetric aminohydroxylation

The asymmetric aminohydroxylation (AA) of alkenes is a related and rapidly expanding area of research, in this case allowing for the direct preparation of vicinal *N*-protected amino alcohols <1996AG(E)451, 1996AG(E)1308, B-1998MI2023, B-2002MI2026>. The importance of the reaction is that it allows direct access to the β -amino alcohol functionality, a component that is abundant in natural products. Since its discovery in 1996 by Sharpless, a great deal of effort has been dedicated to make the technique as reliable, versatile, and convenient to use as its dihydroxylation counterpart <1999AG(E)326, 2003OBC2025>. However, the AA process still lacks the generality and reliability of the AD process, and in many cases problems in selectivities (chemo-, regio-, and enantioselectivity), substrate scope, and catalyst activity have been encountered. Several reviews have discussed specific facets of the AA reaction <1998JA1207, 2000T2561, B-2000MI2024, 2002JCS(P1)2733>.

The first efficient example of asymmetric 1,2-aminohydroxylation of alkenes employs the (DHQ)₂-PHAL AD catalyst system in the presence of chloramine-T trihydrate (TsNCINa) (as the nitrenoid source and oxidant) and water (as the hydroxyl source) to furnish amino alcohols in moderate enantiomeric excess (Equation (15)) <1996AG(E)451>.

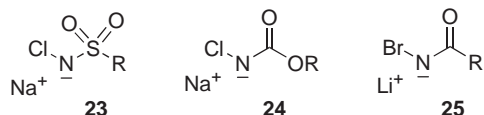


In a more recent study new ligands, consisting of *N*-toluenesulfonyl- α - β -hydroxy amino acids (**22a** and **22b**), were found to induce asymmetry in the AA and AD reactions via the second catalytic cycle <2002AG(E)472>. The authors found that as little as 1.5–2 mol.% of ligand was required to attain the highest possible ee when styrene derivatives were employed in the reaction.



Unlike the AD reaction, strongly electron-deficient alkenes are suitable substrates for the transformation: this is due to the greater polarization of the Os=NTs group compared to that of the Os=O group. Thus, dimethyl fumarate (a poor AD substrate) reacts rapidly to give the 2-hydroxy aspartic acid derivative [<1996ACS649>](#).

In general, the nature of the asymmetric induction in the AA method closely parallels that observed in the AD reaction, thereby suggesting that the factors governing the enantioselectivity of both processes are similar. An additional complexity that is 'not' possible in the AD route is the regioselectivity of the AA reaction: oxidation of unsymmetrical alkenes can, of course, give rise to two regioisomeric amino alcohol products and mixtures of these isomers are frequently obtained in many AD reactions (*vide supra*). There are three main classes of nitrogen source for AD reactions, these being the alkali metal salts of the corresponding *N*-halosulfonamides **23**, *N*-halocarbamates **24**, and *N*-haloamides **25**.



Nitrene equivalents such as (TsNCINa), (MsNCINa), (NsNCINa), *t*-butylsulfonamide [<1999OL783>](#), and 2-(TMS)ethylsulfonamide are also frequently employed as reagents. A drawback of using sulfonamide-derived compounds is that the products generally need harsher deprotection conditions to generate the free amine, although amines protected as the *p*-nitrophenylsulfonamide can be removed under mild conditions. The sulfonamide method also has limited substrate scope, with styrenes and vinyl arenes often being poor substrates. On the other hand, carbamates are frequently efficacious in reactions with styrenes and terminal alkenes. Commonly used carbamate-derived reagents include ethyl, benzyl, *t*-butyl, and 2-(TMS)ethyl carbamate. A difficulty with the carbamates is the removal of unreacted material from the reaction mixture. Amides react well with cinnamates, acrylates, styrenes, and terminal alkenes. Furthermore, the scope of the amide-based AA has improved with the development of a facile monobromination method for primary amides [<2000OL2221>](#). Both amine-substituted heterocycles [<1999AG\(E\)1080>](#) and adenine derivatives [<1998TL7669>](#) can also be used as amino donors in the AA reaction.

2.02.1.3 By Addition to Carbonyl Compounds

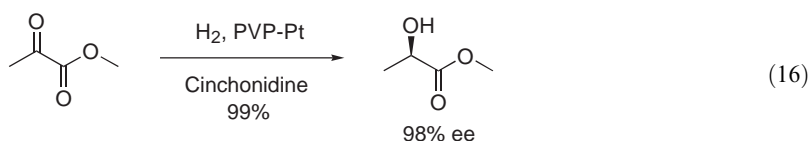
2.02.1.3.1 Reductive addition

There exists a wealth of literature describing the preparation of alcohols via reductive addition to carbonyl compounds, including several recent reviews [<2000JCS\(P1\)2529, 2001TA2225, 2002MI759>](#).

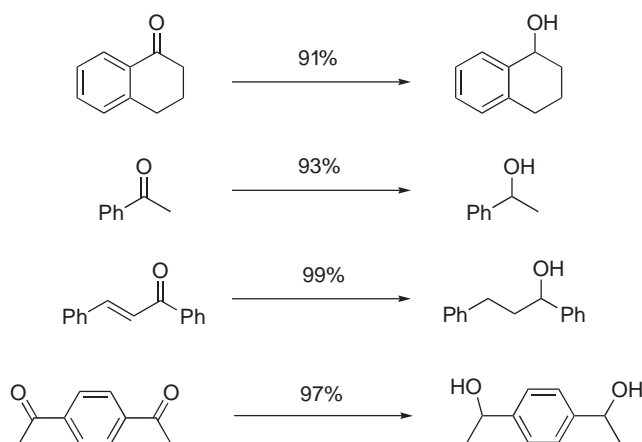
(i) Hydrogenation

Aldehydes, ketones, and esters can all be reduced in the presence of hydrogen to primary alcohols using various conditions, although the reduction of ketones and esters generally requires more forcing conditions.

(a) *Hydrogenation using heterogeneous catalysis.* The use of heterogeneous catalysis in asymmetric synthesis is still relatively rare. Methyl and ethyl pyruvate are reduced enantioselectively by hydrogen in the presence of cinchonidine-treated polyvinylpyrrolidone (PVP)-stabilized platinum species (Equation (16)) [<1998TL1941>](#).



Aromatic ketones and aldehydes are reduced to the corresponding alcohols by hydrogenation in the presence of sub-stoichiometric amounts of a Pd/C–ethylenediamine complex <1998JCS(P1)4043>. Yields are generally greater than 90%, and the process is operationally simple, requiring only a balloon of hydrogen gas to proceed (Scheme 8).

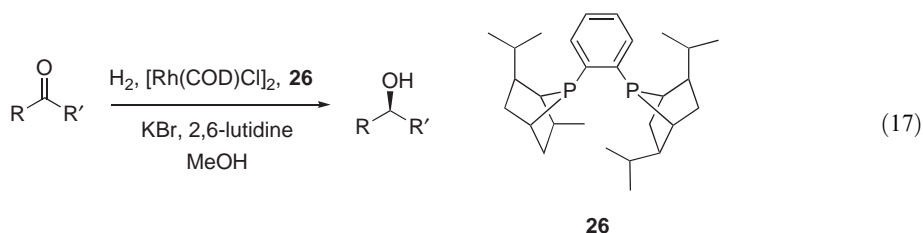


Conditions: 10% Pd/C-ethylenediamine, H₂, MeOH, <24 h

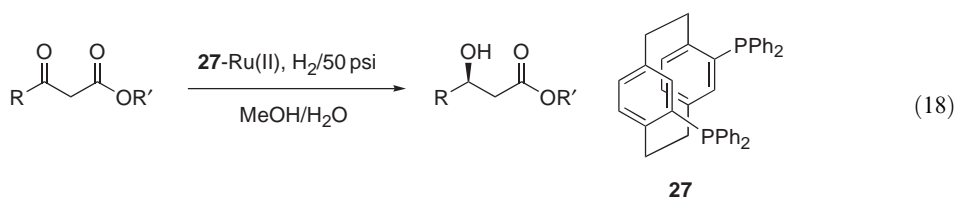
Scheme 8

(b) *Asymmetric hydrogenation under homogeneous catalysis.* The use of soluble rhodium and ruthenium complexes allows for many prochiral ketones to be enantioselectively reduced <1996MI553>. The technique is particularly useful for large-scale reductions. Noyori's (and his co-workers') enthusiasm for this particular synthetic methodology toward carbonyl reduction shows no sign of abating. One interesting account from their lab concerns the diastereoselective reduction of simple ketones using elemental hydrogen, mediated by ruthenium(II) complexes in the presence of 1,2-diamines <1996JOC4872>. Thus, 2-, 3-, and 4-substituted cyclohexanones are reduced by a ruthenium hydride species, which behaves essentially as a bulky hydride, effecting reduction via equatorial attack upon the double bond to give *trans*- and *cis*-alcohols, respectively.

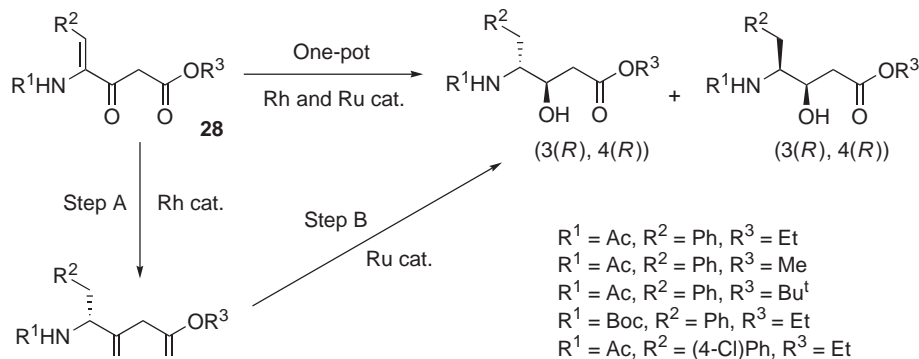
Aromatic methyl ketones are asymmetrically hydrogenated with high levels of enantioselectivity using cationic rhodium complexes and biphosphane ligands **26** <1998AG(E)1100>. For the reaction to exhibit good enantioselectivity (72–96% ee), 2,6-lutidine and KBr must be present in the reaction mixture (Equation (17)).



Diphosphinyl[2.2]paracyclophane (*S*)-PHANEPHOS **27** mediates asymmetric hydrogenation of aliphatic 3-ketoesters using Ru(II) complexes <1998TL4441>. The enantioselectivity of the reaction is high (95–96% ee), with (*R*)-enantiomers usually being the main products (Equation (18)).

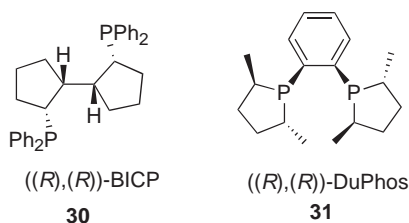


Enaminoketoesters **28** have been converted in good yield and with excellent enantiocontrol into statine analogs via a double asymmetric reduction [<1998JOC428>](#). Thus ester **28** is transformed directly into aminohydroxyester upon reaction with H_2 in the presence of chiral Rh(I) or Ru(II) catalysts in virtually quantitative yield and with excellent enantiocontrol (ee >95%). The (3*R*),4*R*)-isomer is the favored product. The first step of the reaction is hydrogenation of the enamine moiety, determined through the isolation of aminoketoester **29** at lower pressures of hydrogen ([Scheme 9](#)).

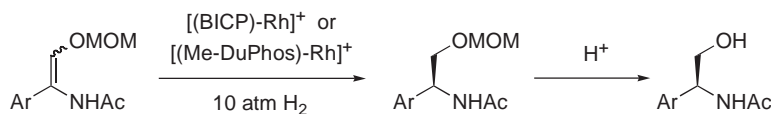


Scheme 9

N-Acetylenamines derived from α -hydroxy-acetophenones are hydrogenated in an enantioselective manner using cationic rhodium complexes based upon chiral ligands ((*R*),(*R*))-BICP **30** and ((*R*),(*R*))-DuPhos **31** [<1998JOC8100>](#).



Thus, MOM-protected hydroxyenamines (prepared in an innovative fashion by reaction of oximes with Fe in acetic anhydride) are converted into deprotected hydroxyamines in quantitative yield and with excellent enantioselectivity ([Scheme 10](#)).



Scheme 10

(ii) Dissolving metal reduction

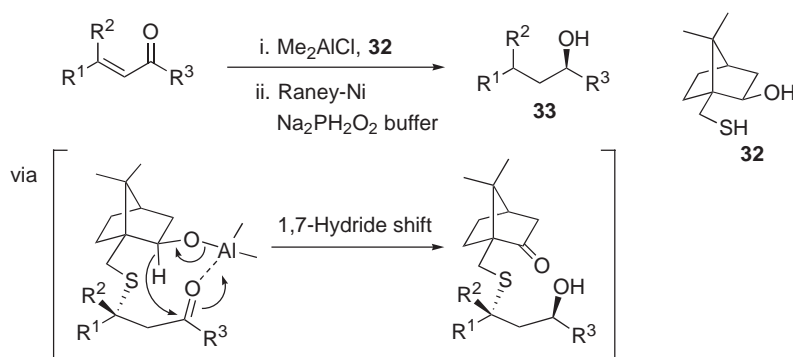
Since the publication of COFGT (1995) [<1995COFGT\(2\)37>](#) little new literature has appeared concerning reduction of carbonyls using dissolving metals; the reader is directed to refer the cited review articles in COFGT (1995) for primary references.

(iii) Reduction using carbon hydrides

Meerwein–Ponndorf–Verley (MPV) reactions continue to occupy the attention of many researchers with growing focus on the asymmetric variants of the reaction; as demonstrated in a recent review [<2002MI759>](#). The classical reaction uses aluminum isopropoxide to form a six-membered cyclic transition state to enable delivery of a hydride from a carbon. Variations upon the theme include

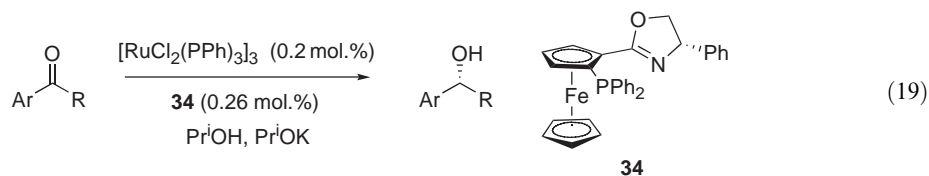
the replacement of aluminum isopropoxide with samarium(IV) and zirconium(IV) oxides (separately) <1995COFGT(2)37>. Both intermolecular and intramolecular (1,5- and 1,7-hydride shifts) asymmetric MPV reductions of carbonyls have been reported <2002MI759>.

α,β -Unsaturated ketones may be reduced by a two-step process into secondary alcohols via the asymmetric MPV process <2000JA1927>. In one example, the reaction is mediated by dimethylaluminum chloride using the hydroxysulfide **32** as an asymmetric hydride source to give alcohols in high enantioexcess (generally = 95% ee and 64–94% yield). The reaction sequence involves asymmetric 1,4-nucleophilic addition of the thiol moiety **32** to the unsaturated ketone (mediated by the Lewis acid) followed by an asymmetric 1,7-hydride shift to generate the alcohol group. Desulfurization using Raney nickel yields alcohols **33** (Scheme 11) <1996JA13103>.

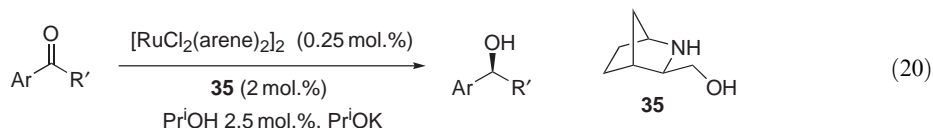


Scheme 11

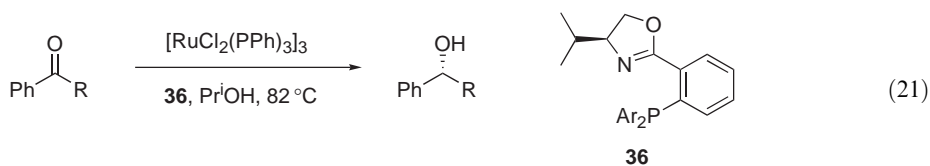
Hybrid phosphinylferrocenooxazolines **34** have been used to effect asymmetric MPV reduction of prochiral ketones <1997JOC6104>. The reduction of aryl alkyl ketones proceeds in good yields (80–92%) and with good enantiocontrol (84–96% ee). In all cases, (*R*)-configured secondary alcohols were obtained from the reaction (Equation (19)).



A chiral ruthenium complex, incorporating nonracemic 2-azanorbornylmethanol **35**, is another example of a useful asymmetric MPV reduction catalyst <1998JOC2749>. Here, ketones are reduced to the corresponding benzyl alcohols with generally high enantiocontrol (83–97% ee) when reacted with KOPr^i in the presence of sub-stoichiometric amounts of $\{\text{RuCl}_2(\text{C}_6[\text{CH}_3]_6)_2\}$ or $[\text{RuCl}_2(p\text{-cymene})_2]_2$ and **35** (Equation (20)).



Langer and Helmchen have investigated the enantioselective MPV reduction of ketones, under the control of asymmetric bidentate ligands **36**, to furnish secondary alcohols in variable yields and with variable enantiocontrol (58–94% ee) (Equation (21)). As is often the case in these reactions, the best results were obtained when aryl ketones were the substrates for the reaction (76% yield and 86% ee) <1996TL1381>.

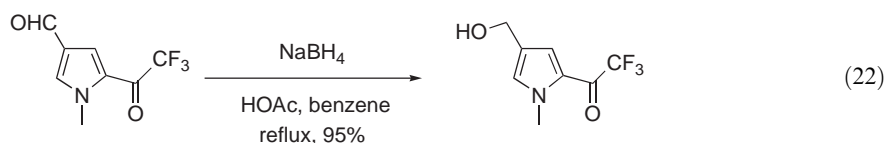


(iv) Reduction using metal hydrides: Boron-based reductants

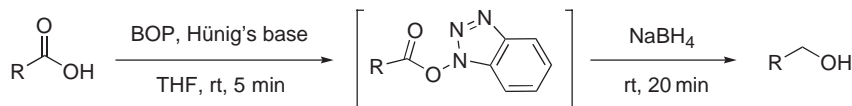
As discussed previously, the majority of carbonyl reductions utilize hydrides, which are chiefly derived from group 13 elements, especially boron and aluminum. There are two main types of reducing agents, neutral (boranes and alanes) and anionic (borohydrides and aluminohydrides): the utility of both types of reagent class has been comprehensively reviewed <2001TA2225, 2001AG(E)40, B-1997MI2021>.

(a) *Boranes and alkylboranes.* The reduction of carbonyls with boranes and alkylboranes has not significantly changed since the publication of COFGT (1995) <1995COFGT(2)37>, partly due to the increase in interest in borohydrides as reducing agents, and the reader is, therefore, directed to that source for primary information. Since carbonyls are reduced by boranes via an intramolecular hydride transfer between the oxygen–boron complex to the carbon, electron-rich multiple bonds are reduced rapidly, due to the strong Lewis acid character of boranes, whilst electron-deficient bonds are often inert. In addition, the reactivity of alkylboranes toward substrates varies as a result of the varying steric demands of the pendant alkyl groups attached to boron. This has been exploited in the asymmetric reduction of carbonyls, using alkylboranes prepared from enantiopure, naturally occurring alkenes. The range of commercially available enantiopure alkylboranes includes Alpine–borane[®], epine–borane, apopinene–borane, isopino–camphenylborane (Icp₂BH), and (1*S*)-diisocaranylborane (dIcr₂BH) <1995COFGT(2)37>.

(b) *Borohydrides.* Lithium borohydrides (LBH) and sodium borohydrides (NBH) are amongst the most commonly used hydride reducing agents, especially for the chemoselective reduction of aldehydes and ketones. One of the reasons for the enduring popularity of these borohydrides is the ease with which the parent reagents can be routinely modified to form either a stronger or a more selective reducing agent. For instance, the combination of NBH with carboxylic acids, such as acetic acid, leads to the generation of sodium acyloxyborohydrides, with triacyloxyborohydrides being less reactive than the corresponding acyloxyborohydrides <1998CSR395>. These reducing agents are capable of selectively reducing aldehydes over even highly electrophilic ketones; this observation is exemplified in the chemoselective reduction of aldehydes in the presence of trifluoromethyl ketone (Equation (22)) <1990T2691> and in the selective reduction of a less sterically encumbered aldehyde in a dialdehyde substrate <1996JA10660>. The chemo-, regio-, and stereoselectivity of the reductions can be regulated by adjusting the stoichiometry of carboxylic acid and borohydride, or by controlled variation in temperature.



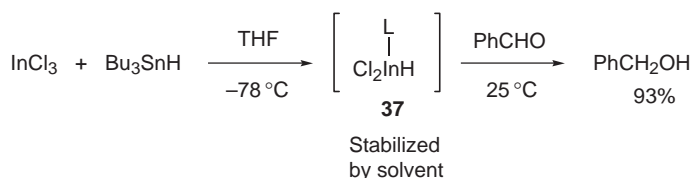
Carboxylic acids may be reduced directly to the corresponding primary alcohols under mild conditions by sodium borohydride via acyl hydroxybenzotriazoles <1998TL3319>. The acids are sequentially treated with BOP, Hünig's base (Pr₂NEt), and borohydride to give excellent yields of alcohols (87–99%). A wide range of functional groups is unaffected under the reaction conditions (although cinnamic acid suffered some reduction at the alkene) (Scheme 12).



Scheme 12

(v) Reduction using metal hydrides: Miscellaneous

Indium trichloride reacts with tributylstannane at low temperature to give dichloroindium hydride 37; this reducing agent (stabilized by solvent) reacts at room temperature with a range of electrophiles to give hydrogenated or hydrogenolyzed products in good yield <1998TL1929>. The reductant exhibits some chemoselectivity with aromatic acetates, nitriles, and nitro compounds unaffected by the process and chalcone is reduced at the alkene only (Scheme 13).

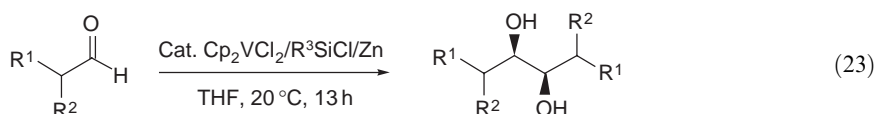


Scheme 13

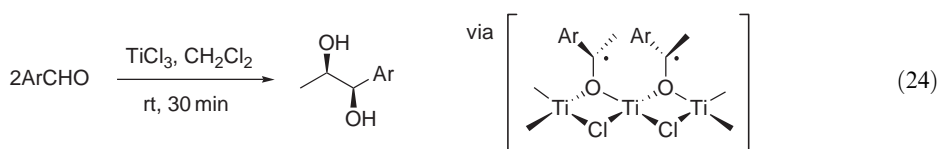
2.02.1.3.2 Stereocontrol in carbonyl reduction

(i) Directed reduction of carbonyl groups

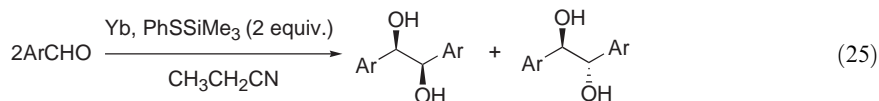
(a) *Pinacol couplings*. Vanadium-mediated diastereoselective pinacol-type couplings have been widely investigated. Thus, a mixture containing TMSCl , Zn metal, and a sub-stoichiometric amount of dichloropentadienylvanadium dichloride mediates the reductive dimerization of a range of aryl and aliphatic aldehydes, in generally excellent yields [<1998JOC2812>](#). The 1,2-diols produced are predominantly of *syn*-configuration, but the level of stereoselectivity is crucially dependant on the solvent, with a more strongly coordinating solvent (DME) leading to poorer diastereoselectivity than a solvent (THF) of weaker coordinating ability ([Equation \(23\)](#)).



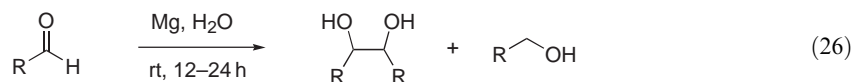
Hydrobenzoins are prepared with very high diastereocontrol ($\text{de} \geq 99\%$) by low-valent titanium-mediated pinacol coupling of aromatic aldehydes ([Equation \(24\)](#)) [<1996TL3035>](#). The selectivity of the reaction is rationalized by the intermediacy of bridged Ti(IV) ketyls.



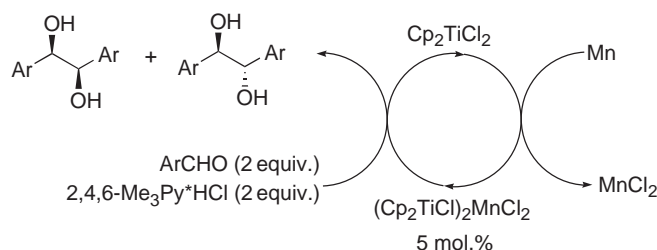
Pinacols are also prepared (albeit with lower selectivity) by reaction of ytterbium(II) phenylthiolate (formed *in situ*) with aromatic aldehydes [<1996TL3465>](#). Although the thiolate is acting as a reducing agent, when it was used in attempted reductions of aldehydes and ketones, complex mixtures of products were obtained ([Equation \(25\)](#)).



A variety of aromatic aldehydes undergo pinacol-coupling reaction when reacted with magnesium in aqueous solution containing a sub-stoichiometric amount of ammonium chloride [<1998JCS\(P1\)3131>](#). Aliphatic aldehydes are inert to the reaction conditions. The 1,2-diols produced by this reaction are often accompanied by reduced products, which in certain circumstances dominate the reaction mixture. The diol products are obtained as a *syn/anti* mixture in which there is a small excess of the *syn*-isomer ([Equation \(26\)](#)).



Aryl aldehydes undergo a titanocene-catalyzed pinacol-like coupling reaction to give primarily *syn*-1,2-diols in good yields <1998JOC2070>. Thus, 2 equiv. of an aldehyde react with a sub-stoichiometric amount of Cp_2TiCl_2 and elemental manganese under buffered conditions to give *syn*-diols ($\geq 96: \leq 4$ dr) via (the authors state) the first example of a catalytic turnover achieved by protonation of a metal–oxygen bond. The authors justify this claim by describing the influence of the buffer upon the diastereoselectivity of the reaction: ranges of pyridinium salts were used and the highest selectivities were observed using the buffer derived from the most basic pyridine (Scheme 14 and Table 4).

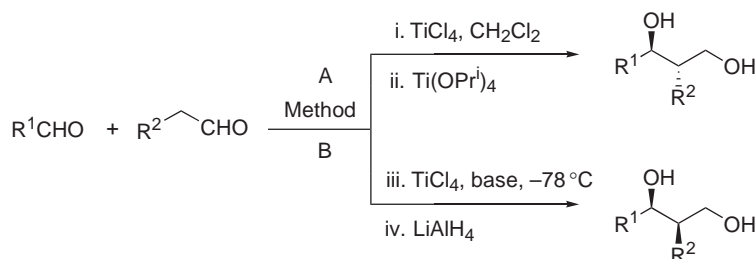


Scheme 14

Table 4 Range of pyridinium salts employed in aryl aldehyde reduction

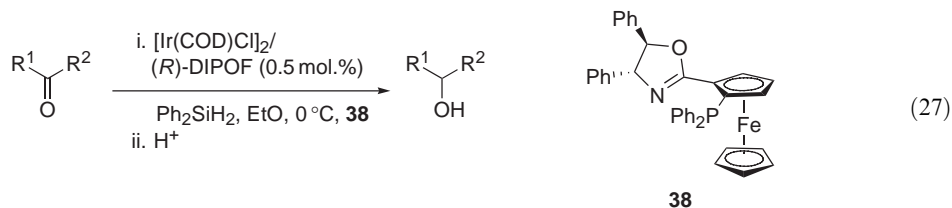
Substrate	Yield (%)	<i>syn:anti</i>
2-MeC ₆ H ₄ CHO	90	97:3
3-MeC ₆ H ₄ CHO	85	97:3
4-MeC ₆ H ₄ CHO	84	97:3
4-ClC ₆ H ₄ CHO	89	97:3
4-BrC ₆ H ₄ CHO	82	98:2
4-MeOC ₆ H ₄ CHO	91	99:1
4-ArOC ₆ H ₄ CHO	85	99:1
4-PhC ₆ H ₄ CHO	87	97:3
4-CH ₂ =CHC ₆ H ₄ CHO	85	96:4
4-(2'-Thienyl)-CHO	82	95:5

(b) *Others*. A “one-pot” aldol-carbonyl reduction procedure allows preparation of 2-alkyl-1,3-diols in generally good yield. *Syn*- or *anti*-products may be obtained (with variable diastereoselectivity) according to judicious choice of enolization conditions (Scheme 15) <1998CC2273>.



Scheme 15

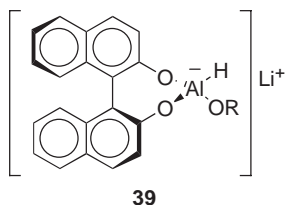
DIPOF, an asymmetric hybrid ferrocene–phosphine/oxazolinyl ligand **38**, is an effective asymmetric mediator in the iridium(I)-catalyzed asymmetric hydrosilylation of ketones [<1996CC847>](#). Thus, reduction of ketones by diphenyl silane furnishes (after acid hydrolysis of the first-formed silyl ether) secondary alcohols in generally moderate enantiomeric excess (9–96%) ([Equation \(27\)](#)).



(ii) Reagent control

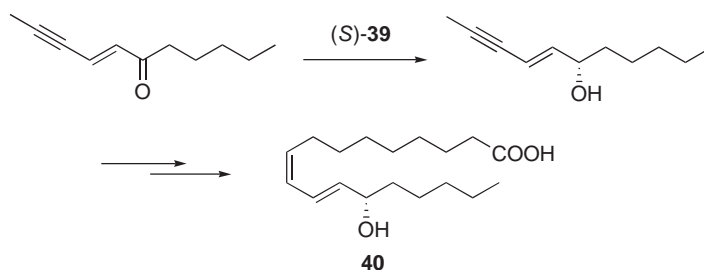
In the past the use of chirally modified alumino- and borohydrides in asymmetric synthesis has been limited. However, many of these chiral alumino- and borohydrides are now often employed as key reagents in the synthesis of significant targets [<2001TA2225>](#). The field of enantioselective hydride reducing agents has further expanded through the use of solid-supported reagents and through the readily available low-cost starting materials, such as LiAlH_4 and NaBH_4 .

(a) *Asymmetric LiAlH_4 modifications.* LAH is extensively used for the preparation of enantioselective reducing agents, in combination with a number of different chiral ligands such as alcohols, amino alcohols, amines, and sulphamides. A popular reagent consisting of an alcohol ligand used in asymmetric synthesis is Noyori's complex; LAH/1,1'-bi-2-naphthol/primary alcohol (BINAL-H) **39**. One drawback to this reagent is its high price and the difficulties associated with recovering and recycling it. However, advantages are that the complex does not disproportionate, have a variety of aggregates, or a variety of conformations.



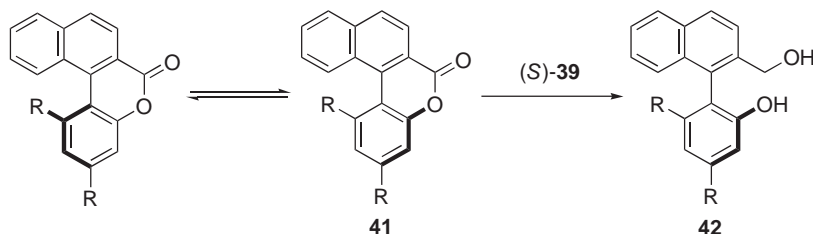
Olah and co-workers [<2000OL3173>](#) have recently described the reduction of 1,1,1-trifluoro-4-phenyl-buten-2-one using (*S*)-BINAL-H to (*S*)-alcohol in 94% yield and 71% ee. (Other groups have reduced the same substrate but only to give a racemic mixture [<2001TA1259>](#).) As a general rule, the nature of the stereoselectivity observed is predictable for phenyl, alkenyl, and alkynyl ketones, and, generally, (*R*)-BINAL-H gives (*R*)-alcohols (and vice versa).

Over the years BINAL-H has been extensively exploited in the reduction of various key prostaglandin intermediates. For example, a series of saturated prostaglandins were obtained employing Noyori's complex in a key-reduction step [<2000BMCL1519>](#). Thus, the naturally occurring fatty acid (*S*)-coriolic acid **40** was prepared by the reduction of the corresponding enynone ([Scheme 16](#)) [<2000T327>](#).



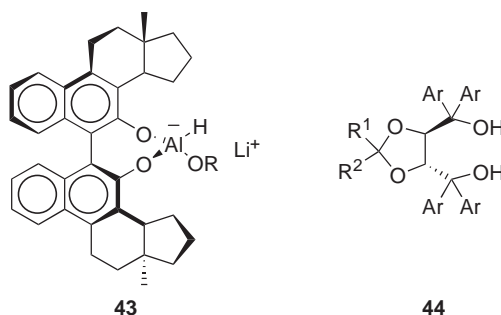
Scheme 16

(*R*)-BINAL-H has been utilized for the multigram enantioselective preparation of 3-methylene-tetrahydropyran, intermediate in the synthesis of neoliacinic acid <1999MI515>. An interesting recent application of BINAL-H is the reduction of configurationally unstable biaryl lactones via dynamic kinetic resolution of the atropoisomers **41** to afford diols **42** in 92% ee (Scheme 17) <1999TA385>.



Scheme 17

Other complexes derived from diols used in enantioselective reductions of ketones include the LAH/bis-sterodial complex **43** <1997JOC7092>, the complex formed from LiGaH₄ with monothio-binaphthol <1999AG(E)335>, and the commercially available, widely-used TADDOL ($\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanols) **44** reagent, the utility of which has recently been reviewed by Seebach <2001AG(E)-92>.

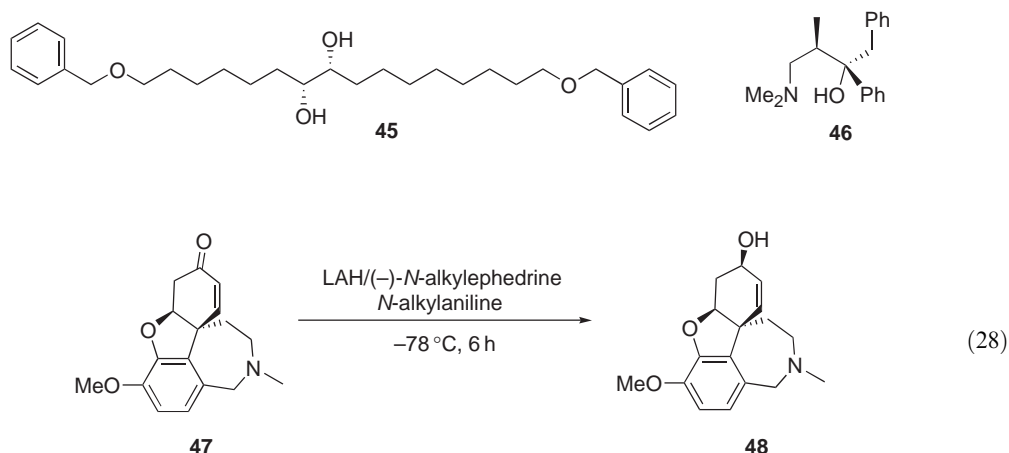


It is noteworthy that complexes of TADDOL/LAH/ethanol have been used to reduce acetophenone, performing equally well as soluble <1996MI459> and polymer-bound reagents <1996HCA1710>. Ligands with large Ar groups (α -naphthyl, β -naphthyl) give rise to low selectivities compared to the parent compound. The reduction of aryl alkyl ketones revealed that stereoselectivities also diminished with the increasing size of the alkyl group. TADDOL/LAH has also recently been employed in the synthesis of the cytotoxic natural product (–)-bifurcadiol <1999TL8359>. The use of the reagent is, in this case, remarkable for the fact that the CBS oxazaborolidine system was not effective in this particular case. Another study found that chiral reducing agents obtained from NaAlH₄ and chiral 1,3- and 1,4-diols were found to give complexes capable of greater stereodifferentiation properties than those formed from 1,2-diols <2000MI460>.

The diol **45**, with its lengthy linear alkyl substituents flanking the vicinal hydroxyl groups, provided (it was hypothesized) a demanding steric hindrance and thus, contribute to the selectivity of ketone reductions using modified LAH reagents incorporating this ligand <1998SC4445, 1998SC977>. Thus, the diol **45**/LAH complex, in the presence of (*R*)-hydrocarpic alcohol or with long-chain alcohols gave high (*R*)-enantioselectivity with aryl ketones.

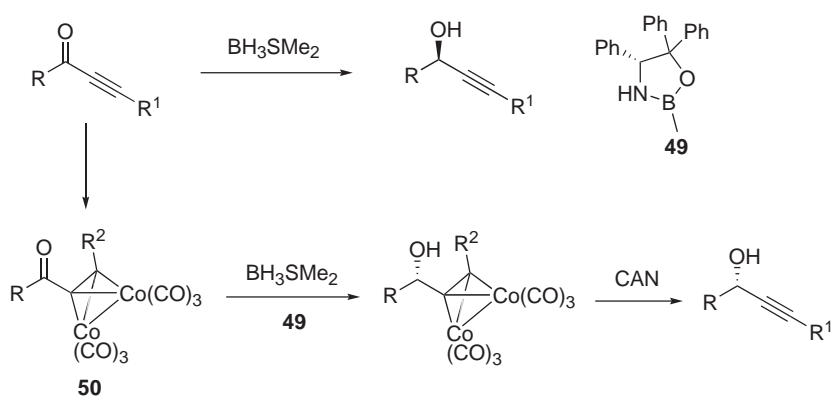
Amino alcohols have also been successfully used as ligands to form chiral reducing complexes with LAH, with perhaps the first (and still best known) such reagent being the commercially available Darvon alcohol **46** (CHIRALD®). Marshall has successfully exploited the LAH/CHIRALD® reagent for the enantioselective reduction of a diverse range of acetylenic ketones with good-to-excellent stereocontrol <1995JOC5550, 1997JOC367, 1998TL1303, 1998TL1493>. Alternative systems include the LAH/(–)-*N*-methylephedrine/*N*-ethyl-2-aminopyridine complex, which

undergoes a tandem enantioselective reduction/kinetic resolution of (–)-narwedine **47** to give (–)-galanthamine **48** (Equation (28)) <1998TL2087, 1999MI425>. Moreover, the reaction can be performed using racemic narwedine, as the (+) form is not reduced. The reducing system has also been used for performing chemoselective reductions of functionalized cyclohexenone to the corresponding cyclohexanol in 83% ee <2001OL201>.



Polymer-supported chiral amino alcohols have also been applied in the reduction of acetophenone, albeit in low ees (43%) <2001TL1673>. Asymmetric auto-inductive reduction of α -amino ketones by LAH, modified with a chiral 1,2-amino alcohol and a chiral additive, has been performed to afford amino alcohols with the same configuration as the ligand <1997AG(E)2458>. Rigid complexes have also been developed for selective reductions <1995TA89, 1999JOC3207>.

(b) *Oxazaborolidines*. The asymmetric carbonyl reduction mediated by enantiomerically pure oxazaborolidines is an established and highly effective synthetic protocol: thus interest continues in the development of this subject area, which has been comprehensively reviewed by Corey <1998AG(E)1987>. For instance, propargyl alcohols may be obtained in high enantiomeric excess by the reduction of alkynyl ketones using (*R*)-phenylglycine-derived oxazaborolidine **49** <1996JOC9021>. Intriguingly, it seems that the same alkynyl ketones may be reduced with the opposite sense of asymmetric induction when their cobalt complexes **50** are employed in the reaction (Scheme 18).



Scheme 18

The oxazaborolidine-mediated asymmetric reduction of *o*-substituted diaryl ketones reveals an interesting nicety concerning the mechanistic nuances of the process. Thus, mono-*o*-substituted benzophenones give (*S*)-configured alcohols when reduced in the presence of catalyst (*S*)-**51**. This observation suggests that the substituted phenyl group is the less sterically demanding group, which is contrary to expectations (Equation (29) and Table 5).

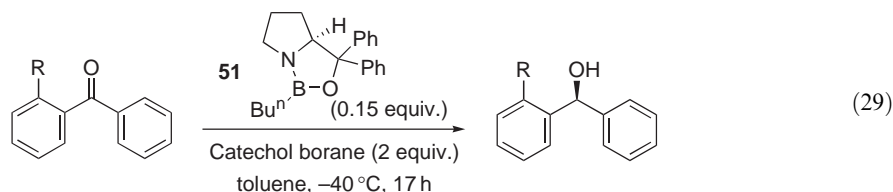
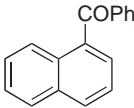
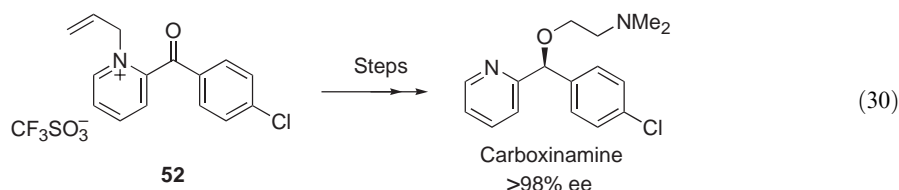


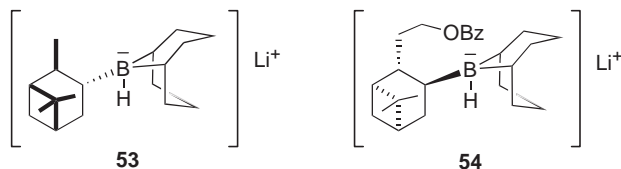
Table 5 Oxazaborolidine-mediated asymmetric reduction of *o*-substituted benzophenones

<i>R</i>	Yield (%)	<i>ee</i> (%)
Me	99	97
Br	90	97
	99	97

The authors suggest that this observation is due to a disfavored steric clash between the *o*-substituent and the carbonyl lone pair. In the same report <1996TL5675>, a preparation of (*S*)-carboxamine (a histamine H₂ antagonist) is described via the reduction of pyridyl-phenones, albeit with low enantioselectivity. 2-Benzoylpyridinium species **52** are, however, reduced with much greater enantioselectivity ($\geq 90\%$ ee), as demonstrated in (Equation (30)).



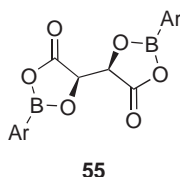
(c) *Asymmetric borohydride modifications.* Chirally modified borohydrides are prepared either by reacting chiral additives with metal borohydrides (NBH or LBH) or by reducing chiral boranes. The first approach is attractive due to the ready availability of NBHs, whilst the latter method is perhaps inclined to be more generally effective and reliable. Borohydrides derived from the reduction of chiral boranes continue to dominate the synthetic literature with Alpine Hydride[®] **53** (obtained by hydroboration of α -pinene with 9-BBN followed by reduction of the resulting borane with RLi), Selectrides[®] (trialkylboron analogs), and NB-Enantride[™] **54** often remaining the reagents of choice.



In addition, research into reductions with chiral additives and borohydrides continues, with common chiral additives used including ammonium salts, monosaccharides, alcohols, amino acids, carboxylic acids, amino alcohols, and oxoaldimines <2001TA2225>. NBH/(*S*)-amino acid complexes have been applied for the reduction of a prochiral ketone in the synthesis of

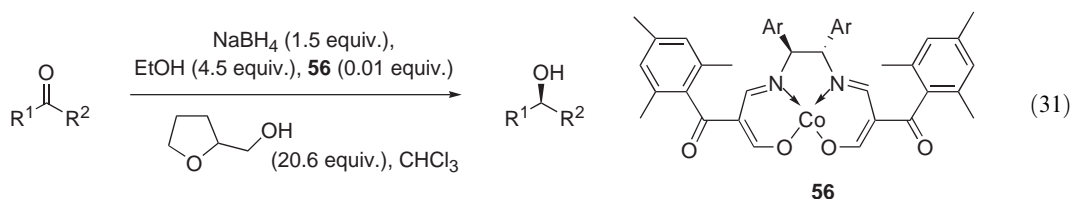
diltazem[®] via dynamic kinetic resolution <1996JOC8586>. Enantioselectivity was only observed when α -amino acids possessing hydrocarbon side chains, such as (*S*)-leucine were used in concert with AcOH as an auxiliary at -30°C .

The modification of NBH with organic acids has not generally proved to be a very successful route for the design of effective new asymmetric reduction processes. Nonetheless, a new chiral reducing system involving a bimetallic Lewis acid complex, derived from LBH and L-tartaric acid/boronic acid **55** has been described <1999BCSJ109>. Trifluoromethyl ketones, benzophenones, and substituted acetophenones have all been reduced using this system with ee values varying from 2–99%. The main advantage of this protocol is the use of inexpensive tartaric acid and the ease of recovering the boronic acid.

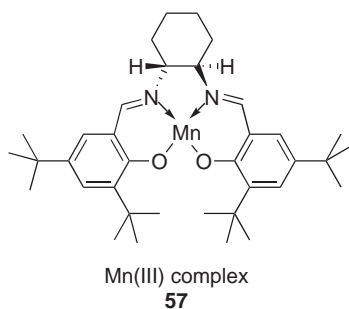


Heterogeneous reductions have been carried out by NBH supported on chiral amino alcohols bound to polymers. However, reduction of acetophenone with polystyrene supported amino alcohols occurred with only moderate enantiocontrol (75% ee) <1995MI749>. Chiral lithium dialkoxyaminoborohydrides have also been employed in the reduction of acetophenone but the reactions proceeded with very low enantioselectivity <1995T3803>.

Mukaiyama and co-workers <1995AG(E)2145> have reported the enantioselective reduction of prochiral aryl ketones by NBH in the presence of substoichiometric amounts of oxoaldimine cobalt(II) complexes **56**. Upon examination of the effects of ligand structure and alcohol additives on asymmetric reductions, the authors found that sterically undemanding substrates were reduced with greatest stereocontrol when ethanol was present, while the presence of methanol was efficacious for ketones of higher steric demand (Equation (31)) <1996SL1076>. Variation in the structure of the oxoaldimine ligand had a pronounced effect: less sterically demanding ketones were reduced most selectively by the cobalt complex whose diamine core bore mesityl rather than phenyl substituents. Overall, the NBH/cobalt complexes have proved to be extremely enantioselective in reducing ketones <1996CL1081> and imines, and recently they have even been used in the desymmetrization of 2-alkyl-1,3-diketones with ee values of up to 99% <2001OL2543>.



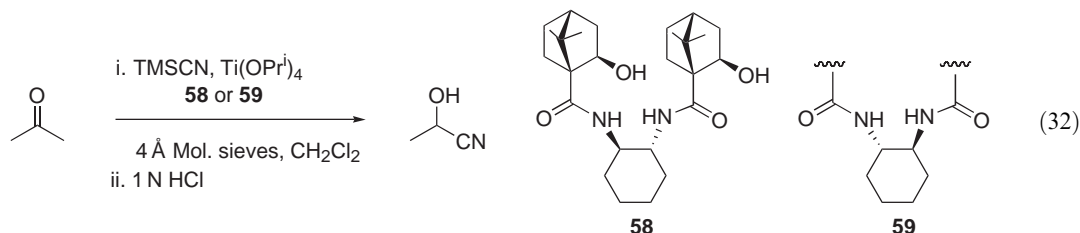
Other oxoaldimine derivatives used include Jacobsen's catalyst **57**, consisting of a Mn(III) complex as opposed to a Co(II) complex, for converting 2-phenylacetylpyridine to the corresponding (*S*)-alcohol <1999TL6665>. Reductions of aromatic ketones have been performed with NBH in water or THF using chiral dendrimers as ligands to give ee values as high as 100% <1999TL2947>.



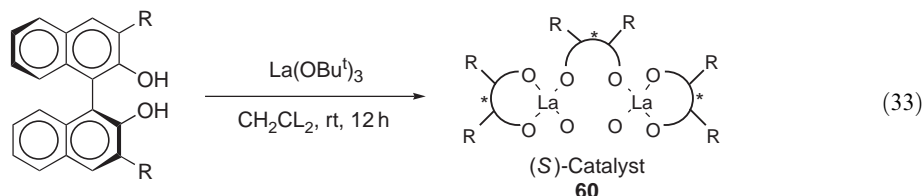
2.02.1.3.3 Alkylative addition

The addition of carbon nucleophiles, such as organometallic reagents, has been, and continues to be, a valuable synthetic methodology for the preparation of alcohols. The diastereoselective addition of organometallic reagents to carbonyl groups is a particularly useful class of this general reaction type and general reviews of the subject area have appeared <1996COS(3)65, 1997COS(4)435, 2000JCS(P1)2529>.

Cyclohexane diamine-derived bis-amides (**58** and **59**) mediate the asymmetric silylcyanation of aldehydes by TMSCN in the presence of tetraisopropyl titanate <1998JOC6772>. Using an optimized procedure, the presence of sub-stoichiometric amounts of ((*R*),(*R*))-bisamide and titanate in the reaction leads (after acidic cleavage of the silyl ether) to (*S*)-cyanohydrins exhibiting generally high enantioexcess. As is often the case, best stereoselectivity was usually observed when aromatic aldehydes were employed in the reaction (Equation (32)).



A range of chiral binaphthol-based ligands have also been shown to mediate an asymmetric trimethylsilylcyanation of aldehydes <1998JCS(P1)2131>. Thus, reaction of aryl aldehydes with TMSCN in the presence of pre-formed chiral lanthanum “binaphthoxides” **60** (Equation (33)) proceeds to give 2-hydroxynitriles in good yield, with at best moderate enantiocontrol (7–73% ee). (*S*)-Configured binaphthols led to (*S*)-hydroxy nitriles.



(i) Organomagnesium and organolithium nucleophiles

Nucleophilic addition has been performed upon 1,2-allenyl ketones to afford 1,2-allenyl alcohols <2000MI850>. The addition of organomagnesium and organolithium reagents to a diverse class of chiral aldehydes and ketones have been performed with high yields and in good-to-excellent diastereoselectivities in the presence of ytterbium(III) trifluoromethanesulfonate [Yb(OTf)₃] <1997BSCF275>. Yb(OTf)₃-promoted additions to alkoxy-substituted aldehydes and ketones occur through a Felkin–Anh-type model (nonchelation control). Samarium triflate [Sm(OTf)₂] <1996JOC5400> and cerium(III) chloride (CeCl₃) <2002TA87> are frequently encountered mediators of the nucleophilic additions of Grignard (and organolithium) reagents to carbonyl compounds.

Chiral 1,2-diols and 1,2-aminoalcohols have been used as additives to enable the enantioselective addition of butylmagnesium chloride to benzaldehyde <2000MC867>. The best selectivity in the formation of 1-phenyl-1-pentanol was observed when substituted 1,2-amino alcohols were added to the organometallic reagent. In one report the distereoselectivity of the alkylation of TBDMS-dihydrotestosterone was influenced by the nucleophilicity of the Grignard reagent <1999SC1065>. More nucleophilic reagents were found to undergo equatorial attack, while weaker nucleophiles proceeded to attack axially.

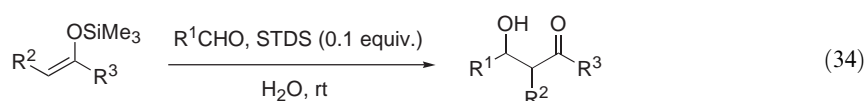
(ii) Organozinc and organocopper reagents

Dialkylzinc reagents are frequently prepared *in situ* by transmetalation of Grignard reagents and ZnCl₂. Organozinc reagents preferentially react with ketones while organocuprates are fairly unreactive, although they do tend to react with aldehydes especially in the presence of zinc

derivatives. Their reactivities can be exploited to allow highly selective reactions to take place. In common with much of the methodology described in this chapter, contemporary methods for preparation of alcohols using these reagents has focused upon asymmetric derivatives of traditional processes; the reader is directed to the review articles available for in-depth discussion of these methods <1995COFGT(2)37, 1996COS(3)65, 1997COS(4)435, 2000JCS(P1)2529>.

(iii) Organolanthanide reagents

Interest continues in the nucleophilic addition reactions of carbonyls by organoceriums, prepared from Grignard and organolithium reagents in the presence of CeCl_3 <2002TA87>, $\text{Yb}(\text{OTf})_3$ <1997BSCF275>, and $\text{Sm}(\text{OTf})_2$ <1996JOC5400> as promoter reagents. A few selected examples include Mukaiyama's aldol reactions, which were carried out in water when scandium tris-dodecylsulfate (STDS) was applied as a Lewis acid <1998TL5389>. Indeed, the catalytic activity of STDS (prepared from sodium tris-dodecyl sulfate and ScCl_3) is lower when the reaction is carried out in organic solvents (Equation (34)).



Complexes formed between sodium triethylgermanide and a range of lanthanide Lewis acids are strong bases, which mediate diastereoselective aldol reactions of ketones over aldehydes <1996SL445>. Even when the aldehyde component contains α -protons, only deprotonation of the ketone is observed.

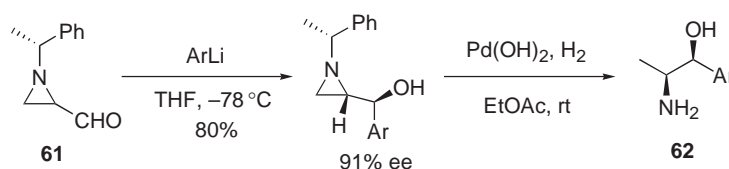
3-Haloesters react with Grignard reagents in the presence of samarium diiodide to give α -substituted cyclopropanols in excellent yield <1996T1953>. Cyclopentanols and cyclohexanols may also be prepared under the same reaction conditions using 5- and 6- haloesters, respectively. In the case of 4-haloesters, substituted cyclobutanols are produced in poor yield, the major product of the reaction being 2,2-disubstituted tetrahydrofurans.

2.02.1.3.4 Enantioselective alkylation

The development of methods for enantioselective nucleophilic attack on carbonyl groups continues to occupy researchers and contemporary investigations focus on stereoselective alkylations via catalytic reagent control <1996COS(3)65, 1997COS(4)435, 2000JCS(P1)2529>.

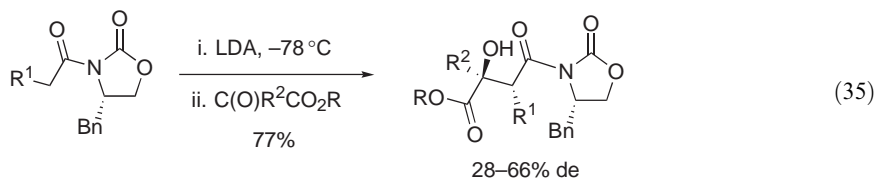
(i) Via organolithiums

In a most original (though substrate-controlled) approach, a series of analogs of ephedra alkaloids have been prepared by a synthetic sequence involving hydrogenolytic reduction of a monochiral aziridine 2-methanol <1996JOC6183>. The reaction path commences with a diastereoselective nucleophilic attack of an aryllithium upon enantiomerically pure aziridine-2-carboxaldehyde **61**. Use of aryllithiums in this nucleophilic addition process gave best selectivities ($\geq 91\%$ de, in favor of *threo*-isomer). Reductive ring-cleavage of the aziridine ring and *N*-debenzylation then occurred smoothly using Pearlman's catalyst to give *syn*-1,2-amino alcohols **62** in good yield. These amino alcohols are analogs of ephedrine; *N*-methylation yields analogs of norephedrine (Scheme 19).

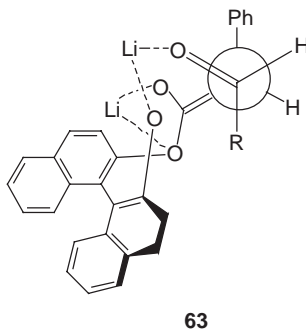


Scheme 19

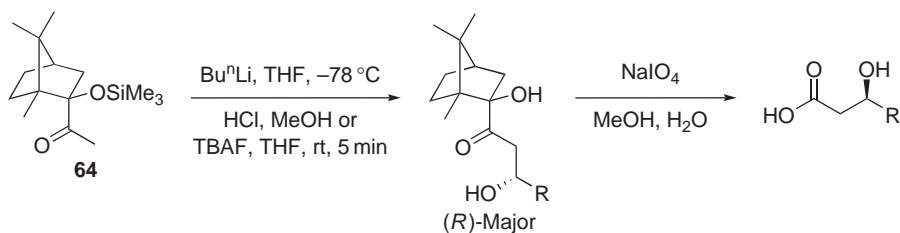
2-Hydroxy-2,3-trisubstituted succinates may be prepared enantioselectively via reactions of oxazolidinone enolates with 2-ketoesters <1996TL8263>. Diastereoselectivities of these aldol reactions are mediocre ($\leq 66\%$ de), although yields are good (Equation (35)).



2'-Hydroxy-1,1'-binaphthyl ester enolates react with aldehydes to give aldol products in good yield and with *anti*-selectivity. The diastereoselectivity of the process ranges from 27–82% (dr = 6391:36–9). The authors propose a chelated transition state **63** invoking a *re-re* interaction of enolate and aldehyde to account for the observed preference for (2*S*),3(*S*)-configured products <1998JCS(P1)637>.



Other researchers also continue to be attracted to solving the “acetate problem” in asymmetric aldol reactions: camphor-derived ketone **64** is one such chiral auxiliary recently proposed <1998AG(E)180>. Thus, the lithium enolate derived from ketone **64** underwent highly diastereoselective reaction with aromatic and aliphatic aldehydes, in good yield, to give aldol products of high enantiopurity (generally $\geq 92\%$ ee). The auxiliary is cleaved destructively by periodate oxidation, regenerating camphor. The authors propose a chelated transition state to rationalize the observed face selectivity (Scheme 20).

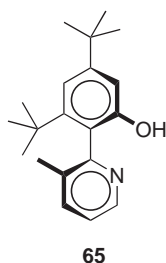


Scheme 20

(ii) *Via organozincs*

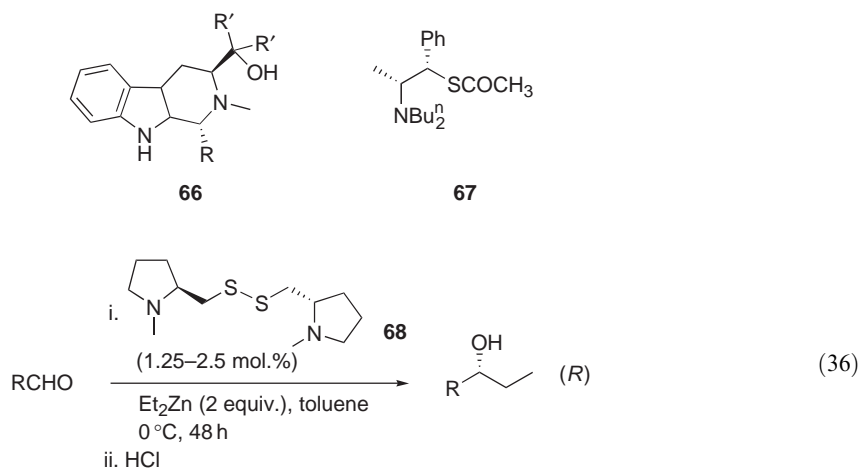
The use of dialkylzincs in enantioselective alkylations of ketones has received a reasonable amount of attention due to their selectivity for carbonyls. In a new slant on the well-known enantioselective addition of diethylzinc to aldehydes, the chiral pyridylphenol **65** has been shown to mediate such a process, but the enantioselectivity of the reaction with aryl aldehydes increases

with reaction temperature <1996JOC8002>. The enantioselectivity of the reaction follows a linear free-energy relationship, and a higher enantioexcess in the product alcohols is observed for more reactive aldehydes. Using (+)-(*R*)-catalyst, (*R*)-configured alcohols were obtained in all cases.

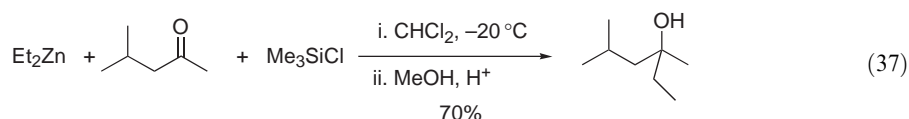


A recent class of aminoalcohols to be studied in asymmetric alkylation of aldehydes by diethylzinc concerns derivatives of the alcohol **66** (obtained from abrine) <1996TL5971>. These derivatives catalyze the alkylation, with variable enantioselectivities (24–98% ee), always in favor of (*R*)-alcohols.

The thionorephedrine derivative **67** catalyzes the enantioselective addition of diethylzinc to aldehydes <1996TL8767>. The enantioselectivities of these reactions are uniformly good. In all cases, (*S*)-alcohols are favored. Another sulfur-containing accelerating ligand useful in asymmetric additions of diethylzinc to aldehydes is disulfide **68**, derived from (*S*)-proline <1996CC645>. The enantioselectivity of additions to representative aldehydes are good-to-mediocre. In all cases, (*R*)-configured alcohols are obtained in yields of 76–96% and 70–99% ee (Equation (36)).

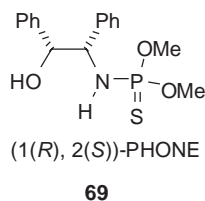


The reaction of a range of dialkylzinc species with ketones is promoted by the presence of silyl chlorides or triflates, leading to the formation of silyl ethers of tertiary alcohols in acceptable-to-good yields <1998JOC1330>. Where aliphatic ketones were used, reduced products (rather than alkylated) were always by-products; aromatic ketones generated these contaminants in generally low yield. Alcohols could be directly obtained from the reaction in one-pot by using an *in situ* acid-catalyzed deprotection (Equation (37)).

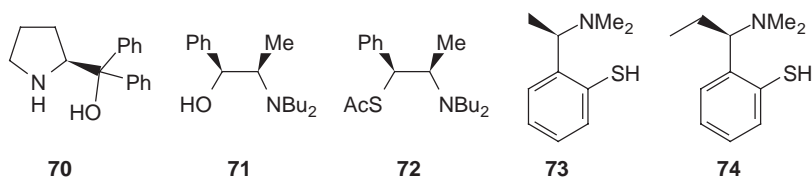


Amino alcohol catalysis of the nucleophilic addition of organozincs to carbonyl compounds has been extended to include cyclopropylzinc reagents <1998JCS(P1)177>. Thus, aldehydes react with dicyclopropylzinc and Ti(OPrⁱ)₄ in the presence of a substoichiometric amount of a chiral aminol to

give substituted cyclopropylmethanols in good yield. The enantiocontrol is good ($\geq 90\%$ ee) when aryl aldehydes are used in the presence of the thiophosphoramidate (1(*R*),2(*S*))-PHONE **69**, but is less impressive using aliphatic aldehydes or simple chiral amino alcohols.

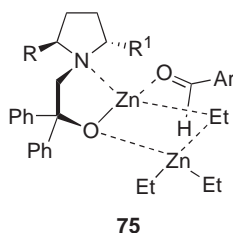


A new ligand class allowing enantioselective addition of vinylzinc reagents to aldehydes has been exemplified. Thus, ligands (**70–74**) catalyze the enantioselective addition of zinc reagents (prepared *in situ* via hydrozirconation and zirconium–zinc exchange) to benzaldehyde, with 95% enantiocontrol in the case of ligand **74**. “Typical” ligands catalyzed the process with much lower stereoselectivity <1998JOC6454>.

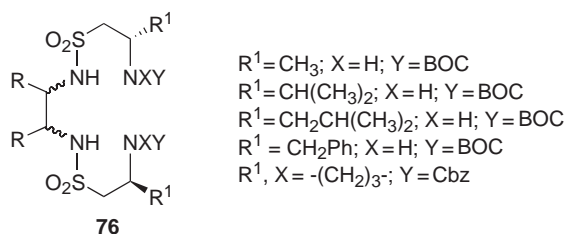


Similar investigations using asymmetric aminothiols have emphasized the influence of nitrogen substituents upon the level of enantioselectivity during such alkylations <1998CC393>. Thus, for instance, valinol-derived ligands exhibit useful enantiocontrol only when the nitrogen atom is disubstituted.

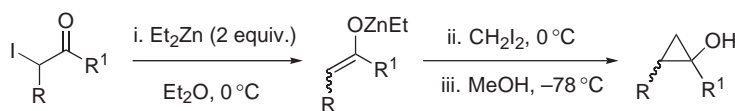
Pyrrolidine 2,5-dicarboxylic acid derivatives have been employed as an asymmetric mediator of the addition of diethylzinc to aryl aldehydes. Yields are high and enantioexcesses of the products are moderate-to-good (61–96% ee). Transition state **75** has been offered to explain the origin of enantioselectivity <1998JCS(P1)2547>.



Chiral diamines react with chiral 2-aminosulfonyl chlorides (obtained from (*S*)-amino acids) to give di(2'-amino)sulfonamides **76**, which mediate asymmetric addition of diethylzinc to aldehydes <1998JOC5312>. Thus, the members of this sulfonamide library act as co-catalysts in the reaction of aromatic and aliphatic aldehydes with diethylzinc and tetra-*i*-propyl titanate, yielding (*R*)-alcohols generally in good yield and with good enantioexcess ($\geq 86\%$ ee).



Ethylzinc enolates (generated *in situ* from 2-iodoketones) may be cyclopropanated via reaction with diiodomethane <1998TL5253>. A wide range of iodoketones undergo the reaction, in variable yield, and the cyclopropanols formed are obtained as predominantly *cis*-isomers (where applicable) (Scheme 21).



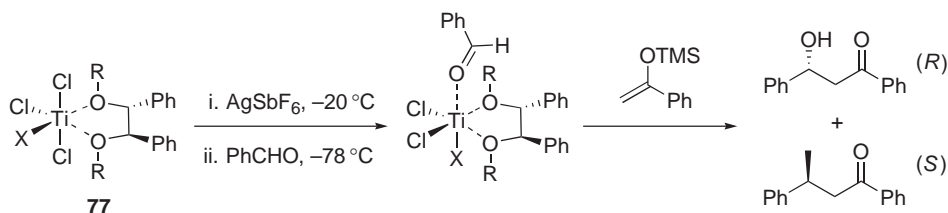
Scheme 21

(iii) *Via organosilanes*

The nucleophilic character of the C—Si bond can be activated through the generation of a positive charge β to the bond, or by the *in situ* formation of hypervalent silicon species, often by reaction with fluoride ion. Denmark and co-workers have reported further details of the aldol reactions of the trichlorosilyl enol ethers of methyl ketones, with emphasis upon catalytic asymmetric aldol processes. Thus, a chiral nonracemic phosphoramidate was employed to catalyze the reaction of trichlorosilyl enol ethers with a range of aldehydes to give the corresponding 3-hydroxy ketones in good yield and in high enantiomeric purity <1998JOC918>. The authors report that trichlorosilyl enol ethers may be prepared routinely by the reaction of the analogous trimethylsilyl enol ethers with silicon tetrachloride in the presence of a mercury(II) salt. Overall, the method constitutes another useful solution to the “acetate aldol” problem.

(iv) *Via titanium*

Chiral cationic titanium-based Lewis acids **77** have been reported to catalyze asymmetric Mukaiyama-like “acetate aldol” reactions. The reactions proceed with mediocre enantiocontrol, but in good yield (Scheme 22) <1998TL727>. Aldol reactions with dienolates and aldehydes can be catalyzed by asymmetric binaphthyl titanates <1995JA12360>.



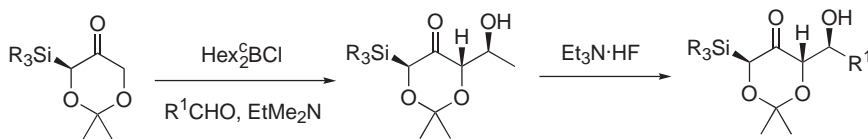
Scheme 22

(v) *Via organoborons*

Alkynyl-, allyl-, and vinylborane reagents are also used in the alkylation of carbonyl compounds. It is now possible to alkylate aryl aldehydes using dialkylboron chlorides in the presence of a base <2000OL255, 2001T1663>. Good yields were obtained when secondary alkyl groups were used, while no reaction occurred with monoalkylboron chlorides. In addition, Kabalka and co-workers <2002T3243> have also developed a system for alkylating certain carbonyls using alkylboron chlorides and alkylboron dichlorides in the presence of oxygen. The reaction appears to be general for all aryl aldehydes, proceeding effectively at 0 °C.

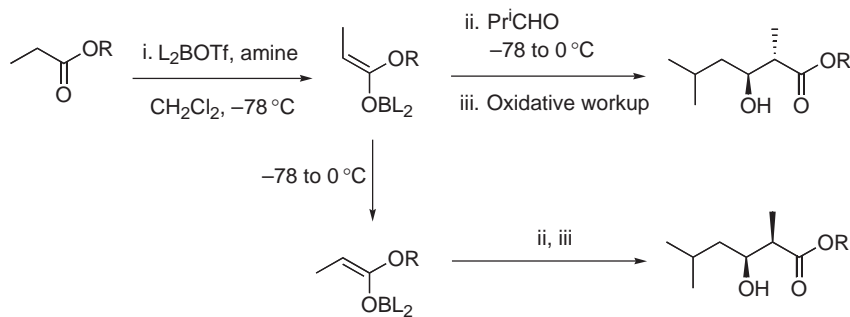
Enantiomerically pure silyl-substituted dioxanones have been shown to undergo highly diastereoselective *anti*-aldol reactions <1996S1095>. Thus, the boron enolate derived from 2,2-dimethyl-4-thexyldimethylsilyl-1,3-dioxan-5-one reacts with a range of aromatic and aliphatic aldehydes with excellent diastereo- and enantioselectivity to give dioxanones in good-to-excellent yield,

via a typical Zimmerman–Traxler cyclic transition state. The desilylation may be effected using HF–triethylamine complex, yielding 1,3-protected *anti*-1,3,4-trihydroxyketones in good yield (Scheme 23).



Scheme 23

Masamune and co-workers <1996JOC2590> have described their observations of aldol reaction between boron enolates of esters and amides, a species previously thought to be relatively unreactive in such reactions (Scheme 24). In addition, esters of 8-phenylmenthol were shown to react with enantio- and diastereocontrol in such aldol reactions, with the levels of control ranging from mediocre (20% de) to excellent (96% de).

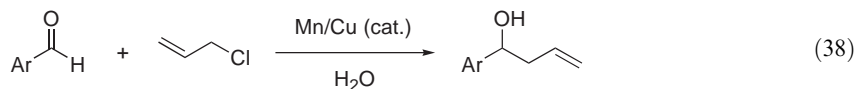


Scheme 24

2.02.1.3.5 Nucleophilic allylation

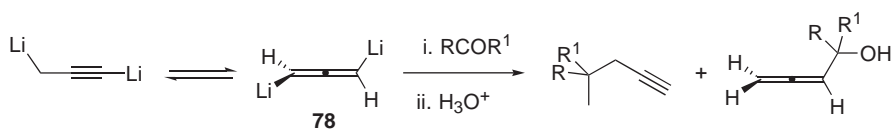
The use of reactions effecting allylation of carbonyl compounds is widespread within synthetic organic chemistry, due to the great flexibility and high stereoselectivity of the processes. The majority of such allylations occur via one of the two procedures, viz., reaction of carbonyls with a mixture of alkyl halides and metals (the Barbier reaction) or by reaction with a preformed allylic metal (or pseudometal in the case of boron and silicon) reagent.

A combination of metallic manganese and copper mediates a Barbier-like reaction of aryl aldehydes with allyl chlorides <1998JOC7498>. This Mn–Cu procedure (notably, no reaction is observed if only one metal is employed) offers greater reactivity than many other metal-mediated allylations in aqueous media. In addition, the presence of acetic acid in the same reaction promotes a pinacol coupling reaction giving dihydrobenzoins in good yield but with poor stereoselectivity (*threo:erythro* = 65:35–39:61). Only aromatic aldehydes undergo this latter process, ketones are unreactive and aliphatic aldehydes are instead reduced (Equation (38)).



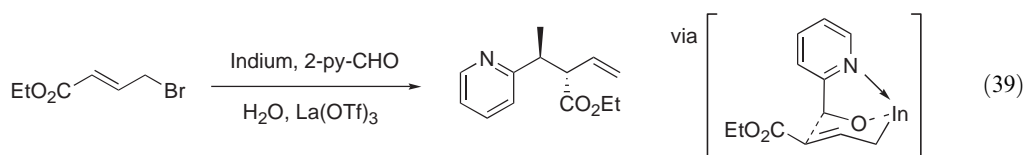
Manganese metal may also be activated by sub-stoichiometric amounts of lead(II) chloride and trimethylsilyl chloride, whereupon Barbier and Reformatsky-type reactions may be carried out <1996TL7040>. The transition metal salt scandium triflate catalyzes allylation of aldehydes with allyltrimethylsilane <1996TL3745>.

Allene reacts with 2 equiv. of BuⁿLi to give 1,3-dilithiopropyne **78**, which reacts with aldehydes and ketones primarily via the propargyl tautomer (rather than the alternative allenyl form), to give homopropargyl alcohols in excellent yield (Scheme 25) <1998TL3935>.



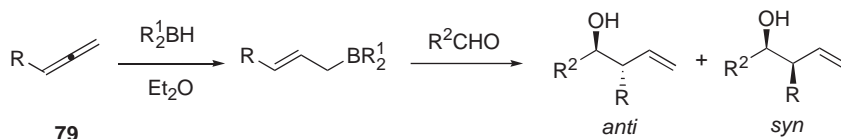
Scheme 25

The use of lanthanum(III) triflate enhances both the rate and stereoselectivity of Barbier-type reactions of 4-bromocrotonate esters with aryl aldehydes [<1996SL263>](#). In most cases, the reaction is stereoselective, and primarily *anti*-homoallylic alcohols are obtained. However, where the substrate possesses an additional ligation point (e.g., in the reaction of 2-pyridinecarboxaldehyde), this stereoselectivity may be overturned ([Equation \(39\)](#)).



2.02.1.3.6 Allylation using boranes, silanes, and stannanes

The use of chiral boranes in the hydroboration of monosubstituted allenes provides a general synthetic route to 3-substituted allylboranes and, subsequently, to nonracemic homoallylic alcohols [<1997TL219>](#). Thus, reactions of allenes **79** with diisopinocampheylborane to give only allylborane products with terminal boron substituents. These boranes react with aldehydes to give *anti*-homoallylic alcohols as the major product, with moderate-to-good enantiomeric excess (74–80% ee) ([Scheme 26](#)).

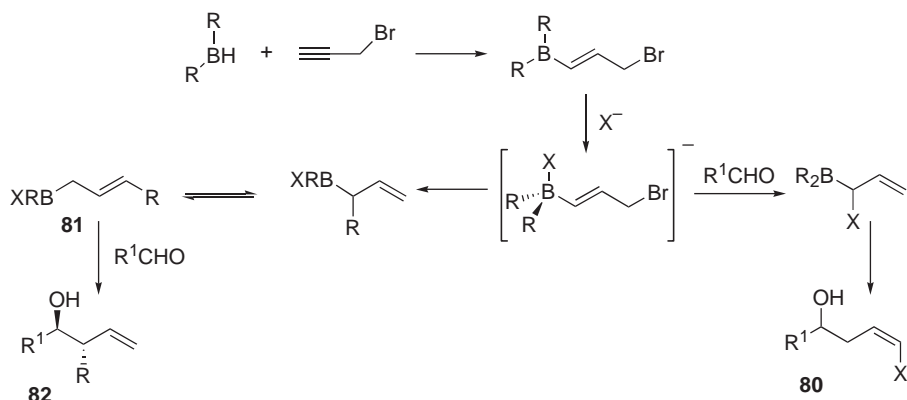


Scheme 26

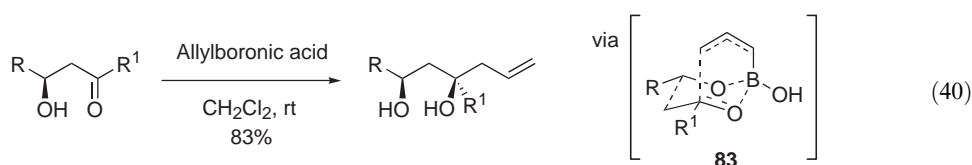
Diisopinocampheylpropargylboranes (obtained upon reaction of metallated 2-alkynes with dIpc_2BCl) react at very low temperature with alkyl and aryl aldehydes to give α -allenyl alcohols in reasonable yields (68–80%) as the only product of the reaction. The enantioselectivity is generally good (87–96% ee), with (*R*)-configured alcohols obtained in all cases [<1996TL4125>](#).

Homoallylic alcohols can be synthesized via a one-pot three-component system based on the regioselective hydroboration of propargyl bromide with dialkylboranes [<2000JOC8767, 2001SL601>](#). The sequence of events commences with the preparation of dialkylborane and hydroboration of propargyl bromide (giving a 2-bromomethyl vinylborane). This is followed by quaternization with tetrabutylammonium bromide, either in the presence of an aldehyde to afford (*Z*)-1-bromoalk-1-en-4-ol **80**, or in the absence of an aldehyde to allow the formation of γ -substituted allylborane **81** ([Scheme 27](#)). This allylborane **81** then nucleophilically attacks an aldehyde leading to an *anti*-homoallylic alcohol **82**.

Although easily prepared (and, in certain cases, commercially available), allylboranes are reactive and, therefore, sensitive species. 3-Hydroxyaldehydes and ketones undergo efficient allylation by allylboronic acid, a much less sensitive reagent. The reaction is diastereoselective (20–84% de), with the highest levels of selectivity being obtained when the carbonyl group bears a phenyl substituent [<1996TL2181>](#). The stereoselectivity of the reaction (in which *syn*-1,3-diols always dominate the product distribution) can be rationalized by a cyclic transition state **83**, which invokes an axial attack upon the chelated carbonyl ([Equation \(40\)](#)).

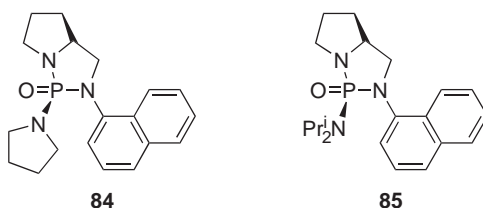


Scheme 27



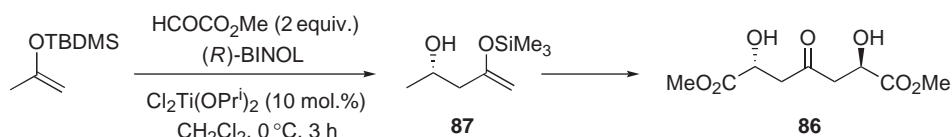
((*S,S*))-*N,N*-Bis(1-methylbenzyl)formamide acts as a Lewis base to catalyze the asymmetric allylation of a range of aryl and aliphatic aldehydes by allyl and crotyl silanes [<1998TL2767>](#). The slow process (typically requiring several weeks) requires stoichiometric amounts of HMPA, but gives homoallylic alcohols in up to 98% ee. Under these reaction conditions aryl ketones react with poor enantioselectivity. Bis(fluorosulfinyl)imide [HN(SO₂F)₂] also catalyzes the allylation of carbonyl compounds with allyltrimethylsilane, in this case by acting as a Brønsted acid [<1996CC581>](#).

Chiral nonracemic phosphoramides catalyze the asymmetric allylation of aldehydes by allyltrichlorosilanes [<1996TL5149>](#). Thus, in the presence of sub-stoichiometric amounts of (*S*)-proline-derived phosphoramides **84** and **85**, aryl aldehydes are allylated in mediocre-to-excellent yield and with moderate enantioselectivity to give homoallylic alcohols.



Where diastereoisomerism is possible, (*Z*)-aryl silanes exhibit a good selectivity for *syn*-homoallylic alcohols, as predicted by the usual six-membered transition state, whereas (*E*)-silanes favor *anti*-configured products. The most interesting feature of the process is the inversion in enantioselectivity witnessed when the alkylamine subunit of catalyst **84** is changed from a pyrrolidine to a diisopropylamine group **85**; when this change is made, the observed selectivity is inverted.

Double asymmetric induction in the titanate-catalyzed asymmetric aldol reaction of silyl enol ethers with methylglyoxalate allows for a highly enantioselective preparation of C₂-symmetric 2,6-dihydroxy-4-oxo heptadioates **86** [<1997TL579>](#). Thus, reaction of the enol ether of acetone with 2 equiv. of methylglyoxalate in the presence of a sub-stoichiometric amount of the (*R*)-BINOL-derived Ti(IV) catalyst proceeds to give diester **86** in good yield and with excellent stereocontrol (>99% ee and >99% de) (Scheme 28). The authors found that the enantiomeric excess of the product was enhanced when compared to the homoallylic alcohol intermediate **87**, which was



Scheme 28

obtained within only 98.5% ee (in favor of the (*R*)-isomer) via reaction of 1 equiv. of glyoxalate with enol ether. Thus, an asymmetric amplification occurs in the second Mukaiyama reaction: theoretical calculations suggest that the second reaction of (*R*)-**87** in the presence of (*R*)-BINOL is ~ 3.4 times faster than that of (*S*)-**87**, thereby allowing a dynamic kinetic resolution.

Enantioselective allylation of aldehydes by organostannanes mediated by chiral catalysts continues to occupy the attention of researchers. Thus, (*R*)-BINAP–silver triflate complex catalyzes the nucleophilic attack by methallyl- and crotyltin species to give homoallylic alcohols in generally good yield and with moderate-to-good enantioselectivity [\[1997SL88\]](#).

Marshall and co-workers [\[1996JOC105\]](#) have maintained their keen interest in the allylations of aldehydes by chiral hydroxylated allylstannanes. Thus, allylstannanes **88** have been utilized in asymmetric stereoselective S_E2' reactions with *syn*-**89** and *anti*-aldehydes to prepare precursors to differentially protected L-talose, D-allose, L-glucose, and D-mannose. The key mechanistic feature of the reaction is a tin–indium transmetalation; the allylindium species produced by such an exchange react with achiral aldehydes to give predominantly *anti*-1,2-dihydroxypent-4-enes (Equations (41) and (42) and Table 6).

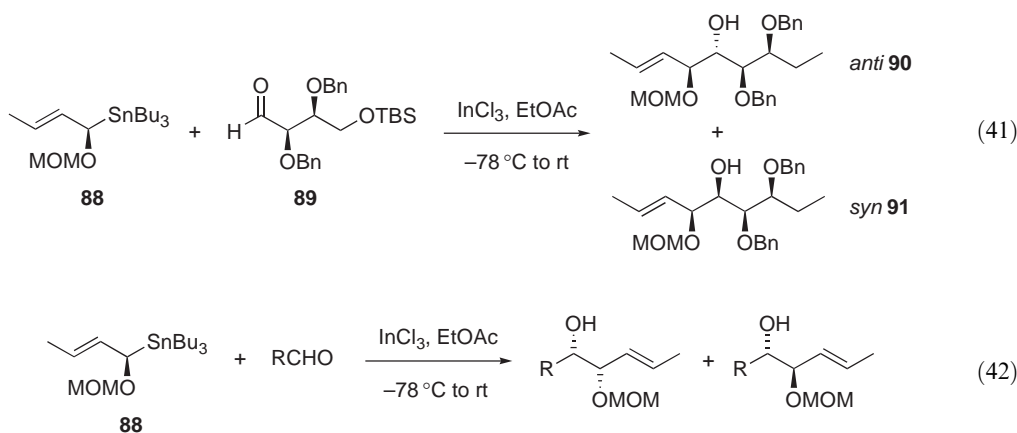
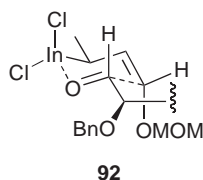


Table 6 Selectivity in the allylation of achiral aldehydes using chiral hydroxylated allylstannanes

<i>R</i>	<i>anti:syn</i>	Yield (87)%
<i>n</i> -C ₆ H ₁₁	95:5	99
<i>c</i> -C ₆ H ₁₁	98:2	95
(<i>E</i>)-BuCH=CH	90:10	85
<i>n</i> -C ₆ H ₁₁ C≡CH	90:10	85

These allylated compounds may be considered to be formal equivalents of differentially protected L-talose **90**, D-allose **91**, L-glucose, and D-mannose. A Zimmerman–Traxler-like cyclic transition state **92**, which rationalizes the observed stereoselectivity is proposed by the authors.



Allylation of aldehydes using tetraallyltin requires no catalyst when polar solvents are used in the reaction. The reaction is mild and efficient, with homoallylic alcohols being produced in generally good yields <1996TL1905>.

Side-chain acyl groups of π -allyltricarboxyliron lactone complexes react with allylstannanes in the presence of a Lewis acid to give homoallylic tertiary alcohols in good yield and with very high diastereoselectivities <1996CC657>. The products of the allylation reaction may be converted into stereodefined buta-1,3-dienes.

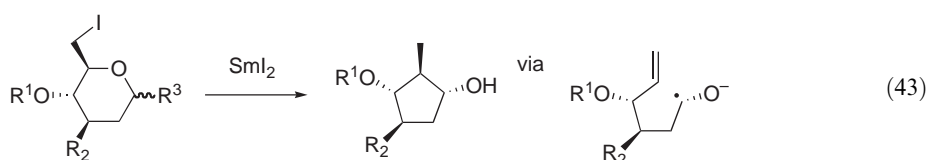
2.02.1.4 By Ether Cleavage

2.02.1.4.1 Ring opening of epoxides

Epoxides are versatile intermediates for the synthesis of alcohols, being easily reduced or opened by a variety of nucleophiles. Attack upon the strained three-membered ring can occur under acidic, basic, or neutral conditions, with Lewis or Brønsted acids usually favoring that product arising from the transition state that best accommodates the positive charge. The corollary is that under neutral or basic conditions, nucleophilic attack generally occurs at the least-hindered site. Contemporary research in the area has been primarily focused on the use of novel activators for ring-opening. For example, cleavage of epoxides can be achieved through the catalytic use of a nonconventional Lewis acid tri(pentafluorophenyl)borane via a hypercoordination of boron <2000OL695>. The area has been reviewed comprehensively and the reader is directed to these works for further details <1995COFGT(2)37, 1998SL337, 2002CSR223>.

(i) Reductive

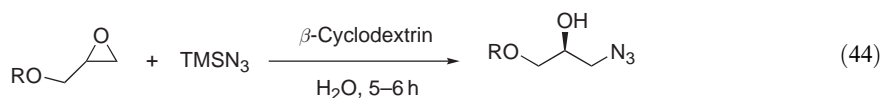
Iodomethylhexose derivatives undergo tandem Grob fragmentation–reductive cyclization, when treated with samarium diiodide (Equation (43)). The first reaction, reductive ring-cleavage liberates an unsaturated aldehyde, which reacts further with SmI_2 via radical cyclization of the intermediate ketal <1996TL5817>. Improved yields are observed when an acetyl leaving group, as opposed to a methoxy group, is present at the anomeric center.



(a) *Reduction by metal hydrides.* Functionalized epoxides undergo reductive ring-opening upon reaction with a mixture of tributylstannane, tributylstannyl iodide, and phosphine oxide <1995TL9357>. The regiochemistry of the reduction depends on the nature of the substituent; adjacent multiple bonds direct reduction to the allylic position.

(ii) Alkylative

(a) *By heteroatomic nucleophiles.* Among the vast number of nucleophiles that have been employed in the ring-opening of epoxides, azides have received considerable attention. The classical reagents for the formation of azidohydrins (precursors to β -amino alcohols) are TMSN_3 or NaN_3 with either a Lewis acid or a transition metal complex. Asymmetric ring-opening can be achieved in the presence of chiral complexes. For example, Jacobsen has shown that chiral (salen) Cr(III) complexes effectively catalyze the asymmetric ring-opening of epoxides with TMSN_3 <1995JA5897, 1996JOC389> via a bimetallic enantioselectivity determining step <1996JA10924>. Other complexes that have been employed include β -cyclodextrin in aqueous media (Equation (44)) <1999TA4261> and ytterbium triisopropoxide <1995CC1021>.

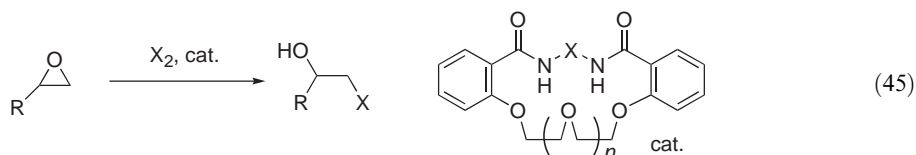


Regioselective azidolysis (addition at the most substituted carbon) of epoxides can be carried under acidic conditions (pH 4.2) with NaN_3 <1999JOC6094>. At basic pH the attack of the azide ion preferentially occurred on the least substituted carbon.

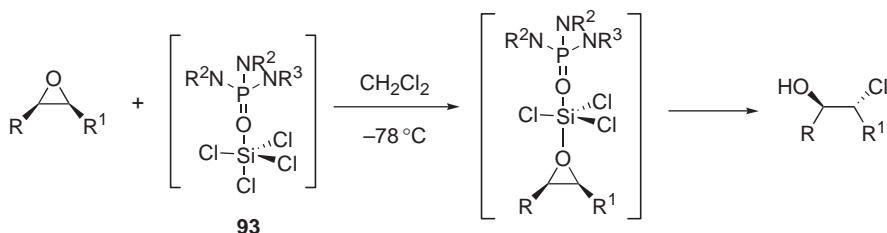
The opening of epoxides with aromatic amines has received little attention possibly due to their high affinity for Lewis acids. One recent method involves stirring a heterogeneous mixture of unactivated commercially available alumina, epoxide, and the aniline derivative in THF at reflux for 6 h <2002TL819>. In the presence of a catalytic amount of Lewis acid $[\text{B}(\text{C}_6\text{H}_5)_3]$ ring-opening of epoxides with various nucleophilic heteroatoms (allyl and propargyl alcohol, aniline, thiophenol) can be achieved <2002TL3801>. Catalytic ring-opening of *meso*-epoxides with anilines can be carried out under mild conditions using bismuth trichloride <2002TL7891>. β -Cyclodextrins <2000SL339>, cerium(III) chloride <2001S831>, and tantalum(V) chloride <2000S1817> have been demonstrated to catalyze the cleavage of epoxides by aromatic amines.

Many techniques are available for the preparation of halohydrins. In a recent study the opening of symmetric and asymmetric epoxides with POCl_3 or PCl_3 in the presence of 4-*N,N*-dimethylaminopyridine and dichloromethane was performed in high yields <2002TL15>. The same protocol can also be used for oxetanes. A mixture of cerium(III) chloride/ NaI in acetonitrile reacts with epoxides to form β -halohydrins <2001TL3955>. Chemoselective epoxide cleavage to bromohydrins in the presence of ketal, benzyloxymethoxy, and trimethylsilyl ether functionalities can be carried out using triphenylphosphonium bromide <2000SL382>.

Macrocyclic diamides mediate the ring-opening of epoxides using elemental iodine or bromine, to give 1,2-hydroxyhalides <1998JOC1455>. In all cases, epoxides were attacked at the least-hindered carbon atom. The authors proposed a macrocycle-mediated *in situ* formation of Br_3^- or I_3^- to rationalize the observations (Equation (45)). Three pyridine-containing macrocyclic dilactams have also been reported as catalysts for the formation of vicinal iodo alcohols <2001T6057>.



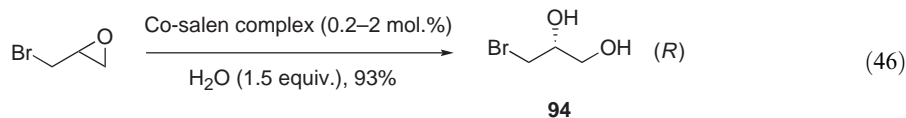
Denmark and co-workers <1998JOC2428> have reported a catalytic asymmetric ring-opening of epoxides utilizing silicon tetrachloride to embrace desymmetrizing halogenative ring-opening of *meso*-epoxides. Thus, symmetrical epoxides react with chlorosilane and a sub-stoichiometric amount of chiral HMPA analog **93** at low temperature to give 1,2-hydroxychlorides in generally excellent yields and with moderate-to-good enantioselectivity (Scheme 29). The reaction, it is postulated, proceeds via formation of a chiral phosphoramidate-stabilized silenium ion.



Scheme 29

An alternative enantioselective ring-opening of *meso*-epoxides, to form TMS ethers of bromo- and iodoalcohols, uses a chiral zirconium complex <1998JA7139>. Titanium complexes using TADDOL and BINOL ligands have also been employed with CuCl_4 or TMSCl to enantioselectively open symmetric and racemic epoxides <1999TA1563>.

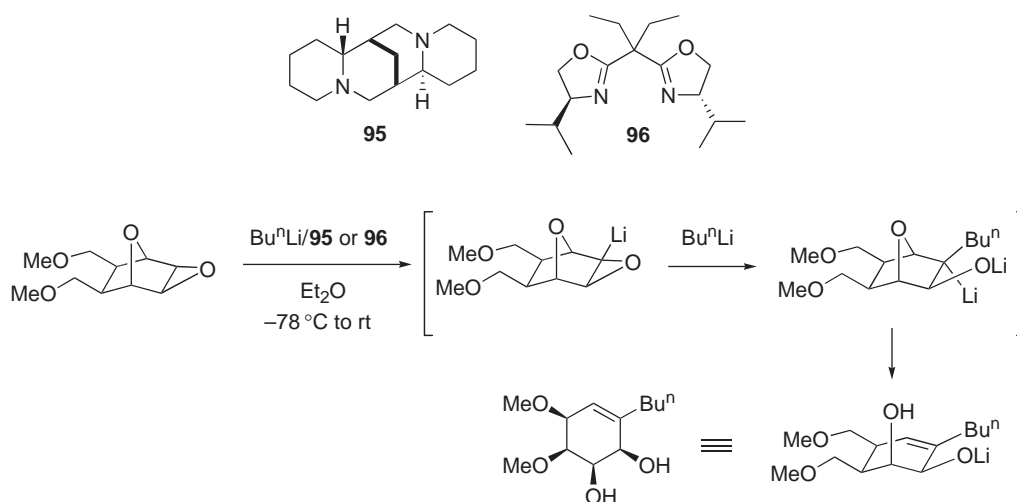
Jacobsen's hydrolytic kinetic resolution (HKR) process has been extrapolated and shown to be adept in the preparation of *epi*-halohydrins of high enantiomeric purity [<1998JOC6776>](#). Thus, ring-opening of racemic halohydrins by water in the presence of the familiar Co-salen complex gives (2(*R*))-bromo diol **94** in nearly quantitative yield and high enantiomeric excess. The results have been rationalized by an *in situ* racemization of *epi*-bromohydrin under HKR conditions (Equation (46)).



β -Hydroxytrifluoroacetamides can be prepared by the ring-opening of epoxides with trifluoroacetamide under solid–liquid phase-transfer catalysis conditions [<1997T4787>](#). Good regioselectivity of ring-opening with amines, hydrazines, and thiophenols can be achieved with the commercially available activator LiNTf_2 [<2002TL7083>](#). β -Hydroxy sulfides are available by the catalytic asymmetric ring-opening of symmetrical epoxides with thiols using a gallium/lithium/bis(binaphthoxide) complex [<1997JA4783>](#). Ring-opening of epoxides can be achieved under high pressure. For example, indoles and pyrroles can react at the 2- or 3-position with asymmetric epoxides to afford alcohols [<1998H1135>](#).

Bis-tributyltin oxide and bis-chlorodibutyl oxides are effective reagents for the regio- and stereoselective ring-opening of (*R*)-(-)-styrene oxide in methanol or *i*-propanol to give β -alkoxy alcohols [<2001SL65>](#). Ytterbium trifluoromethanesulfonate [<2001SL836>](#) and bis(cyclopentadienyl) zirconium dichloride [<2003MI95>](#) can also be used.

(b) *By carbon nucleophiles.* Epoxides derived from dihydrofuran and dihydropyrrole undergo organolithium-induced alkylative double ring-opening to afford acyclic alkene diols and amino alcohols, respectively [<2001OL3401, 2002S1445>](#). Recently the enantioselective alkylative double ring-opening of oxa- and aza-bicyclic alkene epoxides has been described using chiral ligands thus, providing access to substituted cycloalkenediols [<2002AG\(E\)4313>](#). Sparteine **95** and bisoxazoline ligands **96** mediate asymmetric deprotonations with organolithiums Bu^nLi and Pr^iLi . The reaction proceeds by a double ring-opening mechanism with an intermolecular C—C bond-forming step leading to nucleophile incorporation at a vinylic position (Scheme 30).

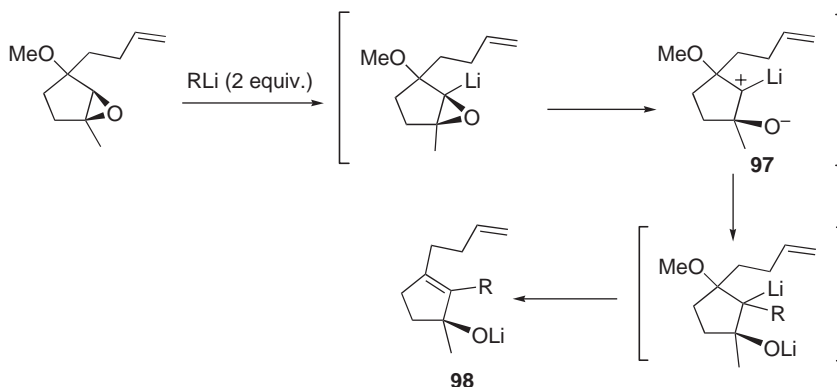


Scheme 30

The regioselective nucleophilic ring-opening of 3,4-epoxy alcohols using organocuprates has been reported [<1997T16139>](#). The reaction proceeds via a six-membered transition state permitting an intramolecular delivery of the nucleophile to C-3 to afford 1,4 diols.

(iii) *Eliminative*

Upon treatment with an organolithium reagent, cyclic α -methoxy epoxides undergo regiospecific conversion to substituted allylic alcohols via β -elimination <1996CC549, 1998SL337>. A feasible explanation is the formation of an α -lithiated epoxide which readily undergoes ring-opening to form an α -alkoxy- α' -alkoxide carbene-like species **97** (Scheme 31). Subsequent insertion of an alkyl group, then elimination of MeOLi leads to the corresponding α - β -unsaturated alcohol **98**. The desymmetrizing, asymmetric eliminative ring-opening of epoxides by chiral lithium amide bases has been reviewed <2002CSR223>.



Scheme 31

2.02.1.4.2 *Vinyl epoxides*

β -Amino alcohols can be obtained from ring-opening of vinyl epoxides by nitrogenous nucleophiles. Normally when vinyl epoxides are treated with sodium azide, a mixture of products is obtained due to a thermal [3,3]-rearrangement of the initially formed allylic azide. However, upon prolonged heating with ammonia and tosic acid, regio- and stereospecific ring-opening of such epoxides occurs <1997TL2027>. Shorter reaction times have been realized through microwave-assisted aminolysis using ammonium hydroxide <1999TL9273, 2001T9225>.

A Lewis acid-mediated, regiospecific opening of vinyl epoxides to give β -hydroxy allyl ethers is possible by reacting equimolar quantities of alcohol and epoxide with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1 mol.%) as the most efficient catalyst <2000TL3892>. Rhodium catalyzes the ring-opening of vinyl epoxides with alcohols and aromatic amines <2000OL2319>.

2.02.1.4.3 *Oxetanes*

As mentioned above the opening of symmetric and asymmetric oxetanes can occur in high yields with POCl_3 or PCl_3 in the presence of 4-*N,N*-dimethylaminopyridine and dichloromethane <2002TL15>. Silyl ethers of 3-oxetanols (prepared by photocycloaddition of aromatic aldehydes and silyl enol ethers) undergo cleavage upon reaction with hydride sources to give 2-hydroxy silyl ethers or 1,2-diols, both of which are obtained with high levels of diastereomeric purity <1996JOC3900>. The reaction is highly *unpoled* and could, formally, be considered to be equivalent to nucleophilic addition of either an α -silyloxycarbanion or an α -aryl- α -hydroxyanion to an aldehyde or ketone. The same reaction type has been exploited via intramolecular nucleophilic substitution to give a variety of heterocyclic structures <1996JOC7642>. The reaction has certain structural requirements, for example, 6-*exo* ring-closure is not favored when the heteronucleophile is oxygen, but proceeds in acceptable yield when sulfur is the nucleophile. In certain cases, dehydration occurs spontaneously, particularly when the heteronucleophile is a phenolic oxygen. In this case, the reaction offers a preparation of 3-substituted benzofurans.

Tebbe-like methylenation of β -lactones gives 2-methylene oxetanes, which undergo an alkylative cleavage in the presence of a base to give homopropargylic alcohols in moderate-to-good yields <1998JOC6782>.

Allylic ethers may be cleaved to give alcohols by treatment with titanates and a Grignard reagent. The reaction proceeds via titanacyclopropane intermediates <1996TL3663>.

2.02.1.5 Miscellaneous Methods of Alcohol Synthesis

2.02.1.5.1 Oxidative methods

The oxidative conversion of alkyl(phenyl)dimethylsilanes has been described <1995JCS(P1)373>. The previously neglected reaction of enol ethers with aqueous H_2O_2 has been examined in depth by Yamamoto and co-workers <1997JOC7174>. Thus, a range of alkyl vinyl ethers reacted with 35% H_2O_2 and cetylpyridinium peroxotungstophosphate (PCWP) to give mainly α -hydroxy acetals, accompanied by hydroxyketone and oxidatively cleaved products.

2.02.1.5.2 From other alcohols

This area of research has seen no significant advances since the publication of COFGT (1995) <1995COFGT(2)37>. Readers are directed to COFGT (1995) and more recent review articles, as detailed in the introduction of this chapter.

2.02.1.5.3 Hydrolytic methods

The recent studies of Davis and co-workers <1996TL4349> into the preparation and reactions of enantiomerically enriched *N*-sulfinyl aziridines have been extrapolated with the report of the use of these compounds to prepare sphingosines. Thus, vinyl aziridine reacts along a bifurcated synthetic sequence involving regioselective hydrolytic ring-cleavage to give both L- and D-sphingosine. Buckminsterfullerene is converted in good yield by a two-step process into dodecahydroxy- C_{60} via sequential reaction with $\text{H}_2\text{SO}_4/\text{SO}_3$ and water <1998JCS(P1)1171>. Thus, in the presence of phosphorus pentoxide, C_{60} is first sulfated to give a hexacyclosulfated fullerene, which is hydrolyzed upon heating in water to the hydroxylated product. Water-soluble fullerlenols may be prepared in "one-pot" via addition of nitrogen dioxide radicals to C_{60} itself <1996T4963>. Polynitrofullerene $\text{C}_{60}(\text{NO}_2)_n$ is produced by the reaction and this species may be hydrolyzed *in situ* to polyhydroxy fullerenes in mediocre overall yield.

2.02.1.5.4 Alcohols from rearrangements

An asymmetric Wittig rearrangement of chromium tricarbonyl complexes of allyl benzyl ethers is mediated by chiral amide bases <1998CC123>. The enantioselectivity of the process is good-to-excellent.

2.02.1.5.5 Others

The mechanism of the conversion of α -nitro ketones to the corresponding α -hydroxy ketones under basic aqueous conditions has been studied <1998HCA1373>. The reaction was discovered serendipitously by the authors whilst they were studying ring-expansion reactions of cyclic α -nitroketones; only α -nitro ketones with acidic protons in the α' -position undergo the reaction and the NO_2/OH exchange was shown to proceed with retention of configuration. The newly incorporated oxygen atom (of the OH group) was shown to originate in the solvent. The product formation is explained by a double $\text{S}_{\text{N}}2$ reaction, via a Favorskii-like cyclopropane intermediate. A systematic study of the ring-opening reactions undergone by endoperoxides has been reported by Little and Schwaebe. Thus, a range of organometallic nucleophiles react with bicyclic endoperoxides to give monoethers of 1,4-cycloalkenyldiols in mediocre-to-good yield <1996TL6635>. When a nonsymmetrical endoperoxide, ascaridole, underwent the reaction, the least-hindered oxygen of the peroxide was attacked selectively. An asymmetric Baylis-Hillman reaction of alkyl vinyl ketones with electron-deficient aromatic aldehydes is catalyzed by proline-derived pyrrolizidine alcohols <1998CC2533>. The reaction proceeds in variable (but generally good)

yield but with mediocre enantioselectivity ($\leq 72\%$ ee). A Baylis–Hillman-like three-component reaction gives 3-hydroxy-2-(phenylthio) methyl esters in good yield and with moderate diastereo-control <1998CC1095>. Thus, reaction of acrylates with lithium thiophenolate in the presence of a range of aldehydes gave primarily *syn*-hydroxyesters. The process was also found to be productive when selenolates were employed rather than thiolates. Highly functionalized 2-hydroxy-methyl acrylates may be prepared by the reaction of methyl propiolate with ketones or aldehydes in the presence of tetrabutylammonium iodide and a zirconium(IV) catalyst <1996SL586>. In effect, the reaction is, therefore, analogous to the Baylis–Hillman reaction. The products of the reaction may be converted into α -methylene β -lactones. A photolytic process allows conversion of *N*-alkylpyridinium halides into *trans*-2,3-aziridino-1-hydroxycyclopent-4-enes in moderate-to-good yields. The methodology was used to prepare analogs of Mannostatin A <1998HCA1095>.

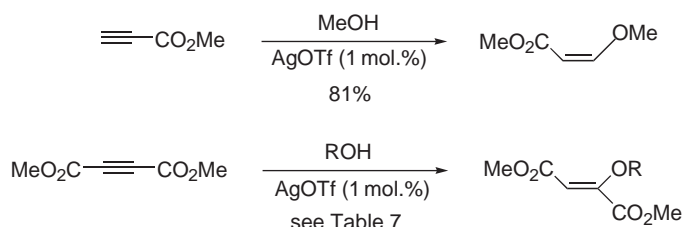
2.02.2 ETHERS

2.02.2.1 Acyclic Ethers

2.02.2.1.1 General methods

The fundamental methodology available for the preparation of acyclic ethers has not been expanded significantly since the publication of COFGT (1995) <1995COFGT(2)37> with the route originally devised by Williamson, involving alkylation of alkoxides or their equivalents, still remaining the general method of choice. Preparative routes previously discussed include the Purdie modification, which utilizes silver oxide as a base to enhance the reaction, thallium ethoxide as an alternative catalyst to silver oxide, and calixarenes to catalyze Williamson-type syntheses of ethers. Other preparative methods previously described for the syntheses of ethers include: (i) the addition of alcohols to alkenes under a variety of conditions; (ii) the reduction of acetals using a range of hydride sources; and (iii) alkylation of acetals and their sulfur and nitrogen hemianalogs. 2-Ketoethers have been prepared via the reaction of substituted vinyl alkoxymethyl ethers with aluminum trichloride. Good yields of symmetrical ethers can be obtained through the reactions of alkyl bromides with dibutyltin oxide in the presence of fluoride ion. Esters of carboxylic acids have been converted into the corresponding ethers by conversion to thionoesters (with Lawesson's reagent) and subsequent reduction with tributyltin hydride <1995COFGT(2)37>.

More recently, enol ethers have been synthesized with high stereoisomeric purity by the silver(I)-catalyzed addition of alcohols to dimethyl acetylenedicarboxylate or methyl propiolate <1996CL727>. Thus, in the presence of sub-stoichiometric amounts of silver(I) triflate, (*Z*)-configured 3-alkoxyfumarates or acrylates are obtained, generally in good yields (Scheme 32). However, it should be noted that care has to be taken in certain cases to avoid hydrolysis of the enol ether or other side reactions (Scheme 32 and Table 7).



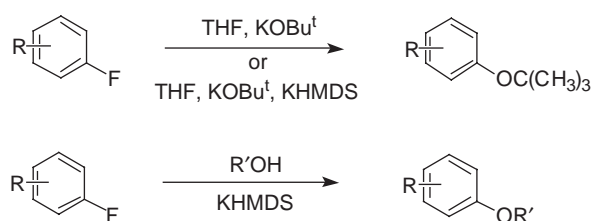
Scheme 32

Tertiary ethers of phenols may be prepared in good yield by *ipso*-nucleophilic substitution of activated aryl fluorides <1998JOC9594>. The method is effective even when using relatively electron-rich arenes, and is applicable to the preparation of a range of chiral ethers (Scheme 33).

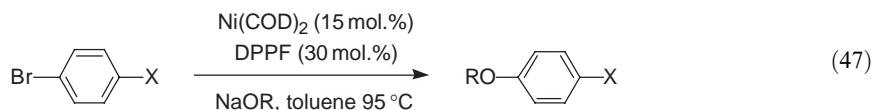
Table 7 Silver(I)-catalyzed addition of alcohols to dimethyl acetylene dicarboxylate

ROH	Time (h)	Yield fumarate (%)
MeOH	4	87
EtOH	7	87
Pr ⁱ OH	20	10 ^a
Bu ^t OH	20	86
Allyl alcohol	20	0 ^b
Propargyl alcohol	20	0

^a Dimethyl oxaloacetate isolated in 38% yield. ^b Claisen rearrangement occurs (81% yield).

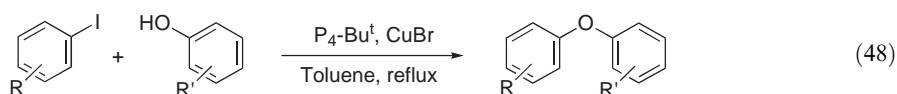
**Scheme 33**

A similar report demonstrates that in the presence of Ni(COD)_2 , *o*-alkylphenols may be prepared in good yields by the direct displacement of aryl halides by alkoxides without the usual prerequisite for strongly electron-withdrawing groups to be present in the aromatic ring <1997JOC5413>. Certain bromides also react with sodium siloxides, yielding silyl aryl ethers in good yield (Equation (47) and Table 8).

**Table 8** Preparation of *o*-alkyl phenols via displacement of aryl halides by alkoxides

X	R	Yield (%)
Bz	Bu ^t	63
CN	Bu ^t	90
Bu ^t	Bu ^t	<1
Bz	Me	76
CHO	Me	55
CN	Me	58
CHO	TBDMS	98
CN	TBDMS	96

Diaryl ethers can be obtained in good yields when phosphazene $\text{P}_4\text{-Bu}^t$ base and copper(I) bromide are used to catalyze the reaction between nonactivated aryl halides and phenols in refluxing dioxane or toluene <1998CC2091>. The authors are unable to assign a precise mechanistic role to the base, but point out that its presence in the reaction medium dramatically enhances the dissolution of the copper(I) salt, which is otherwise only sparingly soluble (Equation (48)).



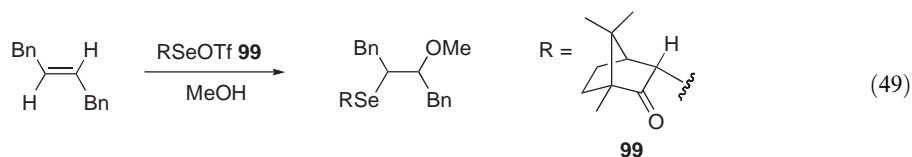
2.02.2.1.2 Specific methods

Certain ethers such as methyl and benzyl ethers possess selective lability, which in turn has enhanced their use as protecting groups, and as a result more preparative methods (discussed below) are available for the synthesis of these ethers compared to their more robust counterparts.

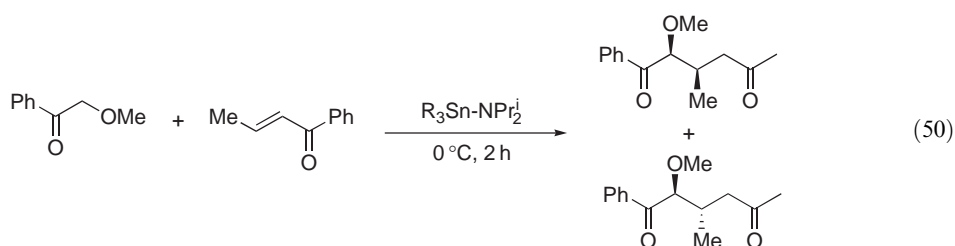
(i) Methyl ethers

Previous procedures to obtain methyl ethers involved the utilization of diazomethane or triethylsilyldiazomethane to etherify alcohols in the presence of Lewis acids such as boron trifluoride etherate. The reaction of difluorocarbene with alcohols to afford 1,1-difluoromethyl ethers was also discussed in COFGT (1995) <1995COFGT(2)37>, as was the preparation of trifluoromethyl ethers with desulfurative fluorination of xanthates.

More recently functionalized methyl ethers have been enantioselectively prepared by 1-methoxy-2-selenenylation of various alkenes upon reaction with chiral camphor-derived selenenyl triflates (Equation (49)) <1998JCS(P1)3123>. For instance, reagent **30** (available from camphor in two steps) reacts with a range of alkenes to give methoxy selenides in good yield but with moderate diastereocontrol (dr = $\leq 94:\geq 6$). It is noteworthy that when nonsymmetrical alkenes were employed as substrates Markovnikoff addition was observed. The authors confirmed the configuration of the product derived from reaction of reagent **99** with styrene as (*R*) by chemical correlation, but did not confirm the absolute stereochemistry of the other products.



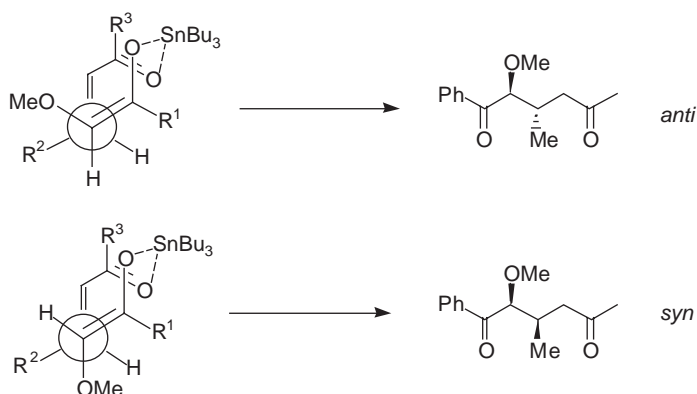
Stannyl enolates of 2-methoxy ketones react in a Michael addition fashion with a range of enones to give 2-methoxy-1,5-dicarbonyl products in reasonable yields with variable diastereoselectivity. Thus, 2,3-*anti*-products are exclusively obtained when tributylstannyl enolates are employed in the reaction, whereas 2,3-*syn*-products are preferred when butyl dichlorostannyl enolates are used (Equation (50) and Table 9) <1998JOC1334>.



Highest levels of *anti*-selectivity were observed when an excess of stannylamide was used. The authors proposed a closed transition state to rationalize the observed diastereoselectivity (Scheme 34).

Table 9 Diastereoselective preparation of 2-methoxy-1,5-dicarbonyl derivatives using stannyl enolates

<i>Tin amide</i>	<i>Yield (%)</i>	<i>syn:anti</i>
Bu ₃ SnNPr ₂ ⁱ	64	0:100
Me ₃ SnNPr ₂ ⁱ	61	9:91
Ph ₃ SnNPr ₂ ⁱ	59	9:91
ClBu ₂ SnNPr ₂ ⁱ	74	50:50
Cl ₂ BuSnNPr ₂ ⁱ	76	79:21
Cl ₂ BuSnNPr ₂ ⁱ (2 equiv.)	84	91:9

**Scheme 34**

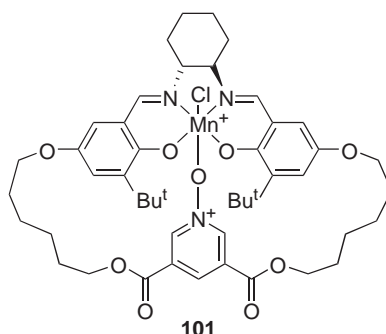
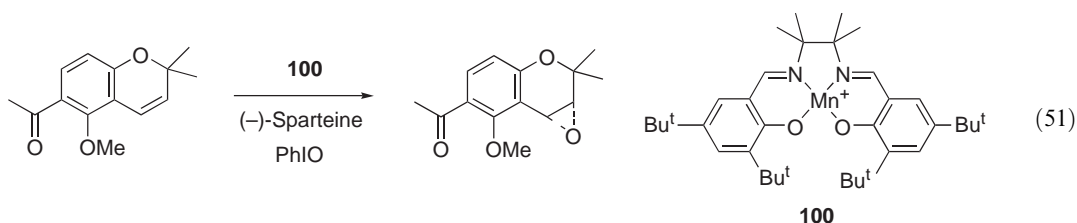
2.02.2.2 Cyclic Ethers

2.02.2.2.1 Oxiranes (epoxides)

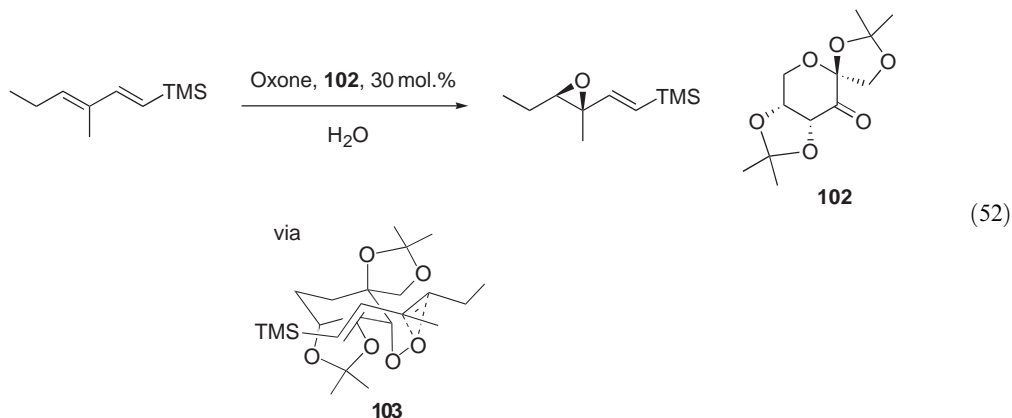
The preparation of this particular class of cyclic ether has received widespread attention as a result of their versatility as synthetic building blocks and several reviews exist detailing their syntheses <1997COS(4)238, 1998JCS(P1)4175, 2000JCS(P1)1291, 2001JCS(P1)2303, 2002JCS(P1)2301>. In general, as well as biocatalytic approaches <1997MI491, 1999MI199, 2001MI247, 2003MI59>, there are two chemical approaches to their preparation; direct and indirect.

(i) Direct synthesis

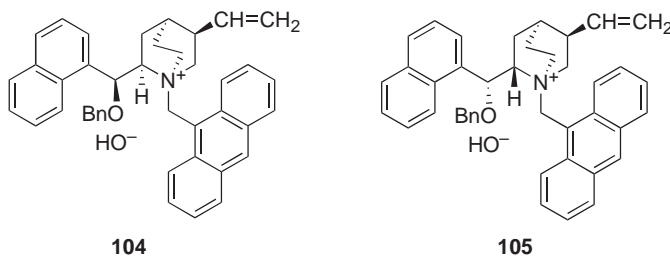
The reaction of alkenes with peracids is a highly attractive route for the preparation of these three-membered ring ethers <1995COFGT(2)37>. Of particular interest in the contemporary literature is the catalytic asymmetric epoxidation of alkenes, often involving Jacobsen–Katsuki-like procedures (Equation (51)). In these reactions, chiral tetradentate ligands are the asymmetric mediators and the high enantioselectivity observed arises from the chirality present on the backbone of the ligand, which in turn induces a chiral twist in (for instance) the manganese–salen complex **100** <1996TL2725>. For current developments in metallosalen-catalyzed asymmetric epoxidations the reader is directed to recent literature <2002MI8, 2001COC663>. The selectivity of this process is affected by other ligands: thus chiral spectator ligands are able to exert an enantioselective effect when the salen ligand itself is achiral. Although much debate has taken place concerning the niceties of the mechanism (and the role of the additive pyridine *N*-oxide) it is now generally accepted that the intermediacy of an oxomanganese–salen complex (typified by **101**) plays a crucial role <1996SL1079, 1997T9541>.



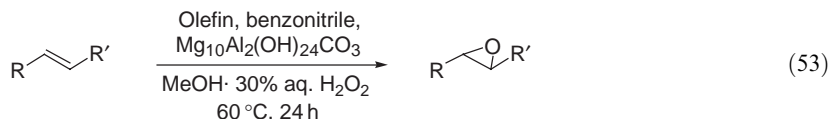
Another enantioselective method for alkene epoxidation, which has been widely-investigated recently, utilizes chiral dioxiranes, generally prepared *in situ* from chiral ketones [<2000S1979>](#). For example, the fructose-derived nonracemic ketone **102** [<1996JA9806>](#) effects enantioselective monoepoxidation of conjugated dienes in the presence of oxone (potassium peroxymonosulfate) [<1998JOC2948>](#). The intermediate chiral dioxirane reacts via transition state **103**, usually giving a monoepoxide (monoepoxide:diepoxide $\geq 12:1$). When unsymmetrical dienes are used, the least-hindered bond normally reacts, whilst with electron-deficient dienes the least electron-deficient position preferentially reacts ([Equation \(52\)](#)). The results of a study into some of the factors controlling the diastereoselectivity of epoxidation of cyclohexane derivatives by dimethyldioxirane have been published [<1996JOC1830>](#).



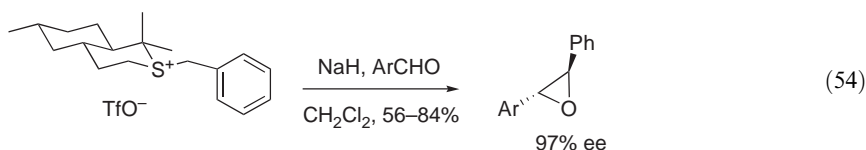
N-Anthracenylmethyl cinchona alkaloid derivatives **104** and **105** catalyze the enantioselective epoxidation of enones by sodium hypochlorite [<1998TL1599>](#). *Trans*- α,β -epoxy ketones are obtained in generally good yields with good diastereoselectivity and good enantiocontrol.



Peroxydicarboximide acid epoxidation of alkenes is promoted by layered hydrotalcite $\text{Mg}_{10}\text{Al}_2(\text{OH})_{24}\text{CO}_3$ <1998CC295>. A range of alkenes is epoxidized in good yield by this two-phase reaction (Equation (53)).



Menthol-derived oxathianes have been employed in an asymmetric synthesis of enantiomerically pure *trans*-diaryl epoxides <1996TA1783>. As judged by NMR, the reaction furnishes enantiomerically pure epoxides directly, as ((*R*),(*R*))-isomers (Equation (54)). If so desired, the precious chiral auxiliary can be recycled in greater than 78% yield.



Chiral difluoro and dihydroxylated pyrrolidines (106–109) catalyze asymmetric epoxidation of allylic alcohols; the enantiomeric purity of the product epoxyalcohols produced is moderate (Equation (55) and Table 10) <1998CC1223>.

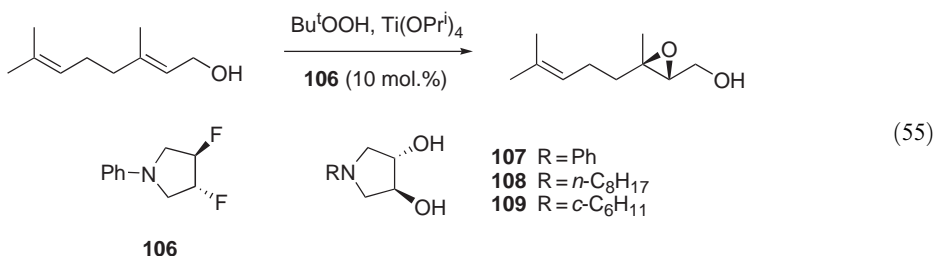
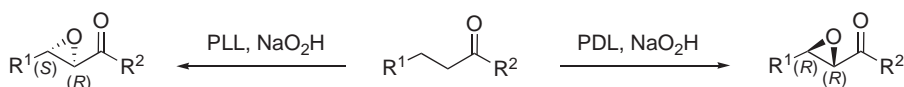


Table 10 Asymmetric epoxidation of allylic alcohols catalyzed by difluoro and dihydroxylated pyrrolidines

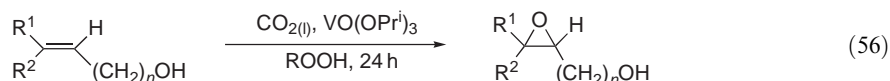
Additive	Temp (°C)	Time (h)	Yield (%)	ee (%)	Configuration
None	−20→20	12	81		Racemic
106	−20→10	0.67	97	25	((<i>S</i>),(<i>S</i>))
108	−20→20	1	68	50	((<i>R</i>),(<i>R</i>))
108	0	1	74	51	((<i>R</i>),(<i>R</i>))
108	−20→20	12	90	66	((<i>R</i>),(<i>R</i>))
108	−80	3	23	27	((<i>R</i>),(<i>R</i>))
109	−20→20	12	87	10	((<i>R</i>),(<i>R</i>))

The Juliá-Colonna epoxidation using polyleucines (L-configured [PLL] and D-configured [PDL]) as chiral mediator was believed to be an efficient asymmetric process only when chalcones were used as substrates. However, Roberts and co-workers <1996CC845> have shown that a much wider range of substrates undergoes epoxidation, some with excellent stereoselectivity (Scheme 35).

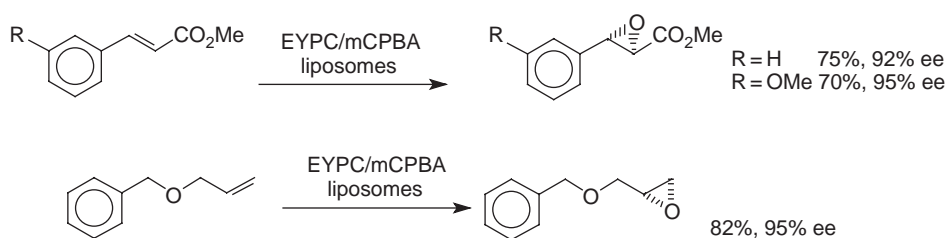


Scheme 35

Allylic and homoallylic alcohols are epoxidized in good yield upon reaction with Bu^tOOH in the presence of a variety of transition metal catalysts in liquid CO_2 <1998CC1015>. Sharpless epoxidation is feasible in this solvent, but the enantioselectivity of the asymmetric epoxidation is low (Equation (56)).

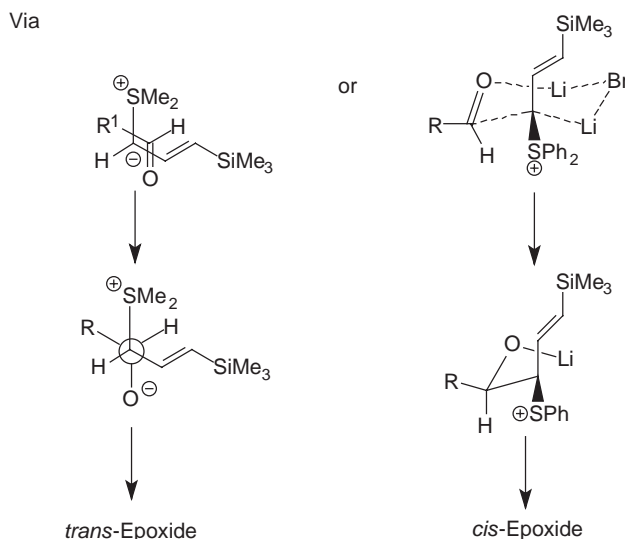
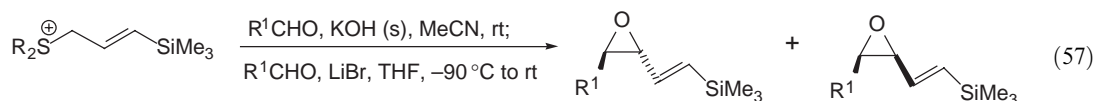


Epoxidation using “liposomized” mCPBA has been reported to be an effective synthetic process <1996TL4751>. A range of alkenes undergoes enantioselective epoxidation using mCPBA encapsulated in liposomes derived from egg phosphatidyl choline (EYPC), some with excellent enantioselectivity. The origins of the stereoselectivity observed lie, it is suggested, in the highly selective interactions between the alkenic substrate and the hydrophobic centers of the liposomes (Scheme 36).



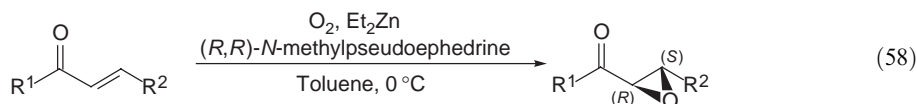
Scheme 36

The work examining the utility of sulfonium salts in epoxidation and aziridination has been extrapolated to allow for synthesis of both *trans*- and *cis*-(trimethylsilyl)vinyl epoxides from aldehydes <1996CC1353>. Thus, (3-trimethylsilyl)allyldimethylsulfonium salts undergo sequential reaction with solid KOH and an aldehyde to give predominantly *trans*-2-trimethylsilylvinyl epoxides, while the analogous diphenylsulfoniums react with KHMDS and aldehydes at low temperature furnishing mainly *cis*-vinyl epoxides (Equation (57)). The authors suggest that the dimethylsulfonium salt reacts via an open transition state to give the thermodynamically favored product, while the diphenylsulfonium salt reacts under aprotic conditions through the ubiquitous six-membered transition state to give the *cis*-configured product (Scheme 37).

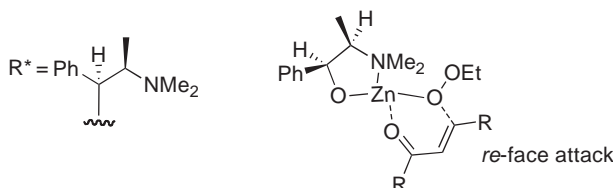


Scheme 37

α,β -Unsaturated ketones may be epoxidized enantioselectively by the combination of oxygen, diethylzinc, and ((*R,R*))-*N*-methyl pseudoephedrine <1996AG(E)1725>. The active species is proposed to be chiral peroxyzinc alkoxide and the overall process is, therefore, analogous to the traditional basic hydrogen peroxide protocol. In all cases, (2(*R*),3(*S*))-epoxyketones were obtained (Equation (58) and Scheme 38).



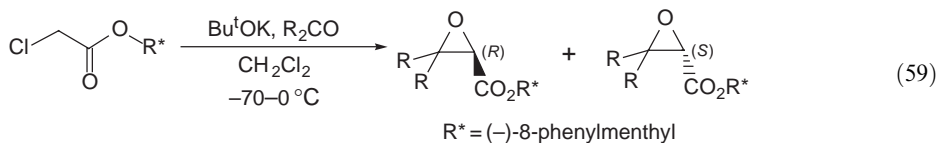
via



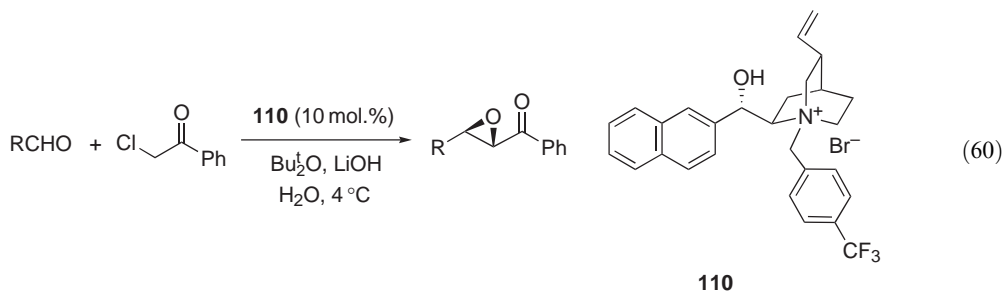
Scheme 38

(ii) Indirect syntheses

The addition of carbanions bearing two leaving groups to carbonyl compounds constitutes a useful preparative entry to epoxides. The best-known example of this type of reaction is the Darzens glycidic ester preparation with chloroacetic acid and ketones <1996CC2411>. In all of the reactions carried out (2(*R*))-configured glycidates predominated and highest enantiocontrol was observed using an (–)-8-phenylmenthyl ester. The authors rationalize the stereoselectivity witnessed as being due to a preference for *si*–*si* approach of the reactants (Equation (59)). When asymmetrically substituted ketones were used in the reactions, mixtures of *cis*- and *trans*-epoxides were obtained.



An asymmetric Darzens reaction between chloroketones and aldehydes yields 2,3-epoxyenones in moderate ee values (42–79%) and a range of yields (43–83%) <1998TL2145>. The reaction is mediated by *N*-(4-trifluoromethyl)benzylcinchonine **110** (Equation (60)).



The Darzens methodology can also be employed in the synthesis of dialkyl 1,2-epoxyalkylphosphonates via the reaction of dialkyl chloromethylphosphonates with carbonyl compounds <1999S207>.

Aggarwal and co-workers [<1998TL8517>](#) have described copper(I)-catalyzed epoxidation via reaction of 2-diazoacetamides in the presence of tetrahydrothiophene (THT). Thus, aryl and aliphatic aldehydes undergo reaction with *N,N*-diethyl-2-diazoacetamide in the presence of sub-stoichiometric amounts of THF and Cu(acac)₂ to give 2,3-epoxyamides in moderate-to-good yield and with good diastereoselectivity (dr *trans*:*cis* = >90:<10) ([Equations \(61\) and \(62\), Table 11](#)).

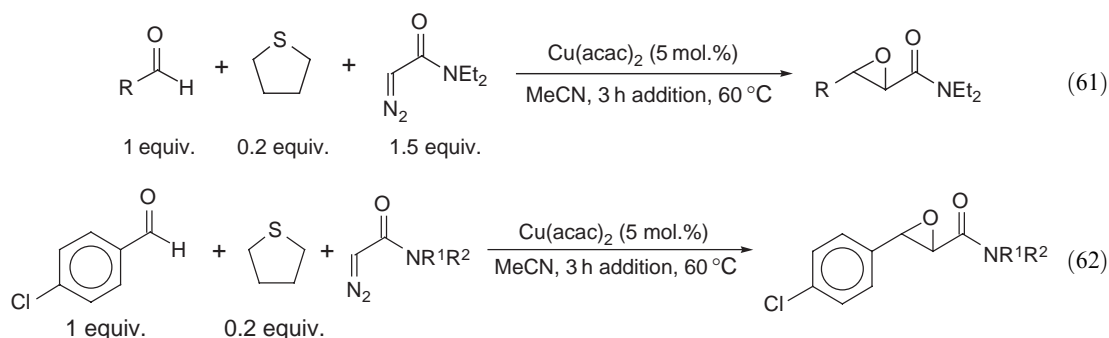
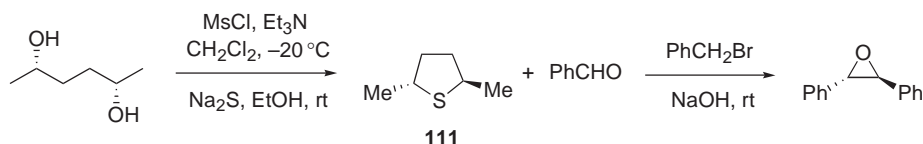


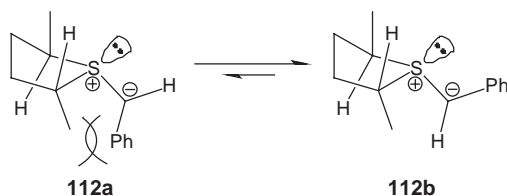
Table 11 Copper(I)-catalyzed epoxidation of 2-diazoacetamides using aliphatic aldehydes

<i>R</i> ¹	<i>R</i> ²	Yield (%)	<i>trans</i> : <i>cis</i>
Et	Et	79	>95:5
Me	Me	78	>95:5
–C ₄ H ₈ –		75	>95:5
Me	OMe	40	>95:5

C₂-Symmetric thiolane **111** mediates an asymmetric Darzens-like epoxidation of aryl aldehydes via a chiral sulfonium ylide **112a**. Predominantly *trans*-((*S*),(*S*))-epoxides are obtained from the process, but diastereo- and enantioselectivities are moderate-to-good. The authors rationalize the observations as proceeding via conformation **112b** of the intermediate chiral sulfonium ylide ([Schemes 39 and 40, Table 12](#)).



Scheme 39

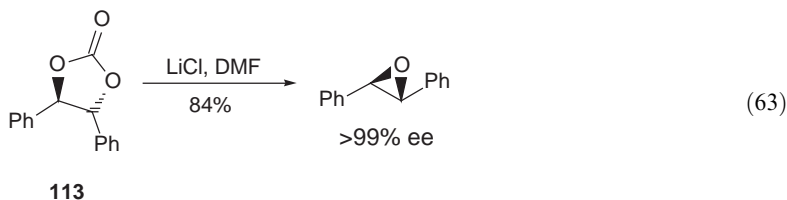


Scheme 40

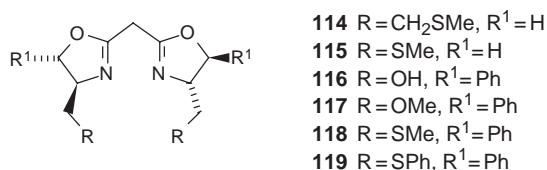
Chang and Sharpless have described a molar-scale preparation of enantiomerically pure stilbene oxide from the corresponding diol [<1996JOC6456>](#). The reaction involves ring-opening of C₂-symmetric cyclic carbonate **113** by chloride ion, followed by decarboxylative ring-closure ([Equation \(63\)](#)).

Table 12 Effect of solvent on asymmetric Darzens-like epoxidation of aryl aldehydes

Solvent	Time (d)	Yield (%)	de (<i>trans</i>) (%)	ee ((<i>S,S</i>)) (%)
9:1 CH ₃ CN:H ₂ O	1	92	88	84
9:1 Bu ^t OH:H ₂ O	2	92	86	88
9:1 Pr ⁱ OH:H ₂ O	8	59	86	90
9:1 EtOH:H ₂ O	3	15	84	94
H ₂ O	4	90	74	86



Chiral bisoxazoline-based catalysts have been reported to mediate asymmetric epoxidation via Tiffenau reaction of phenyl diazomethane with a range of aryl aldehydes in good yield and with high levels of diastereocontrol [<1998JCS\(P1\)2037>](#). Thus, bisoxazolines (**114–119**) were screened in the reaction, but uniformly low ee values were observed (ee = 0–24%). The product 1,2-diarylepoxydes were obtained primarily as *trans*-diastereoisomers (dr = 92–100:8–0 *trans:cis*).



2.02.2.2.2 Oxetanes

(i) Direct Synthesis

The Paternò-Büchi [2 + 2]-photocyclization [<1995COFGT\(2\)37, 1997LA1627, 1998S683, 2000SL1699>](#) of aldehydes and ketones with alkenes continues to be the major direct preparative route to oxetanes. Chiral silyl enol ethers [<1997JA2437>](#), chiral enamines [<1998T4507>](#), and chiral enamides [<1999TL9003>](#) have all been successfully used by Bach and Co-workers with aromatic aldehydes in the diastereoselective Paternò-Büchi for the synthesis of oxetanes.

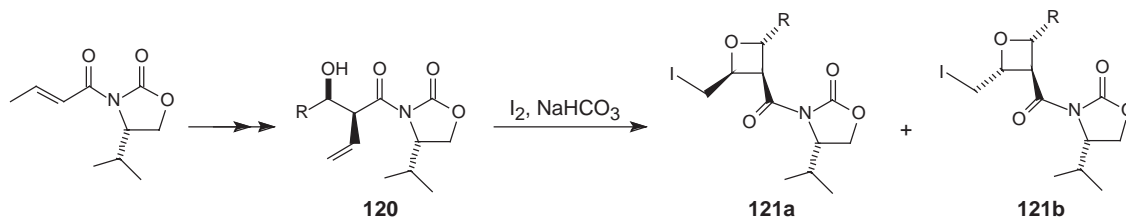
An alternative to directly obtaining oxetanes is cyclization of 1,3-alcohols by transforming one of the two hydroxy groups into a leaving group followed by treatment with a base [<1995S533>](#). However, in this approach the formation of four-membered rings is often hampered by thermodynamic and kinetic barriers. Another problem with this technique is stereoselectivity of the product, which can be overcome by double inversion of the orthoester precursor using acetyl bromide followed by DIBAL reduction [<1999TL8679, 2000JCS\(P1\)711>](#). More recently the stereoselective synthesis of oxetanes has been achieved via Mitsunobu-style procedure using Ziram[®] (zinc *N,N*-dimethyldithiocarbamate), triphenylphosphine, and DEAD [<1996TL3525, 2001JCS\(P1\)2983>](#).

Recently reviewed is the formation of four-membered cyclic ethers through 4-*endo* and 4-*exo* electrophilic cyclizations of unsaturated alcohols using halogens (chlorine, bromine, iodine), haloreagents (NBS, (biscollidineX[−])Y⁺), and seleno reagents [<2002EJOC3099>](#).

(ii) Indirect Synthesis

The synthesis of oxetanes by two-step reactions is usually considerably less straightforward than that of epoxides. This is due to the absence of kinetic acceleration of rate, which is present in epoxide formation. The rate of formation of oxetanes has been estimated to be one hundredth that of the corresponding oxirane reaction, even when the reaction is carried out at 80 °C [<1995COFGT\(2\)37>](#).

The balance between 4-*exo* and 5-*endo* iodoetherification of asymmetric 2-alkenyl-3-hydroxy acid derivatives is complex, being influenced by a variety of structural factors <1997JOC5048>. For example, alcohol **120** (derived from an Evans asymmetric aldol reaction) undergoes 4-*exo*-cyclization upon treatment with elemental iodine, yielding oxetane **121a** as the major product and **121b** as the minor product of iodoetherification (Scheme 41 and Table 13).

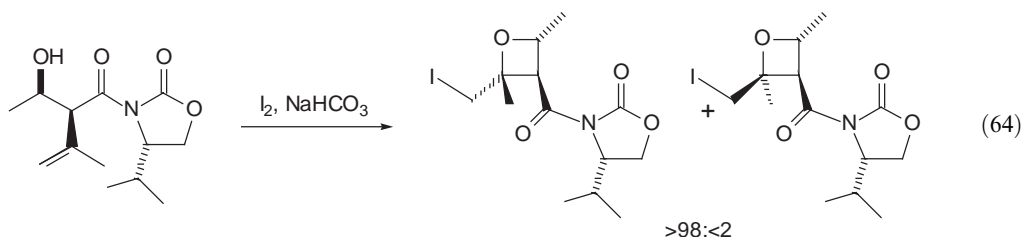


Scheme 41

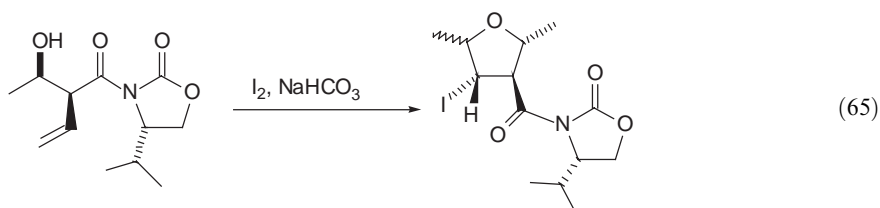
Table 13 Substituent effects on the 4-*exo* iodoetherification of 2-alkenyl-3-hydroxy acid derivatives in the synthesis of oxetanes

<i>R</i>	Yield (%)	121a:121b
Me	47	12:1
Et	48	19:1
Pr ⁱ	40	24:1
Ph	None	None

When the 2-alkenyl fragment bears a substituent, the iodoetherification reaction leads to either oxetane or tetrahydrofuran products, depending on the nature of the substitution. Thus, a methyl group on the “internal” carbon of the alkene leads to a preference for oxetane (Equation (64)).

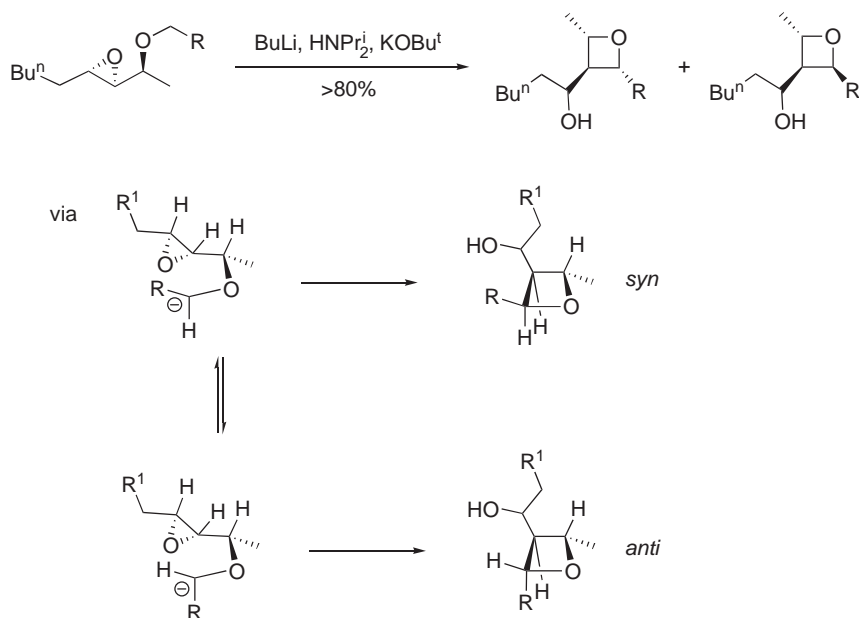


When the terminal carbon of the alkene bears a methyl group, only tetrahydrofurans are produced and with better diastereoselectivity (yield 63–81%) (Equation (65)).



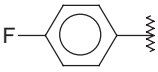

Hydroxyalkyl oxetanes can be prepared in good yield by cyclization of benzylic and allylic glycidols and 1-alkyl-2,3-epoxyalcohols (Scheme 42 and Table 14) <1996JOC4467>.

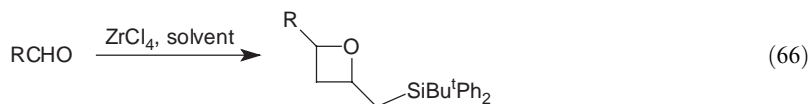
Zirconium(IV) chloride promotes the cycloaddition of allyl silanes to aldehydes, yielding oxetanes in variable yield, and with relatively poor stereoselectivity (Equation (66)) <1996SL1095>.



Scheme 42

Table 14 Preparation of substituted hydroxyalkyl oxetanes

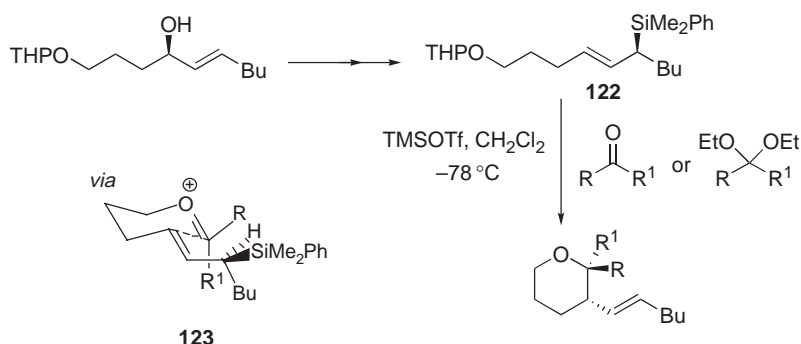
R ($R^1 = \text{Bu}$)	<i>syn:anti</i>
Ph	13:87
	12:88
	2:98
PhS	78:22



2.02.2.2.3 Other cyclic ethers

(i) Tetrahydropyrans

3-Alkenyl-substituted tetrahydropyrans of high enantiopurity can be prepared by the reaction of nonracemic chiral amino- and hydroxyallylsilanes **122** with carbonyl compounds (or their equivalents) <1998JOC6096>. Thus, alcohol **122** (prepared via an elegant, palladium(0)-catalyzed rearrangement of alkoxy- or aminodisilanes) reacts with aldehydes or acetals at low temperature in the presence of TMSOTf to give primarily *trans*-2-alkyl-3-vinyl tetrahydropyrans or piperidines in generally excellent yield and with good enantiocontrol. The authors propose an A-strain-controlled cyclic transition state **123** to rationalize the observed stereochemical preference of the reaction (Scheme 43).

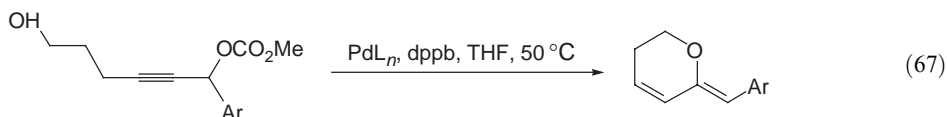


Scheme 43

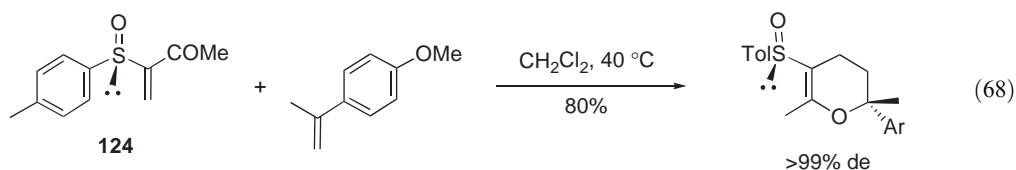
Cis- and *trans* functionalized tetrahydropyrans (and tetrahydrofurans) can also be obtained via an asymmetric Horner–Wadsworth–Emmons reaction with a dialdehyde followed by ring-closure [<2002JOC7226>](#). The strategy is made versatile through the use of different cyclization methods such as; intramolecular Pd(0)-catalyzed allylic substitution or a hetero-Michael addition, leading to different cyclized products.

(ii) Dihydropyrans

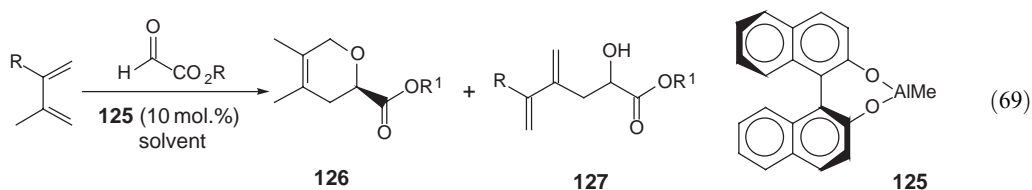
2-Methylene-dihydropyrans may be prepared in moderate yield by means of the reaction of 1-aryl-6-hydroxy-2-hexynyl carbonates with a palladium(0) catalyst ([Equation \(67\)](#)) [<1996SL553>](#).



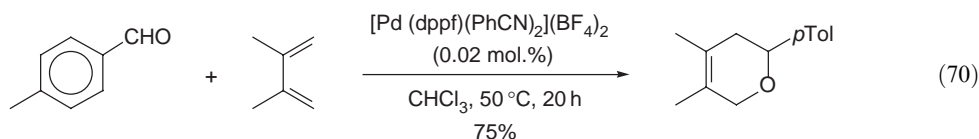
Tolylsulfinyl but-3-en-2-one **124** is an unusually reactive heterodiene, undergoing highly diastereo- and enantioselective cycloaddition reactions with styrenes [<1996TL3687>](#). Thus, electron-rich styrenes react with compound **124** in good yield and with >99% de to afford 3,4-dihydro-2*H*-pyrans ([Equation \(68\)](#)). The reaction of electron-rich alkenes with sulfoxide **124** proceeds with mediocre de. The main factor responsible for the observed stereocontrol (or lack of it) is the nature of the aromatic group.



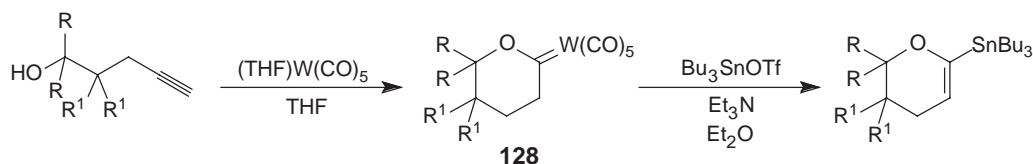
(*S*)-BINOL-derived Lewis acid **125** catalyzes asymmetric hetero-Diels–Alder reaction of glyoxalates and unactivated dienes [<1996CC2373>](#), usually with >90% ee; the cycloadducts **126** are always contaminated by the ene product **127**, leading to low yields ([Equation \(69\)](#)).



Palladium(II) salts mediate hetero-Diels–Alder cycloaddition reactions of aldehydes and unactivated dienes to give 5,6-dihydro-2*H* pyrans in generally good yields [<1996TL6351>](#). The experimental data suggest a stepwise ionic reaction as the operative mechanism ([Equation \(70\)](#)).



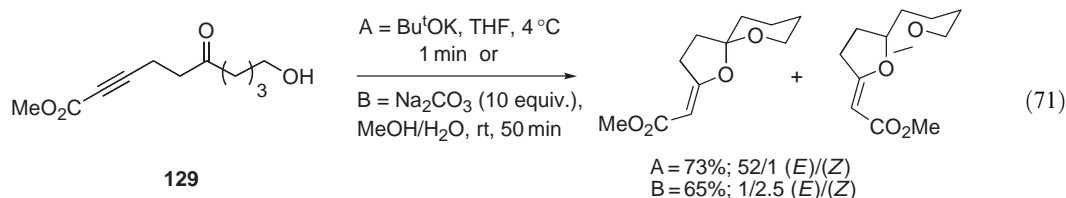
Tungsten dihydropyranylidene carbenes **128** react with tributylstannyl triflate to give 6-tributylstannyl-3,4-dihydro-2*H*-pyrans in excellent yield (Scheme 44) <1996TL4675>. These metal carbenes are conveniently prepared from 1-alkyn-5-ols and tungsten pentacarbonyl–THF complex.



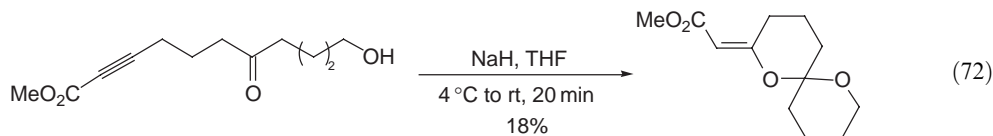
Scheme 44

(iii) Miscellaneous

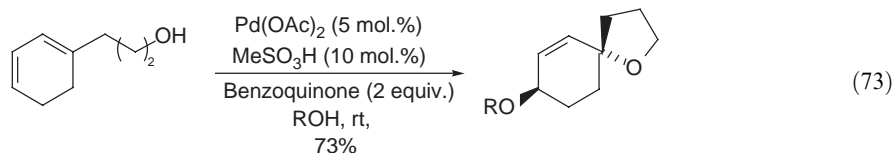
Spiroacetal enol ethers are obtained from the cyclization of 1-methoxycarbonyl-9-hydroxy-5-oxohept-1-yne **129** <1996TL5707>. The stereochemistry of the product of the reaction can be chosen by judicious choice of conditions (Equation (71)).



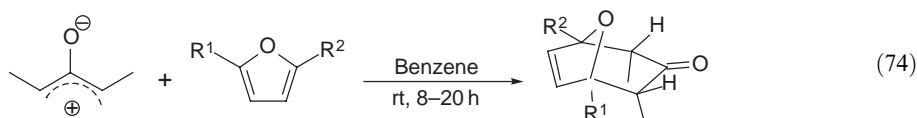
The homologous compounds do not react as efficiently (Equation (72)).



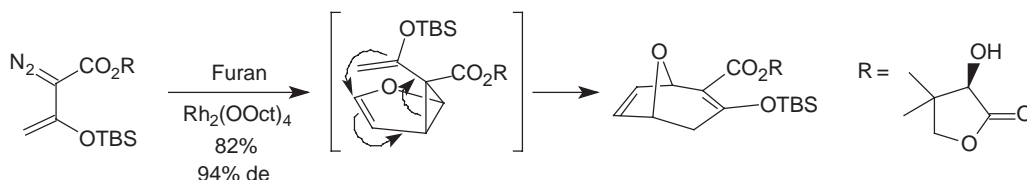
Bicyclic hydropyrans and spiroethers are obtained from palladium-catalyzed intramolecular, 1,4-dialkoxylation of 1- ω -alkoxycyclohexa-1,3-dienes <1998TL1223> (Equation (73)).



The cycloaddition of oxoallyl carbocations (generated from dibromo 2-pentanone with diethylzinc) and furans allows the preparation of bicyclic ketoethers, in moderate yield (Equation (74)) <1996S31>.

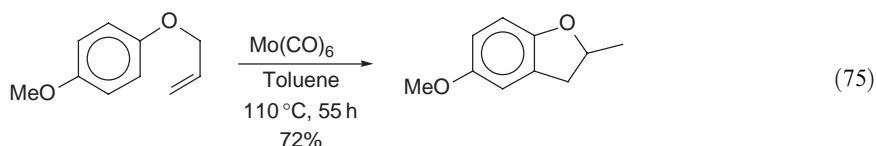


Chiral esters of 2-(1-silyloxyvinyl) diazoacetates react with furans in the presence of rhodium(II) carboxylates to give oxabicyclo[3.2.1]octa-2,6-diene ethers [<1996JA10775>](#). Rather than a [3+4]-cycloaddition, the process is actually a cyclopropanation-Cope rearrangement process ([Scheme 45](#)).

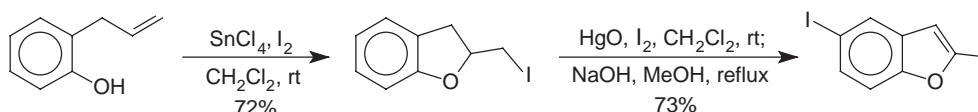


Scheme 45

Allyl aryl ethers undergo a sequential Claisen rearrangement–cyclization reaction when heated with molybdenum hexacarbonyl in toluene to give 2-substituted dihydrobenzofurans [<1997S41>](#) ([Equation \(75\)](#)).

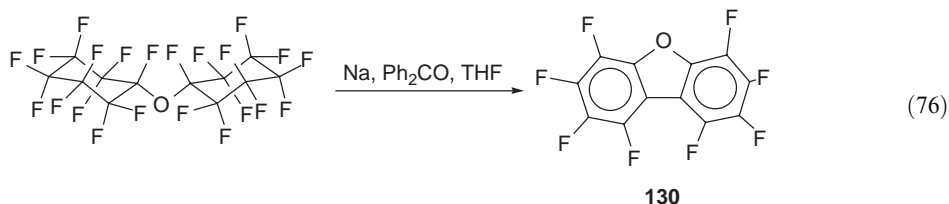


In a similar process, 2-iodomethyldihydrobenzofurans are prepared by the reaction of 2-allyl phenols with tin(IV) chloride and elemental iodine [<1997S23>](#) ([Scheme 46](#)). Dehydroiodination of the reaction products gives benzofurans in good yield. If 1,2-disubstituted alkenes are used in the reaction, the regioselectivity of the etherification is altered and benzopyrans are obtained after dehydroiodination.

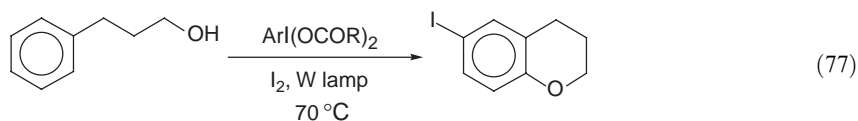


Scheme 46

Octafluorodibenzofuran **130** is prepared by the reaction of perfluorinated dicyclohexyl ethers with benzophenone radical anion [<1998JCS\(P1\)637>](#) ([Equation \(76\)](#)).



(Diacetoxy)iodobenzene reacts with 3-phenyl-propan-1-ol under photolysis, to give dihydrobenzopyrans in acceptable yield, via alkoxy radicals [<1996TL2441>](#). The reaction can be used to prepare flavonoid and vitamin E analogs ([Equation \(77\)](#)).



2.02.3 ALKYL HYPOHALITES

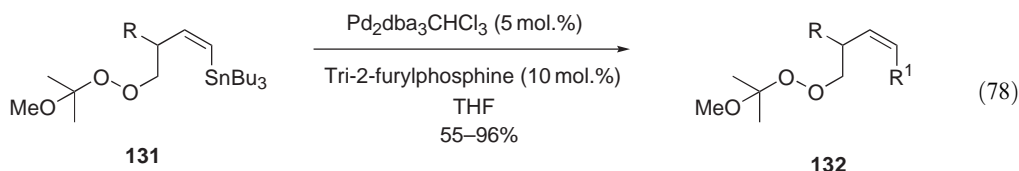
Little has appeared concerning the preparation of this class of chalcogen derivative and the reader is directed to COFGT (1995) <1995COFGT(2)37> for a coverage of the methods available for these compounds.

2.02.4 PEROXIDIC FUNCTIONS

2.02.4.1 Alkyl Hydroperoxides

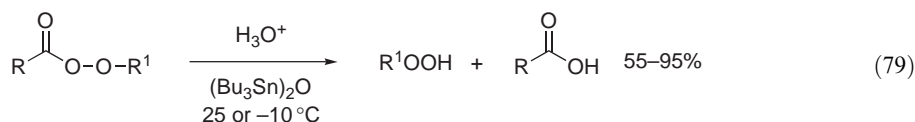
2.02.4.1.1 From equivalents of hydrogen peroxide

Traditional methods for the synthesis of alkyl hydroperoxides rely upon the use of (often concentrated) hydrogen peroxide, leading to potentially hazardous processes. Dussault and co-workers <1998JA7133> have introduced 2-alkoxyprop-2-yl hydroperoxides as stable, masked H_2O_2 -equivalents, thereby simplifying the preparation of alkyl hydroperoxides. The process is exemplified by the reaction shown in (Equation (78)): thus, (Z)-3-stannyl-2-alkenyl hydroperoxides **131** undergo Stille reactions in good yield, to give 2-peroxyacetals **132**, which can be unmasked to give the parent hydroperoxides upon treatment with acetic acid.



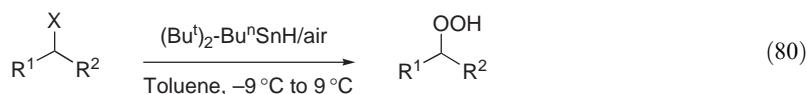
2.02.4.1.2 From peroxy esters

Primary hydroperoxides may be efficiently prepared by the reaction of peroxyesters in the presence of bis(tributyltin)oxide (Equation (79)) <2001SL623>. The reaction is of some utility because primary hydroperoxides are often unstable and few are commercially available. The conditions reported are mild and, in theory, allow for the preparation of a range of primary hydroperoxides: the starting materials for the process are easily prepared by alkylation of the corresponding peroxy acids with alkyl halides <2000JCS(P1)2575>.



2.02.4.1.3 From alkyl halides and oxygen

Nakamura <1995SL525> have reported a reductive oxygenation protocol from the preparation of simple and functionalized alkyl hydroperoxides (Equation (80)). Thus, alkyl bromides or iodides react with oxygen when air is bubbled through a vessel containing the halide and $(\text{Bu}^t)_2\text{Bu}^n\text{SnH}$. The process relies upon sonication, requiring a focused 20 kHz/200 W source rather than the more frequently employed cleaning bath. The reactions proceed cleanly and with good regioselectivity, that is, radical rearrangements are not observed (in contrast to alkane autoxidation, for instance).



2.02.4.2 Dialkyl Peroxides

2.02.4.2.1 From alkyl hydroperoxides

Methods relying upon the reaction of nucleophilic peroxides with electrophiles have continued to dominate the literature concerning the synthesis of dialkyl peroxides. Thus, for instance, water-soluble peroxides have been prepared by the reaction of potassium *t*-butyl peroxide with ω -(trimethylammonium) alkyl halides [<1995JOC5341>](#). The same group have also prepared hydrophilic dialkyl peroxides containing PEG-moieties, by a similar methodology [<1998MI911>](#). These hydrophilic peroxides exhibit antibacterial activity, against both Gram-positive and -negative strains. Other dialkyl peroxides exhibiting antibacterial activity (in this case, against *Trichomonas vaginalis*) were prepared in an analogous manner [<2001MI837>](#).

The synthesis of mixed dialkyl peroxides by the reaction of metal peroxides with halides, under phase-transfer catalysis, is a method of considerable synthetic utility <1991MI137>. A detailed analysis of the kinetics of the process has revealed a pseudo-first-order profile <1996MI11>.

2.02.4.2.2 From 1-peroxy carbenium ions

1-Peroxyethers (monoperoxyacetals) **133** undergo reaction with a range of allyl silanes and stannanes in the presence of Lewis acids, to afford homoallyl peroxides **134** and **135** in good yields (Equation (81) and Table 15) [<2000JOC8407>](#). The process, which proceeds via the apposite 1-peroxy carbenium ion, may be adapted to allow for the preparation of hydroperoxides such as **136**.

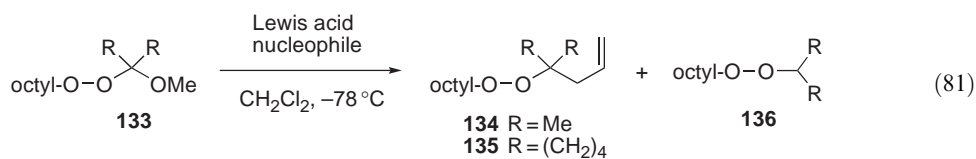
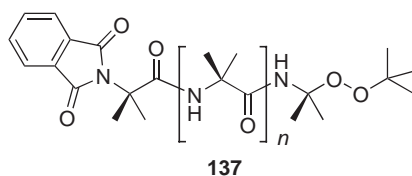


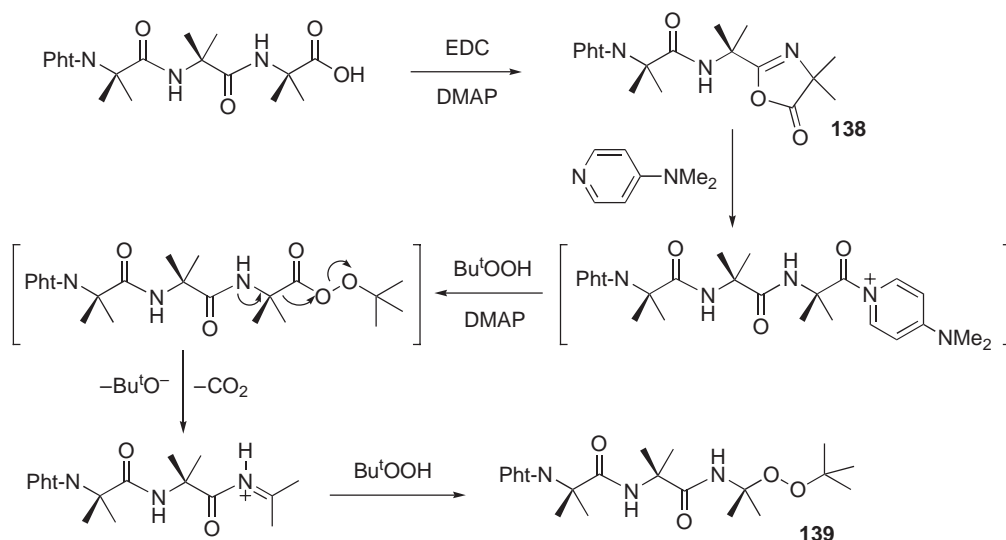
Table 15 Synthesis of homoallyl peroxides from 1-peroxyethers and allyl silane in the presence of Lewis acids

<i>R</i>	<i>Lewis acid</i>	<i>Nucleophile</i>	<i>Product</i>	<i>Yield (%)</i>
Me	TiCl ₄	AllylSiMe ₃	134	86
Me	TiCl ₄	AllylSiBu ₃	134	82
Me	SnCl ₄	AllylSiMe ₃	134	50
Me	Et ₂ AlCl	AllylSiMe ₃	134	10
Me	BF ₃ ·OEt ₃	AllylSiMe ₃	136	60
Me	BCl ₃	AllylSiMe ₃	134	45
-(CH ₂) ₄ -	TiCl ₄	AllylSiMe ₃	135	85
-(CH ₂) ₄ -	TiCl ₄	AllylSiBu ₃	135	80
-(CH ₂) ₄ -	SnCl ₄	AllylSiMe ₃	135	80

2.02.4.2.3 From oxazol-5(4H)-inones

Peptide dialkyl peroxides **137** have been prepared in a serendipitous manner by the reaction of activated peptides with hydroperoxides, in the presence of DMAP and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) ([Scheme 47](#) [<2002HCA3099>](#)).





Scheme 47

Thus, the intermediate oxazol-5(4*H*)-inones **138** reacted with DMAP–Bu^tO₂H to give dialkyl peroxide **139**, rather than the acyl peroxides which were the expected products of the reaction.

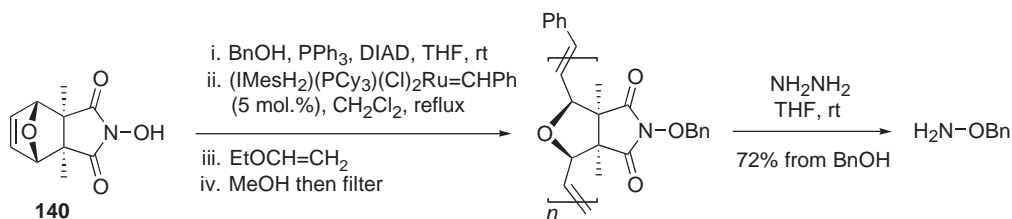
2.02.5 FUNCTIONS BASED ON ROS, ROSe, AND ROTe UNITS

Little has appeared concerning the preparation of this class of chalcogen derivative and the reader is directed to COFGT (1995) <1995COFGT(2)37> for a coverage of the methods available for these compounds.

2.02.6 FUNCTIONS BASED ON THE RON UNIT

2.02.6.1 *O*-Alkylhydroxylamines, RONH₂

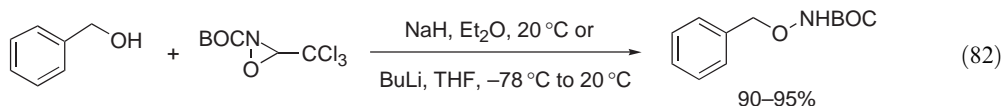
The “capture-release” purification strategy has been modified to good effect in the development of a new method of preparation of a range of *O*-alkylhydroxylamines <2002OL1007>. Thus, in the “capture-ROMP-release” method of Harned and Hanson, sequential Mitsunobu and ROMP reaction of tricyclic, furan-derived succinimide **140** <1971BCSJ1084> generates a polymer which is precipitated from solution with methanol, thereby allowing the removal of the reaction byproducts by filtration (Scheme 48). The resulting resin is treated with anhydrous hydrazine in THF at room temperature to give a range of *O*-alkylhydroxylamines in good yield and with moderate-to-excellent purity.



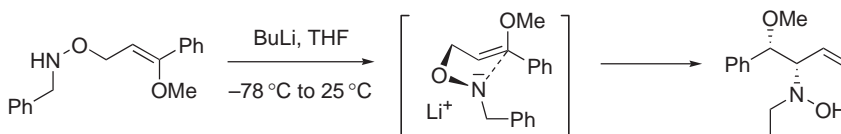
Scheme 48

Oxaziridines have recently been shown to function as useful electrophilic aminators of alcohols, giving *O*-alkylhydroxylamines in good yields. The reaction depends critically upon the nature of the oxaziridine, with electron-neutral oxaziridines (such as 3,3'-di-Bu^t-oxaziridine) requiring

additives (such as DMPU and 18-crown-6) to give these hydroxylamines in good yields <1999JOC6528>. Where electron-deficient oxaziridines are employed (as in the reactions of *N*-BOC-3-trichloromethyloxaziridine), simpler processes are effective, again giving good yields of *o*-alkylhydroxylamines (Equation (82)) <1998TL8845, 2000CC975>.



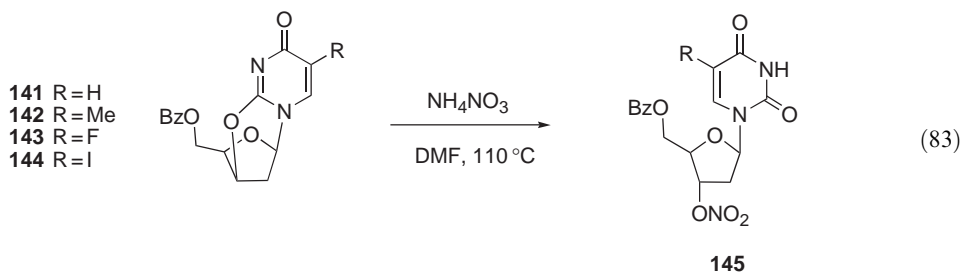
N-Benzyl-*O*-allylic hydroxylamines undergo highly distereoselective intramolecular [2,3]-rearrangement to afford *N*-benzyl-*N*-hydroxyallylamines (Scheme 49) <1999CC2079>.



Scheme 49

2.02.6.2 Nitrate Esters, RONO₂

Nitrooxy pyrimidines **145** have been prepared by nucleophilic ring-opening of the apposite anhydrouridines **141–144**, in poor-to-moderate yields (Equation (83)) <2003JMC995>.

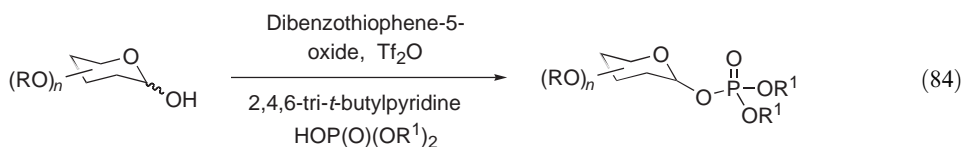


2.02.7 FUNCTIONS BASED ON THE ROP UNIT

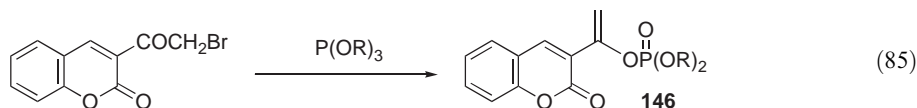
2.02.7.1 Alkyl Phosphates, (RO)_nP(OH)_{3-n}(O)

2.02.7.1.1 Trialkyl phosphates

Trialkyl phosphates derived from carbohydrates have received particular attention (due to their utility as glycosyl donors) since the publication of COFGT (1995) <1995COFGT(2)37>. Thus, monosaccharides react with a suitable phosphate donor (either electrophilic <1981CJC2086, 1982CL1281, 1992MI169> or nucleophilic <1990CJC1063, 1991CJC1462, 1991LA121, 1991TL6175, 1995JOC14, 1998MI471, 1999OL211>) to give the corresponding phosphate. In a recent variation on this theme, Garcia and Yin demonstrated that carbohydrate hemiacetals undergo dehydrative coupling upon reaction with dialkyl phosphates in the presence of a suitable dehydration agent, shown in (Equation (84)) <2000OL2135>. Enantiomerically enriched (ee ≤ 76%) chiral phosphates may be obtained by dynamic kinetic resolution in the reaction of racemic phosphorochloridites with alcohols <2003CC1704>.



The reaction of 3-(2'-bromoacetyl)coumarin with trialkyl phosphites gives vinylphosphate **146** by a Perkow reaction <1998T14407> (Equation (85)). This is in contrast to the reactions of other 2-haloketones, which usually give mixtures of products arising from both Arbusov (giving phosphonates) and Perkow reaction <1961CRV607>.



2.02.8 RO METALLOID FUNCTIONS WITHOUT FURTHER ATOMS ATTACHED TO THE METALLOID

2.02.8.1 Silicon Derivatives, ROSi

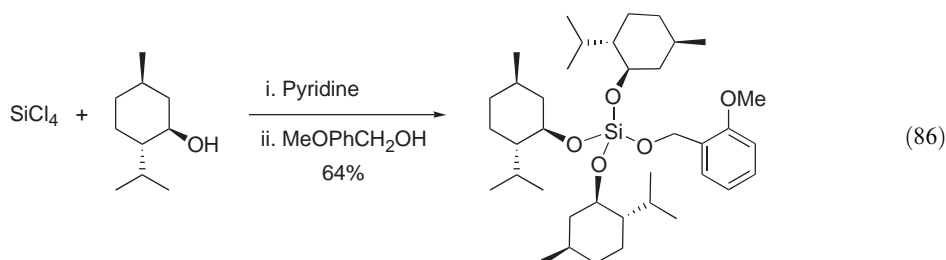
2.02.8.1.1 Trialkoxysilanes, (RO)₃SiH

Trialkoxysilanes derived from primary alcohols may be prepared by the reaction of alcohols with metallic silicon <1994MI15>. Thus, a range of aliphatic alcohols (ethanol, 1-propanol, and 1-butanol) react in the presence of copper(I) chloride at high temperature (240 °C).

2.02.8.1.2 Tetraalkoxysilanes (alkyl silicates), (RO)₄Si

In a reaction which has some similarity to that in Section 2.02.8.1.1, dimethyl and diethyl carbonates react with silica gel in the presence of a KOH catalyst to give tetraalkoxysilanes directly <1993MI442>.

Only the second examples of tetraalkoxysilanes derived from chiral alcohols have been reported <1997JOC4457>. Thus, following on from earlier reports of the reaction of simple tetraalkoxysilanes with carbohydrates <1965LA228>, Clausen and Bols have prepared a range of symmetrical and unsymmetrical tetraalkoxysilanes from the corresponding alcohols and SiCl₄ (Equation (86)).



2.02.9 METAL DERIVATIVES

Little has appeared concerning the preparation of this class of metal derivative and the reader is directed to COFGT (1995) <1995COFGT(2)37> for a coverage of the methods available for these compounds.

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Biographical sketch



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2.03

Alkyl Chalcogenides: Sulfur-based Functional Groups

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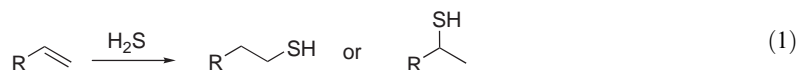
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2.03.1 ALKANETHIOLS

Preparations of alkanethiols have been comprehensively covered in COFGT (1995) <1995COFGT(2)113>. The most extensively developed routes to alkanethiols included the use of alkenes, alcohols, and alkyl halides. Since the publication of COFGT (1995) <1995COFGT(2)113>, a number of new procedures have been reported although alcohols, and to some extent alkyl halides and alkenes, remain the most frequently used precursors. Newly developed approaches to complex and/or natural targets include synthesis 1 β -carbapenem antibiotics, thiosugars, nucleosides, thio-derivatives of amino acids, chelating agents, and chemosensors. An important trend in alkanethiol synthesis is the application of heterocyclic derivatives as substrates or as a masking moiety. At the same time, a number of previously applied synthetic methods have lost their significance, including, for example, synthesis of alkanethiols from phosphorothiolate ions, Bunte salts, xanthates, thiocyanates, or organometallics.

2.03.1.1 Formation from Alkenes

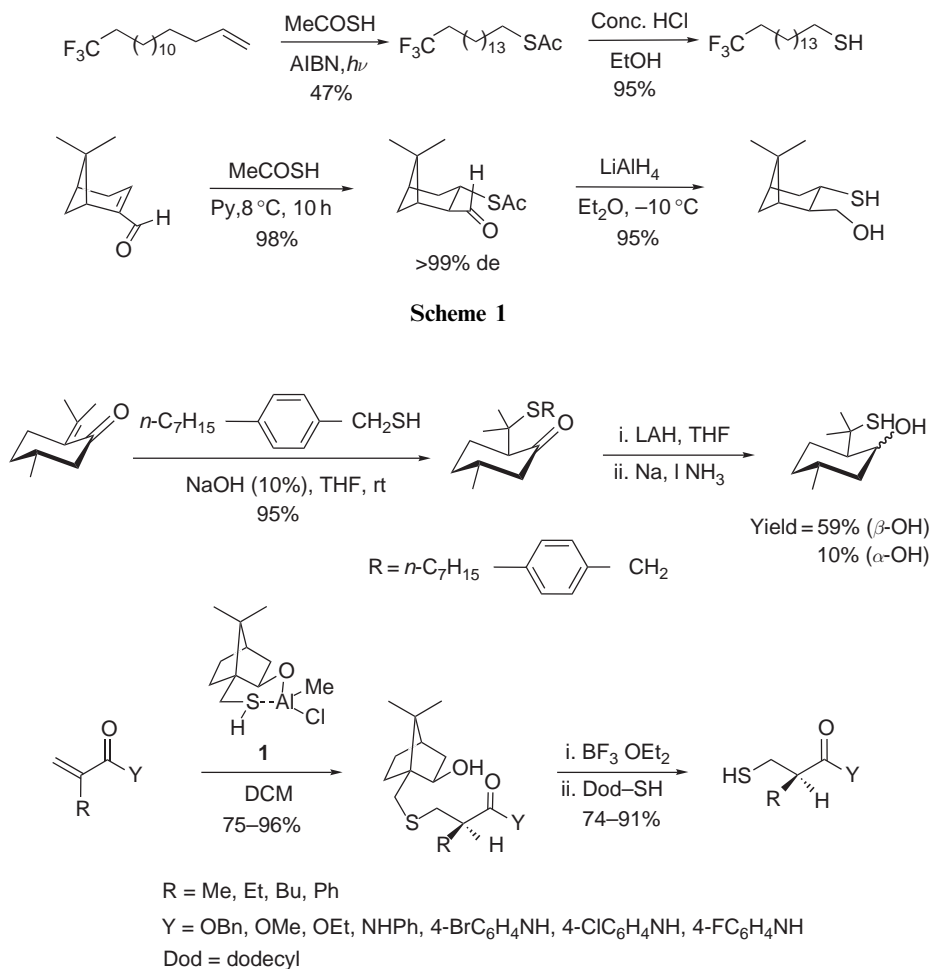
A standard method of thiol preparation from alkenes involves treatment with hydrogen sulfide. By changing the reaction conditions, in particular temperature and catalyst, either of the possible regioisomers can be obtained (Equation (1)).



Indirect methods for conversion of alkenes to thiols are now more attractive. Thus, addition of thioacetic acid across terminal C—C double bond in the presence of AIBN under oxygen-free conditions affords thiol esters, which are typically further converted into thiols under hydrolytic or reductive conditions (Scheme 1) <1999JFC107>. Reaction of thioacetic acid with α,β -unsaturated carbonylic compounds, such as acrylic acids <1997RCB755, 1997RCB1181, 1998JCS(P1)853, 2002BMCL2001> or (–)-myrtenal <2001TA3095> (Scheme 1), easily proceeds without a radical initiator and gives anti-Markovnikov addition products in good yield and high stereoselectivity.

In rare cases when the thioacetate method is unsuccessful, alkanethiols can be prepared by addition of α,β -unsaturated compounds to benzyl mercaptans, such as phenylmethanethiol <2001TA3095>, *p*-methoxyphenylmethanethiol <2002BMC457>, or odourless *p*-heptylphenylmethanethiol. Thus, Michael addition of the latter to α,β -unsaturated ketones under basic conditions and subsequent cleavage of the benzylic C—S bond with sodium metal in liquid

ammonia gives 1,3-mercapto alcohols in good yield (Scheme 2) <2001TL9207>. A similar addition to α -substituted α,β -unsaturated esters and amides using the aluminum complex **1**, containing a chiral odourless thiol, proceeds diastereoselectively. These Michael adducts are converted into β -mercaptoesters and amides via Wagner–Meerwein rearrangement using boron trifluoride etherate and thiol exchange with odorless 1-dodecanethiol (Scheme 2) <2001OL3121>. This method has been used for highly enantioselective synthesis of 1,3-mercaptoalcohols from α,β -unsaturated ketones <2000TL3437>.

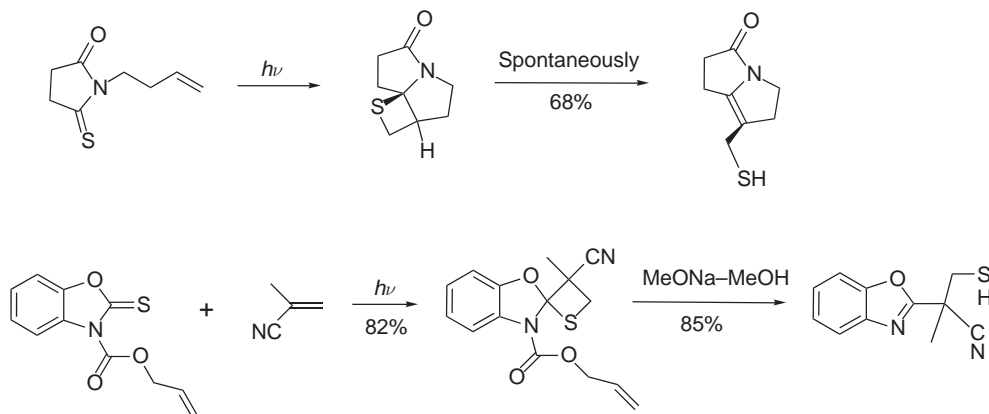


Scheme 2

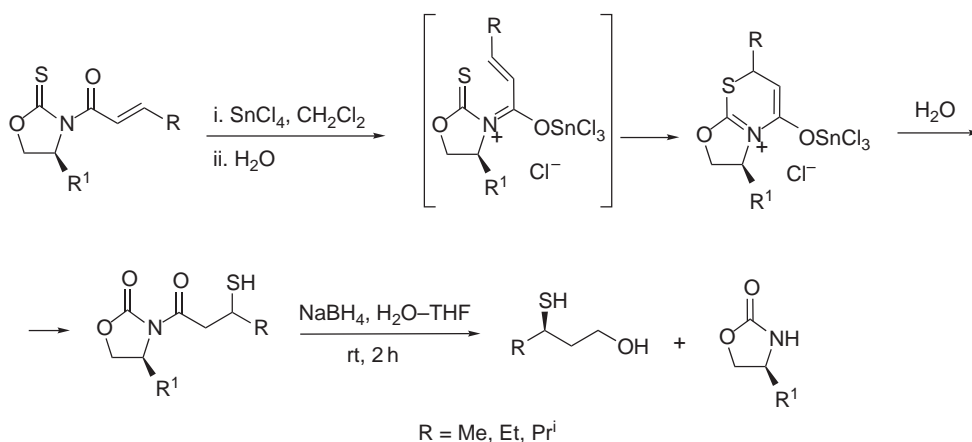
Many thioamides undergo Paterno–Buchi-like [2 + 2]-photocycloaddition with alkenes to give aminothietanes. The latter spontaneously, or on treatment with base, undergo ring opening to afford thiols. Both inter- and intramolecular versions of this reaction are known and used for the preparation of specifically substituted alkanethiols <1995JCS(P1)373, 1997HCA388, 1997JCS(P1)885, 1999CC2371, 1999JCS(P1)1151, 2002H(56)69>. In Scheme 3 this is exemplified by synthesis of 7-mercaptomethyl-1,2,5,6-tetrahydropyrrolizin-3-one <2001OL1781> and 2-(benzoxazolyl-2)-2-cyanopropanethiol <1996JCS(P1)921, 2002HCA2383>. Overall yields vary from moderate to good and cycloaddition is regiospecific.

Another strategy employing heterocyclic thiones and alkenes is electrocyclic intramolecular rearrangement of *N*-enoyl oxazolidine-2-thiones (Scheme 4) <2001JA5602>. Typically 0.01–0.05 M solutions of a chiral oxazolidine-2-thione in CH_2Cl_2 reacts smoothly with SnCl_4 (1–1.5 equiv.) at $-78\text{ } ^\circ\text{C}$ in a few hours to afford the corresponding adduct. Detachment of the chiral auxiliary occurs on treatment with sodium borohydride $\text{THF}-\text{H}_2\text{O}$ to give β -mercapto alcohols in high yield. The process proceeds with high diastereoselectivity and under certain

conditions can also be employed for the preparation of β -mercapto carboxylic acid derivatives. Regeneration of oxazolidine-2-thiones from recovered oxazolidinones can be achieved by treatment with Lawesson's reagent.

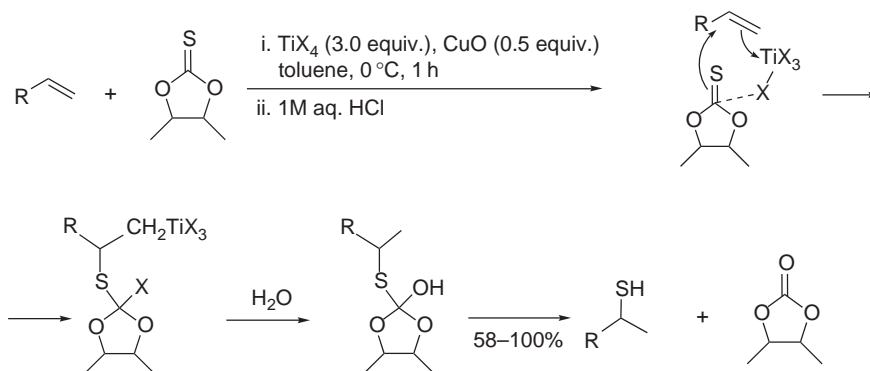


Scheme 3



Scheme 4

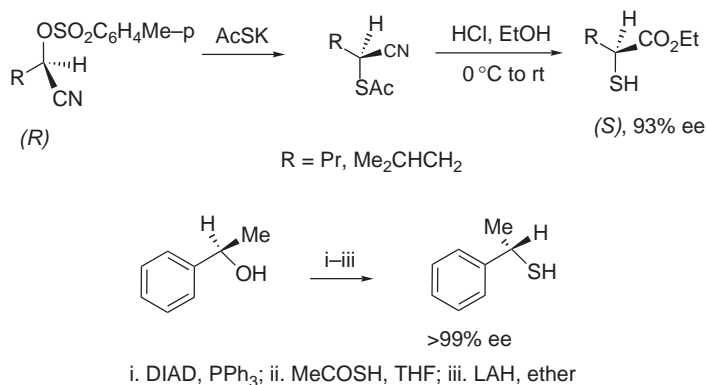
Recently, a convenient method for the direct preparation of secondary and tertiary thiols from the corresponding alkenes was established by using a thiocarbonate, titanium(IV) chloride or fluoride and copper(II) oxide [<2001CL638>](#). Various thiols have been obtained regioselectively (Markovnikov addition) in good-to-excellent yields ([Scheme 5](#)).



Scheme 5

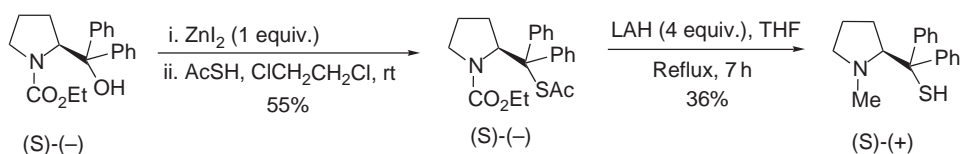
2.03.1.2 Formation from Alcohols

The most reliable and widely used method for alkanethiol preparation is conversion of activated alcohols into thiol esters by reaction with thioacetic (or thiobenzoic) acid or its potassium salt. Subsequent removal of the acyl group under basic, acidic, or reductive conditions gives the thiol in high yield [<1995COFGT\(2\)113>](#). Activation of the hydroxyl group is usually achieved by conversion to the mesylate, *p*-toluenesulfonate or triflate. Mitsunobu reaction using a mixture of DEAD or DIAD and Ph_3P is also productive for this purpose and [Table 1](#) contains details. Importantly, substitution practically always occurs with inversion of configuration. Conversion of tosyl-activated cyanohydrins to 2-mercaptocarboxylates [<1999TA1777>](#) or (*R*)-1-phenylethanol into (*S*)-1-phenylethanethiol provides typical examples ([Scheme 6](#)) [<2001CEJ423>](#).



Scheme 6

There are many variations of the thiolester method. For example, because of the failure to introduce a suitable leaving group into $\text{S}_{\text{N}}1$ active alcohols, a procedure has been developed [<1986TL15>](#) in which such alcohols are converted into corresponding thiol esters by treatment with zinc iodide and thiol acid ([Scheme 7](#)) [<1999TA1551>](#).



Scheme 7

An intramolecular version of the thiolester method is also known. Thiolactone **2**, derived from *N*-protected *trans*-4-hydroxy-L-proline, was effectively converted by reaction with various nucleophiles into 4-mercaptopyrrolidine derivatives ([Scheme 8](#)) [<1995H\(41\)147>](#) (see also [<1996BMCL2575, 1996TL2919, 1998JOC7421, 2001JOC8070>](#)).

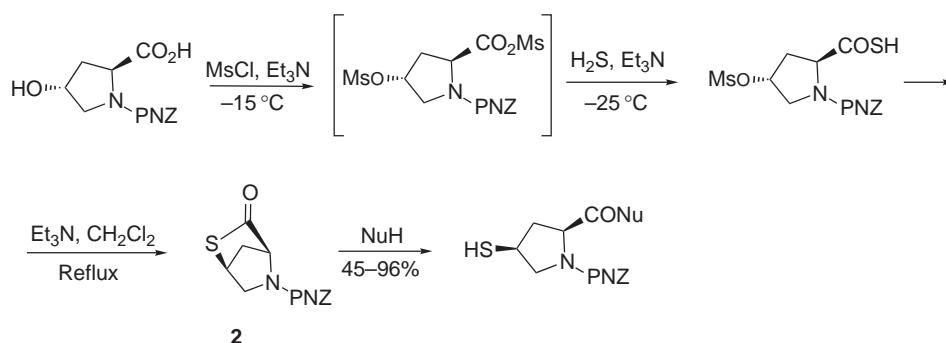
An interesting rearrangement took place when enantiopure β -amino alcohols were subjected to successive mesylation and treatment with 10% aqueous potassium thioacetate ([Scheme 9](#)) [<2001SL1155>](#). It is assumed that such reactivity is caused by intramolecular formation of an intermediate aziridinium salt, which is attacked by thioacetate anion at the more reactive benzylic carbon. The process proceeds with high stereoselectivity and β -aminothiols obtained in this way show excellent activity as chiral catalysts. Application of a similar approach to *trans*-2-(*N,N*-dialkylamino)cycloalkanols leads to *trans*-2-(*N,N*-dialkylamino)cycloalkanethiols [<1998RCB1755>](#).

There is some specificity in the preparation of sugar sulfanyl derivatives that is caused by the proximity of different hydroxyl groups. Thus, in the case of nucleosides their anhydro derivatives can be prepared and effectively used as starting material in reactions with sulfur nucleophiles [<2001IJC\(B\)382, 2002IJC\(B\)379>](#). In such transformations an advantage is gained from the ability of heterocyclic residues, e.g., a uracil moiety ([Scheme 10](#)) [<1997CCC1114>](#), to serve

Table 1 Thiolester synthesis of alkanethiols from alcohols

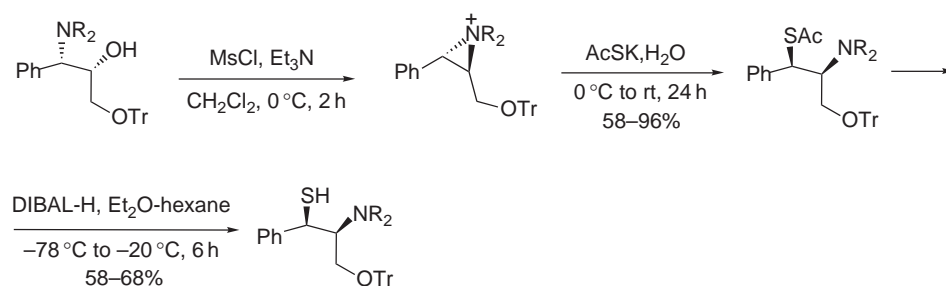
<i>Alcohol substrate</i>	<i>Nucleophile (yield %)</i>	<i>Method of acyl group removal (yield %)</i>	<i>Some target thiols</i>	<i>References</i>
Mitsunobu (Ph ₃ P-DIAD or Ph ₃ P-DEAD)	AcSH, AcSK or PhCOSK in THF or DMF (21–98)	LAH, Et ₂ O; NaOH, MeOH; MeONa, MeOH; NH ₃ , MeOH (68–100)	Tertiary benzylic thiols, thiol containing inhibitors of matrix Metalloproteinases, Sterol-based thiols, 1 β -Methylcarbapenems, Thiosugars	<1995CAR(274)303, 1999BMCL2385, 2000EJO549, 2002CPB415>
Mesylate	AcSNa, AcSK or AcSCs in DMF, MeCN, DMF-toluene or DMF-acetone (65–90)	NH ₄ OH, THF; NaOH, THF; NaOH, MeOH; MeONa, MeOH; NH ₃ , MeOH; K ₂ CO ₃ , MeOH (68–100)	1,2-Sulfinyl thiols, Thiol containing inhibitors of matrix Metalloproteinases, α -Mercapto-carboxylic acid, proline thiols, sterol-based thiols, 1 β -Methylcarbapenems	<1996JAN478, 1997AP268, 1997JAN429, 1999AP111, 2000BMCL95, 2000JAN314, 2000TA3481, 2002HAC77>
Tosylate	AcSK in EtOH, DME or DMF-toluene (63–88)	HCl, EtOH-Et ₂ O; LAH, Et ₂ O; NaOH, MeOH; MeONa, MeOH (68–100)	Chiral α -mercapto carboxylic acids, 1 β -Methylcarbapenems, thiosugars, L-Proline β -amino-thiols	<1995TA1553, 1996AP443, 1999TA1765>
Triflate	AcSK in EtOH or DMF (76–89)	NaOH, H ₂ O; MeONa, MeOH; NH ₃ , MeOH (61–91)	3,3-Difluoro-L-homocystein, thio-sugars, 7 β -Sulfur analogs of paclitaxel	<1995CAR(270)51, 1998BMCL1097>
β -Lactone derivative	AcSK, DMF (90)	6N HCl	2-Phenethylcysteine	<2002MI593>
Alcohol	ZnI ₂ – AcSH	LAH, Et ₂ O (36)	L-Proline-based β -amino tertiary thiol	<1999TA1551>

as a good leaving group. The thiol ester method for preparation of sugar thiols can also be complicated by intramolecular $S \rightarrow O$ <1995T3205> or $O \rightarrow S$ <1998M161> migration of acyl groups in sugar esters as well as intramolecular displacement of neighboring acyloxy group by sulfur <1996CAR(280)145>.



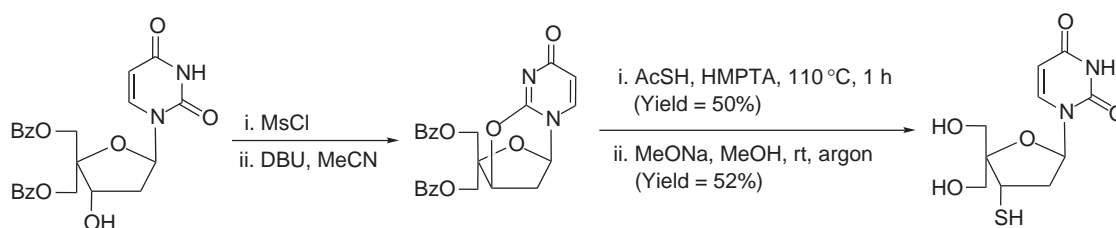
Nu = NMe₂, NHCH₂CH₂Ph, pyrrolidino, *N*-methylpiperazino, NH(4-Me)C₆H₄Me-4, OMe, OCH₂Ph, CH(CO₂Me)₂
 PNZ = *p*-nitrobenzyloxycarbonyl

Scheme 8



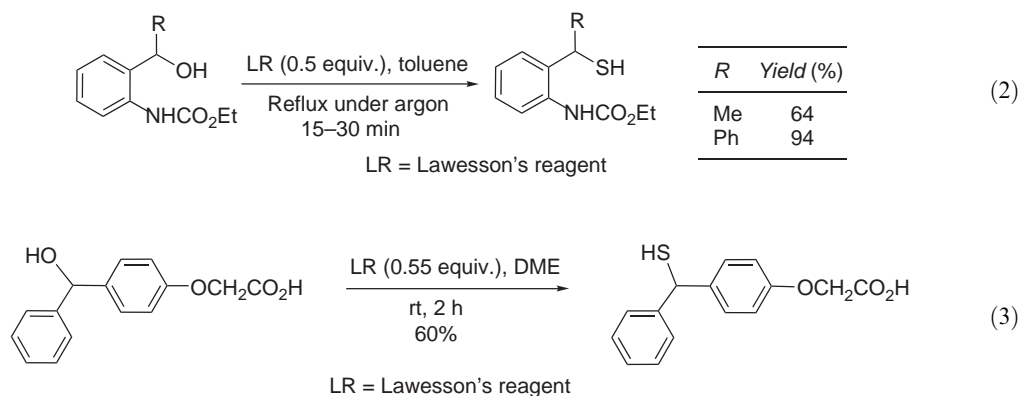
NR₂ = piperidino, dibutylamino

Scheme 9

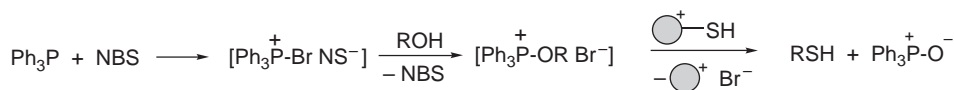


Scheme 10

Since hydroxyl is a poor leaving group, there are few procedures for its direct replacement by an SH function. One method is thiolation of alcohols with Lawesson's reagent <1993JCS(P1)1113>, which was not reviewed in the COFGT (1995). The protocol consists of heating an alcohol with Lawesson's reagent (0.5 equiv.) in toluene <1997JOC1106, 1999TA1551, 2001EJO3553> or dimethoxyethane (Equations (2) and (3)) <1997SC187>. The method gives good results for benzylthiols and tertiary alkanethiols, which are generally formed in moderate-to-high yield. Interestingly, conversion of alcohols into thiols using Lawesson's reagent proceeds with retention of configuration <2001EJO3553>.



Thiols can also be prepared in high yield from the corresponding alcohol using Ph_3P and NBS in acetone followed by addition of polymer supported hydrosulfide (Scheme 11) <2000SL908>. The reaction is conducted under mild conditions as a one-pot synthesis without any trace of dialkyl sulfide formation. Polymer-supported hydrosulfide is more nucleophilic than NaSH and activated alcohols react with hydrosulfide exchange resin much faster than with NaSH. Primary, benzylic and secondary alcohols are equally successful in this type of conversion and it should be noted that alcoholic hydroxyl groups are selectively converted into thiols in the presence of phenols. Secondary alcohols are selectively converted into thiols in the presence of tertiary alcohols. Another one-pot synthesis of thiols using polymer supported hydrosulfide involves preliminary conversion into trifluoroacetates <2000CL1304>.



Scheme 11

Direct conversion of alcohols into alkanethiols by reaction with hydrogen sulfides in the presence of a suitable catalyst was reviewed in COFGT (1995).

Alkanethiols may be prepared from alcohols in many other ways, including preliminary conversion into alkyl halides, isothiuronium salts, *S*-thiocarbamates, and sulfides. These methods are considered below.

2.03.1.3 Formation from Alkyl Halides and Hydrogen Sulfide

Alkyl halides, by analogy with sulfonates and triflates, may be considered as activated alcohols. It is therefore not surprising that methods for conversion of alcohols and alkyl halides into alkanethiols are quite similar (Table 2). In most cases the latter are prepared by reaction of the alkyl halides with potassium or sodium thioacetate and subsequent removal of the acetyl group by one of the procedures mentioned in Table 1. Similar methods can be applied to tertiary alkyl and allyl thiols if the corresponding $\text{S}_{\text{N}}1$ -active halides are treated with zinc thioacetate in aprotic solvents <1997IJC(B)1169>.

Excellent results were also obtained by treatment of alkyl halides with SH-exchange resin in methanol in the presence of equimolar amounts of triethylammonium chloride at room temperature; the procedure worked equally well for primary, secondary, and tertiary alkanethiols, α -mercaptoketones and benzylthiols (Table 2).

2.03.1.4 Formation Using Phosphorothiolate Ion

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

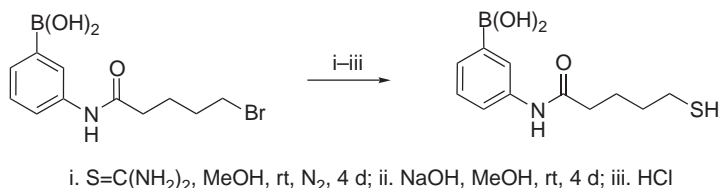
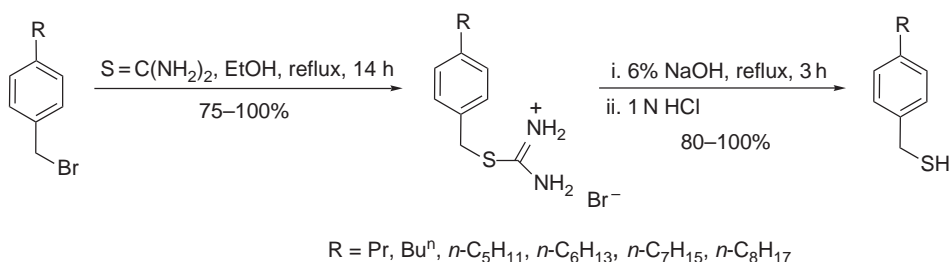
Table 2 Preparation of alkanethiols from alkyl halides

Target thiols	Reagent	Yield (%)	References
Simple alkanethiols (Alk = Bu ⁿ , Bu ^t , hexyl-2, Bn, <i>n</i> -C ₈ H ₁₇)	SH-exchange resin	68–98	<1995S373, 1998JCR(S)212>
ω -Hydroxyalkanethiols	i. AcSK, AcOEt; ii. MeONa, MeOH	90	<1997SC157>
Cinnamenethiol	SH-exchange resin	91	<1995S373>
Propargylthiol	i. AcSNa, THF; ii. LAH, Et ₂ O	i. 82; ii. 97	<1997S518>
α -Mercaptoketones	Method A: i. AcSK, EtOH; ii. conc. HCl or NaOH, MeOH Method B: SH-exchange resin	45–98	<1995SL1143, 2001CPB1660, 1995S373>
Mercaptocarboxylic acid and their esters	Method A: i. AcSNa, EtOH; ii. 6M HCl Method B: SH-exchange resin Method C: i. Trityl thiol in the presence of base; ii. Et ₃ SiH, CF ₃ CO ₂ H	i. 94; ii. 100 92–97	<1999S270> <1995S373, 1995JCS(P1)1247, 1998TA1641, 2000TL2729>
Mercaptocarboxamides	Method A: i. AcSK, MeOH; ii. AcCl, MeOH Method B: SH-exchange resin	i. 80; ii. 76 90	<2001SL1941> <1995S373>
Sugar-based thiols	i. AcSK, DMF; ii. MeONa, MeOH	i. 80–85; ii. 45–56	<1996CAR(280)145, 1998MI61>
Sterol-based thiols	i. AcSNa, acetone; ii. LAH, THF	i. 90; ii. 96	<1996TL29>
Heterocycle-based thiols	Method A: i. AcSK, DMF; ii. NaOH, MeOH Method B: NaSH, EtOH	i. 78; ii. 90 88	<1995AP289, 1998JOC8145> <1997IJC(B)1000>

2.03.1.5 Formation via Isothiuronium Salts and Related Procedures

Preparation of alkanethiols via hydrolytic cleavage of alkylisothiuronium salts is a well-established method. The isothiuronium salts are normally obtained from thiourea and an alkyl halide in hot ethanol. Subsequent heating with aqueous alkali gives the corresponding alkanethiol and urea (Scheme 12) <2001TL9207>. To avoid the formation of sulfides, the hydrolysis is usually conducted under an inert atmosphere; in some cases reductive fission of alkylisothiuronium salts, for instance with zinc in acetic acid, is also possible <1996OPP319>. Cheapness of starting material and high yields are attractive advantages of the isothiuronium method. Recently this method has been successfully used for the synthesis of 2-methylidenepropane-1,3-dithiol <1996AJC1261>, α,ω -hydroxyalkanethiols <1996OPP319>, dithiols <1996JPR327>, alkanethiols with aromatic <1998SC3779, 1998CL603, 1999CC2223, 2001TL9207, 2001TL6065, 2001H(55)1727> and heterocyclic <2002RJOC595> substituents. Interest in specific thiols has been associated with the demands of green chemistry (odorless thiols) <2001TL9207>, electrochemistry (surface-modified gold electrodes) <1996OPP319, 2001TL6065>, and biotechnology (self-assembling vicinal diol receptors) <1999CC2223>.

Along with its advantages the isothiuronium method has several limitations. It is not always effective for the preparation of secondary alkanethiols and does not work at all for tertiary alkanethiols. Its main drawback, due to the harsh conditions, is its inapplicability to the synthesis of thiols containing chiral centers or reactive groups. There are rare examples when these difficulties have been overcome by carrying out both stages at room temperature for several days. An example is the synthesis of *N*-(3-dihydroxyborylphenyl)-5-mercaptopentanamide in which the amide function remains untouched (Scheme 12) <1999CC2223>.

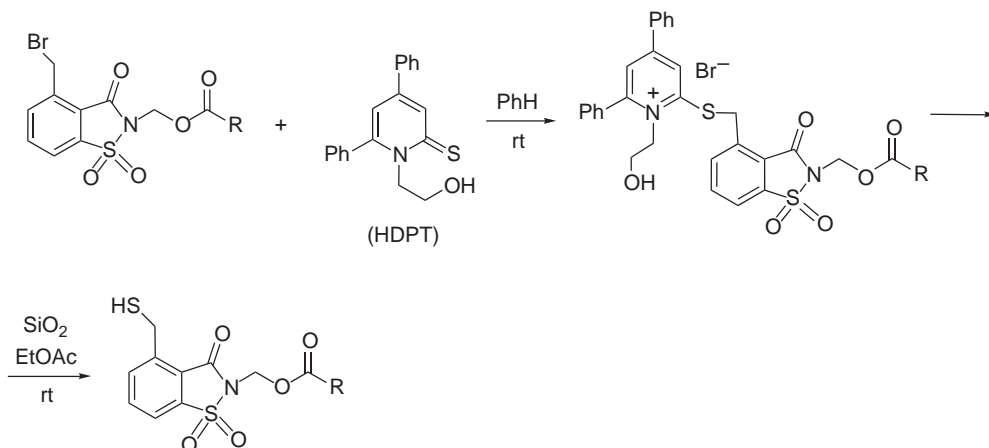


Scheme 12

For preparing isothiuronium salts, alcohols in the presence of strong acid can be used as alkylating agent instead of alkyl halides. This method is especially effective for S_N1-active alcohols, such as di- and trimethoxybenzyl alcohols, which form stable carbocations and react *in situ* with thiourea <1998SC3219>. Subsequent preparation of alkanethiols can be conducted with or without isolation of the isothiuronium salt.

Recently, the preparation of thiol terminated ethylene oxide oligomers and *p*-hydroxyphenethyl thiol has been successfully achieved by conversion of the corresponding alcohols to isothiuronium salts via tosylate intermediates; a procedure starting from alkyl halides did not work in these cases <2003S509>.

Sometimes thiol preparation must be conducted under strictly neutral conditions, which excludes the use of thiourea, many of its heterocyclic analogs (e.g., 1-methylpyridine-2-thione), and thioesters. In such cases, 1-(2-hydroxyethyl)-4,6-diphenylpyridine-2-thione (HDPT) has been recommended by Molina and Katritzky as an excellent thiolating agent. This method has been applied to the synthesis of 4-thiomethylsaccharin from the corresponding benzylic bromide without affecting the sensitive arylsulfonamide group (Scheme 13) <1998TL5309>.



Scheme 13

2.03.1.6 Formation via Bunte Salts

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

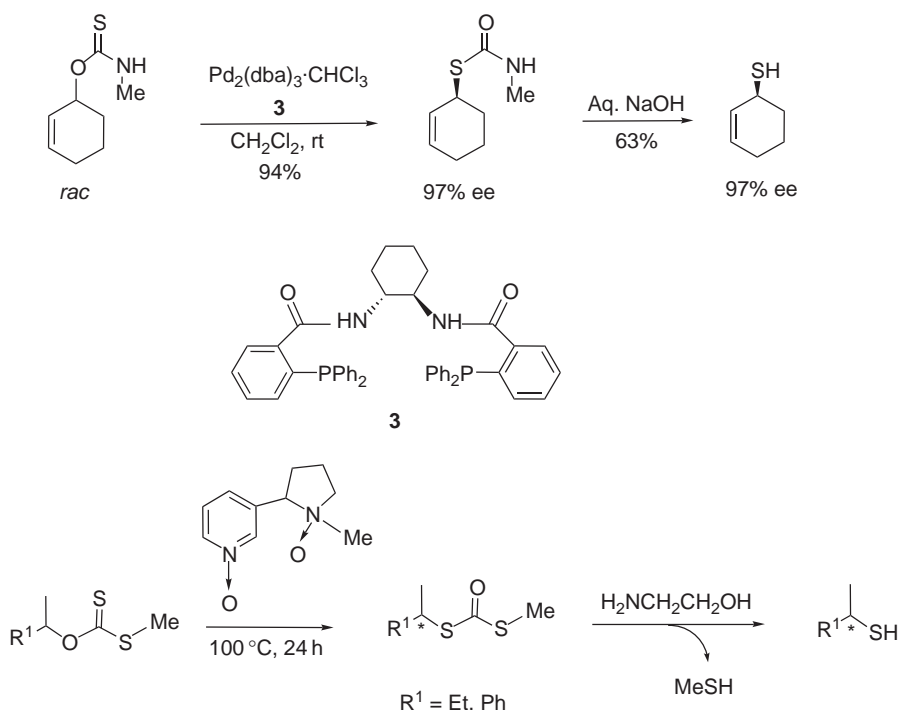
2.03.1.7 Formation via Xanthates and Related Esters

The xanthate method for the preparation of alkanethiols involves two stages: (i) synthesis of the alkyl xanthate and (ii) subsequent cleavage by base hydrolysis or reduction (Scheme 14). Alkyl xanthates are usually prepared by treatment of alkyl halide with potassium ethyl xanthate or similar alkali metal xanthate reagents. The halogen substitution normally proceeds with retention of configuration. In the 1990s, the use of the xanthate method was limited to cases where simpler procedures, e.g., via thioesters, do not work. The preparation of (*R*)- and (*S*)-2-mercaptosuccinic acids from (*S*)- or (*R*)-bromosuccinic acids is a typical example <1998TA1641>.



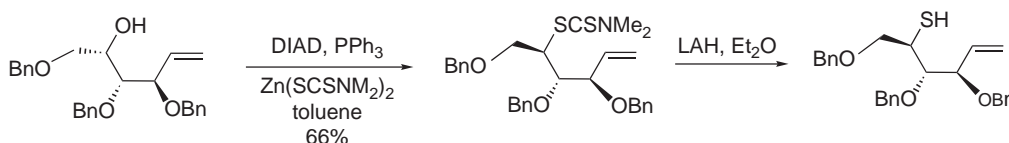
Scheme 14

Methods based on thione–thiol rearrangement provide a useful addition to the xanthate approach. Thus, Pd(0)-catalyzed rearrangement of racemic *O*-allylic thiocarbamates in the presence of the chiral bisphosphane **3** proceeded quantitatively and gave the *S*-allylic thiocarbamates in high yield and with excellent enantioselectivity. Typically, saponification of the *S*-allylic thiocarbamate furnished an allylic thiol with 97% ee (Scheme 15) <1999TA2511>. In a variation of this approach, enantiomerically enriched thiols can be prepared by rearrangement under mild conditions of racemic carbonodithionic *O,S*-dialkyl esters catalyzed by optically active pyridine *N*-oxides, followed by reaction with 2-aminoethanol (Scheme 15) <1995TA1175>. A similar thione–thiol rearrangement of a cyclic thione carbonate was successfully employed for the preparation of 3- and 4-thiopyranose sugars <1995JOC5170>.



Scheme 15

In some instances dithiocarbamates have also been used as convenient precursors to alkanethiols <1996TL707>. Thus, 5-mercapto-3,4,6-tribenzyloxyhex-1-ene was made by Mitsunobu displacement of the corresponding alcohol with ziram (zinc dimethyldithiocarbamate) to give the dithiocarbamate and reduction with LAH gave the thiol in good yield (Scheme 16) <2000MI641>.



Scheme 16

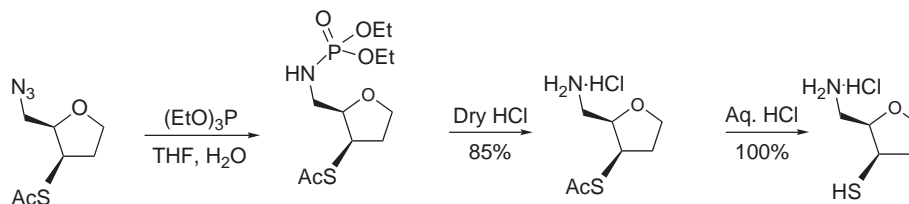
Alkanethiols can also be obtained in good-to-excellent yield by reduction of dithioesters (RC(S)-SR¹) with LAH <1996TL707>.

As mentioned in Sections 2.03.1.1–3, thioesters are versatile thiol precursors and can be prepared from alkenes, alcohols, and alkyl halides. Examples of hydrolytic and reductive conversion of thioesters to thiols are given in Tables 1 and 2 and Schemes 1, 6, 7, 9, and 10. Additionally, a number of new procedures have been developed mainly to avoid disulfide formation or to tolerate other functionalities sensitive to acid or base. Sodium thiomethoxide was successfully used for deprotection of volatile or water-soluble thiols, which are conveniently isolated as the sodium salt <1998TL2693>. This protocol is superior to simple base hydrolysis in that the thiomethoxide can act as a sacrificial reductant preventing oxidation of the desired thiol. Another procedure using TiCl₄/Zn at 0–25°C selectively cleaves the S–Ac bond in thioesters in the presence of other carbonyl groups and protecting groups <2001SL1956>. The removal of allyloxycarbonyl groups from water-insoluble thioesters with diethylamine promoted by a water soluble palladium complex has been reported <2000SL722>. The photochemically removable 3,5-dimethoxybenzoin-*O*-carbonyl group has also been used for the protection of benzylmercaptans <1995JOC1116>.

Conversion of thioacetates into the corresponding thiols under mild and essentially neutral conditions can be achieved by using borohydride exchange resin (3 equiv.) and a catalytic amount of palladium acetate <1995SC2655>.

Thioesters can be hydrolyzed chemoselectively and enantioselectively by piperidine <1999T8039> or by enzymatic cleavage using lipases <1997TA2645>, esterase <1999OL207>, or thioesterase <2001OL283>.

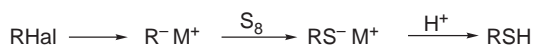
There are cases when labile thioacetate groups need to be retained while other functionalities are modified. Synthesis of 2,5-anhydro-1-amino-1,4-dideoxy-3-thio-*D*-threo-pentitol hydrochloride by conversion of an azido group into a primary amine is an illustrative example (Scheme 17) <2000SC1233>.



Scheme 17

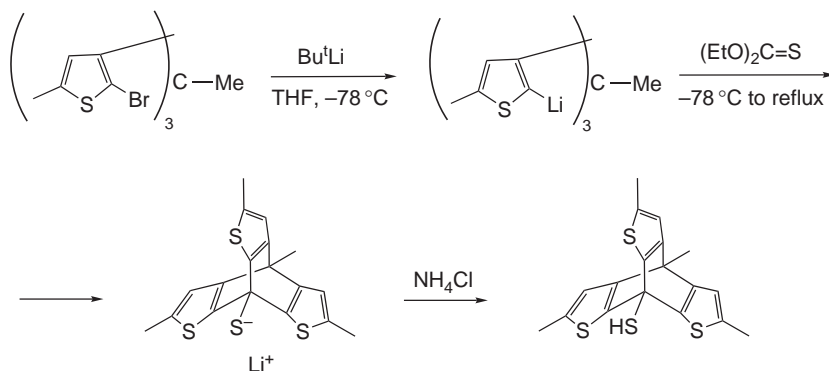
2.03.1.8 Formation Using Sulfur Insertion Reactions of Organometallics

The thiolation of organolithium and organomagnesium compounds with elemental sulfur is a well known but now rarely used method for alkanethiol preparation (Scheme 18). As it was discussed in COFGT (1995) <1995COFGT(2)113>, this approach works best for *t*-alkanethiols and cycloalkanethiols and can also be applied to the preparation of primary and secondary substrates.



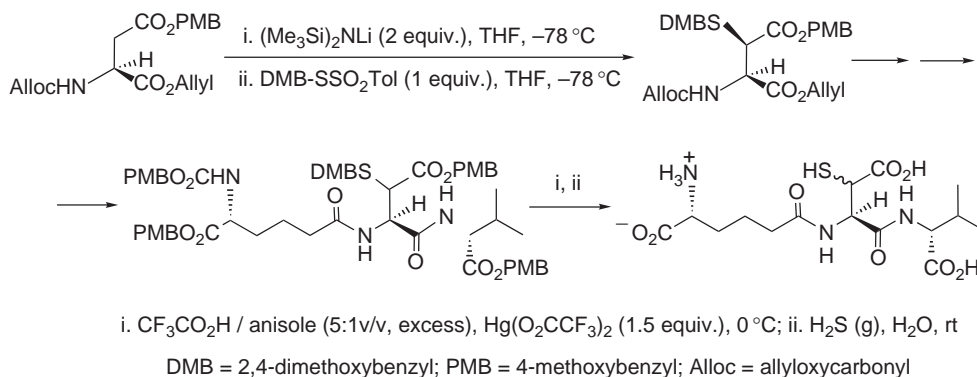
Scheme 18

If an organometallic reagent is treated with diethyl thiocarbonate instead of sulfur the product is a tertiary thiol containing an extra carbon atom. This procedure has been used for the synthesis of sterically hindered thiophenetriptycene-8-thiol (Scheme 19) <1996JA12836>.



Scheme 19

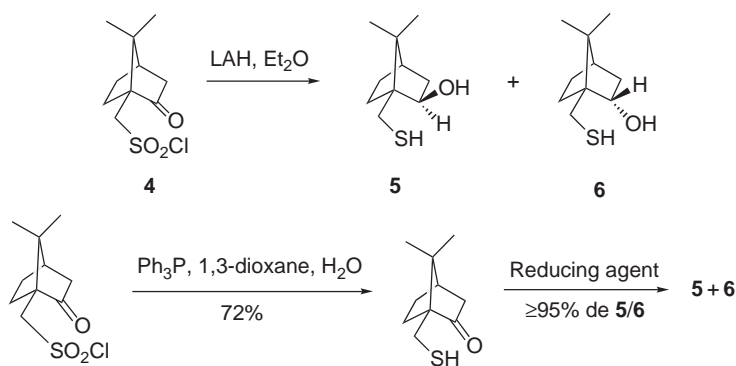
Another modification of alkanethiol synthesis based on organometallic reactions is illustrated by Scheme 20 <1996T12839> which shows a stereocontrolled preparation of protected (2*R*,3*R*)-3-mercaptoaspartic acid and incorporation into a tripeptide. A key step is electrophilic sulfenylation of the lithium derivative with toluene-4-thiosulfonic acid *S*-(2,4-dimethoxybenzyl)ester. After peptide coupling all protecting groups were removed using TFA/anisole/mercury(II) trifluoroacetate, the free thiol being liberated by treatment of the resulting mercury(II) salt with hydrogen sulfide.



Scheme 20

2.03.1.9 Formation from Sulfonyl Halides and Other Sulfonic Acid Derivatives

Alkane sulfonyl chlorides sometimes serve as a convenient source of alkanethiols. Reduction of (+)-10-camphorsulfonyl chloride **4** with excess LAH furnishes a mixture of *exo*-2-hydroxy-10-mercapto-isborneol **5** and its *endo*-isomer **6** (4:1) (Scheme 21) <1979JOC3598, 1986JOC1457, 1995TA2557, 2001JCR(S)405>. This reduction can be performed with high diastereoselectivity (>95% de) in a two-step manner by treatment of compound **4** first with triphenylphosphine and then with LAH, Bu_2AlH or NaBH_4 (Scheme 21) <1998MI378>. This is an important development since the *exo*-isomer **5** is often used to prepare chiral auxiliaries and catalysts for asymmetric synthesis.



Scheme 21

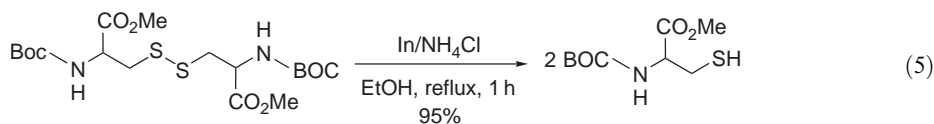
2.03.1.10 Formation by Reductive Cleavage of Disulfides

Alkanethiols and dialkyl disulfides form a redox system and are readily interconverted (Equation (4)).

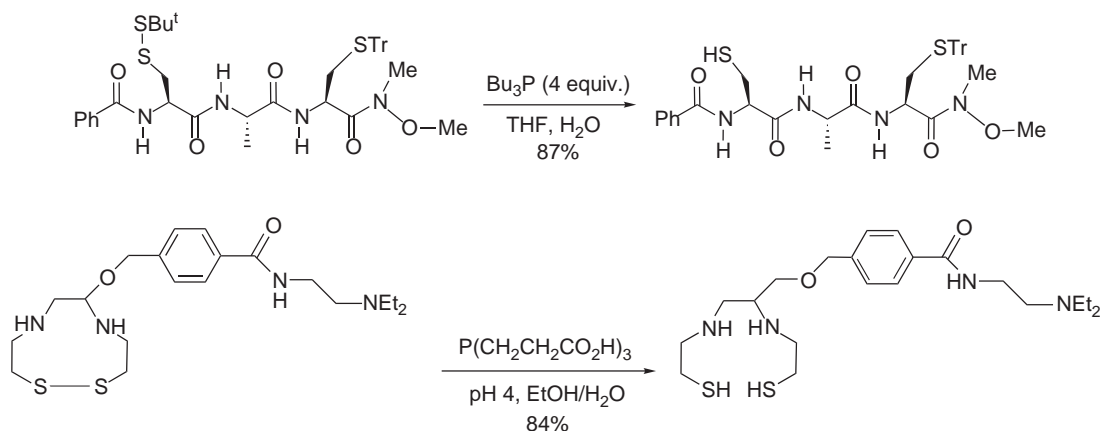


Due to the ease of alkanethiol autooxidation their preparation, especially in alkaline solution, is commonly conducted under an inert atmosphere but even under these conditions the formation of disulfides cannot always be avoided. Fortunately, this is not a serious problem since disulfides are a convenient form for storage of thiols and a method of protection since disulfides can be reductively transformed back to thiols. There are many reducing agents for this purpose and they fall into five types: (i) active metals in proton media; (ii) complex metal hydrides; (iii) trialkyl- and triarylphosphines; (iv) other thiols (so-called thiol–thiol exchange); and (v) other reductants. The reducing agents in each of these groups also differ by their mildness and selectivity.

When a disulfide does not include very reactive substituents, zinc in acetic acid <1995AP277, 1995PHA672, 1996JCS(P1)2237> or sodium in liquid ammonia <2000BMCL597> are the reagents of choice. Recently, Mg/MeOH <1997SC1347> and In/NH₄Cl <2000SC859> were strongly recommended as especially mild and selective reducing systems. They cleave S—S bond in the presence of such easily reducible functional groups as CHO, CO₂R, CN, NO₂, CONR₂, isolated double bonds etc. (Equation (5)).

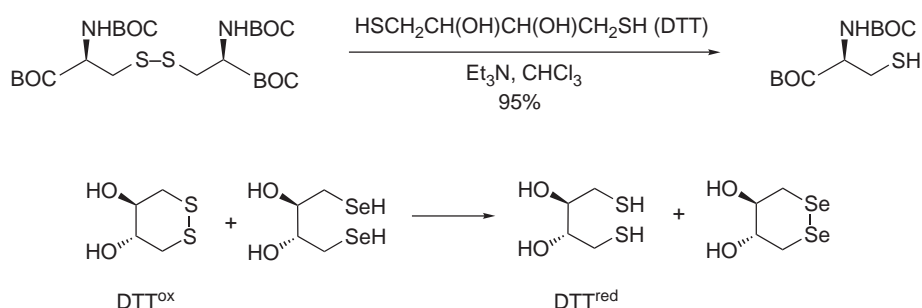


Among complex metal hydrides, LAH is commonly employed for reduction of both symmetrical and unsymmetrical disulfides <1997TA3031, 2001JOC910>. In cases where the substrate contains other readily reducible functionalities and LAH does not provide high selectivity the following milder, mainly borohydride-based, reducing systems have been suggested: ZrCl₄/NaBH₄ <2000SC3905>, LiCl/NaBH₄ <2001JC(B)622>, lithium (2,3-dimethyl-2-butyl)-*t*-butoxyborohydride (LiThxBu^tOBH₂) <2002MI856>. The last reagent reduces S—S bonds in dialkyl disulfides in THF at 0 °C without touching aromatic disulfides, sulfoxides, or sulfones. Trisubstituted phosphines, such as Ph₃P <1998H(48)617>, Et₃P <1997LA165>, Bu₃P <2001TL5801> or hydrosoluble tris(2-carboxyethyl)phosphine <2000JMC190> belong to a class of even milder reducing agents. They are commonly used when selective reduction of S—S bonds by other reagents fail. Two typical examples are shown in Scheme 22.



Scheme 22

Disulfides can be selectively cleaved by other thiols. 2,3-Dihydroxybutane-1,4-dithiol (dithiothreitol, DTT) is commonly used [<1998RCB1547>](#). Treatment of orthogonally protected cysteine and homocysteine derivatives with DTT in the presence of triethylamine leads to cysteine or the corresponding homocysteines in high yield and chemoselectivity (Scheme 23) [<2000BMCL597>](#). In the course of this reaction, DTT is converted into the cyclic oxidized form (DTT^{ox}) from which it can be reformed by reductants such as diselenothreitol (Scheme 23) [<2001HAC293>](#). Such transformations are important for controlling the redox states of protein S—S bonds. Along with DTT other thiols, such as glutathione, 2-mercaptoethanol, or 2-aminoethanethiol, are also employed for this purpose, both *in vivo* and *in vitro* [<2001HAC293>](#). However, since the redox power of these thiols is not strong, excess reagent and a limited pH range are required.



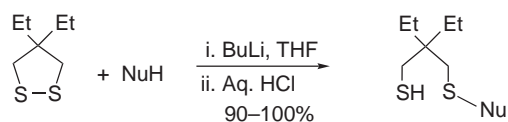
Scheme 23

In addition to reductive cleavage of disulfides, nucleophilic cleavage is also known. C-Nucleophiles such as alkali metal alkynides [<1997RCB199>](#) or metallated heterocycles [<1998HAC281, 1998HAC289>](#) are often used in these reactions (Scheme 24). Only one of the sulfur atoms is converted into a thiol: the second sulfur atom acts as electrophile and adds to the nucleophile. Such conversions are of interest as models for the study of the mechanism of enzyme-reductive acylations of lipoic acid.

Other, less common reagents for S—S bond reduction were reviewed in COFGT (1995) [<1995COFGT\(2\)113>](#).

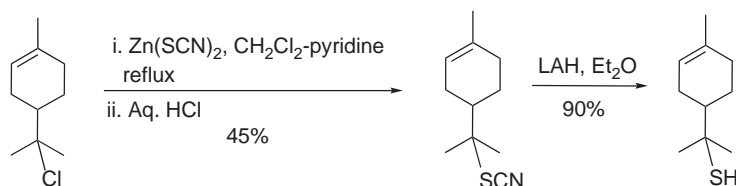
2.03.1.11 Formation from Thiocyanates

Reductive cleavage or acid hydrolysis of alkyl thiocyanates is a convenient preparative method for alkylthiols. LAH and zinc in acetic acid are commonly used reducing agents. For example, *p*-menth-1-enyl-8-thiocyanate on treatment with LAH in dry diethyl ether afforded *p*-menth-1-ene-8-thiol in excellent yield (Scheme 25) [<1997IJC\(B\)1169>](#).



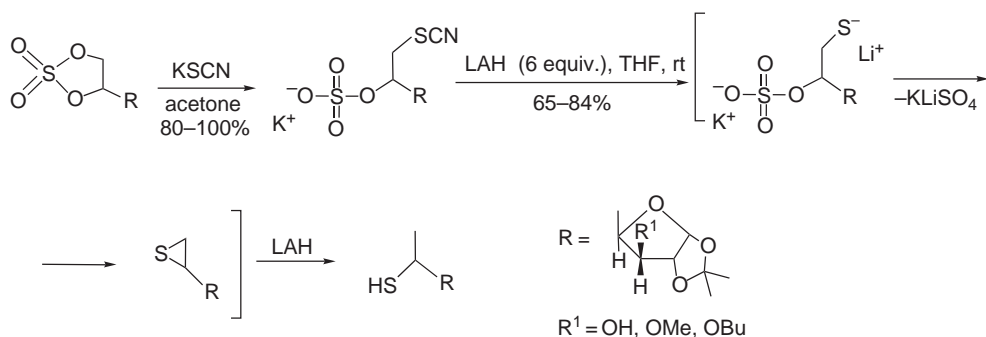
Nu = hexynyl-1, furyl-2, 1-methylpyrrolyl-2, benzofuryl-2, 1-methylbenzimidazolyl-2, 4-methylthiazolyl, 1-methylpyrazolyl

Scheme 24



Scheme 25

Recently, the thiocyanate method has often been used for the preparation of thiosugars <1998CAR(305)33, 1998JCS(P1)3629>. In some instances this process is accompanied by an interesting rearrangement caused by intermediate formation of episulfides and their subsequent reductive ring cleavage (Scheme 26) <1997JOC3944>.



Scheme 26

2.03.1.12 Formation by Dealkylation (Carbon—Sulfur Bond Cleavage) of Sulfides

The preparation of thiols from sulfides (thioethers) is useful when there is a need to remove an *S*-protecting *C*-terminal group. A survey of the most commonly used groups is given in Table 3. Among them are both well-established groups (e.g., Bu^t, Bn, Tr) and those which have been reported quite recently (e.g., quinolyl-2, allyloxycarbonylaminomethyl, *p*-toluenesulfonylvinyl). In general, the advantage of thioethers, compared to thioesters and disulfides, is their higher stability towards many aggressive reagents such as organometallics. This significantly extends the possibilities for various functionalisation procedures.

Commonly, C—S bond cleavage is conducted under reductive or hydrolytic conditions. An exception is the *p*-toluenesulfonylvinyl group which is eliminated by treatment with pyrrolidine via an addition–elimination mechanism. Among reductively removed protecting groups, benzyl is still the most reliable group (see also Sections 2.03.1.1 and 2.03.1.3). Its elimination by sodium or lithium in liquid ammonia usually provides high thiol yields and does not lead to racemization. Recently, elimination of benzyl and allyl groups by the low-valent titanium reagent TiCl₃—Li was reported. However, this procedure has been tested on a limited set of sulfides and gave low yield in some cases. Unlike benzyl, other groups also possessing enhanced stability to acidic and basic reagents have certain inconveniences when removal is required. Thus, *t*-butyl is a good protecting group but its

elimination under acidic conditions is often accompanied by side-reactions as observed for some γ -hydroxy *t*-butyl thioethers <1995T11883>. Removal of *S*-methyl group by Na/NH₃ (liq) normally proceeds only at elevated temperatures and not selectively.

Table 3 Thiol synthesis from sulfides by removal of *S*-protective groups

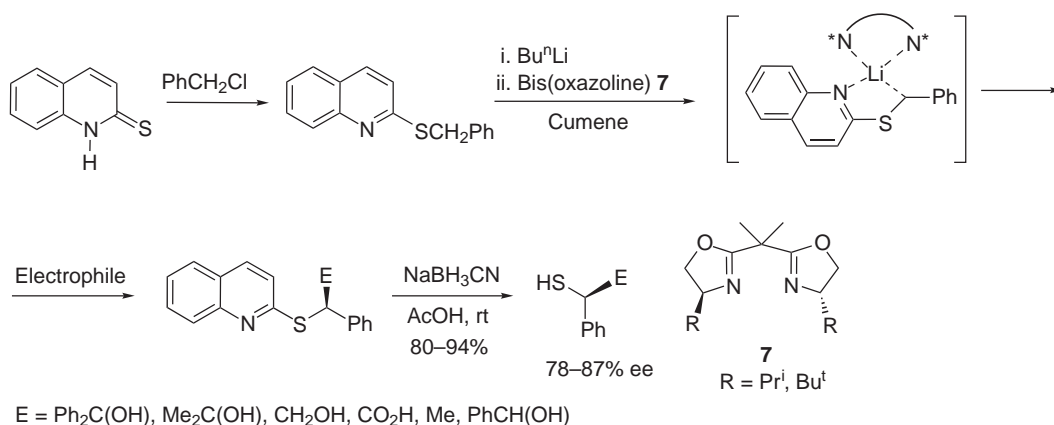
Protective group	Removal conditions	Target thiols	References
<i>t</i> -Butyl	i. Hg(OAc) ₂ , CF ₃ CO ₂ H; ii. H ₂ S	γ -Functionalized thiols	<1995T11883>
Benzyl	Na in liq NH ₃	N ₂ S ₂ -ligands; 4-mercapto-1,3- diols; enantiopure β -hydroxythiols; (<i>S</i>)-2,3-isopropyl- dene-dioxypropa- nethiol	<1996BMCL2399, 1996TL4823, 1998JOC5252, 1997JHC909>
Benzyl	Li in liq NH ₃	Tripod ligands with Ph ₂ P group	<1998EJI1417>
Benzyl	TiCl ₃ -Li, THF	1-Amino-3-mercapto- propylphosphinic acid; cysteine derivatives	<1999RCB1348, 2001JCB(B)1007>
Allyl	TiCl ₃ -Li, THF	Buthane-1-thiol	<2001JCB(B)1007>
Methyl	Na in liq NH ₃	Homochiral camphor annulated pyrroles	<1996TA1269>
Trityl ^a	i. AgNO ₃ -MeOH (EtOH)-pyridine; ii. <i>c</i> HCl	Pseudo-dipeptide- based thiol as antioxidant; sterol-based thiols	<2001BMCL1189, 1997TL2931>
Trityl	Et ₃ SiH, CF ₃ CO ₂ H	Dipeptide-based thiols and N ₂ S ₂ -ligands	<1998BMCL1157, 1999H(51)2849>
Trityl	Na in liq NH ₃	L-Homocysteine	<1999TA4151>
Tetrahydropyranyl	Zr-H ₂ O-MeOH	Benzylic thiols	<2002SC1549>
Tetrahydropyranyl	BF ₃ , Et ₃ N, HSCH ₂ CH ₂ OH- DCM ^b	Diphenylmethane thiols with bulky α -substituents	<1996CL999>
Allyloxycarbonyl aminomethyl	PdCl ₂ (PPh ₃) ₂ cat., Bu ₃ SnH-AcOH, DCM	Benzylic thiols; cysteine derivatives	<1999T6931, 1999T6945>
<i>p</i> -Toluene-sulfonylvinyl	Pyrrolidine, MeCN	Various alkanethiols	<1999JOC6090>
Quinolyl-2	NaBH ₃ CN, AcOH	Thionucleotides; α -functionalized benzylmercaptans	<1999TL1467, 2002EJO1690>

^a cf. Section 2.03.12.7. ^b Earlier reported method using AgNO₃/H₂S for removal of THP was not successful because of low yields (<30%) and a lot of by-products.

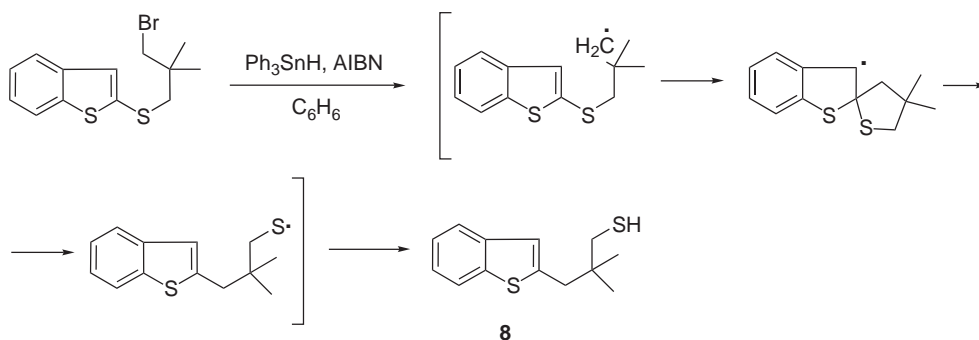
Elimination of the allyloxycarbonylaminomethyl group requires rather expensive reagents and isolation of thiol can be troublesome. Of recently introduced protecting groups the 2-quinolyl group merits special attention. Its attraction is based on the ease of preparation of 2-alkylthio-quinolines from commercially available quinoline-2-thione. 2-Quinolyl groups can be smoothly removed by treatment with NaBH₃CN in acetic acid as is illustrated by the asymmetric synthesis of α -functionalized benzylmercaptans (Scheme 27) <2002EJO1690>. Note that the quinoline heteroatom assists the chiral catalyst **7** in maintaining the configurational stability of the lithium intermediate.

In some cases reductive cleavage of disulfides can proceed via intramolecular radical mechanisms. Thus, treatment of 3-(benzothiophene-2-ylthio)-2,2-dimethylpropyl bromide with Ph₃SnH-AIBN gave the thiol **8** (71% yield) after Smiles rearrangement (Scheme 28) <1999CC75>.

Many other examples of C—S bond cleavage are discussed in Section 2.03.1.13.



Scheme 27



Scheme 28

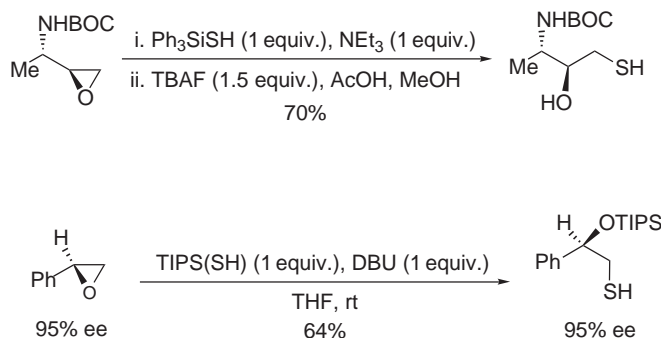
2.03.1.13 Formation by Heterocyclic Ring Cleavage

Heterocyclic compounds are a versatile and extremely useful source of alkanethiols, especially those with complex and nonstandard substituents. There are three general approach to such syntheses: (i) ring cleavage of nonsulfur heterocycles by reaction with *S*-nucleophiles; (ii) cleavage of ring C—S bond in sulfur heterocycles; and (iii) use of the exocyclic thione group in some heterocyclic α -thiones as a source of the SH group. Various examples of the latter were given in earlier sections (see Schemes 3–5, and 27). Therefore, only the first two approaches are considered here.

The ring opening of oxiranes and aziridines by hydrogen sulfide or its potassium salt producing β -hydroxy or β -aminothiols is a typical illustration of the first approach. It has been reviewed in COFGT (1995) <1995COFGT(2)113>. Since both these reagents, besides unpleasant handling, suffer from drawbacks, such as low stereoselectivity and sometimes inapplicability, several alternative reagents have been introduced. One of these is thioacetic acid which reacts with substrates inert towards H₂S such as 1-alkyl-trifluoromethylaziridines producing (after hydrolysis of intermediate thioesters) the corresponding 2-alkylamino-2-trifluoromethyl ethanethiols in good yield <1997RCB1136>. Epoxides can be quantitatively converted into alkanethiols by using hydro-sulfide exchange resin in methanol in the presence of equimolar amounts of triethylammonium chloride at room temperature <1995S373>.

To improve the stereoselectivity of oxirane ring opening, two other novel equivalents of H₂S have been reported recently: triphenylsilanethiol-NEt₃ <1993TL3363, 1999TL3913> and triisopropylsilanethiol-DBU <1998TL4409> (Scheme 29). The TIPS group was found to spontaneously rearrange to oxygen, giving the free mercaptan with TIPS-protected alcohol in a single step. The reaction of epoxide with 1 equiv. of triphenylsilanethiol produced a mixture of *O*- and *S*-silylated hydroxythiols that was desilylated *in situ* with TBAF in AcOH. For both reagents,

the nucleophilic ring opening occurs from the less hindered side of the epoxide. However, the more bulky triisopropylsilylthiolates are considered to be clearly superior to their triphenylsilyl counterparts.



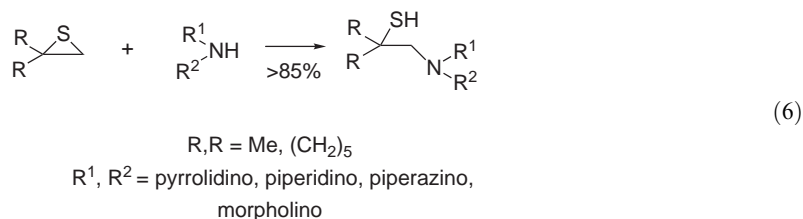
Scheme 29

In some instances, the ring opening of small heterocycles under the action of *S*-nucleophiles is realized as an intermediate step in multistaged reaction. Thus, a THF solution of 1-azabicyclo[1.1.0]butane upon treatment with AcSH afforded 1-acetyl-3-acetylthioazetidine, which was converted into azetidine-3-thiol hydrochloride via acid hydrolysis <2002H(56)433>. Similar examples for aziridines and oxiranes are also known <1998JOC7421, 2001SL1155> (see also Scheme 8).

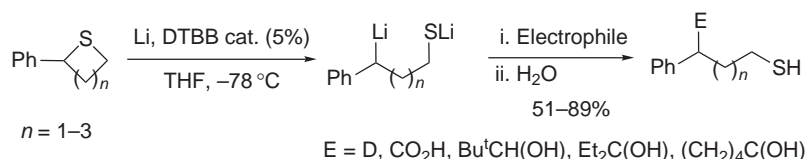
Heterocycles of larger ring size can be opened by sulfur nucleophiles if they are activated. Thus, an *N*-spiroderivative of the piperidinium cation upon treatment with Lawesson's reagent formed the corresponding ω -aminopenthanethiol <1995JOM(496)127>.

Undoubtedly the greatest possibilities for alkanethiol synthesis are connected with C—S bond cleavage in sulfur heterocycles. There are a great variety of such reactions which depend on heterocyclic ring size, nature of reagent, and reaction conditions. Commonly, ring opening is achieved by the action of nucleophiles or reducing agents. However, examples using electrophilic reagents are also known.

The simplest reaction of this type is cleavage of thiiranes using *O*- and *N*-nucleophiles and leading to formation of β -mercaptoalcohols (ethers) and β -aminothiols. For a long time, the latter reaction was usually conducted in aprotic solvents (see e.g., <1996T12745, 1998RJOC583, 2000CHE82>), suffered from low-to-modest yields and often required either prolonged heating or activation by a thiophilic metal cation (e.g., Ag^+). Furthermore, the method has seldom been used to prepare β -amino tertiary thiols. Recently, this procedure has been considerably improved by carrying out the reaction neat. Under these conditions the process is fast and clean, and typically affords the product in yields greater than 85% (Equation (6)) <1999S1106>.

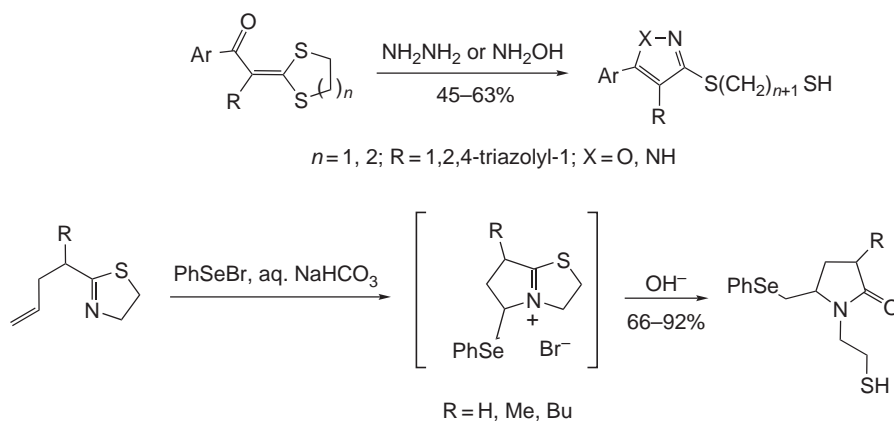


Scheme 30 shows reductive cleavage of the 2-phenyl derivatives of thietane, thiophane, and thiane by lithium in the presence of 4,4'-di-*t*-butylbiphenyl (DTBB) as an electron carrier <1997T5563>. The reaction initially leads to the corresponding sulfur-containing benzylic organolithium compounds, which by reaction with different electrophiles followed by hydrolysis afford functionalized mercaptans in a regioselective manner. The presence of 2-aryl substituents is crucial otherwise stabilization of the intermediate carbanion, and therefore ring opening, is impossible. Similar conversions have also been described for condensed *S*-heterocycles such as thiophthalans, thioisochromans <1996JOC1859>, thiochromans <1995TL4459>, and 1,7-dihydrodibenzothiepine <2001TL2469> (see also review <1997RHA73>).



Scheme 30

When an *S*-heterocycle is appropriately functionalized, ring opening is often accompanied by recyclization which can promote S—C bond cleavage. Normally, these conversions lead to the formation of heterocyclic derivatives of propane-1-thiol or ethanethiol. Examples dealing with α -oxoketene *S,S*-acetals <1995H(41)1653, 1995SC3219, 1995SC3603, 1996JOC1473, 1996SC3115, 1997T17163> and 2-alkenylthiazolines <1999SL733> are shown in Scheme 31. Other examples include ring-opening reactions of thiobutyrolactones <1996CHE158>, 2-cyanothiophanes <1996T3189>, 1,3-oxathioles <1999TL8647, 2000S1681>, 1,3-dithioles <1999JOC9596, 2001OL2185, 2001TL3729>, tetrahydrothiopyranoindoles <1997JCS(P1)2857>, 1,3-dithianes <1995JOC735, 1997M1033>, 2-acyl-1,3-dithiane-*S*-oxides <1995S73>, 1,4-dithiane-2-one <1997TL1371>, 6-methylthiepine-2,5-dione <1996ZN(B)1334>, 1,4-dithiepanes <1999T801>, and imidazo[2,1-*b*]thiazolines <2000OL2877>.

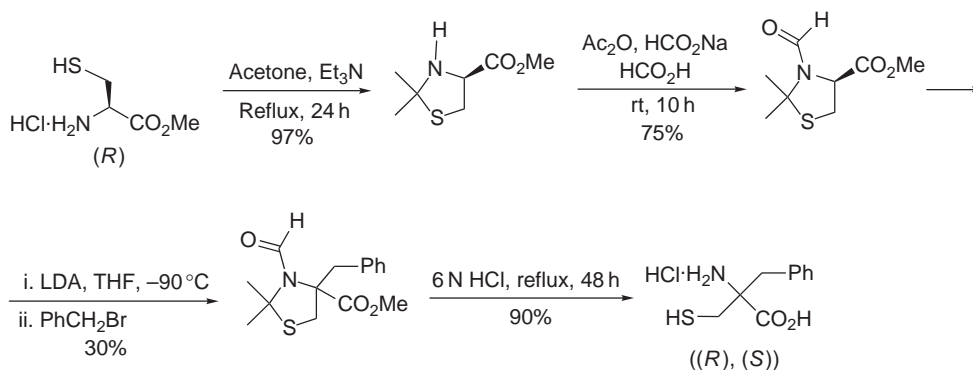


Scheme 31

Heterocyclic ring cleavage of substrates containing several sulfur heteroatoms can be conducted with elimination of one of them. Synthesis of menthanethiol and neomenthanethiol in quantitative yield on treatment of (–)-menthone 1,3-dithiolane acetal with BuLi serves as an illustrative example <1995JPR538>.

From the above examples, it can be seen that heterocycles serve as building blocks, activating and directing moieties in thiol preparation. In many cases they also function as effective protecting groups. This is illustrated by the synthesis of racemic benzylcysteine from (*R*)-cysteine methyl ester via the corresponding thiazoline-4-carboxylates (Scheme 32) <2002MI593>. A similar strategy was employed for the preparation of many other β -aminothiols including cysteine <2001EJO3025, 2002S1499> and isocysteine <1996TL8159> derivatives, L-homocysteine <2000CL468>, antimitotic agent curacin A <1995TL5765, 1996T14543, 1996TL4397, 1997BMCL2657>, 1,1,1-trifluoro-3-aminopropane-2-thiol <1996KFZ12>, and β -cyclopentylaminoethanethiols <1997JPR541>.

It should be noted that some acyclic thiols having multiple bonds, such as $\text{C}=\text{NR}$ or $\text{C}=\text{O}$, can exist as cyclic dimers as they undergo ring-chain tautomerism. A typical example is mercaptoacetaldehyde which exists as 2,5-dihydroxy-1,4-dithiane and on treatment with hydroxylamine gives the oxime of the monomer <1995LA1649>.

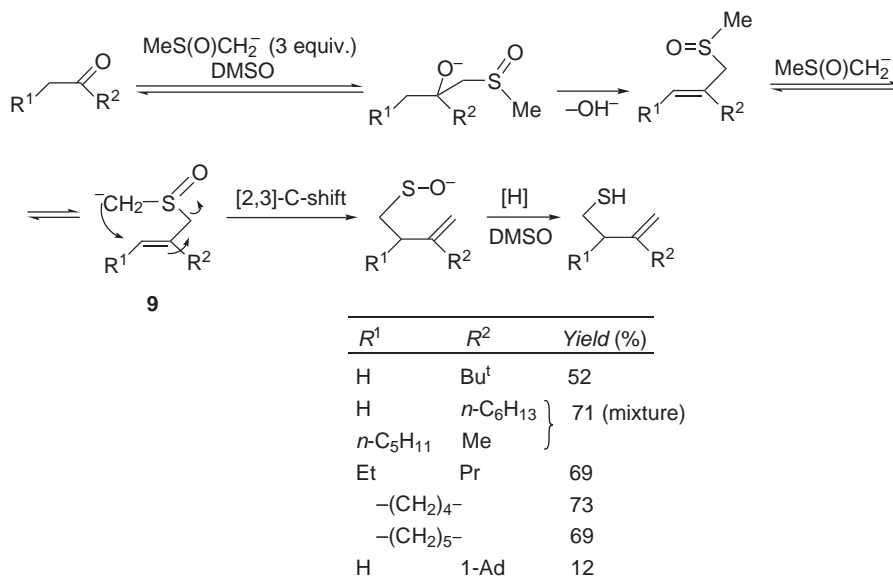


Scheme 32

2.03.1.14 Formation from Aldehydes, Ketones, and Carboxylic Acid Derivatives

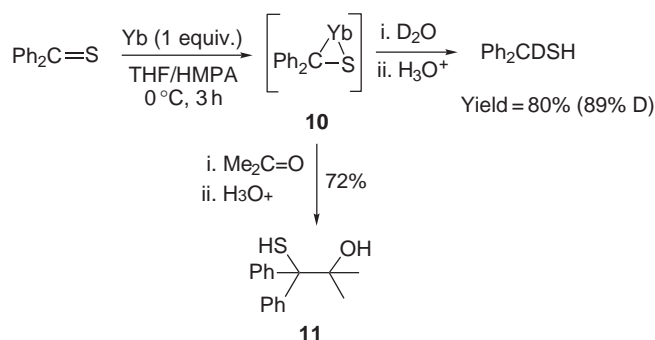
A well-known method for alkanethiol and *gem*-dithiol preparation is by reaction of ketones or their derivatives (e.g., imines, enamines) with hydrogen sulfide in the presence of a reducing agent. This procedure was covered in COFGT (1995) and there have been no further developments.

Among the novel achievements in this field, the most significant is a convenient method for the preparation of homoallyl thiols from ketones by treatment with dimsylsodium in DMSO (Scheme 33) <1998RJOC733, 2000JOC2984>. A key step of the multistaged process is [2,3]-sigmatropic rearrangement of an intermediate allyl sulfinyl carbanions **9** <2002RJOC450>. Yields of thiols are usually good: an exception is thiols carrying bulky substituents (e.g., adamantyl groups) where yields do not exceed 10–12%.



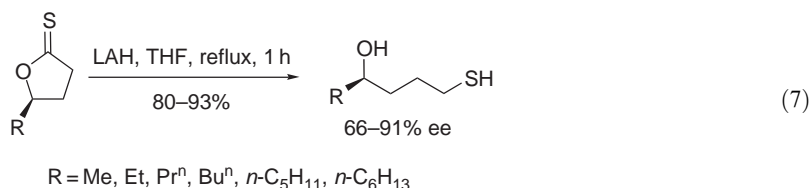
Scheme 33

Thioketones and thioaldehydes are also possible precursors of thiols and this was not discussed in COFGT (1995) <1995COFGT(2)113>. Thus, treatment of thiobenzophenone with ytterbium or samarium metal in THF–HMPA and subsequent quenching with D_2O or acetone affords the α -deuteriated diphenylmethanethiol or β -hydroxythiol **11**, in high yields (Scheme 34) <1996JOC372>. The reactions possibly proceed via intermediate C,S-dianions **10** and are very sensitive to temperature.



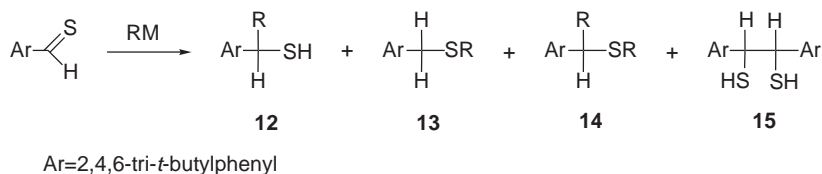
Scheme 34

Stereoselective reduction of the corresponding thiones with LAH or DIBAL-H has proved to be an excellent method for the preparation of camphor-derived compounds with SH functionality in position 2 <1996TA3553, 2001JOC6400>. The LAH reduction of γ -thionolactones leads to the corresponding 1,4-sulfanylalcohols in high yield and enantioselectivity (Equation (7)) <2002TL6267>. This method, starting from readily available racemic γ -lactones, is considered to be superior to other procedures for preparation of 1,4-sulfanylalcohols.



LAH reduction of *O*-propyl thioesters, formed *in situ* by treatment of the corresponding organometallic compounds with *O*-propyl chlorothioformate, has also been used for direct mercaptomethylation of aromatics and heteroaromatics <1999SC201>.

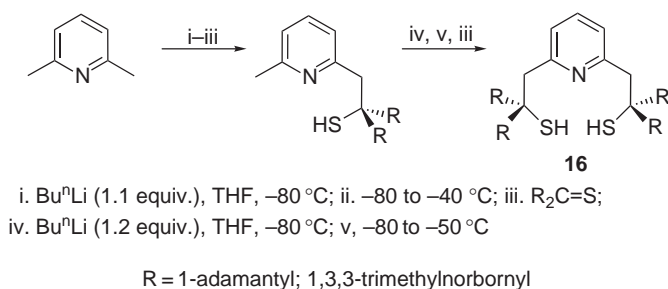
The reactions of thioketones and thioaldehydes, e.g., 2,4,6-tri-*t*-butylthiobenzaldehyde, with Grignard and organolithium reagents affords carbophilic **12**, thiophilic **13**, and double addition products **14** and **15** depending on the organometallic reagent (Scheme 35) <1996BCJ709>. In some cases (e.g., using trimethylsilyllithium, BnMgCl), the corresponding thiols **12** and **15** predominate or are the only product.



RM	Conditions	Yield (%)			
		12	13	14	15
PhMgBr	Et ₂ O, reflux	58	15		
PhMgBr	THF, rt		91		
BnMgCl	THF, rt	50		12	21
Bu ^t MgCl	Et ₂ O, rt		32	12	35
Bu ^t Li	Et ₂ O, rt	7	23	11	12
Me ₃ SiLi	THF, -78 °C	85			
PhLi	Et ₂ O, rt		97		

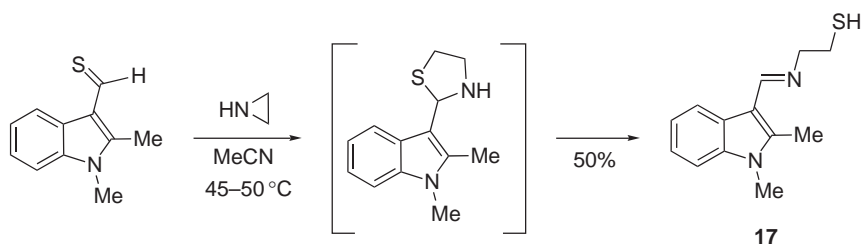
Scheme 35

Similarly, pyridinedithiols **16** have been synthesized in 65–70% overall yield by base-induced two-step addition of 2,6-lutidine to (nonenolisable) thioadamantanone and (*R*)-thiofenchone (Scheme 36) <1997CC1065>.



Scheme 36

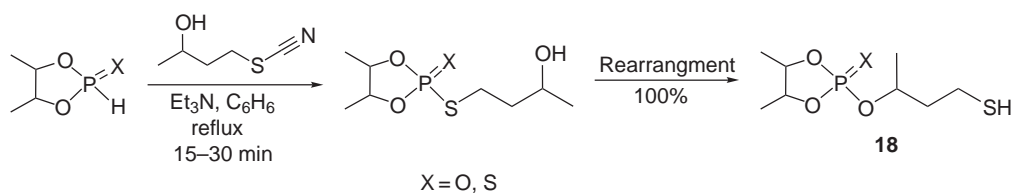
1,2-Dimethylindol-3-carbothioaldehyde reacts with aziridine to afford the rearranged thiol **17** possibly via an intermediate thiazolidine derivative (Scheme 37) <1999RJOC1507>.



Scheme 37

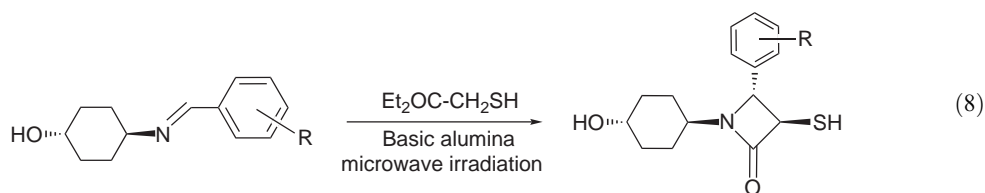
2.03.1.15 Miscellaneous

Several thiol syntheses have been described which cannot be strictly attributed to any specific section. Thus, hydrogen sulfide addition to 1,3-dehydroadamantane (dry Et₂O, rt, 15–20 min) furnishes 1-adamantanethiol in 90% yield <1999RJOC149>. Thiocynoalcohols react with some acid alkylene glycol phosphites and thiophosphites in the presence of Et₃N to give the corresponding hydroxyalkyl alkylene glycol thiophosphates or hydroxyalkyl dithiophosphates. The latter undergo oxy-thiol rearrangement, sometimes spontaneously, to form thiols **18** (Scheme 38) <1996RCB226>.



Scheme 38

Various thiol functionalizations can also serve as useful ways of synthesizing thiols that are inaccessible by other methods. For instance, 3-mercapto β -lactams were obtained from *N*-(4-hydroxycyclohexyl)-arylaldehydes by the reaction with ethyl α -mercaptoacetate on basic alumina with microwave irradiation (>90%) (Equation (8)) <2000SC989>.



An effective procedure for deracemization and stereoinversion of D,L-aminoacids, including cysteine, using porcine kidney D-amino acid oxidase and NaBH₄ has been developed <2002CC246>.

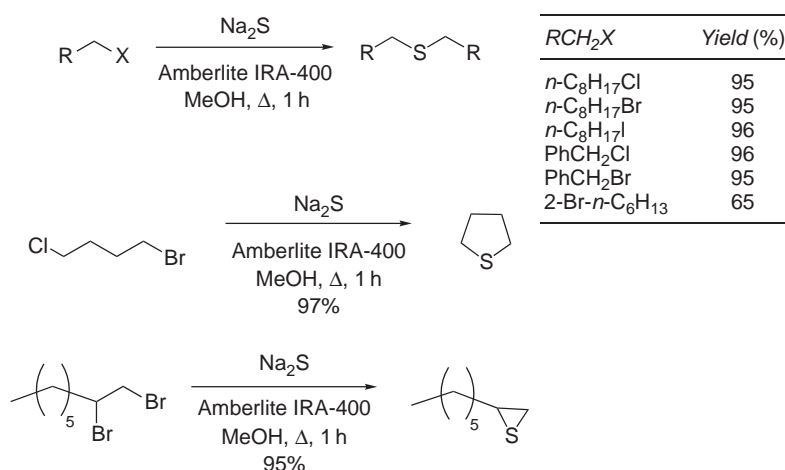
2.03.2 DIALKYL SULFIDES AND THEIR HIGHER-COORDINATED DERIVATIVES

The importance of dialkyl sulfides (thioethers) and their oxidized analogs (sulfoxides and sulfones) in the natural world was highlighted in COFGT (1995) <1995COFGT(2)113>. While the general approaches to synthesis of dialkyl sulfides and their derivatives remain similar to those developed earlier, quite a few modifications of the reaction conditions, the use of new catalysts and asymmetric syntheses have expanded the area significantly. The application of sulfimines and sulfoximines, the nitrogen analogs of sulfoxides and sulfones, in organic chemistry and their biological activity have triggered a growing interest in their synthesis and reactions.

2.03.2.1 Dialkyl Sulfides

2.03.2.1.1 Formation from alkyl halides and metal sulfides

The interaction of alkyl halides with metal sulfides results in symmetrical sulfides with a wide range of substituents. This approach was surveyed in COFGT (1995) <1995COFGT(2)113> and no further advances have been reported on noncatalyzed reactions of alkyl halides with metal sulfides. Recently, it was shown that the use of a catalyst could expand the scope, improve yield, and simplify the procedure for symmetrical dialkyl sulfides preparation. Thus, a commercial anion exchange resin catalyzes the two-phase chemoselective synthesis of sulfides from alkyl halides in good-to-excellent yield (Scheme 39) <1995MI189>. This method has also been shown to be effective for the synthesis of cyclic sulfides in yields higher than previously reported <1995COFGT(2)113>.



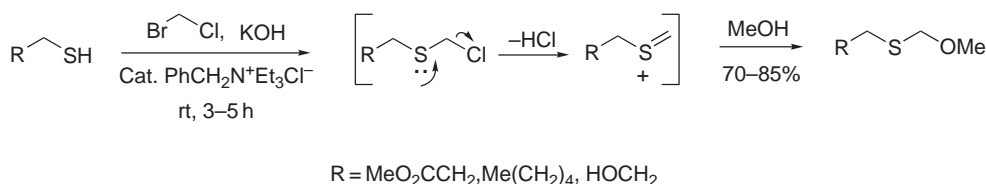
Scheme 39

2.03.2.1.2 Formation from alkyl halides and alkyl thiolates

One of the general and simple methods for thioether preparation is nucleophilic substitution of an alkyl halide with an alkyl thiolate; the thiolate is normally prepared first, often *in situ* by treatment of the thiol with a base (Equation (9)).

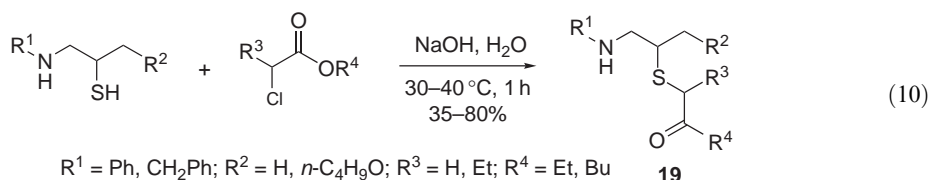


This method was surveyed in COFGT (1995) <1995COFGT(2)113>. The application of each selected procedure can be driven by the choice of the halide component, and/or by the conditions of the thiolate formation (cf. Section 2.03.12). Typically, aqueous or alcoholic solutions of sodium or potassium hydroxide (or alkoxides) are used for thiolate anion generation. Thus, an aqueous solution of potassium hydroxide was used in the synthesis of protected chiral ω -mercapto- α -azido carboxylic acids from 4-methoxy- α -toluene-thiol and ω -bromo- α -azido carboxylic acids in good yields <1998TA2739>. A competitive method of phase-transfer catalysis worked well for the preparation of a number of MOM protected thiols via an intermediate sulfur-stabilized cation (Scheme 40) <1995SL159>.

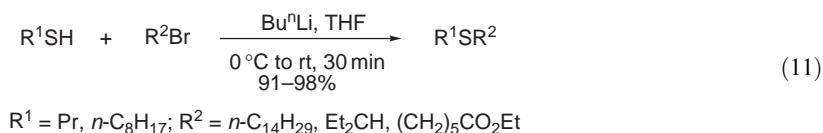


Scheme 40

Functionalized hindered dialkyl sulfides **19** were isolated after reaction of 1,2-aminopropane thiols with the esters of chloroacetic or α -chlorobutanoic carboxylic acid (Equation (10)) <1999SC721>. In a similar way, sodium ethoxide in refluxing ethanol was successfully applied to an improved synthesis of *S*-alkylated cysteine derivatives with branched alkyl chains (30–90% yield) <2001TL1859>.

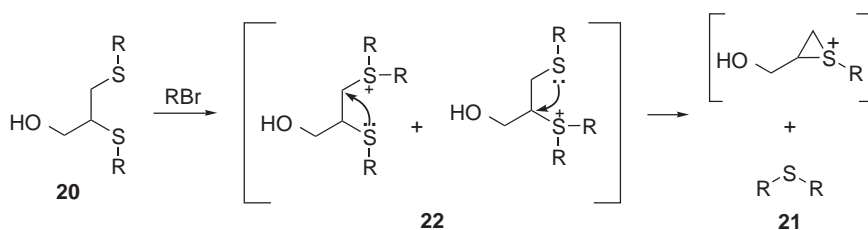
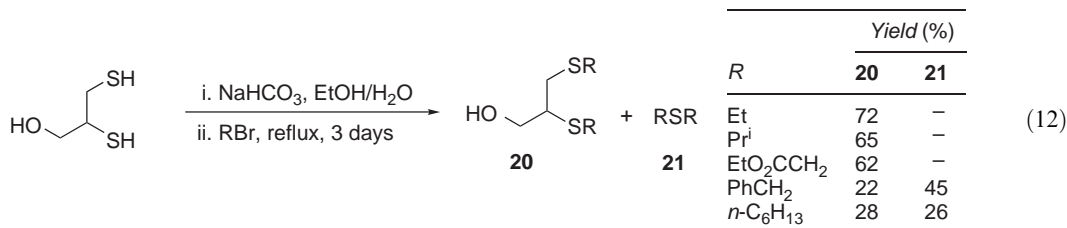


A simple and mild method for synthesis of symmetrical and unsymmetrical sulfides in yields of 89–98% involves addition of alkyl halides or bromo esters to solutions of benzyl, *n*-octyl or cyclohexyl thiol and tetraammonium carbonate or hydrogencarbonate in acetonitrile at ambient temperature <1999SC2611>. Reasonable yields (75–78%) of hindered unsymmetrical dialkyl sulfides were obtained on refluxing zinc *s*-butyl or *t*-butyl thiolates and *t*-butyl bromide in methylene chloride <1998IJC(B)1174>. Unsymmetrical sulfides can be prepared under mild conditions and in excellent yield from thiols and alkyl bromides in the presence of *n*-butyllithium (Equation (11)) <1997TL5953>.



Sodium borohydride exchange resin (BER) has been used as a basic catalyst in the synthesis of unsymmetrical sulfides. Primary alkyl bromides and iodides react rapidly with stoichiometric amounts of hexanethiol in the presence of BER (2equiv.) in methanol at 65°C to give the unsymmetrical sulfides quantitatively <1996MI(1)73>. A new basic clay, synthesized by introducing 3-aminopropyltriethoxysilane into montmorillonite, catalyzes the neat reaction (3–10 h at 95°C) between benzyl chloride and *n*-butyl-, *n*-hexyl-, and *n*-octyl-thiol to afford the corresponding sulfides in greater than 70% yield <1996CCC369>.

One of the diverse rearrangement reactions of 2,3-dimercapto-1-propanol, a well-known ligand for metals, resulted in a series of dialkyl disulfides **20** and symmetrical dialkyl sulfides **21** (Equation (12)) <1996JOC8244>. The proposed mechanism for the formation of the sulfides **21** suggests an alkylsulfonium intermediate **22** (Scheme 41). The second product, a thiaranium cation, can undergo further transformation leading to an alkylmercaptan and acrolein. Other aspects of 2,3-dimercapto-1-propanol rearrangements are discussed in Section 2.03.2.1.5.



Scheme 41

2.03.2.1.3 Formation from alkyl sulfates

Monoalkyl sulfate salts, typically low-yielding alkylating agents, readily form symmetrical sulfides with highly reactive metal sulfides or unsymmetrical sulfides with thiolates. Similarly, more reactive dialkyl sulfates afford symmetrical or unsymmetrical sulfide products. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.2.1.4 Formation from sulfonic esters

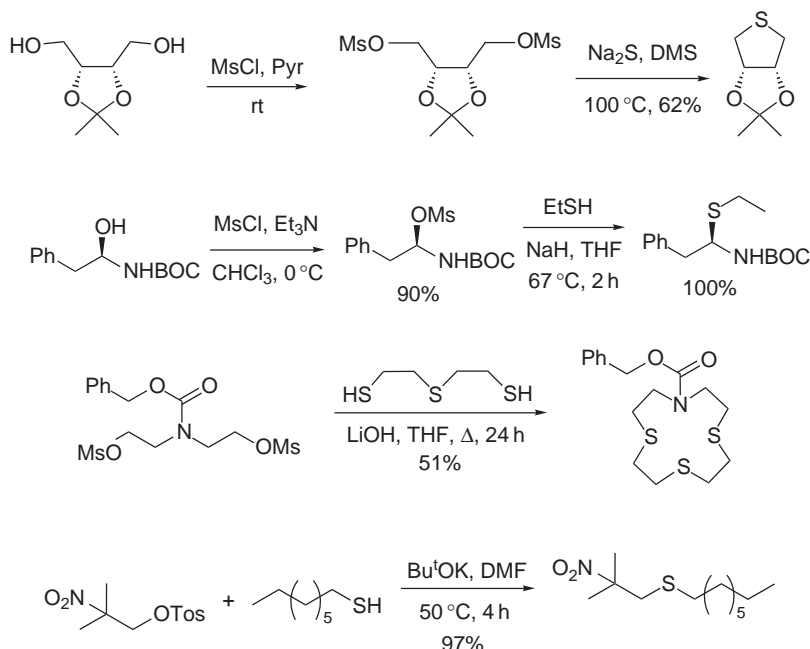
Prior conversion of alcohols into sulfonic esters followed by interaction with thiols has been demonstrated as a convenient approach to the preparation of a great variety of complex sulfides <1995COFGT(2)113>. Esters of sulfonic acids, particularly *p*-toluenesulfonates (tosylates) and methanesulfonates (mesylates), are easily prepared from alcohols (cf. Section 2.03.5.3.1), remain the most employed derivatives in the synthesis of symmetrical and unsymmetrical sulfides, as illustrated by the examples in Scheme 42 <1995TL1223, 1996T3609, 1997CB1279, 1997JMC226, 1998TA2349, 1999JMC4844, 1999TL4795, 1999TL6297, 2001JOC7008, 2002H(57)1399, 2002JCS(P1)1242, 2002TL8359, 2003BMCL859>.

The synthesis of enantiomerically pure C₂-symmetric thiodiglycols in excellent yields from tosylates and sodium sulfide under mild conditions has been reported <1998TA2349>.

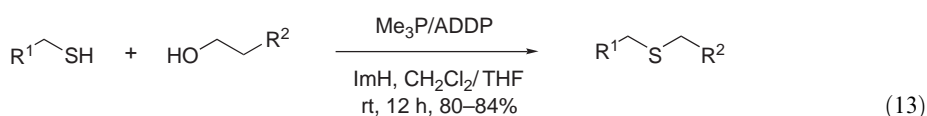
2.03.2.1.5 Formation from alcohols

Direct reaction of alcohols and thiols to form sulfides often requires harsh conditions. Prior conversion of alcohols into the sulfonic esters (cf. Section 2.03.5.3) is one of the ways to milder conditions of interaction with thiols, and to higher yields of the alkyl sulfides <1995COFGT(2)113>. The efficiency of sulfide synthesis from alcohols and thiols can also be achieved by catalysis, and the application of new catalysts has received the most attention during the 1990s. Direct etherification of benzylic alcohols with alkanethiols is catalyzed by the

surfactant-type Brønsted acid dodecylbenzoic acid (DBSA) in water under mild conditions to produce unsymmetrical dialkyl sulfides in high yield <2002CL10>. Various substituted *p*-hydroxybenzylic alcohols were converted into *p*-hydroxybenzylic thioethers in excellent yield by treatment with alkanethiols in the presence of catalytic amounts of CAN <2000JCR(S)266>. Among rare earth metal trifluoromethane sulfonates, ytterbium triflate has been found to be the most efficient catalyst for benzyl thioetherification and affords benzyl alkyl sulfides in good yield; Yb(OTf)₃ could be recovered easily and reused without loss of activity <2002CPB380>. Benzyl and alkyl thiols and hindered alcohols form unsymmetrical alkyl thioethers in good yield in the presence of imidazole (2equiv.) under modified Mitsunobu conditions (cf. Section 2.03.1.2) <1999TL2903>. These conditions are compatible with a wide variety of functional groups including alkenes, acetylenes, silyl ether, and esters, as illustrated in Equation (13).



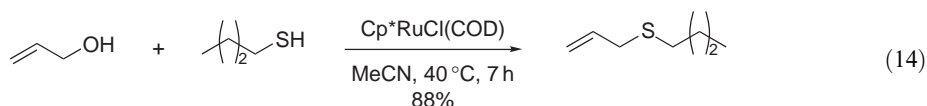
Scheme 42



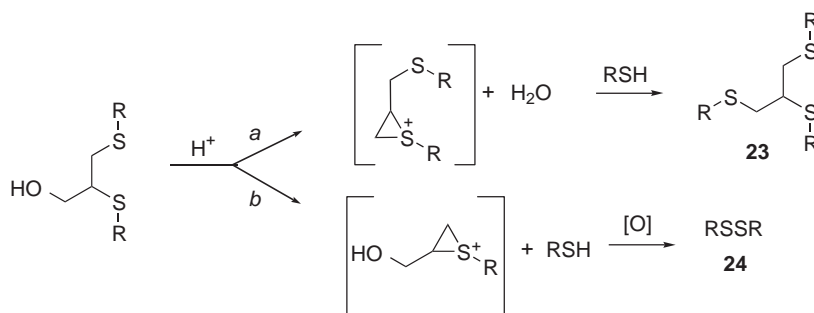
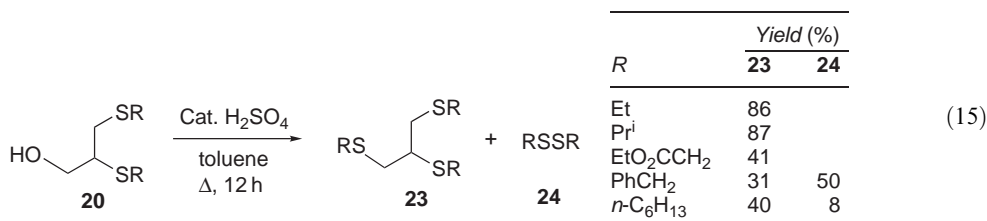
ADDP = 1,1'-(azidocarbonyl)dipiperidine; ImH = imidazole

R¹ = CH₂=CH, R² = Bn; R¹ = Et, R² = HC≡

The general synthesis of allylic sulfides in yield of 70–97% has been achieved using ruthenium-catalyzed allylation of thiols under mild conditions (Equation (14)) <1999JA8657>. This method was also applied to the synthesis of sulfides from thiols and allylic carboxylic esters (Section 2.03.2.1.10).



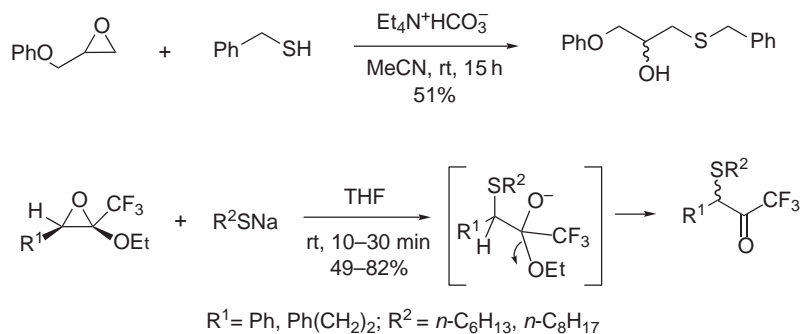
Rearrangement of the sulfide **20**, a carrier of the hydroxy and sulfur functions in the same molecule, occurs under acidic conditions to yield the tris-sulfide **23** and disulfide **24** (Equation (15) and Scheme 41) <1996JOC8244>. The proposed mechanism for sulfide **23** formation includes initial protonation of either (i) oxygen followed by elimination of water (pathway *a*), or (ii) sulfur followed by elimination of thiol (pathway *b*) (Scheme 43).



Scheme 43

2.03.2.1.6 Formation from epoxides

Ring opening of epoxides by thiols is a widely used reaction for synthesis of β -hydroxy thio derivatives. The most common protocols employ opening of the epoxide with thiol in the presence of an acid or a base. The use of metal catalysis allows the enantioselective control induced by optically pure ligands [<1995COFGT\(2\)113>](#). Recently, a variety of reactions of epoxides with thiols in the presence of base or with thiolates have been reported ([Scheme 44](#)) [<1995JCS\(P1\)1913](#), [1996S529](#), [1996SC89](#), [1996TA1797](#), [1997CL15](#), [1997JCS\(P1\)593](#), [1997T4857](#), [1999SC2611](#), [1999TL7015](#), [2000EJO2991](#), [2002CL906](#)>.

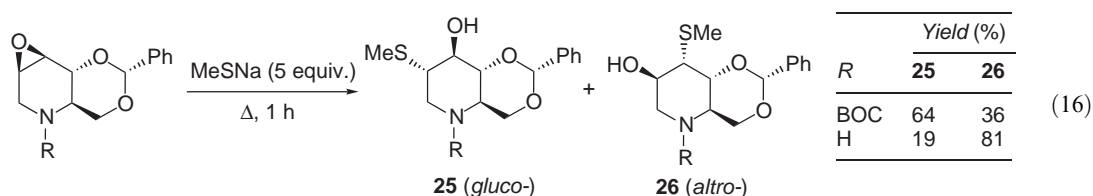


Scheme 44

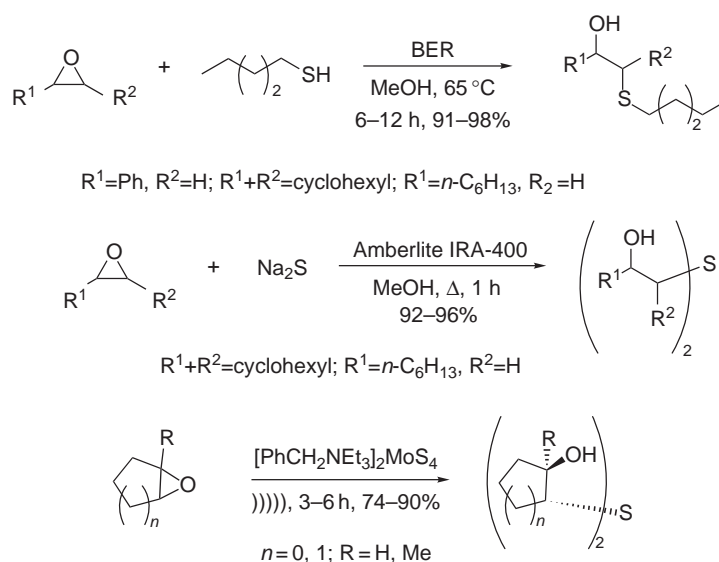
The ring opening of epoxides by thiols under neutral and environmentally friendly conditions has been reported for a one-pot synthesis of β -hydroxy sulfoxides [<2000TL2895>](#) (cf. [Section 2.03.2.2.1.\(i\)](#)).

The desymmetrization of meso epoxides via nucleophilic ring opening is a powerful strategy for establishing two contiguous centers in a single event. Recently, Shibasaki and co-workers achieved an important breakthrough in thiol addition to meso epoxides through the use of a gallium–lithium heterobimetallic binaphthoxide system. Using 10 mol. % of the catalyst and 4 Å molecular sieves, this system was found to effect the addition of *t*-butyl thiol to cyclic and acyclic meso epoxides in enantiomeric excesses of 82–98% [<1997JA4783>](#).

Through the use of a bifunctional thiol, good levels of enantiomeric purity (ca. 85%) are attainable in the chiral (salen)Cr-catalyzed ring opening of cyclopentene oxide and related meso epoxides [<1998JOC5252>](#). The regioselectivity of the stereochemical ring opening of an epoxide can be influenced by the substituents ([Equation \(16\)](#)) [<1995MI843>](#).

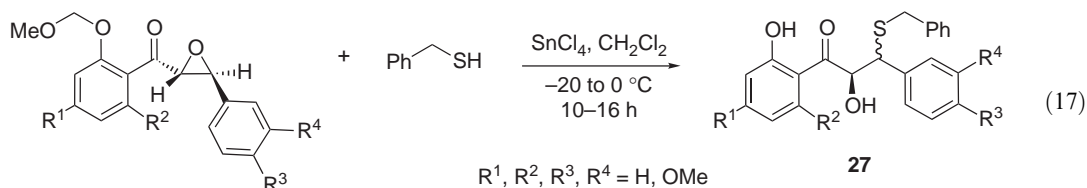


Synthesis of unsymmetrical sulfides from epoxides using BER (cf. [Section 2.03.2.1.2](#)) takes place in excellent yield [<1996MI\(2\)73>](#). Symmetrical sulfides can be prepared from epoxides and a metal sulfide in the presence of an anion exchange resin [<1995MI189>](#) or as a single regioisomer under sonication [<2002JOC9417>](#) ([Scheme 45](#)).



Scheme 45

Protic acid-catalyzed ring opening of epoxides by thiols typically proceeds in moderate yields [<1996CC2747, 1999JCS\(P1\)149>](#). Lewis acid-catalyzed selective ring opening of epoxides has been applied to the synthesis of dihydrochalcones **27** as diastereomeric mixtures (*syn:anti* ca. 2.3:1) with simultaneous removal of an MOM group in 86–93% yield ([Equation \(17\)](#)) [<1997T14141>](#).



The replacement of the oxygen of an epoxide by sulfur gives an episulfide. Reagents and catalysts for this transformation have been extensively explored, as illustrated by the synthesis of cyclohexene episulfide ([Equation \(18\)](#)).



Reagent	Catalyst	Yield (%)	References
KSCN	InBr ₃	87	<2003SL396>
	LiBF ₄	94	<2002JCR(S)176>
	Fe(OTf) ₃	93	<2000BCJ675>
NH ₄ SCN	SbCl ₃	98	<1999JCB605>
	BiCl ₃	98	<1998SC3943>
	P ₄ VP-Ce(OTf) ₄	92	<1999SC3313>
	TiO(TFA) ₃	95	<1998SC3913>
H ₂ NC(S)NH ₂	(NH ₄) ₈ [CeWO ₃₆]·20H ₂ O	96	<2002SC621>
	Montmorillonite K-10	98	<2000JCR(S)122>
	Sn ^{IV} (TPP)(ClO ₄) ₂	93	<1999SC2079>

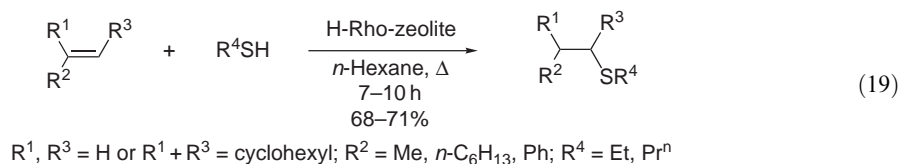
(18)

The reaction of epoxides with triphenylphosphine sulfide in the presence of TFA results in moderate yields of thiiranes <1995JCR(S)102, 1995SC2665, 2000JCS(P1)153>.

2.03.2.1.7 Formation from alkenes

The direct formation of sulfides from alkenes proceeds by addition of inorganic sulfur, hydrogen sulfide, or thiols <1995COFGT(2)113>. In general, Brønsted or Lewis acid-catalyzed addition of thiols across double bonds is known to give thioethers in accordance with the Markovnikov's rule. In the presence of a free radical initiator or on irradiation, thiols have been reported to add to double bonds in *anti*-Markovnikov fashion via a free radical mechanism <1996JCS(P1)921>. The use of hydroboration reagents, developed for this reaction, also results in *anti*-Markovnikov products <1995COFGT(2)113>.

A variety of alkenes react with thiols in the presence of a catalytic amount of H-Rho-zeolite to give *anti*-Markovnikov products which alternatively can be obtained in the presence of a peroxide as a free radical initiator (Equation (19)). Perhaps due to steric constraints, the Markovnikov adduct may not be retained in the zeolite pore, and for this reason only the *anti*-Markovnikov product is isolated <1999SL1921>.



In an interesting example, the reaction of β -alkylthiopropionyl tetrafluoroborates with alkenes in methylene chloride at -40°C (1 h) produced the intermediate cyclic sulfonium salts followed by the cleavage to the Markovnikov products in good yields <1995TL6317>.

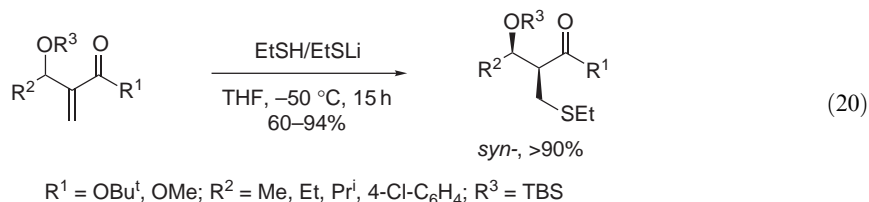
It has been demonstrated that an organic disulfide can add to an unactivated double bond on catalysis with a transition-metal complex. Thus, treatment of dialkyl disulfides with 2-norbornene in the presence of 4 mol.% of Cp**Ru*Cl(COD) in toluene at 100°C (8 h) under argon gave the *vic*-dithioethers in high yield and high stereoselectivity (*exo* 100%) <1999JA482>.

2.03.2.1.8 Formation from electron-deficient alkenes

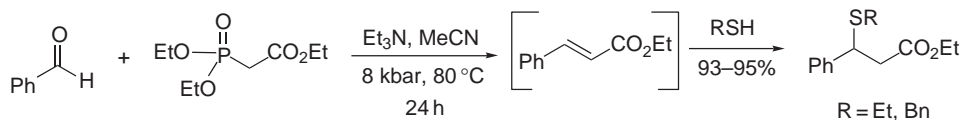
The addition of sulfur nucleophiles to electron-deficient alkenes is a reasonably facile and high yielding transformation compared to formation of sulfides from unactivated alkenes. The Michael addition of thiols to α,β -unsaturated carbonyl compounds is the most frequently used approach <1995COFGT(2)113>. This fundamental reaction was continuously explored during the 1990s. Thiols add to α,β -unsaturated compounds in the presence of a suitable metal salt or a Lewis acid catalyst, or under basic conditions. Enantioselectivity can be controlled using a chiral catalyst. On investigation of a novel tandem asymmetric Michael addition–Meerwein–Pondorf–Verley reduction, Node and co-workers reported that diastereoselective Michael addition of chiral complex **1**

(Scheme 2 in Section 2.03.1.1) to α,β -, and β,β -substituted α,β -unsaturated carbonyl compounds affords the sulfides in high yield and enantiomeric excess of 78–96% <2000JA1927, 2000TL3437, 2001OL3121>.

The synthesis of functionalized β -hydroxy- α -thiomethyl carbonyl compounds via Michael addition of ethanethiol to Baylis–Hillman adducts resulted in high stereoselectivity (Equation (20)) <2002TL6189>. Similarly, the addition of benzylthiol to γ -aminoalkyl-substituted α -methylene- γ -butyrolactones has been accomplished under basic conditions (Et_3N) affording a separable diastereomeric mixture of thioethers (79–80% yield) and in diastereomeric ratio of ca. 80:20 in favor of the *cis*-isomer <2002EJO899>.



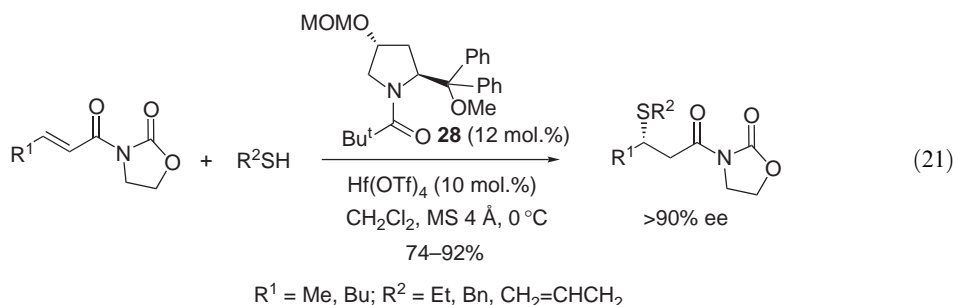
High-pressure-induced domino Horner–Wadsworth–Emmons–Michael reaction has been optimized allowing the one-pot synthesis of β -thio esters from aromatic aldehydes (Scheme 46) <2001SL1395>.



Scheme 46

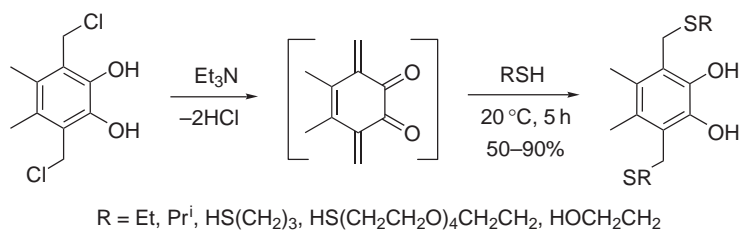
Lewis acid-mediated reaction of α,β -unsaturated carbonyl compounds, which were derived from camphor pyrazolidinone, with thiols under mild conditions provides easy access to β -mercapto adducts in yields greater than 80%. The stereoselectivity of the reaction was up to 95% de when SnCl_4 (1.5 equiv.) was used as the catalyst; the stereoselectivity was reversed on catalysis with TiCl_4 (1.5 equiv.) <2000TL6815>.

The novel chiral Lewis acid hafnium catalysts, readily prepared from $\text{Hf}(\text{OTf})_4$ and, for example, the chiral ligand **28**, have been successfully applied to the asymmetric Michael addition of thiols affording adducts in high yield and enantiomeric excess (Equation (21)) <2001SL983>.



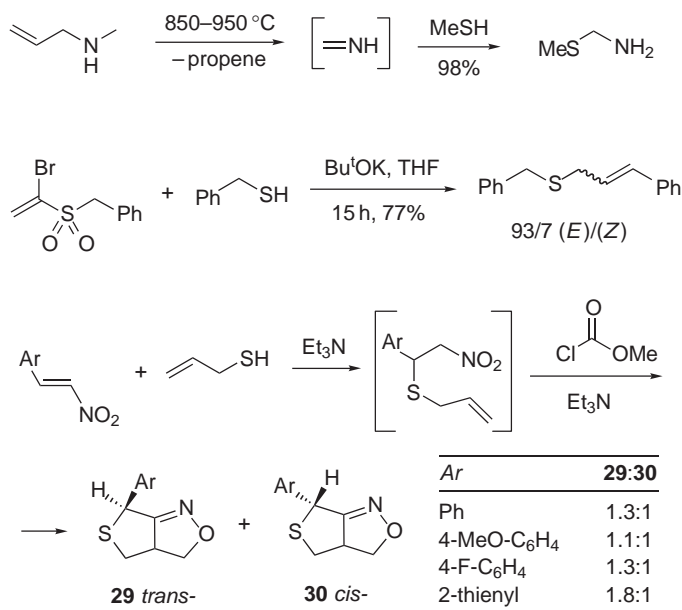
Various β -alkylthio carboxylic acid derivatives are conveniently prepared from thioacetates and α,β -unsaturated compounds, either by borohydride exchange resin Pd-catalyzed transesterification of thioacetates to the corresponding thiols or by catalysis with pyrrolidine, followed by Michael addition <1996SC2189, 1999TL1101>.

An interesting sulfide formation reaction was reported as part of a general route to functionalized catechols. This transformation includes all the components related to Section 2.03.2.1.2 (an alkyl halide, a thiol, and a base) but presumably proceeds via a dehydrochlorinated *para*-quinomethane intermediate followed by Michael addition of thiol (Scheme 47) <1998TL4235>.



Scheme 47

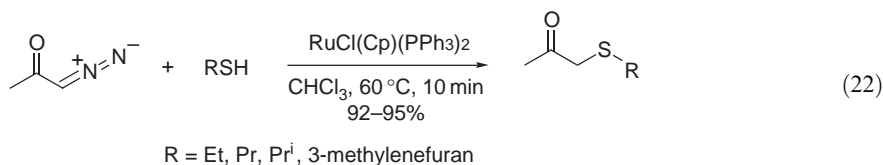
Scheme 48 illustrates some unsaturated substrates that can act as electrophiles in reactions with thiols to give sulfides <1997MI383, 1997SL1043, 1999T12493>.



Scheme 48

2.03.2.1.9 Formation from carbonyl compounds

Sulfides can be formed by direct replacement of the oxygen of a carbonyl group by reductive alkylation with a thiol, either via addition of a sulfide to a carbonyl compound yielding β -hydroxy-substituted sulfides or via α -sulfenylation of a carbonyl compound to α -keto sulfide <1995COFGT(2)113>. α -Sulfenylated carbonyl compounds are important building blocks and practical procedures for stereoselective C—S bond formation in the position α to the carbonyl group are well established. Enantioselective synthesis of α -sulfenylated ketones and aldehydes via α -thiolation of the corresponding hydrazones in very high diastereomeric excess has been reported <1998T10239>. α -Sulfenylation can be performed through α -diazo carbonyl insertion reactions into S—H bonds catalyzed by ruthenium or scandium complexes (Equation (22)) <1997JCS(P1)2455, 1999JCS(P1)3079, 1999TL5255>.

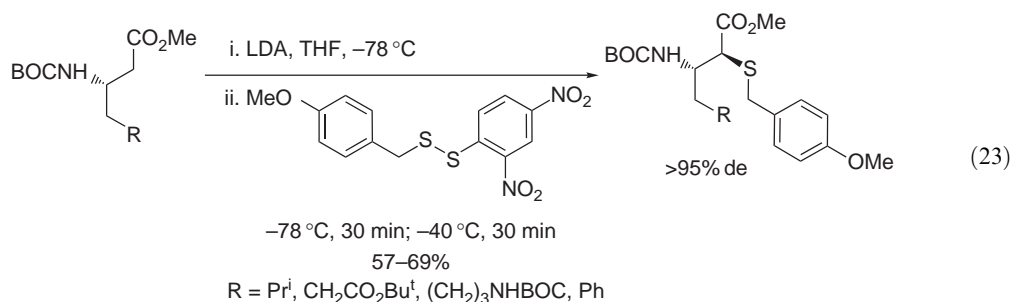


(22)

Synthesis of β -hydroxy- α -methylthio esters in good-to-high yield and with high diastereo- and enantioselectivity has been achieved using the asymmetric aldol reaction of aldehydes and ketene silyl thioacetals [<2001TL6303>](#).

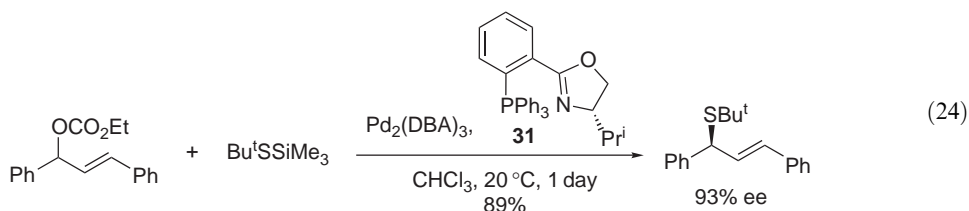
2.03.2.1.10 Formation from carboxyl compounds

Like other carbonyl compounds, carboxyl derivatives are susceptible to α -deprotonation followed by reaction with a disulfide to afford a sulfide [<1995COFGT\(2\)113>](#). This approach has been applied to the synthesis of α -thioalkyl-substituted succinate-base hydroxamic acids and α -phenylsulfanyl alkyl sulfones in good-to-high yields [<1996SC3485, 1999JMC4890>](#). *S*-Arylmethyl benzyl thiosulfonates and *S*-methyl methanethiosulfonates have been reported as convenient α -sulfenylation reagents for carboxylic esters in the presence of $\text{LiN}(\text{TMS})_2$ [<1996T12839>](#) or under phase-transfer conditions [<1997S420>](#). *N*-Protected β -amino esters are selectively α -thiolated using an unsymmetrical disulfide (Equation (23)) [<1997JOC4848>](#).



The sulfenylation–decarboxylation of α -phenylsulfonfylalkyl acetic acids has been reported in moderate yields as an alternative method of synthesis of α -methylthioalkyl phenyl sulfones [<1996SC3485>](#).

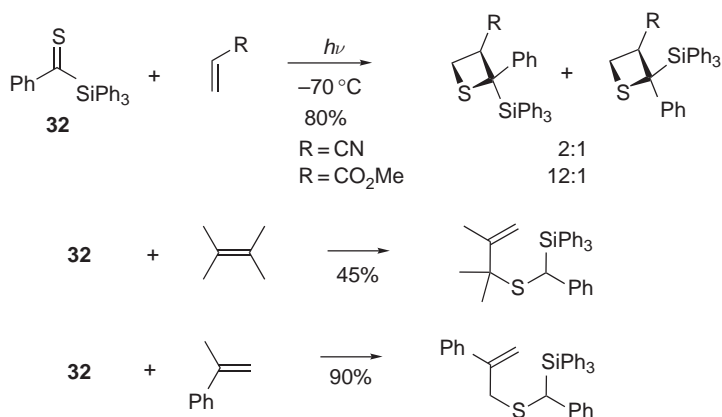
The direct displacement of the carboxylic ester function by a sulfur nucleophile gives a sulfide. For example, the ruthenium-catalyzed reaction of allylic carboxylic esters and thiols affords sulfides in good yield [<1999JA8657>](#) (cf. Section 2.03.2.1.5). The chiral ligand **31** mediated the highly enantioselective formation of the allylic sulfide (Equation (24)) [<1998TA235>](#).



A rare C—C bond replacement by a C—S bond occurred upon irradiation of a mixture of bis(cyclohexylcarboxy)iodobenzene and didodecyl disulfide in methylene chloride at ambient temperature affording 1-cyclohexyldodecyl sulfide [<1995S155>](#).

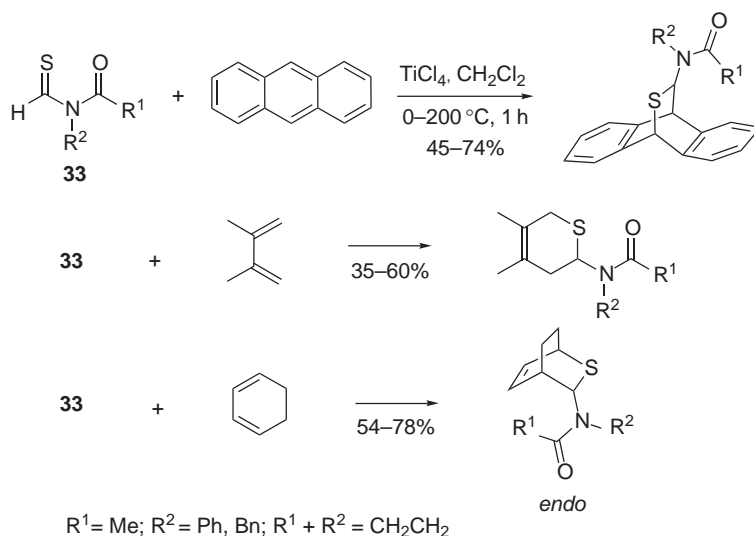
2.03.2.1.11 Formation from thiocarbonyl compounds

Thioketones and thioaldehydes are highly reactive compounds and are generally used as intermediates in the synthesis of sulfides via cycloaddition reactions [<1995COFGT\(2\)113>](#). Thioaldehydes, especially those bearing an electron-withdrawing group, make good dienophiles in the Diels–Alder reaction. This is not the case for the thiocarbonyl compounds bearing strong electron-donating groups, e.g., thioamides. Photo-induced cycloadditions of the readily available and stable thioketone **32** with electron-deficient alkenes gives thietanes in a regio- and highly stereoselective manner, whereas electron-rich alkenes produced ring-opened sulfides (Scheme 49) [<1995JCS\(P1\)2039>](#).



Scheme 49

The first normal electronic demand Diels–Alder reactions of *N*-substituted thioformamides **33** in moderate to good yields has been reported (Scheme 50). The appropriate choice of the nitrogen substituents has been rationalized by an *ab initio* study <1995CC1897>. More detailed coverage of compounds containing tetra-coordinated C with two attached heteroatoms is presented in Volume 4.

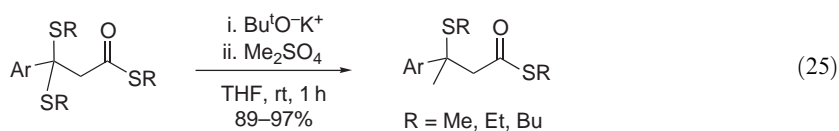


Scheme 50

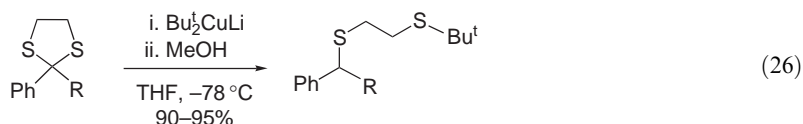
2.03.2.1.12 Formation from thioacetals

Thioacetals are among the most important and popular protecting groups for carbonyl functions. The C—S bond is known to be ambiphilic toward nucleophiles, because the electronegativities of C and S are similar. Accordingly, different reagents or conditions may alter the selectivity of the reaction. Thus, (i) treatment of thioacetals with organolithium reagents leads to the corresponding carbanions; (ii) one C—S bond of a dithioacetal can be selectively cleaved under free radical conditions; and (iii) displacement of one thioalkyl group can be performed with Lewis acid catalysis <1995COFGT(2)113>.

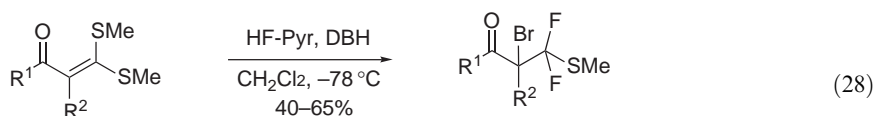
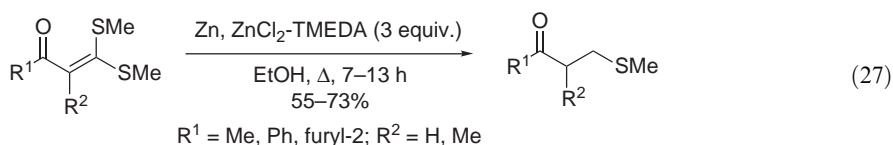
A recent example of carbanion formation illustrates a practical approach to multifunctional sulfides (Equation (25)) <2002S921>.



The first application of a ring opening of dithiolanes by an organocopper reagent is reported (Equation (26)) <1997JOC4568>.



The low-valent titanium iodide reduction of dithioacetals, derived from aromatic aldehydes, afforded the coupling products as *dl*- and *meso*-isomeric mixtures of *vicinal* bis(alkylthio) derivatives in good-to-high yields <2001CL640>. Partial reduction of dithioacetals to the sulfides can be effected in good yield by SmI_2 in benzene-HMPA in the presence of either Bu^tOH or AcOH <1998CPB187>. α -Oxoketene dithioacetals serve as excellent models for regio-, stereo-, and chemoselective reduction and C—C bond formation reactions, as illustrated by controlled conjugate reduction with zinc reagents (Equation (27)) <1996T4679>. Similarly, ketene dithioacetals have been used in the regioselective synthesis of halogenated sulfides (Equation (28)) <1998TL9651>.

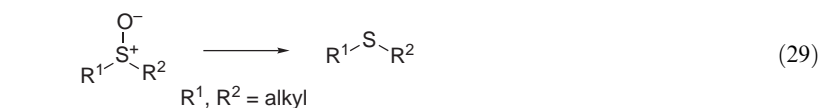


DBH = 1,3-dibromo-5,5-dimethylhydantoin; R^1 = alkyl, Ar; R^2 = Me, Et

Another approach to halogenated sulfides involves the oxidative desulfurization–fluorination of ortho-thioethers $[\text{RCH}_2\text{C}(\text{SMe})_3]$ using tetrabutylammonium dihydrogentrifluoride [$n\text{-Bu}_4\text{NH}_2\text{F}_3$] and 1,3-dibromo-5,5-dimethylhydantoin (DBH) to afford $\text{RCHBrCF}_2\text{SMe}$ in good yield <1996TL7983>.

2.03.2.1.13 Formation from sulfoxides

Sulfoxide reduction is frequently employed in natural product syntheses that require mild conditions, selectivity and functional group tolerance. The straightforward reduction of sulfoxides to sulfides with various reducing agents was surveyed in COFGT (1995) <1995COFGT(2)113>. The need for convenient and inexpensive reagents continues to stimulate the development of new methods, and Equation (29) summarizes the application of new reducing agents. Mild conditions and typically good-to-high yield are the major attributes of these new procedures.

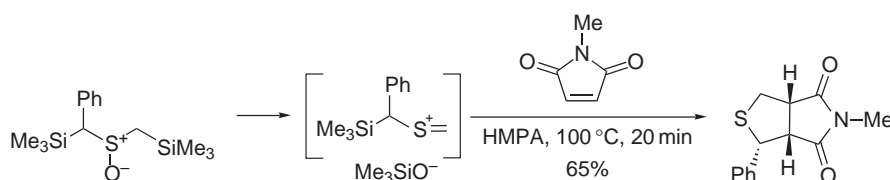


Reagent	Yield (%)	References
SmBr ₂	95–98	<1995MI699>
[ThxBHOBu ^s] ^a	100	<1998OPP63>
WCl ₃ (Nal or Zn)	89–90	<1999S500>
ReOCl ₃ (PPh ₃) ₂	84–95	<1996TL7941>
TiI ₄	84–86	<2000SL1437>
Sm ^b	75–90	<2001SL854>
KI, <i>p</i> -TosH ^c	67–81	<1996SC3619>
2,6-dihoxypyridine	66–98	<2000TL3781>

^a Thx=2,3-dimethyl-2-butyl. ^b Under sonication.

^c In the solid state.

The synthesis of sulfides from sulfoxides by Pummerer rearrangement, which is well known as a useful reaction for the formation of an α -acyl sulfide, was surveyed earlier in COFGT (1995) <1995COFGT(2)113>. An example of the sila-Pummerer rearrangement, which was employed in a novel generation of thiocarbonyl ylides, is shown in Scheme 51 <1995H(40)249>.



Scheme 51

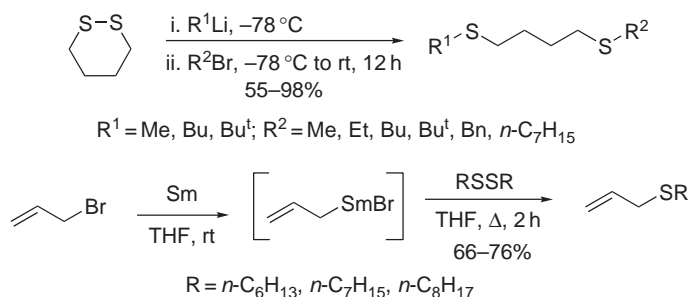
The use of *t*-butyl substituted sulfoxides as sulfenilating agents in reactions with alkenes in the presence of TFA and TFAA resulted in β -trifluoroacetoxythioethers in good yield <1997T15717>.

2.03.2.1.14 Formation from sulfones

Sulfide formation by reduction of a sulfone is often an unfavorable process as the C—S bond cleavage readily occurs. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.2.1.15 Formation from disulfides

The formal expulsion of one sulfur atom from a disulfide with sulfide formation received limited coverage in COFGT (1995) <1995COFGT(2)113>. The direct desulfurization of disulfides has been reported under mild condition in the presence of nonionic superbases P(MeNCH₂CH₂)₃N to afford dialkyl sulfides in moderate-to-good yield <1999HAC544>. An efficient procedure for the preparation of various sulfides has been developed through a simple reaction of a disulfide with a suitable alkyl halide. The reaction is promoted by a reducing agent, e.g., Zn, in the presence of AlCl₃ in aqueous media <2002SC1237> or by titanium chloride derived from Cp₂TiCl₂, and BuⁱMgBr in THF <1999SC1297>. Alkylmagnesium of unactivated alkenes is catalyzed with CpCp*ZrCl₂, and subsequent reaction with disulfides results in asymmetry in the sulfide products in enantiomeric excesses of 30–61% <1998T14617>. Unsymmetrical coupling of disulfides with organometallic compounds is illustrated in Scheme 52 <1995JCS(P1)2381, 1997SC2743, 2001JIC263>.



Scheme 52

Langlois and co-workers have developed the nucleophilic trifluoromethylation of disulfides with trifluoromethane and silicon-containing bases to give trifluoromethyl alkyl sulfides in moderate-to-good yields <2000JOC8848, 2001TL2473>.

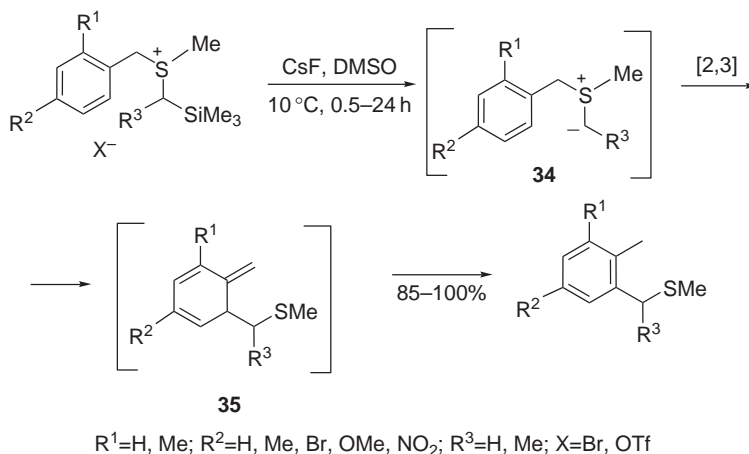
The generation of sulfonium cations $[\text{RS}^+]$ by electrochemical oxidation of a disulfide in the electrophilic substitution of α -alkyl ketones to give α -alkyl sulfanyl ketones has been reported <1998TL4657>.

2.03.2.1.16 Formation from thiol esters

The reduction of thiol esters to sulfides was exemplified in COFGT (1995) <1995COFGT(2)113> and no further advances have occurred in this area.

2.03.2.1.17 Formation from sulfonium salts

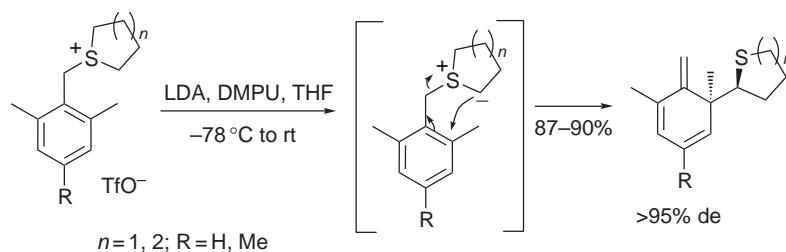
The reduction of sulfonium salts or sigmatropic rearrangements of unsaturated sulfonium ylides are known to produce sulfides <1995COFGT(2)113>. A [2,3]-sigmatropic benzyl migration of the *S*-alkyl ylides **34** to the intermediates **35** followed by conversion into the products of Sommelet–Hauser rearrangement (Scheme 53) has been described <1995JCS(P1)431>.



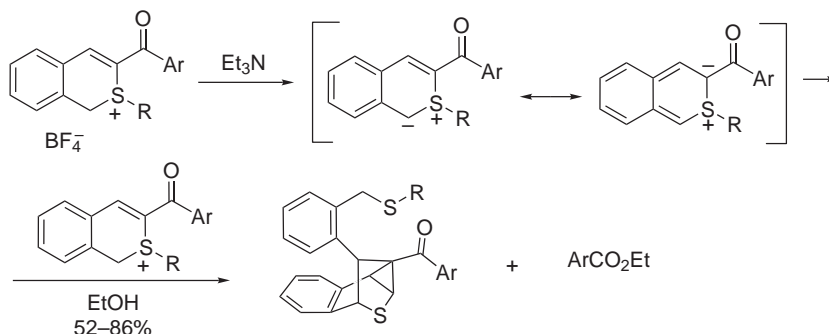
Scheme 53

Similarly, the thia-Sommelet dearomatization of sulfonium ylides produced stable hexatrienes with quaternary stereogenic centers in excellent yield (Scheme 54) <1998JA841>.

2-Thiochromenium tetrafluoroborates give products with a cyclic and an acyclic sulfide in the same molecule through a novel intermolecular cycloaddition (Scheme 55) <1996CC1659>.



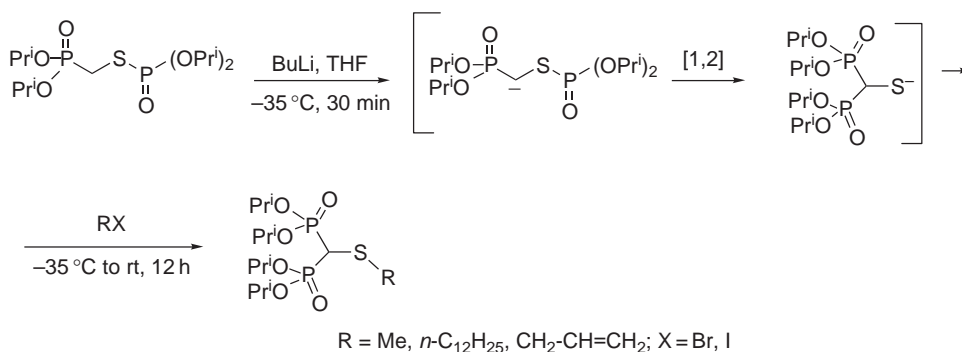
Scheme 54



Scheme 55

2.03.2.1.18 Formation from α -sulfenyl anions

Deprotonation α to a single S requires a strong base; further functionalization of sulfides by C or heteroatom electrophiles occurs [<1995COFGT\(2\)113>](#). An example of α -alkylation of ethylthio-methyl acetate with methallyl bromide in the presence of LDA has been reported (68% yield) [<2001JOC7270>](#). Preparations of α -alkylated sulfides by direct deprotonation with Bu^tLi or Bu^tOK in THF at $-40^\circ C$ has been developed for thiolane and thiane and their reactions with Sn- and Si-containing electrophiles and benzaldehyde; alkyl methyl sulfides were regioselectively deprotonated at the methyl group [<1997TL8615>](#). Recently, the first phosphothiolate-mercaptophosphonate [1,2]-sigmatropic rearrangement was reported via α -deprotonation of a phosphorothiolate (Scheme 56) [<1998T1523>](#).



Scheme 56

2.03.2.1.19 Miscellaneous reactions

Indium- and samarium-catalyzed alkylation of sodium alkyl thiosulfates to sulfides has been developed by Zhang and co-workers <1998JCR(S)130, 1998JCR(S)148, 1998SC493>.

In a reaction similar to that of epoxides with thiols (Section 2.03.2.1.6), nucleophilic ring opening of aziridines yields α -thioalkyl- β -amino-substituted compounds. This approach was used in the asymmetric synthesis of α -functionalized β -amino acids <1995JOC790, 2001SL679>. The nucleophilic ring opening of 2-aryl-3-oxetanols by alkyl thiolates occurs at the less substituted C-4 position affording the diastereometrically pure 3-sulfanyl-1,2-diols in excellent yield <1998EJO2161>. Nucleophilic reactions of cyclic sulfates are known to be superior to their epoxide counterparts. Cyclic sulfates of *vicinal* diols on treatment with KSAc followed by MeONa are transformed in one pot into sugar episulfides in 55–91% yield <1995CC461>.

The addition of trityl thionitrile to unactivated or electron-deficient alkenes by a free radical chain reaction offers a highly regiospecific route to functionalized α -tritylthio oximes in moderate-to-good yield <2001TL4377>.

2.03.2.2 Dialkyl Sulfoxides

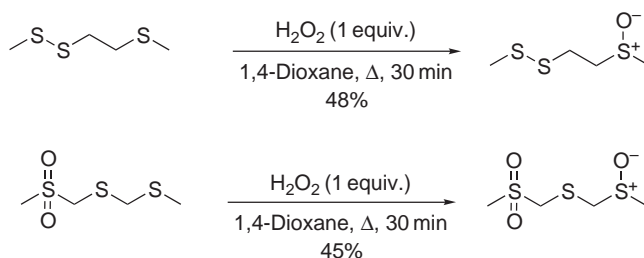
The search for efficient general methods to prepare chiral sulfoxides has been a matter of great interest. Excluding resolution, asymmetric oxidation of sulfides and nucleophilic substitution on chiral sulfur derivatives are the two main methodologies <B-2000MI005>.

2.03.2.2.1 Oxidation of sulfides

The selective oxidation of sulfides to sulfoxides without formation of sulfones requires highly selective methods, whereas complete oxidation to a sulfone can be achieved much more easily. This area is well investigated with regard to oxidizing agents, control of reaction conditions, application of catalysts, and stereoselectivity of oxidation <B-1994MI001, B-1995MI002, B-2000MI005>.

(i) Hydrogen peroxide

The use of hydrogen peroxide without a catalyst under mild conditions results in regiospecific mono-oxidation of multifunctional sulfides to sulfoxides in moderate yields (Scheme 57) <1997AJC683, 1999AJC167>.



Scheme 57

The one-pot synthesis of β -hydroxy sulfoxides from epoxides has been developed into an environmentally friendly methodology using hexafluoroisopropanol as a solvent. The reaction proceeds via ring opening of an epoxide with benzyl thiol followed by oxidation *in situ* with H_2O_2 to give *trans*- β -sulfoxides with moderate diastereoselectivity <2000TL2895>.

(ii) *Hydrogen peroxide and a catalyst*

The selective sulfoxidation of a sulfide by hydrogen peroxide is often carried out with a catalyst. The oxidizing species is usually a peracid derivative of the catalyst <1995COFGT(2)113>. The selective methyltrioxorhenium (MTO)-catalyzed oxidation of sulfides to sulfoxides or sulfones by hydrogen peroxide has been achieved under mild conditions (in ethanol at rt for 1–3 h) and in high yields; the sulfur is selectively oxidized in the presence of other oxidatively sensitive groups <1996BCJ2955>. Rhenium(V) oxo phosphine complexes and MTO have been used as catalysts for chemoselective oxidation of dialkyl sulfides to sulfoxides using commercially available urea-hydrogen peroxide (UHP) complex in acetonitrile at room temperature and sulfone formation was not observed <1998TL5655>. The high-yielding, selective and environmentally benign oxidation of dialkyl sulfides to sulfoxides with UHP is catalyzed by Ti-beta zeolite in acetone at 20 °C <1997CC471>.

An effective sulfide to sulfoxide oxidation procedure with H₂O₂, Ac₂O, and SiO₂ in CH₂Cl₂ avoids overoxidation and represents a simple and inexpensive preparation of glycosyl and non-carbohydrate sulfoxides in high yields <1996JOC8347>.

Mild and efficient flavin-catalyzed hydrogen peroxide oxidation was reported earlier <1995COFGT(2)113>. The kinetics of different flavin catalysts was studied for the flavin/H₂O₂ system which was used in a simple oxidation of thioethers to sulfoxides with short reaction time and quantitative yield <2001CEJ297>.

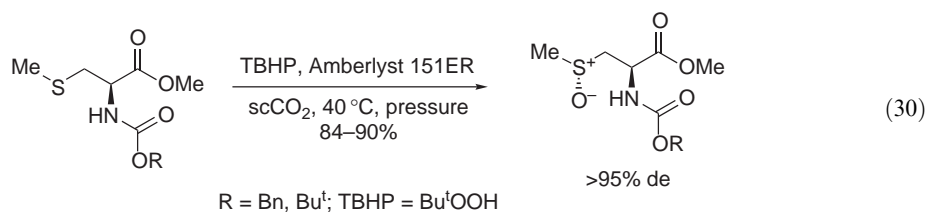
Hydrogen peroxide in conjunction with enantiomerically pure camphor-based sulfonylimines has been used in the catalytic enantioselective oxidation of a range of dialkyl sulfides to sulfoxides under basic conditions in high yield and enantioselectivities (ca. 98%) <1995SL773, 1995TA2911>.

(iii) *Organic peroxides and hydroperoxides*

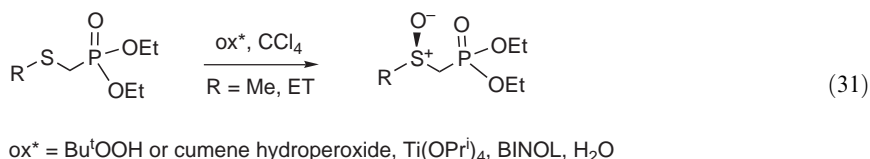
Organic hydroperoxides possess a higher oxidative strength in comparison to hydrogen peroxide <1995COFGT(2)113>. In turn, specific catalysts influence the yield and/or selectivity of oxidation. It was reported that silica gel mediates the reactivity of Bu^tOOH in the environmentally benign oxidation of dibutyl sulfide to the corresponding sulfoxide (1 equiv. of oxidant) or to sulfone (2 equiv. of oxidant) at room temperature in high yield <1995TL3825>.

Asymmetric oxidation of sulfides has become a useful method of preparation of optically active sulfoxides. The most straightforward procedures involve the use of commercially available enantiopure reagents as chiral auxiliaries although not all attempts succeed. For example, (3*S*,4*S*)-Bu^tCH(OH)CH(OH)Bu^t and Ti(OPrⁱ)₄ catalyzed the oxidation of aryl alkyl sulfides to sulfoxides by cumyl hydroperoxide in good-to-high enantioselectivities, whereas dialkyl sulfides gave racemic sulfoxides <1997JOC8560>. Nonracemic dialkyl sulfoxides are accessible through a modified Sharpless kinetic resolution of racemic sulfoxides, and a successful improvement of enantiomeric excess has been achieved <1997TA2473, 1998TA1817>.

A new method for oxidation of sulfides by *t*-butyl hydroperoxide and a resin catalyst in supercritical carbon dioxide (scCO₂) provides high yields and excellent selectivity for sulfoxide formation (Equation (30)) <1999CC247>.



The enantioselective oxidation of commercially available (alkylthio)methylphosphonates by hydroperoxides in the presence of catalytic amounts of complex formed *in situ* from Ti(OPrⁱ)₄, (+)-1,1'-bi-2-naphthol (BINOL) and water gave enantiomeric excesses greater than 98% (Equation (31)) <1999JA4708>.



Furyl hydroperoxides have been employed in the enantioselective oxidation of dialkyl sulfides to sulfoxides under Sharpless-type conditions although in moderate enantiomeric excess <1997TA2141>.

(iv) Peracids

The oxidation of sulfides to sulfoxides by peracids, which possess greater oxidizing power than hydrogen peroxide, is known to proceed at low temperatures and requires strictly equivalent amounts of the reagents <1995COFGT(2)113>. MCPBA is frequently used for the oxidation of sulfides to sulfoxides in low-to-moderate yield <1996TL3223, 1997JOC2432, 2000JMC3304>. Moist magnesium monoperoxyphthalate (MMPP) on alumina <1999OL903> and MMPP on silica gel in methylene chloride <1997S764> (cf. Section 2.03.2.3.1.(i)) are convenient alternatives to MCPBA.

(v) Halogens and halogen compounds

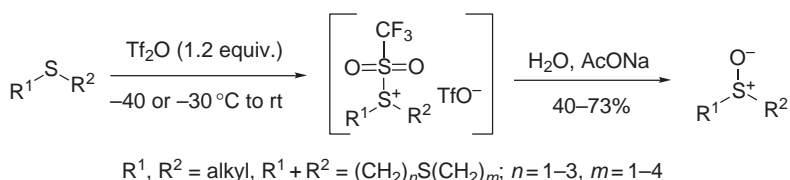
Halogens are known to act as selective oxidants. Some competing reactions such as halogenation and C—S bond cleavage can accompany the oxidation of sulfides to sulfoxides <1995COFGT(2)113>. Dialkyl sulfides give sulfoxides with good selectivity upon bromine-catalyzed oxidation with hydrogen peroxide, or using a stoichiometric amount of bromine in a two-phase system; this oxidation appears to be general with primary, secondary, and tertiary alkyl groups affording sulfoxides in high yields <2001JOC3232>. 4,4-Dibromo-3-methylpyrazole-5-one has been reported to be an electrophilic bromine carrier which neatly transforms dialkyl sulfides into sulfoxides in the presence of AcOH and AcONa at room temperature (79–92% yield) without contamination by sulfones <1997TL4865>.

Sodium periodate continues to be one of the most common reagents for the oxidation of sulfides to sulfoxides and sulfones under mild conditions (methanol–water solution, ambient temperature) and typically in high yield <2002JOC5928>. Wet silica-supported sodium periodate (20% NaIO₄–silica, 1.7 equiv.) was applied to the selective oxidation of symmetrical and unsymmetrical sulfides to sulfoxides by microwave thermolysis (30–150 s) (76–83% yield). The use of 20% NaIO₄–silica (3 equiv.) under the same conditions yielded sulfones in a clean reaction <1997TL6525>.

Tetrabutylammonium periodate effectively oxidizes sulfides to sulfoxides in the presence of AlCl₃ in hot acetonitrile. No over-oxidized products were detected, whereas oxidation in the absence of a Lewis acid produced mixtures of sulfoxides and sulfones <1996BCJ685>.

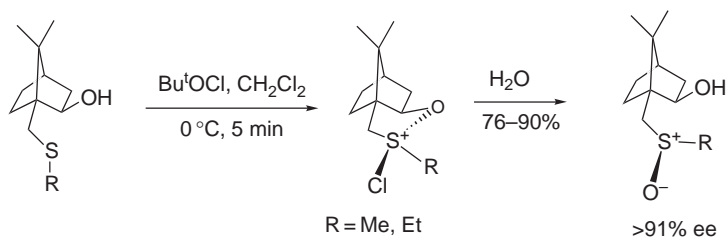
Mild, selective and high-yielding oxidation of sulfides to sulfoxides using *o*-iodobenzoic acid and tetrabutylammonium bromide is compatible with a wide range of functional groups <2003JOC5422>.

A new application of triflic anhydride was found in a selective oxidation of sulfides to sulfoxides (Scheme 58) <1997JOC2483, 2000RCB1415>.



Scheme 58

The oxidation of sulfides by chlorine dioxide has been optimized to achieve the best results with a sulfide-ClO₂ ratio of 2:1 in methylene chloride at room temperature but high yields of sulfoxides are overshadowed by contamination from sulfones <2001RCB432>. *t*-Butyl hypochlorite achieves a highly diastereoselective oxidation of a sulfide to an optically pure sulfoxide via an intermediate alkoxychlorosulfuranes (Scheme 59) <1997H(44)325>.



Scheme 59

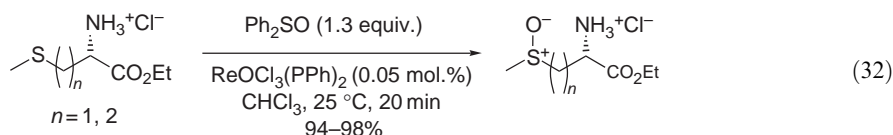
(vi) Nitrogeous compounds

In addition to the previously reviewed applications of ferric nitrate <1995COFGT(2)113>, new procedures have been developed. Oxidation of sulfides to sulfoxides with Fe(NO₃)₃ and silica gel in hexane at 60 °C (1–5 h) affords the dialkyl sulfoxides (72–90% yield) and no evidence of sulfones <1996OPP705>. Fe(NO₃)₃ on clayfen selectively oxidizes dialkyl sulfides on microwave thermolysis under solvent-free conditions producing sulfoxides in high yield <1998SC4087>. Dinitrogen tetroxide and Fe(NO₃)₃ complex was found to be an efficient and selective oxidant of dialkyl and alkyl aryl sulfides to sulfoxides; this reaction proceeds rapidly, sometimes within seconds, affording sulfoxides without overoxidation and in excellent yields <1998SC377>. Bi(NO₃)₃·5H₂O readily effects selective oxidation of sulfides to sulfoxides in good yield in acetic acid at ambient temperature <1998SC939>.

(vii) Other chemical oxidants

An efficient and selective oxidation of sulfides to sulfoxides by air or molecular oxygen is catalyzed by the binary system Fe(NO₃)₃–FeBr₃ and has been applied to multiple types of dialkyl and alkyl aryl sulfides under mild conditions, giving a high yield of sulfoxides in the presence of different functional groups <2001TL7147>. The palladium complex [Pd(PBu₃H)(μ-PBu₃)₂] on exposure to oxygen in THF generates a catalytic system for the selective oxidation of sulfides to sulfoxides (50–83% yield) <1995JOC8365>.

Oxygen transfer from a sulfoxide oxidant provides a mild method for oxidizing sulfides. For example, the rhenium-catalyzed oxidation of sulfides by diphenyl sulfoxide avoids sulfone by-products and is compatible with other functional groups, as illustrated in Equation (32) <1996JOC2260>.



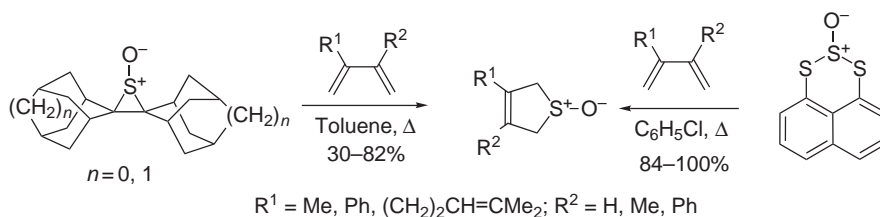
Dibenzyl sulfide and aryl alkyl sulfides are readily oxidized by a solution of pyridine, water, and trichloroisocyanuric acid in acetonitrile to give high yields of sulfoxides without sulfones <2001SC245>. A pyrazine-based polymeric complex of an oxidiperoxochromium(VI) compound has been reported as a mild and versatile oxidant for a variety of functionalities, and sulfides are converted into sulfoxides as exclusive products at room temperature in high yield <1997T7889>. Under similar conditions tetrabutylammonium peroxide selectively oxidizes dialkyl and alkyl aryl sulfides to sulfoxides in nearly quantitative yields <1996SC253>. The oxidation of the ruthenium complex of phthalimidobutyl methyl sulfide with dimethyldioxirane affords the corresponding sulfoxide complex in high yield and high diastereoselectivity <1997CEJ713>.

(viii) Enzymatic oxidation

The enantioselective oxidation of prochiral sulfides by biocatalytic methods is a versatile route for preparation of chiral sulfoxides. Studies of organic sulfide oxidation using enzymes have intensified since 1995. It is known that chloroperoxidase is a useful catalyst because it is readily available, relatively stable, and does not require a cofactor. The general enzymatic approach to the synthesis of dialkyl sulfoxides with high enantiomeric excess has been developed via oxidation of sulfides with hydrogen peroxide and catalysis by chloroperoxidase or cyclohexanone monooxygenase <1997CC439, 1999TA3219, 2002CJC633>. The use of fungi species (*Helminthosporium* and *Mortierella isabellina*) in microbial biooxidation allows the selective synthesis of the (*S*) or (*R*) configuration of the sulfoxides in high yield <1995TA1569, 1999CJC463>.

2.03.2.2.2 Addition to unsaturated compounds

In situ sulfur monoxide can be trapped by dienes and trienes to form cyclic sulfoxides. The thermal decomposition of episulfoxides is a convenient approach to sulfur monoxide and the development of this useful method has been studied by Harpp and co-workers <1995TL201, 1997T12225, 1997JOC8366> and by Grainger and co-workers <2001OL3565> (Scheme 60).



Scheme 60

The hydrohalogenation of electron-deficient 1,2-allenic sulfoxides by AlX_3 and H_2O provides a mild approach to 2-bromo- and 2-chloro sulfoxides (56–89% yield) <2000EJO1939>.

2.03.2.2.3 From sulfur-stabilized carbanions

α -Deprotonation of a dialkyl sulfoxide by a strong base (NaH or AlkLi) gives a sulfinyl-stabilized α -carbanion that reacts with electrophiles affording α -substituted sulfoxide derivatives. New applications involve such electrophiles as carbonyl compounds <1999JIC617, 2002RJOC450>, carboxylic esters <1995T4909, 1997JCS(P2)1649>, imminium salts, <2000EJO1735>, and trithiocarbonates <1999S669>.

2.03.2.2.4 By rearrangements

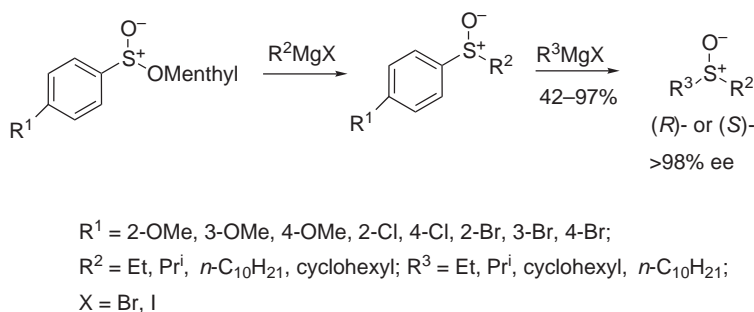
The rearrangement of allyl alkylsulfenyl esters is known to produce the allyl alkyl sulfoxides in the equilibrium process. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.2.2.5 Reduction of sulfones

As for the reduction of sulfones to sulfides (cf. Section 2.03.2.1.14), the formation of a sulfoxide from a sulfone is difficult to achieve. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

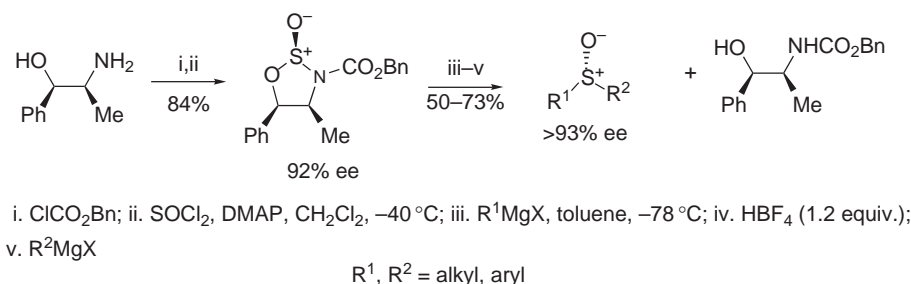
2.03.2.2.6 Sulfinyl group transfer

One of the main strategies for preparation of optically pure sulfoxides is the Andersen synthesis which involves nucleophilic substitution of chiral sulfinate esters by Grignard reagents and proceeds with inversion of configuration at sulfur <1995COFGT(2)113>. Naso and co-workers have shown that the stereospecific sequential displacement of the carbanionic leaving groups from suitable sulfinyl compounds by means of Grignard reagents represents a general and versatile route to chiral nonracemic sulfoxides (Scheme 61) <1999JA4708, 2000JOC2843, 2001JOC5933>. This reaction is associated with inversion of configuration at the final stage.



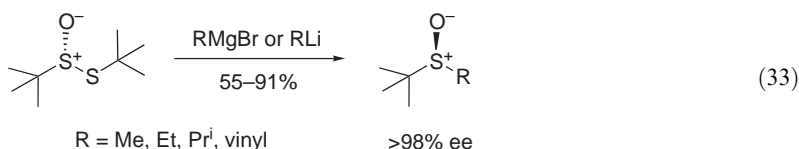
Scheme 61

Ruano and co-workers have developed a sequential one-pot reaction of norephedrine-derived *N*-benzylcarbonylsulfamidite with Grignard reagents affording the chiral sulfoxides in enantiomeric excess greater than 93% (Scheme 62) <2003OL75> (cf. Section 2.03.5.2.9.(vii), Equation (74)). The use of HBF₄ as an electrophilic additive prevents racemization of the sulfoxide.



Scheme 62

Ellman and co-workers have demonstrated that enantiomerically pure *t*-butyl thiosulfinate ester reacts with Grignard or alkyllithium reagents to provide chiral sulfoxides with inversion of configuration at sulfur in good yield (Equation (33)) <1998JA8011> (cf. Sections 2.03.7.3 and 2.03.9.2).



Diacetone D-glucose methodology developed previously <1995COFGT(2)113> has been applied to the synthesis of chiral β-keto sulfoxides <1997JOC287> and C₂-symmetric ethane 1,2-bis-sulfoxides <2000JA7598> with high stereoselectivity.

2.03.2.3 Dialkyl Sulfones

The rich chemistry of sulfones makes them very useful reagents <B-1995MI002, B-1997MI003>. Because of the extensive use of sulfur derivatives in synthetic chemistry, the search is continuing for reagents to carry out these transformations fast and efficiently.

2.03.2.3.1 By oxidation of sulfides and sulfoxides

The most widely used method for sulfone synthesis is oxidation of the corresponding sulfide and is well documented <B-1995MI002>. The presence of other functionalities on the substrate often complicates this oxidation due to the competing reactions.

(i) Oxidation of sulfides

The following requirements for the oxidation of a sulfide to a sulfone are driving the search for new procedures: (i) safe and cheap oxidizing agents and catalysts; (ii) mild and fast oxidation giving exclusively sulfones in quantitative yields; (iii) other functionalities on the substrate not oxidized; and (iv) a facile procedure and easy isolation of products. There have been several reports describing the selective oxidation of sulfides to sulfones (Scheme 63). Dialkyl sulfides are selectively oxidized to sulfones using excess UHP/TFAA <1999SC2235>. Similarly, the oxidation by hydrogen peroxide in the presence of Na₂WO₄ gives sulfones under phase-transfer conditions <1996PJC1121>. Oxidation of dialkyl sulfides by permanganate under solvent-free conditions and microwave irradiation proceeds within minutes in high yield <2001TL5833>. The use of MMPP (cf. Section 2.03.2.2.1.(iv)) represents a simple and efficient method for sulfone synthesis in the presence of other oxidatively sensitive groups such as alkenes <1998SC2983>. Similarly, sulfides are oxidized by hydrogen peroxide in the presence of MTO (cf. Section 2.03.2.2.1.(ii)) affording sulfones in excellent yield <1996BCJ2955>. A binuclear manganese complex catalyzes periodic acid oxidation of sulfides to sulfones under mild conditions; an alkene fragment on the substrate remains unchanged, but an amino group does not survive these conditions <1998TL7055>. The tolerance of an amino group on oxidation of sulfides to sulfones was reported using *p*-toluenesulfonic peracid as the oxidizing agent <1996T5773>.

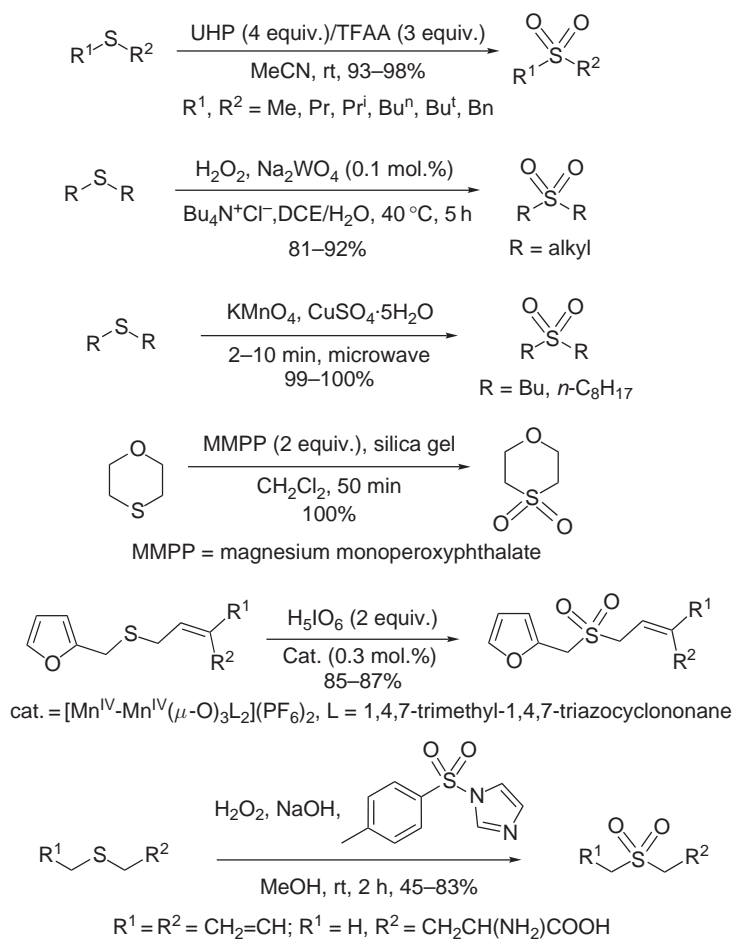
(ii) Oxidation of sulfoxides

Sulfoxides react more slowly with electrophilic oxidants because of the reduced nucleophilicity of the sulfoxide S compared to that of sulfides. Several reports describe the application of mild conditions and convenient oxidants to afford good-to-high yield of sulfones by oxidation of sulfoxides. Silica gel and alumina have been found to mediate the oxidation of dialkyl, alkyl aryl and diaryl sulfoxides by Bu^tOOH or Oxone[®] to give the corresponding sulfones in good yield <1995TL3825, 2000JA4280>. Sodium hypochlorite in acetonitrile readily oxidizes dialkyl sulfoxides at room temperature affording the sulfones in 55–98% yield <1996OPP234>. Similarly, a mixture of oxygen and gaseous chlorine dioxide is reported as an oxidizing agent <2000RJOC1819>.

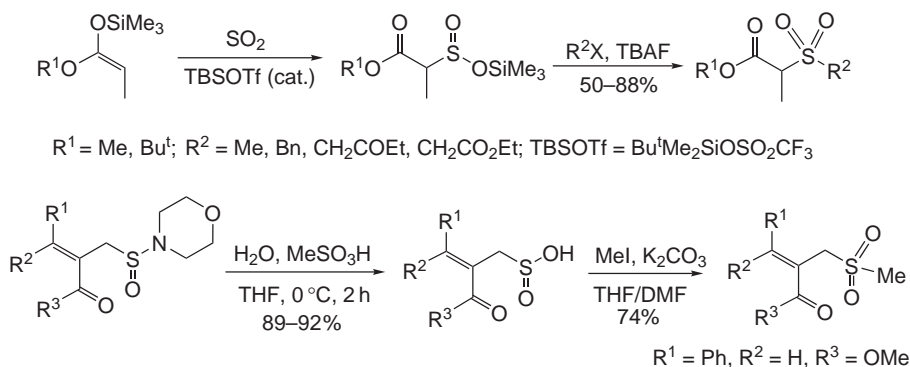
2.03.2.3.2 From sulfinic acids and their derivatives

The synthesis of sulfones via *S*-alkylation of sulfinic acids and their salts has been reviewed <B-1994MI001, 1995COFGT(2)113>. Vogel and co-workers developed a three- and four-component synthesis of open-chain polyfunctional sulfones including an asymmetric version of this transformation via alkylation of sulfinates <2000AG(E)1806, 2001JOC5080, 2002S225, 2002S232>. For example, silyl sulfinates, obtained by ene-reaction of sulfur dioxide with silyl enol ethers, react without purification with electrophiles to generate the sulfones in a one-pot

operation (Scheme 64). Alkylation of the sulfinic acids, generated, for example, from the amide, represents a facile approach to dialkyl sulfones although with some limitations (Scheme 64) <1995BSF196>.



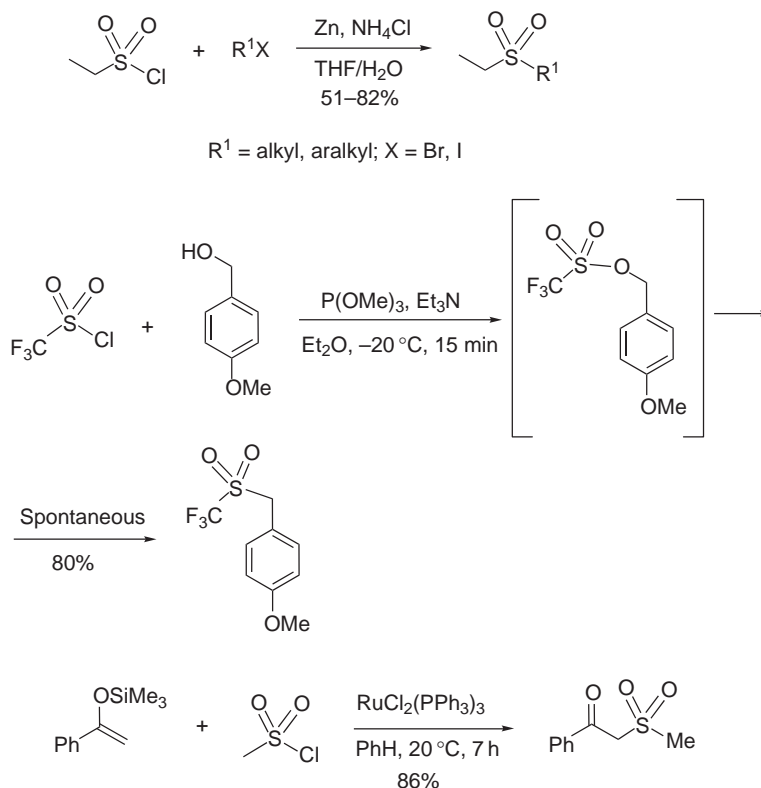
Scheme 63



Scheme 64

2.03.2.3.3 From sulfonic acid derivatives

Alkylation of sulfonyl halides is a well-explored approach to sulfones. Sulfonyl chlorides are the most frequently used reagents for these efficient procedures (Scheme 65) <1997TL5549, 1998SC1785, 1998T1901>.



Scheme 65

A ruthenium(II) phosphine complex catalyzes the addition of sulfonyl chlorides to silyl enol ethers providing a convenient approach to β -keto sulfones in good-to-high yield <1997JCS(P1)783>. Alternatively, β -keto sulfones can be obtained by the reaction of imines, which are readily available from the corresponding ketones, and sulfonyl chlorides via a sulfene intermediate <1994SL1017>. An efficient CsF-catalyzed trifluoromethylation of a methane sulfonic ester with (trifluoromethyl)trimethylsilane has been reported in the synthesis of triflones <1999JOC2873>.

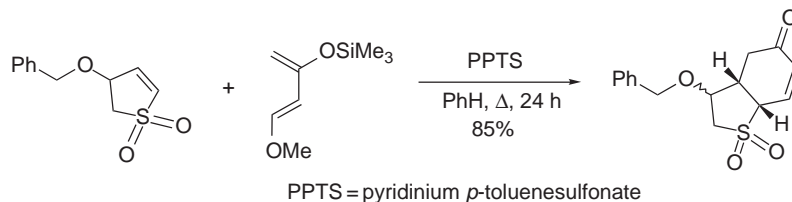
2.03.2.3.4 Via α -sulfonyl carbanions

Nucleophilic reactions of readily formed α -sulfonyl carbanions with a variety of electrophiles are well documented as a convenient route to highly functionalized sulfones <B-1994MI001, 1995COFGT(2)113>. These α -sulfonyl carbanions are usually generated from sulfones by strong bases such as NaH, BuLi, LiHMDS, or under conditions of phase-transfer catalysis. The effect of Bu^tP₄, a strong cation-free base, was used recently for the diastereoselective addition of α -sulfonyl carbanions to aldehydes <1996JOC2690>. *N*-Acyl benzotriazoles have been successfully applied to β -acylation of acyclic and alicyclic sulfones affording β -keto sulfones in good-to-high yield <2003JOC1443>.

2.03.2.3.5 Addition to unsaturated sulfones

(i) Cycloadditions

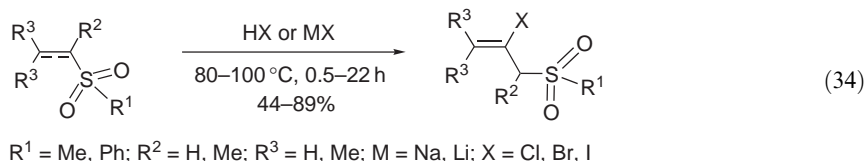
Alkyl vinyl sulfones readily partake in cycloaddition reactions affording the [2+2]-, [2+3]-, and [2+4]-cycloadducts [<1995COFGT\(2\)113>](#). The [2+4]-cycloadditions proceed without catalysis [<2001T201>](#) and are facilitated, for example, by $\text{Zn}(\text{OTf})_2$ [<2001DOKC\(381\)332>](#) or by pyridinium *p*-toluene sulfonate [<1997T8997>](#) (Scheme 66).



Scheme 66

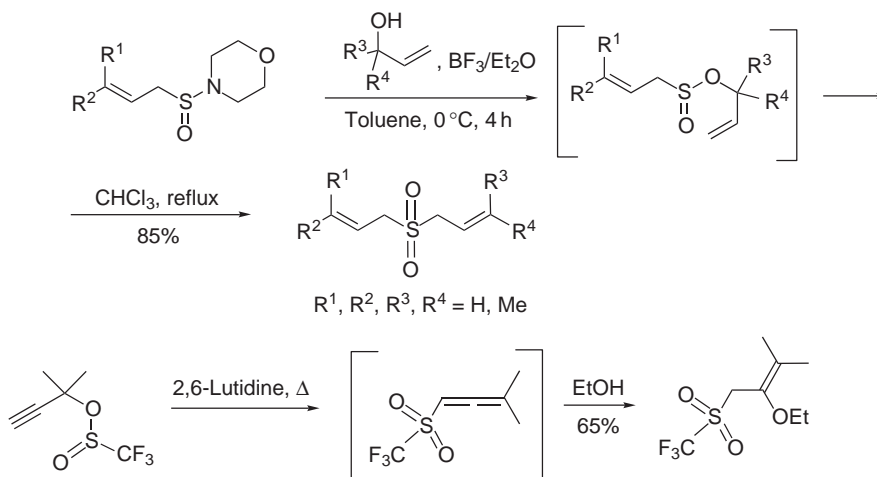
(ii) Conjugate addition

Vinyl sulfones are known to add *O*-, *N*-, *S*-, and *C*-nucleophiles forming alkyl sulfones. Mono-conjugate addition of divinyl sulfone to polyethylene glycol (PEG) has been applied to the synthesis of PEG vinyl sulfones, used in studies of bioconjugation [<2000SC2599>](#). Hydrohalogenation of 1,2-allenic methyl or phenyl sulfones provides a clean route to 2-haloallylic sulfones in good yield (Equation (34)) [<1999JOC1026>](#).



2.03.2.3.6 Rearrangement

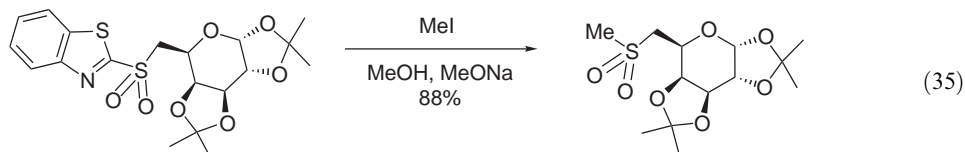
The boron-etherate-catalyzed reaction of the allylic sulfinamides with allylic alcohols opens a route to α, α' -bis-unsaturated sulfones via [2,3]-sigmatropic rearrangement (Scheme 67) [<1995BSF196>](#). Propargylic trifluoromethane sulfinates also undergo [2,3]-sigmatropic rearrangement and solvent addition to form allenyl trifluoromethyl sulfones in good yield (Scheme 67) [<2001TL1391>](#).



Scheme 67

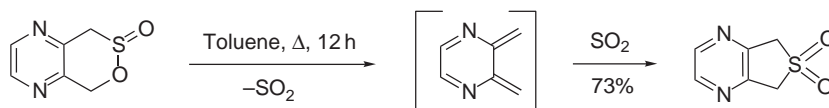
2.03.2.3.7 Sulfonyl group transfer

The ability of aza-aromatic sulfones to undergo nucleophilic substitutions, in the case of benzothiazol-2-sulfonyl derivatives [<1990AHC1>](#), has been applied by Rollin and co-workers to a novel synthesis of sugar sulfones via trans-sulfonylation ([Equation \(35\)](#)) [<1998S1506, 1999MI317>](#).



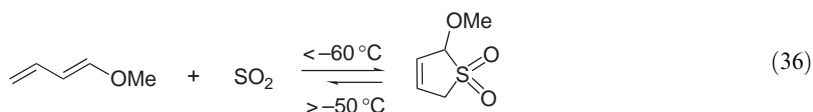
2.03.2.3.8 Reaction of unsaturated compounds and sulfur dioxide

The addition of sulfur dioxide to a diene, both generated from a sultine, has been observed by Chung and co-workers ([Scheme 68](#)) [<2000JOC3395>](#).



Scheme 68

Electron-rich 1,3-dienes such as (*E*)-1-methoxybutadiene add sulfur dioxide below -60°C without catalysis giving the sulfone exclusively ([Equation \(36\)](#)) [<2000CEJ1858>](#). The cycloadduct is unstable above -50°C and undergoes fast cycloreversion liberating the starting diene and sulfur dioxide. This type of sulfone has been extensively studied by Vogel and co-workers [<2001JOC5080>](#).

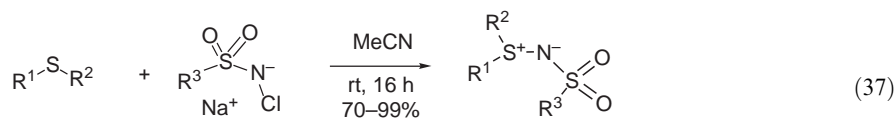


2.03.2.4 Sulfimines

Sulfimines (also known as sulfimides, sulfilimines, or iminosulfurans) are sulfur–nitrogen ylides and can be considered as aza analogs of sulfoxides. Although they are easily accessible and their reactivity is predicted to be intermediate between that of sulfonium ylides and sulfoxides, until recently sulfimines constituted a little studied family of compounds. Interest in sulfimines and the derived sulfoximines is rapidly growing due to their use in organic synthesis and applications based on their biological activity, as summarized in a recent review [<1999SR241>](#).

2.03.2.4.1 The reaction of sulfides with *N*-halo compounds

A broad range of readily available chloramine salts react with a variety of sulfides to form sulfonyl sulfimines in almost quantitative yield; this procedure avoids the formation of sulfoxides which were reported earlier to be inevitable by-products in an aqueous system ([Equation \(37\)](#)) [<2001JOC594>](#). If an aqueous system is used, undesired sulfoxide formation can be minimized using phase-transfer conditions as demonstrated for the synthesis of *N*-tosylsulfimines from thioglycosides and chloramine-T [<2002EJO171>](#).

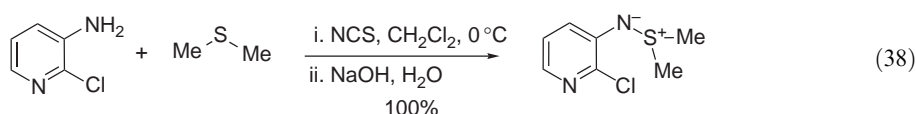


$R^1, R^2 = Me, Et, Bu^t, Bn, CH_2CH_2OH, 4-MeC_6H_4$; $R^3 = Me, Ph, 4-MeC_6H_4, 2-O_2NC_6H_4$

Oxidative amination of methyl trifluoromethyl sulfide by *N,N*-dichlorotrifluoromethanesulfamide gave the corresponding sulfinimine in 92% yield <1998RJOC1117>.

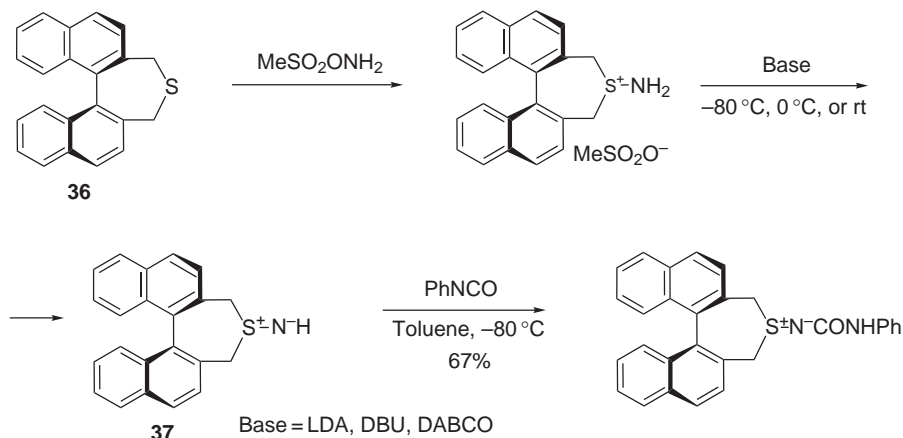
2.03.2.4.2 The reaction of sulfides with amines

N-Chlorosuccinimide is often used for the synthesis of sulfinimines from amines and sulfides (Equation (38)) <2000JHC229>.



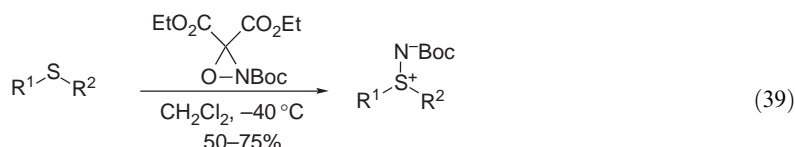
2.03.2.4.3 The reaction of sulfides with hydroxylamine derivatives

O-Mesitylenesulfonyl hydroxylamine reacts with the chiral sulfide **36** affording the asymmetric *N*-unsubstituted sulfinimine **37**, which was investigated in solution for its stability and reactivity (Scheme 69) <1999CC189>.



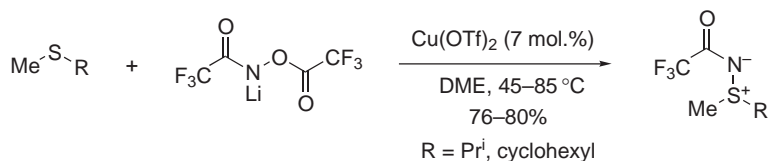
Scheme 69

The use of oxaziridine as a source of electrophilic nitrogen has been reported in a highly efficient amination of sulfides furnishing *N*-alkoxycarbonylsulfinimines (Equation (39)) <2002CC904>.



$R^1 = R^2 = Me$; $R^1 = Bu^t, R^2 = Me$; $R^1 = Bn, R^2 = Et$

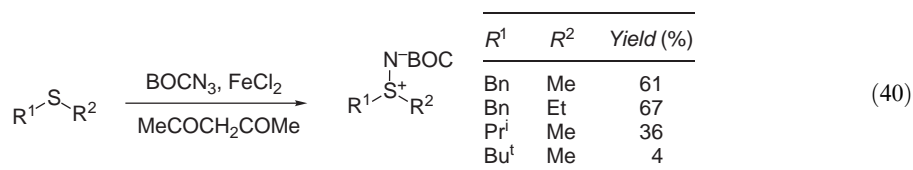
The lithium salt of a hydroxamic acid anhydride serves as a source of electrophilic nitrogen and converts a range of dialkyl and alkyl aryl sulfides to the corresponding *N*-trifluoroacetylated sulfinimes in good yields (Scheme 70) <1999OL149>.



Scheme 70

2.03.2.4.4 The reaction of sulfides with azides

The transfer of a nitrene fragment from an azide to a sulfide leads to a sulfinime. The imidation of sulfides to sulfinimes has been achieved using *N*-*t*-butyloxycarbonyl azide in the presence of FeCl₂; a bulky S-substituent strongly inhibits attack of the nitrene transfer reagent (Equation (40)) <1999EJO1033>.



An (OC)Ru(II)(salen) complex catalyzes the imidation of alkyl aryl sulfides by arylsulfonyl azides in high yield and high enantioselectivity, whereas a dialkyl sulfide (BnSMe) produced the corresponding sulfinime in 36% yield and enantiomeric excess of 66% in a single example <2001TL7071>.

2.03.2.4.5 The reaction of sulfides with sulfamides

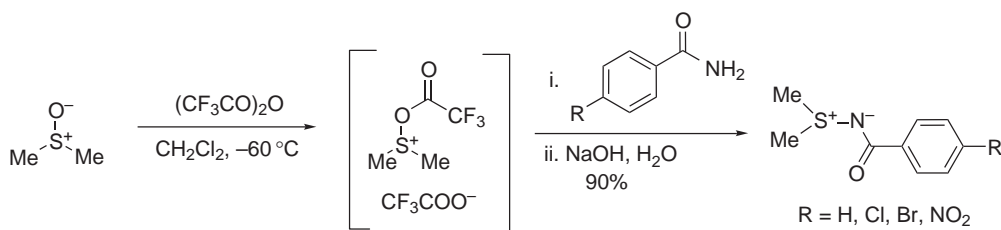
A direct catalytic imidation of sulfides to sulfinimes with [*N*-(*p*-tolylsulfonyl)imino]phenyliodine (TsN=IPh) using a catalytic amount of copper triflate proceeds with a wide range of aryl alkyl and dialkyl sulfides in 50–83% yield. In the presence of a chiral bis(oxazoline) ligand, asymmetric induction occurs to afford the chiral dialkyl sulfinimes although in low enantiomeric excesses <1997JOC6512>. The use of hypervalent iodine has also been reported under mild conditions in the synthesis of *N*-sulfonyl sulfinimes from sulfides, sulfamides, and iodobenzene diacetate in good yields <1999SC4443>. *N*-Perfluoroalkane sulfinimes can be prepared from perfluoroalkane sulfamides, dialkyl sulfides, and lead tetraacetate in good yield <1996JFC81>.

2.03.2.4.6 From sulfoxides

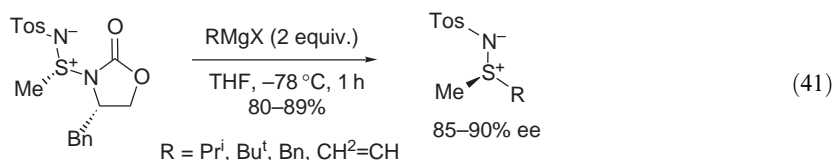
The displacement of a sulfoxide oxygen by a nitrogen nucleophile requires an activator <1995COFGT(2)113>. TFAA has been reported to activate sulfoxides assisting the formation of sulfinimes in high yield (Scheme 71) <1999BMCL1033>.

2.03.2.4.7 Sulfinino group transfer

Optically pure dialkyl *N*-tosylsulfinimes have been prepared from chiral oxazolidinones and Grignard reagents in high yield and high enantiomeric excess (Equation (41)) <1998CC701>. The reaction proceeds with inversion of configuration at sulfur, in a similar manner to sulfinyl group transfer (Section 2.03.2.2.1.(ix)).



Scheme 71



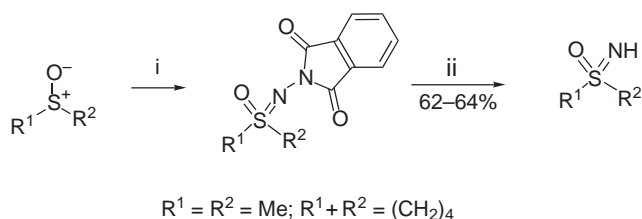
2.03.2.5 Sulfoximines

The versatile chemistry of dialkyl sulfoximines is made possible by the presence of an amphoteric nitrogen, acidic α -protons, and a stereogenic sulfur.

2.03.2.5.1 From sulfoxides

Electrochemical nitrogen-transfer methodology has been applied to the synthesis of sulfoximines from sulfoxides and *N*-aminophthalimide. The chemically difficult removal of the *N*-phthalimido group in sulfoximines can be readily achieved electrochemically (Scheme 72) <2002OL1839>.

In the presence of iodozobenzene diacetate (2 equiv.), *N*-aminourazole (p-urazine) and DMSO furnished 4-(*S,S*-dimethylsulfoximino)-1,2,4-triazole-3,5-dione which was not isolated but used in a variety of cycloaddition reactions <1997JOC3779>.

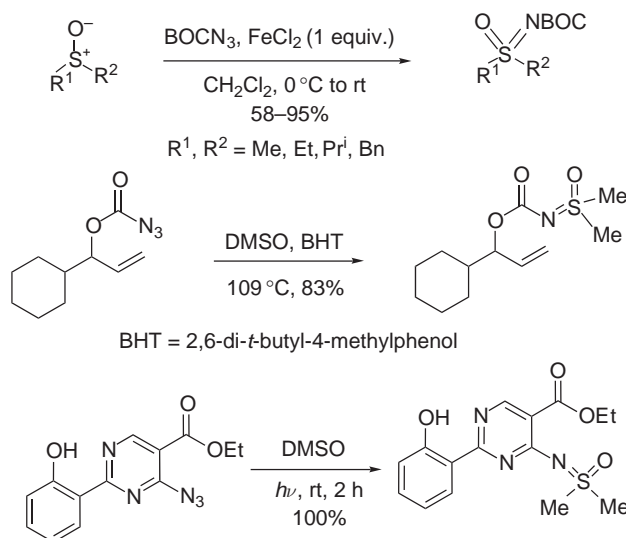


- i. +1.80 V (vs Ag wire), Pt anode, *N*-aminophthalimide (1.3 equiv.), $\text{Et}_3\text{N}^+\text{HAcO}^-$ (1 equiv.), rt, 3.4–4 h
 ii. 10 mA/cm², Pt cathode, MeOH, 0.05 M $\text{Bu}_4\text{N}^+\text{BF}_4^-$, rt, 2 h

Scheme 72

In a direct analogy to the generation of sulfinates from sulfides with perfluoroalkane sulfonyl amides and lead tetraacetate, sulfoxides are converted into sulfoximines in moderate-to-good yield with the same reagent <1995JFC81> (cf. Section 2.03.2.4.5). *O*-Mesitylenesulfonyl hydroxylamine reacts with polyfunctional sulfoxides furnishing the corresponding sulfoximines in good yield <1998BMC1935> (cf. Section 2.03.2.4.3).

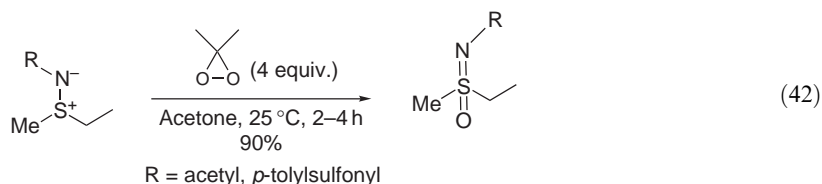
Nitrene transfer from an azide to a sulfoxide is a convenient approach to sulfoxamides (Scheme 73) <1997RCB607, 1997JOC4449, 1998TL5015, 1999JOC1033>.



Scheme 73

2.03.2.5.2 From sulfinimes and sulfonimidoyl chlorides

A straightforward route to sulfoximines involves the oxidation of the parent sulfinimes. The direct conversion of *N*-substituted sulfinimes to the corresponding sulfoximines has been achieved by oxidation with dimethyldioxirane in high yield under mild conditions (Equation (42)) <1997TL5559>.



No new data have been found on the formation of sulfoximines from sulfimidoyl chlorides.

2.03.2.6 Sulfur Diimines

The scattered data in the literature indicate that dialkyl sulfur diimines (or sulfone diimines) can be obtained by the oxidative amination of sulfides or sulfinimes. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

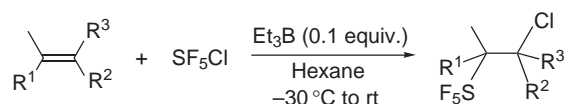
2.03.3 ALKANESULFENYL HALIDES AND THEIR HIGHER-COORDINATED DERIVATIVES

2.03.3.1 Alkanesulfenyl Halides

2.03.3.1.1 Alkanesulfenyl fluorides

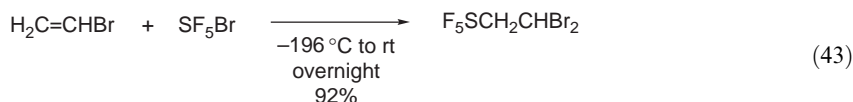
Until now, very few simple alkanesulfenyl fluorides have been described. All of them have been prepared by halogen exchange in alkanesulfenyl chlorides by treatment with KF, AgF, and related reagents, and turn out to be rather unstable. All other representatives belong to higher-fluorinated sulfur derivatives and are usually obtained by direct fluorination of sulfides or by addition of SF₅Cl to alkene substrates <1995COFGT(2)113>. Thus, use of Et₃B as a catalytic initiator allows the

convenient, regiospecific and stereoselective addition of SF₅Cl to a variety of alkenes in high yield (Scheme 74) <2002OL3013>. Similarly, preparation of 1,1-dibromo-2-pentafluorothioethane has been achieved by reaction of vinyl bromide with SF₅Br (Equation (43)) <1996JFC63>, and SF₅CF₂CFBr₂ and SF₅CF₂CF₂Br are obtained in the same manner <1987JFC653>.

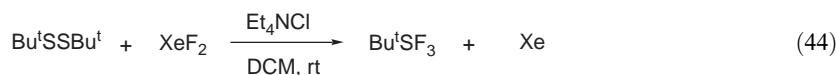


R ¹	R ²	R ³	Yield (%)
H	<i>n</i> -C ₆ H ₁₃	H	95
H	Bu ⁿ	H	98
H	Bu ^t	H	96
H	Et	Et	89
Pr ⁿ	H	Pr ⁿ	95
-(CH ₂) ₄ -		H	98

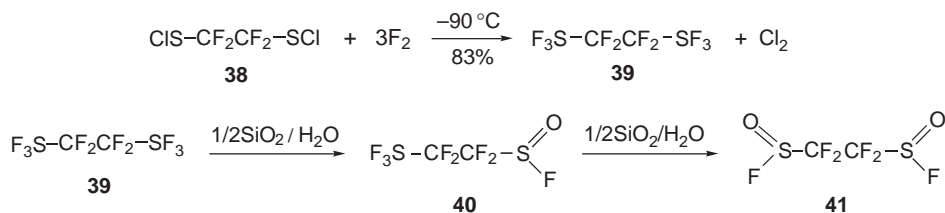
Scheme 74



Oxidative fluorination of di-*t*-butyl disulfide by XeF₂ affords Bu^tSF₃ in ~90% yield (Equation (44)) <2000JFC279>. Apparently, this process is catalyzed by chloride ions since in the absence of Et₄NCl no reaction occurs.



The bis(trifluorosulfur)ethane derivative **39** can be prepared in high yield by low-temperature fluorination of the corresponding chlorosulfenyl derivative **38** (Scheme 75) <1998EJI1035>. Compound **39** is less stable to hydrolysis than CF₂(SF₃)₂ and forms the sulfenyl products **40** and **41**: the initial product **40** can only be observed as an intermediate.

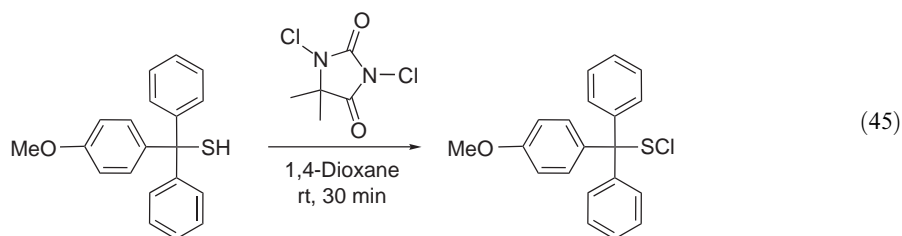


Scheme 75

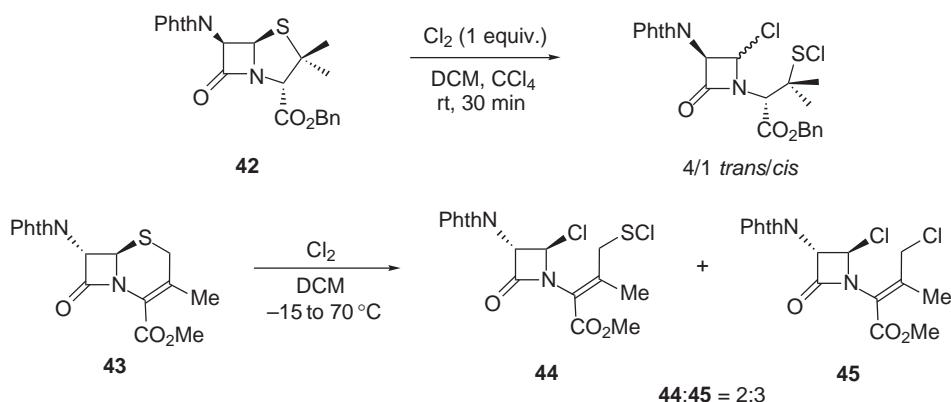
2.03.3.1.2 Alkanesulfenyl chlorides

Alkanesulfenyl chlorides are the most stable and most frequently cited of all the alkanesulfenyl halides. Methods of preparation commonly start from thiols, sulfides (including *S*-heterocycles), disulfides, thiocarbonyl, or alkenes which are subjected to the action of various chlorinating agents such as Cl₂, Bu^tOCl, SO₂Cl₂, and SCl₂ <1995COFGT(2)113>. Recent achievements in this field in general follow these trends.

4-Methoxytritylsulfenyl chloride has been synthesized (76% yield) by treatment of the corresponding thiol with 1,3-dichloro-5,5-dimethylhydantoin (Equation (45)) <2001TL8657>. The use of sulfuryl chloride is also possible as is testified by conversion of ethyl mercaptoacetate into ethyl chlorosulfenylacetate <1996JCS(P1)977>.

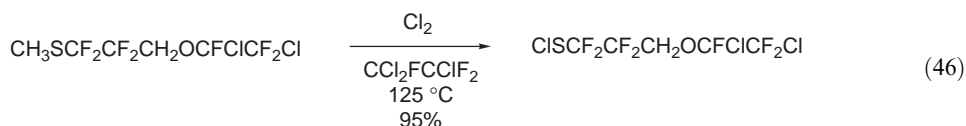


Penam **42** on treatment with chlorine undergoes ring opening with formation of epimeric sulfenyl chlorides <1996CC1989, 2000T6053>. However, the analog **43** under similar conditions behaves differently producing the dichloride **45** in addition to the sulfenyl chloride **44** (Scheme 76). The latter is the only product if sulfuryl chloride is used instead of Cl_2 <1999CC253>.



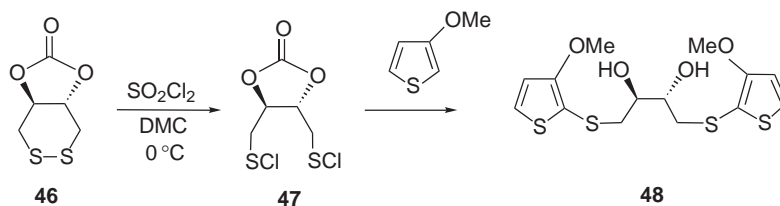
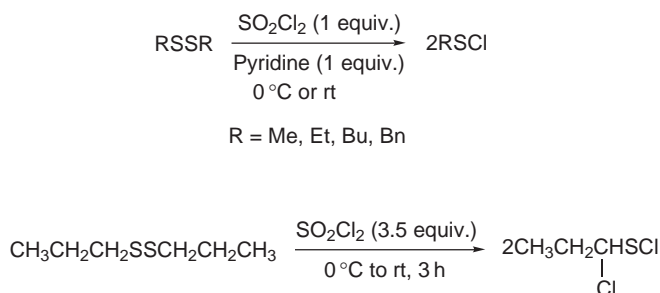
Scheme 76

Transformation of open-chain sulfides into the sulfenyl chlorides usually requires considerably higher temperature (Equation (46)) <1999JFC93>.

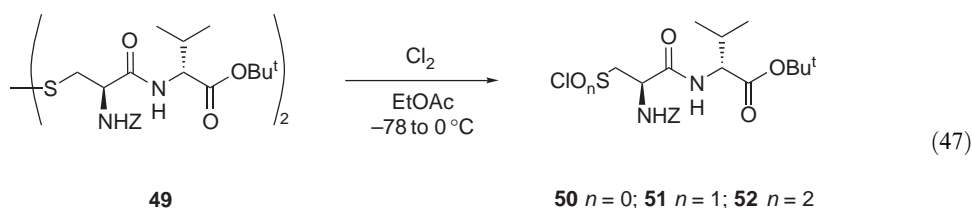


Dialkyl disulfides are often used as high-yielding precursors of sulfenyl chlorides. Normally, the disulfide is treated with an equimolar amount of sulfuryl chloride (Scheme 77) <1996JOC7116, 2000JOC1434, 2001JCS(P1)138>. When excess SO_2Cl_2 is employed, chlorination of an α -methylene group can occur as exemplified by the formation of 1-chloropropane sulfenyl chloride in quantitative yield (Scheme 77) <1997MI4414>. Ring opening of the cyclic disulfide **46** was used to prepare *in situ* the bis(sulfenyl chloride) **47**, which then reacted with 3-methoxythiophene to give the bis-adduct **48** (98% yield) (Scheme 77) <2002S1004>.

Chlorine gas can also be employed to convert disulfides into sulfenyl chlorides. However, the amount of Cl_2 should not exceed 1–3 equiv., otherwise further oxidation takes place. Thus, dipeptide **49** produces the sulfenyl chloride **50** selectively and cleanly but with 3.5 or 7–8 equiv. of chlorine the corresponding sulfinyl chloride **51** or sulfonyl chloride **52** are exclusively formed (Equation (47)) <2001BMCL2111>.

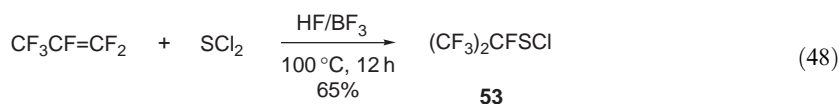


Scheme 77



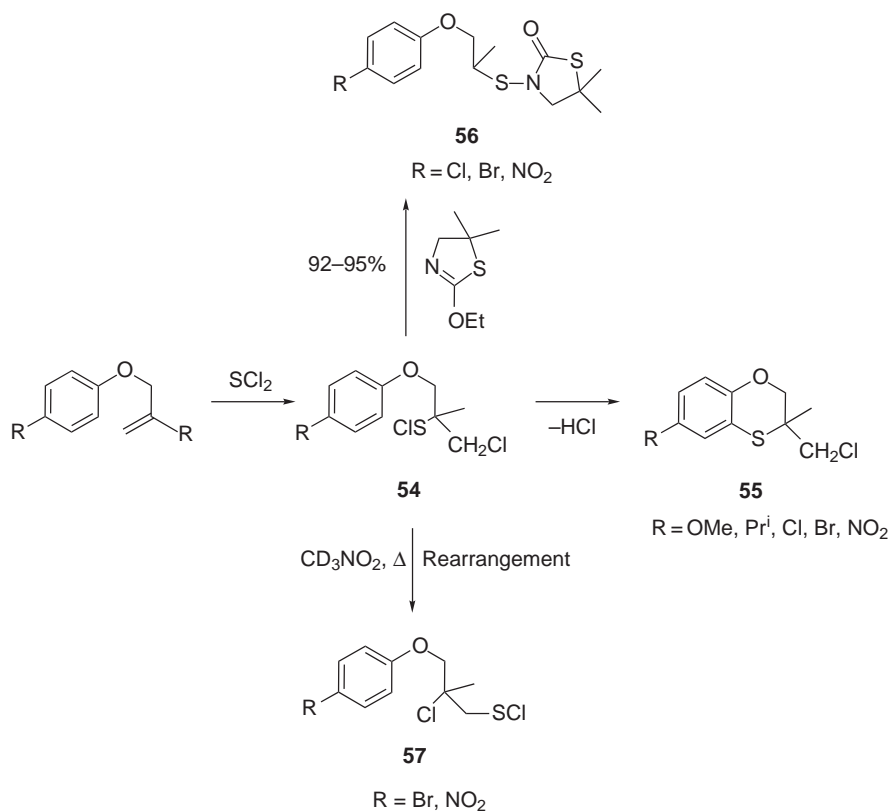
Z = benzyloxycarbonyl

The reaction of hexafluoropropene and SCl_2 in anhydrous HF/BF_3 [<2001JFC325>](#) or HOSO_2F [<1987BAU2194>](#) leads to predominant formation of sulfenyl chloride **53** in good yield (Equation (48)).

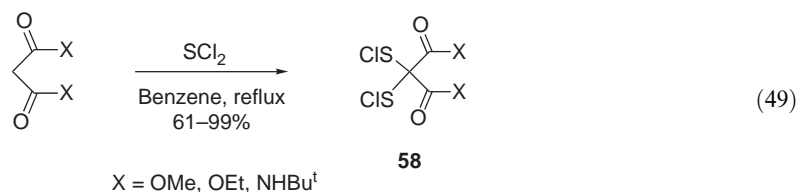


A series of 3-chloromethyl-2,3-dihydro-1,4-benzoxathiins **55** have been prepared in moderate yield by the reaction of several β -methylallyl phenyl ethers with sulfur dichloride. In some cases intermediate sulfenyl chlorides **54** were isolated and characterized as thiazolidine-2-ones **56**. The thermal isomerization of selected sulfenyl chlorides **54** \rightarrow **57** was achieved in good yield (Scheme 78) [<1995JPR283>](#).

Alkanesulfenyl chlorides can also be obtained via direct substitution of hydrogen by chlorosulfenyl in CH-acidic compounds. Thus, malonic acid derivatives on treatment with sulfur dichloride afford *gem*-disulfenyl chlorides **58** in good-to-excellent yield (Equation (49)) [<1990JCS\(P1\)509, 2000EJO2583>](#). Many compounds of this type cannot be purified, but crude products are satisfactory for many synthetic purposes. For compound (**58**; X=OMe) the structure has been determined by X-ray diffraction. The pyridine-catalyzed reaction between malonic acid derivatives and thionyl chloride affords α -chlorosulfenyl chlorides, but the process in some cases is complicated by formation of α,α' -dichlorodisulfides and trisulfides [<2002EJO2039>](#).



Scheme 78



Photolysis of CF_3COSCl has been reported to produce a mixture of trifluoromethane sulfenyl chloride and trifluorochloromethane, but neither of these products were isolated [\[1997JST\(407\)171\]](#).

2.03.3.1.3 Alkanesulfenyl bromides

Very few examples of these reactive compounds have been reported in the 1990s. Methanesulfenyl bromide was prepared and immediately used without isolation by treatment of dimethyl disulfide with an excess of bromine [\[2001JOC910\]](#). Notably, a solution of MeSBr in dichloroethane can be stored at -30°C for up to one month without any appreciable change in reactivity.

It is relevant to point out that sulfides form quite stable molecular complexes of different composition with bromine. Recently, for some of these complexes ($\text{Me}_2\text{S}\cdot\text{Br}_2$, $\text{Me}_2\text{S}\cdot\text{Br}_{2.5}$, and $\text{Me}_2\text{S}\cdot\text{Br}_4$), X-ray measurements have been conducted [\[1999JCS\(D\)79\]](#).

2.03.3.1.4 Alkanesulfenyl iodides

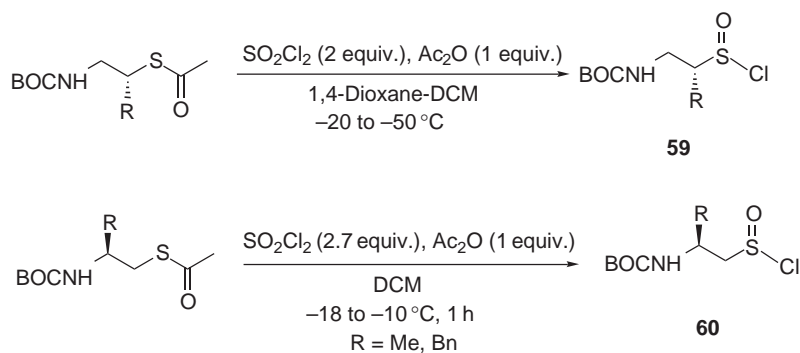
No further advances have occurred in this area since publication of COFGT (1995) [\[1995COFGT\(2\)113\]](#).

2.03.3.2 Alkanesulfinyl Halides

Sulfinyl iodides and sulfinyl bromides are still unknown and sulfinyl fluorides are quite rare and not very useful. In contrast, sulfinyl chlorides are a fundamental building block in organosulfur chemistry and are important for the preparation of many sulfinic acid derivatives, sulfonyl-containing functionalities or enantio-enriched sulfoxides. Recently, methods of preparation and reactions of sulfinyl chlorides have been reviewed [<1999OPP579>](#). **WARNING:** great care should be taken when handling sulfinyl chlorides as they are rather explosive and extremely sensitive to moisture.

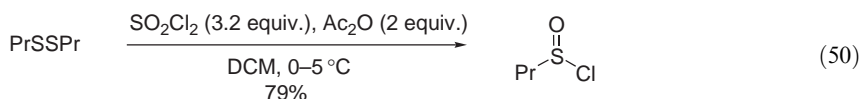
There are two main approaches to the synthesis of sulfinyl chlorides: (i) oxidative chlorination of sulfur substrates, e.g., thiols, disulfides, thioacetates etc.; and (ii) reaction of sulfinic acids or their salts with excess thionyl chloride. Both methods were thoroughly covered in COFGT (1995) [<1995COFGT\(2\)113>](#). Since then these methods have further developed and some useful modifications have been reported.

The β -substituted aminoethanesulfinyl chlorides **59** and **60** were prepared by treatment of BOC-protected β -aminoethane thioacetates with sulfonyl chloride or chlorine. These sulfinyl chlorides were used without further isolation for the preparation of homochiral α - and β -substituted sulfinamides and sulfonamides (Scheme 79) [<1995JOC5157, 1996BMC667, 2000EJO1219>](#). A similar synthesis of a series of *t*-butyl β -chlorosulfinylpropionates has also been described [<1997BMCL2331>](#).

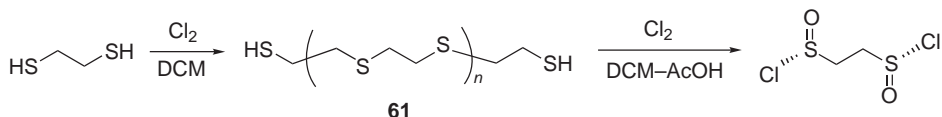


Scheme 79

Dialkyl disulfides can also serve as a source of sulfinyl chlorides. Thus, dipropyl disulfide on treatment with sulfonyl chloride and acetic anhydride furnishes 1-propanesulfinyl chloride as a pale yellow oil (Equation (50)) [<1996JA7492>](#). The same reaction in the absence of Ac_2O leads to formation of sulfenyl chlorides (Section 2.03.3.1.1).

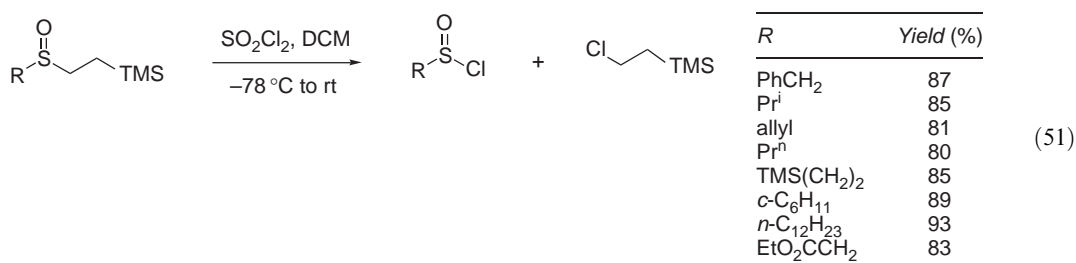


Ethane-1,2-bis-sulfinyl chloride has been obtained in a two-step procedure starting from 1,2-ethanedithiol (Scheme 80) [<2002JOC345>](#). In the first stage the dithiol was treated with chlorine to afford polymer **61**. Subsequent bubbling of chlorine gas through a suspension of polymer **61** in a mixture of DCM and glacial acetic acid gave the desired compound in good yield.

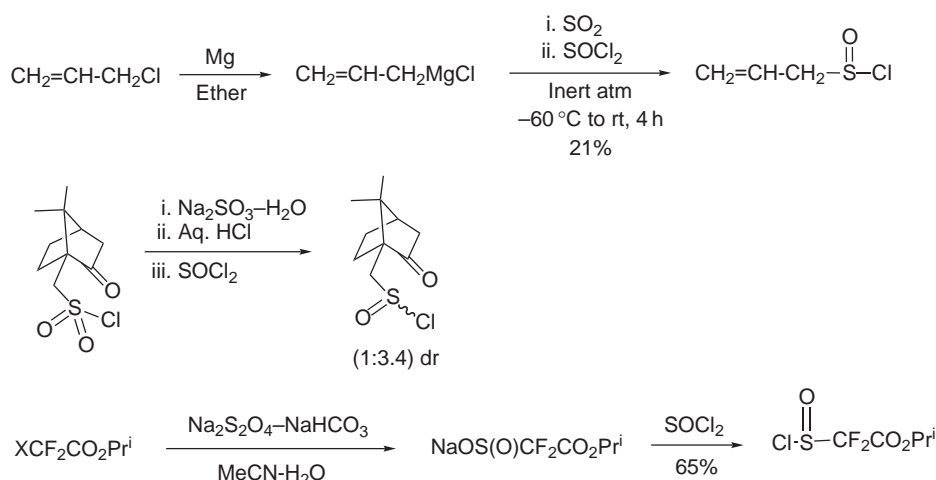


Scheme 80

Another effective route to sulfinyl chlorides is based on the cleavage of 2-(trimethylsilyl)ethyl groups from sulfoxides under oxidative conditions using sulfuryl chloride (Equation (51)) <2001EJO1643>. This method is suitable for most alkane- and arenesulfinyl chlorides but is limited to highly substituted vinylic sulfinyl chlorides.



As indicated above, sulfinyl chlorides can be prepared by chlorination of sulfinic acids or their salts. The latter are usually obtained by Grignard procedures <1997MI4406, 2001JA10127>, sodium sulfide reduction of chlorosulfonyl compounds <1999TA4183>, or reaction of alkyl halides with sodium dithionite <2003JFC59>. Examples are shown in Scheme 81.



Scheme 81

The only representatives of alkanesulfinyl fluorides that have been described since the publication of COFGT (1995) <1995COFGT(2)113> are compounds **40** and **41** (Scheme 75).

2.03.3.3 Alkanesulfonyl Halides

All the four types of alkanesulfonyl halides are well known and stability decreases in the order: sulfonyl fluorides, sulfonyl chlorides > sulfonyl bromides > sulfonyl iodides. In terms of reaction type and starting material, the numerous methods of their preparation can be merged into three large groups: (i) methods involving the formation of C—S(VI) bonds; (ii) methods involving oxidation of various sulfur-containing substrates; and (iii) methods starting from other sulfur(VI) functionalities. In fact, it is not always easy to strictly distinguish between these classifications. Thus, transition from alkyl halides to sulfonyl halides often includes preparation of alkyl sulfonates (method (i)) and further chlorination with PCl₅ or similar reagents (method (ii)). In such cases our assignment of transformation to a particular section is mainly based on the last stage.

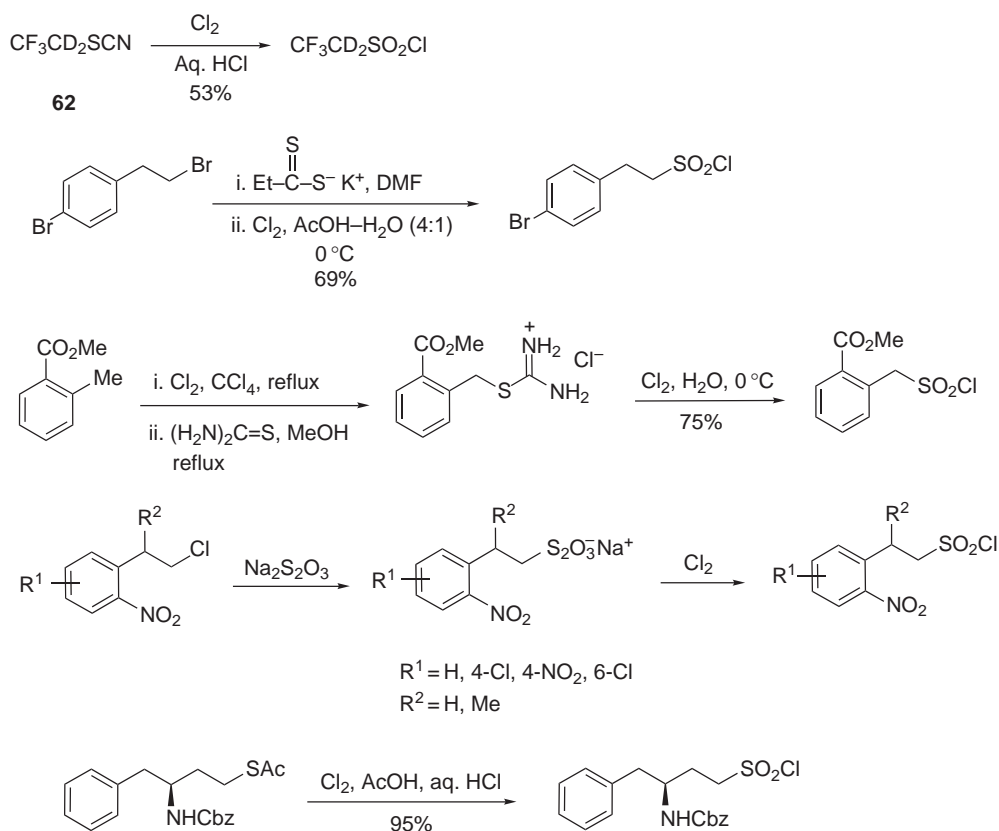
2.03.3.3.1 Carbon–sulfur(VI) bond formation

The most significant versions of this approach are direct sulfochlorination of C–H or metal–C bonds by $\text{SO}_2\text{--Cl}_2$ mixture or SO_2Cl_2 . Both have been discussed in COFGT (1995) <1995COFGT(2)113> and since then no further advances have occurred.

2.03.3.3.2 Oxidation of sulfur-containing moieties

Various sulfur-containing organic compounds can be oxidized to the corresponding sulfonyl chlorides. Among these are thiols, sulfides, disulfides, sulfoxides, sulfones, xanthates, thiosulfates, and isothiuronium salts. As an oxidant chlorine gas in aqueous media is frequently employed although the successful use of iodosobenzene or potassium chlorate has also been reported. Essentially no new synthetic procedures for oxidative preparation of sulfonyl halides have been described since the publication of COFGT (1995) <1995COFGT(2)113>. A short survey of the latest developments in this area is provided below.

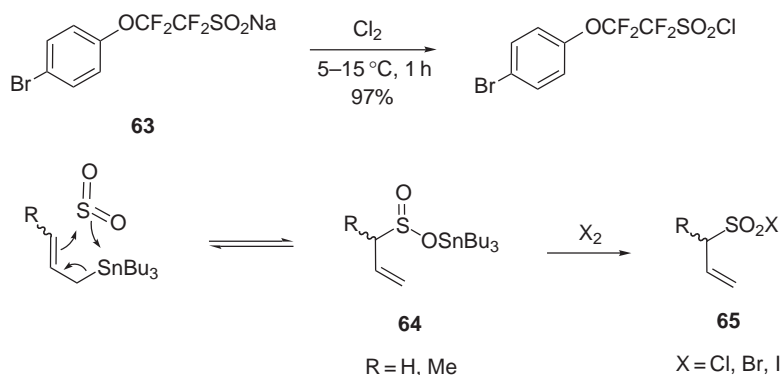
The action of chlorine in aqueous hydrochloric acid on thiocyanate **62** gave 1,1-dideutero-2,2,2-trifluoroethanesulfonyl chloride in moderate yield (Scheme 82) <1998JOC808> (see also <1995CPB1516, 1996CPB122>). Similar examples of oxidation of xanthates <1998BMCL3143>, isothiuronium salts <1998BMCL3683, 2002MI1791>, thiosulfates <1998MI1987>, and thioesters <2000BMCL1159> are shown in Scheme 82. These reactions are usually performed at 0–5 °C or room temperature and isothiuronium salts or thioesters are especially favored as starting compounds.



Scheme 82

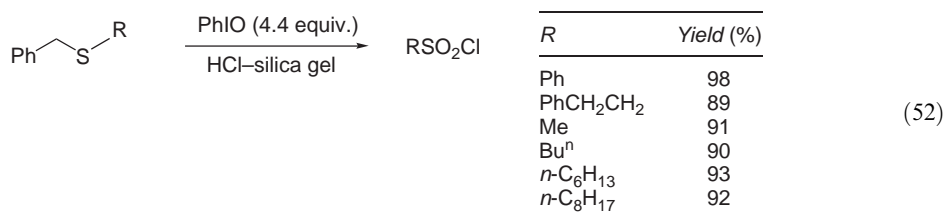
Alkanesulfinic acid salts also produce alkanesulfonyl halides by halogen oxidation. The sodium sulfinate **63** was quantitatively converted to the sulfonyl chloride by treatment with chlorine (Scheme 83) <2000JFC129>. Organotin allylic sulfonates **64**, which can be regio- and stereo-specifically prepared by the metallo-ene addition of sulfur dioxide to allylic stannanes, readily

undergo halogenolysis to yield allylic sulfonyl halides **65** (Scheme 83) <1997TL4493>. Of the latter, only the sulfonyl chlorides were stable to heating; the sulfonyl bromides and iodides underwent a first-order thermal desulfination to yield allylic halides.

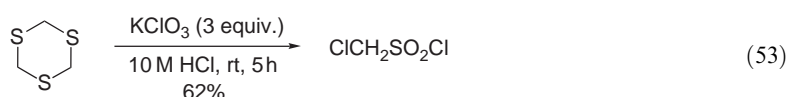


Scheme 83

Various benzylic sulfides were smoothly converted to sulfonyl chlorides in excellent yield by solid-state reaction with hydrogen chloride-treated silica gel and iodosobenzene (Equation (52)) <1998T13737>. Similar oxidation of sulfoxides and disulfides is also possible but in low yield. Sulfones are quantitatively recovered under these conditions.



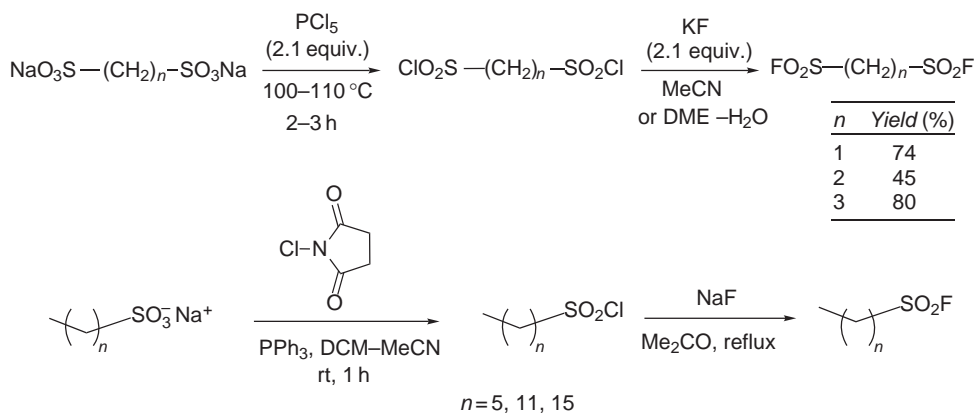
In a modification of the method of El-Hewehi <1964JPR38>, 1,3,5-trithian can be converted into chloromethanesulfonyl chloride by treatment with potassium chlorate (Equation (53)) <1997AJC1027>.



2.03.3.3.3 Preparations of sulfonyl halides from other sulfur(VI) functionality

There are two general methods for synthesizing sulfonyl halides from derivatives of hexa-valent sulfur: (i) methods starting from alkanesulfonic acids and their derivatives and (ii) methods based on halogen exchange reactions. In addition, some compounds are more conveniently prepared by changing other functionalities in already existing sulfonyl halides. The latter to a large extent relates to perfluoroalkanesulfonyl fluorides which are usually obtained by electrochemical fluorination of sulfonyl fluorides.

Conversion of alkanesulfonic acids, or more often their salts, to sulfonyl halides is achieved using a wide range of reagents, such as phosphorus pentahalides, phosphorus trihalides, phosphorus oxyhalides, thionyl chloride, and sulfuryl chlorides. The scope of their application was discussed in detail in COFGT (1995) <1995COFGT(2)113>. Additional examples along with some new reagents and reactions are given below. It is worth noting that the schemes sometimes include several methods of sulfonyl halide preparation. Thus, heating disodium α,ω -alkanebis(sulfonates) with a slight excess of PCl_5 leads to the formation of the bis(sulfonylchlorides) in good yields. The latter were further converted to bis(sulfonyl) fluorides by halogen exchange with potassium fluoride or potassium hydrogen difluoride (Scheme 84) <1994JFC157, 1995JFC61, 1997JFC145>.

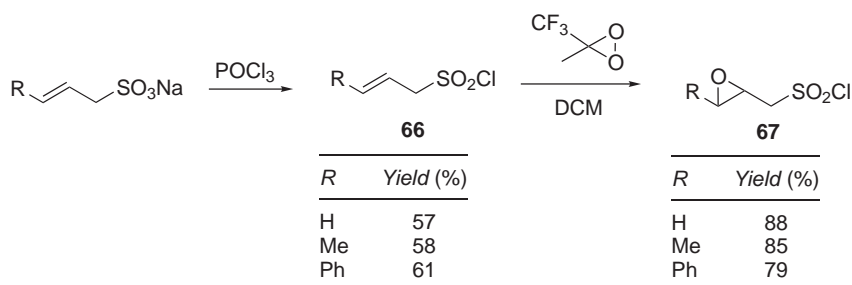


Scheme 84

Hexane- and dodecane- and hexadecanesulfonyl chlorides have been prepared in good yield by treatment of commercially available sodium sulfonates with *N*-chlorosuccinimide in the presence of triphenylphosphine under mild conditions. Alkanesulfonyl fluorides can be obtained from the corresponding chlorides by refluxing in anhydrous acetone with a 10-fold excess of anhydrous sodium fluoride (Scheme 84) <2000BMCL2803>.

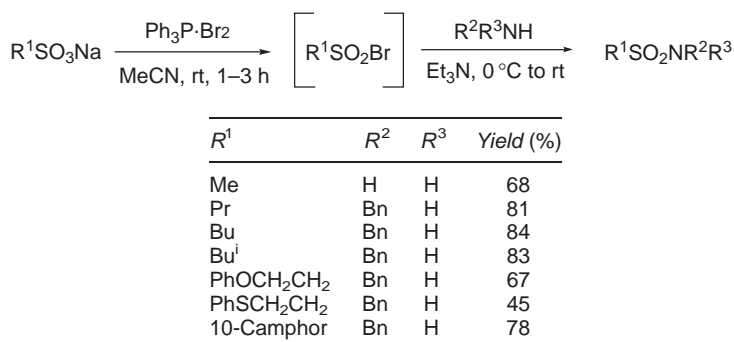
The reaction of methanedisulfonyl fluoride with an *N*-halogenosuccinimide in CCl_4 leads to formation of dihalogenomethanedisulfonyl fluorides [$\text{Hal}_2\text{C}(\text{SO}_2\text{F})_2$ ($\text{Hal} = \text{Cl}, \text{Br}, \text{I}$)] in good-to-moderate yield. Monohalogenomethanedisulfonyl fluorides [$\text{HalHC}(\text{SO}_2\text{F})_2$] can be prepared by treatment of potassium and silver-di(fluorosulfonyl)methanide with chlorine, bromine, or iodine <1994JFC157>.

Phosphorus oxychloride is also widely employed for sulfonyl chloride preparation <1998SL1411, 2000OL2327, 2001BMCL2225>. This method is illustrated by the synthesis of allylic sulfonyl chlorides **66** which after subsequent epoxidation were converted to epoxy sulfonyl chlorides **67** (Scheme 85) <1998SL1411>. Many other conventional oxidizers failed in this case. High-yielding syntheses of (1*S*)-(+)- and (1*R*)-(-)-camphor-10-sulfonyl chlorides have been achieved by treatment of camphor-10-sulfonic acid with thionyl chloride <1997CB879>.



Scheme 85

Despite generally good yields of the sulfonyl chlorides, the reactions of sodium sulfonates with PCl_5 , PCl_3 , or SOCl_2 have several disadvantages. These processes are exothermic, often need a high temperature to complete the reaction and are often incompatible with other functional groups. In addition, stoichiometric amounts of highly toxic and corrosive by-products are formed. In this connection, triphenylphosphine dichloride and dibromide have been suggested as milder and more convenient halogenating reagents for this purpose <1998S423>. In this way a series of alkane sulfonates were smoothly converted into the sulfonyl halides and then, without isolation, into sulfonamides in high to good yields (Scheme 86). Unlike $\text{Ph}_3\text{P}\cdot\text{Cl}_2$ and $\text{Ph}_3\text{P}\cdot\text{Br}_2$, reaction of triphenylphosphine/iodine with sodium sulfonates results in formation of alkyl iodides or thiols, depending on conditions.

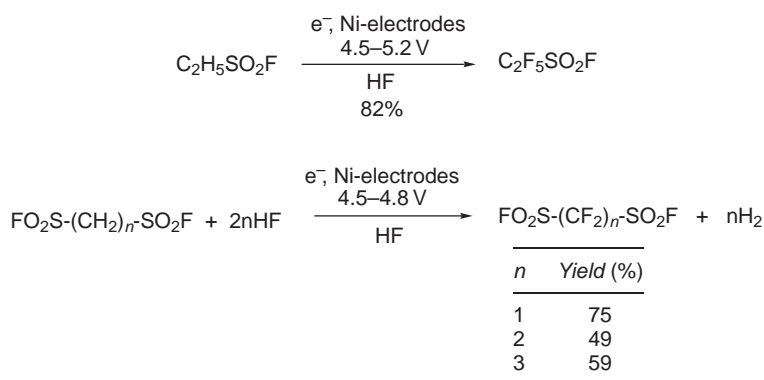


Scheme 86

(1*S*)-Camphor-10-sulfonyl bromide is obtained (93% yield) by treatment of potassium (1*S*)-camphor-10-sulfonate with PBr₅. However, this preparation turned out to be highly capricious and the yields are not reproducible <2000EJO4119>.

As was indicated above (Scheme 84), alkanesulfonyl fluorides are usually prepared via halogen exchange reactions. Additional examples of such transformations include the synthesis of difluoromethyl- <2000JST(550/551)59>, ethyl- <1998JCS(P1)875, 1999ACS1110>, and benzyl- <1998JCS(P1)875> sulfonyl fluorides. The yields commonly vary from good to high, and the reaction can be performed with NaF, KF, or KHF₂ both in aprotic or in protic (H₂O, AcOH) solvents.

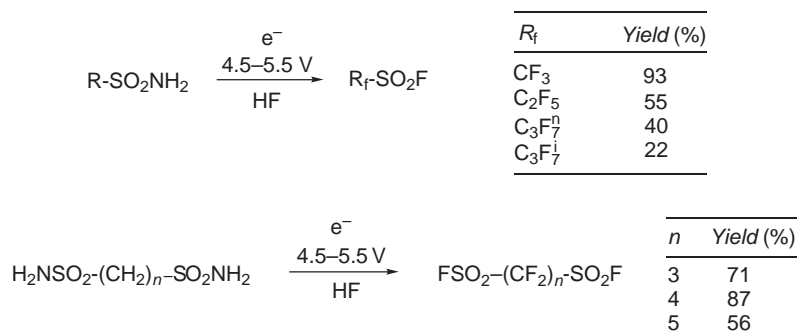
Electrochemical fluorination in anhydrous HF (Simons process) has proved to be a powerful method for conversion of nonfluorinated and partially fluorinated organic compounds into perfluorinated ones. Alkanesulfonyl chlorides and fluorides are typical starting materials for the synthesis of perfluoroalkanesulfonyl fluorides by this method, which has industrial importance (Scheme 87) <1994JFC157, 1997JFC145, 1999ACS1110>.



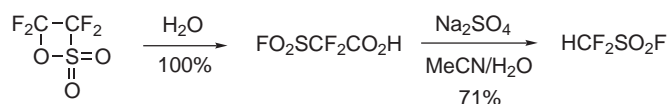
Scheme 87

Even alkanesulfonyl amides and disulfonyl amides under Simons process conditions undergo quantitative fission of S—N bonds to afford the sulfonyl fluorides in good-to-moderate yield; NF₃ and the corresponding perfluoroalkane fluorides are also formed as by-products (Scheme 88) <1996JFC71>.

Another interesting example of sulfonyl fluoride preparation is shown in Scheme 89 <2002CC2098>. This consists of hydrolytic fission of 3,3,4,4-tetrafluoro[1,2]oxathietane 2,2-dioxide (a monomer in the preparation of Nafion ion membrane resin) producing fluorosulfonyldifluoroacetic acid. Subsequent decarboxylation furnishes difluoromethyl sulfonyl fluoride in good yield.



Scheme 88



Scheme 89

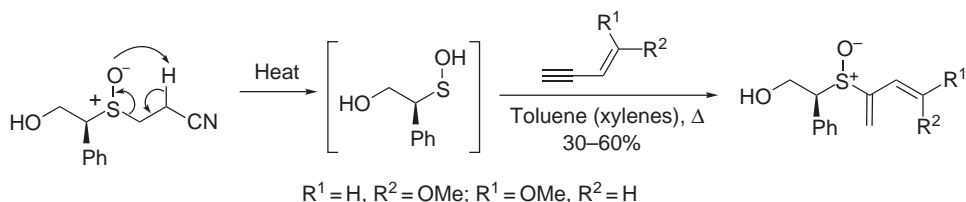
2.03.4 ALKANESULFENIC ACIDS AND THEIR HIGHER-COORDINATED DERIVATIVES

2.03.4.1 Alkanesulfenic Acids

Sulfur in sulfenic acids (RSOH) has an intermediate oxidation number and thus stands between thiols (RSH) and sulfinic acids (RSO_2H). For this reason, sulfenic acids and sulfenates are involved in the oxidation of reduced sulfur compounds such as thiols, sulfides, and disulfides. The great instability of simple alkanesulfenic acids has hampered direct characterization. On the whole, sulfenic acids are easily trapped by alkynes or alkenes to give the corresponding sulfoxides and this indirect method allows reliable characterization. A few sterically hindered alkyl sulfenic acids have been described [<1995COFGT\(2\)113>](#).

2.03.4.1.1 Thermolysis of sulfoxides

Thermolysis of dialkyl sulfoxides is one of the most applicable methods for the synthesis of alkanesulfenic acids. The use of flash vacuum pyrolysis (FVP) has been reported for sulfenic acid generation from sulfoxides. A photoelectron study of the FVP of methyl *t*-butyl sulfoxide allowed determination of the electronic structure and thermal stability of methanesulfenic acid [<1996JA1131>](#). An experimental and computational study addressed structural effects influencing formation from sulfoxides [<2001JOC8722>](#). The formation of chiral sulfenic acids, which are trapped with alkynes, has been utilized in an approach to enantiopure (*E*)- and (*Z*)-3-(alkylsulfinyl)-1-methoxy-1,3-butadienes ([Scheme 90](#)) [<1997JOC4376>](#).



Scheme 90

2.03.4.1.2 Hydrolysis of sulfenyl derivatives

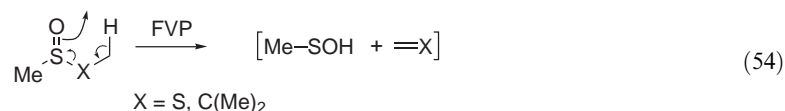
The relatively stable halides, esters, and amides of sulfenic acids are hydrolyzed to the sulfenic acid. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.4.1.3 Oxidation of thiols

Oxidation of a thiol results in a sulfenic acid and immediate trapping affords a sulfoxide. No reports on the subject have been found in the literature since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.4.1.4 Thermolysis of dialkyl thiosulfonates

The thermal decomposition of a dialkyl thiosulfonate produces a sulfenic acid. The process is similar to the formation of sulfenic acids from sulfoxides, which was the subject of a photoelectron study (Equation (54)) <1996JA1131> (cf. Section 2.03.4.1.1).

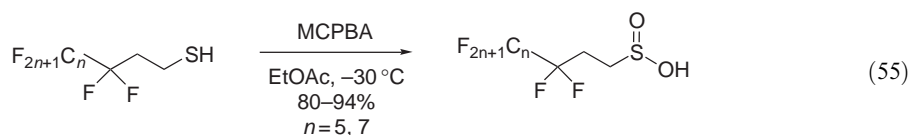


2.03.4.2 Alkanesulfinic Acids

Alkanesulfinic acids are well known but their moderate-to-poor stability makes isolation and characterization difficult, and practical methods for their synthesis are limited <1995COFGT(2)113>.

2.03.4.2.1 Oxidation of thiols

The oxidation of thiols typically gives sulfinic acids in good yield; the reaction proceeds via the intermediate sulfenic acid <1995COFGT(2)113>. This method has been applied to the synthesis of 2-(perfluoroalkyl)ethanesulfinic acids which possess unexpected stability and can be relatively easily purified in the solid state although their more stable salts are preferred (Equation (55)) <2000JFC21>.



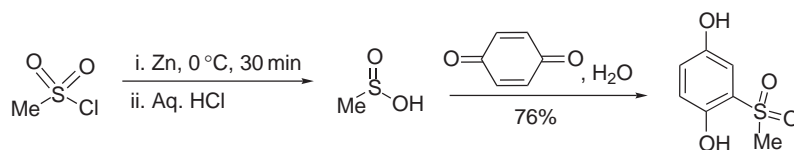
An interesting study of cysteine oxidation by bromine confirmed that the thiol group is the most sensitive site towards oxidation producing the corresponding sulfinic acid <1998JCS(F)1971>. Cysteine is known as a physiological free radical scavenger; thus, it can extend the cell life span and protect against the toxic substances.

2.03.4.2.2 Reaction of organometallics with sulfur dioxide

The most versatile approach to the alkanesulfinic acids involves the condensation of sulfur dioxide with Grignard or organolithium reagents affording the sulfinate salts <1995COFGT(2)113>. However, this method cannot be applied to systems bearing carbonyl functions. For such systems, the new methodology of ene-reaction of sulfur dioxide with silyl enol ethers has been developed by Vogel and co-workers which involves intermediate sulfinic acid derivatives (cf. Section 2.03.4.2.4).

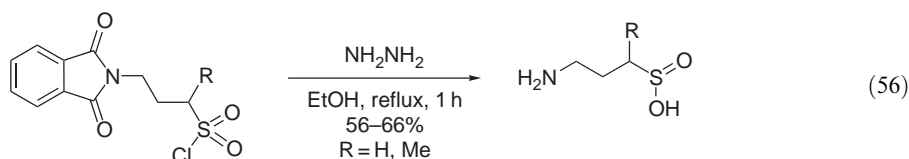
2.03.4.2.3 Reduction of sulfonyl halides

Mild reaction of methanesulfonyl chloride with zinc gives methanesulfinic acid which reacts *in situ* with benzoquinone to form the sulfone (Scheme 91) <2001SI1363>.



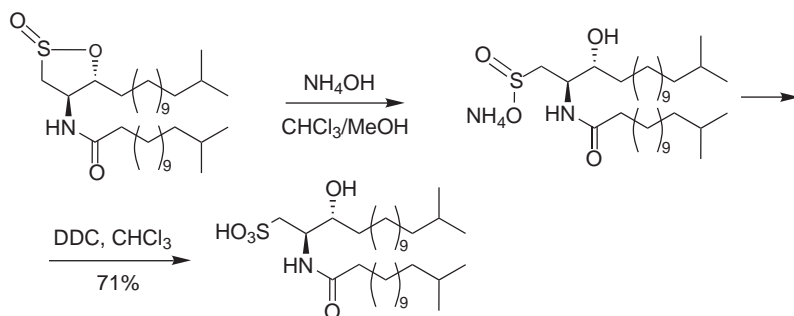
Scheme 91

A series of sulfinic acid analogs of γ -aminobutyric acid (GABA) have been prepared by mild reduction of the sulfonyl chlorides by hydrazine (Equation (56)) <1998BMCL3059>.



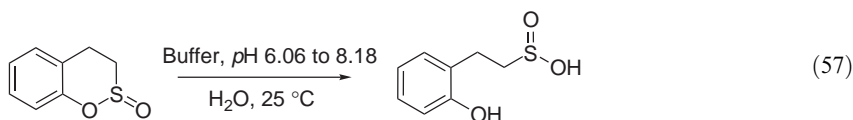
2.03.4.2.4 Hydrolysis of sulfinic acid derivatives

Hydrolysis of a cyclic sulfinate to afford the ammonium salt of a sulfinic acid followed by oxidation *in situ* to the sulfonic acid has been used in the synthesis of new sulfonolipids (Scheme 92) <1999JCS(P1)2467>.

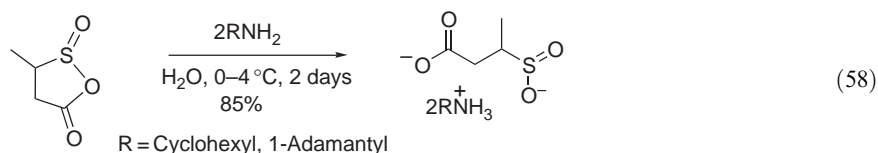


Scheme 92

The ring-opening reaction of a cyclic sulfinate ester with a phenolic leaving group was found to be buffer-dependent and was monitored spectrophotometrically (Equation (57)) <1996BCJ2639>.

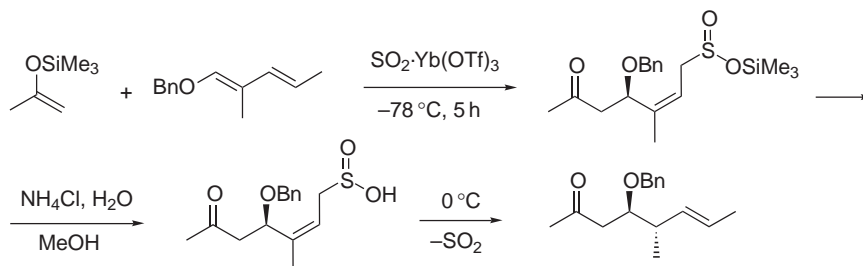


Ring-opening of the cyclic anhydride of a β -(oxysulfinyl)carboxylic acid by primary amines under mild conditions affords bis-salts (Equation (58)) <1997MI258>.



Sulfinic acids are readily formed by hydrolysis of sulfinamides in the presence of methanesulfonic acid (Scheme 64) <1995BSF196>.

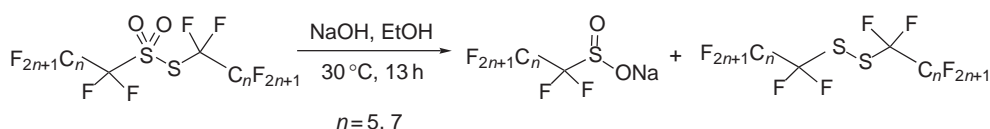
The condensation of an enoxysilane with a 1-benzyloxydiene and sulfur dioxide in the presence of Yb(OTf)₃ generated a silyl sulfinate that was converted *in situ* into the unstable sulfinic acid (Scheme 93) <2001JOC5080>.



Scheme 93

2.03.4.2.5 Reductive cleavage of thiosulfonates

In this well-known method, a thiosulfonate is involved in a nucleophilic attack on the divalent sulfur. The reaction is accompanied by reduction of the sulfonate. Nucleophiles such as thiolate, sodium amide, or a dialkyl phosphite anion are useful in this reaction <1995COFGT(2)113>. Sodium hydroxide was used in the synthesis of sodium salts of (2-perfluoroalkyl)ethanesulfinic acids affording separable mixtures of salt and disulfide (Scheme 94) <2000JFC21>.



Scheme 94

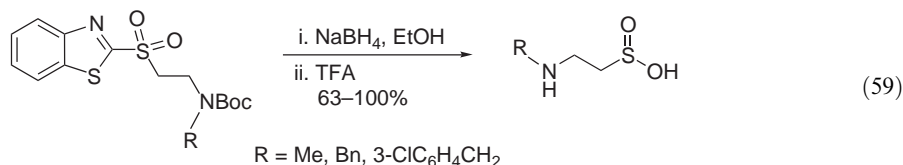
2.03.4.2.6 Addition to double bonds

Addition of thionyl chloride to alkenes has been reported to produce 2-chloroalkane sulfinic acids <1995COFGT(2)113>. No recent advances have occurred in this area.

2.03.4.2.7 From sulfones

(i) Reductive cleavage

Alkyl C—S bond cleavage in a sulfone under reductive conditions gives a sulfinic acid. The reaction typically proceeds on treatment of dialkyl or alkyl aryl sulfones with metallic lithium in methylamine or with metallic sodium in ammonia <1995COFGT(2)113>. The method of reductive cleavage of alkyl benzothiazolyl sulfones with sodium borohydride in alcohol has been applied to the synthesis of sulfinic acid analogs of γ -aminobutyric acid (Equation (59)) <1998BMCL3059> (cf. Section 2.03.2.3.7).



(ii) Base-induced cleavage

The nucleophilic displacement of an alkanesulfonic acid from an alkyl sulfone typically proceeds using cyanide ion, sodium ethoxide, or alkyl thiolates <1995COFGT(2)113>. The γ -sulfonic acid analog of 5-deazatetrahydrofolic acid has been synthesized in 20% yield by a sodium hydroxide-induced cleavage of the phthalimidomethyl sulfone derivative <1999H(51)1789>. The use of sodium thiolates in the preparation of (2-perfluoroalkyl)sulfonic acids from (2-perfluoroalkyl)alkyl sulfones resulted in greater than 90% yield <2000JFC21>.

(iii) Cleavage of small ring cyclic sulfones

A thiirane dioxide reacts with a base or with an organometallic reagent to give the β -substituted alkanesulfonic acids <1995COFGT(2)113>. No recent reports in this area have been found in the literature.

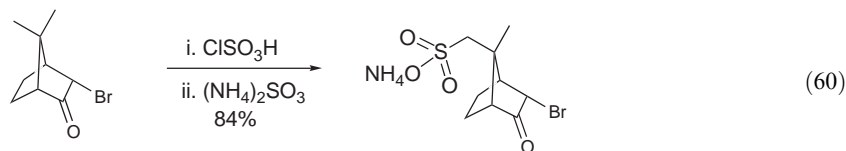
2.03.4.3 Alkanesulfonic Acids

The three main routes to stable sulfonic acids involve (i) addition of a sulfonyl group to a carbon, (ii) the oxidation of an alkyl sulfur compound, and (iii) transformation of an existing sulfonic acid derivative <1995COFGT(2)113>.

2.03.4.3.1 Addition of a sulfonyl group

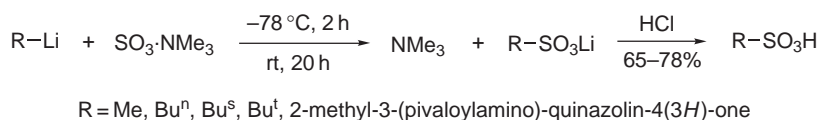
(i) With sulfuric acid derivatives

Sulfonic acid derivatives can be prepared by direct sulfonation of an aliphatic compound with fuming sulfuric acid although this is not a widely used method because of by-product formation and low yield <2002TL2161>. Chlorosulfonic acid and its ester derivatives generally give good yields of the sulfonation products (Equation (60)) <1997S515, 1999EJO91>.



(ii) With sulfur trioxide

The addition of sulfur trioxide across a C—C double bond commonly gives a mixture of products <1995RTC410>; sulfonation with sulfur trioxide occurs readily at the activated α -alkyl position of carbonyl, carboxyl, dialkylamino, and sulfonyl compounds <1995COFGT(2)113>. Sulfur trioxide complexes with dioxane, DMF, or trimethylamine are much milder and easier to handle. A general and efficient method for the preparation of alkyl and aryl sulfonic acids by insertion of sulfur trioxide as a complex with trimethylamine into an Li—C bond has been described (Scheme 95). A similar procedure has been applied to the synthesis of allylsulfonic acid from allylmagnesium bromide <1996JOC1530>.

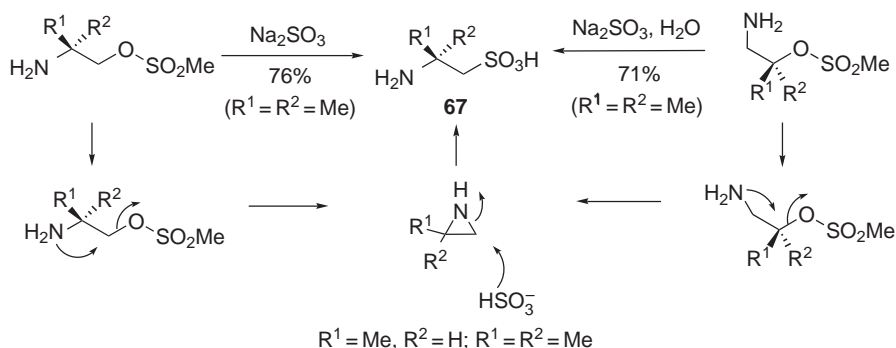
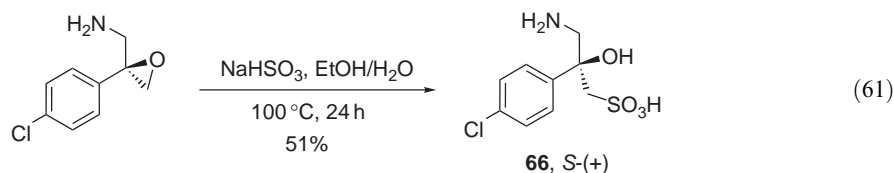


Scheme 95

A three-component alkene-SO₃·DMF-acetonitrile reaction followed by hydrolysis affords 2-aminoalkanesulfonic acids in moderate-to-good yield <2002EJO1407>.

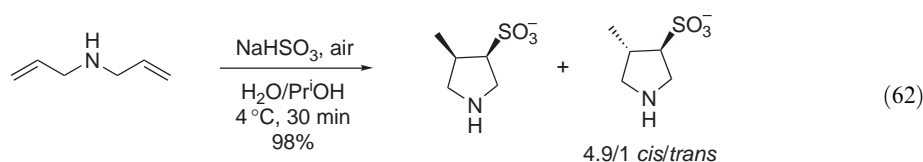
(iii) With hydrogen sulfite ion and sulfites

The most common method for generation of alkanesulfonic acids is the reaction of alkyl bromides with sodium sulfite—the Strecker synthesis <1995COFGT(2)113>. This approach has been reported for the preparation of β-amino-β-aryl-ethanesulfonic acids from the corresponding β-aminopropyl bromides and sodium sulfite in water <1997AJC523>. The interesting biological activities of β-aminoalkanesulfonic acids (taurine analogues) initiated synthesis of their derivatives such as hydroxysaclofen **66** (Equation (61)) <1995T11465> and β-aminopropanesulfonic acids **67** (Scheme 96) <1996TL7319, 2002TA1129>. A mechanism for the chiral (*R*)- or (*S*)-2-aminoalkanesulfonic acid formation by reaction of the corresponding chiral aminoalcohol methanesulfonate with sodium sulfite was proposed by Xu and involves the intermediate aziridine (Scheme 96) <2002TA1129>.



Scheme 96

Diallylamine was converted into the *cis*- and *trans*-pyrrolidinesulfonates by cyclization with sodium hydrogen sulfite in an oxygen-assisted addition which is consistent with the mechanism of addition of bisulfite to alkenes (Equation (62)) <1995JOC5474, 2001JCS(P2)2179>.



(iv) *With sulfur dioxide*

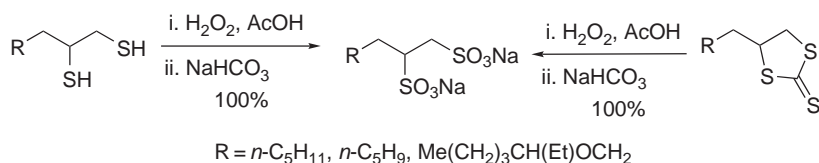
Alkanesulfonic acids can be formed via the sulfonation of alkanes with sulfur dioxide in the presence of oxygen. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.4.3.2 *By oxidation*

The oxidation of an alkyl sulfur compound can involve thiols, sulfides, sulfoxides, and sulfones. In practice, the oxidative reactions of divalent species not requiring forcing C—S bond cleavage (as for thiols and disulfides) are used as synthetic methods.

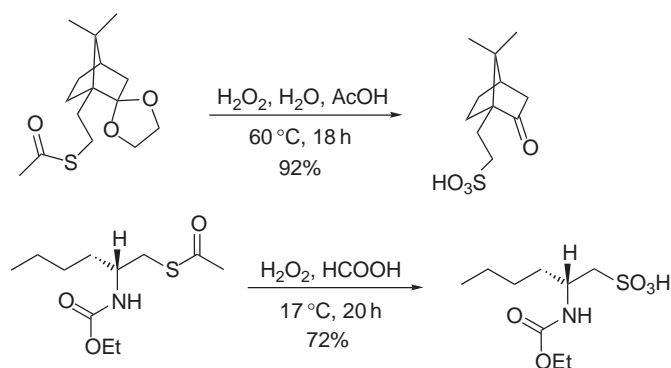
(i) *From thiols, disulfides, and related compounds*

A standard method for alkanesulfonic acid synthesis is the oxidation of thiols and disulfides <1995COFGT(2)113>. Alkane thiols or thiolacetates, which are readily cleaved to the corresponding thiols (cf. Section 2.03.1), are oxidized by oxone forming the alkanesulfonic acids in moderate yield <1995JMC4976, 2003BMCL1381>. The oxidation of 1,2-thiols or cyclic trithiocarbonates by hydrogen peroxide in the presence of acetic acid readily affords alkane-1,2-disulfonic acids isolated as the more stable sodium salts (Scheme 97) <1996ACS158>.



Scheme 97

Thiolacetates are oxidized by hydrogen peroxide in acetic or formic acid to give the corresponding sulfonic acids in high yield; this method is mild and tolerates the presence of other functional groups (Scheme 98) <1999OPP237, 2002HCA1973, 2002JMC567>.

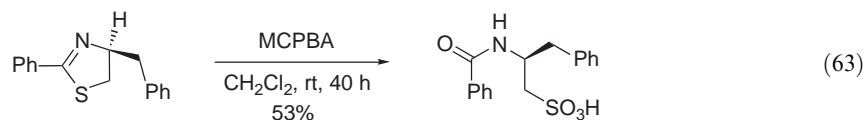


Scheme 98

Irradiation of dimethyl disulfide in a protic solvent in the presence of dioxygen leads to the formation of methanesulfonic acid in 65% yield <1995TL8197>.

(ii) From sulfides and sulfones

In general, the oxidation of alkanesulfides and sulfones to sulfonic acids is of little synthetic value <1995COFGT(2)113>. Aitken and co-workers reported the oxidation of a chiral 2-thiazoline by MCPBA to afford the sulfonic acid in good yield (Equation (63)) <1997JCS(P1)935>.

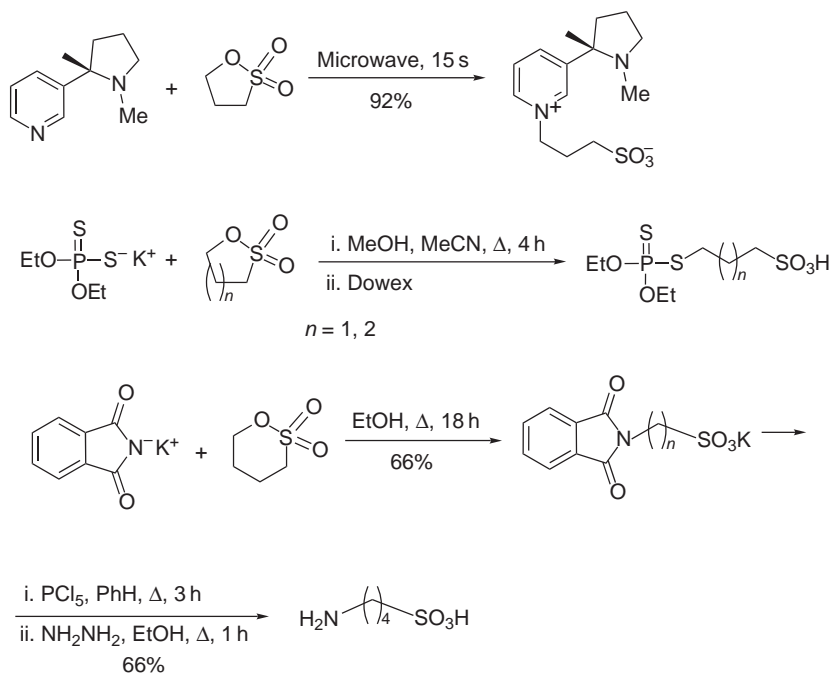


(iii) From sulfinic acids

As indicated in Section 2.03.4.2, moderate-to-poor stability of alkanesulfinic acids makes them less important precursors of sulfonic acids. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

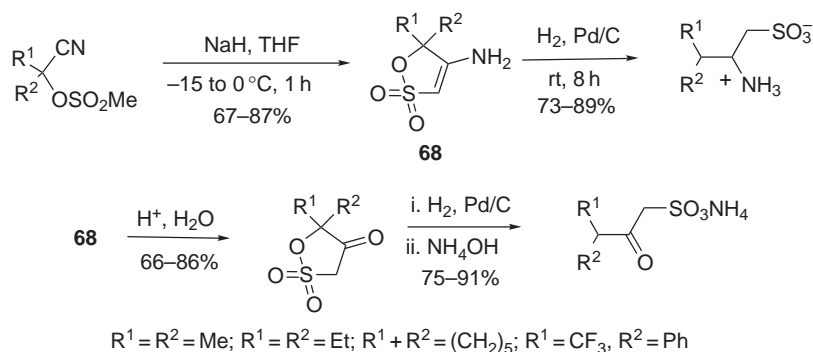
2.03.4.3.3 From sulfonic acid derivatives

Alkanesulfonyl halides, and sulfonate esters and amides are readily hydrolyzed to give the parent acid <1995COFGT(2)113>. The hydrolysis of alkanesulfonyl halides (cf. Section 2.03.3.3) proceeds in acidic or basic solution or on heating in water or methanol <1998ACS42>. The nucleophilic ring opening of cyclic sulfates is a synthetic route to hetero-functional alkanesulfonic acids (Scheme 99) <1998BMCL3059, 1998PS(134/135)137, 1998TL9587>.



Scheme 99

New routes to β -amino and β -keto sulfonic acids have been developed starting from cyanohydrin mesylates (Scheme 100) <1997JOC7021>.



Scheme 100

2.03.5 ALKANESULFENIC ESTERS AND THEIR HIGHER-COORDINATED DERIVATIVES

2.03.5.1 Alkanesulfenic Esters

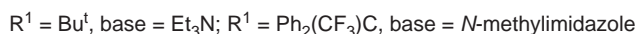
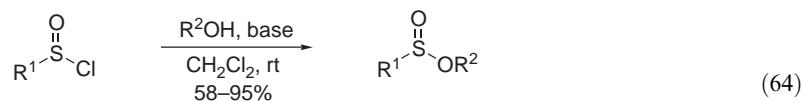
Alkanesulfenic esters are still highly reactive although they possess higher stability compared to the sulfenic acids (cf. Section 2.03.4.1). The most common approach to the alkanesulfenic esters involves the reaction of a sulfinyl halide with an appropriate alcohol. Alkyl sulfinates can undergo selective cleavage of the O—S bond on treatment with an alcohol under acidic conditions to form a new sulfinic acid derivative. A well-known [2,3]-rearrangement of the allylic sulfoxides leads to allylic sulfinates. These methods have been reviewed in COFGT (1995) <1995COFGT(2)113> and no further advances have occurred in this area.

2.03.5.2 Alkanesulfenic Esters

Diastereomeric and enantiomeric sulfinates have recently received considerable interest, mainly due to the fact that they serve as model compounds in studies of nucleophilic substitution at sulfur and are starting materials in the synthesis of sulfoxides (cf. Section 2.03.2.2.1.(ix)) and other optically active sulfinic acid derivatives <B-1997MI004, 1999OPP579>.

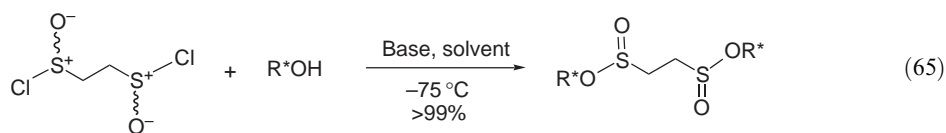
2.03.5.2.1 From sulfinyl halides

The high electrophilicity of the sulfinyl functionality coupled with the good leaving capability of chloride makes sulfinyl chlorides convenient reagents for substitution reactions. Schwan and Stricker surveyed the synthesis of sulfinic acid derivatives from sulfinyl chlorides <1999OPP579>. Sulfinic acid derivative formation via alcohol substitution of sulfinyl chlorides is readily performed in the presence of a base even for sterically crowded sulfinates (Equation (64)). This reaction, once thought to proceed via an S_N2 mechanism, is now generally believed to involve a sulfurane intermediate <1992JOC6789>. The increased stability of sulfinates over their sulfinyl chloride precursors allows comparatively easy isolation and full spectroscopic analysis.



Various chiral secondary alcohols have been used to study the dependence of stereochemical outcome of sulfinic acid derivative synthesis on the nature of the base used to catalyze the reaction. It has been shown that the achiral stereodirecting base effect determined in the DAG methodology <1995COFGT(2)113> is a general behavior in the asymmetric synthesis of sulfinic acid derivatives

<1999TA3177, 1999TL2029>. The DAG methodology was reported in the first example of an enantiodivergent dynamic kinetic resolution with the simultaneous creation of two chiral centers (Equation (65)) <2000JA7598>.



R*	Base	Solvent	Major product	Diastereomeric ratio,	
				((R),(R)):(S),(S)):(R),(S))	
DAG	Pyr	THF	((R),(R))	82:1:17	
DAG	Pr ₂ NEt	toluene	((S),(S))	20:88:12	
DCG	Pyr	THF	((R),(R))	84:1:15	
DCG	Pr ₂ NEt	toluene	((S),(S))	0:85:15	

DAG = Diacetone-D-glucose; DCG = Dicyclohexylidene-D-glucose.

A solution of sodium trifluoromethanesulfinate (sodium triflate) (2 equiv.) and phosphoryl chloride (1 equiv.) in ethyl acetate behaves like an equivalent of $\text{CF}_3\text{S}(\text{O})^+$ cation. It can be used *in situ* to prepare trifluoromethanesulfonates or trifluoromethanesulfinamides (cf. Section 2.03.9.2.2) at room temperature from alcohols or amines <1999T7243>.

2.03.5.2.2 From sulfinic acids

The instability of sulfinic acids and the requirement for the activation of the S—O bond are two drawbacks of this method. Direct esterification can be achieved with a number of reagents <1995COFGT(2)113>. Direct alkylation of the sulfinic acids or their salts with alkyl halides often results in the sulfones <1997TL6197> (cf. Section 2.03.2.3.3), although the use of diazomethane leads to good yields of the methyl esters <1995COFGT(2)113>.

2.03.5.2.3 From alkyl sulfites

The reaction of an alkyl Grignard reagent with a dialkyl sulfite results in formation of a sulfinic ester. This method has been applied to stereocontrolled sulfinate synthesis. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.5.2.4 From disulfides

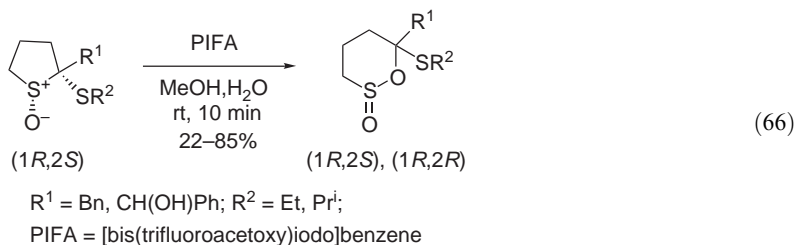
Disulfides are oxidized in the presence of an alcohol to give the sulfinic esters. The most common oxidizing agent is NBS (e.g., <1996BSF1127, 1995COFGT(2)113>) providing good yield for a variety of disulfides and alcohols. The initial transformation of a disulfide into a sulfinyl chloride (cf. Section 2.03.3.2) followed by interaction with an alcohol in the presence of base (cf. Section 2.03.5.2.1) can be used as an alternative synthesis <1999JA10646, 1999JOC1420>.

2.03.5.2.5 From thiosulfonates

A few earlier reports indicated that reductive desulfurization of thiol sulfonic esters can result in the sulfinic esters although not always in good yield. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

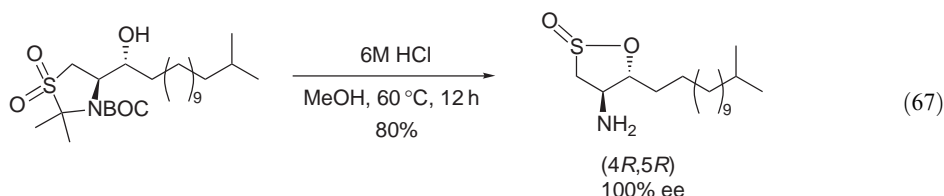
2.03.5.2.6 From sulfoxides

The cleavage of a C—S bond in a sulfoxide in the presence of an oxidising agent and an alcohol can lead to a sulfinic ester <1995COFGT(2)113>. The oxidative ring enlargement occurred with optically pure cyclic (1*R*,2*S*)-2-alkylthio sulfoxides to form two separable diastereomeric cyclic sulfonates (δ -sultines) (Equation (66)) <1999EJO943>. This reaction proceeds with the inversion of configuration at the sulfoxide sulfur and is assumed to involve a bivalent sulfur-catalyst coordination during the course of the oxidation.

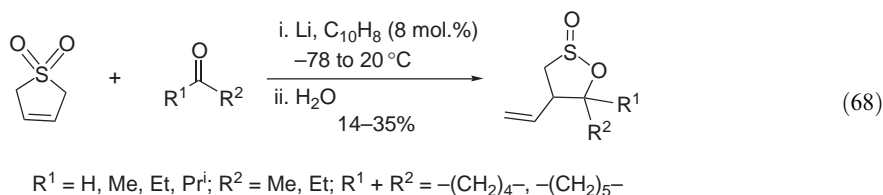


2.03.5.2.7 From sulfones

In a manner similar to earlier results <1995COFGT(2)113>, on treatment with hydrochloric acid, γ -hydroxy sulfones form cyclic sulfonates as exemplified in Equation (67) <1999JCS(P1)2467> (cf. Section 2.03.4).

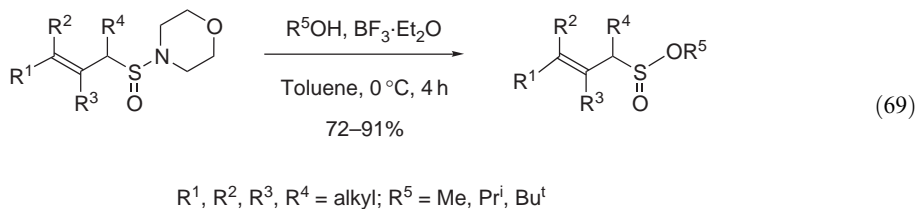


During a study of reductive desulfonylation of sulfones, it was found that the reaction of sulfolene with a carbonyl compound in the presence of excess lithium powder and a catalytic amount of naphthalene leads to cyclic sulfonates in modest yield (Equation (68)) <1995T2699>. As a consequence of the existence of two or three stereocenters in the molecule, the cyclic sulfonates were isolated as a mixture of diastereoisomers which in almost all cases were separated by column chromatography.



2.03.5.2.8 From sulfinamides

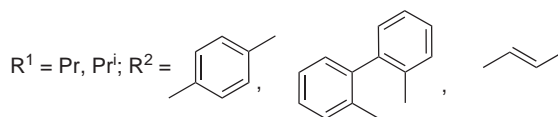
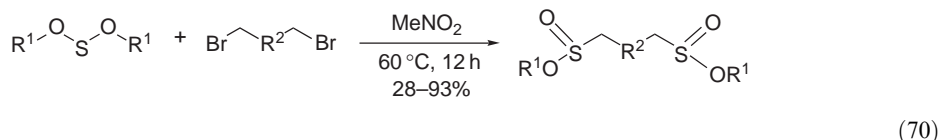
The previously reported reaction for preparing alkyl alkanesulfinates <1995COFGT(2)113> has been developed by the same authors into a method of synthesis for a number of allylic sulfinates (Equation (69)) <1995BSF196>.



2.03.5.2.9 Miscellaneous

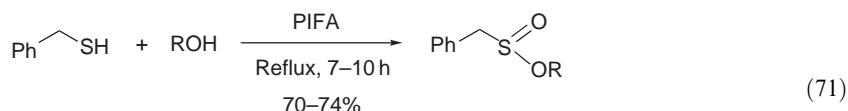
(i) From sulfoxylic dialkyl esters

The dithio-Arbuzov reaction of dialkyl sulfoxylates results in sulfinic esters in moderate-to-high yield (Equation (70)) <1995PS(102)205>.



(ii) From a thiol

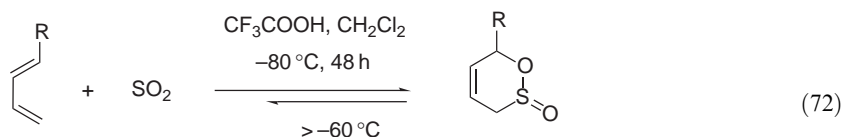
The oxidation of benzyl thiol by a hypervalent iodine compound in the presence of an alcohol leads to a sulfinate and represents a simple procedure, mild conditions, and good yield (Equation (71)) <1997SC1321>.



$\text{R} = \text{Me}, \text{Et}; \text{PIFA} = [\text{bis}(\text{trifluoroacetoxy})\text{i}]\text{benzene}$

(iii) From dienes and sulfur dioxide

The temperature- and catalyst-dependent addition of sulfur dioxide to 1,3-dienes has been extensively studied by Vogel and co-workers <1998JA13276, 1998JOC9490, 2000CEJ1858, 2001CC1214, 2002CEJ1336, 2002HCA761, 2002S225>. It was concluded that the competition between hetero-Diels–Alder and cheletropic additions to form sultines or sulfolenes, respectively (cf. Section 2.03.2.3.8), depends on the nature of the conjugated diene and on the reaction conditions. At low temperature (-80°C) and in the presence of a suitable protic or Lewis acid catalyst, 1,3-dienes add sulfur dioxide highly regioselectively forming exclusively the corresponding 6-substituted cyclic sulfinates (sultines) (Equation (72)). Sultines can adopt two pseudochair conformations, which was established by NMR spectroscopy studies. The instability of such a type of cyclic sulfinates do not allow their isolation.



$\text{R} = \text{Me}, \text{Et}, \text{Bu}^t, \text{Bn}, \text{cyclohexyl}, \text{F}, \text{OAc}, \text{OBz}, \text{SiEt}_3, \text{OMe}$

(iv) From unsaturated alcohols

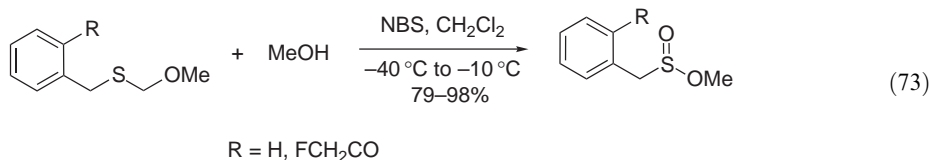
The reaction of an unsaturated alcohol with *N*-sulfinyl-*p*-toluenesulfonamide <1995COFGT(2)113> has been developed into a convenient stereocontrolled synthesis of mono- and bicyclic sulfinates (sultines) in good yields <1995JOC8067>.

(v) From thioketenes

No recent reports have been found in the literature in addition to the example of the oxidation of a thioketene by singlet oxygen described in COFGT (1995) <1995COFGT(2)113>.

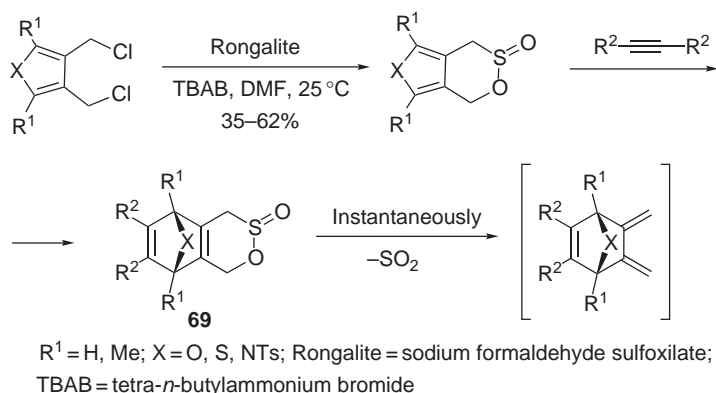
(vi) From methoxymethyl sulfides

The oxidation of substituted aryl or benzyl methoxymethyl sulfides by NBS furnishes the sulfinates in good yield (Equation (73)) <1995SC2871>.



(vii) From o-bis(chloromethyl) heterocycles

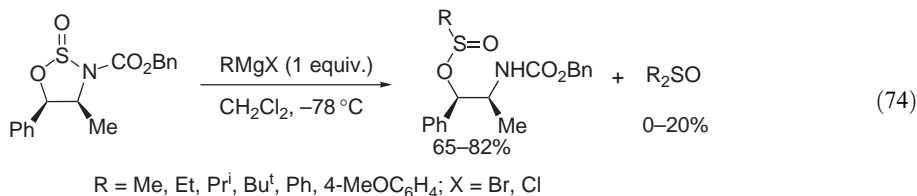
Bis(chloromethyl)thiophene, furan, and pyrrole are readily transformed with sodium formaldehyde sulfoxylate (rongalite) into the corresponding heterocycle-fused sultines (Scheme 101). The sultines react *in situ* with a variety of dienophiles to give the adducts **69** which instantaneously eliminate sulfur dioxide, thus providing the heterocyclic analogs of *o*-quinomethanes for further cycloaddition reactions <1995CC2537>.



Scheme 101

(viii) From a sulfamidite

The reaction of norephedrine-derived *N*-benzylcarbonylsulfamidite with 1 equiv. of an organometallic reagent leads to the sulfinic esters in good yield; symmetric sulfoxides are unavoidable by-products due to high reactivity of the sulfinic esters with Grignard reagents (Equation (74)) <2003OL75> (cf. Section 2.03.2.2.1.(ix)).



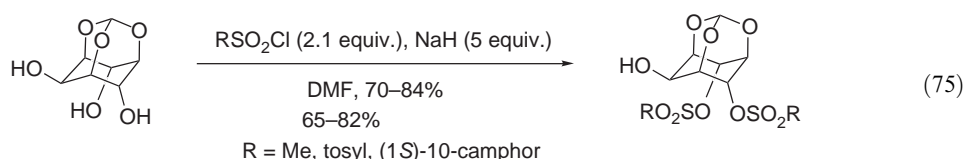
2.03.5.3 Alkanesulfonic Esters

Sulfonic esters are well recognized as a fundamental unit in various fields of organic synthesis, especially as protecting groups and as reagents for the reliable transformation of alcohols into alkylating agents.

2.03.5.3.1 From sulfonyl halides

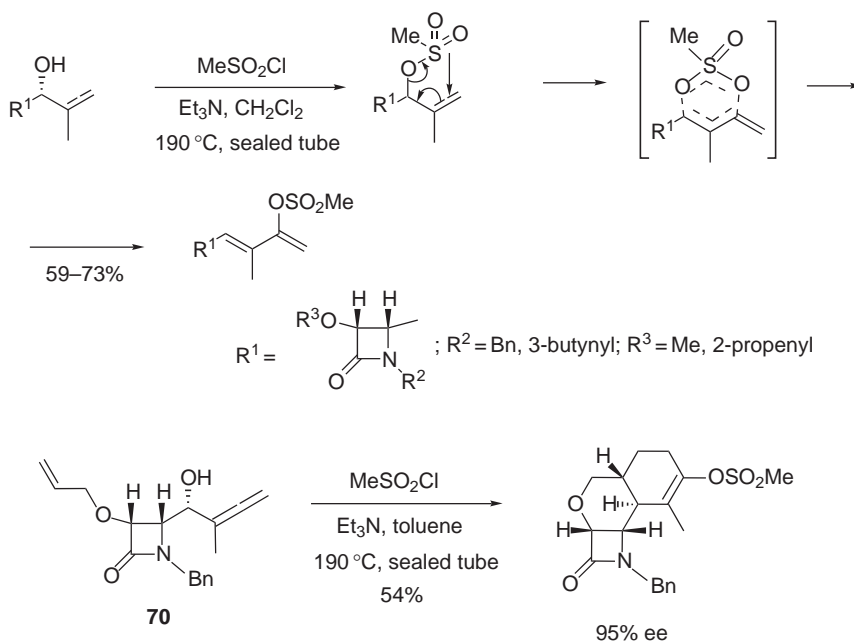
A sulfonyl halide and an alcohol react in the presence of a base to form a sulfonate. Among sulfonyl halides, the sulfonyl chlorides are commonly employed as the acylating agent although in some specific syntheses the sulfonyl fluoride can also be utilized (cf. [Section 2.03.3.3](#)). This method is the most common for protection of the hydroxy function in alcohols, and mesylates, tosylates and triflates are among the widely recognized protecting groups. There are multiple recent reports in the literature on the reaction of methanesulfonyl chloride with a variety of alcohols in the presence of triethylamine [\[1995TL1223, 1998JCS\(P1\)2341, 1999JOC7856, 2000JOC3310, 2000JOC6766, 2000T6223\]](#) or pyridine [\[1995JOC1066, 1995TL8247, 1997JOC7021, 1998JOC6, 2001TL4285\]](#). The reaction is usually performed in methylene chloride affording typically good-to-high yields of mesylates. Mesylation and tosylation can also be carried out in toluene in the presence of triethylamine with a catalytic amount of trimethylamine hydrochloride [\[1999T2183\]](#). This practical and efficient method avoids chlorinated solvents and the excess pyridine which is often required for the reaction completion. Also, this protocol affords the mesylation of less reactive alcohols (e.g., 3-octanol) in greater than 90% yield, whereas the traditional catalysis with triethylamine or pyridine results in less than 10% yield.

Regioselective *O*-sulfonylation has been reported for *myo*-inositol orthoethers. Reaction with methanesulfonyl or tosyl chloride or with (1*S*)-10-camphor sulfonyl chloride in the presence of sodium hydride affords the 4,6-di-*O*-sulfonates in good yield ([Equation \(75\)](#)) [\[2001TL3037\]](#). The requirement of the presence of a metal ion for exclusive functionalization of the C-4 and C-6 hydroxy groups is explained by the stability of the sodium ion–orthoformate chelate thus directing the sulfonylation.

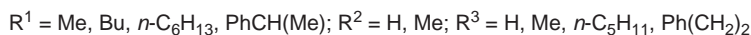
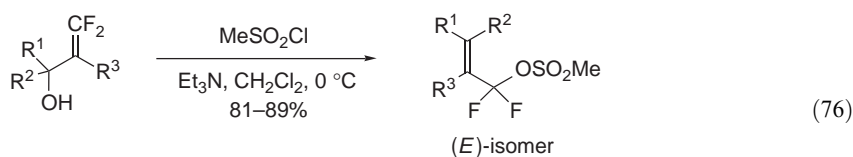


Depending upon the substituents in a substrate, the conditions of sulfonylation of a hydroxy group can favor other transformations of the molecule. On mesylation of allenols, the stereoselective formation of the 1,3-diene occurred via a suggested concerted mechanism involving a six-membered cyclic transition state ([Scheme 102](#)) [\[2002CC1472\]](#). A domino allenol transposition/intramolecular Diels–Alder reaction with high stereoselectivity was observed for the 2-propenyl compound **70** if methylene chloride is replaced by toluene as solvent.

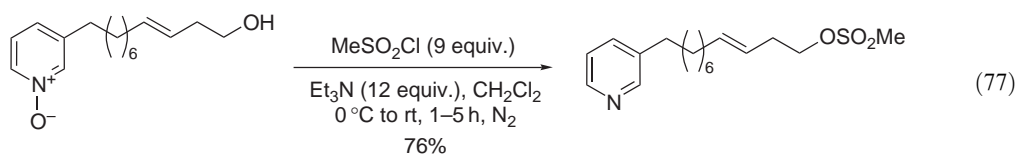
The mesylation of γ,γ -difluorinated allylic alcohols under the usual conditions furnishes the α,α -difluorinated allylic mesylates, possibly by a 1,3-migration of the mesyloxy group after formation of the expected γ,γ -difluorinated allylic mesylates ([Equation \(76\)](#)). This rearrangement was conveniently applied to the construction of trisubstituted allylic alcohols, α,β -unsaturated esters, amides or ketones in good-to-excellent yields with exclusive (*E*) stereoselectivities [\[2001OL743\]](#).



Scheme 102



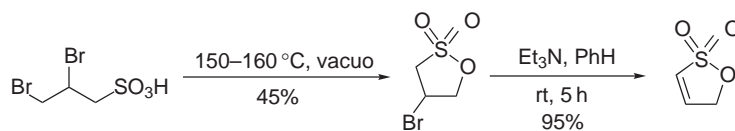
The use of large excesses of methanesulfonyl chloride and triethylamine on mesylation of the hydroxy group on the side chain of pyridine-*N*-oxides leads to deoxygenation of the pyridinium ring (Equation (77)) <1998CL829>.



A practical procedure for chemo- and regioselective conversion of steroid 3-ketones into the corresponding enol sulfonates has been developed with the use of 3-oxa-octafluoropentanesulfonyl fluoride <1996TL8553>. Nonafluorobutanesulfonyl fluoride has been utilized for the preparation of a novel class of vinylphosphonates, α -phosphonyl nonafluorobutanesulfonates <1999TL5337>. Both reactions were catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and were carried out in toluene and THF, respectively.

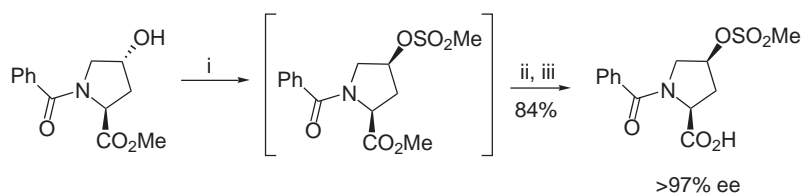
2.03.5.3.2 From sulfonic acids

Heating 3-hydroxypropane or 4-hydroxybutane sulfonic acids in vacuum results in intramolecular cyclization affording the corresponding cyclic sulfonates <1995COFGT(2)113, 1995JOC5474>. In a similar way, β -bromosultone was obtained by a distillative cyclization of 2,3-dibromopropane-1-sulfonic acid followed by treatment with triethylamine to give the propene sultone, which is a substrate for Diels–Alder cycloadditions (Scheme 103) <1999T2245>.



Scheme 103

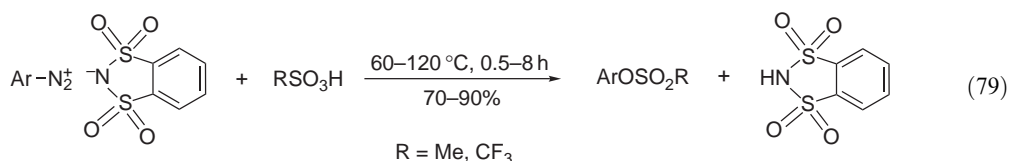
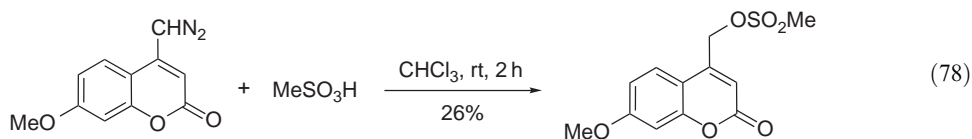
The reaction of a chiral secondary alcohol with methanesulfonic acid under Mitsunobu conditions proceeds with stereochemical inversion in high enantiomeric excess (Scheme 104) <1996JOC7955>.



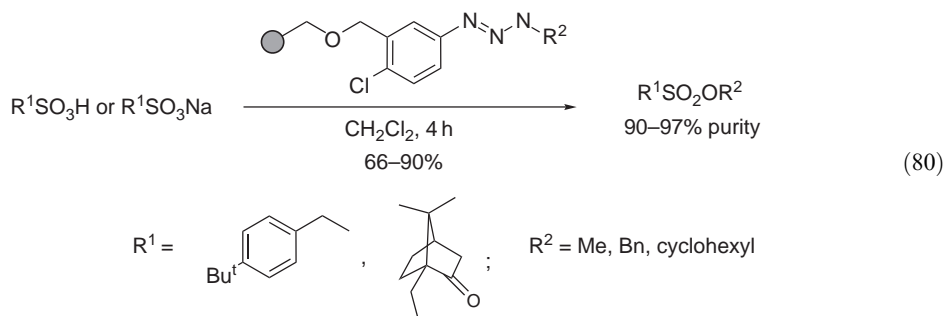
i. MeSO_3H (1.2 equiv.), Ph_3P , (1.2 equiv.), DIAD (1.4 equiv.), Et_3N (0.4 equiv.), toluene, $60-70^\circ\text{C}$, 3 h; ii. NaOH ; iii. H^+
DIAD = diisopropyl azodicarboxylate

Scheme 104

Direct esterification of alkanesulfonic acids can be achieved using a variety of reagents. Diazoalkane derivatives are long known to be efficient alkylating agents as demonstrated by the coumarin derivative shown in Equation (78) <1999JOC9109>. Attempts to prepare this mesylated coumarin from the hydroxy coumarin and methanesulfonyl chloride failed. Methane and trifluoromethanesulfonates have been prepared by thermal decomposition of dry arenediazonium *o*-benzenedisulfonimides in methanesulfonic or trifluoromethanesulfonic acid, respectively (Equation (79)) <1998S90>.

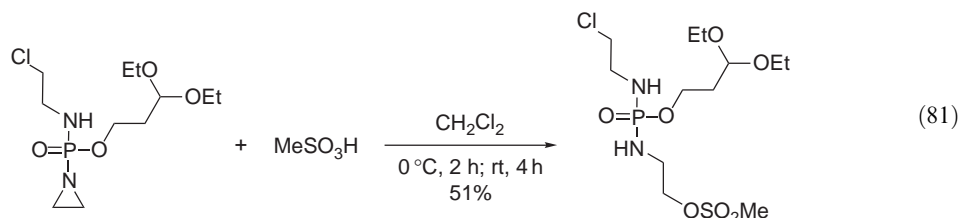


An efficient and selective method for synthesis of sulfonic esters from sulfonic acids or sodium sulfonates using a polymer bound primary triazene as alkylating agent has been developed by Bräse and co-workers (Equation (80)) <2001TL7833>.



Direct esterification of taurine has been accomplished by reaction with ethyl chloroformate in the presence of *n*-butylamine in dioxane to give ethyl 2-aminoethanesulfonate <2001BMC1827>.

Alkylation of methanesulfonic acid by a multifunctional aziridine proceeds without catalysis (Equation (81)) <2000AF843>.

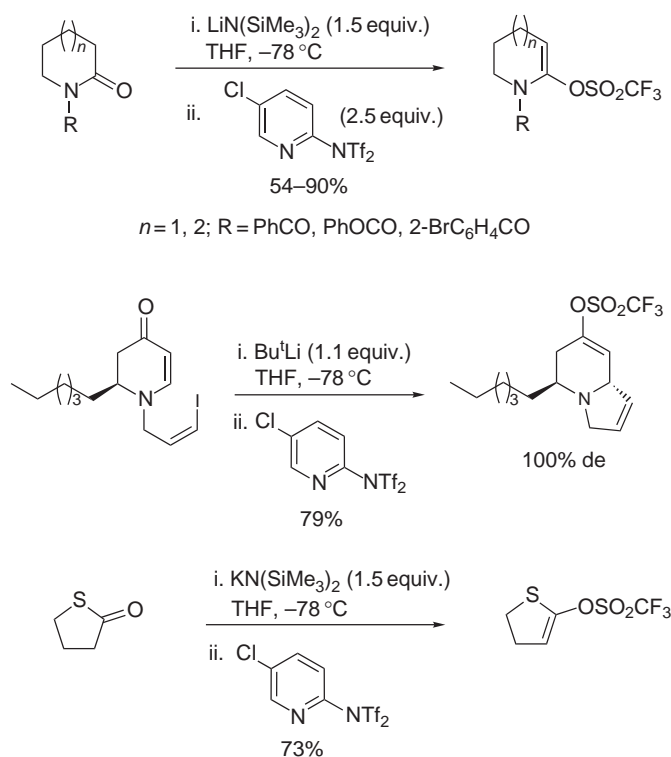


2.03.5.3.3 From sulfenes

On treatment with a base, an alkanesulfonyl chloride can form a sulfene which may undergo cycloaddition to form a cyclic sulfonate <1995COFGT(2)113>. No further advances have occurred in this area.

2.03.5.3.4 From sulfonamides

The utility of 2-[*N,N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins reagent), a convenient alternative to triflic anhydride, is now well recognized in the synthesis of vinyl trifluoromethanesulfonates (vinyl triflates) which are important synthetic intermediates in cross-coupling reactions with various organometallic compounds. Comins reagent has been employed in efficient syntheses of a number of vinyl triflates from carbonyl compounds via enolization (Scheme 105) <1995JOC2656, 1995SL151, 1996JA12248>.



Scheme 105

N-Phenyltriflimide, although ineffective in the reaction with γ -thiobutyrolactone <1995SL151>, reacts regioselectively with a number of enolates to form triflates in good-to-excellent yield (Scheme 106) <1995T5831, 1995T9327, 1997T5233>.



Synthesis of aryl triflates from phenols using *N*-phenyltriflamide under controlled microwave heating (6 min) has been accomplished in good yield. This methodology was applied to both solutions or solid mixtures [<2002OL1231>](#). PEG-supported triflimide and triflamide are efficient new reagents for triflation of aryl alcohols and lithium enolates in high yields [<2000OL477>](#).

The very active mesylating agent 1-methanesulfonyloxy-3-methylimidazolium triflate was effective under essentially mild neutral conditions, whereas other methods for mesylate formation failed (Equation (82)) <1999JOC4069>.



2.03.5.3.5 From sulfones

Thermal rearrangement of keto sulfones and photolysis of cyclic sulfones can lead to the sulfonate esters <1995COFGT(2)113>. No further advances have occurred in this area.

2.03.5.3.6 From sulfur trioxide and alkenes

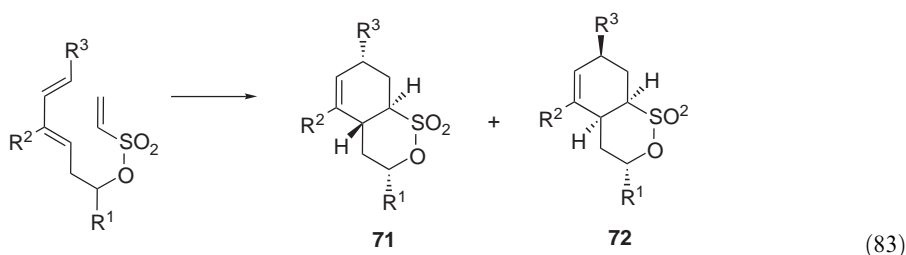
Alkenes can add sulfur trioxide to form cyclic or acyclic sulfonates <1995COFGT(2)113>. No reports on this subject have been found in the recent literature.

2.03.5.3.7 From allylic sulfites

The scattered literature data indicate that allylic sulfites can undergo [2,3]-sigmatropic rearrangement upon catalysis furnishing the sulfonates, or the cyclic sulfites can undergo a related rearrangement into the cyclic sulfates <1995COFGT(2)113>. No further advances have occurred in this area.

2.03.5.3.8 From unsaturated sulfonic esters

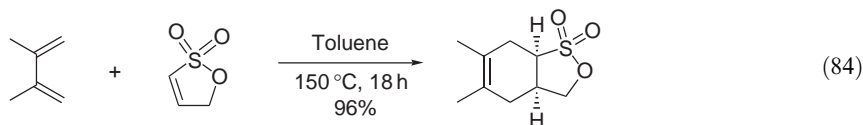
Unsaturated sulfonate esters are very good dienophiles and can be readily transformed into the saturated sulfonates via intra- or intermolecular cycloadditions with dienes. Metz and co-workers investigated the intramolecular [4 + 2]-cycloaddition of vinylsulfonic esters including dependence upon pressure and scavengers (Equation (83)) <1995T711, 2000T873>. Only two diastereomers were formed under both conditions.



R^1	R^2	R^3	13kbar, CH_2Cl_2 , rt		Toluene, BHT, reflux	
			71:72	Yield (%)	71:72	Yield (%)
H	H	H	1:2.3	88	1:1	76
Me	H	Me	1:2	78	1.4:1	64
Bu ^t	Me	H	3.6:1	79	4.7:1	76

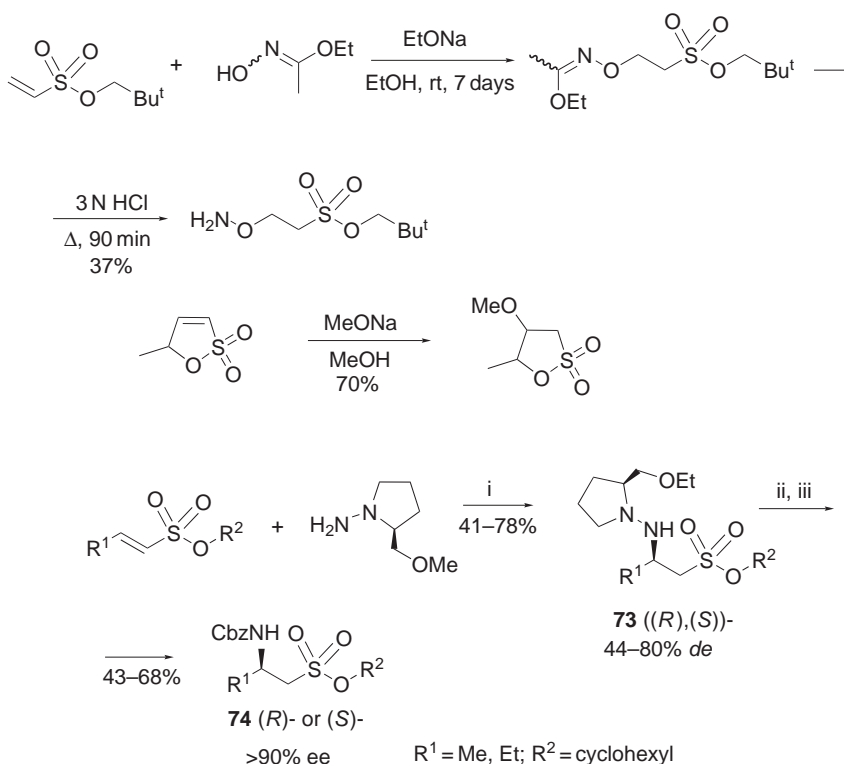
BHT=2,6-di-*tert*-butyl-4-methylphenol.

Intermolecular cycloaddition of an α,β -unsaturated γ -sultone (cf. Scheme 103) has been reported for a number of dienes (Equation (84)). These sultone cycloadducts can be further manipulated by ring-opening at the γ -position by various nucleophiles such as alcohols, amines and thiols <1997CC611>.



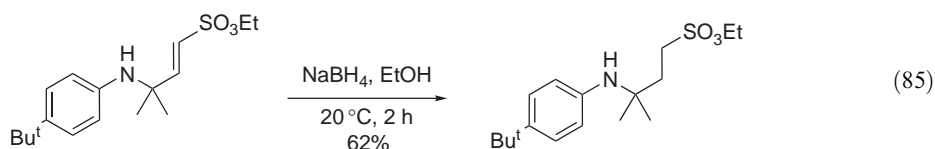
α,β -Unsaturated sulfonates undergo Michael or aza-Michael addition affording adducts in moderate-to-good yield (Scheme 107) <1998SL1411, 2001TL4285, 2002SL304>. The aza-Michael diastereomeric adducts **73** have been separated by preparative HPLC to yield diastereomerically pure β -hydrazinocyclohexylsulfonates which were transformed into the amino-sulfonates **74** in high enantiomeric excess <2002SL304>.

Reduction of vinyl sulfonates by sodium borohydride can give alkyl sulfonates (Equation (85)) <2002CC632>. Reduction of α,β -unsaturated sulfonic esters to the saturated sulfonic esters can also be accomplished by hydrogenation using platinum dioxide <1998JMC1315> or palladium on charcoal <1997TL8627>.



i. ZnBr₂ (0.2 equiv.), MeOH; ii. BF₃·THF (10 equiv.), THF-MeOH, reflux, 5 h;
 iii. CbzCl (3 equiv.), Na₂CO₃ (6 equiv.), CH₂Cl₂-H₂O (4:1), reflux, 1–3 d

Scheme 107



2.03.5.3.9 From diazo compounds

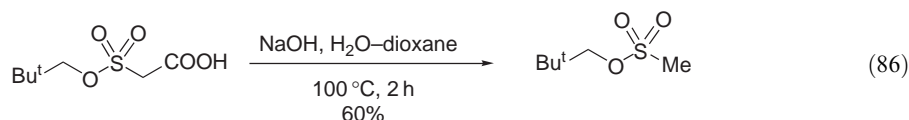
A diazoalkane can react with sulfur dioxide in ethanol to give the ethyl alkanesulfonates. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.5.3.10 From sulfinate esters

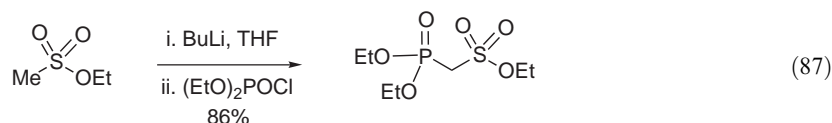
Sulfinate esters are more difficult to prepare than sulfonates and this method has not been developed beyond a single example of sulfinate oxidation by potassium permanganate <1995COFGT(2)113>.

2.03.5.3.11 From sulfonyl esters

Facile decarboxylation of a sulfonyl acetic acid derivative results in the formation of the mesylate (Equation (86)) <1996JOC7250>.



A convenient preparation of a Wittig reagent is afforded by deprotonation of ethyl mesylate followed by interaction with phosphorochloridic acid diethyl ester (Equation (87)) <2003JMC681>.

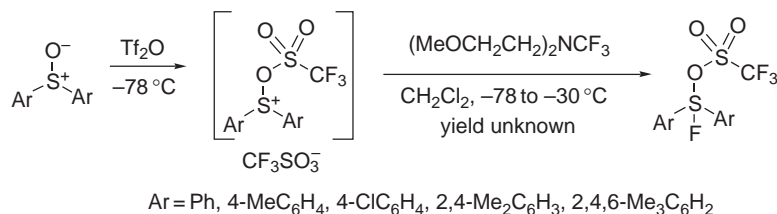


2.03.6 RSOX FUNCTIONS

2.03.6.1 X = Sulfur

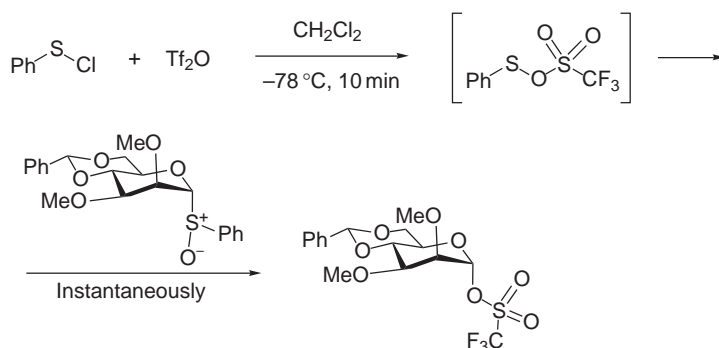
The synthesis of a limited number of highly reactive sulfinic anhydrides was surveyed in COFGT (1995) <1995COFGT(2)113>.

An interesting *S*-fluorination of diaryl sulfoxides was accomplished with bis(2-methoxyethyl)-aminosulfur trifluoride (dexofluorTM reagent) in the presence of triflic anhydride (Scheme 108) <2002JFC169>. The reaction proceeds through the intermediate trifluoxysulfonium triflate and was monitored by NMR.



Scheme 108

The reaction of benzenesulfonyl chloride with triflic anhydride resulted in the sulfonyl triflate, which is a powerful electrophilic reagent, which was used *in situ* (Scheme 109) <1997JA11217, 2000JOC1291>.

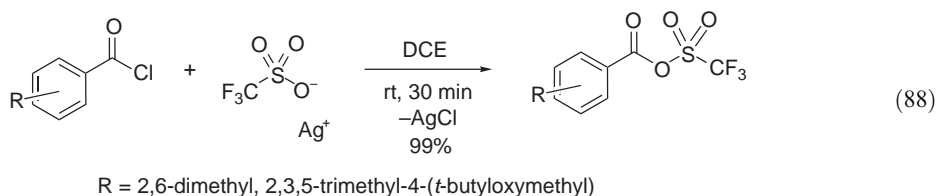


Scheme 109

2.03.6.2 X = Acyl

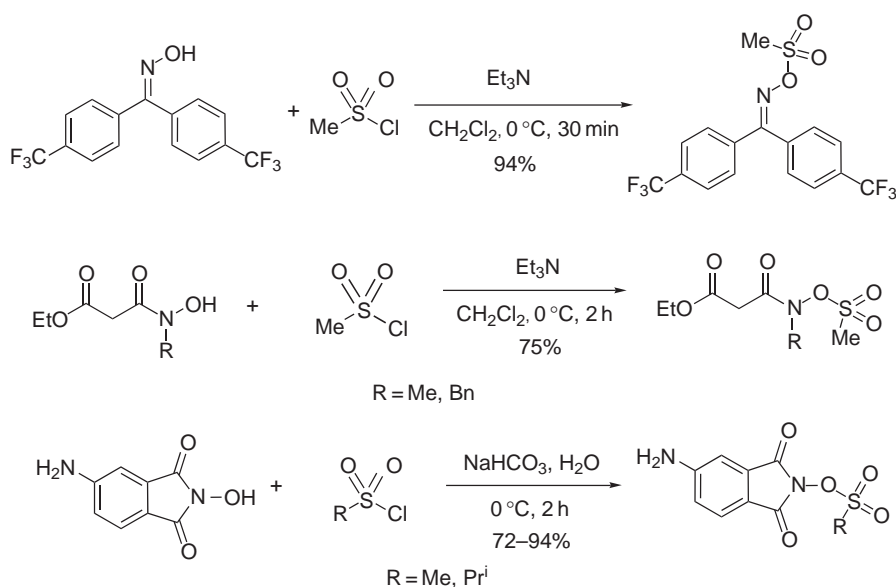
The acylating power of the carboxylic–sulfonic acid mixed anhydrides is often utilized in the activation of the carboxylic acids [<1996RTC321, 2001BMC465, 2002JA2202, 2003BMCL147>](#). A carboxylic acid is typically treated with methane or trifluoromethane sulfonyl chloride in the presence of triethylamine at 0 °C; the mixed anhydride thus formed is used *in situ*.

For mechanistic investigations of aromatic acylation reactions, Effenberger and co-workers prepared solutions of acyl triflates from the substituted benzoyl chlorides and silver triflate (Equation (88)) [<1996JA12572, 2001JA3429>](#).



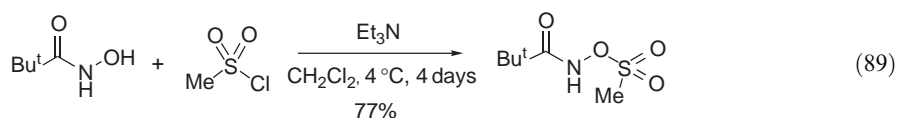
2.03.6.3 X = Nitrogen

The facile reaction of an alkanesulfonyl chloride with the hydroxy group of an *N*-substituted hydroxylamine readily proceeds in the presence of a base furnishing the *O*-sulfonylated compounds in good to high yield (Scheme 110) [<1995JOC5992, 1996BMCL451, 1999BCJ1869, 2000BMCL27>](#).

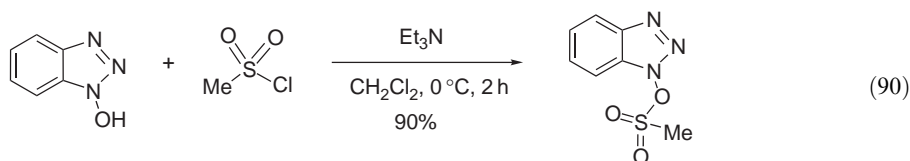


Scheme 110

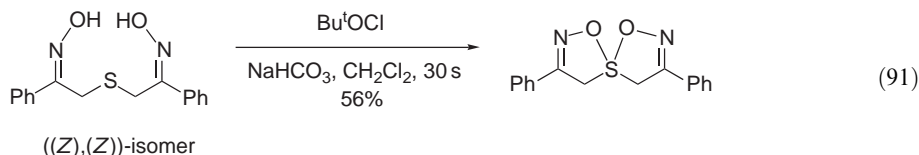
In a similar way, commercially available *t*-butyl-*N*-hydroxycarbamate was converted to the methanesulfonyloxycarbamate (>20 g batches) in 77% yield (Equation (89)) [<1998JOC10040>](#).



A regioselective *N*-mesylating agent has been conveniently prepared from benzotriazol-1-ol and mesityl chloride (Equation (90)) [<1999TL117>](#) (cf. Section 2.03.9.3.3).

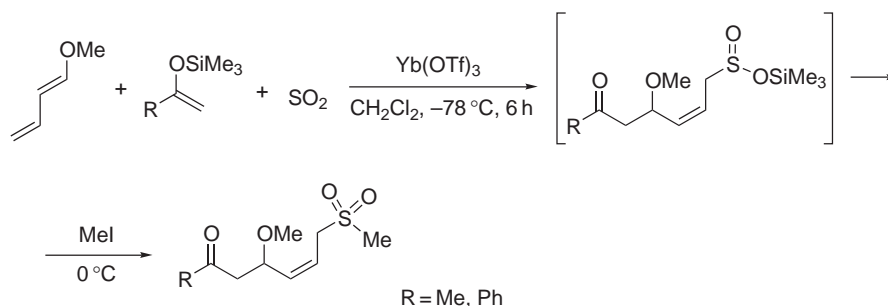


An interesting example of the sulfurane synthesis has been reported by Livant and co-workers (Equation (91)) <1995JOC4153>.



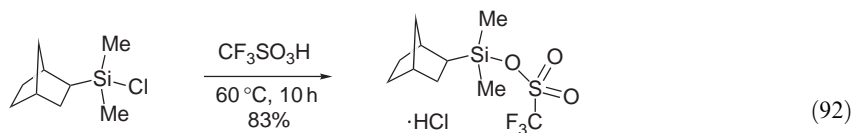
2.03.6.4 X = Silicon

The reaction of sulfur dioxide with a trimethylsilyl enol and 1-methoxybutadiene in the presence of a Lewis acid catalyst generates the trimethylsilyl sulfinates that are converted *in situ* to sulfones (Scheme 111) <1997TL6197, 2001JOC5080, 2001TL673, 2002S225> (cf. Section 2.03.2.3.2).

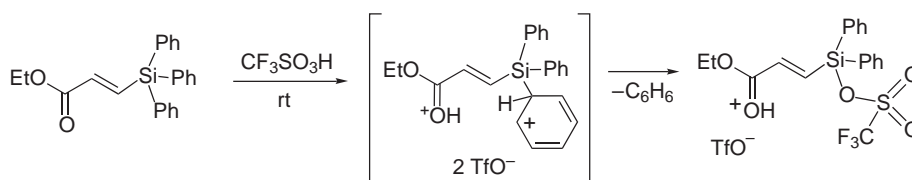


Scheme 111

In order to find a more readily available silyl protecting reagent that retains most of the superior properties of the TBDMS group, Heldmann and co-workers prepared 2-norbornyldimethylsilyl triflate (NDMS triflate) (Equation (92)) <2002SL1919>. This is a very powerful reagent capable of silylating even tertiary alcohols under mild conditions.



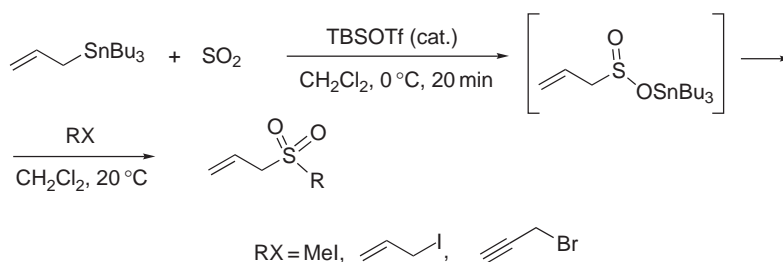
Triphenylsilyl acrylates are protonated by triflic acid initially on the carbonyl group leading to cleavage of a phenyl substituent (Scheme 112) <1999JOC1780>. This transformation is very clean and complete within minutes (monitored by NMR).



Scheme 112

2.03.6.5 X = Tin

The reaction of allyl(tributyl)tin and sulfur dioxide furnishes the tributyltin pro-2-ene-1-sulfinate in a manner similar to the formation of silyl sulfonates (Section 2.03.6.4) (Scheme 113) <2002S225>.



Scheme 113

2.03.6.6 X = Phosphorus

The formation of an $\text{S}-\text{O}-\text{P}$ bond was reported in the synthesis and studies of phosphorus(III) triflates <1995JOC6362, 1996CB465, 1998JOM(567)199, 2002JOM(643-644)516> and mixed phosphonic-sulfonic anhydrides <1996JCR(S)110, 1996TL3533, 1999JCS(P2)2589, 2000T5213>. Both groups of compounds are highly reactive and are used *in situ* for further transformations.

2.03.7 RSSH, R^1SSR^2 , AND RSSX FUNCTIONS AND THEIR HIGHER-COORDINATED DERIVATIVES

This section updates COFGT (1995) <1995COFGT(2)113> on the preparation of aliphatic compounds containing a disulfide linkage. Due to space limitations, a comprehensive survey is not possible and selected examples of the most efficient methods with use of novel catalysts and/or conditions are discussed.

2.03.7.1 Hydrodisulfides and Hydropolysulfides

Alkyl hydrodisulfides can be prepared from thiols and sulfenyl chloride analogs or dialkyl thiosulfones. The reactivity of hydrodisulfides and hydropolysulfides can involve both disulfide and thiol functionalities. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.7.2 Alkyl Disulfides

The most important methods for preparation of disulfides involve the oxidation of thiols and thioalkylation (thiolysis) of sulfur-containing compounds. The oxidation of thiols is mainly employed in the synthesis of symmetrical disulfides, whereas thiolysis is favored for the preparation of unsymmetrical disulfides.

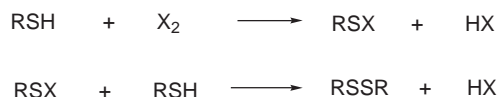
2.03.7.2.1 Oxidation of thiols

Oxidation of thiols is the most common method for disulfide synthesis, mainly because a large number of thiols are commercially available or easily synthesized (Section 2.03.1). Reagents such as halogens, hydrogen peroxide, cerium(IV) salts, permanganates, transition metal oxides, sodium perborate, ferric chloride, sodium chlorite, and nitric oxide have been utilized for oxidation of thiols to disulfides <1995COFGT(2)113>. Since thiols can easily be over-oxidized, a variety of chemical oxidation methods have been developed for the controlled oxidative coupling of thiols to disulfides.

There is still a need for improved general, efficient, and eco-friendly methodologies to synthesize disulfides from thiols. In particular, efficient reactions conducted in the absence of solvents under mild conditions are of importance and recent advances in this area are discussed below.

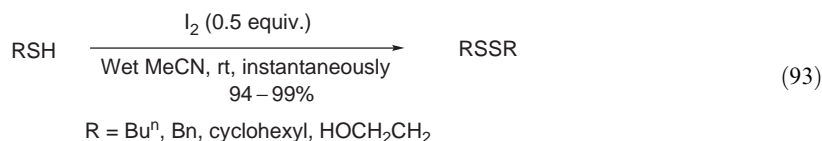
(i) Halogens

The use of iodine or bromine in an inert solvent results in the conversion of a thiol into a disulfide [<1995COFGT\(2\)113>](#). In general, a thiol reacts with a halogen to form an intermediate sulfenyl halide which reacts with a second thiol molecule to yield the corresponding disulfide ([Scheme 114](#)) [<2000OL369>](#). If hydrogen halide is not removed as soon as it is formed, acid promoted side reactions can complicate the oxidation. The reaction can proceed smoothly with a controlled amount of halogen.

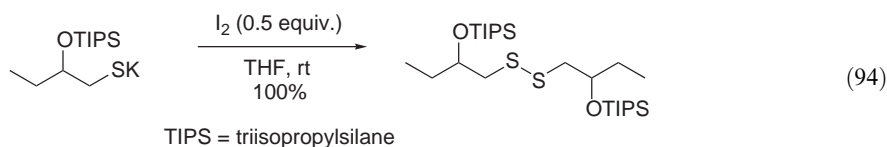


Scheme 114

It has been observed that the oxidative coupling of thiols occurs immediately with iodine in wet acetonitrile at room temperature in high yield ([Equation \(93\)](#)) [<2002JCR\(S\)564>](#).

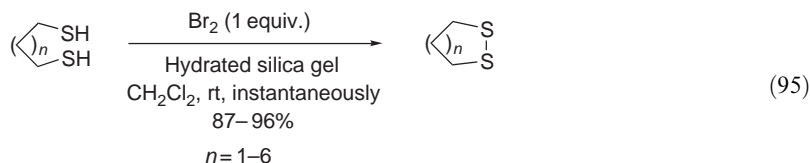


The potassium salt of β -triisopropylsilyloxybutane thiol was quantitatively converted by iodine to the disulfide and the triisopropylsilyl (TIPS) protecting group remained untouched ([Equation \(94\)](#)) [<1998TL4409>](#).



Iodine has also been used in the presence of aqueous sodium bicarbonate solution [<1996JMC596>](#) or potassium hydride in THF [<1998TL4409>](#).

Bromine is also a common reagent for oxidation of thiols to disulfides. An interesting method has been developed using bromine on hydrated silica gel support. This procedure utilizes organic media and does not require a base to suppress acid-promoted side reactions since silica gel acts as both a heat sink and as an HBr scavenger ([Equation \(95\)](#)) [<2002TL6271>](#).



Bromine can also oxidize medium length alkanethiols in the absence of solvent [<1996SC191>](#).

(ii) Peroxides

Although hydrogen peroxide is known to oxidize thiols to disulfides [<1995COFGT\(2\)113>](#), this method often requires long reaction times and strong basic or acidic conditions. Recently, quantitative oxidative conversion of thiols to disulfides by aqueous 30% H₂O₂ in

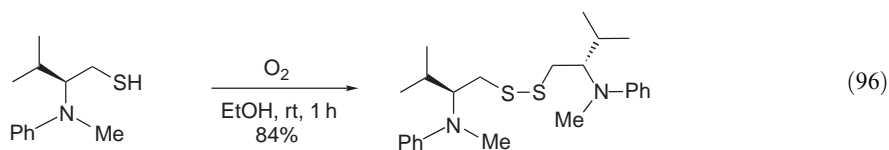
trifluoromethanol has been reported under neutral conditions at room temperature <2000S223>. The solvent is recovered during work-up by distillation as an azeotrope and can be recycled.

(iii) *Diethyl azodicarboxylate*

The use of diethyl azodicarboxylate (DEAD) in the oxidation of thiols to both symmetrical and unsymmetrical disulfides is performed in dry solvent in the dark and can be catalyzed by triphenylphosphine. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

(iv) *Aerial oxidation*

Thiols can be oxidized by air to disulfides. The process can be accomplished in high yield on bubbling air or oxygen through the reaction mixture (Equation (96)) <1998TA3461>. The reaction of thiols with oxygen is sensitive to catalysis by metal ions, and these procedures are described below.



(v) *Miscellaneous organic reagents (chemical methods)*

There are a number of chemical-based methods in addition to those described in COFGT (1995) <1995COFGT(2)113> or discussed above and are based on inorganic metal salts. Air oxidation of thiols is efficiently catalyzed by hydrotalcite clay <1999JCR(S)374>. Selective and simple phase-transfer-catalyzed oxidation of thiols to disulfides proceeds in the system $\text{CBr}_4/\text{K}_2\text{CO}_3/18\text{-crown-6}$ in benzene <1999JCR(S)624>. Elemental sulfur can oxidize alkanethiols quantitatively in the presence of sodium hydroxide and alcohols without contamination by higher polysulfides <1998PS(143)125>. Peroxysulfuric acid (Caro's acid) <1999SC3597> and tetrabutyl ammonium peroxydisulfate under solvent free conditions <2002SC3487> have been used for the efficient oxidative coupling of thiols to disulfides. Thiols can be converted to disulfides using (i) DMSO neat at 110°C <2002S1004>, (ii) nearly neutral reaction conditions in the presence of hexamethyldisilazane <2002SL346>, (iii) trimethylchlorosilane or cyanuric chloride <2002S2513>, or (iv) catalysis by chromatographic neutral alumina <1998JCR(S)472>. Other reagents which have been successfully used include tetrabutylammonium periodate in the presence of AlCl_3 and $\text{BF}_3\cdot\text{Et}_2\text{O}$ <1996BCJ685>, aqueous HIO_3 <2001RJO1340>, trichloromethane <1999T12399>, peroxyxynitrite <2001EJO131>, and diazenecarboxamides <1998JCS(P1)3917>.

(vi) *Oxidation by metal ions/metal oxides*

The use of metal salts for the oxidation of thiols to disulfides is frequently employed either in autocatalysis or in conjunction with an oxidizing agent. Ferric compounds are often used for controlled oxidation and recently some new applications have been reported. Ferric chloride and sodium iodide catalyzed the air oxidative coupling of thiols in acetonitrile at room temperature affording the disulfides in high yield <1999S49>. The oxidation of thiols by molecular oxygen was mediated by iron(III)-ethylenediaminetetraacetic acid in aqueous methanol under environmentally friendly conditions <1997JCR(S)300>. An efficient preparation of disulfides from thiols was described using buffer at pH 7.2 and catalysis by ferric ion exchanged montmorillonite <1997SC2403>. Ferric perchlorate in acetonitrile was reported for the oxidative dimerization of thiols to disulfides at room temperature in good-to-high yield <1998IJC(B)593>.

Another group of the transition metal compounds that can be employed in the synthesis of disulfides, includes chromium(VI)-based oxidants, such as piperazinium dichromate <2002IJC(B)1293>, *n*-butyltriphenylphosphonium dichromate <1997IJC(B)438>, and benzyltriphenylphosphonium dichromate <2000JCR(S)32>. These procedures are mild and selective, the reagents are inexpensive, and yields are good to high. In addition, tetramethylammonium chlorochromate <2002JCR(S)547> and pyridinium chlorochromate <2001SC2777> have been reported for the oxidation of thiols to disulfides under nonaqueous or solvent-free conditions, respectively.

Other metallic species that have been reported for oxidation of thiols to disulfides include tris[trinitratocerium(IV)] paraperiodate <1995OPP216>, cobalt(III) phthalocyaninetetrasulphonamide for catalyzed oxidation by molecular oxygen <2002SC1151>, dichlorodioxomolybdenum(VI) <2002S856> or trichlorooxobis(triphenylphosphine)rhenium(V) <1997JA9309> for catalyzed oxidation by DMSO, and hydrated copper(II) nitrate <1998SC1179> and dinitrogen tetroxide copper(II) nitrate complex <1998SC367>.

A variety of disulfides can be synthesized from protected thiols. For example, from thioacetates via nickel boride (Ni₂B)-catalyzed methanolysis and oxidative disproportionation on borohydride exchange resin (BER) in one pot <1995SL1073> (cf. Section 2.03.2.1.2). In a similar way, samarium diiodide-promoted cleavage of thiobenzoates affords disulfides in one pot under neutral conditions in good yield <2000SC4317>.

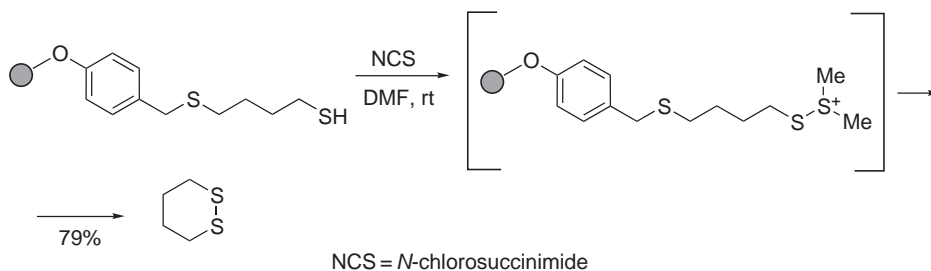
Lee and co-workers have developed a method of oxidation using potassium permanganate and copper sulfate pentahydrate under solvent-free conditions <1998S1587, 2001TL5833>. Solvent-free conditions are also efficient for the oxidative coupling of thiols catalyzed by active manganese dioxide and barium manganate <1999SC2527>.

Sodium iodate on moist neutral alumina in hexane can oxidize medium-to-long chain alkanethiols to disulfides at room temperature in nearly quantitative yield <1998JCR(S)816>. In a similar approach, silica gel and calcium hypochlorite in hexane provide a practical and high yielding method for disulfide synthesis from medium to long chain alkanethiols <1998OPP360>. The oxidative coupling of long chain thiols [C_nH_{2n+1}SH (*n* = 11–15)] to disulfides in high yield has been reported using sodium hypochlorite, *t*-butyl chloride and potassium carbonate in DMF at room temperature <1997IJC(B)819>.

(vii) Miscellaneous methods for the oxidation of thiols to disulfides

Among other alternative methods for the preparation of disulfides from thiols, solid-phase oxidative synthesis, enzymatic oxidation and electrochemical preparation of symmetrical and unsymmetrical disulfides have been reported.

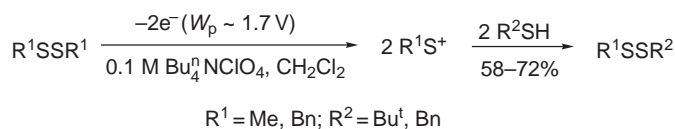
The cyclo-release reaction triggered by a dimethyl(thio)sulfonium moiety has been applied by Zoller and co-workers to the solid-phase preparation of cyclic disulfides (Scheme 115) <2000TL9989>.



Scheme 115

In the enzyme-assisted oxidation of thiols by air, horseradish peroxidase, and mushroom tyrosinase have been reported to produce high yields of symmetrical disulfides in phosphate buffer <1998SC1499>. Disulfides have been formed from thiols under solvent-free conditions on mineral supports activated by hemin (ferriprotoporphyrin(IX) chloride) or by peroxidase <1999JCS(P1)3067>.

An electrochemical method of preparation of unsymmetrical disulfides involves the reaction of the sulphenyl cation, which is formed from a disulfide, with a thiol (Scheme 116) <1997TL3383>.



Scheme 116

Unsymmetrical disulfides can also be obtained as a result of interchange between two different symmetrical disulfides using the electrochemically generated superoxide ion in DMF <1998IJC(B)411>.

2.03.7.2.2 Thioalkylation of thiols (thiolysis)

The thioalkylation of a thiol is often used in the synthesis of unsymmetrical disulfides. Thiolytic reagents such as sulfenyl derivatives, disulfides, thiocyanates, thiosulfonates, and thiosulfonates are among the most frequently reported for disulfide preparation <1995COFGT(2)113>.

(i) With sulfenyl halides

The reaction of a sulfenyl halide with a thiol gives a disulfide. The availability of sulfenyl chlorides (Section 2.03.3.1) enhances the use of this method which was surveyed in COFGT (1995) <1995COFGT(2)113>. No further advances have occurred in this area.

(ii) With sulfenamides

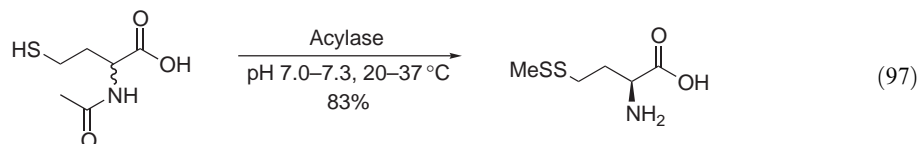
The preparation of unsymmetrical disulfides can be achieved by reaction of a sulfenamide (Section 2.03.9.1) and a thiol. *N*-Sulfenylphthalimides are the most widely used for this purpose. No reports in this area have been found in the literature since the publication of COFGT (1995) <1995COFGT(2)113>.

(iii) With thiocarbamates

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

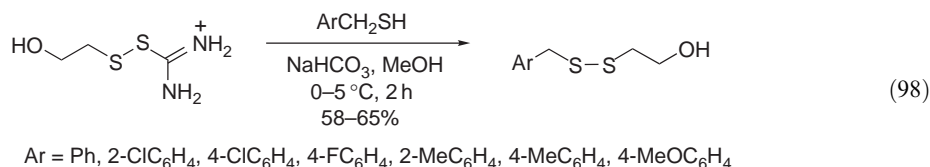
(iv) With thiosulfonates and thiosulfonates

In addition to the previously reported examples <1995COFGT(2)113>, chiral methylthiolation of racemic mercapto-amino acids with methanesulfonic acid *S*-methyl ester has been reported in the presence of acylase from *Aspergillus oryzae* (Equation (97)) <1997TA3197>.



(v) With disulfides

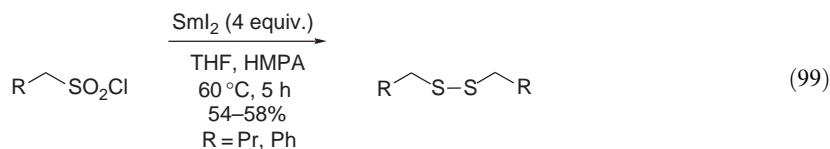
Unsymmetrical disulfides can be synthesized without concomitant formation of the symmetrical products by the reaction of *S*-(2-hydroxyethylthio)isothiuronium chloride with benzyl mercaptans under alkaline conditions (Equation (98)) <2000PS(159)123>.



There are several other methods of thiolysis which were reviewed in COFGT (1995). These are the reactions of thiols with sulfenyl thiocyanates, thiocyanates, thionitronates, thiosulfonic acid salts (Bunte salts), and sulfenyl thiocarbonates. No further advances have occurred in these areas since the publication of COFGT (1995) <1995COFGT(2)113>.

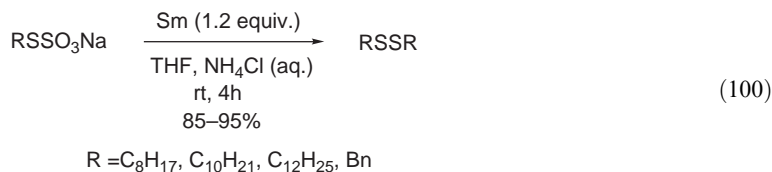
2.03.7.2.3 By reductive coupling of sulfonyl and sulfinyl derivatives

Symmetrical disulfides can be formed by reductive coupling of sulfonyl chlorides. Samarium diiodide has been used for the reduction of aryl and alkyl sulfonyl chlorides to disulfides (Equation (99)) <1997SC85>.



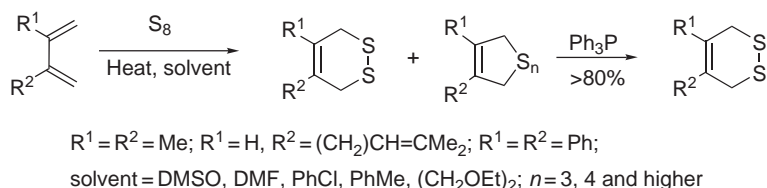
Reductive coupling of alkyl sulfonyl chlorides can be catalyzed by tungsten hexachloride <1999S500> or by molybdenum pentachloride <2001PS(170)211> in high yield, either in the presence of sodium iodide in acetonitrile, or in the presence of zinc in THF.

Reduction of sodium alkyl thiosulfates (Bunte salts) can be mediated by metallic samarium in aqueous media affording disulfides in high yield (Equation (100)) <1999T10695>.



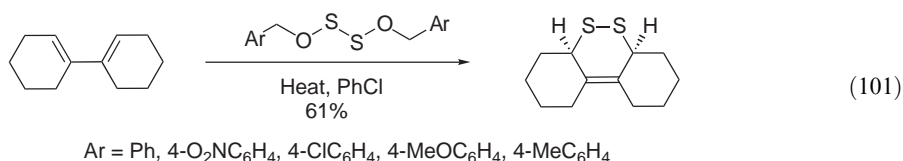
(i) By reaction of alkenes with sulfenylating agents

Sulfuration of dienes has been investigated by Harp and co-workers in a formal [4 + 2]-cycloaddition <1997TL4931, 1998TL9139>. Elemental sulfur reacts on heating and without any other activation with conjugated 1,3-dienes to form the mixture of cyclic di- and polysulfides which was cleanly converted to the disulfide upon treatment with triphenylphosphine (Scheme 117).

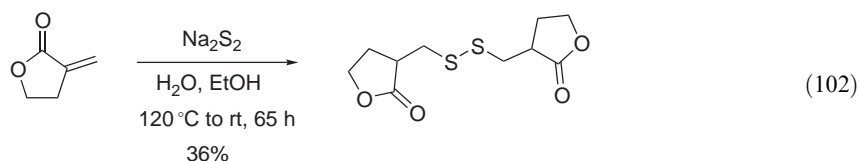


Scheme 117

In an interesting example of trapping diatomic sulfur (generated from dialkoxy disulfides) with 1,1'-bicyclohexane, the disulfide was formed exclusively with no traces of polysulfides (Equation (101)) <1997T12225>.

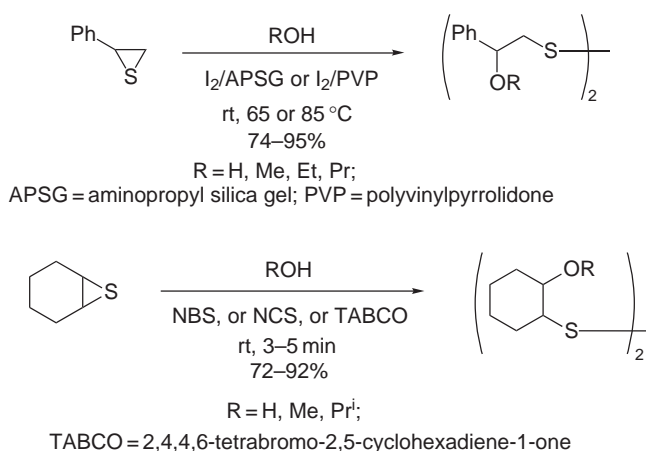


The preparation of a disulfide has been reported in moderate yield by Michael addition of disodium disulfide to 3-methylenedihydrofuran-2-one (Equation (102)) <2001JMC602>.



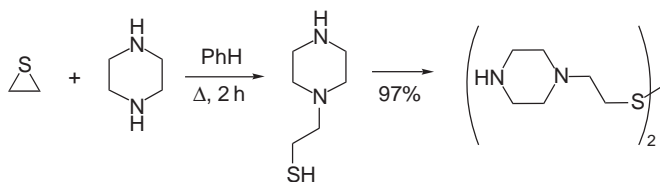
(ii) Via ring opening and coupling of thiiranes

Many examples of thiirane ring opening to give disulfides have been reported <1995COFGT(2)113>. Iranpoor and co-workers have developed a method of nucleophilic ring opening of thiiranes in alcohols or in water by iodine supported on aminopropyl silica gel <2002SC1251>, or on polyvinylpyrrolidone <1997CJC1913>, or by catalysis using NBS, NCS, or TABCO <2002T7037> (Scheme 118).



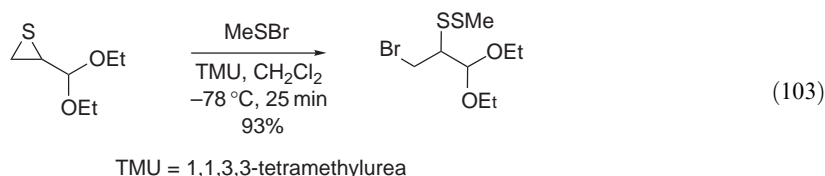
Scheme 118

Heating ethylene sulfide with excess of piperazine can produce a disulfide in one pot via slow oxidation of the intermediate thiol (Scheme 119) <2000JOC3466>.



Scheme 119

Methanesulfonyl bromide has been used to efficiently open a thiirane and produce a versatile brominated disulfide (Equation (103)) <2001JOC910>.



2.03.7.2.4 By reaction with hydrogen sulfide

The reaction of hydrogen sulfide with thiols, sulfonyl chlorides, ketones, aldehydes, imines, and sulfides leads to disulfides <1995COFGT(2)113>. No further advances have occurred in this area.

2.03.7.2.5 By reaction with sodium sulfide

Sodium sulfide has been reported as a convenient reagent mainly for reactions with monohalides affording disulfides, or with dihalides furnishing cyclic disulfides <1995COFGT(2)113>. No recent publications have been found on these transformations.

2.03.7.2.6 By the use of miscellaneous sources of sulfur

(i) Elemental sulfur

A convenient and rapid reaction of alkyl and aryl alkyl halides with sulfurated borohydride resin (SBER) at room temperature produces high yields of symmetrical disulfides <2001TL6741>. The reaction of alkyl halides with sulfur in alkaline medium under phase-transfer conditions has been found to afford disulfides in good-to-excellent yield <1995SC3573>.

(ii) Sulfur dioxide

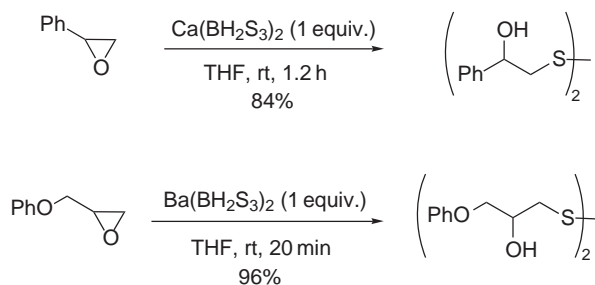
Sulfur dioxide can be employed for the preparation of thiosulfonates from a range of substrates. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

(iii) Sulfur monochloride and dichloride

Sulfur monochloride reacts with unsaturated C—C bonds to furnish symmetrical disulfides <1995COFGT(2)113>. No further examples of the disulfide preparation by this method have been found.

(iv) Sodium borohydride trisulfide (sulfurated sodium borohydride) and other borohydride trisulfides

Sodium borohydride trisulfide (NaBH_2S_3) converts aldehydes, ketones, or epoxides into symmetrical disulfides <1995COFGT(2)113>. The instability of the reagent, which decomposes rapidly in the presence of oxygen or atmospheric moisture, places limitations on its use. Firouzabadi and co-workers have reported the preparation of stable sulfurated calcium and barium borohydrides [$\text{Ca}(\text{BH}_2\text{S}_3)_2$ and $\text{Ba}(\text{BH}_2\text{S}_3)_2$] and investigated their reactivity as reducing reagents <2000PS(159)99, 2000PS(166)83>. With regard to disulfide formation from epoxides, the reactivity and regioselectivity of both reagents is higher than that of NaBH_2S_3 . Substituted epoxides are opened from the less hindered side of the ring and in good yield (Scheme 120).



Scheme 120

(v) Sodium thiosulfate

Sodium thiosulfate has been reported earlier for the preparation of disulfides from alkyl halides <1995COFGT(2)113>. No recent publications have been found.

(vi) Thiolacetic acid

Thiolacetic acid has been employed for the preparation of both symmetrical and unsymmetrical disulfides from alkyl halides and monosulfides, respectively. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

(vii) Trithioalkylphosphine reagents

The literature indicates that trithioalkyl phosphine reagents can be employed as a source of sulfur for the preparation of disulfides <1995COFGT(2)113>. No recent reports have been found on this method.

(viii) Miscellaneous sulfur sources for disulfide formation

Chandrasekaran and co-workers have employed benzyltriethylammonium tetrathiomolybdate as an efficient sulfur transfer reagent for the synthesis of disulfides from alkyl halides <1997CAR(301)221, 1997SC4031>, alcohols <1999T14769>, and epoxides <2002JOC9417>.

Reduction of sodium alkyl thiosulfates to disulfides can be promoted by metallic samarium in the presence of either iodine <1997SC1043> or trimethylsilyl chloride and traces of water <2000SC1917>. Reduction of sodium alkyl thiosulfates using samarium metal in water without an activating agent also affords disulfides in good yield <2002TL8141>.

2.03.7.2.7 Formation of alkyl disulfides by photochemical and thermal reactions

In some cases, photochemical reactions can provide an alternative method for the preparation of disulfides <1995COFGT(2)113>. Recently, microwave-assisted synthesis has been employed for oxidative coupling of thiols to disulfides using clay supported ammonium nitrate (clayan) as a nonmetallic and eco-friendly reagent <2000SC701>.

2.03.7.2.8 From miscellaneous sulfur functionalities*(i) Sulfenyl halides*

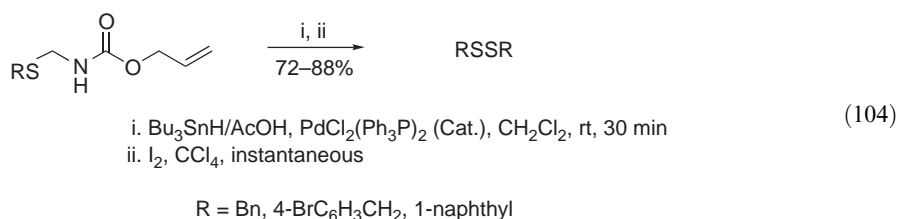
A range of transformations of sulfenyl halides with sulfide nucleophiles result in unsymmetrical disulfides <1995COFGT(2)113>. No further advances have occurred in this area.

(ii) Thiocarbonyl compounds

The reduction of thiocarbonyl compounds by sodium borohydride produces symmetrical sulfides. No recent reports have been found in the literature since the publication of COFGT (1995) <1995COFGT(2)113>.

(iii) Oxidative coupling of sulfides

Cysteins with *S*-allyloxycarbonylaminoethyl (allocam) protecting groups are derivatives of thiols and can be readily transformed into symmetrical disulfides by a sequential cleavage-oxidation process (Equation (104)) <1999T6931>.



(iv) Alkylthiosilanes and alkylthiostannanes

Unsymmetrical disulfides can be prepared from alkylthiostannanes by reaction with sulfur-containing molecules <1995COFGT(2)113>. No recent reports on this method have been found.

(v) Thiocyanates

Reductive dimerization of organic thiocyanates to disulfides can be assisted by benzyltriethylammonium tetrathiomolybdate <1995JOC7142>, tetrabutylammonium fluoride <1999TL6489>, or titanium tetrachloride-samarium metal system <1997SC2721>.

(vi) Vinyl sulfides

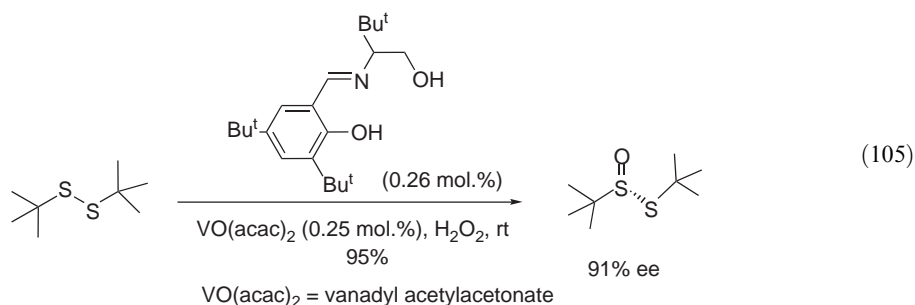
A single example is described in COFGT (1995) <1995COFGT(2)113> and no other reports have been found.

(vii) Disulfides

Disproportionation of two disulfides can be promoted by nitric oxide in the presence of oxygen and results in the formation of unsymmetrical disulfides <1999BMCL2161, 2000CPB1524>.

2.03.7.3 Alkanethiosulfonates and Thiosulfonates

The principal method of thiosulfinate preparation involves oxidation of disulfides. The oxidizing agents used in this method are often those that are employed for the oxidation of thiols to disulfides <1995COFGT(2)113>. Ellman and co-workers have reported the first example of the catalytic asymmetric oxidation of *t*-butyl disulfide to *t*-butanesulfinic acid in high enantiomeric excess (Equation (105)) <1997JA9913, 1998JA8011> (cf. Sections 2.03.2.2.6 and 2.03.9.2).



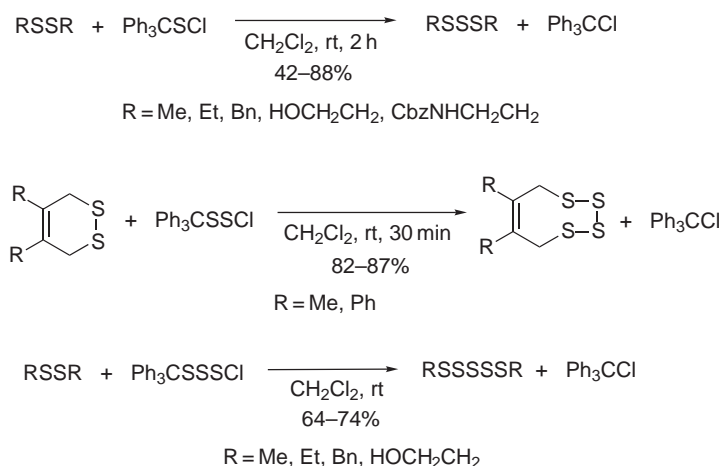
Enantioenriched thiosulfonates have been obtained by dioxygenase and chloroperoxidase catalyzed oxidation of disulfides <2002CC1452>.

The rhenium catalyst [Re(O)Cl₃(PPh₃)₂] with sulfoxides can oxidize cyclic disulfides to thiosulfonates, whereas acyclic disulfides yielded thiosulfonates <1997JA9309>. Thiosulfonates can also be produced from disulfides using dinitrogen tetroxide supported on polyvinylpyrrolidone <2002T5179>.

The synthesis of methanethiosulfonates from alkyl halides and the sodium salt of methanesulfonic acid has been reported in an approach to thiol-specific modifying reagents <1998JOC9614, 1999BMCL2303, 2000BMC1957, 2002CEJ4129>. Reductive zinc coupling of two molecules of a sulfonyl chloride in the presence of acetyl chloride has been reported as a practical procedure in the preparation of thiosulfonates <1998SL894>.

2.03.7.4 Alkyl Trisulfides and Polysulfides

Trisulfides and polysulfides can be prepared by the reaction of a suitable dithiol with sulfur <1995COFGT(2)113>. Harpp and co-workers have developed a general route to polysulfides via treatment of disulfides with various thiosulfenate species (Scheme 121) <2000TL7169, 2000TL7809, 2001TL8607>.



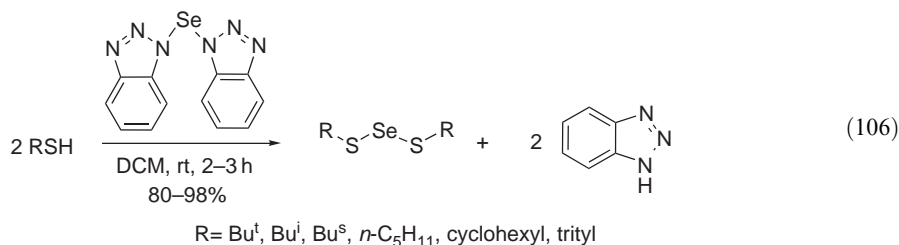
Scheme 121

2.03.8 RSe AND RSTe FUNCTIONS AND THEIR HIGHER-COORDINATED DERIVATIVES

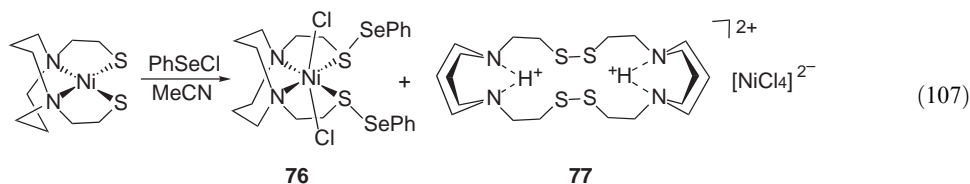
2.03.8.1 Sulfenyl Selenides

Most of the principal methods for alkane sulfenyl selenide preparation reviewed in COFGT (1995) <1995COFGT(2)113> were based on reactions of thiols with a selenium reagent. Among the latter were selenocarbonyl compounds, phenylselenenyl chloride, heterocycles with an

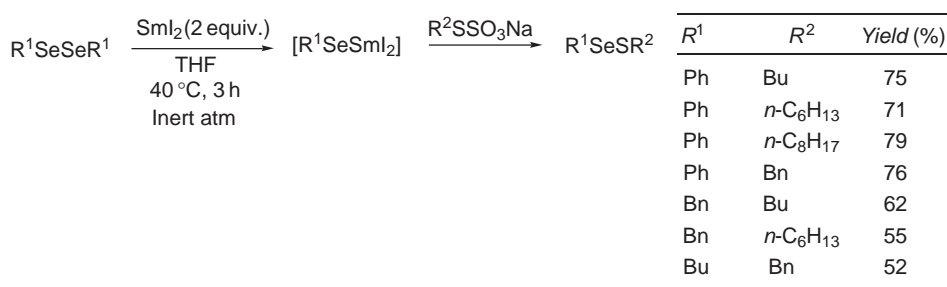
Se—N ring bond, selenium transfer agents, selenous acid, selenosulfates and diaryl selenides. In the 1990s very limited development of these methods has been reported. A unique selenium-transfer reagent, bis(benzotriazol-1-yl)selenide, has been effectively employed for the preparation of dithioselenides (Equation (106)) <1997TL8829>. An earlier procedure involving treatment of thiols with selenous acid gives only moderate yields of dithioselenides contaminated with other products.



The nickel-bound selenosulfide **76** was obtained in 55% yield, together with a small amount of the bis-disulfide **77**, by reaction of [*N,N'*-bis(mercaptoethyl)-1,5-diazacyclooctane]nickel(II) with PhSeCl in MeCN solution (Equation (107)) <1999CC2473>.



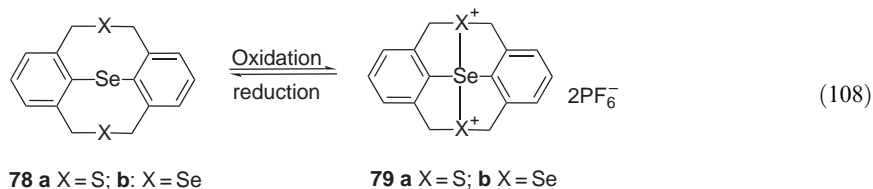
A novel synthesis of selenosulfides from diselenides using samarium diiodide has been described <2000JCR(S)374>. The diselenides are reduced by SmI₂ to produce samarium selenolates, which then react with sodium alkylthiosulfates or phenylsulfenyl chloride (Scheme 122). The advantages of this method are mild conditions, simple operation and generally good yields.



Scheme 122

2.03.8.2 Higher-coordinated RSSe Functionality

The first compounds with multicentered bonds involving two different chalcogens have recently been obtained <1996T10375, 1999CL723>. Thus, oxidation of the sulfur- or selenium-bridged diphenyl selenides **78** with NOPF₆ (2 equiv.) gave the cyclic selenurane salts **79** which contain two selenonium or two sulfonium cations at the apical positions. These selenuranes **79** can be readily reduced back to the neutral selenides **78** upon treatment with PhSH, Ph₃P, phenothiazine or SmI₂, i.e., **79a,b**, act as oxidizing agents (Equation (108)).

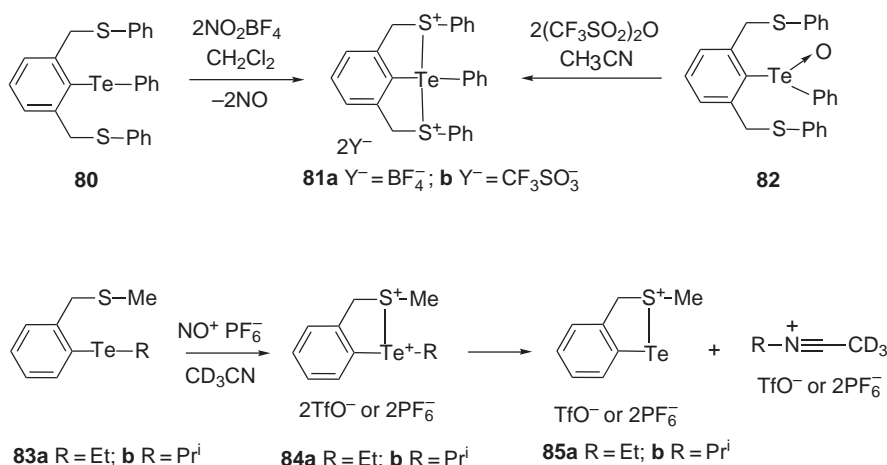


2.03.8.3 Alkanesulfenyl Tellurides

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.8.4 Higher-coordinated RSTe Functionality

The first representatives of this type of compounds have been obtained by the methods shown in Scheme 123 <1998PS(136)471, 1999CL723> (see also <2000AG(E)1318>). The diaryl telluride **80** is readily oxidized by NOBF_4 (2 equiv.) at -78°C under argon to produce tellurane dication 2BF_4^- salt **81a** in 92% yield. Similar treatment of telluroxide **82** with trifluoromethanesulfonic anhydride resulted in its conversion to the triflate salt **81b** <1998PS(136)471>. X-ray structure determination of salt **81a** revealed that the hypervalent tellurium is at the center of a distorted trigonal bipyramid with two apical sulfonio ligands connected via transannular bonds.



Scheme 123

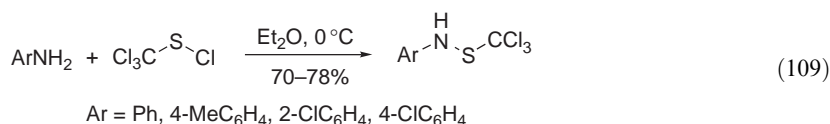
The reaction of ethyl or isopropyl 2-(methylthiomethyl)phenyl telluride **83a,b** with Tf_2O (1 equiv.) or NOPF_6 (2 equiv.) in CD_3CN at -40°C leads to the tellurathia dications **84a,b**. However, on raising the temperature above 20°C , dealkylation occurred giving the tellurasulfonium salts **85a,b** <1999CL723>.

2.03.9 RSN FUNCTIONS AND THEIR HIGHER-COORDINATED DERIVATIVES

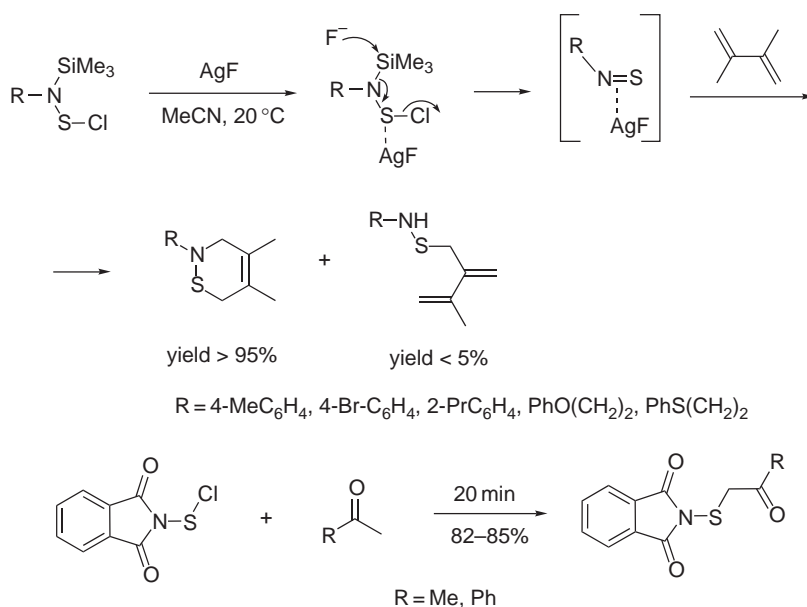
2.03.9.1 Alkanesulfenamides

2.03.9.1.1 From sulfenyl halides

Sulfenyl halides readily react with ammonia or primary and secondary amines forming sulfenamides <1995COFGT(2)113>. This method has been utilized in the synthesis of trichloromethane-sulfenamides (Equation (109)) <1997TL487>.



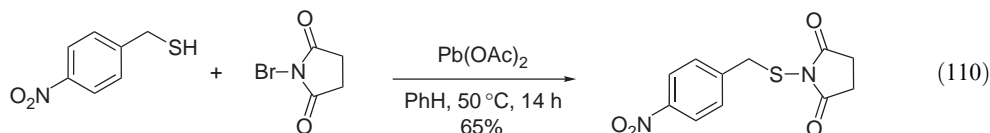
An alternative approach involves the reaction of halosulfenamides with nucleophiles such as alkenes or ketones (Scheme 124) <1996JCS(P1)1825, 1997TL5041>. The reaction of *N*-trimethylsilylamino sulfur chlorides with dimethylbutadiene in the presence of silver ion possibly proceeds via transient metal-coordinated thionitroso species and results in 1,2-thiazines formation.



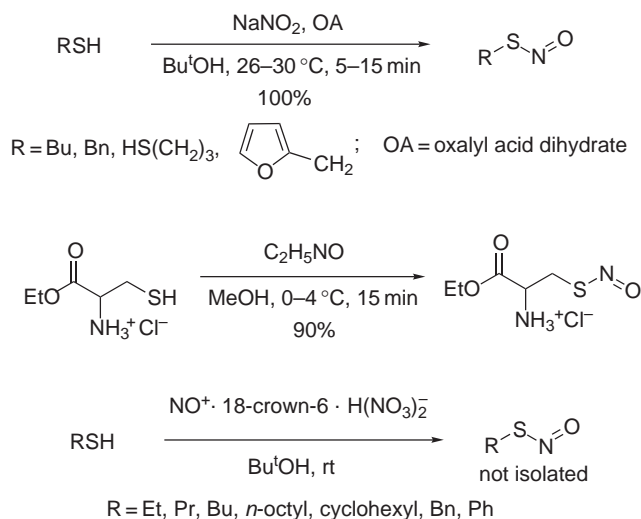
Scheme 124

2.03.9.1.2 From thiols

The reaction of a thiol and a nitrogen-containing reagent can result in the formation of a sulfenamide. The interaction with amines involves activation of either the thiol or the amine. Chlorinating conditions for the reaction of a thiol with an amine, or involvement of the activated form of an amine, such as *N*-bromosuccinimide, effect the formation of sulfenamides (Equation (110)) <1995JCS(P1)1685>.



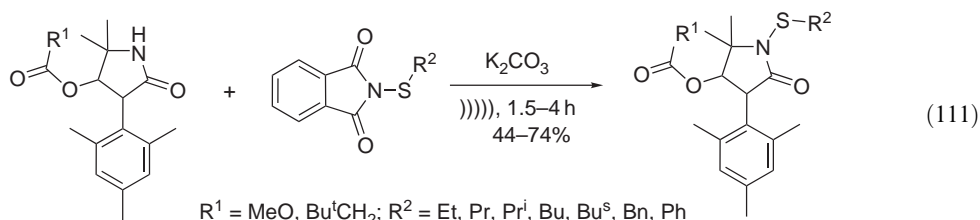
The synthesis of *S*-nitrosothiols has received considerable attention because of their potential role in nitric oxide storage and transfer in physiological processes. Thiols readily react with nitrosating agents such as sodium nitrite, ethyl nitrite, or the 18-crown complex of nitric oxide, affording *S*-nitrosothiols which are typically unstable on storage (Scheme 125) <1997BMCL1393, 1999JCR(S)668, 1999SC2277, 2001CJC830, 2001JMC2035, 2001JOC6064, 2002CEJ380>.



Scheme 125

2.03.9.1.3 From *N*-thiophthalimides

A simple and efficient method of sulfenamide synthesis is the nucleophilic reaction of an amine with an *N*-thiophthalimide [<1995COFGT\(2\)113>](#). Ultrasound has been successfully utilized in the *N*-sulfenylation of dihydropyrrolidones (Equation (111)) [<2002H\(57\)909, 2003BMC489>](#).

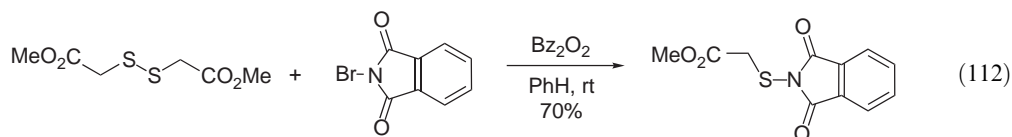


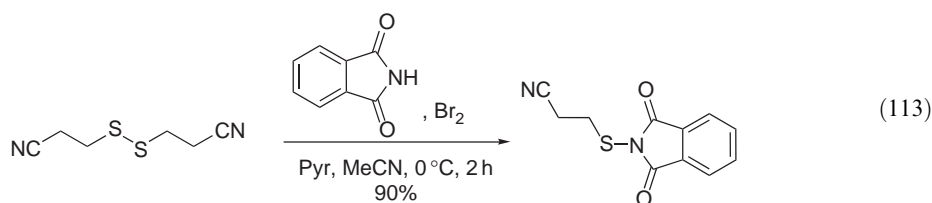
2.03.9.1.4 From sulfenyl thiocyanates

The reaction of sulfenyl thiocyanates with amines can result in sulfenamides. The reaction proceeds most efficiently with secondary amines. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.9.1.5 From disulfides

Sulfenamides can be formed from symmetrical disulfides by treatment with lithium dialkylamides [<1995COFGT\(2\)113>](#). An oxidizing agent can favor the formation of a sulfenamide from a disulfide. The *N*-phthaloylsulfenamide formation by coupling the disulfide with *N*-bromophthalimide in the presence of dibenzoyl peroxide proceeds in good yield ([Equation \(112\)](#)) [<1996JCS\(P1\)977>](#). Similarly, 2-cyanoethyl disulfide reacted with bromine and phthalimide in pyridine to form the sulfenamide in high yield ([Equation \(113\)](#)) [<1997T14411>](#).





2.03.9.1.6 From thionitrites

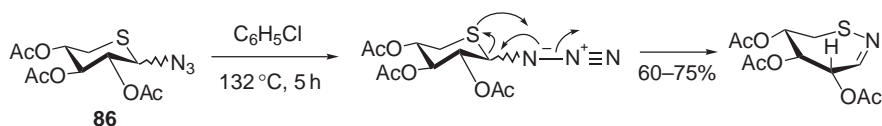
The reaction of an amine and a thionitrite can produce a sulfenamide. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.9.1.7 From thiocarbonyl compounds

1,3-Cycloaddition of a thioketone to diazomethane furnishes a thiadiazoline. No further reports of this method have been found since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.9.1.8 From sulfides and thiiranes

Sulfides and thiiranes react with nitrogeous compounds to form sulfenamides <1995COFGT(2)113>. An interesting intramolecular rearrangement has been reported for acetylated 5-thio-D-xylopyranosyl azide **86**. Thermolysis of both anomers resulted in ring enlargement giving 4,5,6-triacetoxytetrahydrothiazepine (Scheme 126) <1999MI833>.



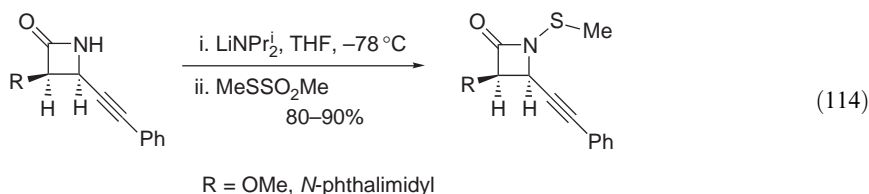
Scheme 126

2.03.9.1.9 From thiostannanes

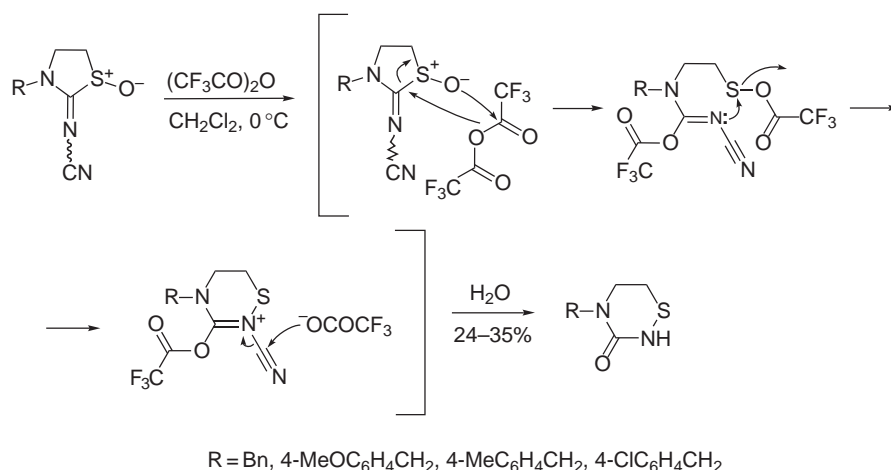
Thiostannanes have been shown to react with NBS furnishing sulfenamides. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.9.1.10 Miscellaneous

A convenient thiomethylation of lactams by methyl methanethiosulfonate has been utilized by Turos and co-workers as part of an approach to inverted penems (Equation (114)) <1995JOC4980, 1998JOC8898, 2000T5571> (cf. Section 2.03.3.1.1).



The reaction of 3-alkyl-2-(*N*-cyanoimino)thiazolidine-1-oxides with TFAA resulted in a ring enlargement to give cyclic sulfenamides in moderate yield (Scheme 127) <1997SL316>.



Scheme 127

2.03.9.2 Alkanesulfinamides

The most general approaches to alkanesulfinamides involve: (i) cycloadditions of sulfoximines, (ii) coupling of a sulfinyl chloride with an amine, and (iii) oxidation of sulfenamides. Optically pure sulfinamides, which are analogous to sulfinate esters, are prepared through a substitution reaction with an optically pure nitrogen compound. Also in keeping with the chemistry of sulfinate esters (Section 2.03.5.2), the reaction between an optically active sulfinamide and an organometallic reagent proceeds with inversion of configuration at sulfur to generate optically active sulfoxides <1999OPP579, B-2000MI005>.

2.03.9.2.1 Cycloaddition reactions of sulfoximines

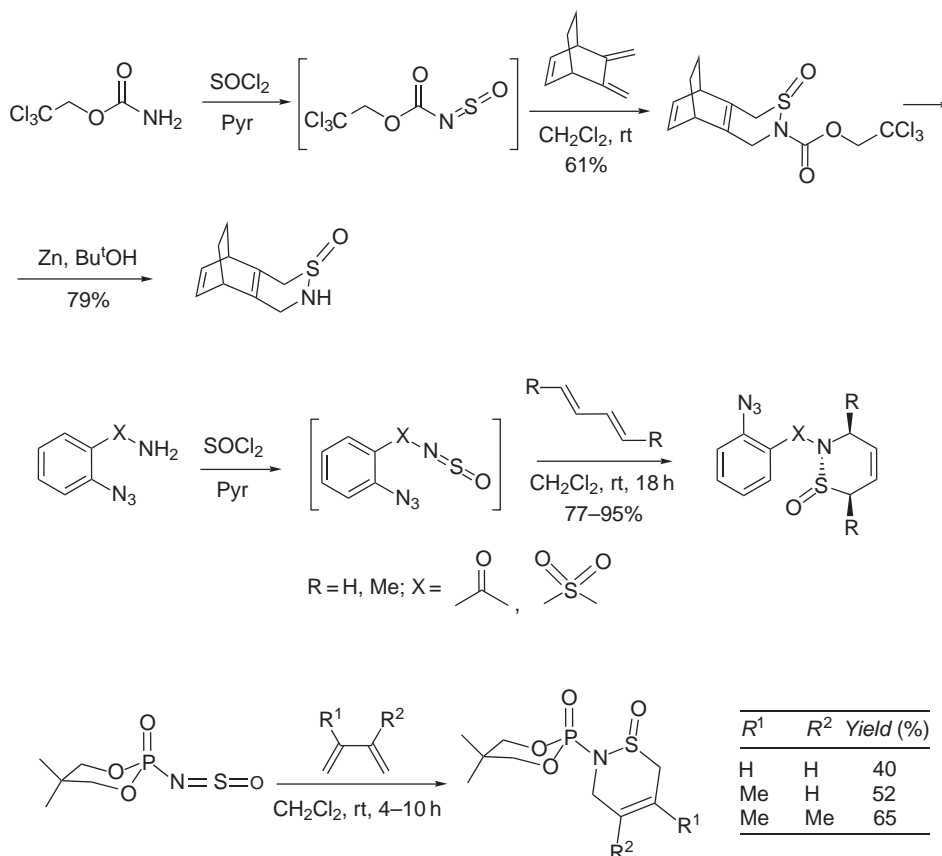
The formation of cyclic sulfinamides by [4+2]- or [2+2]-cycloadditions is well documented <1995COFGT(2)113>. A few interesting recent examples of [4+2]-cycloaddition reactions are shown in Scheme 128. Sulfoximines can be formed *in situ* by reaction of an amine or an amide with thionyl chloride in pyridine; the selectivity of hetero-cycloaddition has been established by X-ray crystallography <1998JOC1372, 2000TL10107, 2001TL4183>.

2.03.9.2.2 From sulfinyl chlorides

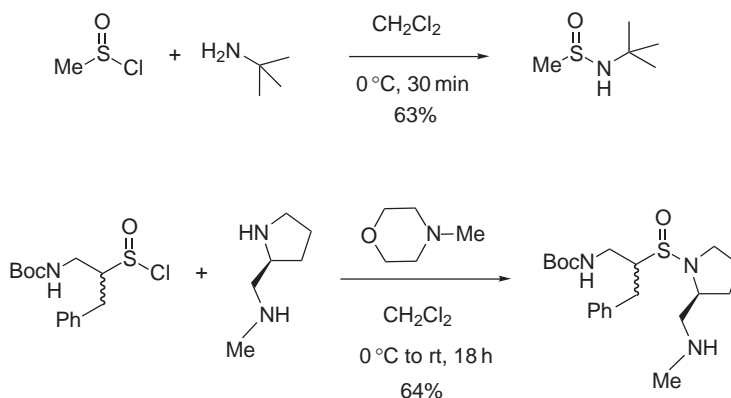
Sulfinyl chlorides readily react with amines furnishing sulfinamides, typically in high yield. The utilization of this direct method is influenced by the availability and reactivity of sulfinyl chlorides (Section 2.03.3.2). Sulfinyl chlorides couple with primary or secondary amines under mild conditions to form sulfinamides in good yield (Scheme 129) <1995JOC5157, 2002BCJ223>. Excess amine can act as an HCl scavenger, otherwise the reaction is usually carried out in the presence of *N*-methylmorpholine <1997BMCL2331, 1996BMC667>.

2.03.9.2.3 From sulfenamides

The oxidation of sulfenamides by MCBPA has frequently been reported as a convenient approach to sulfinamides. The reaction proceeds under mild conditions in high yield, and in the last example shown in Scheme 130 even with excess oxidizing agent <1995JA4218, 1997SL316, 1997TL487, 1997TL5041>.



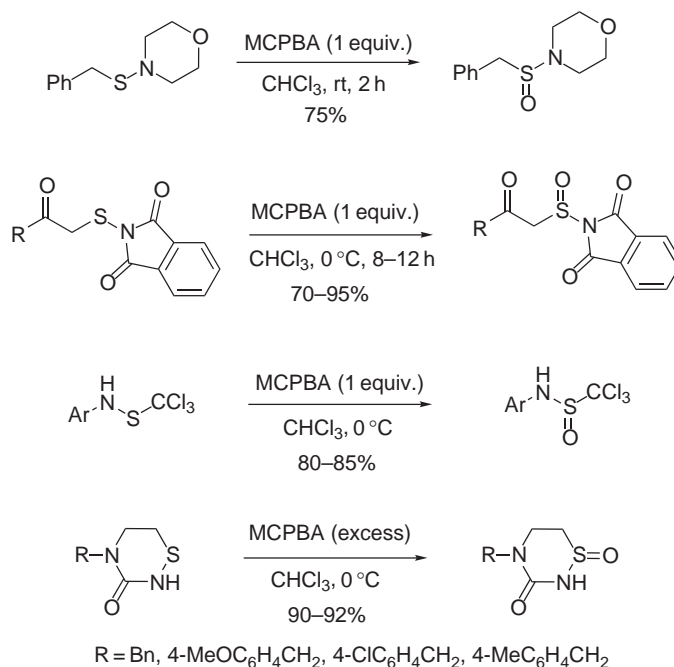
Scheme 128



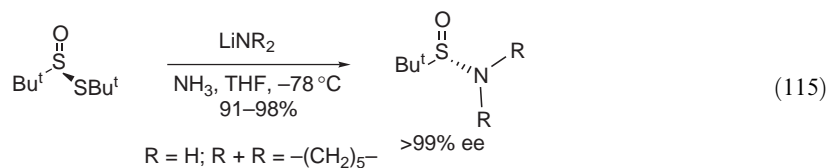
Scheme 129

2.03.9.2.4 Miscellaneous methods of alkanesulfonamide preparation

Ellman and co-workers developed a route to chiral sulfonamides through the reaction of an optically enriched thiosulfonate (Sections 2.03.2.2.6 and 2.03.7.3) with lithium amides to afford the stable *t*-butanesulfonamides in high yield and selectivity (Equation (115)) <1998JA8011>.

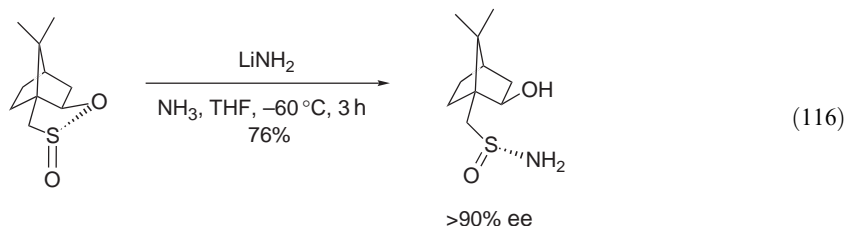


Scheme 130



(115)

A convenient approach to 10-isobornylsulfinamide from a sultine precursor involves lithium amide [<1999TA4183>](#) or lithium hexamethyldisilazide [<1999JOC8724>](#) and results in good yield and enantioselectivity ([Equation \(116\)](#)).



(116)

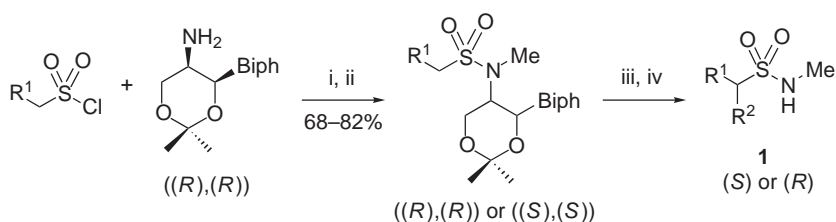
The synthesis of trifluoromethanesulfinamides has been demonstrated by two interesting approaches: one involves the reaction of trimethyl(perfluoroalkyl)silanes and *N*-sulfinylamines in the presence of fluoride ions [<2002TL3029>](#) and the other employs sodium triflate and phosphoryl chloride (cf. [Section 2.03.5.2.1](#)) in a reaction with primary and secondary amines [<1999T7243>](#).

2.03.9.3 Alkanesulfonamides

2.03.9.3.1 From other sulfur(VI) functionality

The most obvious approach to alkanesulfonamides is reaction of sulfonyl chlorides with ammonia and amines. Indeed, this is one of the most frequently reported methods, if the formation of the starting sulfonyl chloride is possible [<1995COFGT\(2\)113>](#). Various linear and nonlinear primary

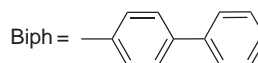
alkylamines readily form the corresponding *N*-mesylated derivatives by reaction with mesyl chloride in the presence of triethylamine <2001CL712>. The reaction of alkanesulfonyl chlorides with chiral amines provided a route to chiral α -substituted *N*-methylsulfonamides in high enantiomeric excess (Scheme 131) <1998HCA1329>.



i. Et₃N, CH₂Cl₂, 0 °C to rt; ii. BuLi (1 equiv.), THF, 0 °C, MeI;

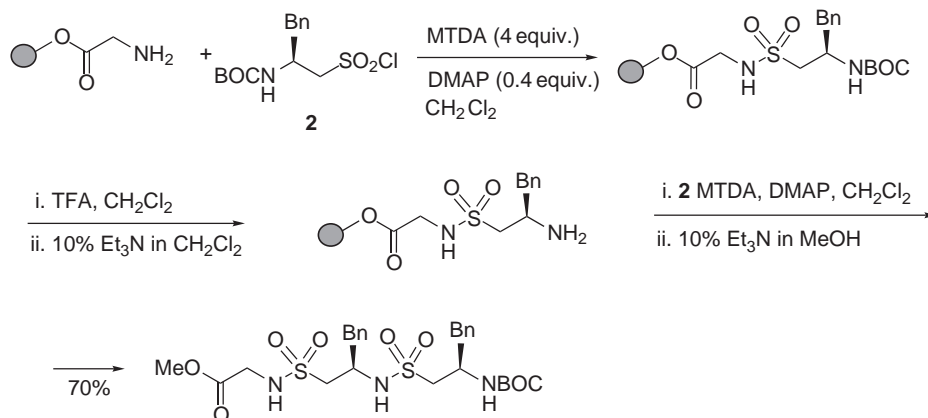
iii. HMPA (1 equiv.), BuLi (1.1 equiv.), -70 °C, R²X (1.5 equiv.); iv. HCl, 100 °C

1	R ¹	R ²	Yield (%)	ee (%)
(R)	Me	Bn	55	>98
(R)	Et	Bu	63	>98
(R)	Et	Bn	53	94
(S)	Et	Bn	55	95
(R)	Pr ⁱ	Me	53	94
(R)	Pr ⁱ	Bn	56	91



Scheme 131

Chiral β -sulfonopeptides have been synthesized both in solution and in the solid phase by the reaction of a chiral sulfonyl chloride with an amine (Scheme 132) <1996TL8589>.



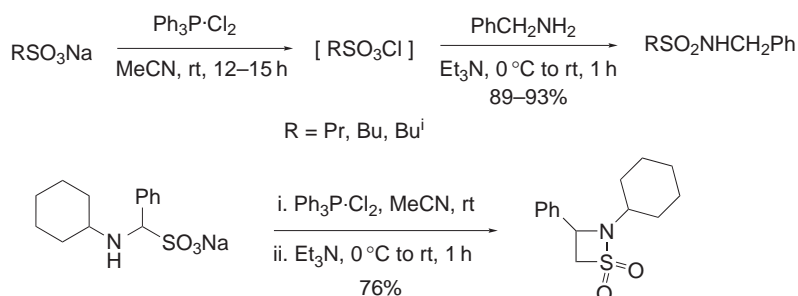
MTDA = methyl trimethylsilyl dimethyl ketene acetal; DMAP = 2,4-dimethylaminopyridine

Scheme 132

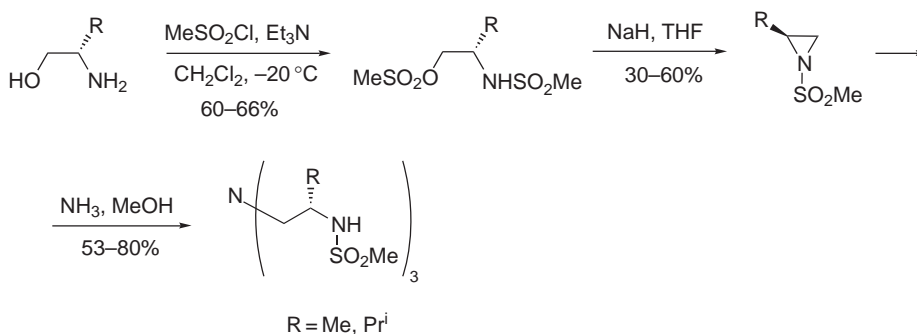
The formation of a sulfonyl halide *in situ* from a sodium sulfonate and a triphenylphosphine dihalide has been utilized in an efficient synthesis of sulfonamides, including an intramolecular cyclization (Scheme 133) <1998S423>.

Although the conventional conditions for reaction between a sulfonyl chloride and an amine commonly involve the presence of triethylamine, sodium hydride can be used as an HCl scavenger as demonstrated in the mesylation of aryl pyridyl amines <1999JCS(P1)1505>.

Enantiopure tripodal tetradentate C_3 -symmetric sulfonamides have been conveniently prepared starting with chiral aminoalcohols by utilization of the standard protocol of mesylation and cyclization followed by aziridine ring opening under mild conditions (Scheme 134) <1997TA2655>.



Scheme 133



Scheme 134

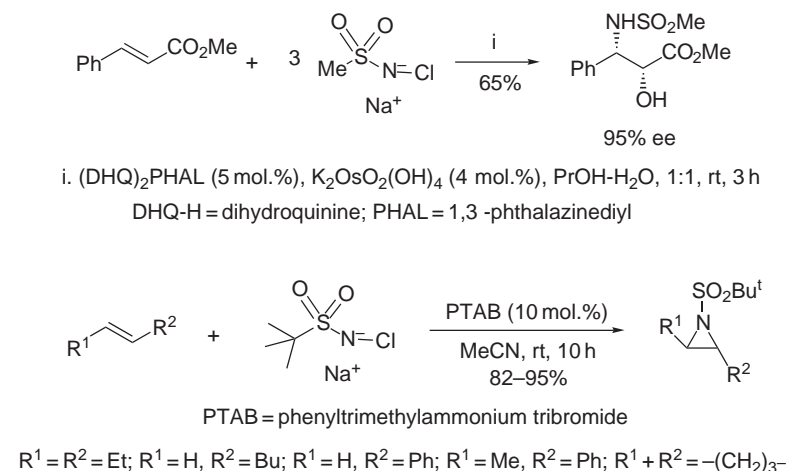
An interesting novel example of a three-component reaction between an alkene, a sulfonyl chloride, and a nitrogen source is the stereoselective synthesis of *N*-sulfonylaziridines (Equation (117)) <2002JOC2101>. Asymmetric aziridination of the styrene was found to proceed smoothly with a chiral nitridomanganese complex when a sulfonyl chloride was employed as an activator in the presence of a silver salt affording *N*-sulfonylaziridines with moderate enantioselectivity.



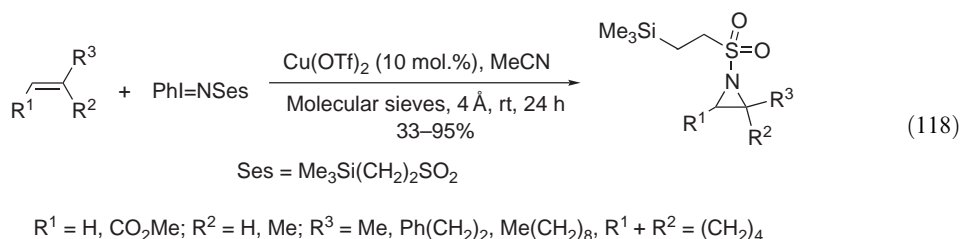
Sharpless and co-workers utilized *N*-chloramine salts of methyl- and *t*-butyl-sulfonamide (Section 2.03.9.3.2) as an efficient nitrogen source for the catalytic aminohydroxylation and aziridination of the alkenes (Scheme 135) <1996AG(E)2810, 1999OL783, 1999TL5151>. The S—N bond in the products is easily cleaved under mild acidic conditions, allowing facile liberation of the amino group. Aminohydroxylation of α,β -unsaturated amides results in competitive regioselectivity and is substrate dependent.

The trimethylsilylethanesulfonyl (Ses) protecting group, initially developed by Weinreb <1998OS161>, is now widely used in numerous applications including the synthesis of

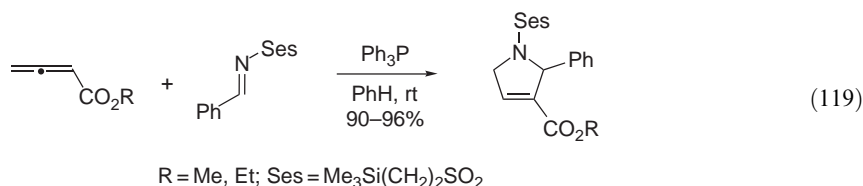
N-(Ses)aziridines which are convenient precursors for the preparation of substituted α -amino acids and oligosaccharides. Dauban and Dodd reported a new Ses-iminoiodinane reagent for the preparation of *N*-(Ses)aziridines (Equation (118)) <1999JOC5304>. In the presence of a catalytic amount of Cu(I) or Cu(II) triflate, a slight excess of the iodine reacts with alkenes to form *N*-(Ses)aziridines in moderate-to-good yield.



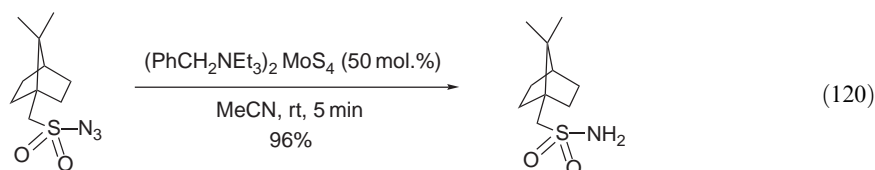
Scheme 135



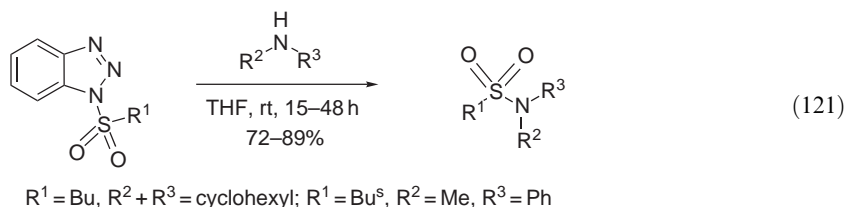
The triphenylphosphine-catalyzed reaction of alkyl 2,3-butanedioates with *N*-(Ses)imine gave a [3 + 2]-cycloadduct in excellent yield (Equation (119)) <1998JOC5031>.



Sulfonamides can be prepared by reduction of sulfonazides by benzyltriethylammonium tetrathiomolybdate (Equation (120)) <1995JOC7682>.



Katritzky and co-workers applied benzotriazole methodology to achieve a convenient synthesis of alkyl, aryl, and heteroaryl secondary and tertiary sulfonamides in good yields (Equation (121)) <2004JOC1849>.



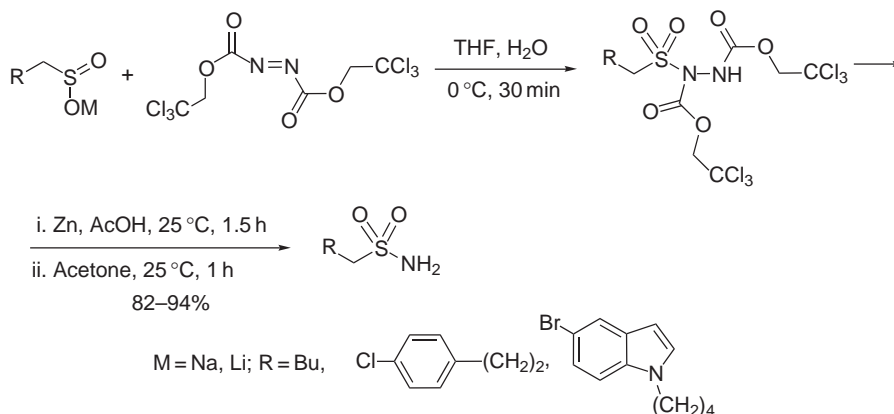
2.03.9.3.2 By oxidation of sulfenyl and sulfinyl derivatives

MCBPA was reported as the most common reagent for oxidation of sulfenamides or sulfinamides to sulfonamides. *N*-Sulfenyl dihydropyrrolidones (cf. [Section 2.03.9.1.3](#)) were oxidized by MCBPA in dichloromethane at room temperature affording the sulfonamides in high yield [<2003BMCL489>](#).

The relatively stable *t*-butylsulfinamides can be oxidized to the *t*-butylsulfonamides by MCBPA or NaIO_4 and RuCl_3 [<1997JOC8604>](#), by H_2O_2 in the presence of LiOH [<1995H\(41\)2737>](#), or by NaOCl under the conditions of phase-transfer catalysis [<1995JOC2831>](#). Interest in the synthesis of *t*-butylsulfonamides was initiated by Weinreb, who reported the utility of the *t*-butylsulfonyl group (Bus) for the protection of primary and secondary amines [<1997JOC8604>](#). The Bus group is capable of withstanding strong metalation conditions and also is easily cleaved.

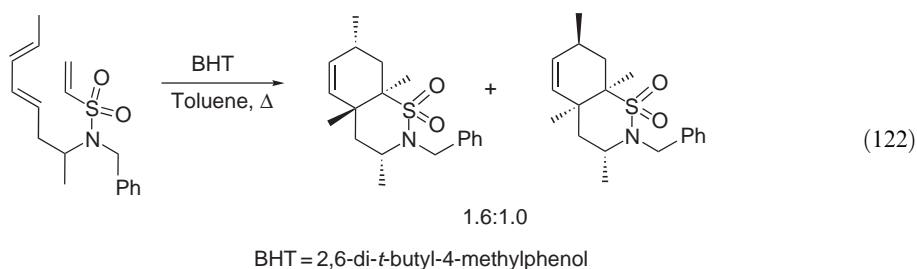
2.03.9.3.3 Miscellaneous methods

Aliphatic and aromatic sulfinic salts react with bis(2,2,2-trichloroethyl) azodicarboxylate to form sulfonylhydrazides which are smoothly cleaved under reductive conditions affording sulfonamides in good yields ([Scheme 136](#)) [<2002TL4537>](#).

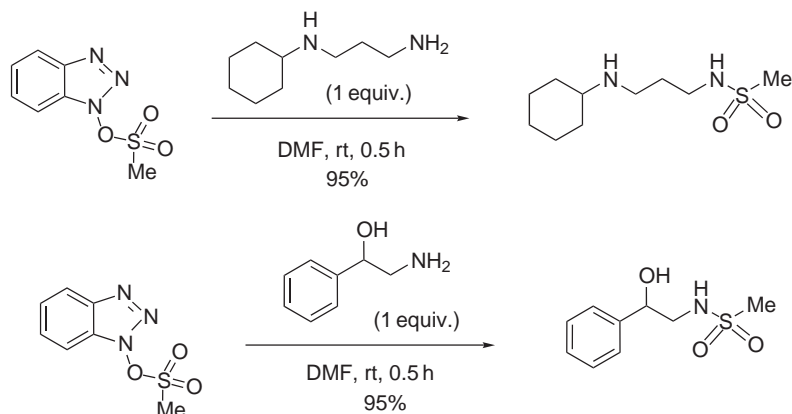


Scheme 136

Intramolecular [4 + 2]-cycloaddition of a vinylsulfonamide results in formation of two diastereomers ([Equation \(122\)](#)) [<2000T873>](#).



1*H*-Benzotriazol-1-yl methane sulfonate has been utilized as an efficient reagent for selective mesylation of primary amino groups (Scheme 137) <1999TL117>.



Scheme 137

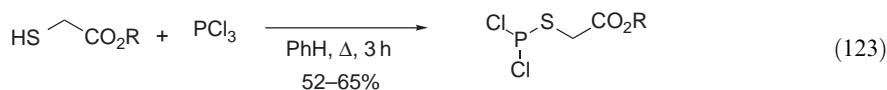
2.03.10 RSP, RSAs, RSSb, AND RSBi FUNCTIONS AND THEIR HIGHER-COORDINATED ANALOGS

2.03.10.1 Alkanethiophosphines and Their Higher-coordinated Analogs

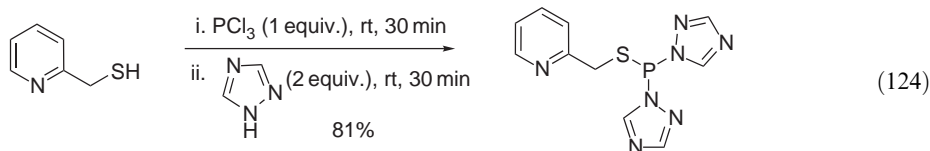
Compounds containing P—S bonds have been extensively studied in the synthesis of deoxyoligonucleotide analogs and naturally occurring lipids, in the development of specific immunoassays, in coordination chemistry and in numerous applications as pesticides <1995COFGT(2)113, 1996JOC4272, 1998PS(132)155, 1999JCS(P1)1477, 2000PS(166)1, 2001MI1615>. In agreement with the survey in COFGT (1995) <1995COFGT(2)113>, the reaction of a thiol with a phosphorus reagent and alkylation of a thiophosphorus compound are the principal approaches to formation of a S—P bond.

2.03.10.1.1 From thiols

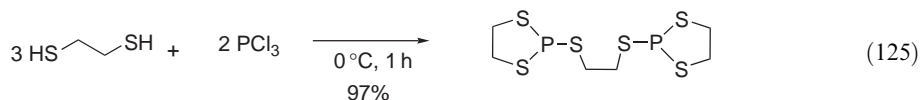
Alkanethiophosphines can be prepared by reaction of a thiol with a phosphorus trihalide (normally trichloride), with a dichloro- or a chlorophosphine, or with a phosphine containing leaving groups other than chloride. The reaction of 1 equiv. of a thiol with phosphorus trichloride smoothly produces the dichlorophosphinothioates (Equation (123)) <1995RJGC324>.



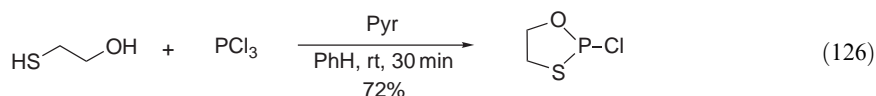
Complete substitution of phosphorus trichloride by two different nucleophiles, first 2-picolythiol (1 equiv.) followed by 1,2,4-triazole (2 equiv.) affords in one-pot 2-picolythiophosphoro-bis(triazolide) (Equation (124)), which was used in the synthesis of phosphorothioates of 2'-deoxyriboligonucleotides <1997IJC(B)1000>.



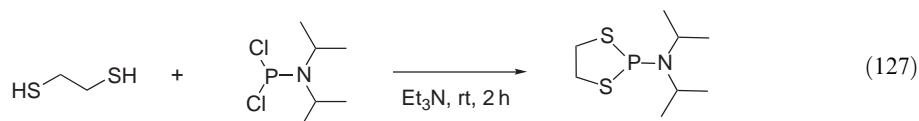
The reaction of phosphorus trichloride with a thiol (3 equiv.) can afford the trisubstituted compounds as demonstrated by the synthesis of *S,S'*-bis(1,3,2-dithiaphospholane)-1,2-ethane-dithiol (Equation (125)) <2000PS(166)1>.



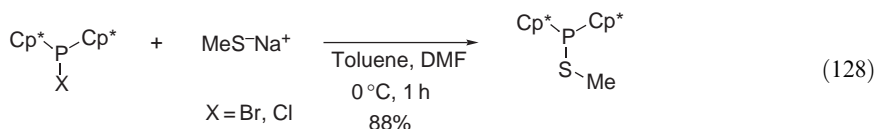
The reaction of PCl_3 with 1 equiv. of a reagent containing two different nucleophilic functional groups, such as 2-mercaptoethanol, can result in the displacement of two chlorides with formation of a cyclic compound (Equation (126)) <1995JA12019>.



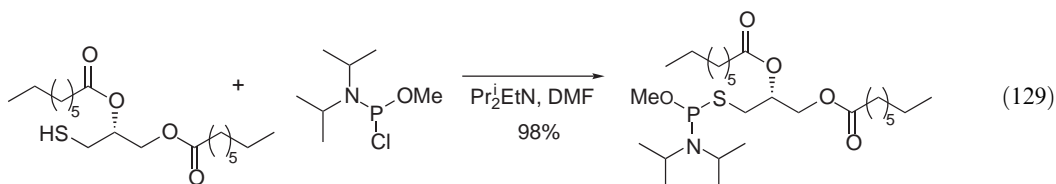
In a similar way, 1,3,2-dithiaphospholanes can be formed by the reaction of ethane-1,2-dithiol with an appropriate dichlorophosphine (Equation (127)) <1998CC2611>.



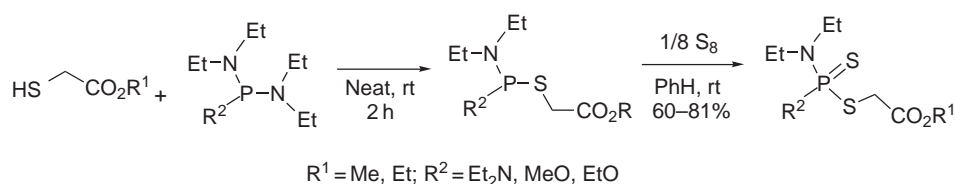
In an example with one leaving group on phosphorus, methylthio-bis(Cp^*)phosphane is formed from bromo- or chlorobis(Cp^*)phosphane and sodium methanethiolate (Equation (128)) <1996PS(111)185, 1998EJ1331>.



If there are other leaving groups, such as dialkylamino or alkoxy, attached to P in a chlorophosphane, the chloride is selectively displaced by a thiol (1 equiv.) to form a thiophosphoramidite in high yield (Equation (129)) <1997BMCL1235>.



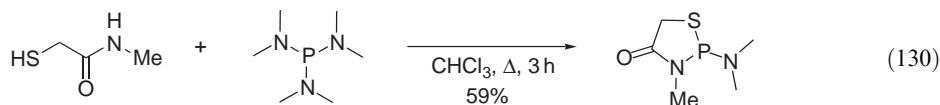
In the absence of a competitive chloride displacement, other leaving groups can be substituted with the formation of an S–P bond. Phosphorus triamidates and phosphorodiamidites readily react with mercaptoacetic acid esters under oxygen-free conditions to give the phosphoramidothioates *in situ*. A subsequent exothermic reaction with sulfur affords dithiophosphates (Scheme 138) <1995RJGC324>.



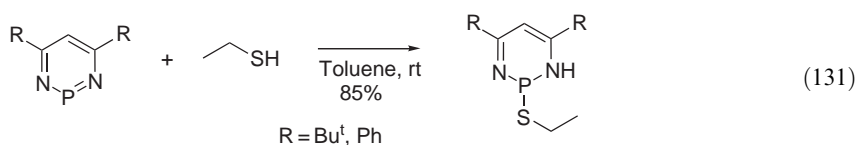
Scheme 138

In a similar way, mono displacement of a pyrrolidinyl substituent in a phosphorodiamidite by ethanedithiol monoacetate has been used in a synthesis of thymidine phosphorothioamidites <1996JOC4272>.

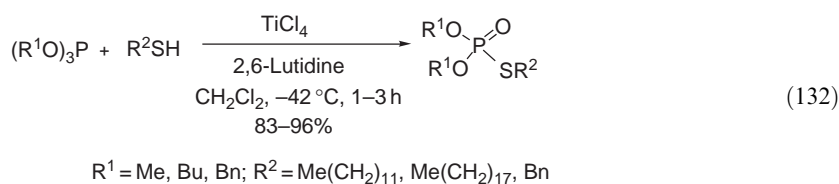
The displacement of leaving groups other than chloride can also result in a cyclic compound. Tris(dimethylamino)phosphane reacts with *N*-methylthioglycolamide to give dialkylaminothiazaphospholidinone in good yield (Equation (130)) <1995LA1555>.



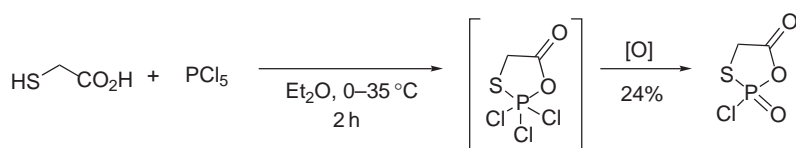
In an interesting example employing a cyclic phosphine, the highly reactive 1,3,2-diazaphosphinines readily add ethanethiol at room temperature to give 2-ethanethio-1,2-dihydro-1,3,2-diazaphosphinines (Equation (131)) <1996JA11978>.



Phosphites form phosphoric thiol esters (phosphorothioates) by a redox-type reaction with thiols in the presence of tellurium(IV) chloride (Equation (132)) <1995SI243>.

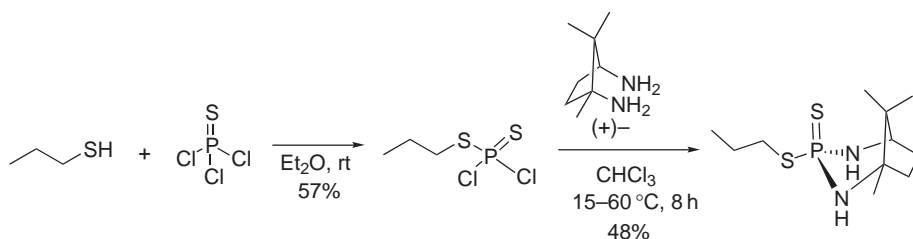


The reaction of phosphorus pentachloride with mercaptoacetic acid results in a cyclic oxathio-phospholane in moderate yield, presumably by oxidation *in situ* of the highly reactive trichlorophosphorane intermediate (Scheme 139) <1998RJGC1965>.



Scheme 139

Thiophosphoryl chloride reacts with one equiv. of propanethiol to form thiophosphorodichloridates, which can cyclize with a chiral diamine with retention of configuration (Scheme 140) <1996PS(114)123>.



Scheme 140

$$\text{R-P(=O)(Cl)}_2 \xrightarrow[\text{60-65\%}]{\text{i, ii}} \text{R-P(=O)(S-C(=O)Me)}_2\text{-NH-CH}_2\text{-CH}_2\text{-CO}_2\text{Me}$$

$$\text{R = Bu, Ph}$$

 (133)

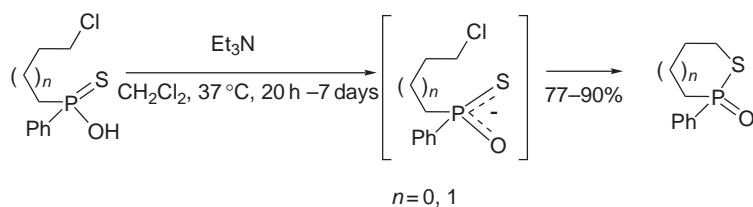
$$\begin{array}{ccc}
 \text{CF}_3\text{CH}_2\text{O}-\text{P}(=\text{O})(\text{Cl})_2 & \xrightarrow[\text{Et}_2\text{O}, 0-5^\circ\text{C to rt, 14 h}]{\text{EtSH (2 equiv.), Et}_3\text{N (2 equiv.)}} & \text{CF}_3\text{CH}_2\text{O}-\text{P}(=\text{O})(\text{SEt})_2 \\
 & & 30\%
 \end{array}$$

$$\begin{array}{ccc}
 \text{R}_f\text{O}-\text{P}(=\text{O})(\text{Cl})_2 & \xrightarrow[\text{Et}_3\text{N, Et}_2\text{O}]{\text{RSH}} & \text{R}_f\text{O}-\text{P}(=\text{O})(\text{SR})_2 \\
 & & 0-5^\circ\text{C to rt, 14 h} \\
 & & 19-41\%
 \end{array}$$

$\text{R} = \text{Et, Pr; R}_f = \text{CF}_3\text{CH}_2, \text{C}_7\text{F}_5\text{CH}_2, \text{C}_3\text{F}_7\text{CH}_2, (\text{CF}_3)_2\text{CH}$

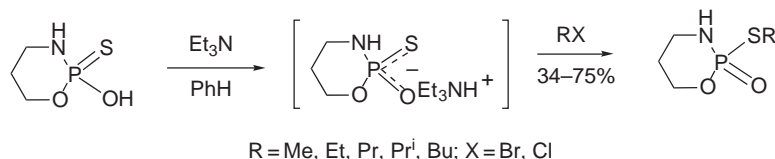
Scheme 141

S-Alkyl phosphorothioates can be prepared by alkylation of the sulfur atom of a phosphorothioate [<1995COFGT\(2\)113>](#). The alternative S—O intramolecular alkylation of chlorophosphinothioic acids in the presence of triethylamine produces *S*-alkylated compounds exclusively via the intermediate thiophosphinate anions ([Scheme 142](#)) [<1999JCS\(P1\)1347>](#).



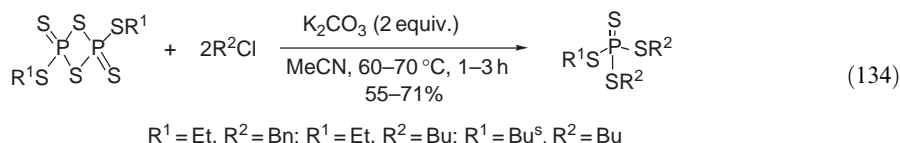
Scheme 142

In a similar way, alkylation of the tetraammonium salt of 2-hydroxy-2-thio-1,3,2-oxazaphosphorinane with alkyl halides results in the exclusive formation of 2-alkylthio-2-oxo-1,3,2-oxazaphosphorinanes (Scheme 143) <1995RCB2147>.



Scheme 143

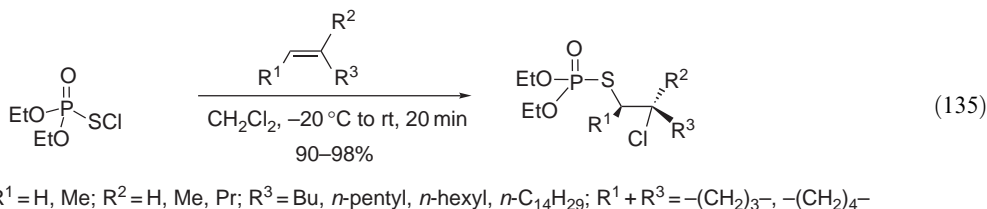
Dithiadiphosphetanes can be alkylated in the presence of potassium carbonate to form tetra-thiophosphates with mixed substituents (Equation (134)) <1998PS(132)85>.



2.03.10.1.3 Addition to carbon-carbon double bonds

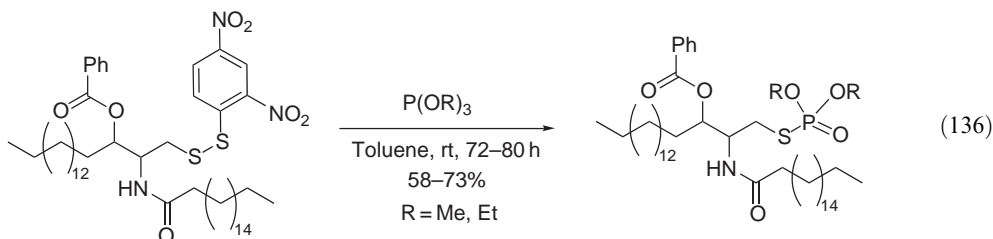
Phosphinodithioic acids can be alkylated by alkenes, enol esters, or enol acetates to give Markovnikov products. 1,3-Dienes and phosphinodithioic compounds can form [4 + 2]-cycloadducts or the anti-Markovnikov products by addition to the terminal position of a diene. Those methods have been reviewed in COFGT (1995) <1995COFGT(2)113>.

Phosphoranesulfonyl chloride reacts with aliphatic alkenes to give *S*-(2-chloroalkane)-*O,O*-diethylphosphates, which are convenient precursors for thiirane synthesis (Equation (135)) <1997HAC429>.



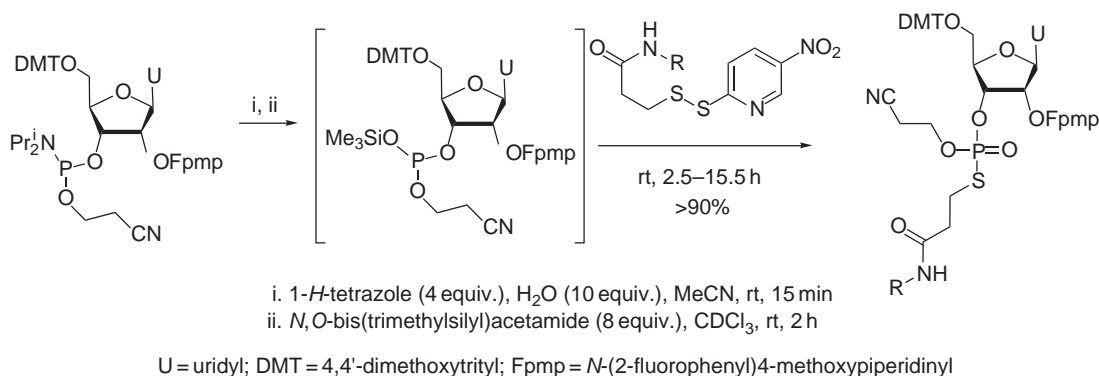
2.03.10.1.4 From disulfides

The S—S bond of a disulfide can be cleaved by a phosphorus reagent to form an S—P bond. This approach has been used in Arbuzov-type reactions to afford thiophosphates in the synthesis of thiophospholipids (Equation (136)) <1996MI85>.



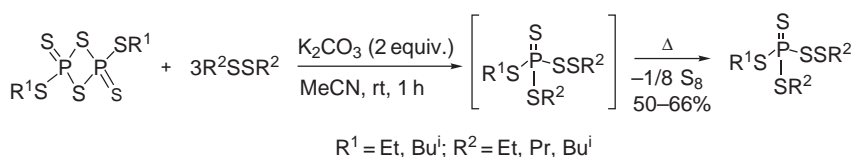
Michaelis–Arbuzov chemistry has been used both in solution and on solid supports to prepare *O,S*-dialkyl-3'-*O*-nucleosidyl phosphorothiolate triesters by cleavage of the S—S bond in *S*-alkyl-*S*-5-nitropyridyl disulfides, which provides a faster reaction and better yield than the symmetrical disulfide 3,3'-dithiopropionic acid di(*N*-succinimidyl ester) (Lomant's reagent) (Scheme 144) <1998TL7975>.

Dithiadiphosphetanes react with disulfides in the presence of potassium carbonate to form pentathiophosphates, which are thermally unstable and readily eliminate sulfur during distillation



Scheme 144

to afford tetrathiophosphates in good yield (Scheme 145) <1998PS(143)133> (cf. Section 2.03.10.1.2).

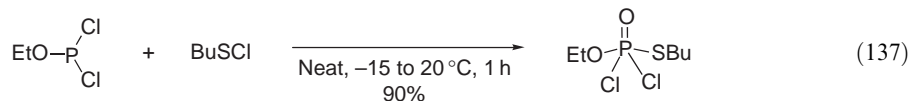


Scheme 145

2.03.10.1.5 From sulfenyl chlorides or sulfenates

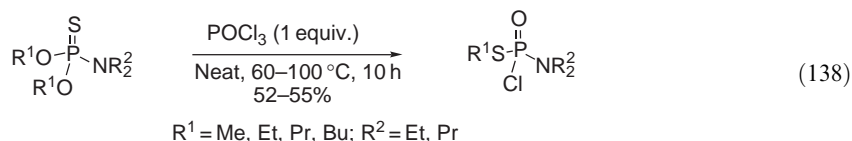
The reaction of alkyl phosphites and sulfenyl chlorides produces thiophosphates. In a manner similar to earlier examples <1995COFGT(2)113>, this method has been used for the synthesis of thiophospholipids <1995LA1467>.

Ethyl dichlorophosphite readily reacted with butylsulfenyl chloride to give dichlorophosphorothioate in high yield (Equation (137)) <2000RCB1593>.

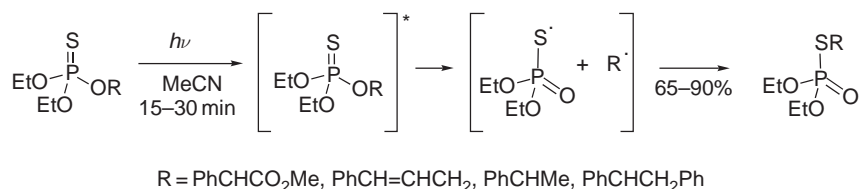


2.03.10.1.6 By rearrangement

Chlorination of *O,O*-dialkyl-*N,N*-dialkyl thiophosphoroamidates using phosphorus oxychloride proceeds with rearrangement to give *S*-alkyl-*N,N*-dialkyl chlorophosphates in good yield (Equation (138)) <1995PS(101)91>. In a similar way, the isomerization-chlorination reaction of *O,O*-dialkyl thiophosphoramidates has been employed to afford the corresponding 3-alkyl chlorophosphates <1996HAC207>.

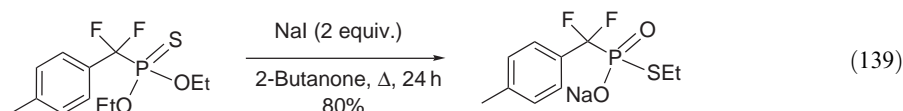


The photoirradiation of thionophosphates in acetonitrile leads to thiophosphates through an established nonchain radical pathway (Scheme 146) <2001JCS(P1)323>. This behavior of thionophosphates is unlike that of the related phosphates, which react via an ionic dissociation-recombination pathway.



Scheme 146

Sodium iodide has been found to be an effective reagent to induce the thiono–thiolo rearrangement of *O,O*-diethyl difluoromethylenephosphonothioate (Equation (139)) <2000JOC5858>.



2.03.10.1.7 Miscellaneous

(i) From alcohols

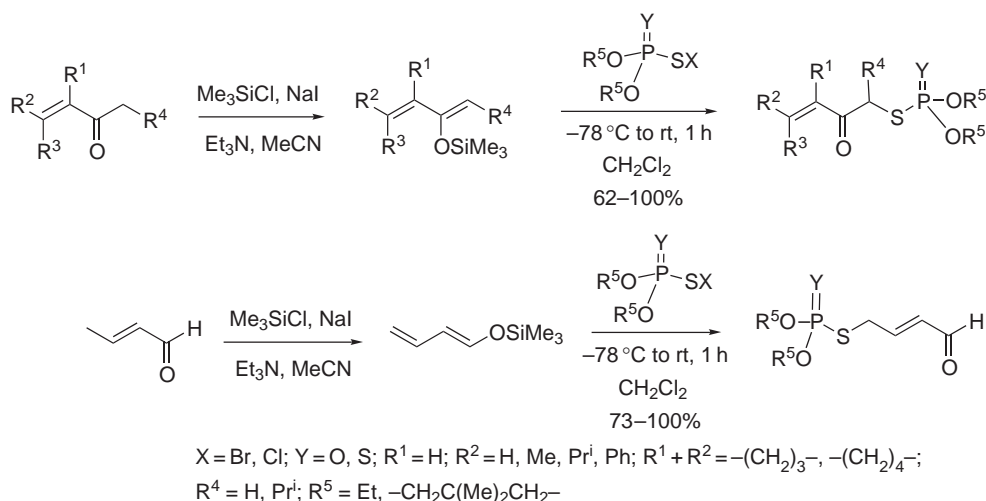
The reaction of alcohols with phosphinodithioic acid derivatives or with phosphorus pentasulfide results in *S*-alkyl phosphinodithioates. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

(ii) From carbonyl compounds

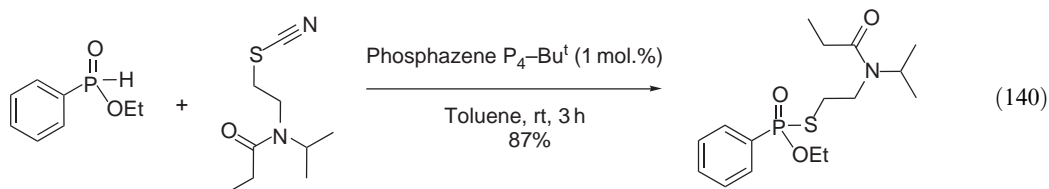
O-Silylated dienolates of α,β -unsaturated ketones and aldehydes can be thiophosphorylated by *O,O*-dialkyl chloro- or bromothiophosphonates to give thio- and dithiophosphates in high yield (Scheme 147) <1999S844>.

(iii) From thiocyanates

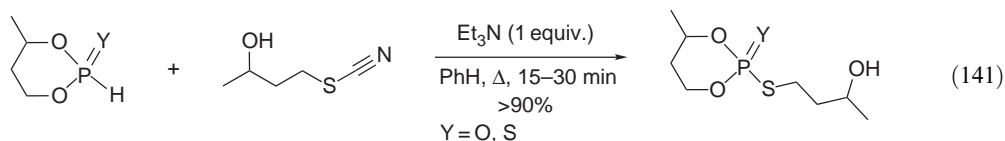
Renard and co-workers have developed a mild and efficient method for thiocyanate addition to H-phosphine oxides by catalysis with the hindered non-nucleophilic base phosphazene ($\text{P}_4\text{-Bu}^t$) (Equation (140)) <2002CEJ2910>.



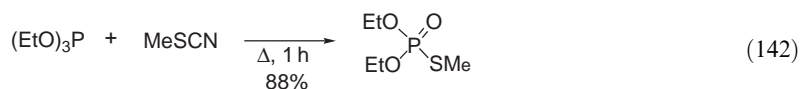
Scheme 147



The reaction of phosphites or thiophosphites with thiocyanato-alcohols produces thiophosphates in high yield (Equation (141)) <1996RCB226>.



Arbuzov reaction of triethyl phosphite with methyl thiocyanate gave the phosphorothiolate in good yield (Equation (142)) <2003JFC161>.



(iv) From thioamides

An Arbuzov-type reaction is known for the formation of thiophosphates from trialkyl phosphites and *S*-alkylthiosuccinimides. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

(v) From ortho-esters

Ethyl ortho-formate reacts with phosphorus pentasulfide to give triethyl dithiophosphate <1995COFGT(2)113>. No further advances have occurred in this area.

(vi) From epoxides

Ring cleavage of an epoxide by the trimethylsilyl derivative of a dithiophosphate was reported in the formation of an *S*-alkylated product <1995COFGT(2)113>. No new data on this subject have been found.

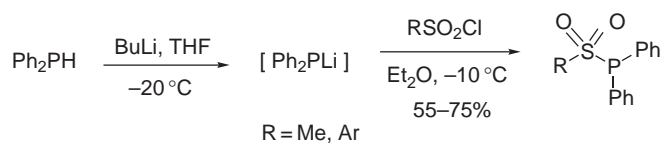
(vii) From thiiranes

Formation of an S—P bond has been reported during thiirane cleavage by triethyldichlorophosphorane. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

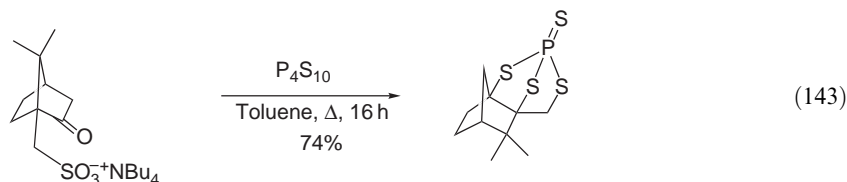
(viii) From sulfonyl chlorides and sulfonic acids

Lithiated diphenylphosphine reacts with mesyl chloride and arylsulfonyl chlorides affording sulfophosphamides (Scheme 148) <1997TL3735>.

The first chiral tetrathiophosphate has been synthesized by reacting tetrabutylammonium camphorsulfonate with P_4S_{10} (Equation (143)) <1997TL6457>. This product was characterized by X-ray diffraction data, but the mechanism of its formation has not been elucidated.



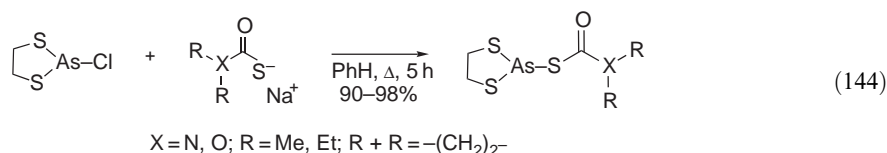
Scheme 148



2.03.10.2 Alkanethioarsenates and Their Higher-coordinated Analogs

2.03.10.2.1 From arsenic halides

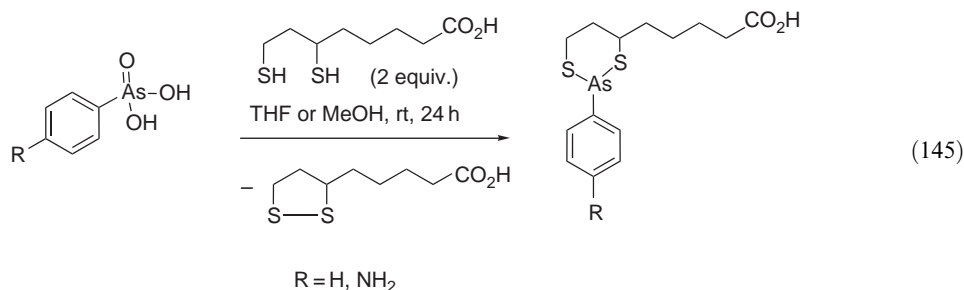
2-Chlorodithioarsolane was synthesized by the direct reaction of arsenic trichloride with ethanedithiol <1995COFGT(2)113>. In turn, this compound reacts with dithiocarbamic or dithiocarbonic acid sodium salt to afford the dithioarsenic alkylthiocarbamates or carbonates (Equation (144)) <1998PS(134/135)345>.



2.03.10.2.2 From arsenoxides

Arsenoxides and thiols react with the formation of alkyl thioarsenates <1995COFGT(2)113, 2002PS(177)497>. This method has been applied to the synthesis of dithiaarsolanes <1999AF944> and *S,S',S'*-arsanetriyl-tri-L-cysteine <1995PS(105)109> for biological tests on antihelmintic activity and as chemotherapeutic agents, respectively.

Dihydrolipoic acid smoothly reduces arylarsonic acids with formation of the As(III) compound and lipoic acid (Equation (145)) <1998EJI61>.



2.03.10.2.3 From aminoarsines

Aminoarsines have been used in the synthesis of thioarsenates by reaction with thiols or with dithiols. No further advances have been made since the publication of COFGT (1995) <1995COFGT(2)113>.

2.03.10.2.4 From tetraalkyldiarsines

An earlier publication reported the reaction between tetramethyldiarsine and disulfides as an approach to functionalized glucopyranoses with potential anticancer activity <1995COFGT(2)113>. No further publications have been found on the subject.

2.03.10.3 Alkanethioantimonates and Their Higher-coordinated Analogs

The literature records that a simple addition of antimony trichloride to thiols affords thioantimonates. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

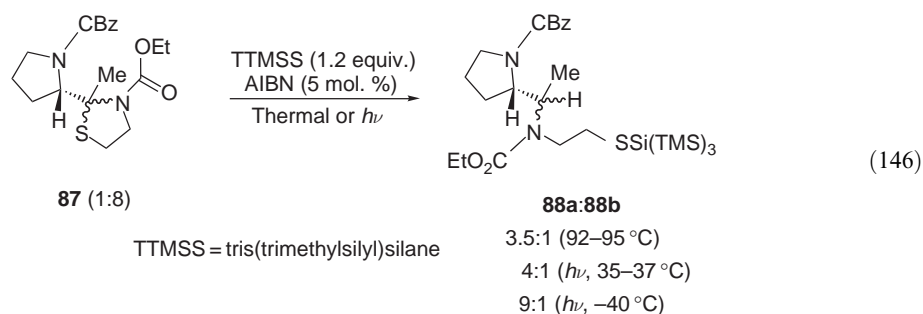
2.03.10.4 Alkanethiobismuthates and Their Higher-coordinated Analogs

The formation of thiobismuthates from bismuth oxide by reaction with thioglycolate or from bismuth nitrate and a thiol has been described <1995COFGT(2)113>. No other examples have been found since the publication of COFGT (1995).

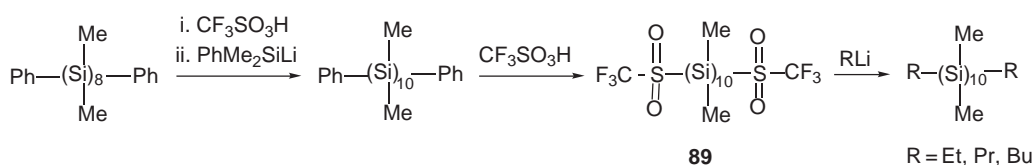
2.03.11 RSSi AND RSB AND RELATED METALLOID FUNCTIONS AND THEIR HIGHER-COORDINATED DERIVATIVES

2.03.11.1 Alkanethiosilanes

The COFGT (1995) survey of alkanethiosilanes included preparations from alkanethiols, alkyl sulfides, disulfides and thiocarbonyl compounds. Since then very few new reports on this topic have appeared. In one report 2-substituted 1,3-oxathiolanes, 1,3-dithiolanes and 1,3-thiazolidines were reacted with tris(trimethylsilyl)silane (1.2–1.8 equiv.) in the presence of AIBN (5 mol.%) under photolytic conditions <1996SL237>. This resulted in C–S bond homolytic cleavage and formation of C–H and S–Si(TMS)₃ bonds. When the 2-substituent is a tertiary chiral group, asymmetric 1,2-induction is observed. Thus, the ratio of diastereomeric products **88a:88b** upon reductive cleavage of compound **87** increases from 3.5:1 under thermal conditions to 9:1 on photolysis (Equation (146)).

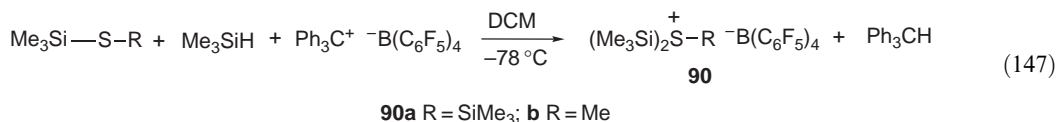


In another study, mesomorphic 1,10-dialkylpermethyldeasilanes were prepared starting from 1,8-diphenylpermethyloctasilane. In this multistep conversion, the terminal bis-trifluorosulfonyl derivatives **89** were formed in good yield and easily reacting with organolithium reagents (Scheme 149) <1998CL345>.



Scheme 149

The first example of silylsulfonium ions **90a,b** have been prepared as a long-lived species by the method shown in Equation (147) and unequivocally characterized by ^1H , ^{13}C , and ^{29}Si NMR spectroscopy <2000JOC7646>. Earlier claims of the preparation of silylsulfonium ions were incorrect.

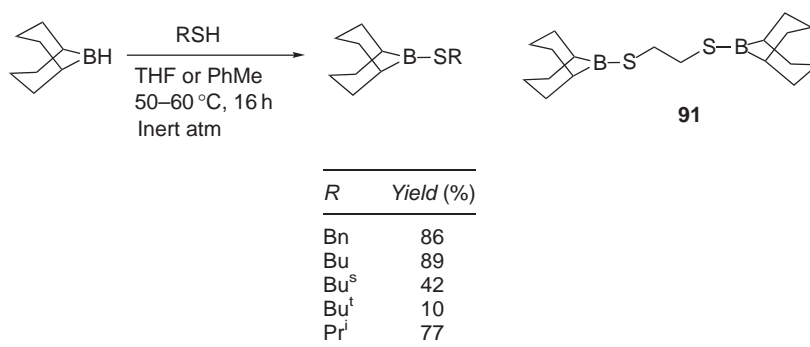


2.03.11.2 Alkanethioboranes

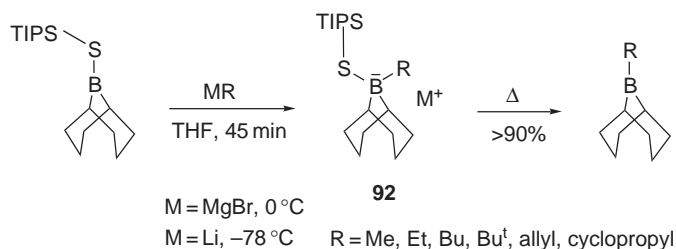
Although alkanethioboranes are known to be versatile reagents for the introduction of thio groups, the number of publications devoted to their preparation is still not large. The main synthetic procedures are based on the use of boranes, haloboranes or alkylboranes, which are usually reacted with an alkanethiol.

2.03.11.2.1 Boranes and haloboranes

Recently, 9-alkylthio-9-borabicyclo[3.3.1]nonanes have received special attention as useful reagents for cross-coupling synthesis of unsymmetrical sulfides <1996JOM(525)225> and thio-boronation of unactivated terminal alkynes <1993JA7219>. This is due to the robust nature of the 9-BBN moiety, which functions efficiently as spectator ligand in many such transformations. The common procedure for 9-RS-9-BBN preparations consists of treatment of 9-BBN-H with the corresponding thiol. Yields are usually high for linear alkanethiols but diminish for branched thiols (Scheme 150) <1988CB1137, 1993JA7219>. Reactions of 9-BBN-H with ethane-1,2-dithiol or TIPS-SH afford **91** (96%) <1988CB1137> and (TIPS)S-9-BBN (85%) <2000TL3537>. The latter has been proposed as an effective reagent for organometallic synthesis of various 9-BBN derivatives (Scheme 151). The (TIPS)S-9-BBN is superior to *B*-MeO-9-BBN for this purpose because of the higher stability of the intermediate 'ate' complexes **92**.

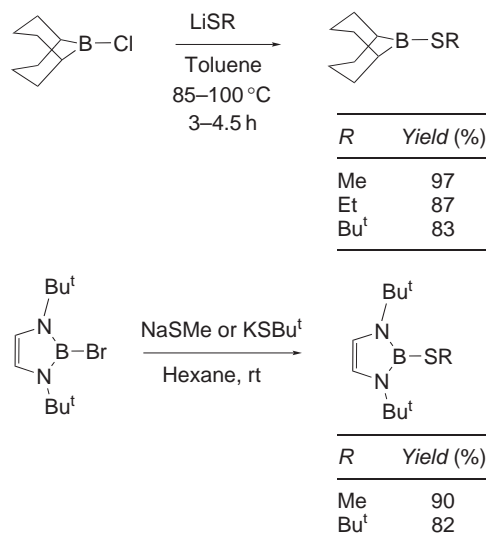


Scheme 150



Scheme 151

In some cases such as introduction of bulky alkylthio groups, boron halides and alkali metal thiolates are the preferred starting materials. For example, the yield of 9-*t*-butyl-9-BBN rises to 87% compared to 10% for the reaction of 9-BBN-H with *t*-butylmercaptan (Scheme 152) <1988CB1137>. Another notable example is synthesis of 2-alkylthio-1,3,2-diazaboroles from 2-bromo-1,3,2-diazaborole and sodium alkylthiolates (Scheme 152) <2001JCS(D)3459>.

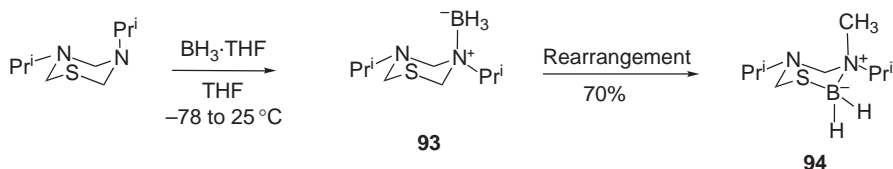


Scheme 152

2.03.11.2.2 Miscellaneous boron-containing compounds

A number of alkanethioboranes can be conveniently prepared by exchange of the groups attached to boron. For instance, (butylthio)diphenylborane has been obtained in 65% yield by disproportionation of an equimolar mixture of BuSBBu₂ and BuOBPh₂ under slow distillation conditions <1996RCB2592>. Reaction of B(SMe)₃ with Me₃SiCN yields the disubstituted complex B(CN)₂(SMe)·NCSiMe₃ as the major product. The latter on treatment with NMe₃ affords the complex B(CN)₂(SMe)·NMe₃ whose structure has been confirmed by an X-ray study <2000JA7735>.

Perhaps, the most interesting example of this type of conversion is reaction of 3,5-dialkyl-1,3,5-thiadiazacyclohexanes with BH₃·THF resulting in initial formation of N·BH₃ complexes **93** that rearrange to 1,3,5,6-thiadiazaboracyclohexanes **94** (Scheme 153) <1999EJI2063>. The same rearrangement was also observed for N·BH₃ and N·BHCl₂ complexes of 1,3,5-dithiaazacyclohexanes <1993CB863>.



Scheme 153

2.03.12 RS-METAL FUNCTIONS AND THEIR HIGHER-COORDINATED DERIVATIVES

Metal thiolates play an important role in the chemistry of organosulfur compounds. In particular, they are widely used as nucleophiles for synthesis of thioethers and thioesters, as ligands for metal complexes and as precursors for disulfide preparation. Many of these conversions have biological

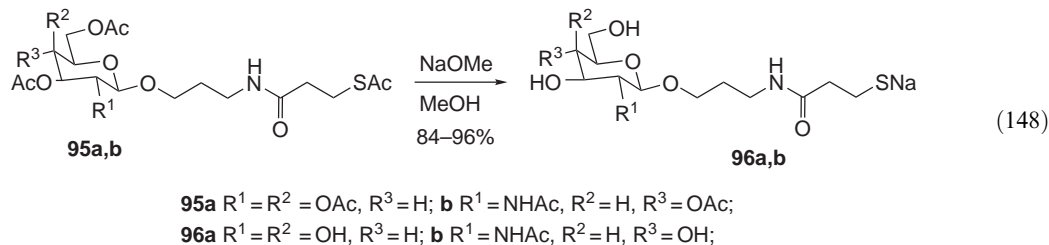
significance. Recently metal thiolates and their complexes have found a growing application in various cross-coupling reactions and as chiral auxiliaries in enantioselective syntheses. Metal-thiolate bonds are responsible for the spontaneous formation of self-assembled monolayers upon dissociative adsorption of alkylthiols and dialkyl disulfides on metal surfaces <1997SC157>.

Since the publication of the review in COFGT (1995), the methods for preparation of alkali and alkali earth metal thiolates are mostly unchanged. In contrast, the volume of information available on heavy metal thiolates has considerably increased. These circumstances are reflected in the following review. Apart from selected exceptions, this survey does not include the numerous data on metal complexes with participation of sulfides and other non-thiolate sulfur derivatives.

2.03.12.1 M = Sodium

Sodium thiolates are commonly prepared by ionization of alkanethiols using sodium hydroxide, sodium alcoholates, sodamide, sodium hydride, or sodium metal. Sodamide and sodium hydride require use of nonprotic solvents (e.g., THF), whereas for both sodium hydroxide and alcoholates a protic solvent is preferred. Since alkyl thiolate anions are readily oxidized, their preparation is normally conducted under an inert atmosphere. Thus, sodium ethanethiolate is obtained as a colorless solid (>90% yield) by stirring ethanethiol with sodium pellets in THF at room temperature for 2 days <1995JCS(D)3699>; hexane or heptane can also be used as a solvent <2001RJGC1883>. Sodium hydride in THF has been employed for the preparation of polystyrene functional resins with side-chains linked to the polymer through a sulfide linkage <2001CJC1049>.

Another procedure for sodium alkanethiolate preparation consists of deacylation of alkyl thioesters by treatment with sodium methoxide or similar bases. For example, the monosaccharides **95** were converted into the *S*-sodium salts **96** for further preparation of cyclodextrin-based glycoclusters (Equation (148)) <1999CL69> (see also <2000T9909, 2001BMCL2651, 2002T3655> and Section 2.03.1.7). It should be noted that in these and many other cases sodium alkylthiolates are obtained *in situ* without isolation.



2.03.12.2 M = Lithium

The simplest way to prepare lithium alkanethiolates is treatment of alkanethiols with butyllithium. EtSLi and Bu^tSLi have been prepared in homogeneous phase from a commercial hexane solution of butyllithium by addition of the thiol in slight excess at -60°C and evaporation at room temperature to obtain noticeably pure salts <1996H(43)1893>. Some specific lithium alkanethiolates can be prepared by reductive cleavage of sulfur heterocycles by lithium (Section 2.03.1.12, Scheme 30) and by thiolation of organolithium compounds using inorganic sulfur or other sulfur derivatives (Section 2.03.1.8). Lithium alkanethiolates are often used as nucleophiles in substitution and addition reactions <1996H(43)1893, 2001TL2469, 2002JOC1008>.

2.03.12.3 M = Potassium

There is little information on potassium alkanethiolates: they can be prepared in a similar way to their sodium counterparts. Thus, bubbling of low boiling mercaptans through a mixture of concentrated aqueous potassium hydroxide and an aromatic hydrocarbon in which 18-crown-6 is dissolved leads to formation of complexes $[\text{K}(18\text{-crown-6})\text{SR}]$ which are soluble in aromatic solvents at elevated temperatures. These complexes can be used as active catalysts for the

preparation of alkyl vinyl sulfides by addition of alkanethiols to acetylenes <1996JPR172, 1996JPR264>. The complex [K(18-crown-6)SBU] has been isolated and subjected to an X-ray study. It is the first structurally characterised potassium salt of a monodentate thiolate that is monomeric.

2.03.12.4 M = Magnesium

Magnesium thiolates can be prepared by the addition of an alkanethiol to ethylmagnesium bromide in THF <1995COFGT(2)113>. An alternative procedure consists of sulfur insertion into an organomagnesium species <2001RJGC1883> (see also Section 2.03.1.8). Since magnesium thiolates are highly reactive they are not normally isolated.

2.03.12.5 M = Copper

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)113>.

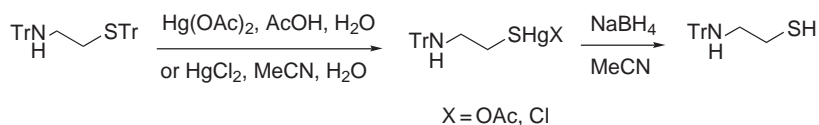
2.03.12.6 M = Zinc

Zinc thiolates can be prepared by reductive cleavage of disulfides using zinc dust in hydrochloric acid <1995COFGT(2)113>. In more recent procedures, alkanethiols have been used as starting compounds. In a typical protocol the corresponding thiol (2equiv.) was stirred with ZnO or ZnCO₃ (1 equiv.) in dry C₆H₆ under reflux in a Dean–Stark apparatus, the solvent was removed under reduced pressure and the residual zinc salt dried over P₂O₅ (Equation (149)) <1996CAR(285)159>. Reaction of thiols with zinc sulfide also leads to formation of zinc mercaptides <1998IJC(B)1174>. The latter are usually used for preparation of *S*-glucosides from glucosyl halides <1996CAR(285)159> or thioethers containing bulky alkyl groups <1998IJC(B)1174>.



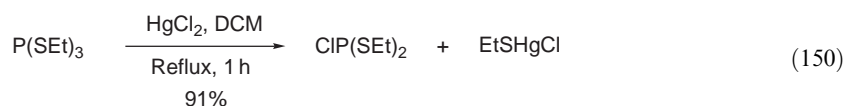
2.03.12.7 M = Mercury

Mercury thiolates are formed and often isolated upon deprotection of tritylthio <2001JOC7615> or *t*-butylthio groups <1995T11883, 1996BMCL2053> by mercury diacetate or dichloride. Free thiol can be obtained by cautious addition of NaBH₄ to an alkaline suspension of the mercury salt (Scheme 154) <2001JOC7615> or by the action of hydrogen sulfide <1995T11883, 1996BMCL2053>.



Scheme 154

Treatment of triethyl trithiophosphite with HgCl₂ gives ethylthiomercury chloride in high yield as a colorless solid (Equation (150)) <1999RJGC662>.



2.03.12.8 M = Gold

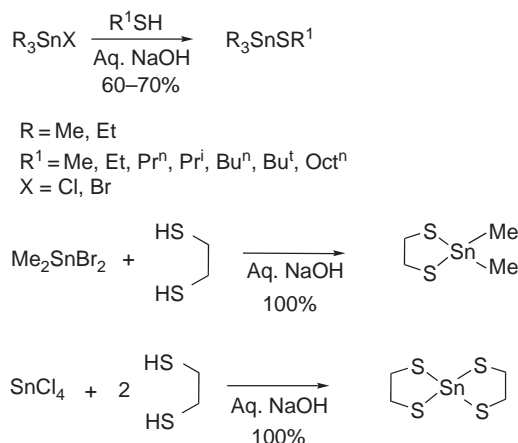
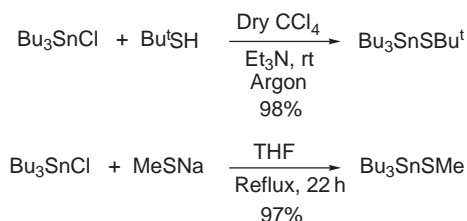
Common methods for the preparation of gold thiolates are based on reactions of trialkylgold or dialkylgold halides with thiols <1995COFGT(2)113>. Since the publication of COFGT (1995) only limited progress has occurred in this area. In particular, attention has been directed to self-assembly of alkylthiols and dialkyl disulfides on gold surfaces, which is thought to include formation of gold thiolates <1997SC157>.

2.03.12.9 M = Silver

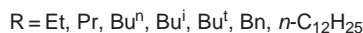
Silver thiolates are usually formed by selective removal of *S*-trityl groups by AgNO₃ in MeO-H(EtOH)-pyridine solution <1997TL2931, 2001BMCL1189>.

2.03.12.10 M = Tin

Alkylthio compounds of tin were not considered in COFGT (1995), although they have been known for a long time. Common ways for preparing compounds of the type R₃SnSR¹, R₂Sn(SR¹)₂, and RSn(SR¹)₃ consist of reaction of the corresponding organotin halides with thiols in the presence of base. This method provides equally good yields for the synthesis of acyclic, heterocyclic, and spiro-compounds with S—Sn bonds (Scheme 155) <1965JCS1192>. Since alkylthio compounds of tin, in marked contrast to the corresponding silicon derivatives, are not hydrolyzed by water, the procedure can be conducted conveniently and more cheaply in aqueous solution. However, in several instances the aqueous methods gave lower yields (30–50%), presumably due to formation of some insoluble polymeric organotin oxygen compounds. In view of this, nonaqueous procedures are preferable as they provide nearly quantitative yields of the target compounds (Scheme 156) <1995SC1831, 1997T1025, 2002JA4874>.

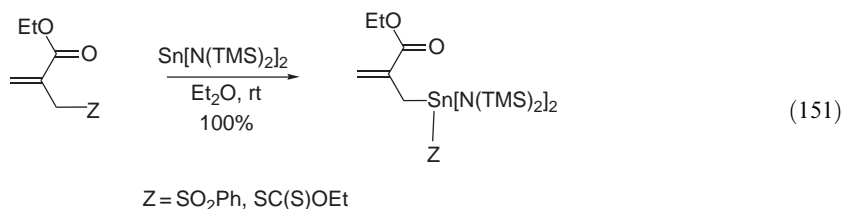
**Scheme 155****Scheme 156**

Many alkylthio compounds of tin are quantitatively obtained by thiolysis of alkyltin alkoxides and oxides in benzene or toluene (Scheme 157) <1967JOM(7)85>. Notably, this protocol does not require the use of a base.

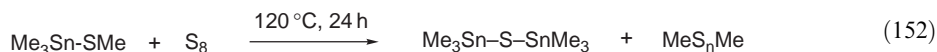


Scheme 157

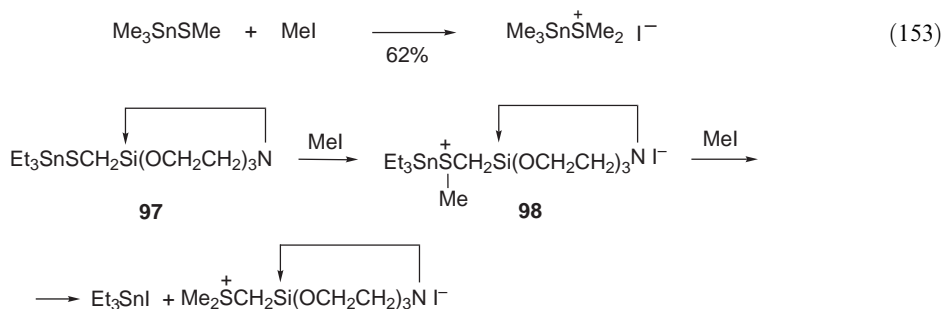
In one example, compounds with S—Sn bonds have been prepared by insertion of a stannylene [$\text{Sn}(\text{N}(\text{TMS})_2)_2$] into a C—S bond (Equation (151)) <1997BSF959>.



In an attempt to produce organotin disulfides, elemental sulfur was heated with alkylthiotrimethyltins <1965JCS1192>. Instead of the expected Me_3SnSSR , however, bis(trimethyltin) sulfide was isolated (53%) together with the organic sulfide and disulfide (Equation (152)).



Methylthiotrimethyltin and methyl iodide react upon warming to produce dimethyl(trimethylstannyl)sulfonium iodide as a stable crystalline solid, which can be recovered unhydrolyzed from aqueous solution (Equation (153)) <1965JCS1192>. In contrast, a similar attempt to prepare iodide **98** from the silatrane derivative **97** failed, possibly due to cleavage of the Sn—S bond in the desired sulfonium salt (Scheme 158) <1999RJGC560>.



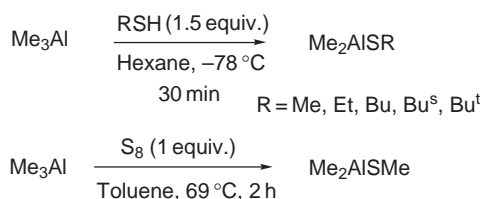
Scheme 158

Alkylthio compounds of tin and especially trialkylstannyl alkyl sulfides are widely employed as reagents for cross-coupling sulfide synthesis <1995S717, 1995CAR(277)231, 1996MI(2)73, 1997T1025, 1997EJM409, 1998JCS(P1)1935, 1998MI647, 2001JCS(P1)1413, 2002BMCL1663, 2002BMCL3171, 2002TL3645> including alkylthio derivatives of carbohydrates <1996CAR(286)107>.

2.03.12.11 M = Aluminum

Aluminum thiolates can be prepared starting from either aluminum halides or trialkylaluminum. Thus, in accordance with a typical protocol dimethylaluminum alkanethiolates were obtained

(without isolation) by stirring trimethylaluminum and the corresponding thiol in hexane solution <1977JOC3960, 1995JOC2942>. In the case of dimethylaluminum methanethiolate, the reaction of trimethylaluminum with equimolar amounts of sulfur also gave the desired product (Scheme 159) <1995JOC2942>.



Scheme 159

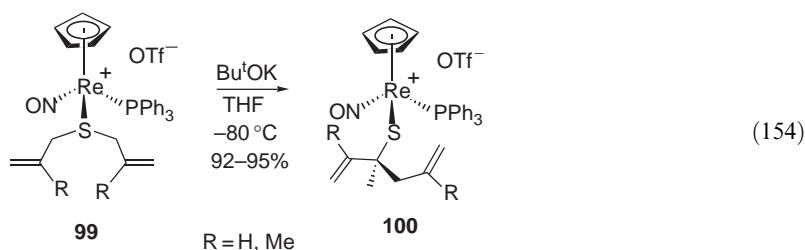
Dialkylaluminum alkanethiolates are often used for the mild conversion of lactones <1995TL1459, 1997JOC1310, 2002OL859, 2002TL3621> or esters <1977JOC3960, 1995JOC2942, 1998PS(136)561, 1999JCS(P1)1631> into *S*-alkyl esters.

2.03.12.12 M = Lead

Despite the highly thiophilic nature of lead, little is known about its alkylthiolates. A rare example is the preparation of ethylthiotrimethyllead (53%) by reaction of trimethyllead chloride with ethanethiol in aqueous alkali <1965JCS1192>.

2.03.12.13 M = Rhenium

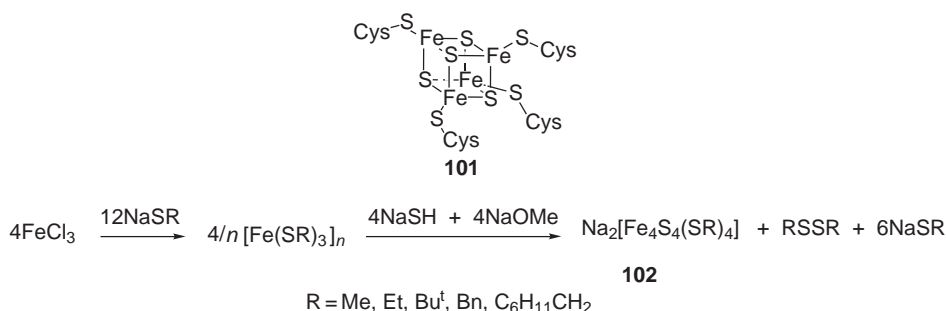
Rhenium triflate complexes with dipropargyl or diallyl sulfide ligands (e.g., **99**) on treatment with Bu^tOK in THF rearrange within a few minutes to the thiolate complexes **100** in excellent yield. This reaction proceeds with high diastereoselectivity and **100** can be further transformed by detaching the thiolate ligands to give nonracemic organosulfur compounds (Equation (154)) <1994JA3655>.



2.03.12.14 M = Iron

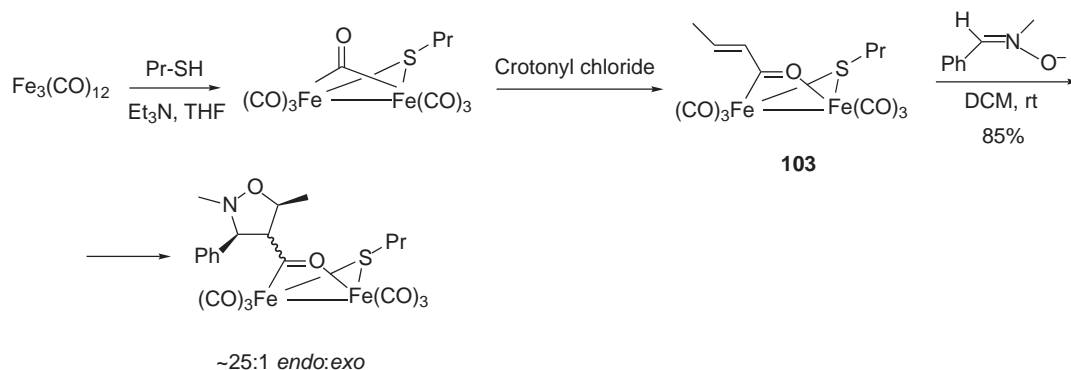
Simple iron(II) thiolates can be obtained by reaction of sodium alkylthiolate with FeCl₂ or FeCl₃ <1927CB2318, 1984IC1816>. In the latter example the primarily formed Fe(SR)₃ is easily reduced by excess thiol to Fe(SR)₂. Thiols are inert to metallic iron, but mechanically activated iron at high temperature reacts with alkanethiols to produce small amounts of Fe(SR)₂ (R = Buⁿ, Bu^t, *n*-C₁₂H₂₅, Bn) <1998RCB2316>. Iron thiolates are highly insoluble green solids similar to that of other metal (II, III) mercaptides for which polymeric structures have been proposed.

Iron thiolates are important derivatives because of their relationship to iron–sulfur proteins, which constitute one of the classes of metalloproteins and metalloenzymes. The active site of some iron-sulfur proteins consists of an approximately cubic Fe₄S₄^{*} cluster with Fe and S^{*} at alternate vertices. In these structures cysteinyl sulfurs act as terminal ligands to iron as shown in structure **101**. Model complexes of the type **102** have been prepared in accordance with Scheme 160 <1973JA3523, 1980JA4694, 1981JA4054>.



Scheme 160

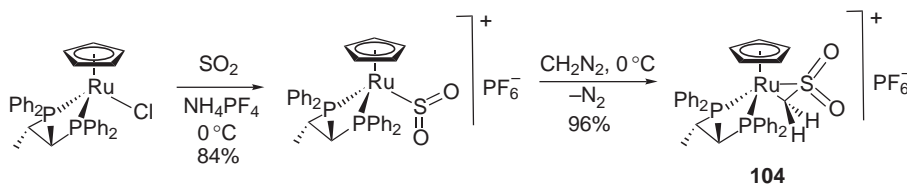
Diiron acyl complexes of type **103** containing an alkyl thiolate ligand can be prepared by interaction of triiron dodecacarbonyl with a thiol. They have recently been suggested as useful dipolarophiles reacting with nitrones in a regio- and stereoselective manner (Scheme 161) <1995JA4431, 1997JA3399, 1999AG(E)1116>.



Scheme 161

2.03.12.15 M = Ruthenium

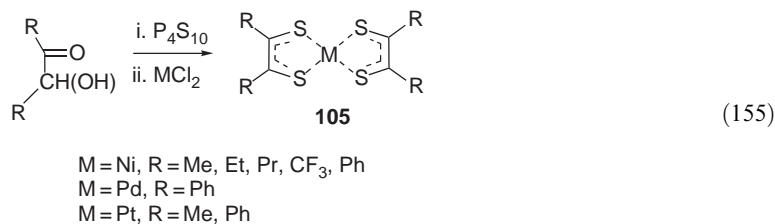
Recently, enantiomerically pure ruthenium-sulfene complex **104** has been prepared from a ruthenium chloride precursor (Scheme 162) and was used to carry out C—C coupling reactions on treatment with carbon nucleophiles <2000EJI287>.



Scheme 162

2.03.12.16 M = Nickel, Palladium, and Platinum

Bis-dithio- α -diketone complexes of nickel, palladium and platinum **105**, which formally include a metal-mercaptide unit, have been prepared in moderate to good yields starting from α -hydroxy ketones (Equation (155)) <1965JA1483>. All compounds are crystalline and air stable, and the methyl-substituted complexes are vacuum sublimable.



The [N,N'-bis(mercaptoethyl)-1,5-diazacyclooctane]nickel (Equation (107), Section 2.03.8) was obtained as an air-stable purple powder in good yield by treatment of 1,5-bis(mercaptoethyl)-1,5-diazacyclooctane with nickel acetylacetonate in toluene <1990IC4364, 1999CC2473>.

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Biographical sketch



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2.04

Alkyl Chalcogenides: Selenium- and Tellurium-based Functional Groups

T. KATAOKA and S. WATANABE

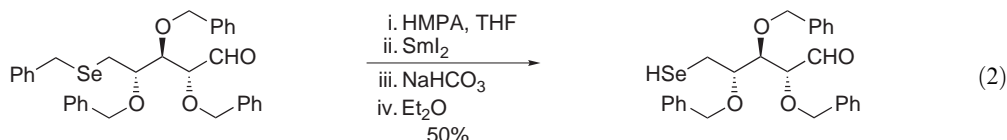
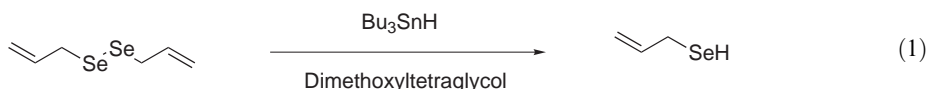
Gifu Pharmaceutical University, Gifu, Japan

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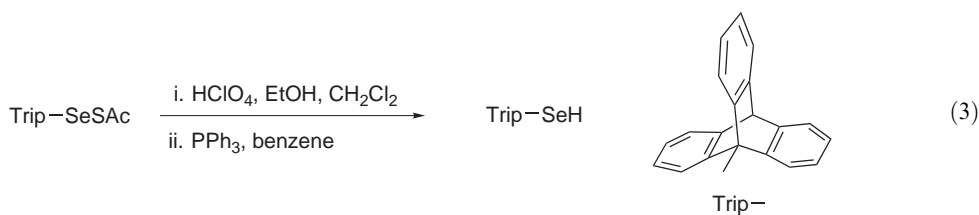
2.04.1 ALKANESELENOLS (RSeH) AND ALKANETELLUROLS (RTeH)

Selenols are more powerful nucleophiles than the corresponding thiols and are important reagents for further functional group transformations. In addition, they have reducing activities towards a number of organic functionalities. Typical synthetic methods for alkaneselenols are described in chapter 2.04 of COFGT (1995) <1995COFGT(2)277>, and subsequently some types of alkaneselenols have been prepared as their metal salts by the same methodology <2002PS597, 2001HAC293, 1999EJI873>.

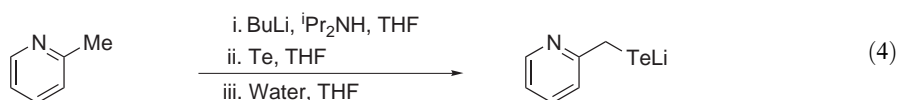
Allylic selenols (2-propene-, 2-butene-, 3-methyl-2-butene-, and 2-methyl-2-propeneselenol) are formed by the reductive cleavage of the corresponding diallylic diselenide with Bu_3SnH . β,γ -Unsaturated selenols are very unstable compounds at room temperature in the absence of a radical inhibitor (Equation (1)) <2002OM68>. Samarium iodide was also used for the formation of alkaneselenol through a radical reaction. Treatment of 2,3,4-tri-*O*-benzyl-5-benzylseleno-5-deoxyribose with SmI_2 in THF affords 2,3,4-tri-*O*-benzyl-5-deoxy-5-hydro-seleno-D-ribose in 50% isolated yield in a process most likely involving intramolecular homolytic substitution at the selenium atom in the selenosugar (Equation (2)) <2000T3995>.



Acetyl triptycene-9-thioselenate was hydrolyzed with perchloric acid followed by treatment with triphenylphosphine to give triptycene-9-selenol through the corresponding thioselenenic acid (Equation (3)) <2002CC2810>.



Alkanetellurols are prepared in a similar way to alkaneselenols <1995COFGT(2)277>. Lithium 2-picolytellurolate was obtained by the reaction of lithiated 2-picoline with elemental tellurium (Equation (4)) <2002PS597>.



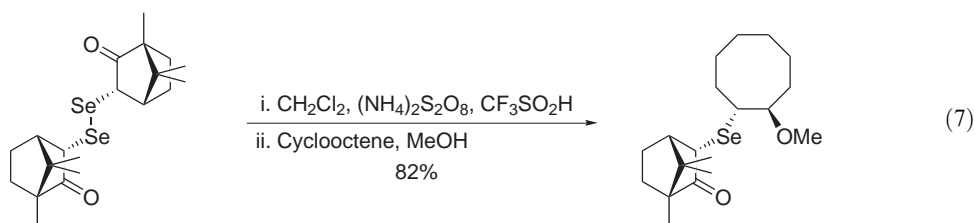
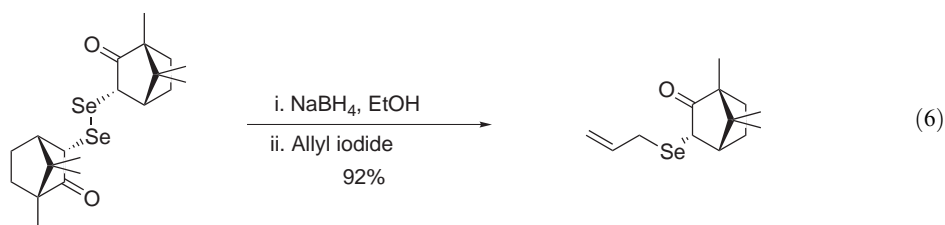
2.04.2 DIALKYL SELENIDES (R^1SeR^2), DIALKYL TELLURIDES (R^1TeR^2), AND THEIR HIGHER-COORDINATED DERIVATIVES

2.04.2.1 Alkyl Selenides and Alkyl Tellurides

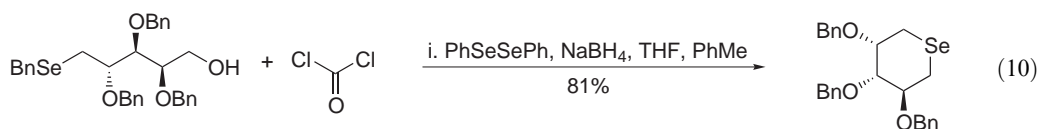
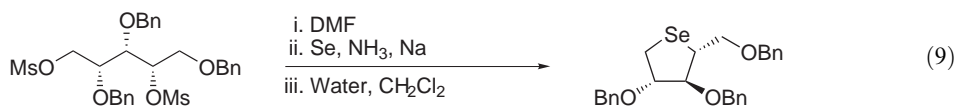
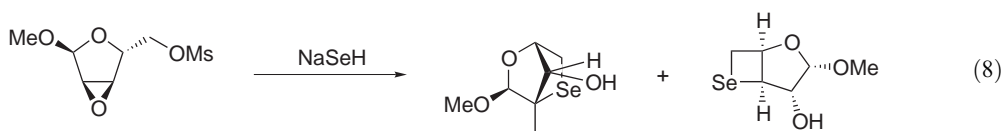
The versatility of selenides, one of the most important selenoorganic functional groups, arises from their facile transformations. In particular, selenides can act as nucleophiles or electrophiles toward reagents. The stabilization of carbanions, carbocations, and radicals to the α -seleno moiety is also well known. The detailed preparations of alkyl selenides are described in COFGT (1995) (chapter 2.04.2.1) <1995COFGT(2)277>. The reactions of alkyl halides with (i) sodium selenide and its equivalent <2002EJO3198, 2001HAC293, 1998SL971, 1995ZOB99>; (ii) alkaneselenolate anions derived from diselenides <2000SC1731, 1999JCR(S)280, 1997SC609, 1996CPB2223>, selenocyanate <2000SC377>, Se and a carbanion <1997JOM(533)197>; and (iii) a diselenide and a carbanion <1996TL8015> are representative of the syntheses of the selenides.

As the versatility of chiral compounds is increasing, several types of optically active compounds that are used as precursors and catalysts bearing a selenide component have been prepared by known methods. An optically active selenide that catalyzes asymmetric epoxidation was obtained from the reaction of lithium selenide with chiral ditosylate (Equation (5)) <2001CC2350>.

Camphor diselenide is considered to be a useful intermediate for forming several chiral selenides. The reaction of the sodium selenolate formed from camphor diselenide and sodium borohydride with allyl iodide afforded the chiral allyl selenide in a high yield (Equation (6)) <1999T3191>. Alternatively, using the reaction with ammonium persulfate, the easily available diselenide derived from (1*R*)-(+)-camphor was converted into camphorselenenyl sulfate. This chiral electrophilic selenium reagent reacted with alkenes in MeOH to afford selenomethoxylated adducts regioselectively in good yields and with moderate-to-good facial selectivity (Equation (7)) <1998TL2809, 2000EJO3451, 2000OL3007>.

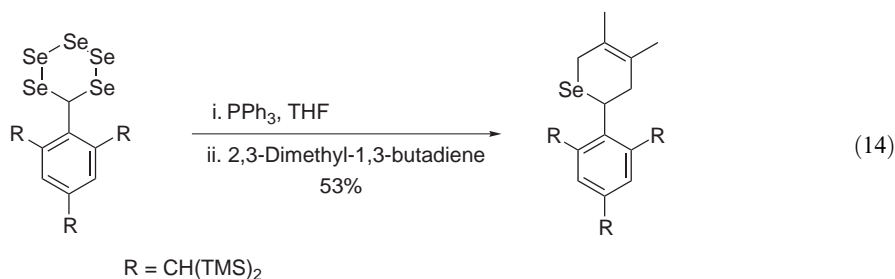
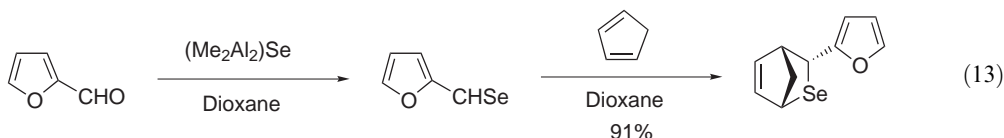
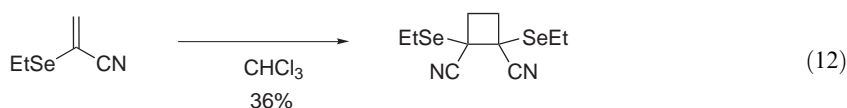
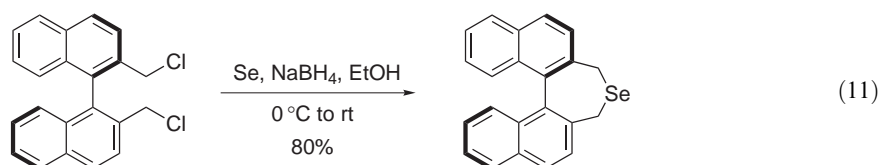


Cyclic selenides with polychiral centers are derived from sugar derivatives. Sodium hydrogen selenide readily attacks methyl 2,3-anhydro-5-*O*-mesyl- α -D-ribofuranoside to yield selenabicyclics as pure enantiomers (Equation (8)) <1999PS429>. 2,3,5-Tris-*O*-(phenylmethyl)-D-xylitol dimethanesulfonate, which was prepared from L-xylitol, reacted with sodium selenide in DMF to give the chiral selenolane derivative in 80% yield (Equation (9)) <2002JA8245>. 2,3,4-Tri-*O*-benzyl-1,5-dideoxy-5-seleno-D-pentopyranose sugars are readily prepared by thermolysis of 2,3,4-tri-*O*-benzyl-5-benzylseleno-D-ribofuranoside, 2,3,4-tri-*O*-benzyl-5-benzylseleno-D-xylitol, and 2,3,4-tri-*O*-benzyl-5-benzylseleno-D-arabinose in transformations that involve an intramolecular nucleophilic attack of the benzylseleno moiety with a concomitant loss of carbon dioxide and phenylselenolate (Equation (10)) <2000T3995, 2003BCJ381>.

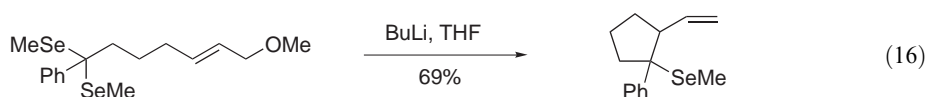
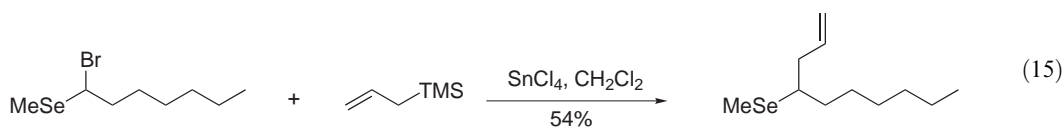


A novel enantiomerically pure selenide bearing a binaphthyl skeleton was synthesized by the reaction of (1*R*)-2,2'-bis(chloromethyl)-1,1'-binaphthalene, which was derived from (*R*)-1,1'-bi-2-naphthol via multiple steps, with sodium selenide in a good yield (Equation (11)) <2000SC2975>.

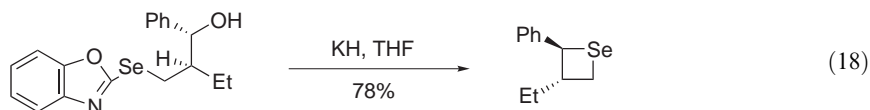
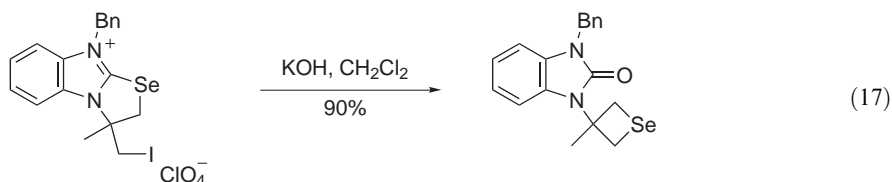
Gentle reflux of a chloroform solution of a vinyl selenide caused [2 + 2]-dimerization to give the head-to-head dimers as an (*E*)/(*Z*)-isomeric mixture (Equation (12)) <1997LA541>. Dihydrosele- nins were prepared by [4 + 2]-cyclization of selenoaldehydes with 1,3-butadienes. Furyl selenoal- dehyde reacted with cyclopentadiene to give an adduct (Equation (13)) <1999JOC1565>. A selenoaldehyde protected by the Tbt (2,4,6-tris[bis(trimethylsilyl)methyl]phenyl) group, which was generated by the deselenation of a cyclic polyselenide mixture with triphenylphosphine, reacted with 2,3-dimethyl-1,3-butadiene to afford a cyclic selenide (Equation (14)) <1997T12167>.



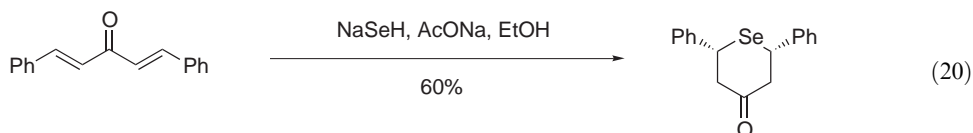
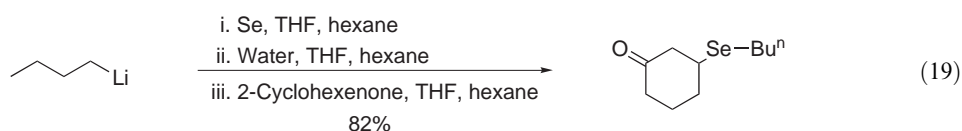
α -Haloselenides were cleanly transformed into homoallyl selenides upon reaction with allyltri- methylsilane in the presence of tin tetrachloride (Equation (15)) <1995JOC6141>. A selenoacetal bearing an allylic ether in a side-chain reacted with butyllithiums and the resulting α -selenobenzyl- lithium reagent underwent an intramolecular S_N2' reaction to give 1-methylseleno-2-vinylcyclo- pentanes (Equation (16)) <2000SL1443>.



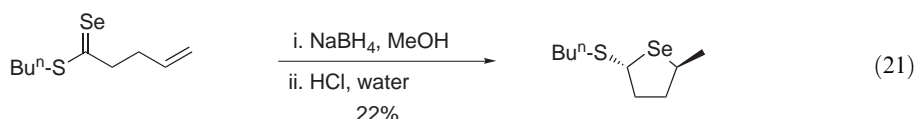
The selenetane ring was prepared utilizing a characteristic of benzimidazole chemistry. The treatment of an (iodomethyl)selenazolobenzimidazolium perchlorate with potassium hydroxide in CH_2Cl_2 gave the selenetanylbenzimidazolone in a high yield (Equation (17)) <1999RJOC730>. A selenetane was afforded in 78% yield upon treatment of (3-hydroxypropyl)selenide with a 1.5 molar amount of potassium hydride in THF. This selenetane may be formed via a spiro intermediate whose ring opens into a selenolate anion followed by intramolecular nucleophilic displacement (Equation (18)) <1998H633>.



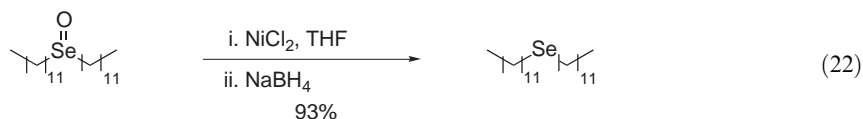
Alkenes conjugated to electron-withdrawing groups (e.g., CHO, RCO, CO₂R, CN) reacted rapidly with alkylselenenols and tellurols generated *in situ* to give the corresponding β -chalcogeno aldehydes, ketones, esters, and nitriles (Equation (19)) <2002TL1625>. 4-Selenanones were obtained from 1,4-pentadien-3-ones and sodium hydrogen selenide via a double Michael addition reaction (Equation (20)) <2001SC3429>.



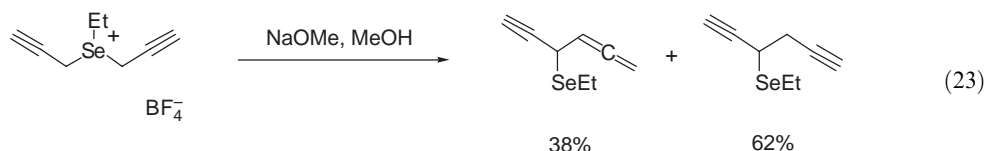
Reductive cyclization of γ,δ -unsaturated selenothioic acid *S*-esters with sodium borohydride proceeds via δ,ϵ -unsaturated selenols to afford tetrahydroselenophenes (Equation (21)) <1996CC1461>.



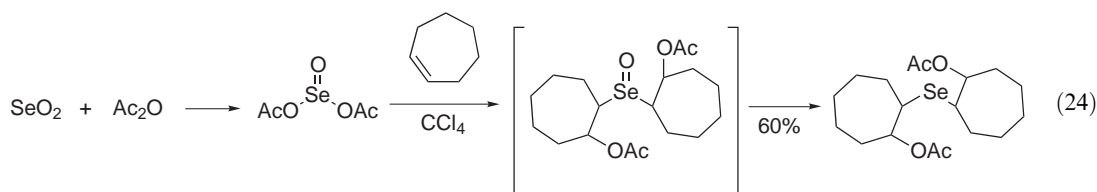
Deoxygenation of a variety of acyclic selenoxides has been accomplished with nickel boride in THF at 0–5 °C in nearly quantitative yields. The deoxygenation probably proceeds by an oxidative-addition and reductive-elimination mechanism (Equation (22)) <1998TL3829>.



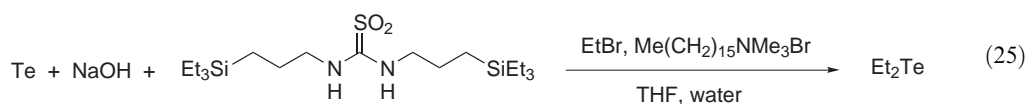
The bis- γ -substituted and unsubstituted propargylic selenonium salts underwent [2,3]-sigmatropic rearrangement of the corresponding selenium ylides to afford an allen-yne selenide and diyne selenide on the treatment with sodium methoxide (Equation (23)) <2001TL2911>.



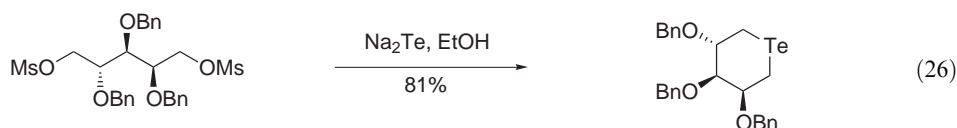
Alkenes react with SeO₂-Ac₂O reagent to form acetoxyselenated compounds in fair yields. It is probable that the SeO₂-Ac₂O combination produces an intermediate seleninyl acetate that reacts with two equivalents of the alkenes to produce the respective selenoxides. However, it is not clear how the selenide is formed from the selenoxide (Equation (24)) <1997SC267>.



Alkyl tellurides are prepared in a similar way to alkyl selenides [<1995COFGT\(2\)277>](#), and symmetrical and unsymmetrical tellurides are formed from alkyl halides and dipotassium ditelluride generated by the reduction of elemental tellurium with hydrazine and potassium hydroxide via dialkyl ditelluride [<1996SUL49, 1995ZOB1145>](#). Tellurium was reduced by *N,N'*-bis[3-(triethylsilylpropyl)]thiourea *S,S*-dioxide under phase-transfer conditions and reacted with ethyl bromide to form diethyl telluride ([Equation \(25\)](#)) [<2002RJGC55>](#).



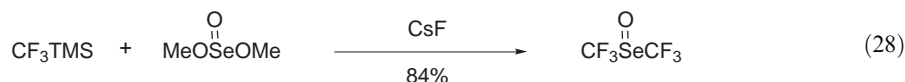
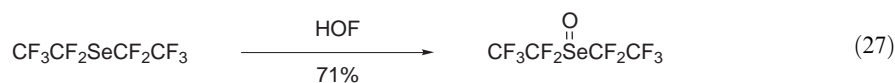
2,3,4-Tri-*O*-benzyl-1,5-dideoxy-5-telluro-D-arabinose and 2,3,4-tri-*O*-benzyl-1,5-dideoxy-5-telluro-L-arabinose were readily prepared by treatment of D- and L-2,3,4-tri-*O*-benzyl-1,5-di-*O*-methanesulfonylarabitol with sodium telluride in ethanol ([Equation \(26\)](#)) [<2002TL3799>](#).



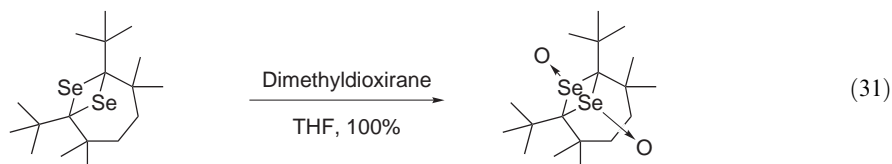
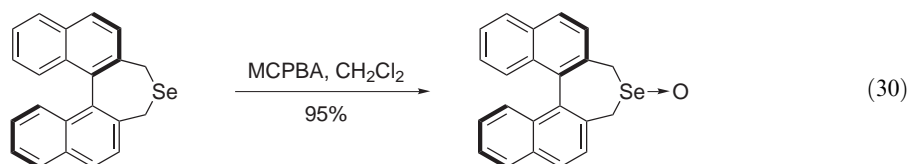
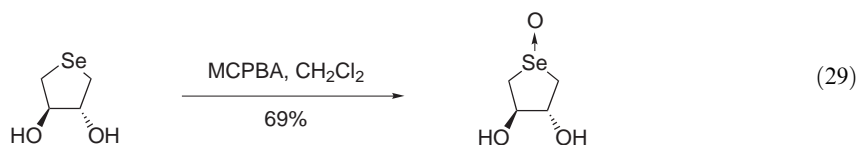
2.04.2.2 Alkyl Selenoxides and Alkyl Telluroxides

Selenoxides have provided useful intermediates for a variety of synthetic applications. Seleninyl compounds suffer mild and easy thermal *syn*-elimination to give unsaturated alkenes in good yields. Furthermore, the oxidation of allylic selenide leads to a facile formation of an allylic alcohol via a selenenic ester generated by [2,3]-sigmatropic rearrangement. More information on the properties and syntheses of selenoxides and telluroxides is given in COFGT (1995) (chapter 2.04.2.2) [<1995COFGT\(2\)277>](#) which covers the literature up to 1995.

Fluoroalkyl selenoxides were prepared by oxidation of perfluoroalkyl selenide with hypofluorous acid without a solvent ([Equation \(27\)](#)) [<2000JFC\(102\)301>](#). Bis(trifluoromethyl) selenoxide was prepared in 84% yield by the reaction of (trifluoromethyl)trimethylsilane with methyl selenite in the presence of caesium fluoride ([Equation \(28\)](#)) [<1999JOC2873>](#).



A new class of water-soluble redox reagent (*trans*-3,4-dihydroxy-1-selenolane Se-oxide) developed for the purpose of the redox control of protein structures, was prepared by MCPBA oxidation of the corresponding selenide ([Equation \(29\)](#)) [<2000CL1440>](#). A new C_2 -symmetrical chiral selenoxide, which was used for the asymmetric oxidation of sulfides to sulfoxides, was obtained in a high yield from the reaction of the corresponding selenide with MCPBA ([Equation \(30\)](#)) [<2000SC2975>](#). The conversion of 1,6-di-*t*-butyl-2,2,5,5-tetramethyl-7,8-diselenabicyclo[4.1.1]octane to the corresponding diselenoxide was performed in high yield by oxidation with dimethyldioxirane ([Equation \(31\)](#)) [<2000JOC1799>](#).



No further advances have occurred in the preparation of alkyl telluoxides since the publication of COFGT (1995) [<1995COFGT\(2\)277>](#).

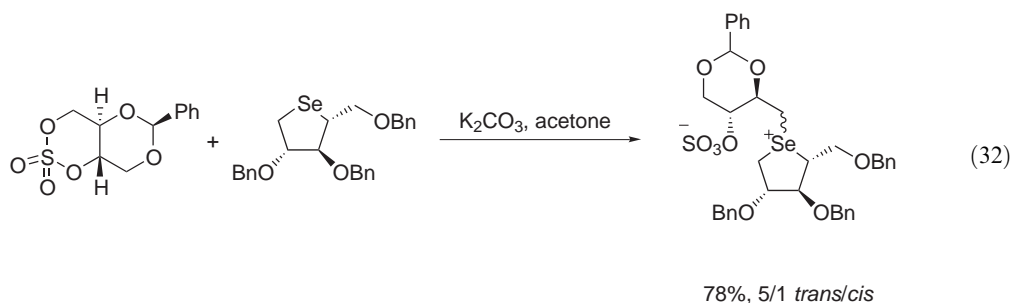
2.04.2.3 Alkyl Selenones and Alkyl Tellurones

No further advances have occurred in this area since the publication of COFGT (1995) [<1995COFGT\(2\)277>](#).

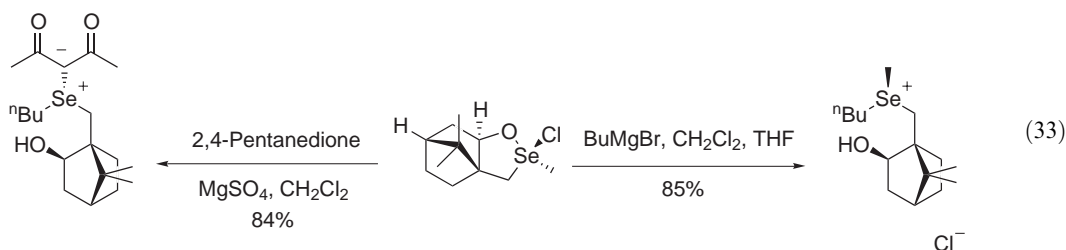
2.04.2.4 Alkyl Selenonium Salts and Alkyl Telluronium Salts

Selenium cations in selenonium salts are attacked by nucleophiles to form the hypervalent selenium compounds, selenuranes. Since the selenonio group is a good leaving group, S_N2 reactions with nucleophiles also occur. Alternatively, selenonium ylides are formed by the reaction of selenonium salts with bases. Several examples of the preparation of alkyl selenonium salts are indicated in COFGT (1995) [<1995COFGT\(2\)277>](#), and their synthesis through the alkylation of the corresponding selenides is a typical method [<2001RJGC1883, 1996ZOB1802, 1995H1127>](#).

The synthesis of a cyclic selenonium salt, which is the precursor of a selenonium analog of the naturally occurring sulfonium ion, saaoacinal, has been achieved by the reaction of seleno-arabinitol and cyclic sulfate, which was derived from D-glucose in 78% yield as a mixture of two diastereomers (Equation (32)) [<2002JA8245>](#).

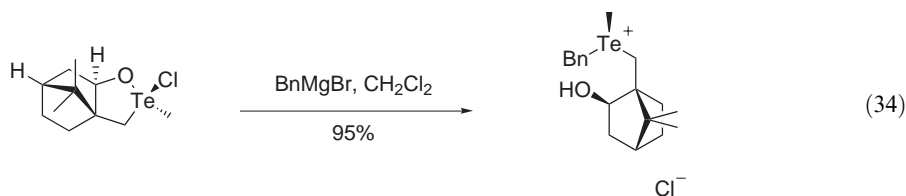


An enantiomerically pure selenonium salt was prepared in a good yield and selectivity by the reaction of the chiral chlorooxaselenurane of 2-*exo*-hydroxy-10-bornyl compound with a Grignard reagent [<2001SC2441>](#). Alternatively, the reaction of chlorooxaselenurane with acetylacetone gave the selenonium ylide as a single isomer (94% yield) in the presence of triethylamine (Equation (33)) [<1995CL379>](#).



Alkyl telluronium salts were prepared in a similar manner to the selenonium salts. The alkylation of alkyl tellurides [<1997JMAC1697>](#) and the exchange of counteranions in telluronium salts [<2002EJO2701, 2002JCS\(D\)3763>](#) has been reported.

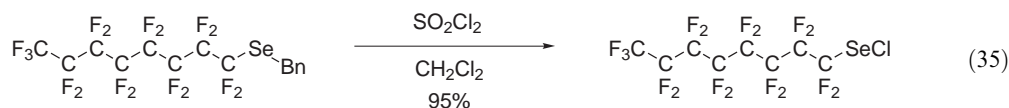
An enantiomerically pure benzyl telluronium salt was prepared in a high yield and selectivity by the reaction of a chiral chloroalkoxytellurane bearing the 2-*exo*-hydroxy-10-bornyl group as a chiral ligand with a Grignard reagent (Equation (34)) [<1998JOC5423, 1997TA3357>](#).



2.04.3 ALKANESELENYL HALIDES AND THEIR HIGHER-COORDINATED DERIVATIVES (RSeHal), SELENINYL HALIDES (RSe(O)Hal), SELENONYL HALIDES (RSe(O)₂Hal), AND CORRESPONDING TELLURIUM COMPOUNDS

Alkaneselenenyl halides act as good electrophiles and react with several nucleophilic reagents to afford selenide derivatives. Usually, the halogenation of selenocyanates or diselenides with a stoichiometric amount of halogen or a sulfuryl chloride affords alkaneselenenyl halides. Typical synthetic methods for the corresponding alkaneselenenyl and tellurenyl halides are described in COFGT (1995) [<1995COFGT\(2\)277>](#).

It has been reported that the reaction of benzyl perfluorooctyl selenide with chlorine, or sulfuryl chloride, produced perfluorooctyl selenenyl chloride and represented an easy route to perfluoroalkyl selenyl chlorides because of the easy cleavage of the benzyl–selenium bond using chlorine or sulfuryl chloride (Equation (35)) [<2001SL1260, 2002CCC1262>](#).



No further advances have occurred in this area except on alkaneselenenyl halides, since 1995.

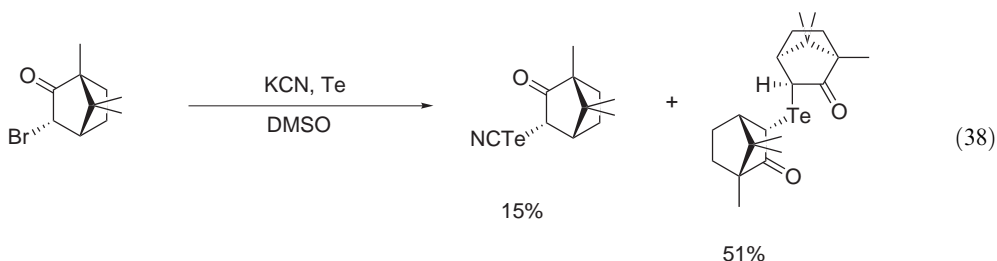
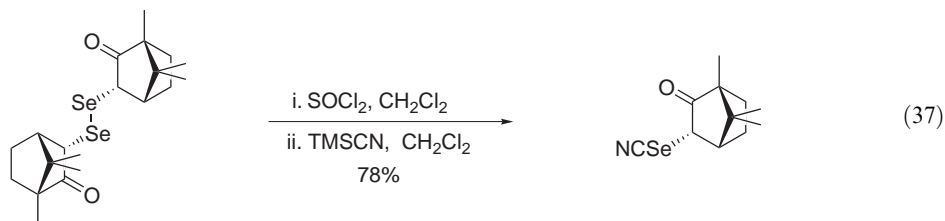
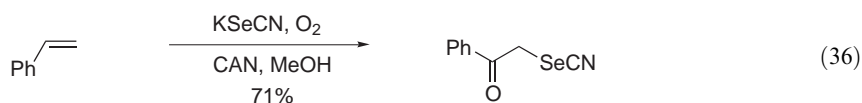
2.04.4 ALKYL SELENOCYANATES (RSeCN) AND ALKYL TELLUROCYANATES (RTeCN)

The selenium atom of alkyl selenocyanates is the preferential site of attack for several nucleophiles, and selenocyanates can be used instead of alkaneselenenyl halides. Mainly alkyl selenocyanates are obtained from the reactions of a selenocyanate anion with alkyl halides or sulfonates. More information on the properties and syntheses of alkyl selenocyanates and tellurocyanates is given in COFGT (1995) [<1995COFGT\(2\)277>](#), and there have been some reports on the preparation of alkyl selenocyanates using potassium selenocyanate with alkyl halides [<2002CL934, 1997PS43, 1995AG\(E\)1627, 1995LA211, 1995CJC113>](#).

Selenocyanation of styrene and indole mediated by cerium(IV) ammonium nitrate (CAN) in the presence of oxygen afforded the corresponding selenocyanates in moderate-to-good yields (Equation (36)) [<2002EJO2363>](#). A chiral camphorselenocyanate was prepared in 78% yield

by chlorinolysis of the corresponding diselenide using sufuryl chloride followed by treatment with trimethylsilyl cyanate (Equation (37)) <1995JOC703>.

The reaction of potassium tellurocyanate with 3-bromocamphor in hot DMSO gave a complex mixture of products from which only 15% of the desired tellurocyanate, as well as 51% of the telluride, was isolated (Equation (38)) <1995JOC4657>.

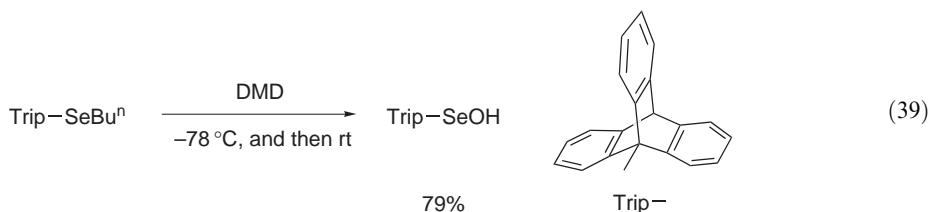


2.04.5 FUNCTIONS BASED ON THE RSeOH UNIT AND ITS HIGHER-COORDINATED DERIVATIVES—SELENENIC, SELENINIC AND SELENONIC ACIDS (RSeOH, RSeO₂H, RSeO₃H), AND CORRESPONDING TELLURIUM ACIDS

2.04.5.1 Alkaneselenenic Acids and Alkanetellurenic Acids

Selenenic acids are unstable and produce diselenides and seleninic acids disproportionately and rapidly. They function as electrophiles and undergo 1,2-additions to alkenes to afford β -hydroxy selenides. More information of the properties and syntheses of alkaneselenenic and alkanetellurenic acids is given in COFGT (1995) (chapter 2.04.5.1) <1995COFGT(2)277>.

9-Triptyceneselenenic acid, which is sterically protected by the 9-triptycyl (Trip) group, is the first isolable alkaneselenenic acid. The oxidation of butyl 9-triptycyl selenide with dimethyldioxirane (DMD) followed by debutenization gives the acid after recrystallization (Equation (39)) <1999JOC1084>.

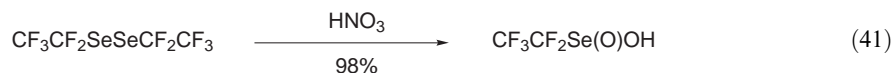
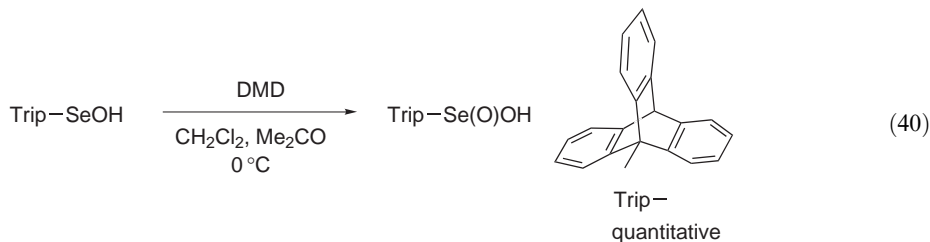


There have been no reports on the synthesis of alkanetellurenic acids, since 1995.

2.04.5.2 Alkaneseleninic Acids and Alkanetellurinic Acids

The general preparative procedures for alkaneseleninic acids and alkanetellurinic acids are described in COFGT (1995) (chapter 2.04.5.2) <1995COFGT(2)277>.

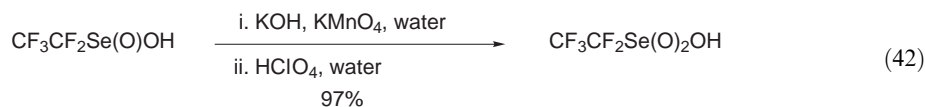
9-Triptyceneseleninic acid was prepared quantitatively by the oxidation of the corresponding selenenic acid with dimethyldioxirane at 0 °C in CH₂Cl₂–Me₂CO (Equation (40)) <1999JOC1084, 2001HAC198>. Oxidation of dipentafluoroethyl diselenide with concentrated nitric acid afforded the corresponding seleninic acid in 98% yield (Equation (41)) <1995CB423>.



No reports of the synthesis of alkanetellurinic acid have been published, since 1995.

2.04.5.3 Alkaneselenonic Acids and Alkanetelluronic Acids

There have been few new results on the preparation of alkaneselenonic acids. Pentafluoroethylseleninic acid is oxidized by potassium permanganate in a slightly alkaline aqueous solution to give the potassium salt of the selenonic acid, which was converted into the free acid by treatment with perchloric acid (Equation (42)) <1995CB423>.



No alkanetelluronic acid has been prepared.

2.04.6 FUNCTIONS BASED ON THE R¹SeOR² UNIT AND ITS HIGHER-COORDINATED DERIVATIVES—SELENENATES, SELENINATES, SELENONATES, AND RELATED FUNCTIONS (R¹SeOR², R¹Se(O)OR², R¹Se(O)₂OR²), AND CORRESPONDING TELLURIUM COMPOUNDS

General information on alkaneselenonic acid esters and alkaneseleninic acid esters is given in COFGT (1995) (chapter 2.04.6) <1995COFGT(2)277>, and no further advances have occurred on alkaneselenonic and alkaneseleninic acid esters since 1995.

The ethyl ester of a selenonic acid was prepared in 68% yield from the reaction of the silver salt of pentafluoroethylselenonic acid with ethyl iodide in CHCl₃ (Equation (43)) <1995CB423>.

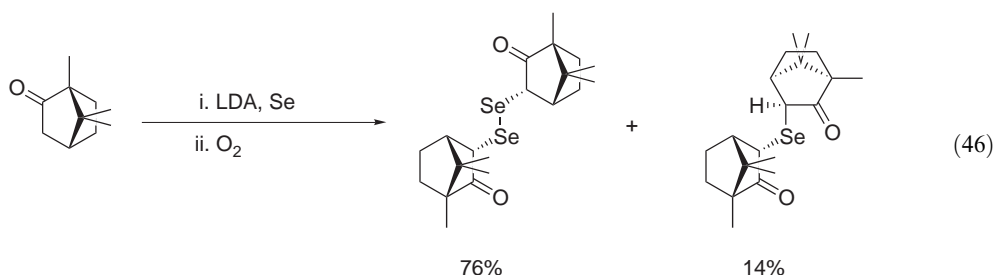
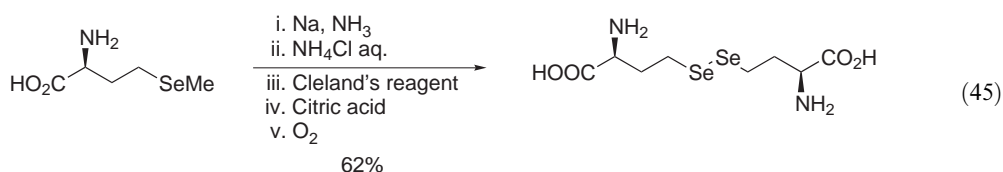
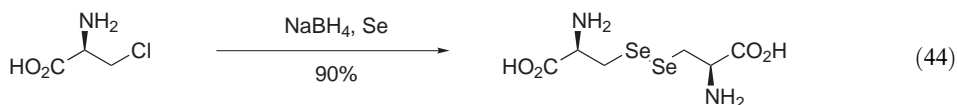


Esters of tellurenic acid, tellurinic acid, and alkanetelluronic acid have not been reported.

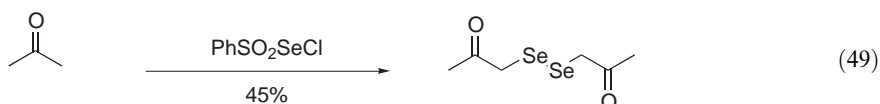
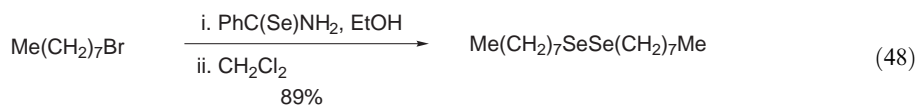
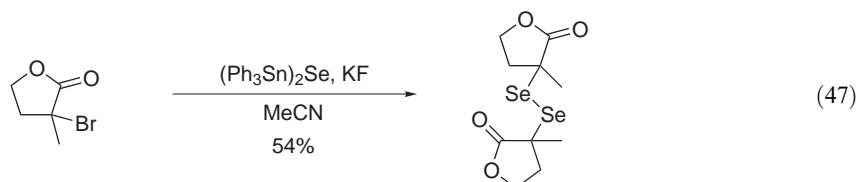
2.04.7 ALKYL DISELENIDES (R¹SeSeR²) AND ALKYL DITELLURIDES (R¹TeTeR²)

Diselenides play a key role, since they are stable, easily handled, and reactive enough to produce electrophilic, nucleophilic and radicophilic species, and are utilized as versatile starting materials for the transformation of functional groups. General information on alkyl diselenides is given in COFGT (1995) <1995COFGT(2)277>. The alkylations of lithium, sodium or potassium diselenides with electrophiles <2002JCR(S)160, 2002JA5960, 2000JCS(P1)723, 1997SC553, 2001HAC293>, the oxidation of selenols or selenolates <2002PS597, 2001SC1507> derived from the reduction of

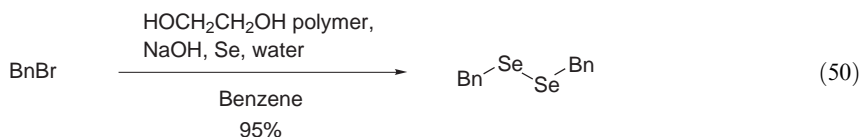
selenocyanates <2000JMC3906, 1997JMC2991, 1997T12147, 1997TL3079, 1995TL5711, 2000AG(E)1669>, and radical reactions <2001TL3881, 1996T11163> are recent typical examples of methods for their preparation. Furthermore, chiral diselenides are prepared from optically active organoselenium compounds by known methods without racemization. Thus, L,L-selenocystine was prepared by the reaction of sodium diselenide with 3-chloro-L-alanine in 60% yield (Equation (44)) <2001BMCL2911, 2001JA5140>. The oxidation of L-selenohomocysteine, which was derived by the reaction of L-selenomethionine with sodium in liquid ammonia, gave L-selenohomocystine in 62% yield (Equation (45)) <2000BMCL2471>. The reaction of camphor enolate with elemental selenium, followed by aerial oxidation, afforded chiefly the *endo*, *endo*-dicamphoryl diselenide with a small amount of the corresponding selenide (Equation (46)) <1995JOC703>.



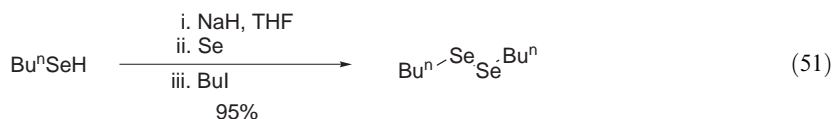
Bis(triphenylstannyl) selenide, which is prepared from sodium hydrogen selenide and triphenyltin chloride in the presence of a fluoride ion, is a useful reagent for the preparation of symmetrical α -selenoesters from the corresponding α -haloesters (Equation (47)) <2001SUL203, 1998S1137>. As selenium transfer reagents, arylselenoamides react with a variety of alkyl halides in ethanol under mild conditions to give dialkyl diselenides in excellent yields. Similarly, alkyl halides can be transformed to dialkyl diselenides upon treatment with selenourea (Equation (48)) <1995JOM19>. The novel electrophilic selenium transfer reagent phenylsulfonylselenyl chloride (PhSO_2SeCl) was prepared and reacted with enolizable carbonyl compounds to yield α -seleno ketones and diselenides (Equation (49)) <1995CC195>.



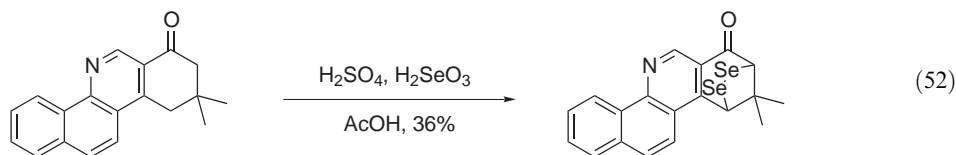
A simple, rapid and efficient method for the synthesis of dibenzyl diselenides under microwave irradiation has been reported. The reaction of benzyl bromide with sodium selenide in the presence of polyethylene glycols with irradiation gave dibenzyl diselenide in 95% yield (Equation (50)) <2000SC325>.



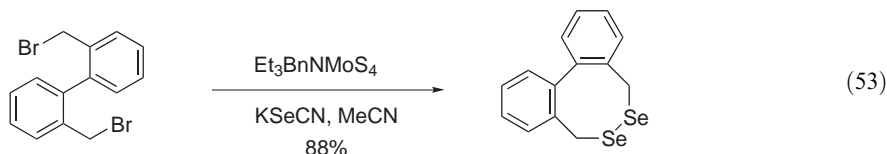
The successive reactions of butaneselenol with a strong base, elemental selenium, and butyl iodide afforded dibutyl diselenide in high yield via the metal salt of butyl diselenol (Equation (51)) <1999AG(E)2245>.



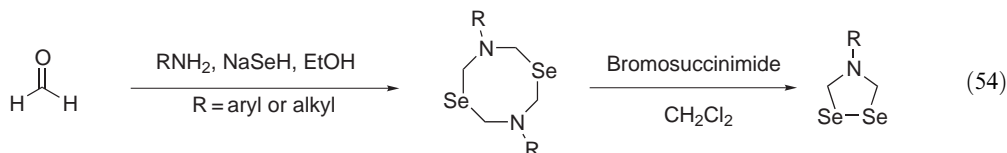
The selenous acid oxidation of 2-aryl-7,7-dimethyl-5,6,7,8-tetrahydro-5-quinazolones leads to cyclic diselenides containing a new ring system (2,3-diselenabicyclo[3.2.1]octane) in 36–70% yield (Equation (52)) <1999EJO1585>.



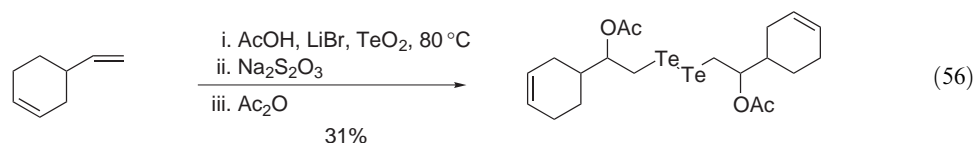
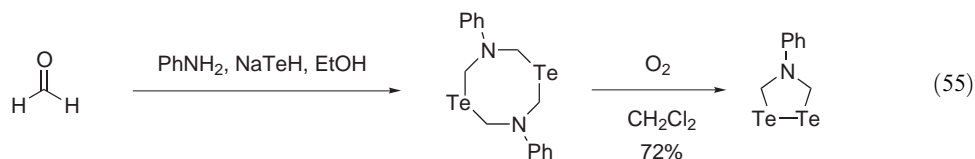
A variety of functionalized selenocyanates generated *in situ* from the corresponding alkyl halides undergo a facile reductive coupling on treatment with benzyltriethylammonium tetrathiomolybdate under very mild conditions to give the corresponding diselenides in very good yields (Equation (53)) <1997CC1021>.



The oxidation of 3,7-disubstituted 2*H*,6*H*-tetrahydro-1,5,3,7-diselenadiazocines, prepared by the reaction of formaldehyde with sodium hydrogen selenide and an aryl- or alkylamine in EtOH, afforded 4-substituted 1,2,4-diselenazolidines in modest yields (Equation (54)) <1995CL277>.

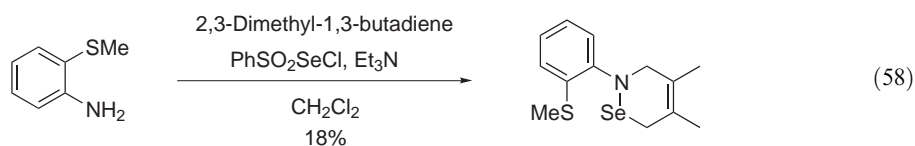
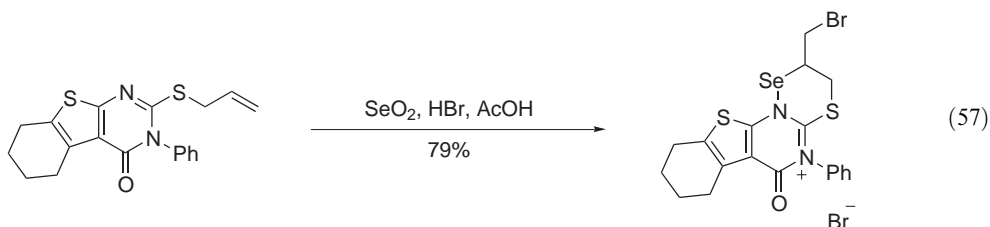


Alkyl ditellurides are prepared in a similar way to alkyl diselenides. Treating tellurium with potassium hydroxide and hydrazine followed by methyl iodide gave 45% of dimethyl ditelluride <1996ZOB1579, 1995SUL59>. The synthesis of novel five-membered cyclic ditellurides (4-aryl-1,2,4-ditellurazolidines) was achieved by treating 3,7-diaryl-2*H*,6*H*-tetrahydro-1,5,3,7-ditellura-diazocines, which were prepared by the reaction of formaldehyde with sodium hydrogen telluride and amines, with oxidizing agents. The oxidative ring contraction of the heterocycles may proceed through the formation and subsequent fragmentation of bicyclic ditellura dications (Equation (55)) <2000CL870>. Tellurium(IV) oxide reacted with nonconjugated dienes in acetic acid at reflux temperature in the presence of lithium halide or iodine to give the corresponding *vic*-diacetates in moderate yields. Reaction at 80 °C followed by reduction of the mixture with aqueous sodium thiosulfate gave bis(β -acetoxyalkyl)ditellurides as the main products (Equation (56)) <1995JOM(487)55>.



2.04.8 RSeN FUNCTIONS AND THEIR HIGHER-COORDINATED DERIVATIVES, AND CORRESPONDING TELLURIUM COMPOUNDS

An outline of the preparation of RSeN and RTeN functions and their higher-coordinated compounds is presented in COFGT (1995) (chapter 2.04.8) [<1995COFGT\(2\)277>](#). Two types of alkane selenenamide have been synthesized. A 2-(allylthio)thieno[2,3-*d*]pyrimidine derivative reacted with selenium dioxide and hydrogen bromide in acetic acid to give a cyclic selenenamide in 79% yield (Equation (57)) [<1998UKZ128>](#). The reaction of phenylsulfonylselenenyl chloride, a useful electrophilic selenium transfer reagent, with arylamines in the presence of triethylamine and dimethylbutadiene afforded 1,2-selenazine derivatives, providing the first evidence for the Diels–Alder trapping of selenonitroso intermediates ($\text{Ar}-\text{N}=\text{Se}$) (Equation (58)) [<1995CC195>](#).



The preparation of alkane seleninamides and selenonamides has not been reported except for 2,4,4-trimethyl-3-isoselenazolidinone-1-oxide [<1987JA5549>](#) and 1,1,1-trifluoro-*N,N*-dimethylmethaneselenonamide [<1990CB685>](#).

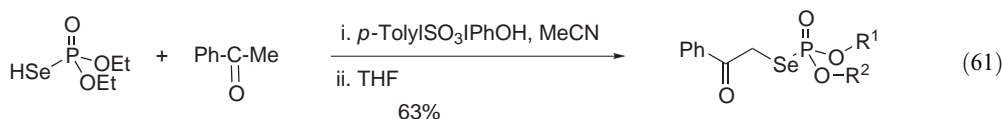
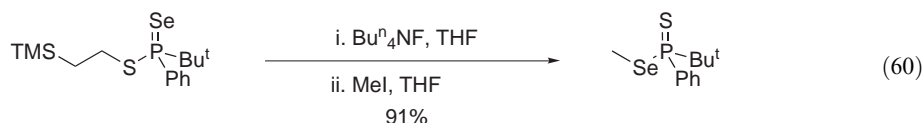
Alkane tellunenamides, telluninamides, and tellunonamides have not been reported, and no further advance has occurred in this area of alkane selenimides and tellurimides since 1995.

2.04.9 RSeP, RSeAs, RSeSb, AND RSeBi FUNCTIONS AND THEIR HIGHER-COORDINATED ANALOGS, AND CORRESPONDING TELLURIUM COMPOUNDS

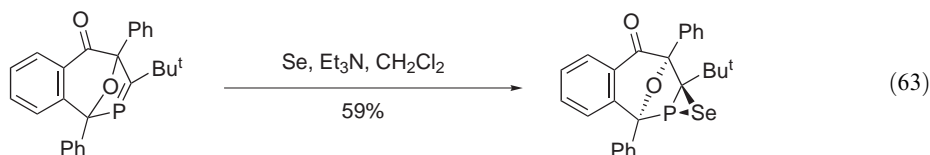
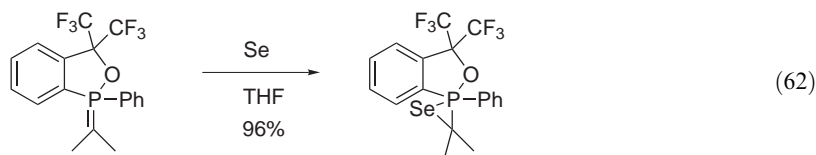
The preparations of RSeP, RSeAs, RSeSb, and RSeBi functions and their higher-coordinated analogs are summarized in COFGT (1995) (chapter 2.04.9) [<1995COFGT\(2\)277>](#). There are also a few reports on the typical bond formation between selenium and phosphorus and between tellurium and phosphorus or arsenic by the reactions of diorganyl dichalcogenides with tetraorganyl diphosphane or diarsane [<1999ZAAC2085, 1995JOM\(493\)189>](#). Alkyl phosphoroselenoates are synthesized by the reactions of phosphoroselenoic acids with alkyl halides in the presence of amines (Equation (59)) [<2001BMC1525, 2000HAC292, 1995PJC1027>](#).



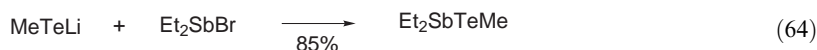
The alkylation of selenothiophosphinic acid salts, which were derived from the reactions of selenothiophosphinic acid *S*-(2-trimethylsilyl)ethyl esters with an ammonium fluoride, by an alkyl halide proceeded at the selenium atom to give the corresponding *Se*-alkyl esters (Equation (60)) <2002CL914>. One-pot reactions of ketones, [hydroxy(tosyloxy)iodo]benzene and potassium *O,O*-dialkyl selenophosphates led to the formation of the corresponding *Se*-(β -oxoalkyl) *O,O*-dialkyl selenophosphates under mild conditions and in a good yield (Equation (61)) <2001JCR(S)156>.



Treatment of a phosphorus ylide, which was prepared by the deprotonation of the corresponding phosphonium triflate bearing the Martin ligand by 2,4,6-trimethylphenyllithium, with 1.6 equiv. of elemental selenium in THF successfully afforded the selenaphosphirane in 96% yield (Equation (62)) <2002JA9706>. The reaction of the polycyclic phosphalkene with elemental selenium led stereoselectively to the selenaphosphirane derivatives (Equation (63)) <2000T6259>.



Diethyl(methyltelluro)stibine was synthesized by the reaction of lithium methanetellurolate with bromodiethylstibine in 85% yield (Equation (64)) <1995JOM(493)189>.

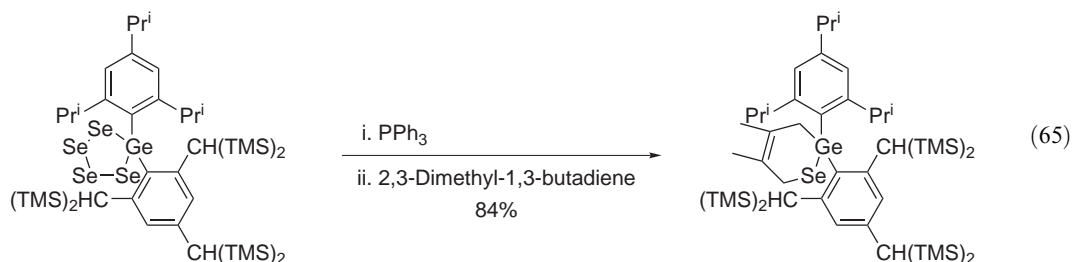


There have not been any reports on the formation of RSeAs, RSeSb, RSeBi, and RTeBi, since 1995.

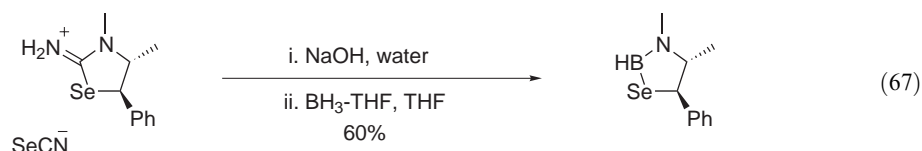
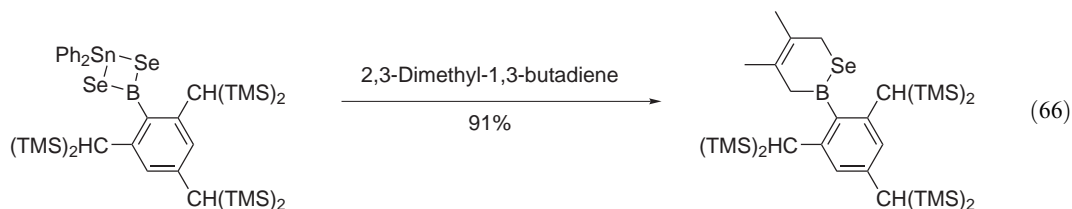
2.04.10 RSeSi, RSeGe, RSeB, AND RELATED METALLOID FUNCTIONS AND THEIR HIGHER-COORDINATED DERIVATIVES, AND CORRESPONDING TELLURIUM COMPOUNDS

Typical preparations of RSeSi, RSeB, and related tellurium compounds are summarized in COFGT (1995) (chapter 2.04.10) <1995COFGT(2)277>.

Dechalcogenation of the novel 1,2,3,4,5-tetraselenagermolane with triphenylphosphine gave diaryl-substituted germaneselone followed by [4 + 2]-cycloaddition with 2,3-dimethyl-1,3-butadiene to afford the corresponding adduct (Equation (65)) <1999JA8811>.



Thermolysis of the novel four-membered 1,3,2,4-diselenastannaboretanes in the presence of 2,3-dimethyl-1,3-butadiene gave the corresponding [4 + 2]-cycloadduct via an arylselenoxoborane (Equation (66)) <1998CC2495>. Treatment of (4*R*,5*R*)-(+)-3,4-dimethyl-5-phenyl-2-iminium-selenazolidine selenocyanate with sodium hydroxide followed by reaction with borane afforded the corresponding boraselenazolidine in 60% yield (Equation (67)) <1997TA3903>.



The reaction of lithium butanetellurolate, prepared from butyllithium and elemental tellurium, with chlorosilanes led to the corresponding tellurobutyl-substituted silanes (Equation (68)) <2001MI31>.



There have been no reports on the formation of RSeSi, RTeGe and RTeB derivatives, since 1995.

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2.05

Alkylnitrogen Compounds: Amines and Their Salts

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2.05.1 INTRODUCTION

This chapter is intended to provide an overview of major areas in the synthesis of alkylamines, material being selected chiefly from the period 1995–2003 and being representative rather than exhaustive. Earlier work-up to 1995 is covered in COFGT (1995) <1995COFGT(2)297>. Several reviews form a useful background to this chapter: the chemistry of vicinal diamines has been reviewed <1998AG(E)2580>, as has the synthesis of secondary amines <2001T7785>, and reductive amination of carbonyl compounds with borohydride and boranes <2002OR(59)1>.

For many years, chiral amines and their derivatives have been used as ligands in asymmetric synthesis, e.g., in asymmetric reduction involving metal hydrides <2001TA2225>, and work continues unabated in this area.

Increasingly, complex polyamines are being prepared using solid-phase synthesis, a method that has several advantages over solution-phase procedures, especially ease of purification and automation <2000S1189>. One such example is a synthesis of the spermine alkaloid kukoamine A on a solid support of 2-chlorotriyl resin <1998TL5117>.

2.05.2 ILLUSTRATIVE METHODS FOR THE INTRODUCTION OF NITROGEN

2.05.2.1 Replacement of Hydrogen by Nitrogen Using Aminating Reagents

Electrophilic amination has been reviewed <1997SL741>, extensions of the use of *t*-butyl azodicarboxylate being notable. The Sharpless–Kresze allylic amination procedure has been applied to a fused cyclopentene and enabled the stereocontrolled introduction of an amino group in a total synthesis of the antitumor alkaloid agelastatin <1999JA9574>. Allyl amines containing an *N*-phenyl group were formed by the addition of phenylhydroxylamine to a heated solution of an alkene in dioxane containing an iron salt <1997JA3302>. Cycloalkenes have been converted into the corresponding allylic *p*-toluenesulfonamide (up to 67% ee) by the reaction with $\text{PhI}=\text{NTs}$ catalyzed by a chiral 3,3',5,5'-tetrabromosubstituted (salen)manganese(III) complex <2001TL3339>. Allylic amidation of cholesteryl acetate using $\text{PhI}=\text{NTs}$ and a Ru(II)-salen complex afforded the 7-substituted *N*-tosyl sulfonamide derivatives in an $\alpha:\beta$ ratio ranging from 1:1.1 to 1:2.3 <2002CC124>.

2.05.2.2 Use of Ammonia and Amines

Although direct *N*-monoalkylation of primary amines is often unsatisfactory because of the difficulty of preventing further alkylation, some improved procedures have been developed. Thus, treatment of a primary amine in dimethyl sulfoxide with solid K_2CO_3 and the appropriate amount of an alkyl bromide (either 1 or 2 equiv.), typically at 80 °C, afforded high yields of the corresponding secondary or tertiary amine, respectively <1999SC2085>. Primary amines can usually be satisfactorily prepared by the action of sodamide (CAUTION) on primary alkyl halides.

A useful alkylation of a primary amine involves its conversion into the corresponding 2,4-dinitrobenzenesulfonamide and treatment either with an alkyl halide and K_2CO_3 , or with an alcohol under Mitsunobu conditions to give the dialkyl sulfonamide that is then cleaved to the secondary amine using mercaptoacetic acid and a base <1997TL5831>. These deprotection conditions do not cleave a 2-nitrobenzenesulfonamide group (which requires sodium naphthalenide); thus, a wide variety of diamines can be prepared using the mononitro- and dinitrobenzenesulfonamide protecting groups. Arrays of primary and secondary amines have been prepared by using an *N*-BOC-*o*-nitrobenzenesulfonamide linker that permits alkylation of the amine in its resin-bound form using Mitsunobu reactions <2003TL4153>.

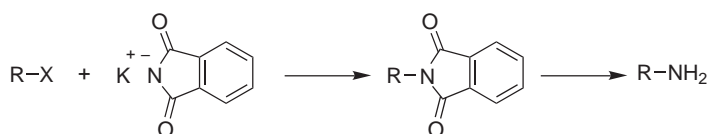
Unlike primary amines, tertiary amines can often be efficiently prepared by reacting one molar equivalent of an alkylating agent with a secondary amine. A solid-phase synthesis of tertiary amines involved alkylation of a secondary amine with Merrifield resin followed by quaternization with a suitable alkyl halide and subsequent dequaternization with release of the tertiary amine using morpholine <2001TL1383>.

The palladium-catalyzed amination of aryl halides has been reviewed <1997SL329>. Mechanistic studies led to the amination of aryl iodides with primary amines to give mixed alkyl aryl secondary amines, often laborious to prepare by more traditional methods <1997SL329>.

The alkylation of tertiary amines, the Menshutkin reaction, is usually efficient.

2.05.2.3 Gabriel Synthesis

Primary amines are often prepared by means of the Gabriel synthesis <1968AG(E)919>. In the classical reaction, the phthalimide anion, particularly its potassium salt, is reacted with an alkylating agent followed by a second step involving the removal of the phthaloyl group (Scheme 1). Alkyl halides and alkyl sulfonates are commonly employed as alkylating agents.



Scheme 1

The *N*-alkylation step has been widened by the use of Mitsunobu reactions <1981S1>, which (where applicable) usually proceed with excellent inversion of configuration. A useful two-step preparation of allylic amines involves the treatment of an allylic alcohol with phthalimide in the presence of diisopropyl azodicarboxylate (DIAD) and Ph₃P, followed by cleavage with hydrazine or methylamine, in a modified Gabriel synthesis <1995S756>. Modified Gabriel syntheses have been developed using methyl *t*-butyl iminodicarboxylate and di-*t*-butyl iminodicarboxylate <1977CC758, 1983JCS(P1)2983, 1987S275>. Alkylation can be conducted in DMF or DMSO (20–60 °C). Specific monodeprotection can be accomplished using either basic conditions or acidic conditions (trifluoroacetic acid). The use of the sodium salt of diethyl *N*-(*t*-butoxycarbonyl)phosphoramidate allows the corresponding *N*-alkyl derivatives to be deprotected by the treatment overnight with benzene saturated with dry HCl <1982S922>. Reaction of 1,3-diphenylallylethyl carbonate with benzylamine in the presence of a Pd-complex of a chiral ferrocenyl pyrazole afforded the corresponding secondary amine in 99% ee <1996JA1031>.

A recent extension of the Gabriel synthesis involves reduction of an alkyl phthalimide (obtained by *N*-alkylation of phthalimide itself) with NaBH₄ and subsequent *O*-protection to give the corresponding *o*-(tetrahydropyranoxymethyl)-*N*-alkyl benzamide which was deprotonated with KOBu^t and reacted with another alkyl halide to give the *N,N*-dialkyl benzamide which with acetic acid was cleaved to the secondary amine <1998TL5017>.

2.05.3 AMINES FROM OTHER AMINES

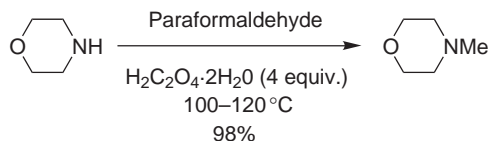
2.05.3.1 Alkylation at Nitrogen

In many cases, direct *N*-alkylation by an alkyl halide is either unsatisfactory or not possible. Some exceptions are discussed in Section 2.05.2.2 and a few follow here. Thus, intramolecular alkylation of an amine is usually an efficient route to a cyclic amine (Section 2.05.5). Secondary amines have been prepared in high yields by the treatment of a primary amine with an alkyl halide in DMF in the presence of 1 equiv. of CsOH·H₂O and 4 Å molecular sieves, the caesium salt suppressing over alkylation <2002JOC674>. Allylamines have been prepared by allylic displacement of a benzo-triazole group by a secondary amine, catalyzed by Pd(OAc)₂–PPh₃ <1998JOC5232>. Microwave-induced amination of aryl bromides either with morpholine or benzylamine proceeds in 4 min when a temperature of either 130 °C or 180 °C is maintained <2002S1597>. Alkyl and aryl

azides undergo reductive monoalkylation (60–90%) upon treatment with Zn and allyl bromide in DMF at room temperature <1999SL551>. A useful alternative approach for the preparation of primary and secondary amines involves blocking (i.e., protection, which may also activate the nitrogen atom), monoalkylation, and subsequent deprotection. Suitable blocking groups include phthalimido (Gabriel reaction, Section 2.05.2.2) resulting in primary amines; aryl sulfonyl <B-68MI205-01, B-75MI25-01> (Hinsberg synthesis), trifluoromethylsulfonyl <1973TL3839>, and phosphoramidate <1977AG(E)107> groups have all been used to convert primary amines into secondary amines by controlled monoalkylation.

Other common routes involving alkylation include the Eschweiler–Clarke procedure, both in its conventional form, the reductive methylation of primary and secondary amines with formaldehyde and formic acid, in newer variants such as the use of borohydride reagents in place of formic acid <1980JOC357, 90TL5595>. Mannich-type reactions, involve the condensation of an enolizable carbonyl compound with an iminium ion, the most well-known process being a condensation involving formaldehyde, dimethylamine, and a ketone under acidic conditions. Both Eschweiler–Clarke and Mannich processes are discussed below in further detail.

Conventional Eschweiler–Clarke *N*-methylations of amines employ formaldehyde and concentrated formic acid. Alternatives to this toxic and corrosive mixture have been developed and include *p*-formaldehyde and oxalic acid dihydrate in the absence of solvent, usually at 100 °C for 1 h, then 120 °C for 20 min (at which temperatures decomposition into formic acid, the actual reducing agent, occurs) (Scheme 2) <2002SC457>.

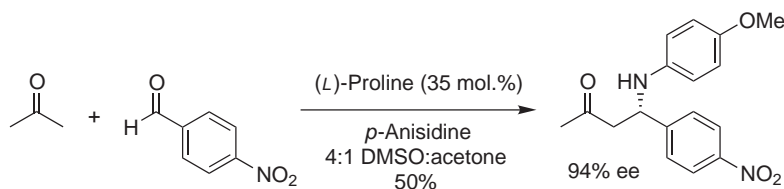


Scheme 2

Reductive methylation of primary and secondary amines has been achieved in excellent yields at room temperature using aqueous 37% formaldehyde and decaborane <2001SC3417>. Reductive methylation of secondary amines to give the corresponding *N*-methylated tertiary amines, including those that are sterically hindered, can be achieved under mild conditions using aqueous formaldehyde and sodium phosphite without reduction of ethynyl, ester, or cyano groups <2000SC3353>. Eschweiler–Clarke *N*-methylations of a variety of alkylamines and cycloalkylamines were found to proceed much more rapidly under conditions of microwave irradiation; procedures for monomethylation and for *N,N*-dimethylation are described <1996SC3919>.

Tertiary homoallylic amines have been prepared in a one-pot procedure by the condensation of an aldehyde with a secondary amine in the presence of Ti(OPrⁱ)₄ to give an intermediate aminoalkoxy titanium complex that reacts with an organometallic reagent prepared from In or Zn and a reactive halide such as an allylic bromide or alkyl iodoacetate <2000OL1851>.

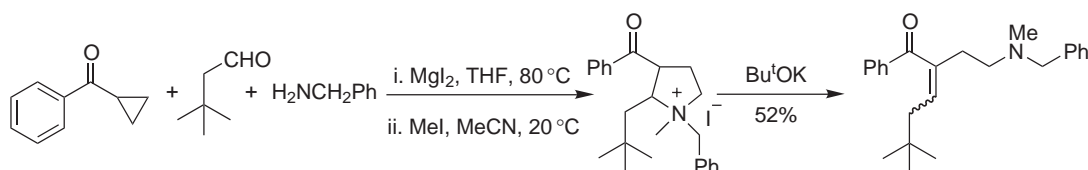
Modern variants of the Mannich reaction have been reviewed <1998AG(E)1044>, as have vinylogous Mannich reactions <2001T3221>. Three-component Mannich-type reactions involving an aldehyde, an amine, and a ketone are efficiently catalyzed by dodecylbenzenesulfonic acid in water at 20 °C affording β -aminoketones, often in yields much higher than those obtained by using traditional catalysts in organic solvents <1999OL1965, 2001T2537>. Preparation of β -aminoketones via the Mannich reaction can be improved by using microwave irradiation <2000SL341>. Mannich-type condensation of an aldehyde and a primary amine with 1-methoxy-2-methyl-1-trimethylsilyloxypropene can be conducted in methanol with InCl₃ as the recoverable catalyst <2002OL3647, 2000T3227>. The variant of the Mannich reaction in which a hydrazone reacts with an iminium ion derived from an aldehyde or a secondary amine has been extended in its scope by appropriate selection of experimental conditions, e.g., a 2 M solution of the hydrazone in toluene at 80 °C <2000CC1585>. Proline-catalyzed asymmetric Mannich reactions permit the condensation of a ketone, an aldehyde, and an amine in 99% ee in favorable cases (Scheme 3) <2002JA827>. A catalytic asymmetric Mannich reaction proceeded in up to 96% ee by the reaction of an acetone, an aldehyde, and a *p*-anisidine in the presence of 35 mol.% of L-proline <2000JA9336>. In a variation of



Scheme 3

the Mannich reaction, a ketone reacts with benzyl azide in the presence of $\text{CF}_3\text{SO}_3\text{H}$ to give the corresponding α -phenylaminomethyl ketone via acid-promoted rearrangement of benzyl azide to the *N*-phenyliminium cation, which effects aminoalkylation of the ketone <2000JA7226>. β -Amino ketones and esters have been prepared by a one-pot Mannich-type condensation of an aldehyde, an imine, and a silyl enol ether in water, promoted by InCl_3 <1998TL323>.

The addition of an α,β -unsaturated enone group as part of an *N*-alkylation involved a three-component reaction promoted by MgI_2 to give, after quaternization, a pyrrolidinium salt that underwent Hofmann elimination (Scheme 4), in which the (*E*)-configuration predominated <2002OL4333>.



Scheme 4

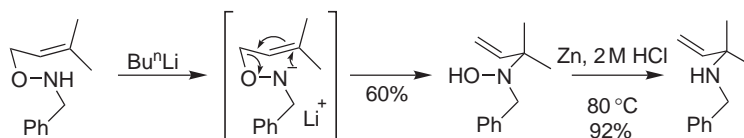
Addition of a primary or secondary amine to a vinyl silane, or *N*-vinylimidazole, or *N*-vinylcarbazole in an atmosphere of CO and H_2 at a total pressure of 100–110 bar in the presence of a rhodium catalyst affords aminosilanes and 1,2-diamines, respectively <1999T7177>. Certain allylic, tertiary amines were prepared by palladium-catalyzed three-component couplings involving a secondary amine, a vinylic halide, and a terminal alkene <1995T6635>. A limited study of asymmetric palladium-catalyzed amination of two allylic alcohols using chiral phosphine ligands containing pyridine and aminomethyl pyrrolidine units afforded tertiary amines in up to 94% ee <1998SL49>.

An unusual preparation of tertiary amines involved ozonolysis of a terminal alkene followed by the addition of a secondary amine to the monosubstituted ozonide so obtained <1995T5019>.

The synthesis of polyamines has been reviewed <2000S1189>, *N*-alkylation being the most widely used approach. In order to maximize monoalkylation either an excess of amine can be used, or *N*-protection (e.g., by tosylation or phthaloylation) can be employed, usually with good control. Both those protective groups have been used in a synthesis on 1,3-polyamines.

1-Acetonyl-1-aminocyclopropanes resulted in high yield from the reaction of 1-acetonyl-1-tosyloxycyclopropanes with primary or secondary amines <1999SL1053>.

Intramolecular *N*-alkylation as part of a [2,3]-sigmatropic rearrangement of an *N*-benzyl-*O*-allylhydroxylamine leads to the *N*-allylhydroxylamine that can be reduced to the corresponding allylamine (Scheme 5) <1998CC2235>.



Scheme 5

Polyamines, including 4,8,19,23-tetraazahexacosane-1,26-diamine, have been prepared by the dialkylation of bis(aminopropyl)amine and its derivatives using α,ω -dimesylates as the *N*-alkylating agents <1997SC2833>.

2.05.3.2 Alkylation at Carbon

Since direct carbanion formation adjacent to nitrogen is not favored, modification of an amine to give an electrophilic α -carbon atom that can be attacked by a nucleophile (e.g., Mannich reaction) is a common tactic.

Secondary and tertiary amines have been prepared by the addition of organozinc reagents derived from alkyl bromides to the adducts obtained by mixing an aldehyde, a secondary amine, and benzotriazole, formally the result of addition of the organozinc to an iminium species <1998T7167>. A related procedure that results in 5-(*N,N*-dialkylamino)-2-alkenoate esters involves the addition of organozinc reagents derived from bromocrotonate esters to the adducts obtained by mixing an aldehyde, a secondary amine, and benzotriazole, formally the result of γ -addition of a zinc dienolate to an iminium species <2003SC693>.

Functionalized amines have been obtained by the amidoethylation of the anions of Horner–Wittig reagents by aziridines that contain an electron-withdrawing group at nitrogen <1995S44>.

2.05.3.3 Dealkylation

Dealkylation of amines, in particular demethylation, has been of value in the synthesis and elucidation of natural products, especially alkaloids. In the preparation of a primary amine by the D  l  pine reaction, a primary halide is treated with hexamethylenetetramine to give the (mono) quaternary salt that is then hydrolyzed. Allylamines have been deallylated using 2-mercaptobenzoic acid and 5 mol.% of Pd(dba)₂/DPPB <1995TL1267>.

Secondary amines have long been prepared by the dealkylation of tertiary amines using cyanogen bromide, the von Braun reaction. One of the best methods of dealkylating tertiary amines involves treatment with α -chloroethyl chloroformate, usually followed by methanolysis. A recent variant involves treatment of a tertiary aliphatic amine with PhOC(S)Cl at 20  C to give a thiourethane which with dimethyl sulfate affords an iminium salt that was hydrolyzed in boiling water to give the hydrogen sulfate salt of the secondary amine <1998TL4387>.

N-Debenzylation of tertiary *N*-benzylamines with aqueous cerium(IV) ammonium nitrate (CAN) afforded the corresponding secondary amines in high yields, only monodebenzylation being observed even when the tertiary amine contained more than one *N*-benzyl group <2000CC337>. Allylated primary and secondary amines were deprotected by treatment with *p*-MeC₆H₄SH in the presence of AIBN in benzene at reflux; the thiyl radical promotes conversion of the allylic amine into the enamine via two consecutive hydrogen abstractions. Subsequent polar addition to the enamine afforded the thioaminal that then underwent fragmentation <2002CC216>. *N,N*-Dibenzylamines were readily monodebenzylated using either CAN or DDQ <2000SL77>.

Tertiary amines containing an *N*-hydroxyethyl group were selectively dealkylated by treatment with SOCl₂ in THF, followed by excess KCN in THF:DMSO <1999TL3709>.

Amino-Claisen rearrangement of *N*-(1,1-disubstituted-allyl)anilines using *p*-TsOH as the catalyst afforded 2-(3,3-disubstituted-allyl)anilines <2001S621>. *o*-Allylamines were also obtained from amino-Claisen rearrangements proceeding in moderate yields from *N*-allylamines using Et₂O·BF₃ <1995S1287>.

2.05.3.4 Deprotection

Selective cleavage of *N*-BOC protective groups has been achieved using AlCl₃ <1999S66>; thus, (*S*)-CbzNH(CH₂)₄CHNH₂CO₂Me was obtained in 92% yield from the derivative protected with BOC at the nitrogen site of the amino acid. Sn(OTf)₂ also deprotected an *N*-BOC group on a variety of amines <2003SC445>. Deprotection of *N*-BOC groups has

also been accomplished using SnCl_4 in an organic solvent; an acid-labile thioamide group was found to be unaltered <1996CC2509>. LiBr in acetonitrile provides a mild procedure for the selective cleavage of an alkoxycarbonyl group (BOC, Cbz) in *N,N*-dicarbonyl-protected amino compounds <2003JOC743>.

Aliphatic and aromatic amines bearing an *N*-trichloroethoxycarbonyl (Troc) group can be deprotected using indium powder and NH_4Cl in aqueous ethanol at reflux <2002SL883>.

Deprotection of sulfonamides (in up to 84% yield) to give secondary amines has been accomplished using $\text{KF}\text{--}\text{Al}_2\text{O}_3$ with microwave radiation <1999SL1745>. The 2-pyridyl sulfonyl group can be cleaved from the pyridine-2-sulfonamide of an alkyl- or arylamine by treatment with Mg in methanol at 0°C <2001SC2209>, a significant improvement upon *p*-toluenesulfonamide desulfonylation.

N-Allylamines and benzylamines were deprotected in THF at reflux using a low-valent titanium reagent prepared from Li and TiCl_3 <1995SC813>.

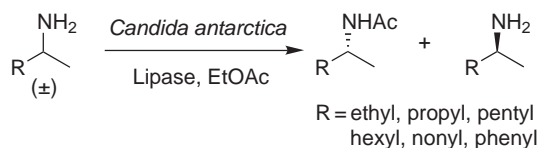
Deprotection of *N*-phenylfluoren-9-yl (Pf) groups in tertiary amines has been accomplished by heating with iodine (60% w/w) in methanol at reflux <1999SL614>.

5,8-Ditrityl-1,5,8,12-tetraazadodecane has been prepared by terminal bis-protection of 1,5,8,12-tetraazadodecane with trifluoroacetyl groups, followed by internal protection with trityl groups, and lastly removal of the trifluoroacetyl groups using NaOH <1998SC3451>.

N-H-Aziridines have been obtained from the corresponding *N*-trityl aziridines by reductive deprotection using $\text{Et}_3\text{SiH}\text{--}\text{TFA}$ <2001JOC7542>. Deprotection of *N*-tritylated vinyl aziridines to give the corresponding *N-H*-vinyl aziridines has been achieved using either TFA or HCOOH <2002T5979>.

2.05.3.5 Miscellaneous

Kinetic resolution of chiral aliphatic and arylalkylamines in up to 97.5% ee for the (*R*)-enantiomers and up to 99.9% ee for the (*S*)-enantiomers, and chemical yields of 50–80%, was achieved using immobilized *Candida antarctica* lipase and ethyl acetate as the acyl donor (Scheme 6) <2001SC569>.



Scheme 6

Primary amines have been obtained in up to 94% ee by the alkylation of imines using the phase-transfer chiral catalyst (2(*S*))-1-methyl-1-[*N*-(diphenylmethylene)]-2-hydroxymethyl pyrrolidine hydrazone iodide <1995TA1225>.

One-pot decarboxylation of α -amino acids has been achieved by reaction with *N*-bromosuccinimide in water at pH 5 to give the intermediate nitrile that is reduced *in situ* by subsequent addition of NiCl_2 and NaBH_4 <2003SL542>.

Ring-closing metathesis of enantioenriched allylamines provides *N*-protected cyclic allylamines in excellent yields (five- and six-membered rings) <2002JOC6896>. Cyclohexenylamines have been prepared by ring-closing metathesis of 1-allyl-4-pentenylamines using Grubbs' ruthenium carbene catalyst <1998SL891>.

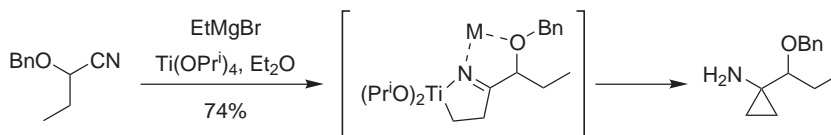
N-Alkyl-*o*-nitroanilines are efficiently prepared by microwave irradiation of a mixture of *o*-chloronitrobenzene derivatives, a primary amine and Et_3N <2002SC2657>.

Propargylic amines have been prepared in moderate-to-good enantioselectivities by the addition of the Grignard reagent of (trimethylsilyl)acetylene to *N*-(BOC)-tetrahydro-2*H*-1,3-oxazines in the presence of $\text{BF}_3\cdot\text{OEt}_2$ followed by a sequence to effect the removal of the chiral auxiliary <1999JCS(P1)1943>.

2.05.4 FUNCTIONAL GROUP MANIPULATION

2.05.4.1 By Amination of Organometallic Reagents

A wide variety of carbanions derived from organometallic species can be aminated, although Grignard reagents and organoboranes generally give higher yields than organolithiums or dialkylzinc reagents. Cyclopropylamines have been prepared by the reaction of a Grignard reagent with a nitrile, believed to proceed via ring contraction of a five-membered chelate (Scheme 7) <2002JOC3965>.



Scheme 7

N-Tosyl allylamines are formed in moderate yields by the reaction of allylstannanes with PhI=NTs and 10 mol.% of Cu(OTf)_2 as the catalyst <2001SC2463>. A similar amination of allyl silanes using PhI=NTs and Cu(OTf)_2 or $\text{Et}_2\text{O}\cdot\text{BF}_3$ has been described <1997SC2753>.

Amines are obtained by the reaction of diarylzincs or triarylzincates with acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime or *O*-methylhydroxylamine in the presence of CuCN <1999SC3989>.

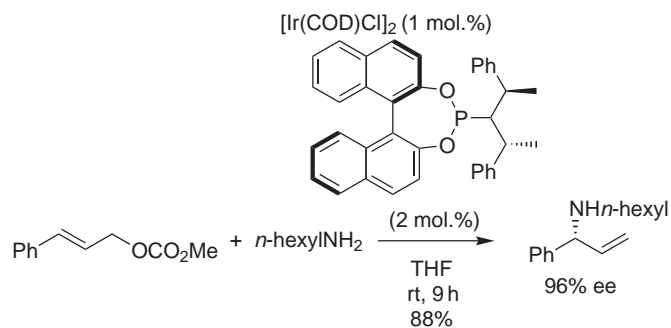
Oxidative decomposition of lithium and zinc amidocyanocuprates afforded moderate yields of amines via electrophilic amination <1997S545>.

2.05.4.2 Amines from Alkenes and Alkynes

Recent advances in the transition metal-catalyzed amination of alkenes have been reviewed <2002SL1579>. Primary amines have been prepared (62–88%) by the reaction of *O*-(mesitylsulfonyl)hydroxylamine with the intermediate $\text{RCH}_2\text{CH}_2\text{ZrCp}_2\text{Cl}$, obtained by hydrozirconation of RCH=CH_2 with Schwartz's reagent (HZrCp_2Cl) <1995JOC1912>. Hydroamination of vinyl arenes with secondary amines proceeds to give predominantly the β -phenethylamines (the anti-Markovnikov product) using $[\text{Rh(COD)}(\text{DPEphos})]\text{BF}_4$ as the catalyst <2003JA5608>.

Photoamination of substituted buta-1,3-dienes in the presence of 1,4-dicyanobenzene produces radical cations, which undergo 1,4-addition of NH_3 to give the corresponding amines <1997JCS(P1)217>.

Allylic esters undergo hydroamination by amines in the presence of an iridium–phosphoramidite complex to give the internal allylamine, typically in $\geq 95\%$ ee (Scheme 8) <2002JA15164>.



Scheme 8

N,N-Dialkylcyclopropylamines have been prepared by the coupling of terminal alkenes with *N,N*-dialkylcarboxamides mediated by $\text{CITi(OPr}^i\text{)}_3$ <1997JOC1584>.

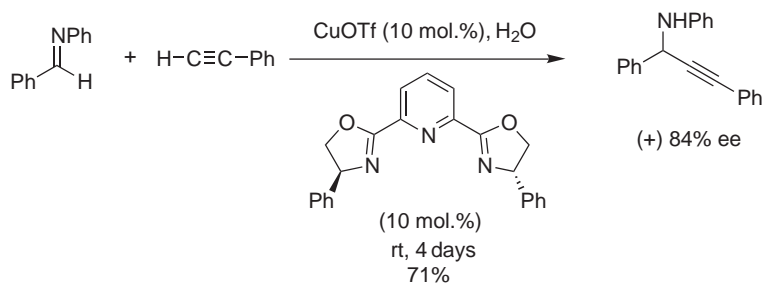
Bromosulfonamidation of alkenes using ((*S,S*))-dimethyl-*N*-(*p*-toluenesulfonyl)-sulfilimine and NBS provides the *trans*-addition products in modest yields <2001SL851>.

Dimethyltitanocene is an inexpensive catalyst that effects the hydroamination of alkynes with primary aryl- and alkylamines; reduction with LiAlH_4 of the reaction solution affords the amine <1999AG(E)3389>. Primary amines have been prepared in moderate yields by the hydroamination of alkynes using α -aminodiphenylmethane as an ammonia equivalent and dimethyltitanocene as the catalyst, giving the imine that is hydrogenated *in situ* (H_2 , Pd-C) <2000OL1935>.

Secondary amines can be prepared by the addition of an *n*-alkylamine (or benzylamine) to an internal alkyne in the presence of $\text{Cp}_2^*\text{TiMe}_2$ as the catalyst <2002JOC1961>.

Several pharmacologically active secondary and tertiary 1-(3,3-diarylpropyl)amines have been prepared from 1,1-diarylethenes, a primary or secondary amine, CO, and H_2 in the presence of $[\text{Rh}(\text{COD})\text{Cl}]_2/\text{PBu}_3$ as catalyst, the hydroformylation followed by reductive amination proceeding in one overall operation <1999T1915>. In a variation of the above process, 1,4-diamines were prepared by the reaction of methyl allyl chloride, a secondary amine, CO, and H_2 in the presence of $[\text{Rh}(\text{COD})\text{Cl}]_2$ as catalyst, in a one-pot nucleophilic substitution–hydroformylation–reductive amination sequence <1999T3917>; in a similar procedure, heterocyclic allylic amines have also been converted into the corresponding 1,4-diamines <1999T9801>. Tertiary α,ω -diamines result from the bis(hydroamino-methylation) of α,ω -dienes using CO and H_2 in the presence of $[\text{Rh}(\text{COD})\text{Cl}]_2$ as the catalyst <1998S71>.

Propargylamines have been prepared typically in 90–96% ee by the addition of phenyl acetylene to a Schiff base in toluene in the presence of 10 mol.% of CuOTf and a pybox catalyst; interestingly, the addition also gave good enantioselectivities (80–91% ee) when conducted in water (Scheme 9) <2002JA5638>.



Scheme 9

α -Branched amines have been prepared in one pot by the addition of an organolithium to an aldimine obtained by hydroamination of a terminal alkyne with an aliphatic primary amine in the presence of $\text{Cp}_2\text{Ti}(\eta^2\text{-Me}_3\text{SiC}\equiv\text{CSiMe}_3)$ <2003TL3217>. Symmetrical internal alkynes have been shown to undergo hydroamination by primary amines in the presence of various titanocene complexes; subsequent reduction with NaBH_3CN in the presence of ZnCl_2 furnishes the secondary amine <2002SL799, 2002EJO1213>. Such hydroamination reactions can also be enhanced by microwave irradiation <2001EJO4411>.

2.05.4.3 Amines from Halides

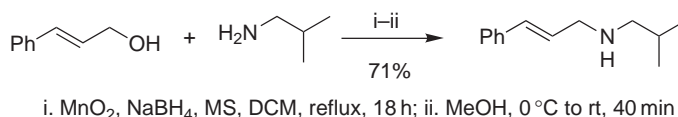
In many cases, direct alkylation of ammonia or a primary amine is not efficient, owing to over alkylation. Some exceptions to such processes are described in Section 2.05.2.2. A useful advance is the reaction of a primary alkyl halide with a 2- or 4-nitrobenzenesulfonamides to give in near quantitative yields a *N*-alkylated sulfonamide that can be deprotected by treatment with thiolate in DMF to give the *p*-methoxybenzyl secondary amine <1995TL6373>.

2.05.4.4 Amines from Hydroxyl Compounds and Their Derivatives

Mitsunobu-type conditions have proved useful for conversion of alcohols into amines. Reaction of alcohols with NaN_3 and 2 equiv. of Ph_3P in 1:4 CCl_4 –DMF at 90°C afforded the corresponding primary amines in excellent yields (85–95%), a procedure claimed to avoid hazardous

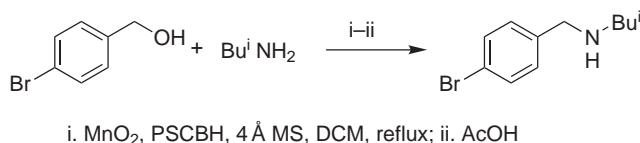
reagents, although the reaction proceeds through the azide intermediates that are not isolated <2000SC2233>. A solid-phase synthesis of primary amines used a polymer-bound iminodicarbonate that underwent *N*-alkylation by a primary or secondary alcohol under Mitsunobu conditions; release of the primary amine was then effected using TFA in CH₂Cl₂ <2000TL6537>. *N*-Benzoylation of secondary aliphatic amines on a solid support was achieved by the conversion of secondary amine into the corresponding ammonium iodide salt prior to treatment with benzyl alcohol under Mitsunobu conditions <2000TL1841>.

A useful one-pot alkylation of an amine using an alcohol employs a system of MnO₂–NaBH₄ and permits secondary and tertiary amines to be prepared simply and in good yields (Scheme 10) <2002TL7337>.



Scheme 10

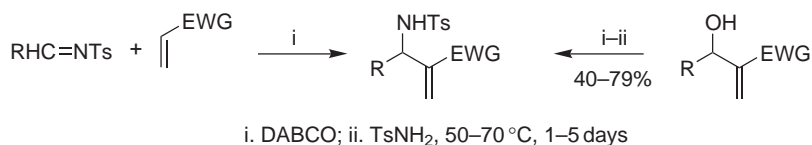
Alcohols have been converted directly into both secondary and tertiary amines by a one-pot process involving MnO₂ as the oxidant to give the imine, which undergoes *in situ* reduction by polymer-supported cyanoborohydride (PSCBH) resulting in the amine (Scheme 11) <2001OL1637>.



Scheme 11

The Ritter reaction continues to be a useful route to amines, especially from tertiary alcohols; those react with chloroacetonitrile in AcOH–H₂SO₄ to give the corresponding *N*-chloroacetyl-*t*-alkylamines, which are then heated with thiourea in EtOH–AcOH at reflux temperature to furnish the *t*-alkylamine <2000S1709>. *p*-Substituted benzhydrylamines have been prepared by the reaction of benzhydrols with phenyl carbamate to give the carbamate intermediates, which were subsequently hydrolyzed <2000S667>.

Baylis–Hillman adducts of *N*-tosylimines are valuable intermediates, for example, in the synthesis of β -lactams; *N*-hexylimines can themselves be used in a Baylis–Hillman-type reaction (Scheme 12). However, pure *N*-tosylimines are often difficult to prepare, and an alternative route (Scheme 12) proceeds via conjugate addition to give the DABCO salt which undergoes *in situ* displacement by TsNH₂ <2002SL173>.



Scheme 12

A versatile route to primary amines involves reaction of a primary alcohol (which may be allylic) or a secondary alcohol with cyanomethylenetriethylphosphorane and *p*-TsNH₂ to give the sulfonamide that can be cleaved to the primary amine with sodium naphthalenide; farnesylamine was so prepared in 59% yield <1996TL2457>. Primary and secondary alcohols react with 2- and 4-nitrobenzenesulfonamides under Mitsunobu conditions to give in high yields *N*-alkylated sulfonamides that can be deprotected by treatment with thiolate in DMF to give the *p*-methoxybenzyl secondary amine <1995TL6373>.

Various (*Z*)-allylic amines were obtained in good yields when the alkene geometry of (*Z*)-3-monosubstituted-2-alkenyl carbonates was completely retained during allylic amination in the presence of piperidine and a catalytic amount of $[\text{Ir}(\text{COD})\text{Cl}]_2$ and $\text{P}(\text{OPh})_3$ at 50°C <1999OL265>.

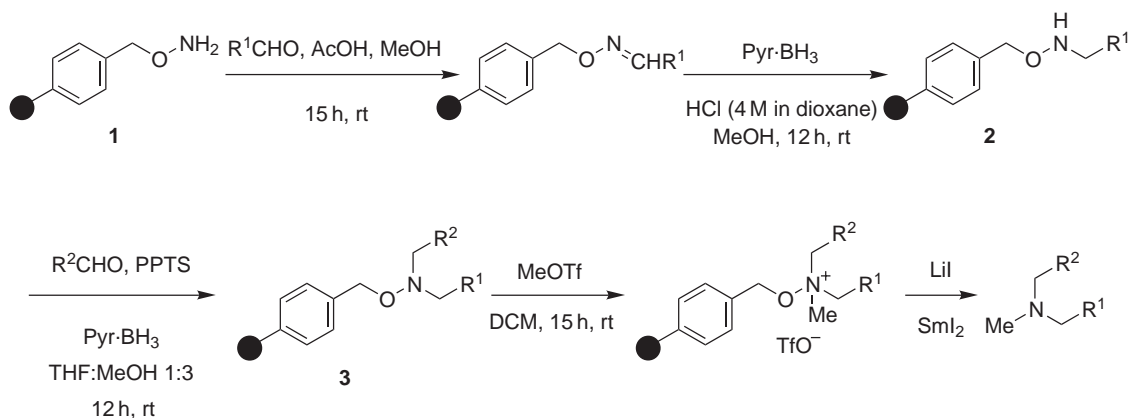
(1(*S*),2(*S*))-1,2-Diamino-3-cyclohexene has been prepared from (1(*S*),2(*S*))-1,2-dihydroxy-3-cyclohexene (obtained by enzymic resolution) by reaction with NaH followed by CCl_3CN to give the ((*S*),(*S*))-trichloroimidate. This underwent a twofold Overman rearrangement to the bis(trichloroacetamide), which was subsequently hydrolyzed and converted into the dihydrochloride salt of (1(*S*),2(*S*))-1,2-diamino-3-cyclohexene <2001S863>.

2.05.4.5 Amines from Acetals and Ketals

There have been no significant developments since the publication of COFGT (1995) <1995COFGT(2)297>.

2.05.4.6 Amines from Aldehydes and Ketones

Reductive amination has recently been reviewed <1999RCR55> (see <2001OL1745> for key methods and literature in 1999 and 2000). Over alkylation in solid-phase reductive aminations can be minimized by preforming the imine before adding the reductive agent <1999BMCL1567>, or by conversion of the amine into the amide, followed by reduction with borane <1997S778>. Reductive aminations in the form of solid-phase synthesis have been widely used to prepare libraries of compounds. In this way a $-\text{CH}_2\text{NH}-$ group is created, and can mimic the biological effect of an amide group; typical conditions have employed sodium cyanoborohydride and acetic acid in DMF <1998BMCL433, 1999CEU2787>. A novel solid-phase synthesis of tertiary methylamines involves cleavage of the $\text{N}-\text{O}$ bond of resin-bound alkoxyammonium intermediates that are formed by sequential reductive alkylation steps, starting with a resin-bound equivalent of *O*-benzylhydroxylamine (Scheme 13) <2001TL133>.



Scheme 13

Tertiary methylamines were also prepared by a closely related earlier method, in which the *N*-BOC derivative of alkoxyamine **1** was deprotected with NaH in DMF, alkylated, and then deprotected with 20% TFA in CH_2Cl_2 to give the analog of derivative **2** that was then reductively alkylated using R^2CHO and $\text{NaBH}(\text{OAc})_3$ in THF giving the analog of derivative **3**, which was quaternized (MeOTf) prior to cleavage of the resin using Et_3N <2000TL6635>. *N,N*-Dimethyl tertiary amines have been prepared in good-to-excellent yields by reductive amination of an aldehyde or ketone in absolute ethanol at 25°C using $\text{Ti}(\text{OPr}^i)_4$ and Et_3N <1995JOC4928>.

Monomethylation of primary amines can usually be achieved using *p*-formaldehyde and sodium methoxide (to form the imine) followed by reduction with NaBH_4 <1996JMC2586>. Ketones and aromatic aldehydes can be reductively aminated by a variety of amines using

HCOOK and $\text{Pd}(\text{OAc})_2$ as the catalyst in DMF on the imine prepared *in situ* using 4 Å molecular sieves <2003SL555>; such carbonyl compounds have also been aminated using polytrimethylhydrosiloxane as the reducing agent and $\text{Ti}(\text{OPr}^i)_4$ as the activator <2000SL1655>.

N-Methyl secondary amines were formed in good yields by the reductive alkylation of methylamine with an aldehyde or a ketone, using NaBH_4 and $\text{Ti}(\text{OPr}^i)_4$ <2003SC1411>. *N*-Benzyl secondary amines were obtained by reductive amination of ketones or aldehydes using benzylamine–borane <2002SC443>. Secondary amines have been conveniently prepared from a primary amine and an aldehyde or a ketone using Mg in methanol, with Et_3N –AcOH as a buffer <1996JCS(P1)265>.

Aliphatic and cyclic ketones are usually excellent partners for reductive amination. Ketones usually only give the monoalkylated product with a primary amine. Even diaryl ketones will react in the presence of a Lewis acid. Pyruvic acid, and other α -ketoacids, afford α -amino acids by reductive amination. Despite the extensive enolization of 1,3-diketones and β -ketoesters, those can also be satisfactory substrates, an enamine intermediate being implicated with β -ketoesters. Aromatic and heteroaromatic amines have been reductively alkylated by hindered aliphatic aldehydes <1996JOC6720, 1998BMCL301>.

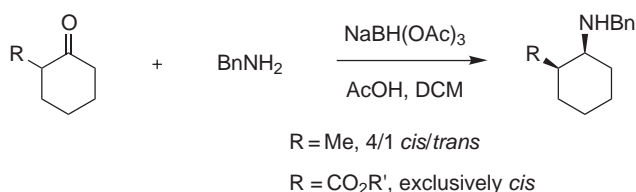
Reductive amination of an aldehyde or a ketone with ammonia or an amine in the presence of a reducing agent is a venerable and general route to amines. Reductive aminations that employ borohydride and boranes have been extensively reviewed <2002OR(59)1>. Strongly acidic conditions reductive alkylations using NaBH_4 continue to find use; TFA is well known, and more recently aqueous H_2SO_4 –THF mixtures have been described <1998JOC7727>. Ketones can be converted into the corresponding primary amines using ammonium formate with a $\text{Cp}^*\text{Rh}(\text{III})$ catalyst in methanol at 70 °C, which is a much lower temperature and also with a higher chemoselectivity than the original Leuckart–Wallach reaction, conducted mostly above 180 °C <2002JOC8685>. Reaction of an aldehyde with BOC- NH_2 and TsNa in the presence of HCO_2H afforded the corresponding α -amidoalkyl sulfone that with NaBH_4 in THF at room temperature underwent reductive elimination to give RCH_2NHBOC <2001TL5093>.

The reductive alkylation of amines with α,β -unsaturated carbonyl compounds was efficiently achieved by adding $\text{Zn}(\text{BH}_4)_2$ to the imines preformed on silica gel <1998JOC370>. Reductive aminations using sodium borohydride (typically in an alcohol as solvent) have advantages over $\text{Na}(\text{CN})\text{BH}_3$ of being less toxic and of not usually requiring acid because NaBH_4 readily reduces imines. NaBH_4 can be added to complete imine reductions when $\text{Na}(\text{CN})\text{BH}_3$ <1998JOC7207, 1999S1541> or $\text{NaBH}(\text{OAc})_3$ <1993JOC5918> has been used initially. Solvent-free reductive amination of carbonyl compounds using sodium borohydride supported on wet montmorillonite K 10 clay and facilitated by microwave irradiation furnishes high yields of the corresponding amines <1998T6293>.

Although ureas do not undergo reductive alkylation under typical conditions (owing to the weakly nucleophilic nitrogen atoms), reaction of an aldehyde with ureas does lead to monoalkylation upon treatment with Me_3SiCl in acetic acid followed by addition of NaBH_4 <1998TL1107>.

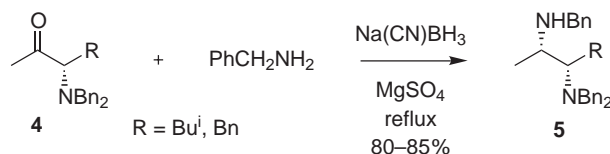
Reductive amination can be achieved by the treatment of an amine and an aldehyde with benzotriazole, followed by the reduction of the intermediate (which is usually isolated) with NaBH_4 <1989JCS(P1)225>.

Sodium triacetoxyborohydride is a general, mild, and selective reducing agent for reductive amination of aldehydes and ketones, and often gives higher and fewer side products than $\text{NaBH}_3\text{CN}/\text{MeOH}$, borane–pyridine, or catalytic hydrogenation (Scheme 14) <1996JOC3849>. However, limitations were observed in attempted reactions involving aromatic or unsaturated ketones. In the reaction of tropinone with benzylamine, $\text{NaBH}(\text{OAc})_3$ afforded the *endo*-benzylamine in high diastereoselectivity.



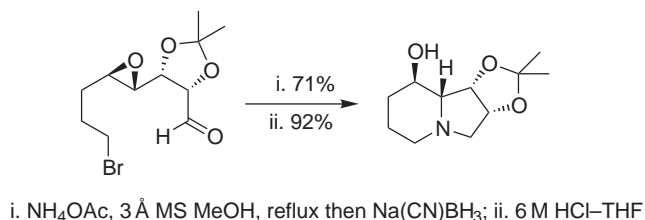
Scheme 14

Reductive amination using sodium cyanoborohydride was described in 1971 by Borch and co-workers <1971JA2897>. While a popular reagent, sodium cyanoborohydride is extremely toxic; HCN can be liberated, and so reactions must be performed in a well-ventilated hood. PSCBH has been used to generate a library of secondary amines from aldehydes and primary amines <1998JCS(P1)2239>. Amino ketones **4**, prepared in enantiomerically pure form from α -amino acids, undergo stereoselective reductive amination (Scheme 15) to give the enantiopure *syn*-1,2-diamines **5**, with a diastereoisomeric ratio of 95:5 <1999TL2741>.



Scheme 15

Reductive amination of an epoxy aldehyde was effected with spontaneous ring closure to give the indolizine ring system of (–)-swainsonine, after acidic deprotection (Scheme 16) <1997JOC1112>.

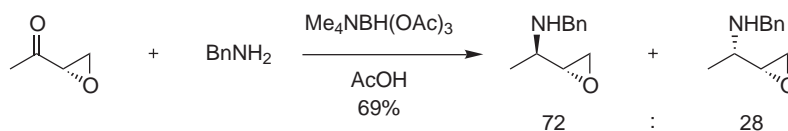


Scheme 16

Sodium borohydride finds only limited use in solid-phase reductive amination because of its ease of reducing aldehyde and ketones. However, $\text{NaBH}(\text{OAc})_3$ is quite widely used, typically in DMF containing 1% acetic acid <1997JA3288, 1999AG(E)2902>. A variety of amino bicyclo[2.2.2]octane derivatives have been prepared by means of reductive amination of intermediates bound to Wang resin <1995SL1017>.

Reductive amination of 2-methylcyclohexanone in benzylamine using $\text{NaBH}(\text{OAc})_3$ gave predominantly the *cis*-amine, probably via an enamine intermediate, rather than an imine <1996TL3977>. 2-(Carboalkoxy)cyclohexanones gave exclusively the *cis*-aminoesters <1992OPP685>.

Reductive amination of α -epoxyketones with benzylamine was achieved using tetramethylammonium triacetoxyborohydride (Scheme 17) <1994CC633, 1996TL4525>.

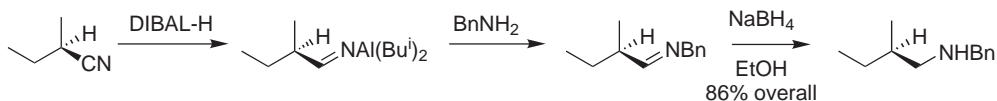


Scheme 17

The reducing power of borane–amine complexes is influenced by the basicity and steric features of the amine ligand. Borane–pyridine has found use in solid-phase reductive aminations <1999CC1341, 1997BMCL2639>. The borane–pyridine complex in acetic acid media reduces imines and iminium salts in preference to carbonyl groups; primary amines undergo reductive alkylation using both aliphatic and aromatic aldehydes, although usually with some bisalkylation. Reductive alkylation with borane–pyridine in methanol can be improved in the presence of 4 Å

molecular sieves <1995JOC5995>. The use of pyridinium *p*-toluenesulfonate (PPTS) and borane–pyridine permits the reductive amination of aldehydes with hydroxylamines <1997SL859>. An improvement on borane–tetrahydrofuran for reductive amination is the use of $\text{Me}_2\text{S}\cdot\text{BH}_3$ with $\text{Ti}(\text{OPr}^i)_4$ and TiCl_4 <1997ACS351>.

A one-pot reductive amination of nitriles with DIBAL involved *trans*-imidation by the addition of a primary amine, prior to further reduction to the amine (Scheme 18) <1998TL3451>. This method also afforded chiral 1,2-amino alcohols from cyanohydrins <1996TA1723>.



Scheme 18

Reductive amination promoted by Bu_3SnH in DMF at room temperature is satisfactory for a variety of aldehydes and ketones <2000SL556>. The system of PhSiH_3 (stoichiometric reducing agent) and Bu_2SnCl_2 (catalyst in 2–10 mol.%) in THF at 20 °C is effective for reductive aminations involving anilines and dialkylamines, but not for monoalkylamines <2001OL1745>.

Titanium(IV) isopropoxide has been used in the reductive amination of aliphatic ketones <1997T14369>, cycloalkanones <1999SL1322>, bicyclic ketones <1995T11183>, and α -substituted aldehydes <1998JOC2548, 1997TA779, 1995JMC1778>. Reductive amination of cyclic ketones with a primary or secondary amine has been achieved using HCOONH_4 and 10% Pd–C in yields of around 70% <2002T5669>.

Reductive amination of ketones and aldehydes with aminohydrosilanes such as $\text{Et}_2\text{NSiHMe}_2$ in the presence of a catalytic amount of a Lewis acid (e.g., TiCl_4 , but ZnI_2 for aliphatic aldehydes) afforded tertiary amines in moderate-to-high yields <2001SL1617>. Dimethylcyclohexanamines were obtained in 86–99% ee by reductive amination of the imines derived from dimethylcyclohexanones and (*R*)-(+)- or (*S*)-(–)-1-phenylethylamine, followed by hydrogenolysis of the chiral auxiliary <1997S1325>.

Primary amines containing a (trimethylsilyl)methyl group have been obtained from a three-component condensation of an aldehyde, $\text{LiC}\equiv\text{CSiMe}_3$ or $\text{ClMgCH}_2\text{SiMe}_3$, and hexamethyldisilazane promoted by LiClO_4 (CAUTION) <1998TL8071>.

A one-pot preparation of primary (*E*)-allylic amines involved treatment of diethyl methyl phosphonate with Bu^nLi followed by a nitrile and then an aldehyde. The α,β -unsaturated imine so obtained was reduced *in situ* with NaBH_4 to give the primary (*E*)-allylic amine <1995TL281>.

Homoallylic amines have been prepared by a one-pot condensation of an aldehyde with a carbamate and allyl trimethylsilane in the presence of borontrifluoride etherate <1997TL997>. A library of homoallylic amines was prepared using a key one-pot Lewis acid-promoted *N*-acyliminium coupling of a solid phase-bound carbamate, an aldehyde, and an allyl silane <1999TL1601>. 3-Alkenylamines, 4-alkenylamines, and 3-allenylamines have been prepared by transamination respectively of α -vinylaldimines, α -allylaldimines, and α -allenylaldimines induced by KO^tBu and subsequent hydrolysis with aqueous oxalic acid <1997T10803>.

N,N-Bis(but-3-enyl)amines were prepared from 1-(triphenylphosphoroylidene aminoalkyl)benzotriazole using an aza-Wittig reaction with an aldehyde followed by a double displacement with two molar equivalents of allylmagnesium bromide <2002JOC7530>.

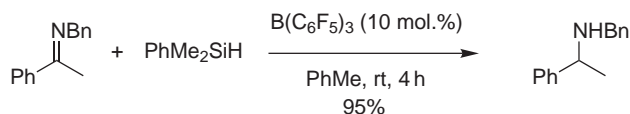
Fluorinated amine hydrochlorides were prepared by conversion of fluorinated aldehydes and ketones into the corresponding *N*-benzylic imines that were isomerized to *N*-benzylidene derivatives that were then hydrolyzed with 4 M hydrochloric acid <1996JOC6563>.

2.05.4.7 Amines from Imines

2.05.4.7.1 By reduction

Asymmetric transfer hydrogenations of several heterocyclic imines using $\text{HCOOH}\text{--}\text{Et}_3\text{N}$ as the hydrogen source have been achieved in up to 99% ee using a chiral rhodium complex generated from $[\text{Cp}^*\text{RhCl}_2]_2$ and (1(*S*),2(*S*))-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine <1999OL841>.

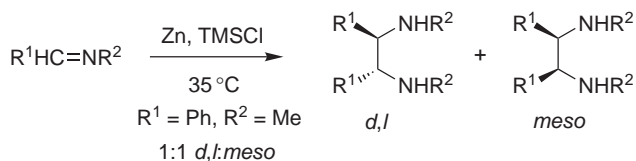
Hydrosilylation of imines has been accomplished with Et_3SiH , or a related silane, in the presence of a nickel(II) catalyst comprising the thiosemicarbazone of an *o*-hydroxy benzaldehyde <1995S419>. A wide range of benzaldimines and ketimines are reduced to the corresponding imines by PhMe_2SiH in the presence of $\text{B}(\text{C}_6\text{F}_5)_3$ as the catalyst, probably via a silyliminium hydridoborate intermediate that undergoes hydride transfer with loss of $\text{B}(\text{C}_6\text{F}_5)_3$ (Scheme 19) <2000OL3921>. A wide variety of imines can be reduced to the corresponding amines using polymethylhydrosiloxane in ethanol at room temperature in the presence of *n*-butyltris(2-ethylhexanoate)tin as the catalyst, alkenes, alkynes, alkyl bromides, epoxides, esters, and nitriles being inert under the reaction conditions <1997T16349>.



Scheme 19

Enantiopure (1*S*,2*S*)-1,2-diaryl-1,2-diaminoethanes can be conveniently prepared by the diastereoselective reduction of 2,2-spirocyclohexane-4,5-diaryl-2*H*-imidazole with $\text{Li}-\text{NH}_3$ followed by resolution with L-(+)-tartaric acid <1995TA3>. Reductive dimerization of imines using lithium metal afforded the 1,2-diamines, sometimes in high de <2001SC3587>. However, this method has the disadvantage and potential hazard of requiring lithium perchlorate in 5 M concentration for the generation of the imine or iminium salt that is to undergo reductive dimerization <2001SC3587>. Typically, $(\text{Me}_3\text{Si})_2\text{NH}$ was used to obtain primary 1,2-diamines, and $\text{Me}_3\text{SiNEt}_2$ to obtain diethyl-substituted tertiary 1,2-diamines. Reductive coupling of Schiff bases to the vicinal diamines has been achieved using samarium catalyzed by Cp_2TiCl_2 ; the *dl*:*meso* ratio varied from 60:40 to 90:10 <1997SC1483>.

Reduction of imines with indium in the presence of NH_4Cl afforded good yields of the corresponding amines (Scheme 20) <2001SC1581>, as does the reduction of imines with $\text{Zr}(\text{BH}_4)_4$ at room temperature <2000SC4387>. Reduction of imines to amines using $\text{Zn}(\text{BH}_4)_2$ supported on silica gel is a very simple and efficient process <1997JOC1841>. Reduction with $\text{Zn}(\text{BH}_4)_2$ of enantiopure imines derived from (*R*)- α -methylbenzylamine gives the corresponding amines, generally in moderate de <2000TA2555>. Polymethylhydrosiloxane activated by ZnCl_2 is a convenient means of reducing imines to amines, and 1-aza-1,3-dienes to the corresponding allylamines <1999SC3981>. *C*₂-Symmetric diamines result from the reductive coupling of imines using $\text{Zn}-\text{Me}_3\text{SiCl}$, an inexpensive procedure suitable for large-scale preparations (Scheme 20); the mixture of *meso*- and *d,l*-stereoisomers can be treated with lithium and isoprene which by isomerization of the *meso* form produces an improved yield of the useful *d,l*-isomer (78% for $\text{R}^1 = \text{Ph}$ and $\text{R}^2 = \text{Me}$) <1998SL873>. Addition of HMPA to SmBr_2 in THF enables ketimines to be reduced to the corresponding amines at 20 °C <2001OL2321>.



Scheme 20

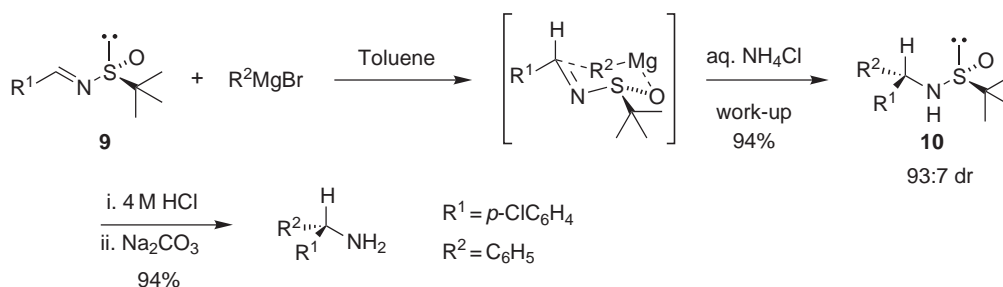
Secondary amines free from the common side products of over alkylation and carbonyl starting materials have been prepared by transimination of a resin-bound aldehyde with a solution-phase primary amine to give a solution-phase imine that undergoes reduction with resin-bound borohydride to furnish the secondary amine in solution <2002OL4611>.

Tertiary amines have been prepared in a one-pot procedure by the reduction of an imine with $\text{Bu}_2\text{SnClH}-\text{HMPA}$ and subsequent alkylation of the intermediate tin amides <1995JOC2677>. Reductive cyclization with NaBH_4 of the imine derived from benzaldehyde and 3-bromopropylamine afforded *N*-benzylazetidine in 68% yield on a 91-gram scale <2001SC565>.

alcohols by reaction with SnCl_2 and *N*-chlorosuccinimide afforded the homoallylic sulfonamides <2002SL2113>. Barbier-type alkylation and allylation of enantiopure imines derived from amino acids has been achieved using metallic samarium and a catalytic amount of iodine with the appropriate alkyl or allyl halide at room temperature, in favorable cases the reaction being highly diastereoselective <1999T13947>. The reaction of *N*-phenylsulfonyl aldimines with arylboronic acids, catalyzed by rhodium complexes, afforded diarylmethylamine derivatives in high yields <2000SL1637>. An imine or hydrazone that contains a terminal unsaturated site such as vinyl- or trimethylsilyl-ethynyl undergoes cyclization to the corresponding cycloalkylamine derivative induced by $(\eta^2\text{-propene})\text{Ti}(\text{OPr}^i)_2$ <1996CC533>. The latter reagent when combined with Pr^iMgBr reacts with alkynes to give a titanium–alkyne complex that underwent addition to imines to give allylic amines in generally high yields <1995TL5913>.

α -Arylalkylamines have been prepared by the addition of Grignard reagents to *N*-(diethoxyphosphoryl)aldimines followed by the cleavage of the diethoxyphosphoryl group with 20% aqueous HCl <1999S930>.

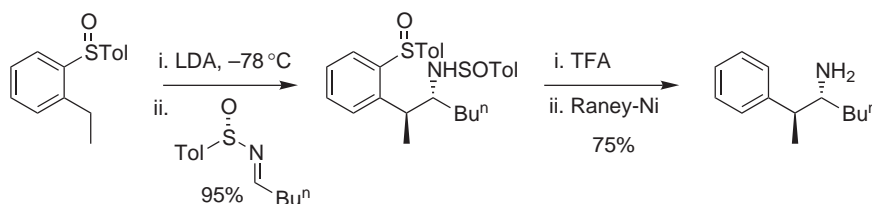
The asymmetric synthesis of amines bearing an α -stereogenic center is an important goal, and has been achieved mainly by asymmetric reduction of a ketimine or by asymmetric addition of a carbanion to an aldimine. An advance in the latter approach employs *N*-*t*-butanesulfinylimines <2002ACR984, 2003PAC39>; the *t*-butanesulfinyl group activates the imine moiety toward nucleophilic addition, acts as a powerful chiral directing group, and is readily cleaved by acid. α -Branched amines and α -trifluoromethylamines have been so prepared, the former both conventionally and also using a support-bound sulfinamide. A typical procedure involved reaction of the inexpensive (R_S)-*t*-butanesulfinamide with an aldehyde mediated by CuSO_4 to give the sulfinyl aldimine **9** that underwent addition of a Grignard reagent to give the sulfinamide **10** that can be efficiently cleaved to the amine hydrochloride salt or the free amine (Scheme 22) <1999T8883, 1997JA9913, 2002SL303>. For $R^1 = \text{Et}$ and $R^2 = \text{Me}$, the amine hydrochloride was obtained in 97% yield <1999T8883>. Chelation control operates with ArMgBr in toluene, but reversal of enantioselectivity was observed using PhLi in THF, and was accounted for by a pathway involving an open transition state.



Scheme 22

Reaction of organometallic reagents with 1-aza-1,3-butadienes <1997SL1321> gave the products of either 1,2- or 1,4-addition depending considerably on the nature of the ligand transferred from the organometallic reagent; typically, butyl and phenyl groups were transferred with 1,4-addition, whereas 1,2-addition of 2-furyl and 2-thienyl groups was observed.

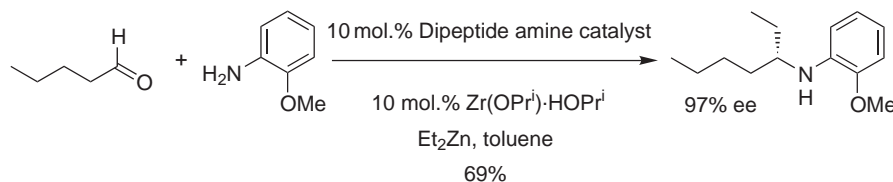
Enantiopure single diastereoisomers of aryl-substituted amines have been prepared by highly stereoselective addition of the lithio derivative of a sulfoxide to a (*S*)-*N*-*p*-toluenesulfinylimine and subsequent desulfinylation (Scheme 23).



Scheme 23

Addition of Bu^iLi to an enantiopure triethylmethylsulfinamide-derived aldimine established the chiral center in the first asymmetric synthesis of (*R*)-didesmethylsibutramine, of potential use in CNS disorders <2002OL4025>.

Amines have been prepared in very high ee by a one-pot imine formation followed by zirconium-catalyzed asymmetric addition of a dialkylzinc (Scheme 24) <2001JA10409>.



Scheme 24

Enantioselective addition of MeLi to benzaldehyde 4-anisidine imine gave the corresponding amine in up to 70% ee in the presence of an enantiopure tridentate amino ether catalyst <1995TA2527>.

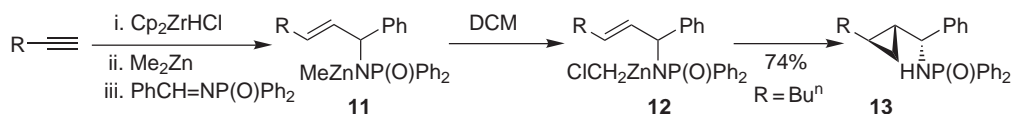
Ethylmagnesiumation of a series of aldimines and ketimines catalyzed by 10 mol.% of Cp_2ZrCl_2 afforded the corresponding amines bearing an α -ethyl group, thereby permitting the preparation of amines with a quaternary α -carbon atom <2001EJO3677>. α,α -Disubstituted amines incorporating a nitrogen heterocycle have been prepared in up to 97% ee by the addition of a Grignard reagent to a ketimine followed by oxidative cleavage of the chiral auxiliary <1997JOC5537>.

((*R*),(*R*))-Di-*t*-butylethanediamine has been prepared by the addition of *t*-butylmagnesium chloride to the chiral bis-imine prepared from glyoxal and (*S*)-methylbenzylamine <1999S228>.

Primary 1-alkenyl (or alkynyl)-3-methylcyclohex-2-enamines were obtained by the addition of a Grignard reagent to the *N*-phenylsulfinimine obtained from the reaction of heptan-2,6-dione with *N,N*-bis(trimethylsilyl)phenylsulfenamide <1998SC3279>.

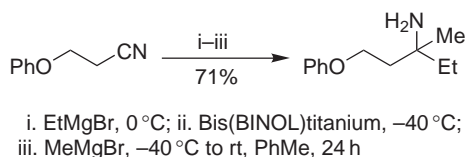
Secondary amines have been prepared by the addition of dimethylcuprate–boron trifluoride reagents to the *Si*-face of imines derived from (*S*)-1-phenylethylamine, generally with moderate diastereoselection <1996T12571>.

Aminocyclopropanes have been prepared stereoselectively by a three-component reaction involving hydrozirconation of an alkyne followed by *in situ* transmetalation with Me_2Zn and addition to *N*-diphenylphosphinoylimine (Scheme 25). The amide **11** that is formed evidently inserts into the solvent CH_2Cl_2 to give intermediate **12** which via intramolecular carbenoid insertion and hydrolysis affords the amino cyclopropanes **13** <2001JA5122>.



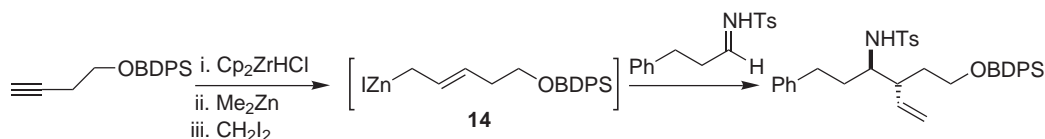
Scheme 25

An enantioselective tandem nucleophilic addition of two organometallic species to an *O*-protected cyanohydrin has been achieved using a bis(BINOL)titanium catalyst (Scheme 26) <1999TA1961>.



Scheme 26

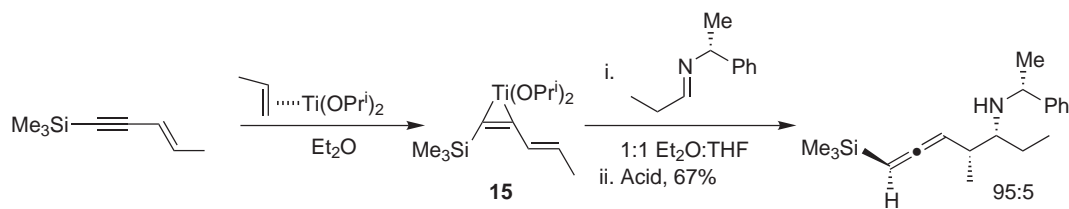
Homoallylamines have been prepared from *N*-trimethylsilyl derivatives of aromatic aldimines and *B*-allyldiisopinocampheylborane (D-Ipc₂BAl) in up to 94% ee by the addition of one molar equivalent of water during the asymmetric allylboration <1999AG(E)825>. Homoallylamines in up to 82% ee were obtained by the reaction of allyltributylstannane with an imine in the presence of a π -allylpalladium chloride catalyst complex derived from β -(-)-pinene <1998JA4242>. Homoallylamines are also obtained by the addition of the organoytterbium reagent formed from allyl bromide and Yb to a Schiff base in the presence of a catalytic amount of Me₃SiCl <2001SC273>. Allylation of cyclic aldimines using an allylic zinc reagent prepared by the addition of allylzinc bromide to an enantiopure lithiated bisoxazoline afforded the corresponding homoallylic amine derivatives in 77–99% ee <1996JA8489>. Homoallylic amines have been prepared in a three-component reaction of an aldehyde with a primary amine and an allyltributylstannane, conducted in water and in the presence of sodium dodecylsulfate, and mediated either by Sc(OTf)₃ <1998CC19> or by SnCl₂·2H₂O <2002JCS(P1)1157>. Homoallylic amine derivatives were obtained from an acyclic aza-[2,3]-Wittig sigmatropic rearrangement, induced by *n*-butyllithium, of an appropriately substituted allylic amine derivative <1995CC1835, 1997JCS(P1)1517>. Chiral β -substituted homoallylic amines resulted from addition to imines derived from α -phenylethylamine of an allylic titanium intermediate prepared from an allylic halide, Ti(OPr^{*i*})₄ and Pr^{*i*}MgCl <1995JOC8136>. Homoallylic amines have also been prepared by hydrozirconation of an alkyne followed by *in situ* transmetalation with Me₂Zn to give the methyl vinylzinc, which with CH₂I₂ forms the corresponding allylic iodozinc species **14** that adds to an *N*-phosphinoyl or *N*-sulfonyl aldimine (Scheme 27) <2001OL2773>.



Scheme 27

Propargylic amines can be conveniently prepared by the addition of trimethylsilylacetylene to an imine in the presence of a catalytic amount of [IrCl(COD)]₂ <2001OL4319>.

Silylated enynes were readily converted into enyne–titanium alkoxide complexes (e.g., **15**), which add to an imine to give the allene (95:5 ds, Scheme 28) <2000JA7138>.



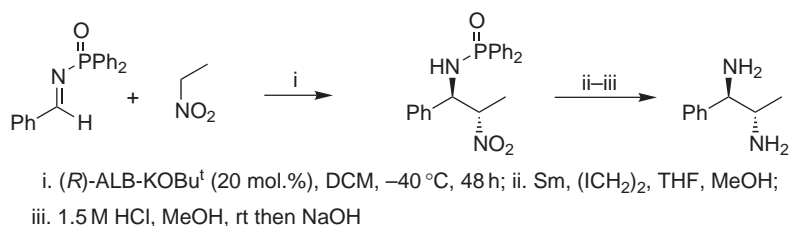
Scheme 28

(α,α' -Diperfluoroalkylated)diamines and α -perfluoroalkylated amines have been prepared by the addition of a perfluoroalkylated Grignard reagent to an *N*-(α -aminoalkyl)benzotriazole in the presence of BF₃·OEt₂ <1997TL7015>.

2.05.4.7.3 By addition of other carbon nucleophiles

The addition of carbon-centered radicals to imines and related compounds has been reviewed, formation of five- and six-membered rings being common <2001T5461>. An alkyl radical R[•] can be added to an imine of the type ArCH=NTs by treatment with RI, Zn, and saturated aqueous NH₄Cl in dichloromethane at 20 °C, the resulting radical ArCHRN[•]Ts undergoing reduction by zinc to ArCHRN(–)Ts prior to protonation <2000CC2059>. Free radical cyclizations involving nitrogen have also been reviewed, intramolecular addition of a radical to an imine having found

use in many syntheses <1997T17543>. Enantioselective addition of a source of cyanide (HCN or TMS-CN) to imines has been achieved in up to 95% ee using the new chiral heterobimetallic complex $\text{Sc}(\text{BINOL})_2\text{Li}$ <2001TA1147>. Enantioselective addition of silyl enol ethers to a Schiff base has been achieved in up to 95% ee <2001T861>. Addition of a chiral lithium enolate equivalent of methyl acetate to various Schiff bases afforded the corresponding β -aminoesters in up to 94% de <2001T875>. Asymmetric addition of the anions of enantiopure alkyl sulfoxides to imines derived from perfluorinated aldehydes provided an efficient route to stereochemically defined α -fluoroalkylamino compounds <1998T12789>. *N*-substituted-1,2-nitroamines have been prepared in up to 88% ee by using the heterobimetallic catalyst, $\text{AlLi}[(R)\text{-binaphthoxide}]_2$, in the first examples of enantioselective and diastereoselective catalytic nitro-Mannich reactions. The products can be converted into the corresponding chiral 1,2-diamines by reduction (Scheme 29) <2001SL980>. The nitro-Mannich reaction proceeds with up to 10:1 diastereoselection in favor of the *anti*-isomer for the addition of alkyl nitronate anions to *N*-4-(methoxybenzyl) (PMB) imines <1998JOC9932>.



Scheme 29

1,2,3-Triamines have been prepared by addition of trimethylsilyl-2-phenylnitronate to a substituted α -aminoimine followed by reduction with $\text{NaBH}_4\cdot\text{NiCl}_2\cdot 6\text{H}_2\text{O}$ and separation of the diastereoisomers <2003JOC1418>. Iminoaldol reactions of ketene silyl acetals with imines provides a useful route to β -aminoesters, precursors of β -lactams; such additions are promoted by cation exchange resins, especially Amberlyst[®] 15 DRY <2000SL1828>. The imino-ene reaction can be a powerful method of incorporating nitrogen, either as a substituent, or as part of a newly constructed heterocyclic ring; the imino-ene reaction has been reviewed <1995S347>.

2.05.4.7.4 By isomerization

A catalytic asymmetric synthesis of amines in up to 44% ee involved conversion of a methyl ketone into an *N*-benzylimine which was then isomerized using a chiral alcohol such as (2*S*)-*N*-tritylaziridine diphenylcarbinol to the Schiff base which was hydrolyzed to give the chiral secondary amine <1995TL3917>. 3-Alkenylamines, 4-alkenylamines, and 3-allenylamines have been prepared by transamination respectively of α -vinylaldehydes, α -allylaldehydes, and α -allenylaldehydes induced by KOBu^t and subsequent hydrolysis with aqueous oxalic acid <1997T10803>.

2.05.4.8 Amines from Oximes and Their Derivatives

Primary amines can be obtained from both aldioximes and ketoximes by reduction with LiAlH_4 , but other reagents and procedures are notable, including diborane, $\text{NaBH}_3\text{CN-TiCl}_3$, and catalytic hydrogenation. Arylmethylamines were obtained by the reduction of aromatic oximes using a combination of NaBH_4 supported on Amberlite IRA 400 and $\text{Ni}(\text{OAc})_2$ <1995SC863>. $\text{NaBH}_4\text{-I}_2$ reduces *O*-acyl derivatives of aldioximes and ketoximes to the corresponding primary amines <1995SC3503>. An asymmetric synthesis of (1*S*,2*R*)-1-amino-2-indanol, a significant component of indinavir, the HIV-protease inhibitor, proceeded via catalytic reduction of the enantiopure α -hydroxy oxime <1998SL51>.

2.05.4.9 Amines by Addition to α,β -Unsaturated Carbonyl Compounds

Conjugate addition of amines to electrophilic alkenes is often an effective *N*-alkylation procedure; it has been enhanced by using both high pressure and a lanthanide catalyst <1996T13557>. Conjugate addition of amines to electrophilic alkenes can be conducted in water, under mild conditions and using a catalytic amount of InCl_3 <1998SL975>. Water-promoted conjugate addition of secondary amines to α,β -unsaturated esters and ketones is greatly assisted by microwave irradiation <2000SC643>. Glycosyl β -aminoesters have been prepared by the stereoselective conjugate addition of benzylamine catalyzed by TBAF that enhances the nucleophilicity of the amine <2002TA21>. β -Aminoesters were also obtained by the conjugate addition of enantiomerically pure 4-methoxyphenethyl-substituted lithium amides to an α,β -unsaturated ester, the resulting amine being oxidized with CAN to give an imine that was hydrolyzed with acid <2000SC1779>. Asymmetric conjugate addition of lithium amides to α,β -unsaturated esters afforded the corresponding β -amino-substituted esters in up to 99% ee using 1.8 equiv. of ((*R*),(*R*))-1,2-dimethoxy-1,2-diphenylethane <2003JA2886>. Catalytic enantioselective addition of an arylamine to an α,β -unsaturated amide derivative in the presence of a chiral oxazoline-derived Lewis acid afforded the β -amino carbonyl compound in up to 95% ee <2001CC1240>. A variety of aliphatic amines (either primary or secondary) undergo *N*-alkylation by α,β -unsaturated esters, ketones, and acrylonitrile catalyzed by $\text{Bi}(\text{OTf})_3$ to give the corresponding tertiary amines <2003SL720>. Asymmetric crotylation of *N*-benzoylhydrazones with (*E*)- and (*Z*)-crotyltrichlorosilane afforded respectively the *syn*- and *anti*-homoallylamine derivatives in high de and around 90% ee <2003JA6610>. A one-pot synthesis of β -amino esters proceeded in high diastereoselectivity when (*S*)-valine methyl ester was reacted with an aldehyde and a silyl enolate in the presence of $\text{Yb}(\text{OTf})_3$ <1996TL1691>. Alkylation of secondary amines by α,β -unsaturated ketones was achieved in excellent yields using $\text{CeCl}_3 \cdot 7\text{H}_2\text{O} \cdot \text{NaI}$ supported on silica gel <2001JOC9052>. β -Haloaryl- β -amino acid derivatives (>95% ee) can be prepared by the addition of lithium *N*-benzyl-*N*- α -methyl-4-methoxybenzylamide, a homochiral equivalent of ammonia, to α,β -unsaturated esters, followed by oxidative deprotection with CAN <2000SL1257>.

2.05.4.10 Amines from Hydrazines and Related Compounds

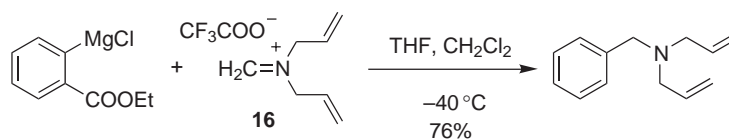
Amines and hydrazines can be obtained from oximes and hydrazones respectively by reduction with $\text{LiCl}-\text{NaBH}_4$ on an Amberlyst[®] 15(H+) support <1999SL409>.

The *N,N*-bond of chiral trisubstituted hydrazines has been cleaved with excess $\text{THF} \cdot \text{BH}_3$ to give the corresponding amines in high ee <1998SL1182>.

A synthesis of (2(*S*),12'(*R*))-2-(12'aminotridecyl)pyrrolidine, a defense alkaloid of the Mexican bean beetle, was synthesized from (*R*)-proline, the stereogenic center in the chain being constructed by 1,2-addition of methyllithium to the SAMP-hydrazone of an aldehyde <2000S510>.

2.05.4.11 Amines from Iminium Salts

Aminomethylation of functionalized organozinc and Grignard reagents using iminium salts (e.g., **16**) afford bisallylamines (Scheme 30) <2000S941>. Such iminium salts were prepared by the reaction of R_2NH with aqueous HCHO to give $\text{R}_2\text{NCH}_2\text{NR}_2$, which with Tf_2O in CH_2Cl_2 affords salt **16** or the corresponding diphenyliminium salt.



Scheme 30

A highly diastereoselective one-pot synthesis of 1,3-diamines involved the aminoalkylation of enamines by preformed iminium salts to give the quaternary iminium salts that were then reduced *in situ* using NaBH_4 , an (*E*)-butenyltrimethylsilane affording predominantly the *anti*-diastereoisomer

<1997SL177>. In a related sequence, a highly diastereoselective one-pot synthesis of Mannich bases involved reaction of an enamine with an iminium salt, the latter generated from a secondary amine and an aldehyde mediated by NaI/Me₃SiCl/Et₃N <1997SL974>. 1,3-Diamines have also been prepared diastereoselectively by the reduction of such Mannich bases, *O*-mesylation, displacement of the mesylate with azide, and reduction of the azido group <2002SI365>.

Homoallylic amines were formed by nucleophilic addition of allyl silanes to an *N*-tosyliminium species prepared *in situ* from a ketone or aldehyde and TsNH₂ mediated by SnCl₂ <1999CC1075>.

2.05.4.12 Amines from Nitriles

2.05.4.12.1 By reduction of nitriles

Nitriles have been reduced to amines by many methods, especially by catalytic hydrogenation and by metal hydrides. Aliphatic and aromatic nitriles have also been reduced to nitro derivatives using hydrazinium monoformate in the presence of Raney-nickel <2002T2211>.

trans,trans-Homofarnesylamine has been prepared from farnesyl bromide by reaction with NaCN and subsequent reduction of the resulting nitrile with LiAlH₄ <1995SC413>.

2.05.4.12.2 By reduction, then addition

Homoallylamines (up to 90% ee) were prepared by the reaction of a chiral allylboron reagent such as (Ipc)₂BCH₂CH=CH₂ with the *N*-borylimine obtained by the reduction of a nitrile with LiEt₃BH <1999SL1987>.

2.05.4.12.3 By addition, then reduction

Addition of an organolithium reagent to benzonitrile catalyzed by CuBr followed by trapping with TBSCl afforded the silylated imines that underwent reduction with THF·BH₃ to give phenylalkylamines <1998SC4067>. When the reduction was carried out using 1,3,2-oxazaborolidines, phenylalkylamines in up to 79% ee were obtained <1998SC4067>.

1-Aryl-substituted primary cyclopropylamines are formed in moderate-to-good yields by the reaction of aromatic nitriles with Et₂Zn in the presence of MeTi(OPrⁱ)₃ and LiOPrⁱ and LiI via a presumed azatitanacyclopentane intermediate <2003OL753>. In a variant on the above, a nitrile reacted with (ethylene)Ti(OPrⁱ)₂, prepared from EtMgBr and Ti(OPrⁱ)₄, to form an oxatitanacycle that underwent ring-contraction to the 1-substituted cyclopropylamine mediated by BF₃·OEt₂ <2001CC1792>.

2.05.4.13 Amines from Azides

The Staudinger reaction of an azide with a phosphine gives an iminophosphorane that with an aldehyde can undergo an *in situ* aza-Wittig reaction to furnish the imine. This strategy has been accomplished on a polymer support, with further reaction of the imine with either NaBH₃CN or an organometallic reagent to give a range of primary and secondary amines <2001SL1565>.

Azides are efficiently reduced to primary amines by a variety of systems including Zn–NiCl₂·6H₂O–THF <1997SL1253>, zinc and ammonium chloride <2002SC3279>, and Sm–NiCl₂·6H₂O <2002SC189>. Of the hydride systems for the reduction of azides, the use NaBH₄/CoCl₂·6H₂O in water at 25 °C is notable for high yields and scope, unsaturated sites, and acetal groups remaining intact <2000S646>; NaBH₄–LiCl is effective in the range 0 to 25 °C <2001SC4495>, as is NaBH₄–ZrCl₄ <2000SC3559>. NaBH₄ and a catalytic amount of tin(IV) 1,2-benzenedithiolate is effective in reducing primary, secondary, tertiary, aromatic, and heteroaromatic azides to primary amines in excellent yields in an aqueous buffer at 15 °C <2000OL397>. Primary, secondary, and tertiary azides, including cycloalkyl and benzylic azides, were reduced to the corresponding primary amines by BHCl₂·SMe₂ <1995TL7987>. Alkyl azides have been reduced to the corresponding alkylamines under neutral and mild conditions using Me₃SiCl–NaI <1997TL6945>.

N-Protected-1,2,3-triaminopropanes have been prepared from diamino alcohols or aminodiols via hydrogenolysis of diazido intermediates over 5% Pd–C <1998SI113>.

A total synthesis of the pyridine alkaloid niphatesine C involved a Friedel–Crafts acylation of a 2-substituted thiophene with 5-(3-pyridyl)pentanoic acid chloride; in the final step the terminal amino group was obtained by hydrogenolysis of an azide <1995JCS(P1)2323>.

(*S*)-*N*-Benzoyl *s*-butylamine has been prepared via azidation of (2(*S*),(*R*_S))-(-)-1-(*p*-tolylsulfinyl)butan-2-ol under Mitsunobu conditions followed by reduction of the azide and sulfonyl groups, the latter to a sulfide that was then reductively cleaved using Raney-nickel over hydrogen <1998JCR(S)666>.

2.05.4.14 Amines from Nitro Compounds

A wide range of aliphatic and aromatic nitro compounds are reduced to nitro derivatives using hydrazinium monoformate in the presence of a catalytic amount of zinc dust <2003SC281> or Raney-nickel <2002T2211>; nitrile, carboxylic acid, ester, phenolic, halogen, and ethylenic groups remained unaltered.

Primary aromatic amines were obtained in high yields by reduction of aromatic nitro compounds with indium in aqueous ethanolic ammonium chloride, ester, nitriles, amide, and halide substituents being unaffected <1998SL1028>. Aromatic nitro compounds can be converted into the corresponding *N*-(*t*-butoxycarbonyl)- or *N*-(ethoxycarbonyl)-amines by treatment with Sn and NH₄Cl and either (BOC)₂O or ClCO₂Et respectively, during sonication <2002SL771>.

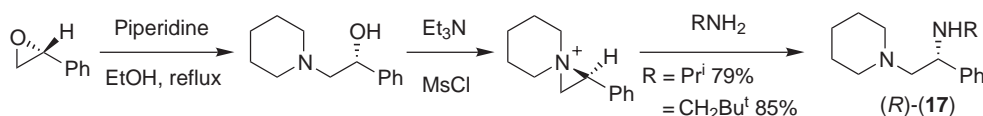
Primary amines have been prepared (78–92%) by the reduction of nitro compounds with ZrCl₄/NaBH₄, at 0°C to room temperature for aliphatic amines, and at reflux for aromatic ones <2000SL683>.

A nitro group can be selectively reduced in the presence of cyano, carboxylic acids, amide groups, or halogen by treatment with NaH₂PO₂ and FeSO₄ with microwave radiation <2000SL993>.

The reduction of tertiary alkylnitro compounds to the corresponding amines has been reviewed <1995S1053>. Hydrogenation over Raney-nickel, usually in methanol or ethanol, can be a convenient method for the preparation of such amines in excess of 50 g quantities.

2.05.4.15 Amines from Epoxides

Koga introduced chiral diamines, including those of type **17**, as chiral bases for asymmetric deprotonation. Diamines **17** have recently been prepared in an efficient process in which an aziridinium species derived from styrene oxide undergoes ring opening by an amine that itself may be chiral (Scheme 31) <2001S693>.



Scheme 31

A one-pot synthesis of enantiopure 1,2-diamines proceeded by the treatment of (*R*)-styrene oxide with a secondary amine followed by Et₃N to give the aziridinium intermediate that is then treated *in situ* with Et₃N and a primary amine or ammonia <1998JCS(P1)1483>.

The aminolysis of epoxides is an important route to β-aminoalcohols; it has been conducted with many reagents, but Ca(OTf)₂ is a recent development that avoids some of the disadvantages of metal perchlorates or lanthanide triflates <2002T5979>.

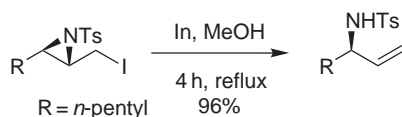
2.05.4.16 Amines from Aziridines

Primary *s*-alkylamine hydrochlorides have been prepared by ring-opening of 2-alkyl- and 2,3-dimethyl-*N*-(diethoxyphosphoryl)aziridines at the less hindered carbon atom with copper-modified Grignard reagents and subsequent hydrolysis with 20% HCl at reflux <1997T4935>.

Enantiopure β -aryl(heteroaryl)alkylamines have been prepared from *N*-tosyl alkylaziridines and Grignard reagents by regioselective ring-opening followed by desulfonylation with Mg in ethanol <2001TA2517>.

Reductive cleavage of, or nucleophilic attack on aziridines can provide useful routes to amines. Thus, a fused aziridine was converted by methanolysis into a 4-amino-pentopyranoside <1997T14369>.

Enantiopure allylic amines can be synthesized efficiently by the treatment of 2-iodomethyl *N*-tosyl aziridines with metallic indium (Scheme 32) <2001SL1608>. Chiral 5-amino-1,3-dienes can also be prepared by a corresponding 1,4-elimination <2001SL1608>.



Scheme 32

1,2-Diamines containing *N*-aryl and *N'*-tosyl groups have been obtained in excellent yields by the treatment of *N*-tosyl aziridines with primary arylamines in the presence of a catalytic amount of LiClO₄ <2002SL53>. Activated *N*-tosyl aziridines reacted with benzylamine in acetonitrile to give the expected 1,2-diamines in enantiomerically pure form, but in methanol dialkylation of benzylamine occurred giving C₂-symmetric triamines <2002SL269>. 1,2-Diamines were also obtained in >90% yield by the ring-opening of aziridines with anilines in the presence of 10 mol.% of BiCl₃ <2003SC547>.

1,2-Halo-*N*-tosylamines were efficiently prepared by the ring-opening of *N*-tosyl aziridines with InX₃ (X = Br, Cl, or I) at ambient temperatures <2001SL1417>.

Alkylation of lithiated β -sulfonyl acetals with *N*-tosyl aziridines derived from amino acids followed by acid-catalyzed cyclization afforded enantiomerically pure 2-alkyl-1,4-bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines <1998SL55>.

Dialkyl [[2-(bromomethyl)aziridin-1-yl]methyl]phosphonates have been synthesized by the reaction of 1,3,5-trialkylhexahydro[1,3,5]triazine with dialkyl phosphites, subsequent bromination followed by reductive ring closure with NaBH₄ <1998SL180>.

Addition of lithiated 4-methoxybenzylisocyanide to enantiopure amino acid-derived *N*-tosyl- and *N*-diphenylphosphinoylaziridines afforded *N*-protected 3-isocyanooamines that upon acidic hydrolysis afforded differentially protected 1,3-diamine derivatives <1999TA1001>.

Allylic amines have been obtained by the treatment of a sulfonate ester of an aziridinemethanol with telluride ion, obtained by reduction of elemental tellurium; during the reaction tellurium(0) is re-formed and may be reused <1997JOC7920>.

2.05.4.17 Amines from Carboxylic Acids and Their Derivatives

Conventional methods for the conversion of RCOOH into RNH₂ include the Schmidt reaction, involving the addition of hydrazoic acid to give the isocyanate RNCO that is hydrolyzed *in situ*; the same isocyanate intermediate is involved in the Curtius reaction. (\pm)-*trans*-Cyclopentane-1,2-diamine has been prepared from *trans*-cyclopentane-1,2-dicarboxylic acid via a twofold Curtius rearrangement <2000SC2593>. The monoamine oxidase inhibitor *trans*-2-phenylcyclopropylamine has been synthesized as the (1(*R*),2(*S*))-enantiomer by a modified Curtius degradation of (1(*R*),2(*R*))-(-)-*trans*-2-phenylcyclopropane carboxylic acid, obtained by asymmetric cyclopropanation of styrene with dicyclohexylmethyl diazoacetate <1999SC567>.

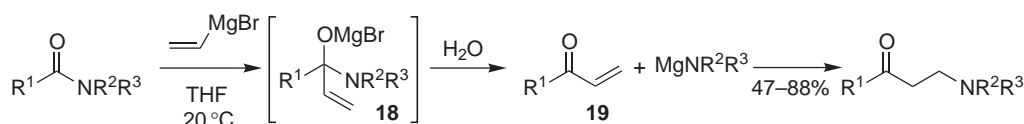
2.05.4.18 Amines from Amides

Direct reduction of amides to amines is the most important method. Reduction of amides to secondary amines has been achieved with Zr(BH₄)₄ at room temperature <2000SC4387>, an advantage over Zn(BH₄)₂ and (*n*-Bu)₄NBH₄ which usually require heating at reflux. Primary, secondary, and tertiary amines have all been prepared efficiently by reduction of the corresponding amide with a hydrosilane in the presence of a transition metal catalyst such as Ru₃(CO)₁₂ or

an amine complex such as $\text{Os}_3(\text{CO})_{12}\cdot\text{Et}_2\text{NH}$ <2001TL1945>. A wide range of tertiary amines have been prepared by the reduction of the corresponding tertiary amide with two molar equivalents of Ph_2SiH_2 catalyzed by 0.1 mol.% of $\text{RhH}(\text{CO})(\text{PPh}_3)_3$ at room temperature, the method being tolerant of ester and epoxide groups <1998TL1017>.

Reduction of an *N*-protected amide with DIBAL followed by *O*-silylation afforded an *N,O*-acetal trimethylsilyl ether, the precursor of a presumed *N*-acyliminium ion, to which a variety of carbon nucleophiles can be added in the presence of a Lewis acid, resulting in an α -alkylated amine <2002CC1064>.

Cyclopropylamines were obtained by the reaction of dialkyl carboxamides with 1.0 equiv. of methyltriisopropoxytitanium and 1.1 equiv. of a Grignard reagent; this protocol afforded higher yields than previous procedures in which 2.0 equiv. of the Grignard reagent and 1.0 equiv. of $\text{Ti}(\text{OPr}^i)_2$ were used <1997SL111>. Conversion of *N,N*-dialkylformamides into functionalized aminocyclopropanes involved reaction with a titanacyclopropane intermediate, obtained via transmetallation of an organozinc reagent <2002SL879>. ^{15}N -Labeled diethylenetriamine, [^{15}N]-dien], and ethylenediamine, [^{15}N]-en], have been synthesized from ^{15}N -glycine by amidation-reduction sequences using trityl as the *N*-protecting group <1997S410>. β -Aminoketones have been prepared by the addition of vinylmagnesium bromide to an amide, the reaction being thought to proceed via the tetrahedral intermediate **18** that undergoes elimination to the α,β -unsaturated ketone **19** which then undergoes addition (Scheme 33) <2000OL11>.



Scheme 33

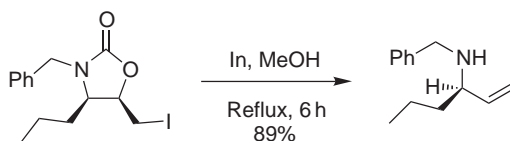
Unsymmetrical *N,N'*-disubstituted α,ω -diaminoalkanes have been prepared by reduction of *N*-(ω -arylaminoalkyl)amides with $\text{THF}\cdot\text{BH}_3$ <1998SC1625>.

N,N-Dialkylaminobutylamines can be prepared by a general method involving reaction of a dialkylamine with chloroacetyl chloride followed by a chain extension to give the 3-cyano-*N,N*-dialkylpropanamide which is reduced with LiAlH_4 <1998SC4257>.

N-Alkylactams have been reduced in high yields to the corresponding cyclic amines using lithium *N,N*-dialkylaminoborohydrides <1999OL799>.

2.05.4.19 Amines from Heterocycles by Cleavage of a Heterocyclic Ring

Allylic amines in high ee were obtained by the indium-mediated reductive cleavage of 5-iodomethyl-2-oxazolidinones, obtained via nucleophilic ring-opening of a 2,3-epoxy alcohol with a primary amine (Scheme 34) <2001TL6385>. A closely related method used telluride ion (obtained from Te and NaBH_4) to cleave reductively mesylates corresponding to the iodides in Scheme 34 <1999TL2255>.



Scheme 34

2.05.4.20 Amines from Other Functional Groups

Secondary amines were formed by deoxygenation of nitrones using lithium powder, $\text{NiCl}_2\cdot 2\text{H}_2\text{O}$ and 10 mol.% of 4,4'-di-*t*-butylbiphenyl (DTBB) in THF at room temperature <2001S427>; the use of $\text{NiCl}_2\cdot 2\text{D}_2\text{O}$ afforded the mono- α -deuterated secondary amine. Reductive cleavage of

N—N and N=N bonds using polymethylhydrosiloxane and (BOC)₂O in the presence of a catalytic quantity of 10% Pd—C provides a one-pot conversion of aromatic hydrazines and azo compounds into *N*-(*t*-butoxycarbonyl)amines <2002SL1561>.

Hydroxylamines have been reduced to the corresponding amines by indium powder in a mixture of ethanol and aqueous ammonium chloride heated at reflux <2003OL1773>. Tertiary and aromatic amine oxides have been efficiently deoxygenated by *O*-formylation using formic pivalic anhydride and subsequent base-induced deformylation <1999SL623>.

Allylamines in up to 93% ee have been obtained by [2,3]-sigmatropic rearrangement of allylic selenimides, obtained by reaction of a chiral allylic chloroselenurane with the *N*-lithio derivative of a primary amine <1996JOC2932>.

The preparation of homoallylamines by the reaction of an enamine with allyl bromide mediated by indium was greatly accelerated by the addition of one molar equivalent of acetic acid <1997CEJ1064>. Allylic and propargylic amine derivatives have been obtained by the addition of a vinyl or ethynyl organometallic reagent to the nitron derived from D-glyceraldehyde to give the corresponding hydroxylamines that are deoxygenated with Zn—Cu(OAc)₂ and deprotected <1996TA1887>. Enantiomerically pure α -substituted propargylamines were prepared by the reaction of dialkyl alkynylalane–triethylamine complexes in the presence of Me₃Al with various oxazolidines derived from (*R*)-phenylglycinol in two steps <2000JOC6423>.

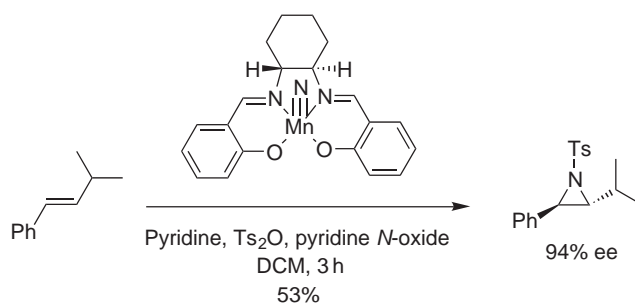
2.05.5 CYCLIC AMINES

2.05.5.1 Aziridines

Aziridines are important as intermediates that can undergo ring-opening and rearrangement, and in the generation of chiral ligands and auxiliaries; applications of aziridines in synthesis have been reviewed <2000S1347>, as has the asymmetric synthesis of aziridines <1997TA1693>. Common starting materials include derivatives of 1,2-amino alcohols, epoxides, alkenes (e.g., via cyclic sulfate formation or nitrene addition), and more recently, azirines and imines. Aziridines have been prepared from 2*H*-azirines, versatile intermediates in synthesis <2001EJO2401>. An intriguingly simple method of preparing aziridines in the absence of catalysts, metal-based reagents, or stoichiometric oxidants is by electrochemical oxidative aziridination of an alkene with an amine, taking place at a Pt anode at +1.80 V <2002JA530>.

Preparation of aziridines from epoxides is a very useful approach, especially since the latter are readily available. 2,3-Epoxy alcohols undergo attack by azide, and if followed by the protection of the primary hydroxy group and subsequent ring closure, e.g., using Ph₃P, functionalized aziridines can be obtained with inversion at both stereogenic centers compared with the epoxy alcohol <1998S109>. Conversion of epoxides into aziridines using iminophosphoranes in the presence of ZnCl₂ or ZnI₂ was found to be the most satisfactory for terminal and cyclic epoxides <1996JCS(P1)1167>. (*R*)-1-Benzyl-2-trifluoromethylaziridine has been prepared in enantiopure form by the reaction of (*S*)-3,3,3-trifluoropropene oxide (75% ee) with benzylamine, recrystallization of the amino alcohol to enantiopurity, and ring-closure using Ph₃PCl₂ and Et₃N <1997TA2933>. *N*-Sulfonyl aziridines have been prepared by ring-opening of epoxides with *p*-toluenesulfonamide under the conditions of solid–liquid phase transfer catalysis to give β -sulfonamidoalcohols that were *o*-tosylated prior to cyclization with K₂CO₃ <1999T6387>.

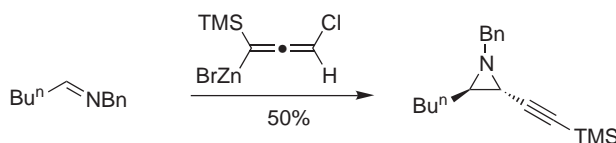
Aziridination of alkenes, especially enantioselectively, continues to be an important route to aziridines. The chloramine salt of *t*-butylsulfonamide is a useful nitrogen source in the aziridination of alkenes because the *t*-butylsulfonyl group can be cleaved under reasonably mild acidic conditions (CF₃SO₃H in CH₂Cl₂ in the presence of anisole) <1999OL783>. The copper-catalyzed asymmetric aziridination of alkenes commonly employs PhI=NTs, but improvements in both chemical yield and ee have been reported using *p*-NO₂C₆H₄SO₂N=IPh and aryl-substituted alkenes <1997TA3563>. Copper-poly(pyrazolyl)borate catalysts have shown promise for the aziridination of styrenes using PhI=NTs; recent developments using sodium tris(3,5-dimethylpyrazolyl)borate and CuCl have provided a few examples of the aziridination of cycloalkenes and 1-octene to give racemic *N*-tosyl aziridines <2001OL1423>. An asymmetric aziridination of styrene derivatives has been achieved in up to 94% ee using a chiral nitridomanganese complex that has the same template as Jacobsen's catalyst for the asymmetric epoxidation of alkenes (Scheme 35) <1998AG(E)3392>.



Scheme 35

Aziridination of alkenes has been achieved in water using chloramine-T and iodine with 10 mol.% of a quaternary ammonium salt [<2001JCS\(P1\)3186, 1998T13485>](#). Rhodium-catalyzed aziridination of alkenes using $\text{H}_2\text{NSO}_3\text{CH}_2\text{CCl}_3$ in the presence of $\text{PhI}(\text{OAc})_2$ and MgO has the advantages of (i) employing a crystalline sulfamate ester that is an optimal source of nitrogen, (ii) applicability to a wide range of alkenes, and (iii) potential cleavage by Zn to *N*-H-aziridines [<2002JA13672>](#). Atkinson's substituted quinazoline systems effect asymmetric transfer of nitrene equivalents into alkenes; the use of β -trimethylsilylstyrene afforded an intermediate 2-silyl derivative which with CsF underwent desilylative elimination of the chiral quinazoline moiety to give 3-phenylazirine which in the presence of KCN afforded (2(*R*),3(*S*))-2-cyano-3-phenylaziridine in 83% ee [<1997JCS\(P1\)897>](#). *N*-Sulfonyl aziridines have been prepared by the bromine-catalyzed reaction of an alkene or an allylic alcohol with anhydrous TsNCINa [<1998JA6844>](#).

Carbenoid insertion into imines has attracted increased interest, especially regarding asymmetric variants. The reaction of imines with ethyl diazoacetate catalyzed by $\text{Cu}(\text{OTf})_2$ to give aziridines has been thoroughly studied [<1995CC1401>](#). The reaction of ethyl diazoacetate with imines is also catalyzed by other Lewis acids including $\text{Et}_2\text{O} \cdot \text{BF}_3$ [<1996JOC8358>](#). Sulfur ylides (acting as carbenoid equivalents) permit the asymmetric aziridination of imines using phenyl diazomethane, diazoesters, and diazoacetamides in up to 95% ee with a $\text{Rh}_2(\text{OAc})_4$ catalyst [<2001JCS\(P1\)1635>](#). Rhodium-catalyzed asymmetric aziridinations of imines mediated by achiral sulfur ylides has provided 1,2,3-trisubstituted aziridines in up to 97% ee [<1996JOC8368>](#). Benzyl-stabilized *S*-ylides were found to react irreversibly with imines, whereas ester- and amide-stabilized *S*-ylides reacted reversibly [<2001JCS\(P1\)3159>](#). Aziridines have been prepared by using the asymmetric methylenide transfer reagent (*S*)-*S*-methyl-*S*-(*p*-tolyl)-*N*-(*p*-tosyl)sulfimide, the highest enantiomeric enrichment reported being 38% ee [<1998JCS\(P1\)3399>](#). Asymmetric addition of ethyl diazoacetate to an imine in the presence of a vaulted biphenanthrol (VAPOL) catalyst afforded the corresponding *cis*-disubstituted aziridines in up to 99% ee [<1999JA5099>](#). β -Phenylvinylaziridines have been prepared by catalytic aziridination of *N*-sulfonylimines with cinnamyl bromide mediated by Me_2S and in the presence of K_2CO_3 under solid-liquid phase-transfer conditions [<1996JCS\(P1\)867>](#). A similar procedure was successful using *N*-sulfonylimines and sulfonium salts derived from 4-bromocrotonate esters [<1996JCS\(P1\)2725>](#). *cis*-Vinyl and *cis*-ethynyl aziridines are formed in high yields by reaction of unactivated *N*-aryl- or *N*-alkylimines with *S*-ylides in the presence of Me_3SiCl or $\text{BF}_3 \cdot \text{OEt}_2$ [<1997CC1231>](#). Aziridines have been prepared by a three-component coupling of an aliphatic aldehyde, an aliphatic amine, and ethyl diazoacetate catalyzed by $[\text{Ir}(\text{COD})\text{Cl}]_2$ [<2000CC625>](#). *trans*-Alkynyl-substituted *N*-H-aziridines were obtained in high diastereoselectivities by the addition of an allenylzinc carbenoid, obtained from a propargylic bromide, ZnBr_2 , and LDA , to an imine (Scheme 36) [<2002EJO1385>](#).



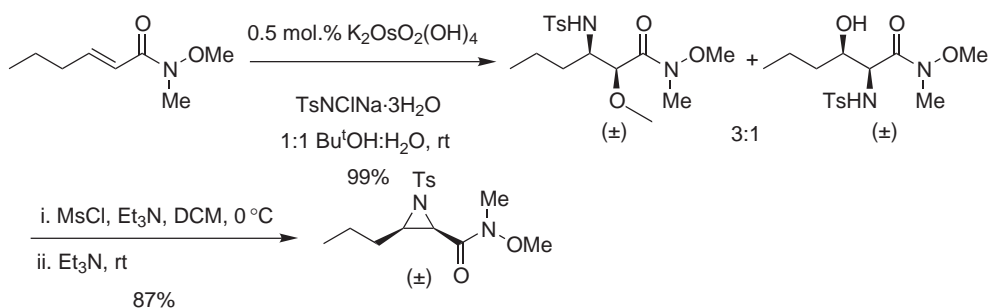
Scheme 36

Trifluoromethyl-substituted aziridines result from the Lewis acid-catalyzed reaction of trifluoromethyl-substituted imines with ethyl diazoacetate [<2001SL679>](#). The resulting aziridines undergo ring opening at the carbalkoxy carbon atom to give single diastereoisomers of esters containing

both trifluoromethyl and amino groups at the β -position. Predominately *cis*-2,3-disubstituted aziridines resulted in moderate yields from the $\text{Ln}(\text{OTf})_3$ -catalyzed reaction of ethyl diazoacetate with imines <1999T12929>.

Cyclisation of *N*-BOC-protected β -amino alcohols to give enantiomerically pure *N*-protected aziridines can be efficiently achieved in one step using TsCl and powdered KOH at reflux <1997SL893>. Vinylic aziridines result from the cyclization of 1,4-aminoalcohols using Mitsunobu conditions <1998SL247>. 2-Vinyl aziridines have been obtained by palladium-catalyzed cyclization of amino allenes <1999JOC2992>. *cis*-2-Vinyl-3-alkyl aziridines are formed by the conversion of (*Z*)-4-(*N*-arylsulfonyl)amino-4-alkylbut-2-en-1-ols into the corresponding mesylates, which are cyclized using 4 mol.% of $\text{Pd}(\text{PPh}_3)_4$ <1999JCS(P1)2155>. Starting with *N*-tosyl-L-serine, Grignard addition led to a ketone which by adaptation of previous work <1984JA1095> was reduced and then cyclized to give the enantiopure *N*-tosyl aziridine <2001SL1602>. Aziridines have been prepared in up to 70% ee by asymmetric transfer hydrogenation of aryl-substituted 2*H*-azirines catalyzed by a metal complex derived from $[\text{RuCl}_2(p\text{-cymene})]_2$ and an enantiopure amino alcohol <2002CC1752>.

cis-3-Substituted aziridine-2-carboxamides are formed by aminohydroxylation of α,β -unsaturated amides of *trans*-configuration with $\text{TsNCINa}\cdot 3\text{H}_2\text{O}$ and $\text{K}_2\text{OsO}_2(\text{OH})_4$ mixtures to give a regioisomeric mixture of hydroxysulfonamides that undergo ring closure upon mesylation and subsequent treatment with Et_3N (Scheme 37) <1997AG(E)2637>.



Scheme 37

Aziridine-2,2-dicarboxylates have been prepared in up to 80% ee by the addition of *N,O*-bis(trimethylsilyl)hydroxylamine to α,β -unsaturated malonates in the presence of $[\text{Cu}(S,S)\text{-Bn}(\text{-box})](\text{OTf})_2$ <2002TA1407>.

The first enantioselective addition of an organolithium reagent to an azirine has been described, 3-(2-naphthyl)-2*H*-azirine affording the corresponding 2,2-disubstituted aziridine in up to 17% ee <2002TA1957>.

A multiply substituted aziridine has been obtained by the self-condensation of an oxiranyl carbaldimine induced by LDA ; a new variety of aza-Darzens reaction is postulated in which deprotonation at the epoxide carbon atom adjacent to the imine group gives an anion that attacks the imine of another molecule, leading via intramolecular opening of an epoxide ring to the aziridine as a single diastereoisomer <2001OL1527>.

Both 2,3-*cis*- and 2,3-*trans*-*N*-arylsulfonyl-2-ethynylaziridines have been synthesized in high ee by the successive treatment of α -amino acids with $\text{Ph}_3\text{P}=\text{C}(\text{Br})\text{CO}_2\text{Me}$, DIBAL , $\text{MsCl}-\text{Et}_3\text{N}$, and then NaH in DMSO to effect aziridine ring formation, followed by KOBu^t in THF to induce dehydrobromination resulting in the alkynyl substituent <1998TA3929>.

2-Substituted (*S*)-aziridines have been conveniently prepared by (*R*)-oxynitrilase [EC 4.1.2.10]-catalyzed addition of HCN to an aldehyde to give an enantiopure cyanohydrin that is *o*-sulfonylated and then reduced at the nitrile function by LiAlH_4 to give the intermediate amine that rapidly cyclizes <1995TA283>. Asymmetric syntheses of 2-aryl aziridines have been achieved by the addition of a sulfur ylide to an enantiopure *N*-sulfinylimine, followed by removal of the sulfinyl group by MeLi at -78°C <1996TA3407>. The *t*-butylsulfinyl group was found to be the most satisfactory.

cis-3-Substituted-2-silylaziridines are formed by the addition of $\text{Me}_3\text{SiCHN}_2$ to *N*-sulfonylimines in 1,4-dioxane at 40°C ; the silyl group undergoes replacement with retention of configuration in the presence of a fluoride source and a suitable electrophile <2000OL4107>. *cis*-3-Substituted-2-silylaziridines have also been prepared by the addition of bromoazide to an imine; this affords a useful route to the *N*-*H*-aziridines <2000JCS(P1)1173>.

(2(*R*),3(*S*))-(-)-2-Phenyl-3-methylaziridine has been prepared by the reaction of (1(*R*),2(*S*))-(-)-norephedrine with PCl_5 to give the (1(*S*),2(*S*))-(+)-1-chloro-1-phenyl-2-propylamine hydrochloride, by inversion of configuration and subsequent ring-closure (NaOH at 80 °C <1997TA2877>. This protocol has been extended to the synthesis of *cis*-1,2,3-trisubstituted aziridines in >98% ee from (1(*R*),2(*S*))- or (1(*S*),2(*R*))-(+)-norephedrine via the corresponding *N*-(arylidene)- β -chloroamines <2000T7299>. Aryl aziridines have been prepared by the reaction of Schiff bases with a diazocompound using $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2(\text{THF})]^+[\text{BF}_4]^-$ as the catalyst <1998JOC6839>.

C-Alkylation of sulfinyl aziridines was achieved by sulfoxide–magnesium exchange using EtMgBr followed by addition of a primary alkyl halide in the presence of CuI . The alkylated aziridines were hydrogenolyzed over $\text{Pd}(\text{OH})_2$ to give enantiopure secondary amines bearing a quaternary chiral center <2000TL6495>.

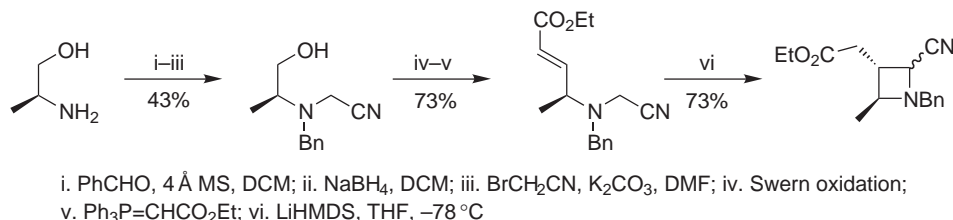
Intramolecular aziridination of bromoalkenes mediated by NaH in DMF afforded the *cis*-2,3-disubstituted 2-ethynyl aziridines <2002JA15255>.

Aminoalkyl aziridines have been prepared by the reaction of 1-aminoalkylchloromethyl ketones with a primary amine in the presence of TiCl_4 to give the corresponding enantioenriched 1-aminoalkylchloromethyl ketimines that were reduced to the *syn*-diamine derivative prior to cyclization induced by MeLi <2001JOC2764>.

The trisaziridine methyl *cis*-9,10;*cis*-12,13;*cis*-15,13-triepipiminoctadecanoate has been prepared as a mixture of diastereoisomers by the treatment of the corresponding triepoxide with NaN_3 followed by PPh_3 <1999EJO661>.

2.05.5.2 Azetidines

Enantiopure 2-cyanoazetidines have been prepared from β -aminoalcohols by conversion into *N*-cyanomethyl derivatives which were then oxidized to an intermediate aldehyde that underwent Wittig olefination; the α,β -unsaturated ester so formed was then subjected to an intramolecular base-induced conjugate addition to give separable diastereoisomers (Scheme 38) <2003SL726>. Enantiopure 2-cyanoazetidines have also been prepared from β -amino alcohols by a 4-*exo-trig* ring closure of a lithiated α -aminonitrile with displacement of chloride <2002SL297>.



Scheme 38

3-Bromoazetidines were formed in 4-*endo-trig* cyclizations by the addition of bis(collidine) bromonium(I) hexafluorophosphate to allylic tosylamides that have a terminal alkyl or aryl substituent <2000EJO3007>.

(2(*S*),4(*S*))-Azetidine-2,4-dicarboxylic acid has been prepared by the reaction of (*S*)-1-phenylethylamine with dimethyl-2,4-dibromopentanedioate, separation of the isomers, and subsequent hydrogenolysis and hydrolysis <1995JCS(P1)693>.

1,2,2-Trisubstituted azetidines were prepared by ring expansion of 2,2-disubstituted 1-methoxycyclopropylamines to 1,4,4-trisubstituted 2-azetidinones using AgBF_4 , and subsequent reduction with LiAlH_4 <1996JOC6500>.

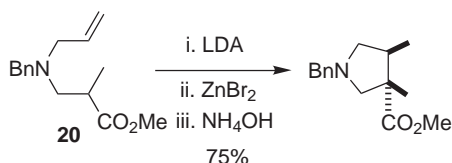
2.05.5.3 Pyrrolidines

Many cyclizations that afford pyrrolidine rings are known. 2-Substituted pyrrolidines have been obtained by the base-induced cyclization of the methanesulfonates of enantiomerically enriched

4-hydroxynitriles <1995SC1155>. Dynamic resolution of 2-lithiopyrrolidines, using an excess of a commercially available derivative of prolinol, afforded 2-substituted pyrrolidines in around 95% ee <2002AG(E)3887>.

3-Substituted pyrrolidines have been obtained by tin–lithium exchange on a homoallylamine to give an α -aminoorganolithium that underwent 5-*exo-trig* cyclization and subsequent trapping by electrophiles <1996JA5322, 1995TL2157>. Other 3-substituted pyrrolidines have been prepared by the cyclization of *N*-(benzylidene)- and *N*-alkylidene-homoallylamines with electrophiles including bromine and PhSeBr; that can be followed by reductive debromination with Bu₃SnH and AIBN, or deselenylation with Ph₃SnH <1995CC2029>.

Pyrrolidine-3-carboxylates were formed diastereoselectively by intramolecular carbocyclization of zinc enolates derived from β -(*N*-allyl)-aminoesters **20** (Scheme 39) <2002SL919>.



Scheme 39

Ring-closing olefin metathesis (RCM) of unsymmetrical diallylamines using Grubbs' catalyst afforded 3-substituted pyrrolidines <2002SL1889>. (*S*)-Homoproline has also been prepared by RCM using Grubbs' catalyst, but here the required diallylamine derivative was obtained by conjugate addition of (*S*)-*N*-allyl-*N*- α -methylbenzylamide to *t*-butyl sorbate <2002SL1146>. Chiral 2-substituted pyrrolidines have also been prepared by ring-closing metathesis of unsymmetrically substituted diallylamines <2002SL731>.

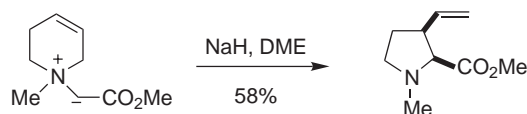
Chiral hydroxylated pyrrolidines have been prepared by the reaction of an unsaturated epoxy alcohol with *N*-benzylhydroxylamine to give the intermediate ω -unsaturated hydroxylamine, which undergoes a reverse-Cope cyclization to give an amine oxide that is hydrogenolyzed to give the 3,4-dihydroxylated pyrrolidine <2000SL1408>. C₂-Symmetric 3,4-diphenylpyrrolidines have been prepared by the condensation of 2,3-diphenylsuccinic acid with primary amines at 220°C to give the cyclic imides followed by reduction with NaBH₄–I₂ in THF at reflux <2000S703>. The same reducing system was effective in the reduction of cyclic imides to give the corresponding enantiopure 3,4-dihydroxypyrrolidines <1998CC1223>. 3,4-Disubstituted pyrrolidines, predominantly of *cis*-stereochemistry, were formed by the addition of TsSePh to dialkylallylammonium salts followed by dequaternization <1997SL1420>. 3-Oxysubstituted pyrrolidines were obtained by a radical [3 + 2]-cycloaddition of iodomethylene-*N*-tosylaziridine with a vinyl ether in the presence of AIBN or other initiator <2003JOC3184>.

2,4-Disubstituted pyrrolidines, with the *trans*-diastereoisomer predominating, were formed by Lewis acid-mediated radical cyclizations of substituted *N*-chloropent-4-enylamines <2001JCS(P1)891>.

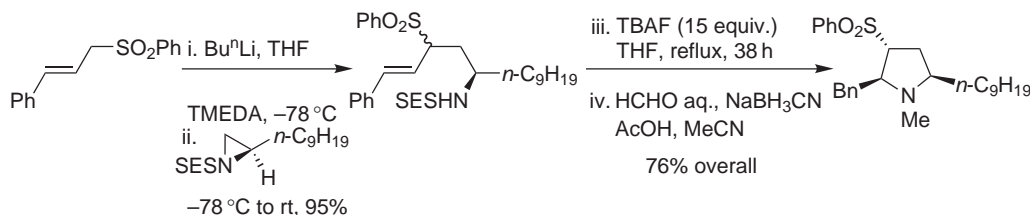
trans-3,4-Disubstituted pyrrolidines bearing a C(4)-protected hydroxy group were obtained in high de by the asymmetric 1,3-dipolar cycloaddition of an azomethine ylide containing a chiral group on the nitrogen atom to a 3-benzyloxy-substituted alkenoylcamphorsultam <2001TA1977>. One such cycloadduct was used to prepare a glycosidase inhibitor. Completely *endo*-selective cycloadditions have been described using the azomethine ylide obtained from the ring opening of (2(*R*),3(*R*))-[3-phenylaziridin-2-yl]prop-2-enoate in reaction with a variety of dipolarophiles <1995S1147>. *trans*-3,4-Disubstituted pyrrolidines bearing two vinyl groups have been prepared by radical cyclization of bis(allenes), linked via an NTs group, with *p*-TsBr or *p*-TsSePh in the presence of AIBN <2001CC1306>. The first enantioselective syntheses of vicinal 3,4-difluoropyrrolidines have been described; treatment of the bistriflate of an *N*-substituted (3(*S*),4(*S*))-dihydroxypyrrolidine with Bu₄NF at –80 to 20°C afforded the corresponding (3(*R*),4(*R*))-difluoropyrrolidines <1998CC1223>.

[3,2]-Sigmatropic rearrangement of didehydropiperidinium ylides has been shown to be a viable route to 3-ethenyl proline derivatives, the conditions used suppressing products of elimination (Scheme 40) <2000SL1208>.

A new type of cyclization, probably proceeding via isomerization to the vinylic sulfone, has provided substituted pyrrolidines with stereocontrol (Scheme 41); subsequent oxidative transformation of the sulfonyl group into the ketone permitted the total synthesis of (+)-preussin <2001SL1602>.

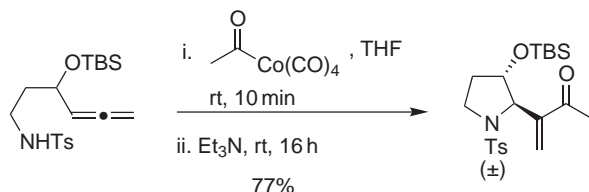


Scheme 40



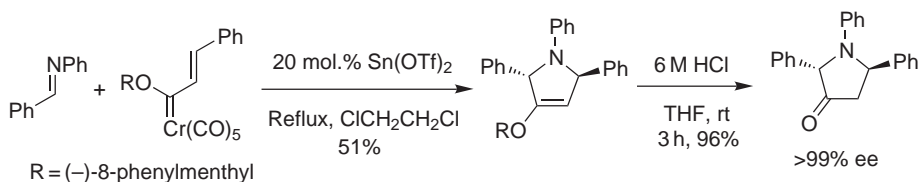
Scheme 41

Acylation–cyclization reactions of allenes with acylcobalt reagents provided an efficient route to pyrrolidines [<1995T12939>](#). This has been extended by using an α -oxy substituent (Scheme 42) which resulted in pyrrolidines in high diastereoselectivity [<2001SL532>](#).



Scheme 42

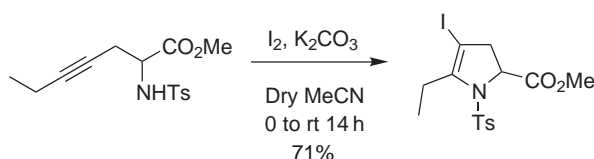
The synthesis of 2,5-disubstituted pyrrolidines has been reviewed [<1996TA927>](#). A ring-contraction protocol provided 2,5-disubstituted pyrrolidines from 3-hydroxy piperidines, themselves obtained from 2-methoxypiperidines and allyltrimethylsilane in the presence of ZnCl_2 [<2001SL45>](#). ((*R*),(*R*))-*trans*-2,5-Diphenylpyrrolidine (>98% ee) has been prepared by the asymmetric reduction of 1,4-diphenyl-1,4-butanedione with Ipc_2BCl to give the appropriate C_2 -symmetric diol that was converted into the dimesylate which is cyclized with allylamine prior to deallylation mediated by Wilkinson's catalyst $[(\text{Ph}_3\text{P})_3\text{RhCl}]$ [<1995TA409>](#). An asymmetric [3 + 2]-cycloaddition of an alkenyl Fischer carbene complex with an imine afforded, after hydrolysis, substituted 3-pyrrolidinones which in the case of phenyl substituents were obtained virtually enantiopure (Scheme 43) [<2001JA7182>](#).



Scheme 43

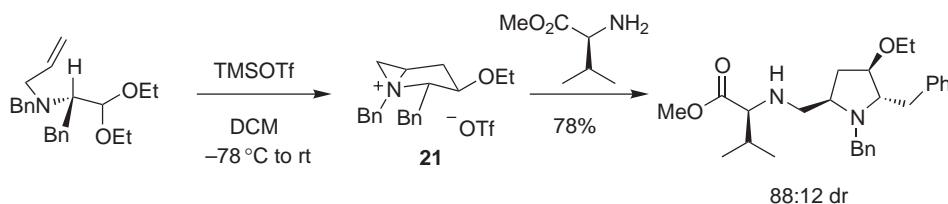
2,5-Disubstituted 3-iodopyrrolidines were formed by the treatment of (*E*)-homoallylic tosylamides with iodine, the *cis*-isomer being generally obtained in the absence of base, but K_2CO_3 or NaHCO_3 led predominantly to the 2,5-disubstituted *trans*-isomer, by suppression of HI that catalyses the isomerization (Scheme 44) [<1996CC915>](#).

Enamines derived from methyl acetoacetate reacted with cyclic sulfate esters of *vic*-diols to give polysubstituted pyrrolidines containing a vinylogous amide unit [<2003SL675>](#). Treatment of *N*-protected 5-aminopent-1-ene derivatives with tosyl iodide afforded β -iodosulfones that undergo



Scheme 44

ring closure to pyrrolidines upon treatment with DBU [<1997SL1441>](#). 3,3,4-Trisubstituted pyrrolidines have been prepared by a zirconium-catalyzed diene cyclization of substituted diallyl amines that proceeded in up to 86% ee [<1997JA7615>](#). Polysubstituted pyrrolidines have been prepared by a cationic cyclization leading to an aziridinium salt (e.g., **21**), which then undergoes attack by C- or N-nucleophiles (Scheme 45) [<2001CC966>](#).



Scheme 45

Substituted pyrrolidines, amongst other *N*-heterocycles, have been formed by the cyclization of the appropriately substituted 1-amino or 1-amidoalkyl radical [<1996S913>](#). *cis*-(2(*R*),3(*S*))-3-Hydroxyproline has been synthesized in 52% overall yield in eight steps, a crucial diastereoselective step being the SnCl_4 -mediated addition of allyltrimethylsilane to an *N,O*-protected L-serinal [<2002TA1103>](#). Treatment of *N,N*-bis(tosylmethyl)benzylamines with SmI_2 affords azomethine ylides that are trapped by alkenes to give pyrrolidines (41–87%) [<1999SL590>](#). *N*-Tosylpyrrolidines have been prepared by the reaction of *p*-toluenesulfonamide with electrophilic alkenes of suitable chain length that bear a terminal iodo group, in an *N*-alkylation-cyclization protocol [<1999SC2175>](#). Pyrrolidines possessing an exocyclic methylene group have been prepared by reductive cyclization of a 1-propargyl-substituted pyrrolidine-2-carboxaldehyde catalyzed by $\text{Ni}(\text{COD})_2$ conducted in the presence of Et_3SiH and Bu_3P [<2000JA6950>](#). 2-(2-Bromovinyl)-substituted pyrrolidines were prepared by cyclization of γ -allenic tosylamides catalyzed by 10 mol.% of $\text{Pd}(\text{OAc})_2$ in the presence of LiBr and K_2CO_3 , with $\text{Cu}(\text{OAc})_2$ as the oxidant [<2000JA9600>](#).

2-Substituted and 2,2-disubstituted pyrrolidines have been prepared by the reaction of an aldehyde or a ketone with 3-chloropropylamine followed by the treatment of the chloroimine with lithium and a catalytic amount of 4,4-di-*t*-butylbiphenyl [<2001JOC6207>](#).

1,2,3-Trisubstituted pyrrolidines have been prepared by diastereoselective cyclizations of imines bearing the 2-(thiomethyl)-3-trimethylsilyl-1-propenyl terminator mediated by TiCl_4 [<2001JOC5237>](#).

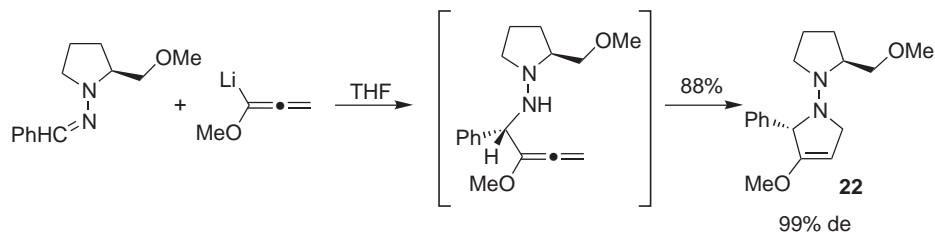
N-Propargylic-*N*-allylic sulfonamides underwent rhodium-catalyzed cycloisomerization to give unsaturated pyrrolidines containing a substituted 3-exomethylene group [<2000JA6490>](#).

N-(α -Benzotriazolylalkyl)alkenylamines, prepared by reacting α,δ -unsaturated amines bearing a δ -methoxycarbonyl group with benzotriazole and an aldehyde, reacted with SmI_2 to give substituted pyrrolidines containing a methyl ester [<1996SL39>](#).

2.05.5.4 Pyrrolines

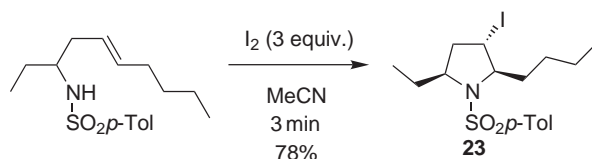
1-Substituted 1-pyrrolines were obtained in excellent yields by hydroamination–cyclization of 1-amino-4-pentyne derivatives with a mixed catalyst containing silicon and samarium [<1996JA9295>](#). Substituted 1-pyrrolines have been prepared by ruthenium-catalyzed intramolecular oxidative ring closure of substituted 4-pentenyl-1-amines [<2002JA186>](#). 1-Pyrrolines were formed by reductive cyclization of a nitroarene by CO catalyzed by $\text{Ru}_3(\text{CO})_{12}$ in the presence of

1,10-phenanthroline <1995JOC8328>. 3-Pyrrolines **22** have been prepared in at least 99% ee from the SAMP-hydrazones of aldehydes by reaction with α -lithio methoxy allene. The α -allenylhydrazine underwent cyclization to compound **22**, which could be reductively cleaved to the chiral 3-pyrroline by alkylation with ClCO_2Me followed by hydrogenolysis (H_2 , Raney-nickel, 50°C , 50 bar) (Scheme 46) <1999TL5009>.



Scheme 46

3-Cyanodihydropyrrole derivatives have been prepared by the reaction of (1-cyanocyclopropyl)diphenylphosphine oxide and an *N*-monosubstituted amide with NaH in xylene at $130\text{--}165^\circ\text{C}$ under nitrogen <1996CC511>. 3-Iododihydropyrroles (e.g., **23**) were formed by 5-*endo-dig* iodocyclizations of homopropargylic sulfonamides (Scheme 47); *trans*-2,5-disubstituted pyrrolidines were obtained in the presence of a base, but in its absence isomerization occurred giving the *cis*-isomers <2001JCS(P1)1182>. The electrophilic driving force of the cyclizations means that they are not regarded as exceptions to Baldwin's rules of ring closure.



Scheme 47

2-Substituted 3-pyrrolines (64–93% yields) have been prepared by cyclization of (*Z*)-allylic mesylates with NaH in DMF <1999SL228, 1999JCS(P1)2155>.

5-Methyl- Δ^1 -pyrroline and 2,5-dimethyl- Δ^1 -pyrroline have been prepared by the reaction of the dianion of ethyl acetoacetate with an *N*-phosphorylated aziridine followed by hydrolysis and decarboxylation with acid to give the γ -aminoketone that underwent cyclization with K_2CO_3 <1998SC1127>. The formation of 4,5-dihydropyrroles was found to be favored under $\text{Rh}_2(\text{OAc})_4$ -catalyzed reactions of Schiff bases with methyl styryl diazoacetate, whereas 2,5-dihydropyrroles predominate when $\text{Cu}(\text{OTf})_2$ was used as the catalyst <2003JA4692>.

Enantiopure 3-aminopyrrolidines were prepared from L-glutamic acid that was converted by a short sequence into an aminodimesylate that effected dialkylation benzylamine with ring closure <1998SC3919>.

2-Aryl-1-pyrrolines were prepared by the addition of the Grignard reagent derived from 1-(3-bromopropyl)-2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane to an aromatic nitrile, and subsequent cyclization using K_2CO_3 <1996SC3097>.

2.05.5.5 Pyrrolizidines

Cyclization to give a pyrrolidine ring is a central feature in the synthesis of many pyrrolizidines. 3-Methyl-substituted pyrrolizidines were formed by cyclization of a secondary amine bearing unsaturated termini using a mixed catalyst containing silicon and samarium <1996JA707>.

The photo-induced addition of *N*-alkylpyrrolidines, by generation of the corresponding α -aminyl radical, to electrophilic alkenes can proceed with high facial selectivity, and by using (5(*R*))-5-menthyloxy-2(5*H*)-furanone as the acceptor, succinct routes to (–)-isoretronecanol and (+)-laburnine were established <2000EJO2227>.

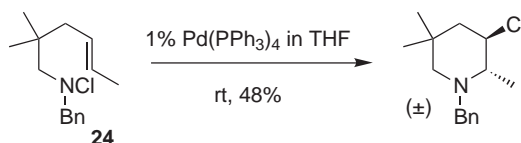
A stereocontrolled route to either enantiomer of dihydroxyheliotridane proceeded via an intramolecular 1,3-dipolar cycloaddition involving a terminal alkene and an ylide from an *N*-benzylaziridine carboxylic ester <1995CC2291>.

2.05.5.6 Piperidines

As with pyrrolidines, cyclizations provide many useful routes to piperidines. Treatment of *N*-protected 6-aminohex-1-ene derivatives with tosyl iodide afforded β -iodosulfones that underwent ring closure to piperidines upon treatment with DBU <1997SL1441>.

Enantiopure 3-aminopiperidines were prepared from L-glutamic acid, which by a short sequence was converted into an aminodimesylate that reacted with benzylamine <1998SC3919>.

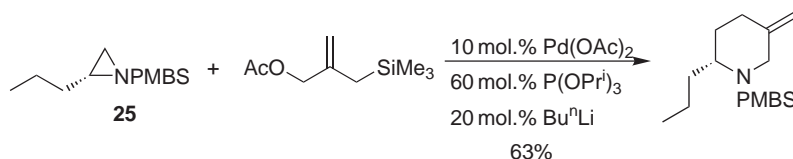
N-Substituted 3-chloropiperidines were formed by palladium-catalyzed cyclization of an unsaturated *N*-chloroamine (e.g., **24**) (Scheme 48) to give a 2-chloromethylpyrrolidine that underwent rearrangement to the thermodynamically more stable 3-chloropiperidine <2002CC720>.



Scheme 48

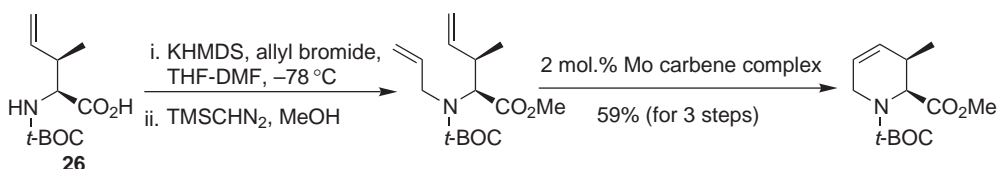
N-Substituted 3-chloropiperidines were also formed by the ring closure of *N*-chloro-*N*-(4-pentenyl)amines catalyzed by CuCl <2000S1561> or by SmI₂ <2001TL7771>; the anticipated 2-chloromethylpyrrolidines were not obtained, but presumably cyclized to the corresponding aziridinium species which underwent attack by chloride ion to give the more thermodynamically stable 3-chloropiperidine. Another route to 3-chloropiperidine derivatives involves cyclization of *N*-chlorinated 5-aminopent-1-ene derivatives with a catalytic amount of Bu₄NI <2002EJO3171> or with 10 mol.% of CuCl <2002EJO1848>.

A [3+3]-cycloaddition reaction of aziridines (e.g., **25** with Pd–trimethylenemethane complexes afforded a synthesis of piperidines containing a 3-exomethylene unit (Scheme 49); the product was converted into (–)-pseudoconhydrine <2001SL1596>. *n*-Butyllithium acted as the reducing agent.



Scheme 49

Ring-closing metathesis has become an important method for the construction of nitrogen heterocycles, including unsaturated piperidines. 3-Substituted pipercolinic esters were prepared from the acid **26** (obtained by Kazmier–Claisen rearrangement of a crotyl ester) by *N*-allylation followed by esterification and ring-closing metathesis (Scheme 50) <1998JOC3158>. Related strategies using Grubbs' catalyst have also succeeded and by incorporating a 2-(3-pyridyl) substituent in the acyclic precursor, a total synthesis of (*S*)-anatabine was achieved <2000SL1646>. Similarly, an oxygenated side chain at the 2-position led via ring-closing metathesis (using Grubbs' catalyst) to a 3,4-dehydropiperidine that was converted into (+)-sedamine <2000SL1461>.



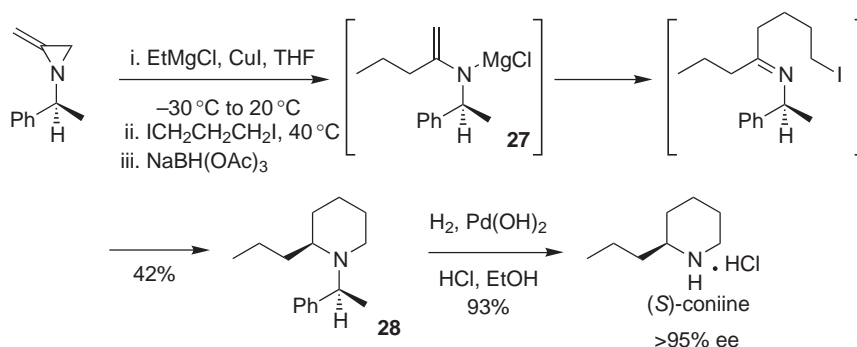
Scheme 50

Ring-closing metathesis of a chiral amine obtained by the conjugate addition of (*S*)-*N*-allyl-*N*- α -methylbenzylamide to an unsaturated ester forms the basis of a synthesis of (*S*)-homopipericolic acid <2002SL1146>. A similar approach furnished (*S*)-coniine <2002SL1146>.

The piperidine ring has been constructed by a double alkylation of a cyclic sulfate with a stabilized *C,N*-dianion of an amide to give a δ -oxygenated amide that is cyclized and reduced <2000SL1360>. A similar strategy was used to prepare (+)-sedridine <1997SL22>.

Polysubstituted piperidines in enantiopure form have been prepared by a sequence involving a silyloxy Cope rearrangement of an Evans aldol product to give a 7-oxo-2-enimide that was condensed with a primary amine to give a tetrahydropyridine that was hydrogenated to the corresponding piperidine <1999EJO3353>.

Piperidines, and (*S*)-coniine in particular (Scheme 51), have been prepared by ring-opening of an enantiopure 2-methyleneaziridine with an organocuprate followed by trapping of the metalloenamine **27** with an alkyl halide and subsequent reductive cyclization to give compound **28**, which by hydrogenolysis afforded the alkaloid in $\geq 95\%$ ee <2001CC1784>.



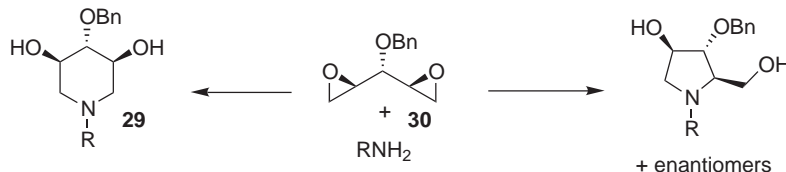
Scheme 51

A versatile synthesis of 2-substituted piperidin-3-ols involves application of the SAMP/RAMP hydrazone methodology to the α -alkylation of a chiral glycol aldehyde hydrazone with subsequent 1,2-addition of an organolithium; the chiral auxiliary is reductively cleaved using THF·BH₃ prior to reductive cyclization using NaBH₄ <2002TA587>.

N-Substituted piperidin-3-ols have been conveniently prepared by sequential treatment of pyrrolidinemethanol derivatives with (CF₃CO)₂O, then heating with Et₃N to effect ring expansion via the aziridinium intermediate, and lastly the hydrolysis of the trifluoroacetate group with aqueous NaOH <1999EJO1693>.

3-Hydroxy-2-phenylpiperidines have been prepared by a Lewis-acid-catalyzed hetero-ene reaction of (*S*)-*N*-benzyl-*N*-(4-methylpent-3-enyl)phenylglycinal proceeding with appreciable diastereoselectivity <1997S475>.

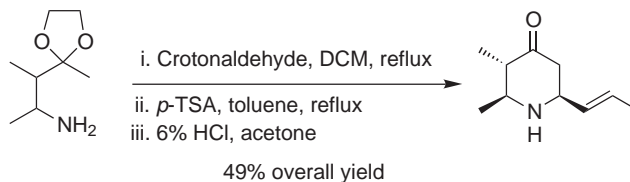
Aminocyclization of bis-epoxides (e.g., **30**) favors the 6-*endo-tet* piperidinol **29** when conducted in water at 50 °C (Scheme 52) <2000SL193>.



Scheme 52

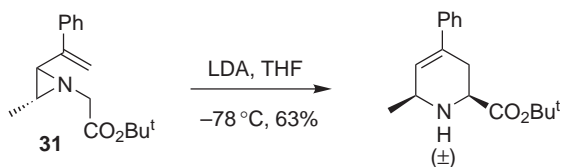
Enantiopure derivatives have been prepared by 6-*exo-trig* cyclization of γ -hydroxy- α,β -unsaturated sulfones with Et₃N <2000SL53>. Derivatives of nipecotic acid have been prepared by thermolysis of 1,2-oxazines to give 1-aza-1,3-butadienes that undergo intermolecular trapping by *n*-butyl vinyl ether <2002SL863>. 2-Methylpiperidine has been resolved using the appropriate enantiomer of mandelic acid; each enantiomer of 2-methylpiperidine was used to prepare an enantiomerically pure *trans*-2, 6-disubstituted piperidine by metallation of the *N*-BOC piperidine and subsequent alkylation <1999SC1747>. 2-Vinylpiperidines have been prepared by the treatment of an

N-allylic benzotriazole with *n*-butyllithium followed by 1-bromo-3-chloropropane to give the alkyl chloride that is displaced by heating with a primary amine followed by cyclization with $\text{Pd}(\text{OAc})_2\text{-PPh}_3$ <1999JOC6066>. Enantiocontrolled syntheses of *cis*-2,6-disubstituted piperidines have been achieved by the desymmetrization of *meso*- η -(3,4,5)-dihydropyridinylmolybdenum complexes, for example, by reaction first with allylmagnesium chloride, and subsequently with a lithium enolate <2003JA2878>. Enantio-enriched *cis*-2,6- and *trans*-2,6-trisubstituted tetrahydropyridines have been prepared by reaction of a chiral allyl silane containing an α -aminoester terminus with an aldehyde in the presence of MgSO_4 to generate the imine *in situ*, followed by addition of TiCl_4 to achieve cyclization <2003JA626>. An intramolecular reaction provided a route to highly substituted piperidines (Scheme 53), subsequent treatment with acid effecting equilibration to a single major diastereoisomer <2000TL9797>.



Scheme 53

Oxime ethers derived from the commercially available enantiomers of 1-phenylbutanol underwent highly diastereoselective additions of Grignard reagents to give hydroxylamines that after N—O bond cleavage and cyclization were converted into coniine and pseudoconhydrine <1997JOC746>. Syntheses of (+)- and (–)-dihydropinidines involved a diastereoselective addition of an organocerium reagent (prepared from the addition of CeCl_3 to the Grignard reagent prepared from 5-bromopent-1-ene) to an imine derived from the appropriate enantiomer of phenylglycinol. A subsequent Wacker oxidation and reductive cyclization with concomitant cleavage of the chiral auxiliary furnished the enantiopure piperidine alkaloids <1999JCS(P1)2791>. *N*-Tosylpiperidines have been prepared by the reaction of *p*-toluenesulfonamide with electrophilic alkenes of suitable chain length that bear a terminal iodo group, in an *N*-alkylation-cyclization protocol <1999SC2175>. 4-Phenylpiperidines have been formed by [2,3]-aza-Wittig rearrangement of vinyl aziridines such as the derivative **31** (Scheme 54), in this case only a single diastereoisomer being isolated from the reaction using a 1/1 *cis*/*trans* isomeric mixture of aziridine **31** <1995JCS(P1)2739>.

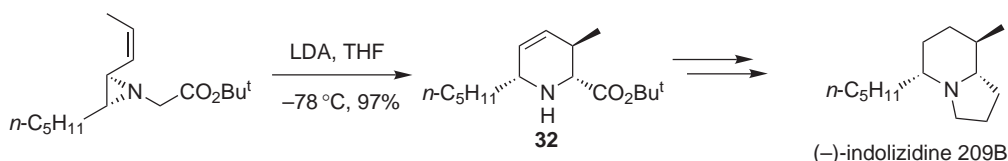


Scheme 54

A formal total synthesis of (–)-paroxetine, a 3,4-disubstituted piperidine that is a selective serotonin re-uptake inhibitor, involved an enantioselective ring expansion of a trisubstituted prolinol and subsequent radical dehalogenation <2002EJO3543>. (–)-Pseudoconhydrine has been prepared from L-proline by a ring expansion that proceeds in 57% yield <1997SL905>.

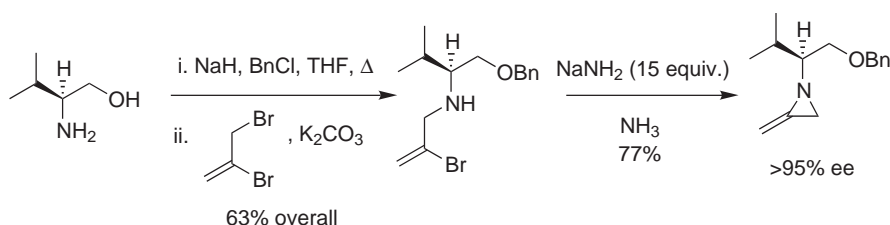
2.05.5.7 Miscellaneous

Syntheses of substituted 1-azabicyclo[1.1.0]butanes have been reviewed <1997SL1029>. Vinyl aziridines underwent an efficient aza-[2,3]-Wittig rearrangement to give the tetrahydropyridines **32** (Scheme 55) that have been converted into the dendrobatidae alkaloids, (–)-indolizidines 209B and 209D <1995T9747>.



Scheme 55

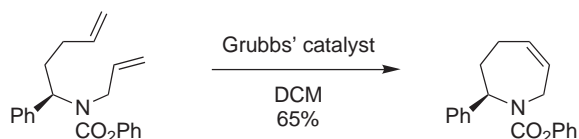
3,4,5,6-Tetrahydropyridines were obtained by organolanthanide-catalyzed intramolecular hydroamination–cyclization of aminoallenes [<1998JA4871>](#). Methyleneaziridines ($\geq 95\%$ ee) have been prepared from enantiopure β -amino alcohols by *N*-alkylation with 2,3-dibromopropene followed by ring closure with NaNH_2 (Scheme 56) [<1996TA3397>](#).



Scheme 56

A route to enantiomerically enriched 2*H*-azirines involved β -elimination of a sulfonyl group, e.g., treatment of (2(*S*),3(*S*))-*N*-(*p*-tolylsulfinyl)-2-carbomethoxy-3-phenylaziridine with LDA followed by MeI [<1995JA3651>](#).

Ring-closing metathesis has been used to prepare five-, six-, and seven-membered nitrogen heterocycles (Scheme 57) [<2000CC1771>](#).



Scheme 57

2.05.6 ASYMMETRIC SYNTHESIS OF AMINES

This topic was briefly reviewed in COFGT (1995) [<1995COFGT\(2\)297>](#). In this edition, asymmetric syntheses of amines and their derivatives have been placed in the appropriate sections concerning key functional groups or ring systems. For example, in [Section 2.05.5.1](#) the preparation of aziridines includes paragraphs on their asymmetric syntheses by enantioselective aziridination of alkenes and by enantioselective carbenoid insertion into imines.

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Biographical sketch

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2.06

Alkyl Nitrogen Compounds: Compounds with N—Halogen, N—O, N—S, N—Se, and N—Te Functional Groups

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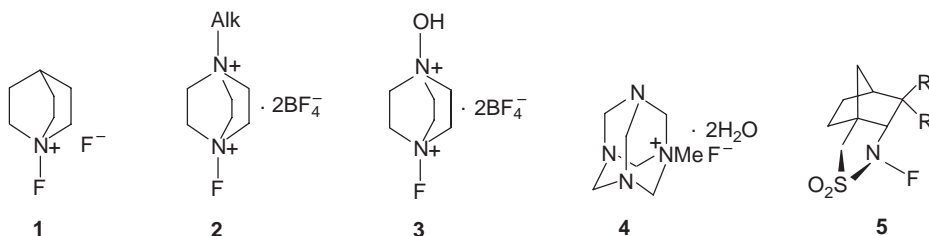
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2.06.1 *N*-HALOGENOALKYLAMINES: $RNHHal$, R^1R^2NHal , $RNHal_2$, AND SALTS THEREOF

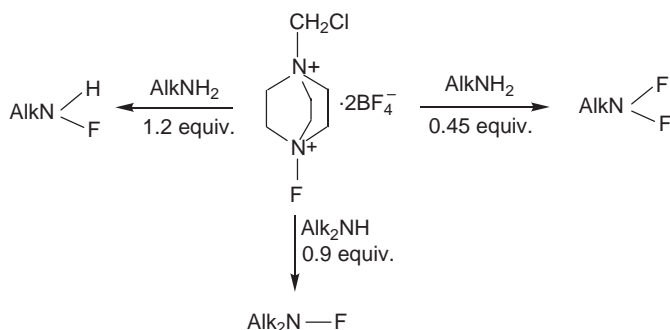
2.06.1.1 *N*-Fluoroalkylamines: $RNHf$, R_2NF , RNF_2 , R_3N^+F

N-Fluoroalkylamines and *N,N*-difluoroalkylamines have rightfully received much attention as fluorinating agents. Synthesis and synthetic applications of such compounds have been reviewed [<B-1999M1001, 1998JCS\(P1\)1577, 1998JFC\(87\)1, 1996CRV1737>](#), and polyfluorinated oxaziridines as a specific source of *N*-fluoroamines have been reviewed [<1996CRV1809>](#). Cyclic *N*-fluoroalkylamines such as *N*-fluoroquinuclidinium fluoride **1**, selectfluor[®] (**2**; $Alk=CH_2Cl$), 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **3**, methylhexamethylene-tetraamine fluoride **4**, and *N*-fluoro-2,10-camphorsultams **5** have widely been used in the 1990s as highly regioselective fluorinating agents.



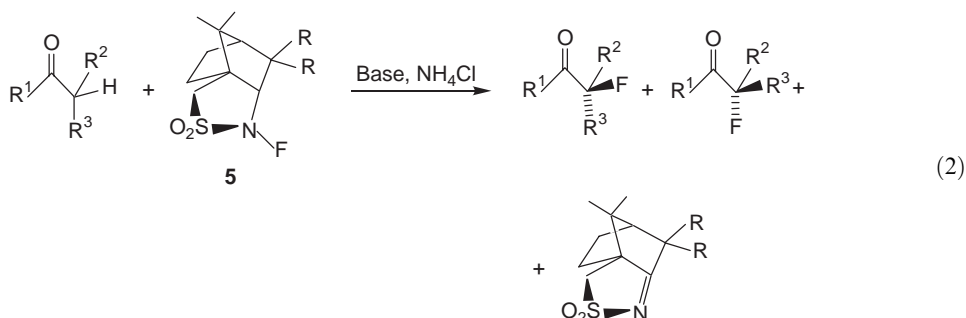
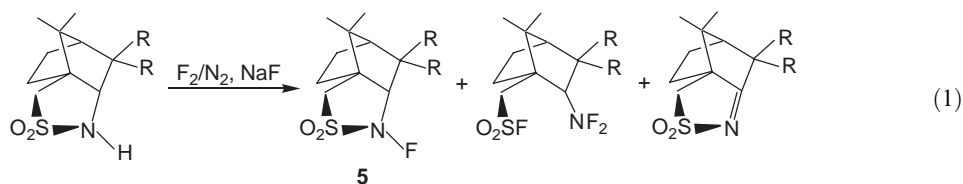
2.06.1.1.1 Primary and secondary *N*-fluoroalkylamines: $RNHF$, R_2NF

Selectfluor[®] (**2**; $\text{Alk} = \text{CH}_2\text{Cl}$), methods of synthesis of which were reviewed in COFGT (1995) <1995COFGT(2)333>, fluorinates amines in quantitative yield <2001CC1196>. The reaction between selectfluor[®] and primary or secondary amines proceeds in either DMF or DMA solution at 0–25 °C. The rate of fluorination in the case of primary amines depends upon the molar ratio of reagents (Scheme 1) and was determined by ^{19}F NMR. The products are stable at temperatures below 0 °C. The authors <2001CC1196> emphasized that the mechanism of electrophilic *N*-fluorination of amines is still unclear. An interesting application of selectfluor[®] in the fluorination of linear and cyclic alkanes has been reported <2000CC959>.

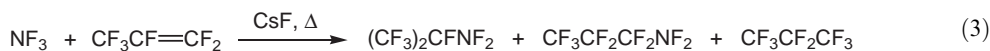


Scheme 1

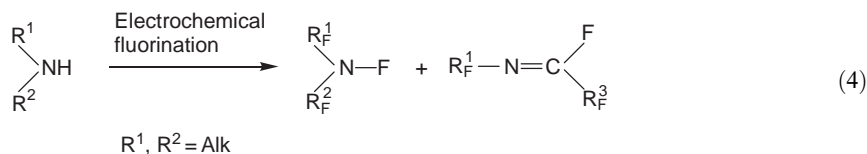
N-Fluoro-2,10-camphorsultams **5** are synthesized by fluorination of the corresponding camphorsultams at –40 °C with 10% fluorine/nitrogen in $\text{CHCl}_3\text{--CFCl}_3$ solution in the presence of sodium fluoride to scavenge HF <1998JOC2273>. The yields of the monofluorinated products vary between 25% and 67%. The process is accompanied by secondary transformations leading to products of dehydrofluorination and N–S bond cleavage–polyfluorination (Equation (1)). Asymmetric fluorination of kinetic enolates by *N*-fluorosultams **5** takes place at –78 °C (Equation (2)) and is completed at 0 °C (Equation (2)) <1998JOC2273>.



N-Fluorination of 2-substituted aziridines by fluorine/NaF supported by freon 113 gave a mixture of both stereoisomers, which are characterized by a high barrier of nitrogen inversion <1998IZV1110>. For the *trans*-3-trifluoromethyl-2-methoxycarbonylaziridines, Prati and co-workers <1998JFC(89)177> have developed a stereodirected version of the process. The structure of the product was confirmed by “aromatic solvent induced shift” on the protons. Fluoroalkenes are efficiently fluorinated by nitrogen trifluoride in the presence of caesium fluoride (Equation (3)) <2000JFC(101)115>.

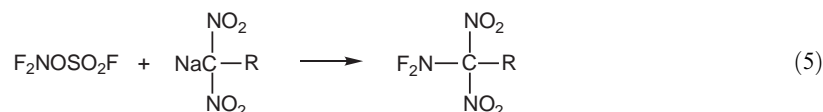


Electrochemical fluorination is a new approach to *N*-fluoroalkylamines (Equation (4)) <2000JFC(106)35, 2000JFC(105)149>. Accumulation of *N*-fluorodialkylamines is accompanied by formation of the corresponding imines. Although the yields of this process are low, the method undoubtedly has high potential.



2.06.1.1.2 *N,N*-Difluoroalkylamines: RNF_2

As described in COFGT (1995) <1995COFGT(2)333>, the possible approaches to *N,N*-difluoroalkylamines are either stepwise fluorination of amines and imines or radical difluoroamination of alkenes with tetrafluorohydrazine. A new approach to the title compounds has been described by Fokin and co-workers <1996DOK(346)358>. *N,N*-Difluoroalkylamines were synthesized by difluoroamination of dinitroalkanes with *N,N*-difluoro-*O*-fluorosulfonylhydroxylamine. The former reagents were introduced in the reaction in the form of sodium salts, and acetonitrile was determined to be the optimum solvent. To avoid direct fluorination of the sodium salts, the process was carried out below -20°C <1996DOK(346)358>. The maximum yield (70%) was achieved after 2 h although the exothermic conversion of the salts was very quick (Equation (5)). The author considers the process to be an electrophilic amination <1996DOK(346)358>.



2.06.1.1.3 *N*-Fluoro quaternary salts: $\text{R}_3\text{N}^+\text{F}$

These types of compound, including 1–4, have been used as reagents for highly efficient electrophilic fluorination (Scheme 1). Synthetic approaches to such compounds have been reviewed <2000CC959, 1999TL2673, 1998JCS(P1)1577, 1996CRV1737>.

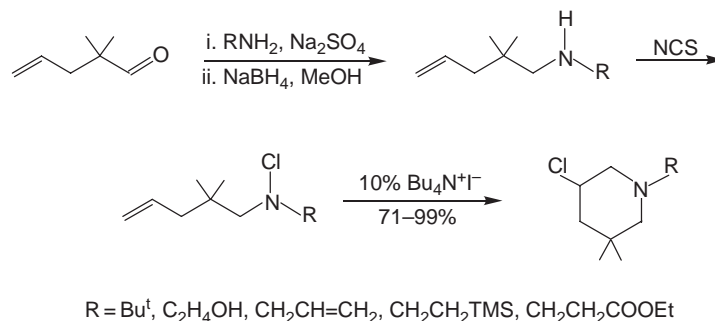
2.06.1.2 *N*-Chloroalkylamines: RNHCl , R_2NCl , RNCl_2 , $\text{R}_3\text{N}^+\text{Cl}$

Reviews by Koval <2001ZOR327, 2000ZOR1437, 1998ZOR807> and by Ura and Sakata <B-2002MI002> reflect the achievements in synthesis and applications of *N*-chloroalkylamines in the 1990s.

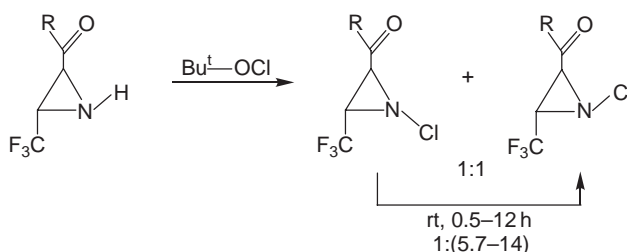
2.06.1.2.1 Primary and secondary *N*-chloroalkylamines: RNHCl , R_2NCl

Synthesis of secondary *N*-chloroalkylamines by the reaction of a corresponding amine with *N*-chlorosuccinimide (NCS) was widely used in the 1990s and reviewed in COFGT (1995) <1995COFGT(2)333>. Gottlich and Noack <2002EJO3171, 2001TL7771> applied this method to unsaturated dialkylamines. The total synthesis of these compounds starting from aldehyde condensation with morpholine, followed by reaction with allyl bromide and formation of the corresponding unsaturated aldehydes and amination, resulted in the unsaturated secondary amines. Subsequent *N*-chlorination employed NCS at 0°C . The products were cyclized (Scheme 2) using tetrabutylammonium iodide <2002EJO3171> or samarium iodide <2001TL7771>. The latter gave lower yields (36–54%). NCS achieved quantitative *N*-chlorination of *N*-allyl-*N*-(5-phenylpent-4-ene)amine at room temperature <1999T6465>. *N,N*-Dichlorotosylamine aminochlorinate

activated alkenes via an intermediate *N*-chloroaziridine <2001T8407, 2000OL2249>. Chlorination of 3-trifluoromethyl-2-carbamoylaziridines by *t*-butyl hypochlorite at -80°C in methylene chloride gives a mixture of *N*-chloroaziridine stereoisomers <1998JFC(89)177> which, unlike similar *N*-fluorinated aziridines <1998JFC(89)177>, are characterized by a low barrier to nitrogen inversion. This resulted in formation of *cis* and *trans* isomers with a tendency to *cis* \rightarrow *trans* conversion upon storage at room temperature (Scheme 3).

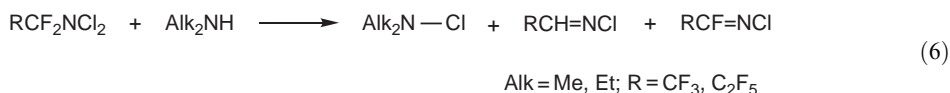


Scheme 2

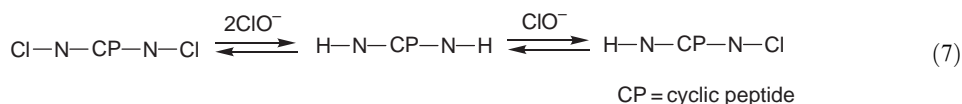


Scheme 3

N-Chlorination of oxazolidine followed by dehydrochlorination was used as a new synthetic approach to oxazoline <2000TL9787>. *N*-Chloro- and *N,N*-dichlorodifluoroalkylamines can act as chlorinating agents toward dialkylamines in accordance with Equation (6) <1994IC4407>.



Prutz <1999MI107> has reported the use of hypochlorous acid for chlorination of cyclic peptides. The equilibrium process is pH dependent and can result in chlorination at one or two sites depending upon the ratio of ClO^- in the system (Equation (7)).



The kinetics of *N*-chloramine decomposition in alkali solution has been studied <1996JPO447>.

2.06.1.2.2 *N,N*-Dichloroalkylamines: RNCl_2

N,N-Dichloro-2-butylamine has been synthesized by condensation of 2-butylamine with excess NCS powder at room temperature <2001JPC2085>.

2.06.1.2.3 *N*-Chloro quaternary salts: R_3N^+Cl

Synthetic methods for *N*-chloro quaternary salts were reviewed in COFGT (1995) <1995COFGT(2)333>. New applications of these compounds include catalysis in biochemical synthesis <2001ACA3, 1999TL1389>.

2.06.1.2.4 *N*-Perchloryamines: R_2NClO_3

There were no publications on these derivatives since the publication of COFGT (1995) <1995COFGT(2)333>.

2.06.1.3 *N*-Bromoalkylamines: $RNHBr$, R_2NBr , $RNBr_2$, R_3N^+Br

Synthetic methods for the title compounds were reviewed in COFGT (1995) <1995COFGT(2)333>. Some new applications of *N*-bromo quaternary salts include catalysis in biochemical synthesis <2001ACA3>.

2.06.1.4 *N*-Iodoalkylamines: $RNHI$, R_2NI , RNI_2

There were no publications on the title compounds presenting new methods in the 1990s.

2.06.2 HYDROXYLAMINES AND RELATED FUNCTIONS

2.06.2.1 *N*-Alkylhydroxylamines: $RNHOH$, R^1R^2NOH , and Salts Thereof

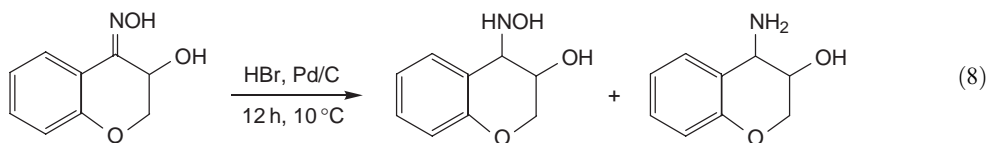
2.06.2.1.1 *N*-Alkylhydroxylamines: $RNHOH$

(i) Oxidative methods

Oxidation of amines is a long known method for the preparation of monoalkylhydroxylamines and the examples described recently do not go beyond the scope of those presented in COFGT (1995) <1995COFGT(2)333>. One of the latest examples has been presented by Vallee and co-workers <2003TA525>. Oxidation of the drug clonidine proceeded via the formation of a dialkylhydroxylamine which was hydrolyzed to an alkylhydroxylamine <2002CHE1469>.

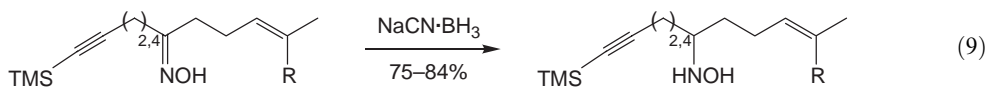
(ii) Reductive methods

The most attractive feature of this protocol is its possible stereoselectivity. Stereoselective reduction of 3-hydroxy-4-chromanone oxime using Pd/C and acid targeted the corresponding aminoalcohol <2000TL8021>. A wide variety of acids, including hydrohalogenic, sulfuric, nitric, acetic, and trifluoroacetic acids, were investigated and hydrobromic acid was found to be the most selective. The hydroxylamine was formed as a result of incomplete conversion of oxime into amine (Equation (8)).

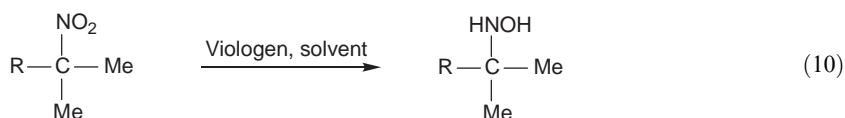


Another efficient oxime reducing agent is borane-pyridine complex which is utilized for the synthesis of polymer-supported hydroxylamines <1998TL9211>. Synthesis of the oxime precursor starts with chloromethylcopoly-(styrene-1%-divinylbenzene) resin condensation with 4-hydroxybenzaldehyde

followed by the reaction with hydroxylamine hydrochloride. The mild process of aminolysis takes place in tetrahydrofuran (THF) at room temperature within 10 h. Reduction of alkyl oximes by sodium cyanide–borohydride under acidic conditions gives alkylhydroxylamines in high yield (Equation (9)) <1996T11601>.



Rhodium(I) hydrogenation systems convert 1-acetonaphthanone oxime into the enantiomeric hydroxylamines <1999CRV1069, 1995CC1767>. High stereoselectivity of addition is achieved not only with an individual oxime as starting compound but also with transition metal–catalyzed systems using a mixture of (*E*)- and (*Z*)-oximes. Reduction of tertiary nitro compounds to alkylhydroxylamines (89–95% yield) by sodium dithionate catalyzed by 1,1'-dialkyl-4,4'-bipyridinium (V^{2+}) (Viologen) proceeds in $\text{H}_2\text{O}-\text{CH}_2\text{Cl}_2$ or $\text{H}_2\text{O}-\text{CH}_3\text{CN}$ solution at 35°C <1995JOC6202>. Aromatic nitro compounds are partially converted to the corresponding amines under similar conditions (Equation (10)).



1-Nitrodecane was readily reduced to the alkylhydroxylamine (90%) within 7 h using SnI_2 in HCl solution <1994MC62>.

2.06.2.1.2 *N,N*-Dialkylhydroxylamines: Alk_2NOH

(i) Oxidative methods

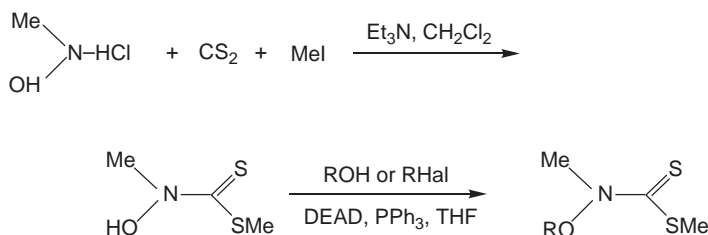
Oxidation using hydrogen peroxide–metal catalyst is a traditional route to *N,N*-dialkylhydroxylamines from dialkylamines. Goti and Nannelli <1996TL6025> oxidized dibenzylamine into dibenzylhydroxylamine using H_2O_2 supported by methyltrirrhodium catalyst. Another oxidizing agent used in the same study was urea–hydrogen peroxide complex: besides dialkylhydroxylamine the corresponding nitron was formed. Imidazoline oxidation/hydrolysis led to clonidine synthesis <2002CHE1469>.

(ii) Reductive methods

Reduction of oximes to the corresponding hydroxylamine epimers is achieved by the action of sodium cyanoborohydride at pH 4.0. The products undergo reversible cyclization to the corresponding *N*-oxides <1995JOC5803>. In chloroform solution the equilibrium shifts slowly toward *N*-oxide giving a 1:9 ratio of hydroxylamines: *N*-oxide. Borohydrides in combination with iridium or rhodium complexes catalyze the reduction of nitrones to hydroxylamines in moderate to good yield depending upon the ligands stereostructure <2000CC409>. Hydrogenation–cyclization of an unsaturated oxime gives hydroxylamine as a mixture of stereoisomers <1995JOC5803>. LiAlH_4 is efficient for hydrogenation of nitrones to hydroxylamines <2001T1119, 1995JOC4743>. An intramolecular reductive cross-coupling of nitrones catalyzed by SmI_2 in THF strictly at -78°C gives an excellent yield of hydroxylamine <2002AG(E)1772>. Intramolecular reductive cross-coupling was also applied to the synthesis of biologically active compounds <2000JCS(P1)3487>. Intermolecular reductive coupling of nitrones and functionalized ethylenes catalyzed by ZnI_2 has been reported <1999JOC3790>. Alkynes catalyzed by Zn(II) gave new propargylic hydroxylamines <2002AG(E)3054>. Urea is an efficient reducing agent for nitrones <2003TL2817>. *N,N*-Diphenylthioureas containing strong electron-withdrawing groups (e.g., CF_3) act as a Lewis acid catalyst in the addition of TMSCN and ketene silylacetales to nitrones <2003TL2817>.

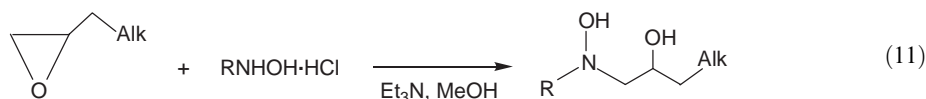
(iii) From alkylation: C—N bond formation

N-Alkylation is a very efficient and extensively utilized general approach to *N,N*-disubstituted hydroxylamines. For example, *N*-methylhydroxylamine hydrochloride is alkylated by carbon disulfide–methyl iodide in THF to give *N*-methyl-*N*-dithiocarbamoylhydroxylamine in quantitative yield <2001SL688>. Subsequent treatment with either an alcohol or an alkyl halide gives the corresponding *O*-alkylhydroxylamines (Scheme 4). The latter have been used for generation of alkoxyradicals.

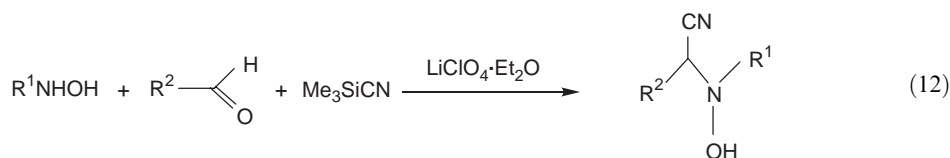


Scheme 4

Benzylhydroxylamines are alkylated by sugars in high yield <2003T4261, 1999TL9375>. An interesting but seldom used approach to *N,N*-dialkylhydroxylamines is alkylation of hydroxylamines by epoxides. Monosubstituted epoxides react with alkylhydroxylamine hydrochlorides in methanol in the presence of triethylamine at room temperature to give the products in 50–93% yield (Equation(11)) <1998TL9089>.



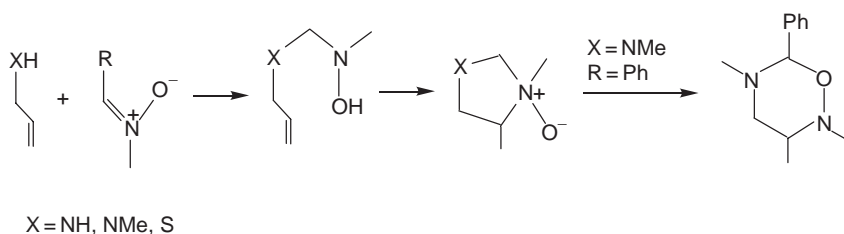
The reaction of arylhydroxylamines with aldehydes and trimethylcyanosilane under the action of 5 M lithium perchlorate–diethyl ether at room temperature gives α -cyanohydroxylamines (88–97%) (Equation (12)) <2000TL2471>.



Aldehydes condense with 2,3-bis(hydroxylamino)-2,3-dimethylbutane to produce cyclic bis-hydroxylamines <2001JCS(P2)1453>. The reaction of hydroxylamine with 1,4-diols under the action of methyl or trialkylsilylsulfonyl chloride is a reliable general approach to the corresponding stereospecific hydroxylamines <1999TL2853, 1997JOC3119>. Among recent examples is a study of the ene reaction of nitroso compounds leading to dialkylhydroxylamines <2003OBC1389>. Quantum chemical methods suggest that the reaction is a stepwise process involving polarized diradical intermediates. Cycloaddition of ketohydroxylamine to cyclopentadiene under oxidative conditions with subsequent ring opening by the action of Pd(II) complex results in a mixture of *N,N*-disubstituted hydroxylamine regio- and stereoisomers <2003JOC139>.

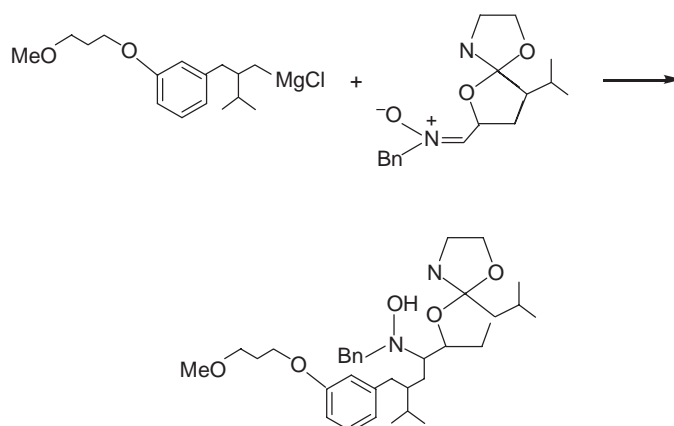
(iv) Nucleophilic addition to nitrones

Nucleophilic addition to nitrones has been employed by Knight and co-workers <1997TL8545, 1997TL8549, 1997TL8553> to form *N,N*-dialkylhydroxylamines. In particular, they studied the reaction of nitrones with *N*-alkylallylamines (and allylthiols) at low temperature. Upon storage at room temperature, the functionalized alkylhydroxylamines underwent cyclization to imidazolidine *N*-oxides or oxadiazinanes (Scheme 5).



Scheme 5

Addition of Grignard reagents to nitrones, such as pyrroline-*N*-oxide, results in stereoselective formation of products in accord with the most preferable orientation of the two and five substituents of the cyclic hydroxylamine [<2000TA2339>](#). In nucleophilic additions to nitrones such as *C*-cyclopropylaldonitrones at low temperature, Grignard reagents were more favorable than Lewis acids [<2001JCS\(P1\)599>](#). The addition of allylindium bromide to nitrones, the unorthodox example, resulted in the formation of hydroxylamines in 75–90% yield [<2000TL9311>](#). Phosphorylated hydroxylamines can be synthesized from D-glyceraldehyde-derived nitronium and diethyl phosphite at -20°C in a process employing *t*-butyldimethylsilyl triflate [<2001TL3033>](#). In a synthesis of the renin inhibitor SPP-100 Dondoni employed an interaction between nitronium and Grignard reagent at low temperature (-40°C and -10°C) to achieve good yields (62–77%) of dialkylhydroxylamine with high stereoselectivity in favor of the (*R*)-isomer (Equation (13)) [<2001TL4819>](#). Transmetalation of magnesium with cerium chloride in the Grignard reagent followed by the same procedure gave the hydroxylamine in 51% yield and similar stereoselectivity.

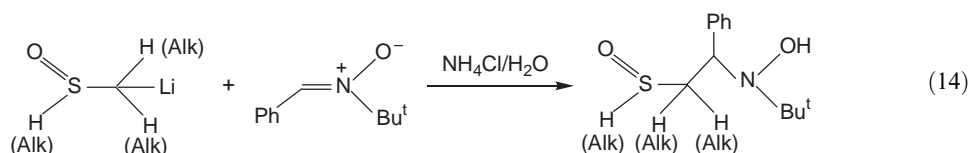


(13)

Ab initio methods have been used to investigate nucleophilic addition of a Grignard reagent to chiral nitrones [<2001T8125>](#) and suggest that chelation is a major factor governing stereoselectivity of the process [<1999TA1867, 1998T12301, 1998JOC5627>](#).

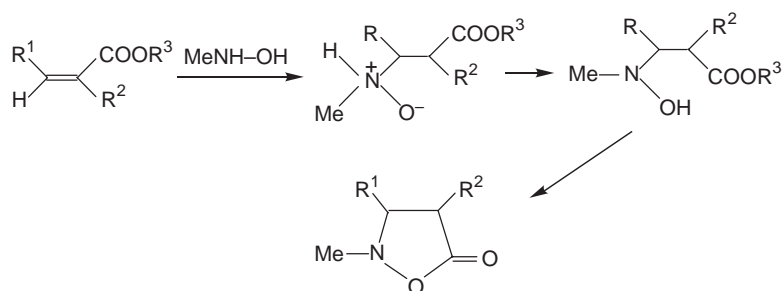
(v) From addition of alkyllithium reagents to nitrones

Metallated by lithium, thiazole, furan, imidazole, thiophene, and their benzoderivatives reacted readily with nitrones to give the hydroxylamines in high yield and high diastereoselectivity favoring the *syn* structure [<1998MI001>](#). In contrast, pretreatment of nitrones with diethylaluminum chloride leads to formation of *anti*-isomers. 4-Phenylpyrroline-*N*-oxide reacted stereospecifically with phenyllithium to give the corresponding *trans*-hydroxylamine [<2000TA2339>](#). The presence of Et_2AlCl in such reactions results in inversion [<2002TL459, 2000TA2339>](#). Adams and Paterson [<2000JCS\(P1\)3695>](#) reported a new approach to enantiopure 1,2-oxazine derivatives by the reaction of chiral nitrones with lithiated allene in THF at -78°C [<2000JCS3695>](#). Lithiated siloxypyrroline added to nitronium in 55% yield [<1998EJOC2361>](#). Addition of α -lithiated sulfoxides to bulky *N*-*t*-butyl-*O*-phenylnitronium gave the corresponding product in greater than 95% diastereoselectivity (Equation (14)) [<2001TL9011>](#).



(vi) From addition of *N*-alkylhydroxylamines to alkenes

Nucleophilic addition of hydroxylamines to alkenes as an approach to *N,N*-disubstituted hydroxylamines has received a new impulse in the 1990s. Usually the process is initiated by a base and takes place in a polar or low-polar solvent at ca. 20 °C to give the corresponding hydroxylamines in several hours with high yields. Such processes have been used for the synthesis of new enantiopure β -aminoacids <2002JOC2402> and nucleosides <1999JOC4>. Niu and Zhao <1999JA2456> proposed a mechanism of the process (Scheme 6).



Scheme 6

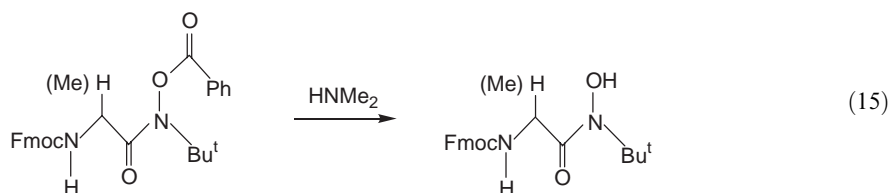
Addition of *N*-alkylhydroxylamines to allylamines in acidic aqueous solution gives a mixture of oxadiazinanes and aminohydroxylamines. This process can be slow even on heating <1997TL8545>.

(vii) From nitroxides

Nitrile oxides can be oxidized to intermediate nitrosocarbonyl species that react as dienophiles in hetero-Diels–Alder reactions. Extremely reactive and unstable nitrosocarbonyl intermediates are formed by mild oxidation of nitrile oxides or alkylchloroximes by methylmorpholine *N*-oxide and trapped by 2,3-dimethyl-2-butene to produce unsaturated hydroxylamines in high yield <1998TL3233, 1996TL1909>.

(viii) From rearrangements

Intra- and intermolecular rearrangements of *N*-alkyl-*O*-allylhydroxylamines leading to *N,N*-dialkylhydroxylamines take place under the action of BuLi–THF <1998CC2235>. There is an interesting example of new peptide bond formation from a hydroxamic acid derivative that proceeded via intramolecular rearrangement (Equation (15)) <2000OL1399>. The yields of hydroxylamines were 82–96%.



(ix) *From nitro compounds*

Nitro compounds have recently proved to be a good source of *N,N*-disubstituted hydroxylamines: 2- and 2,5-substituted nitrobenzenes were allylated by allyl bromide in aqueous acetonitrile solution under the action of indium. Caesium carbonate was found to be the most efficient facilitator of the process <2001SC2277>.

2.06.2.1.3 Alkylhydroxylamine salts: RN^+H_2OH , R_2N^+HOH

Synthetic methods for these compounds were reviewed in COFGT (1995) <1995COFGT(2)333>.

2.06.2.2 *N*-Oxides: R_3NO and Salts Thereof

2.06.2.2.1 *N*-Oxides: R_3NO

Synthetic approaches to *N*-oxides were thoroughly reviewed in COFGT (1995) <1995COFGT(2)333> and this area has not attracted much attention since. A new method has been described by Ciganek <1995JOC5803> and is based on cycloaddition of unsaturated Grignard reagents to nitrones. The process is highly stereoselective and presents an opportunity to carry out subsequent stereocontrolled reduction to amines. *N*-Oxides are side products in the reactions of ethanolamines with monosubstituted epoxides <2000IZV575> (see also <2001JCS(P1)1475, 2000TL5423>).

2.06.2.2.2 Salts of *N*-Oxides: R_3N^+OH , $R_3N^+OR^2$

No methods for these compounds have been described since they were reviewed in COFGT (1995) <1995COFGT(2)333>.

2.06.2.3 *O*-Substituted *N*-Hydroxylamines: R^1NHOR^2 , $R^1N(OR)_2$

2.06.2.3.1 *N*-Alkoxy primary amines: R^1NHOR^2

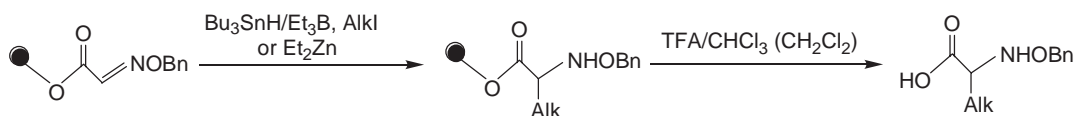
(i) *Reductive methods*

Reduction of *O*-alkyloximes, which is considered to be one of the most convenient methods, employs reducing agents similar to those described for *N*-alkyl(aryl)hydroxylamines (Section 2.06.2.1.2): these are $BH_3 \cdot THF$ <1997TA497>, BH_3 ·pyridine in HCl – $EtOH$ solution <1998CC2235>, $NaBH_3CN$ in HCl <1995T1277>, etc. Keck and co-workers <1996JOC8366, 1999JA5176> performed reduction–radical addition–cyclization sequences with *N*-alkoxyoximes of condensed rings. The processes took place with thiophenol in toluene at 27 °C and UV irradiation to yield (73–91%) the corresponding *N*-alkoxyamines. The process is characterized by high diastereoselectivity. Hydrolysis of aminodicarbonyl compounds under basic conditions followed by reduction on Pd/C in methanol affords α -amino acids (50% yield) <1997TL1841>. Generally, methods do not differ significantly from those considered in COFGT (1995) <1995COFGT(2)333>.

(ii) *From radical addition to oxime ethers*

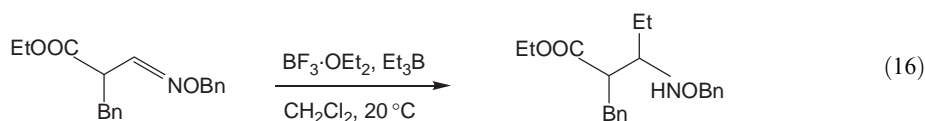
Radical addition to oxime ethers has been applied successfully to the synthesis of a variety of *N*-alkoxyamines. Solid-phase reactions can be induced by traditional radical initiators such as BEt_3 <1999JOC2174, 1998T11431>, BEt_3/O_2 <2001JCS(P1)1290>, $BF_3 \cdot OEt_2$ <1998TL631, 1998T11431>, Bu_3SnH/BEt_3 <1999JOC2174, 1998T11431>, and other organotin initiators <1996JOC8186> or by newer ones such as $ZnEt_2$ in CH_2Cl_2 at low temperature (–78 °C)

<2000OL1443>, $\text{Zn}(\text{OTf})_3$ <1998T11431>, and $\text{Yb}(\text{OTf})_3$ <1998T11431>. The latter publication presents highly efficient solid-phase processes that give *N*-alkoxy- α -amino acids upon cleavage of the resin by TFA in CHCl_3 or CH_2Cl_2 at 20 °C (Scheme 7) <2000OL1443>.



Scheme 7

The synthesis of β -amino acids from sultam derivatives proceeded via radical alkylation using $\text{BF}_3 \cdot \text{OEt}_2 / \text{BEt}_3 / \text{AlkI}$ in CH_2Cl_2 or toluene <1999OL569>. Similar conditions of radical addition to *O*-alkyloximes were applied in other studies <2003OBC381, 1997JCS(P1)2633, 1998TL631>: a typical example is presented in Equation (16).



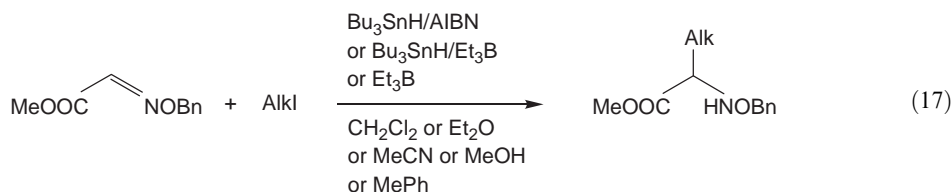
Naito and co-workers <1998T11431> have proposed a mechanism of radical alkylation–reduction by the system $\text{Bu}_3\text{SnH} / \text{AlkI} / \text{BEt}_3 / \text{BF}_3 \cdot \text{OEt}_2$ according to which BF_3 coordinates with nitrogen followed by a radical *C*-alkylation and subsequent reduction by Bu_3SnH . The parent imines with *O*Alk, Tos, Ar, and NAr substituents on the imine nitrogen reacted with alkyl iodide upon initiation by $\text{BEt}_3 / \text{O}_2$ <2001JCS(P1)1290>. The nature of the alkyl substituent on the α -carbon atom influences the reaction time substantially. More data regarding this type of processes can be found in a review <2001T2461>.

(iii) From radical addition–cyclization

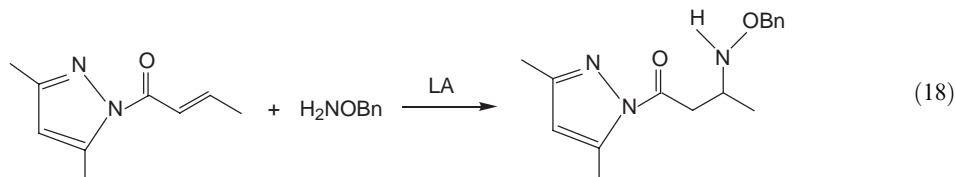
Radical addition–cyclization has been studied using a wide variety of *O*-alkyloximes and was induced most efficiently by $\text{Bu}_3\text{SnH} / \text{BEt}_3$ <1995TA1547, 1999JA5176>, $\text{Bu}_3\text{SnH} / \text{AIBN}$ <2000T5819, 1999JOC2003, 1998JOC9164, 1998T5883, 1998JOC201, 1995JA7289, 1995TL253>, and SmI_2 <1998T5883>. The protocol was successfully applied to the synthesis of ethers derived from sugars such as D-glucose, D-galactose, and D-xylose <2000T5819>. The system $\text{Bu}_3\text{SnH} / \text{AIBN}$ achieved good yields (>70%), even with bulky biologically active molecules <1995JA 7289, 1998JOC9164>. A review of addition of carbon-centered radicals to imines has been published <2001TL5461>.

(iv) By C–N bond formation

C–N bond formation processes can lead to *N*-alkoxy primary amines in several ways. The reaction of 2-hydroxy-2-methoxyacetic acid with hexyloxyamine and alkyl iodide was carried out using Bu_3SnH , BEt_3 and MgSO_4 in CH_2Cl_2 at 25 °C. The process takes place with or without Bu_3SnH , although the presence of this initiator makes the reaction more efficient. This method has been extended to the synthesis of α -amino acid derivatives (Equation (17)) <2000T2413>.



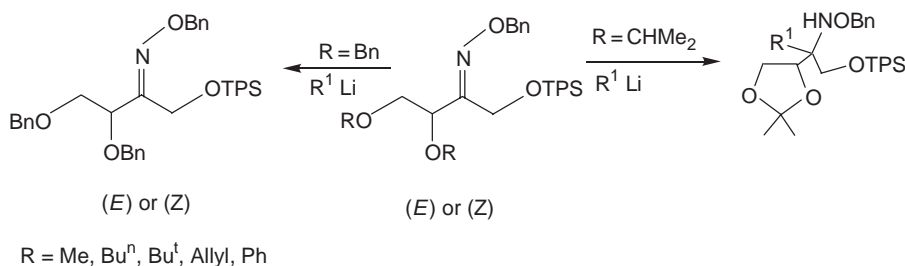
When the reaction of an oxime with Pr^{I} was initiated by triethylborane, the ratio of α -alkylated ($\text{Alk} = \text{Pr}^{\text{I}}$ or Et) amino acid formed depended substantially on solvent and temperature. Diethylzinc was also a radical initiator but of somewhat lower efficiency than BET_3 <2000T2413>. Sibi and co-workers <1998JA6615> have presented the first example of enantioselective addition of *O*-alkylhydroxylamines to alkenes under the action of chiral Lewis acids. The latter components were prepared from *gem*-bisoxazolinecyclopropane and $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$. At -60°C a yield of 60% was achieved in 21 h, whereas at -80°C the same yield was obtained after 72 h. The reaction was highly stereoselective being 96% and 97%, respectively, for the (*R*)-isomer (Equation (18)). At the highest temperature studied, the reaction gave only 59% total yield within 2 h and stereoselectivity was substantially lower (61%). The switch from MgBr_2 to $\text{Y}(\text{OTf})_3$ or $\text{Yb}(\text{OTf})_3$ resulted in a faster process but with a high ratio of the (*S*)-isomer (59% and 41%, respectively).



Chiral rare earth metal phosphate complexes catalyze efficiently the conjugate addition of alkoxyamines to alkenes with good yields (57–81%) and variable stereoselectivity (12–69%) <2002T8321>.

(v) *From addition of organometallic reagents to oxime ethers*

Addition of organometallic reagents to oxime ethers is another method for preparation of alkoxyamines which can efficiently be stereocontrolled. It is achieved by reaction of chiral *O*-alkyloxime ethers with alkyllithium and results in formation of a mixture of (*E*)- and (*Z*)-cyclic or open chain alkoxyamines (Scheme 8) <1997TL1841>. (*E*)-isomers of *O*-alkyloxime ethers react more diastereoselectively than the (*Z*)-isomers. The authors <1997TL1841> explain this effect in terms of different mechanisms for (*E*)- and (*Z*)-isomers. The former proceed via a cyclic complex with lithium coordination to nitrogen and oxygen atoms, whereas the latter may react via a noncyclic transition state.



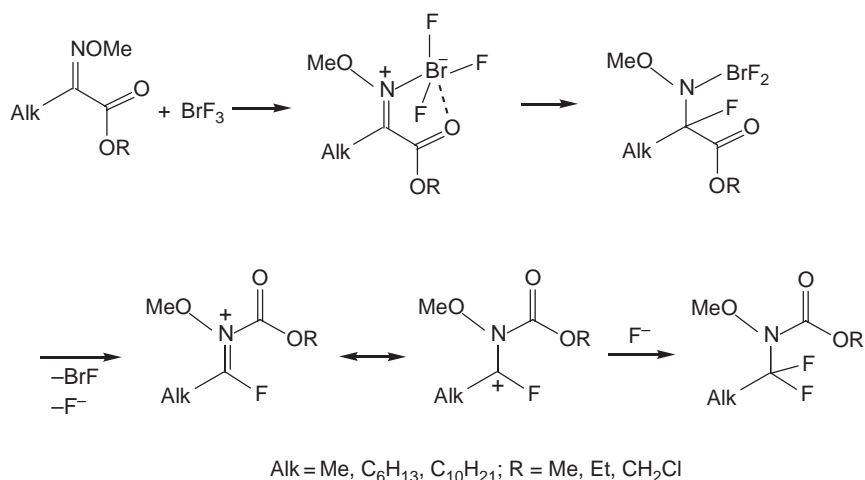
Scheme 8

(vi) *From rearrangement in oxime ethers*

Rearrangement of oxime ethers using bromine trifluoride allowed Rozen and Ben-David <2001JOC496> to synthesize *N*-difluoroalkyl-*N*-alkoxycarbamates in yields of 22–65% (Scheme 9). The reaction took place in CFC_3 at 0°C and was completed in 15 min.

(vii) *Intramolecular cycloaddition of oximes*

Intramolecular cycloaddition of oximes is a highly stereoselective process and takes place selectively with (*Z*)-isomers <2003OBC1122>.



Scheme 9

(viii) Hydrolysis of oxaziridines

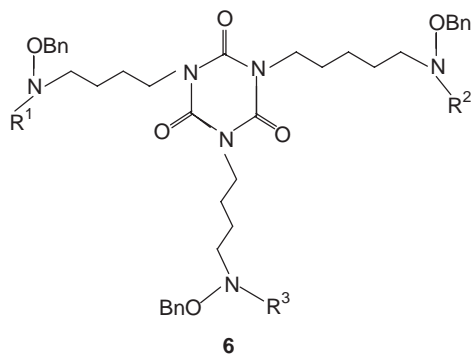
Hydrolysis of oxaziridines in acidic solution is claimed to be a general method for preparation of *N*-alkyl(cycloalkyl, aryl)hydroxylamines <2000DEP10061623>.

2.06.2.3.2 *N*-Alkoxy secondary amines: R¹R²NOR³*(i) From O-alkylation of N,N-dialkylhydroxylamines*

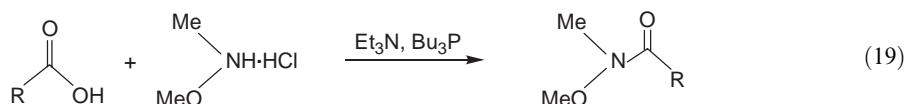
O-Alkylation of *N,N*-disubstituted hydroxylamines has been accomplished in high yield <2001SL688> by reaction of alkanols with *N*-methyl-*N*-hydroxydithiocarbamate using DEAD and PPh₃ in THF. The products were used for tin-free generation of alkoxy radicals. *O*-Alkylation of hydroxylamine under oxidative conditions was carried out in a synthesis of pyridomacrolidin <2003OL2351>.

(ii) From C—N bond formation

The number of publications devoted to this approach to the title compounds is growing rapidly due to its high efficiency not only in the laboratory but also in industrial processes. The traditional reaction of the corresponding secondary amine with alkyl halides is still used for the synthesis of sophisticated compounds such as aminoalkyl-substituted triazinetriones **6** <2003JOC191>.



A simple general method of preparation from carboxylic acids and *N,O*-dimethylhydroxylamine hydrochloride has been described by Banwell and Smith <2001SC2011>. Reaction occurs in dichloromethane in the presence of Et₃N, Bu₃P, and (2-pyridine-*N*-oxide) disulfide at 18 °C to give hydroxamic acid esters in moderate to high yields (Equation (19)).



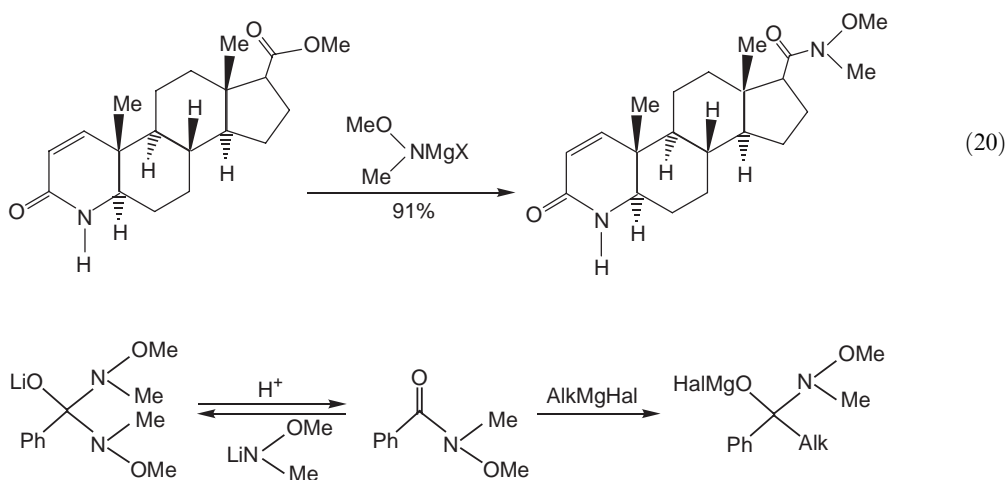
The reaction of *N,O*-dimethylhydroxylamine with acids to form *N*-alkoxyamines can also be carried out using HBTU/DIEA <1998TA1855>, *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate <1995CC1255>, or in a one-pot two-step process via conversion of the acid into an *S*-2-pyridyl thioate followed by reaction with *N,O*-dimethylhydroxylamine hydrochloride under the action of Et₃N <2001MI421>. Hydroxylamine esters upon exposure to carboxylic acid chloroanhydrides in the presence of pyridine give *O*-acylhydroxamic acids that have been used as precursors of di- and tripeptides <2003OL2203, 1997T10433>.

The reaction of *O*-alkylhydroxylamine with pivaloyl chloride followed by *N*-alkylation with methyl iodide in the presence of sodium hydride gives the corresponding *N*-alkoxy secondary amines (60%) <2000OL1345>. A similar procedure with *N*-alkylation involving alkyl halides was used for isoxazolidinone synthesis <1997T10433>.

Cyclic β -amino acid precursors were synthesized by the addition of *N*-alkylhydroxylamines to pyrrolidinone enoates catalyzed by chiral Lewis acids <2000OL3393>.

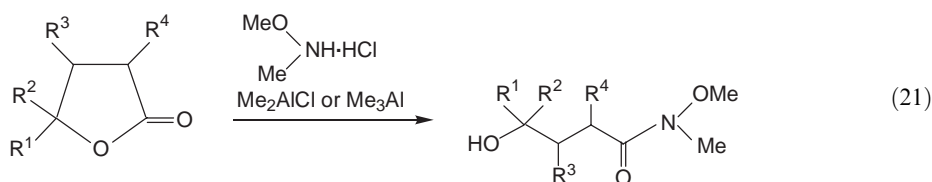
Hydroxamic acid esters were accumulated as intermediates in the synthesis of biologically active compounds. Aminolysis of the carbonyl group carbon atom by *N,O*-dimethylhydroxylamine involved the support from the Weinreb reagent <1997TL5115, 1997TL5119>.

An important commercial approach to *N*-alkoxyamines is direct conversion of esters. A large-scale process was developed for a drug candidate for benign prostatic hyperplasia by a Merck group <1995TL5461>. The ester was treated with ethylmagnesium bromide followed by the addition of *N*-methyl-*N*-methoxyamine hydrochloride in THF at 0 °C which resulted in quick formation of the corresponding amide (91% yield) (Equation(20)). Related studies of *N*-methyl-*N*-methoxyamides with Grignard reagents and with lithium *N*-methoxy-*N*-methylamine resulting in products of nucleophilic addition (Scheme 10) have been described <1995TL5461>.



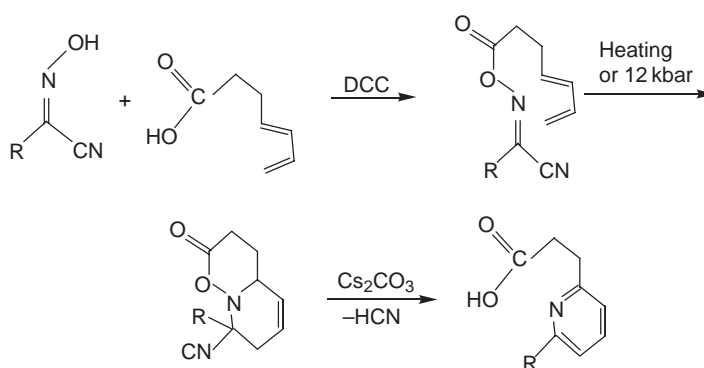
Scheme 10

A similar transformation of an ester into an *N*-methyl-*N*-methoxyamide was achieved using dimethylaluminum chloride <1997TL2685>. Treatment of a mixture of various lactones and *N*-methyl-*N*-methoxyamine hydrochloride with dimethylaluminum chloride or trimethylaluminum resulted in lactone ring opening, followed by aminolysis and formation of *N*-methyl-*N*-methoxy- γ -oxyamides with good to high yields and low recovery of the starting materials (Equation (21)) <1997TL2685>.



(iii) From addition of oximes to alkenes

Intramolecular hetero-Diels–Alder addition of oximes to alkenes gives valuable biologically active compounds or their precursors. The oximes act as dienophiles with reliable regiochemical control <2000OL4007>. Highly polarized oximes react with open chain diene acids and DCC upon heating or under high pressure in toluene. These cycloadducts (35–74%) were subjected to N–O bond scission–decyanation, using caesium carbonate in DMF resulting in the aromatic product (Scheme 11) <2000OL4007>.



Scheme 11

A mixture of butyl-4-hexylketoxime stereoisomers reacted with benzyl acrylate at high temperature in xylene to give an intermolecular cycloadduct in the form of the (Z)-isomer <1999OL681>.

(iv) Intramolecular cyclization of oximes

Intramolecular cyclization of α -iodoacetalketoxime in the presence of *N*-Bu₃SnCl/NaBH₃CN/AIBN in *t*-butanol at elevated temperature gave the *N*-methoxymorpholine derivative <1997TL2745>.

(v) Cycloaddition of hydroxamic acids to dienes

Intramolecular nitroso-Diels–Alder cycloaddition of hydroxamic acid <1995JOC6191> to 2-substituted butadienes is induced by Et₄N⁺IO₄[−] at 0 °C, giving the cycloadducts in 75–80% yield <2000OL1473>.

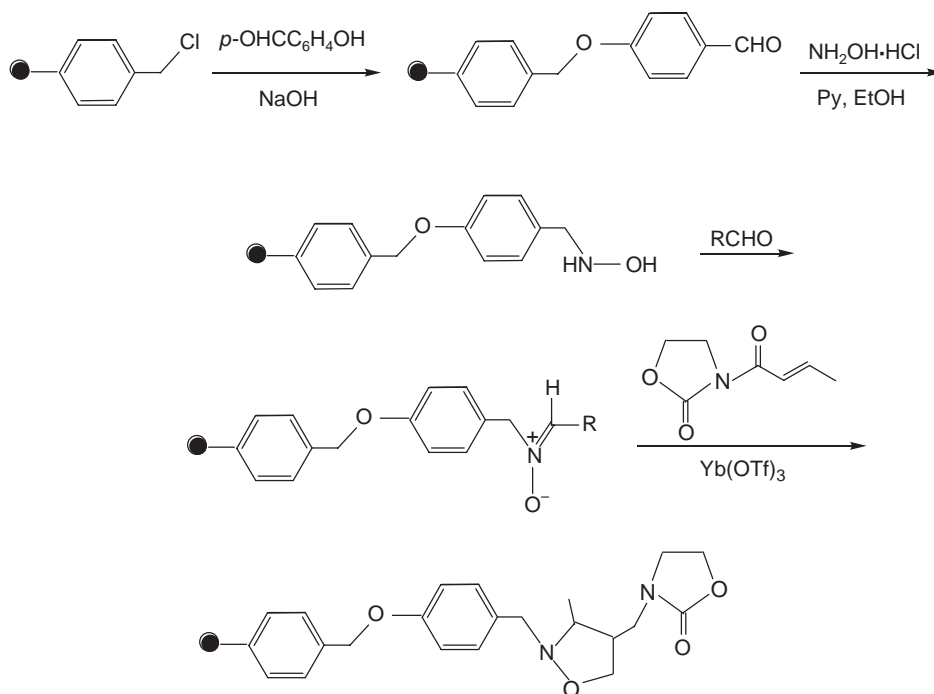
(vi) *O*-Alkylation of nitrones and nitroxides

Nitrone alkylation has been described for substituted pyrroline-*N*-oxides and subsequent reaction with 2,2'-azobisisobutyronitrile proceeded at 80 °C to give α -C- and *O*-alkylation products <2000MM8106>. Anthracene nitroxide is alkylated readily by methyl radicals <2001MI1800>. 2,2,6,6-Tetramethyl-1-piperidinyloxi (TEMPO) <1996JOC1194> has been used as a chemical and biochemical radical detector. The method is based on the reaction of TEMPO with alkyl radicals which gives *N*-alkoxyamines <2003OL2899, 2003JA8655>. The scavenging of protein-based radicals

by TEMPO \cdot was monitored by MS <2003JA8655>. Thermolysis of *N*-alkoxyamines with TEMPO, 2,2,4-trimethyl-2*H*-imidazole-1-oxide (TMIO), etc. generated efficient radical initiators in the synthesis of polyethylene, polybutadiene, polystyrene, and other polymers <2003IEC3662, 2003MM5792>. Termination of such radicals by *O*-alkylation was a key to controlling polymerization. Trapping of nitroxides in the processes of polymerization was studied with ^{15}N -labeled species <2003JOC7322>.

(vii) 1,3-Dipolar addition of nitrones to alkenes

1,3-Dipolar addition of nitrones to alkenes has received increasing attention since the publication of COFGT (1995) <1995COFGT(2)333>. Aspects of this reaction were reviewed by Martin and Jones <B-2002MI001>, Cardona and co-workers <2001EJO2999>, and Gothelf and Jorgensen <2000CC1449>. Grigg and co-workers <1984JCS(P1)41, 1984JCS(P1)47> established the oxime-nitron prototropy. An example of synthesis of nitrones via *N*-alkylhydroxylamines on a solid support is presented in Scheme 12 <1998TL9211>. The nitron condenses with 3-(2-buteneyl)-1,3-oxazoline-2-one, catalyzed by $\text{Yb}(\text{OTf})_3$, leading to polymer-supported isoxazolidine (Scheme 12 <1998TL9211>).



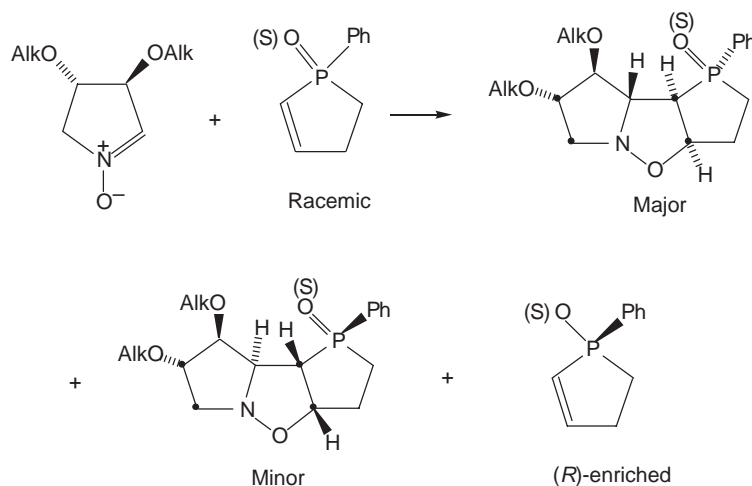
Scheme 12

EPR studies of nitrones and quantum chemical calculations emphasized thermodynamically and kinetically highly favorable addition of radicals to the C-site of the dipole <2003OBC1591, 2001JCS(P2)875, 2001JPC7096>. There is a large number of examples of intramolecular dipolar cycloaddition of nitrones. Among conditions of reaction that play the most important role are temperature <2003T2899>, solvents <2001TL6719, 2000TL9239>, and catalysts. Most reactions were carried out at room temperature or even at -78°C , and only a limited number of processes took place at an elevated temperature. Zhu and co-workers <2003T2899> emphasize much higher regio- and stereoselectivity at lower temperature. The reaction can proceed without a catalyst within several hours <2003T4113, 2003OBC684, 2003T2899, 2003CAR(338)673, 2003OL1475, 1998T5695, 1997TL2299, 1997JCS(P1)1581, 1997T13855, 1997T1787, 1995T8605, 1995T5689, 1995T2979>. Catalysts that have been investigated include Et_3N <1996T14311>, BuOK <1999TL25>, $\text{BF}_3\cdot\text{Et}_2\text{O}$ <2000TL9239, 1996CC2137>, Ipc_2BCl <1998JOC6348>, $\text{Al}(\text{III})$ <2000TL9239, 1999JA3845, 1998T12301>, PhSeBr <1996T6811>, ZnCl_2 <1998EJO2513>, ZnBr_2

<2003OBC2336, 1998JOC2371, 1998TA1759>, ZnI_2 <1999JOC3790>, SnCl_4 <1996T8889>, Cu(II) <1999JOC2353, 1996JOC346>, Ni(II) <1998JA12355>, Ti(II) <2000CC1449, 1997JOC2471, 1996JA59>, Pd(II) <1999JOC5017, 1996TL5947, 1996JA59>, and Yb(III) <1998JA5840>. Chiral Ti(IV) complex catalysis of enantioselective addition of nitron to alkenes depends substantially upon the ligands <2002JA2888>. In some instances Lewis acids do not initiate the reaction <1997T403>. Protection of alkenes can play an important role in stereocontrol of cycloaddition <2002EJO1941, 2000OL2475, 2000T323>.

The problem of alternative coordination of nitrones to alkenes has been discussed. NMR has proved to be the most informative method for elucidating the regio- and stereochemistry of products <2003T2899, 2003CAR(338)673, 2001JCS(P1)3382, 2000EJO3633, 1997JCS(P1)3043>. Models of the cycloaddition process have been investigated using semi-empirical and *ab initio* methods <2002T3667>.

Substituted 1-pyrroline-*N*-oxides reacted under mild conditions with methylenecyclopropane to give regioselective products with high thermal stability <1996TA1659, 1995JOC4743>. This regiospecific nitron cycloaddition and similar processes <2000EJO3633, 1997JOC3119> have been explained in terms of the preferred orientation of alkenes toward nitrones in the transition state <1995JOC6806>. Nitrones reacted with maleic acid ester with less pronounced stereoselectivity <2000EJO3633>. A fruitful approach to 1,3-dipolar cycloaddition of cyclic and acyclic nitrones to highly asymmetric phenyl-2-phospholene oxide and thiooxide was investigated by Brandi and co-workers <1994JOC1315>. The excess racemic mixture of phospholene reacted with enantiopure pyrroline-*N*-oxide to form two diastereomeric tricyclic structures along with phospholene or thiophospholene (*R*)-enantiomer (Scheme 13). The orientation of alkoxy substituent in the nitron determines the positioning of phospholene toward a dipole in the transition state and threefold to 10-fold excess of the former product over the latter.



Scheme 13

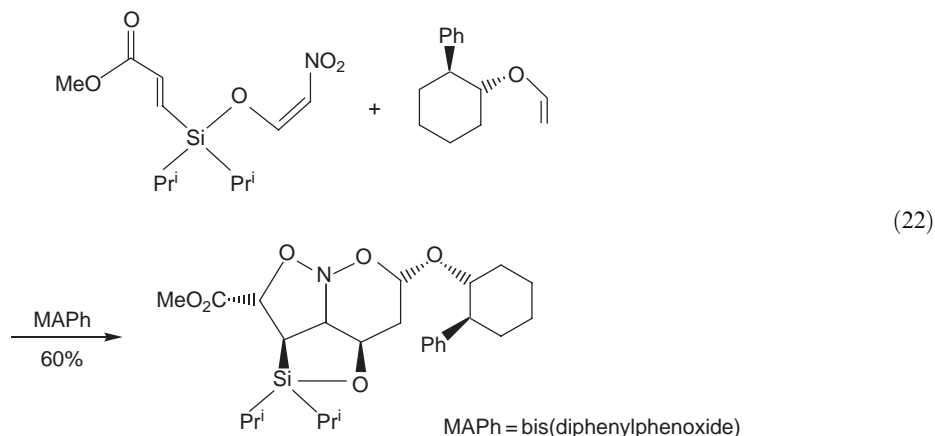
Aggarwal and co-workers <2003OBC684> have studied stereocontrol in intramolecular nitron cycloadditions. Some original approaches to intramolecular nitron cycladdition have been presented <2001CEJ1845, 2001EJO3313, 1995T89, 1995S1171>. A new type of nitron-aldol reaction leading to β -hydroxynitrones that react with methyl acrylate to give cycloadducts has been described <2002CEJ5652>. Other synthetic applications include aminoalkoxypyrrolidinones <1996T7875>, hydroxyindolizidines <2002EJO1941>, aminosaccharides <2003OL1475, 2003CAR(338)673, 2001TL8893, 2001TL7497>, precursors to pyrrolizidine, and indolizidine alkaloids <1999TL2853>.

(viii) Cycloaddition of *N*-oxides to alkenes

Cycloaddition of *N*-oxides to unsaturated sugars in the presence of formaldehyde in ethanol at 50 °C gives the corresponding bicyclic oxazolidine derivative <2003CAR(338)673>.

2.06.2.4 *N,N*-Dialkoxyamines: $\text{RN}(\text{OR}^1)_2$

Denmark and co-workers <1997JOC1668, 1997JA125, 1995JOC3205> have made a valuable addition (Equation (22)) to the synthetic routes to *N,N*-dialkoxyamines reviewed in COFGT (1995) <1995COFGT(2)333>.



2.06.2.4.1 Salts of *O*-substituted *N*-alkylhydroxylamines: $\text{R}^1\text{N}^+\text{H}_2\text{OR}^2$, $\text{R}^1\text{N}^+\text{H}(\text{OR}^2)_2$

No new methods or examples have been reported since the publication of COFGT (1995) <1995COFGT(2)333>.

2.06.2.4.2 *N*-Chloro-*N*-alkoxyamines: $\text{R}^1\text{N}(\text{Cl})\text{OR}^2$

No new methods or examples have been published since the publication of COFGT (1995) <1995COFGT(2)333>.

2.06.2.5 *N*-Sulfonyloxyamines $\text{R}_2^1\text{NOSO}_2\text{R}^2$ and Related Compounds

The title compounds were synthesized by an imino version of the Diels–Alder reaction. The reactions of *O*-tosylated oximes with dienes have been discussed in a review <2001T6099>.

2.06.2.6 *N*-Phosphinyloxyamines: $\text{RNH—O—P}(=\text{O})\text{R}_2$, $\text{R}_2\text{N—O—P}(=\text{O})\text{R}_2$

The methods for preparation of these compounds are reviewed in COFGT (1995) <1995COFGT(2)333> and no new methods have been reported since then.

2.06.2.7 *N*-Siloxyamines: $\text{R}_2\text{NOSiAlk}_3$ and *N,N*-disiloxyamines— $\text{RN}(\text{OSiAlk}_3)_2$

2.06.2.7.1 From addition of siloxy amines to alkenes

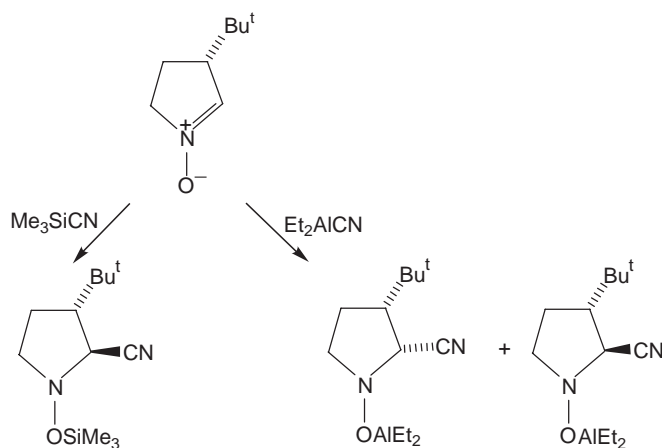
The addition of *N,O*-bis(trimethylsilyl)hydroxylamine to α,β -alkenylmalonic esters proceeds smoothly at -40°C . Hydrolysis removes the *N*-trimethylsilyl protecting group to give *N*-alkyl-*O*-trimethylsilylhydroxylamines (57–75%) <2001JOC8657>.

2.06.2.7.2 From silylation of hydroxylamines

The OH group of *N,N*-dialkylhydroxylamines can be protected by silylation using tributylsilyl chloride in DMF (yield 93%). Some products were deprotected by TBAF in dry THF (yield 65–70%) <1999JOC4>.

2.06.2.7.3 From addition of silanes to nitrones

N-Siloxamines can be synthesized by condensation of nitrones with trimethylsilyl cyanide (TMSCN) <2003TA367> or trimethyl(trifluoromethyl)silane <1999TL25>. The stereoselectivity was high and in favor of the *trans* isomer (*trans*:*cis* > 20:1) (Scheme 14).



Scheme 14

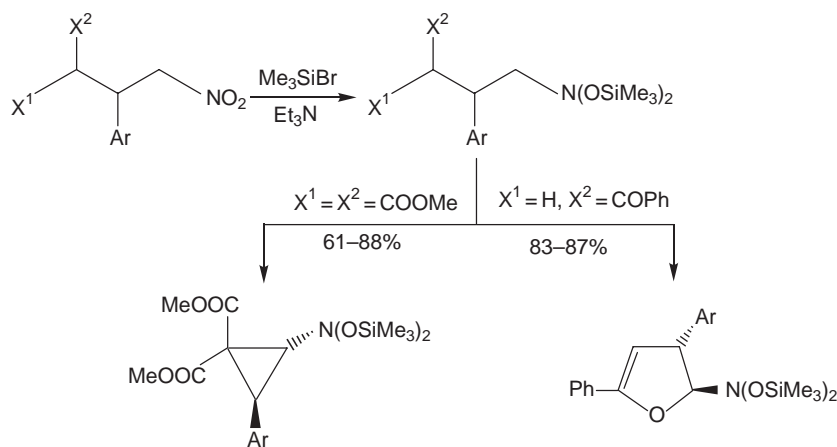
Reaction between acyclic nitrones containing aromatic substituents and TMSCF₃ is initiated by Bu^tOK, proceeds at –78 °C, and gives trifluoromethylated hydroxylamines (yields 54–89%) <1999TL25>. Zinc iodide initiates the silylation of nitrones by chiral ketene silylacetal in THF at –78 °C with yields of 35–63% <2000JCS(P1)3695>.

2.06.2.7.4 From silylation of nitroalkanes

An elegant synthesis of *N*-alkyl-*N,N*-bis(trimethylsiloxy)amines has been described <2000JOC8826, 2000EJO3229, 1999TL5075>. Nitroalkanes react with trimethylsilyl bromide in the presence of TEA at –30 °C. The nature of the substituent on the γ-C influences decisively the reaction pathway as shown in Scheme 15. These products are a source of β-nitrooximes <1999S1767>. Some secondary nitroalkanes under comparable conditions give *N,N*-bis(trimethylsilyloxy)enamines <2002JA11358, 2001JOC3196, 1998S181> and other interesting derivatives <2002HCA3489>.

2.06.2.8 *N*-Aluminumoxyamines: R₂NOAlAlk₂

Unlike highly stereoselective trimethylsilyl cyanide addition to nitrones (Section 2.06.2.7.3), diethylaluminum cyanide did not show stereoselectivity <2003TA367>. Under comparable conditions, addition resulted in formation of *trans* and *cis* isomers or shifted substantially toward *cis* isomers under treatment of the reaction mixture with aqueous sodium bicarbonate (Scheme 14).



Scheme 15

2.06.3 THIOHYDROXYLAMINES AND RELATED FUNCTIONS

2.06.3.1 Thiohydroxylamines: R_2NSH

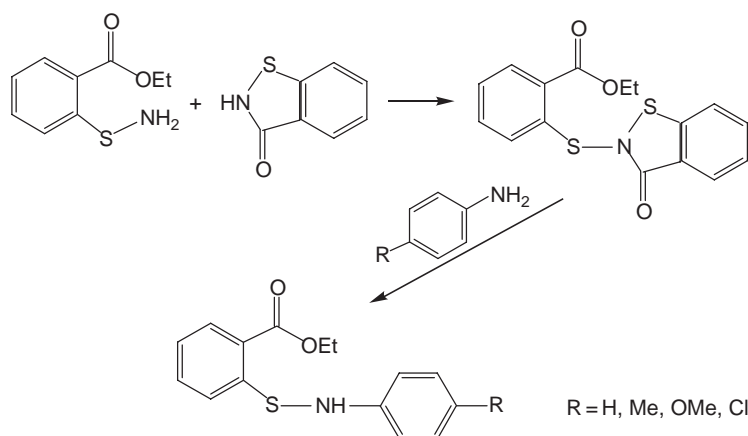
These products are formed by thermolysis of *N,N*-dialkyl-*S*-alkylthioamines <1998JPO407, 1996MI353>.

2.06.3.2 Sulfenamides: R^1NHSR^2 , R_2NSR^2

2.06.3.2.1 Primary sulfenamides: R^1NHSR^2

Methods for primary sulfenamides were reviewed in COFGT (1995) <1995COFGT(2)333> and these remain the most widely used approaches. Recent examples are synthesis of trichloromethylsulfenamides from trichloromethylsulfenyl chloride and arylamines <1997TL487> and application of a novel *m*-terphenyl protecting group, which can stabilize the corresponding sulfenyl iodide but allow it to react with amines and form stabilized sulfenamides <2001TL4875>. Ring substituents influence the rate of aniline substitution at sulfur (Scheme 16) but have little effect upon the generally high yields (63–99%) <2002T3779>.

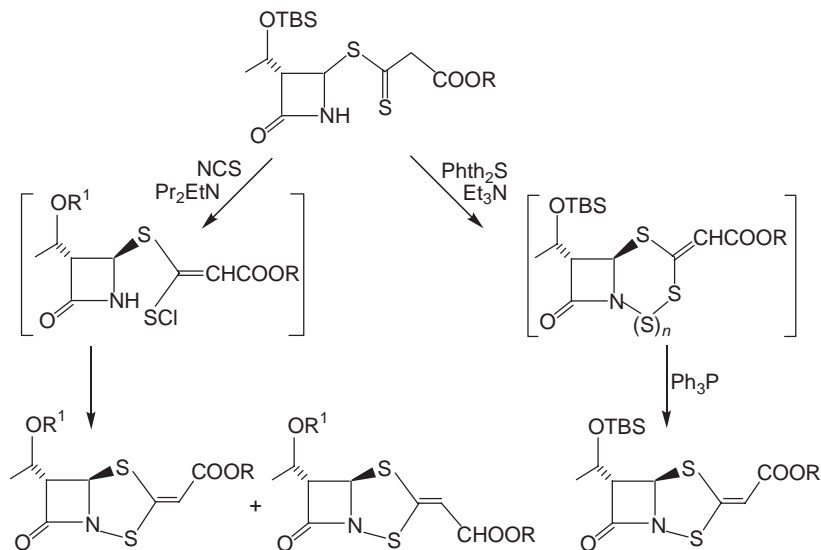
N-*t*-butylbenzenesulfenamide was prepared by the reaction of *t*-butylamine with benzenesulfenyl chloride <2003T6739>.



Scheme 16

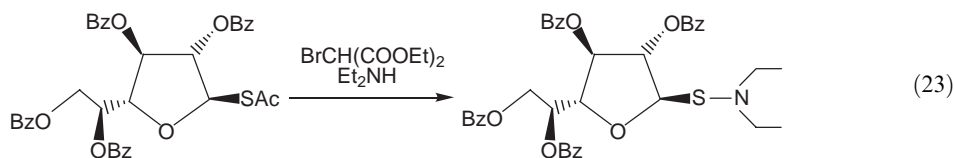
2.06.3.2.2 Secondary sulfenamides: $R_1^1NSR^2$

Beyond the methods presented in COFGT (1995) <1995COFGT(2)333> the formation by reaction of a secondary amino group with either a sulfonyl chloride or alternatively via a polythio cycle is mentioned here (Scheme 17) <1991TL3771>. The former approach results in a mixture of stereoisomers, whereas the latter approach is stereoselective.

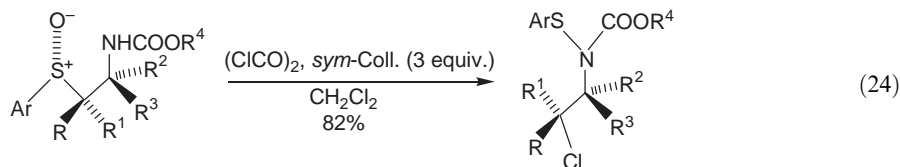


Scheme 17

Aminyl radicals can be formed from sulfenamides, prepared from arylsulfonyl chlorides <1997TL6301>. The competitive interaction between *S*-acetylgalactofuranose, bromomalonate, and diethylamine resulted in the formation of the *N,N*-diethylsulfenamide (72%) (Equation (23)) <2000CAR(328)287>.



Nonoxidative chloro-Pummerer reaction of *N*-alkoxycarbonyl- β -sulfinylamines with oxalyl chloride in the presence of *sym*-collidine proceeded at -50°C to give β -chlorosulfenamides with high diastereoselectivity (Equation (24)) <2001TL3985, 1997TA2811, 1996TL6005, 1995TL7301>. Zanda and co-workers <2001T6511> applied this protocol in the synthesis of a pepstatin analog. Among recent examples is methylation of *N*-acylsulfenamides in the presence of NaH in THF to give the corresponding *N*-methyl-*N*-acylsulfenamides <2003T303>.



2.06.3.2.3 Sulfenamide salts: $R_3^1N^+SR^2$, $R_2^1N-S^+R_2^2$

Methods are reviewed in COFGT (1995) <1995COFGT(2)333> and no new methods have been reported since then.

2.06.3.3 Derivatives of Thiohydroxylamines: $RN(X)SY$

Methods are reviewed in COFGT (1995) <1995COFGT(2)333> and no new methods have been reported since then.

2.06.3.3.1 $RNH-SY$ and R_2N-SY , with $Y = \text{halogen}$

Methods are reviewed in COFGT (1995) <1995COFGT(2)333> and no new methods have been reported since then.

2.06.3.3.2 $RNH-SY$, R_2N-SY

Methods are reviewed in COFGT (1995) <1995COFGT(2)333> and no new methods have been reported since then.

2.06.3.3.3 Disulfenamides: $R^1N(SR^2)_2$

Methods are reviewed in COFGT (1995) <1995COFGT(2)333> and no new methods have been reported since then.

2.06.3.4 Dialkylaminosulfur Trifluorides: R_2NSF_3

The major representative of these compounds is diethylaminosulfur trifluoride (DAST), the synthesis of which is reviewed in COFGT (1995) <1995COFGT(2)333>. Recent examples of DAST <1999CC215> application have been reviewed <1999JOC7048, 1998JCS(P1)1577>.

2.06.3.5 Sulfenamides: $R^1NHS(O)R^2$, $R_2^1NS(O)R^2$, and Derivatives Thereof

Some synthetic aspects of sulfenamides have been presented as a part of a wider review <2003CRV3651>.

2.06.3.5.1 Redox methods

Oxidation of trichloromethylsulfeneamide by MCPBA <1996TL7933> in dichloromethane at 0°C (80–85% yield) <1997TL487> is an example of this well-known approach to sulfenamides. More information is available in COFGT (1995) <1995COFGT(2)333>.

2.06.3.5.2 From substitution at sulfur(IV)

COFGT (1995) <1995COFGT(2)333> gives a full account of this method.

2.06.3.5.3 Other general methods

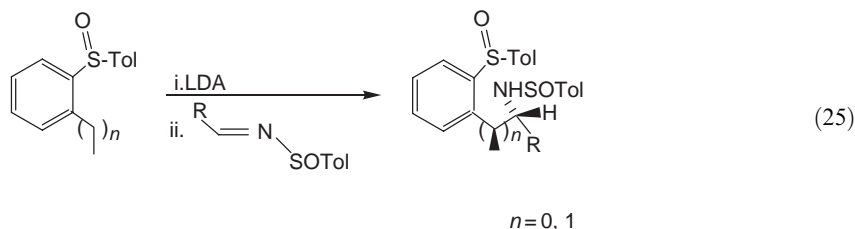
Some additional methods for the preparation of the title compounds can be found in Sections 2.06.3.5.6 and 2.06.3.5.8.

2.06.3.5.4 Derivatives of sulfenamides

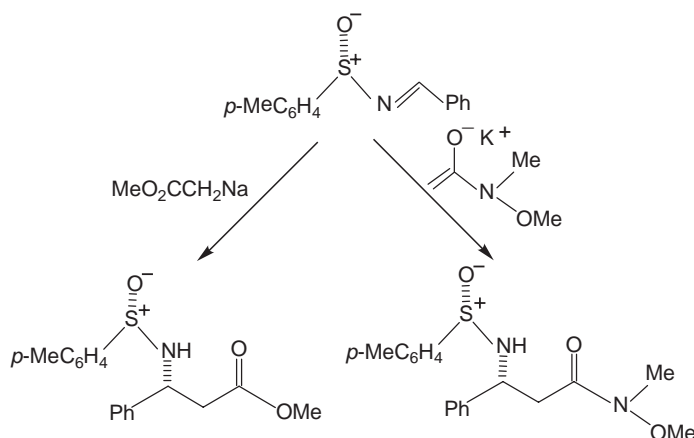
COFGT (1995) <1995COFGT(2)333> gives an up-to-date account of these methods.

2.06.3.5.5 From sulfinimines

Synthesis of sulfinimines and their use in sulfenamide preparation has been reviewed [<1999JOC1278, 1998CSR12>](#). Alkylation of sulfinimides, which was not discussed in COFGT (1995) [<1995COFGT\(2\)333>](#), has become an efficient approach to the title compounds. Ruano and co-workers [<2003OL677>](#) made a significant observation on the stereoselectivity of *N*-sulfinimine benzylation which can be promoted by a sulfinyl group in the *ortho* position. This study revealed that very high stereoselectivity can only take place in the case of identical *S*-configurations of both *N*-sulfinimide and 2-*p*-tolylsulfinyltoluene or 2-*p*-tolylsulfinylethylbenzene ([Equation \(25\)](#)).



Bis- β -amino acids have been synthesized by the addition of the sodium enolate of methyl acetate to a bisulfinimine in THF at -78°C [<1998TA3919>](#). Another synthetic approach involves the addition of methyl acetate [<1995JOC7037>](#) or *N*-alkyl-*N*-alkoxyacetamide [<2003OL925>](#) to sulfinimines ([Scheme 18](#)) with high stereoselectivity.



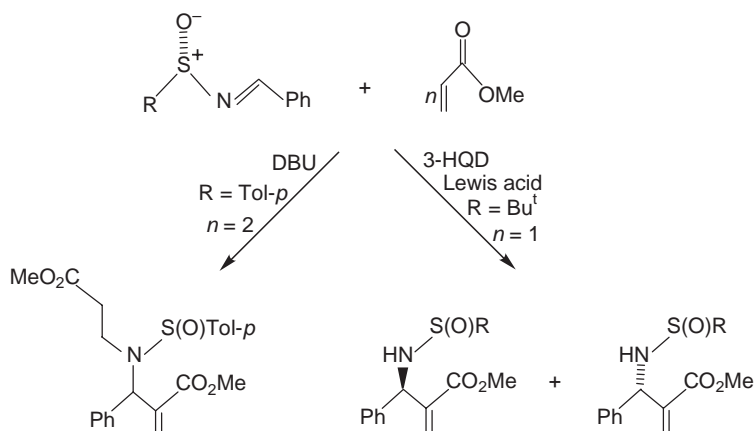
Scheme 18

Enantiomerically pure *N*-sulfinimines were alkylated, in accordance with the Baylis–Hillman reaction, by methyl acrylate [<2002TL1577>](#). This slow reaction proceeded at room temperature in seven days under the catalysis of 3-hydroxyquinuclidine (3-HQD) and various Lewis acids ([Scheme 19](#)) to give the products in moderate to good yield. A similar reaction using DBU resulted in double addition of methyl acrylate to sulfinimine and formation of the adduct as a diastereomeric mixture ([Scheme 19](#)) [<2002TL1577>](#).

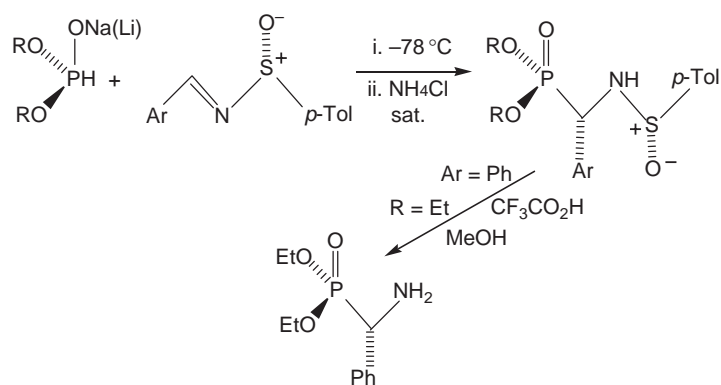
2.06.3.5.6 From phosphorylation of sulfinimines

Lefebvre and Evans [<1997JOC7532>](#) described phosphorylation of enantiopure sulfinimines by lithium or sodium dialkylphosphites in THF at -78°C . This achieved very high diastereoselectivity and total yield ([Scheme 20](#)).

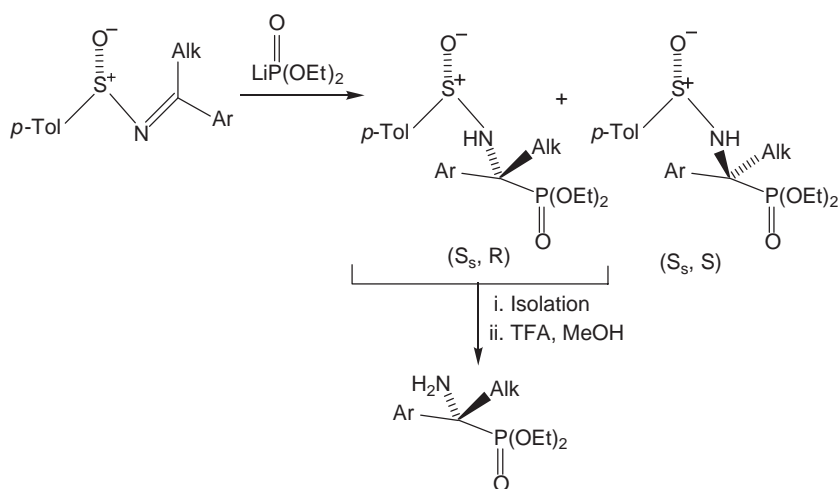
Another diastereoselective phosphorylation of enantiopure sulfinimines has been described by Davis and co-workers [<2001OL1757>](#). This is the first example of an asymmetric synthesis of α -alkyl- α -amino(aryl)methylphosphonate derivatives (71–97%) ([Scheme 21](#)).



Scheme 19



Scheme 20



Scheme 21

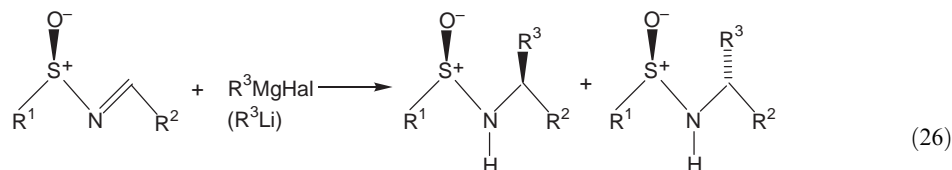
Halomethyl phosphonates and sulfinimides produce α-chloro-β-phosphonosulfonamides as a mixture of stereoisomers [<2003JOC6894, 2003JOC2410>](#). Under the action of a base the same reagents give a mixture of stereoisomeric phosphonosulfonamides in the form of aziridines [<2003JOC6894, 2003JOC2410>](#).

2.06.3.5.7 From hydrocyanation with dialkylaluminum nitriles

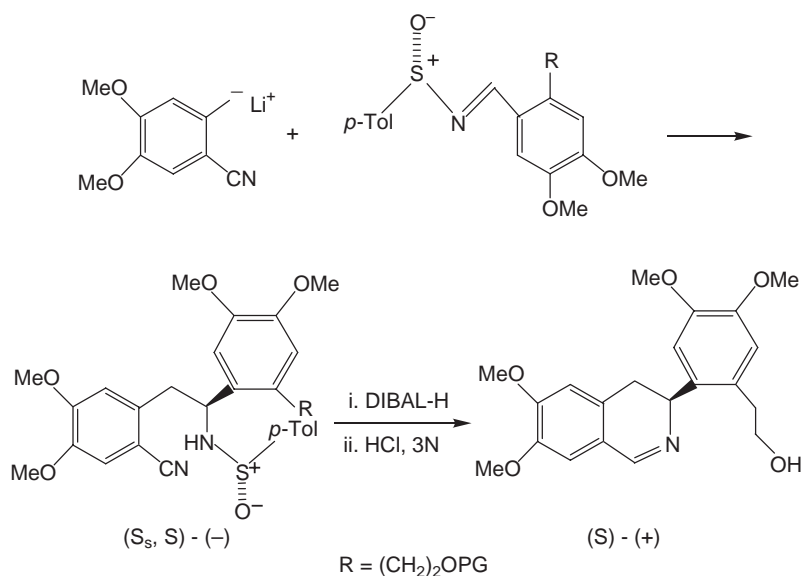
Davis and co-workers [<2002JOC7802>](#) synthesized *N*-sulfinylamino nitriles in yield of 70–80% by the reaction of sulfinimines with dialkylaluminum nitrile and isopropanol.

2.06.3.5.8 From reactions with Grignard and alkyllithium reagents

Grignard reagents have proved to be efficient reagents for preparing alkylsulfinimides (Equation (26)). In most cases the process is highly diastereoselective [<1999T8883, 1999JOC3396, 1999JOC12, 1998JA8011, 1997JA9913, 1997TA591>](#).

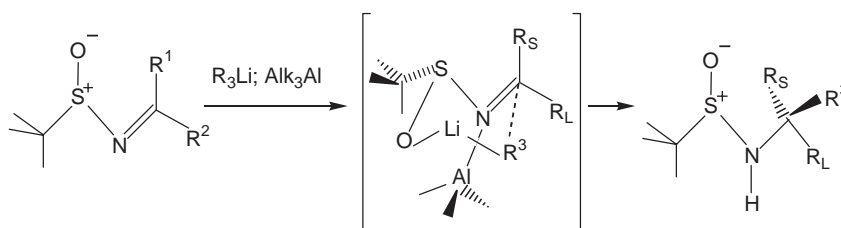


Similar results with lower diastereoselectivity were achieved using alkyllithium reagents [<1999T8883, 1999JOC12>](#) (26). Grignard reagents have induced transformation of bulky sulfinimides into sulfonamides [<2003TA2827>](#). Synthesis of *N*-sulfinylaziridines has been discussed [<2002T7135, 1997TL5139>](#). Ellman and co-workers have studied stereoselective approaches to and transformations of sulfinamides [<2003JCO590>](#) and β -oxysulfinamides [<2003JA11276, 2002JA6518>](#). In the former case the process was carried out under the action of Grignard reagents followed by resin capture of the products. In the latter case the product structure (*syn* or *anti*) was dependent upon the reducing agent (catecholborane or LiBHET_3) and reaction conditions. Condensation of furyllithium with sulfinimines has been carried out in toluene at -78°C in the presence of AlMe_3 [<2001TL1433>](#). Alkyl addition to sulfinimines is also accomplished with lithium, sodium, or titanium enolates [<1999JOC12>](#). The limitations of Bischler–Napieralski and Pictet–Gams reactions [<B-1998MI121>](#) can be overcome by an approach worked out by Davis and Mohanty [<2002JOC1290>](#). These authors carried out the synthesis of tricyclic molecules of specific natural alkaloids *xylopinine* and other cyclic systems [<2000OL3901>](#) via the step of sulfinimide alkylation with alkyllithium (Scheme 22).



Scheme 22

Cogan and Ellman <1999JA268> studied 1,2-addition of organometallic reagents to *t*-butyl-sulfinilimines targeting sulfinamides with α,α -dibranched amines. Sulfinimines react with phenylmagnesium bromide in dichloromethane at -48°C in very low yield, whereas the process with phenyllithium in toluene gave 65% of the product with (*R_s*,*R*) to (*R_s*,*S*) ratio 94:6. The dominating diastereomers in the former and latter cases were opposite. Even higher yields were achieved in the reaction of sulfinimines with a mixture alkyl(aryl)lithium/trialkylaluminum (61–100%) (Scheme 23). The authors <1999JA268> concluded that sulfinimine alkylation took place not via alkyl transfer from the *N*-aluminate complex but from alkylolithium–sulfinimine six-membered cyclic intermediate activated by *N*-aluminate complex. High stereoselectivity of the process is explained in terms of kinetic factors.

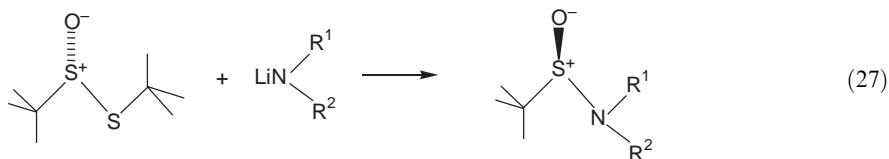


Scheme 23

Barrow and co-workers <2001TL2051> determined that similar processes involving Grignard reagents or alkylolithium were highly dependent on reaction conditions. For example, in THF and dichloromethane solution diastereoselectivities were opposite. This effect is explained by the formation of a different reaction intermediate than the one presented by Ellman (Scheme 23).

2.06.3.5.9 From thiosulfate ester

Lithium amides react efficiently with thiosulfate esters in THF in the presence of piperidine and, according to Ellman and co-workers <1998JA8011>, the corresponding sulfinamides are the products of inversion at sulfur. The yields are 89–98%, with the rate of racemization less than 0.1% (Equation (27)). It is noteworthy that lithium bis(trimethylsilyl)amide does not react with thiosulfate esters <1998JA8011>.



2.06.3.6 Sulfonamides: $\text{R}^1\text{NHSO}_2\text{R}^2$, $\text{R}_2\text{NSO}_2\text{R}^2$

Studies of sulfonamide synthesis and applications during the 1990s can be found in a number of reviews and original publications <2003CRV3651, 2003CRV811, 2001T7575, 2001JCS(P1)1729, 2001T7053, 2001T6651, 2000JA12055, 2000T5259, 1999T1, 1998T10927, 1998TA1883>. Biochemical aspects have been discussed <2003T7047, 2003TL5715, 2003TL4195, 2003BMC3301, 2003BMC2191, 2003MI216, 2000JMC41, 1998JCS(P1)2959, 1997CRV787>. In many cases the SO_2R fragment is used as an amine protecting group in a multistep synthesis and is removed in a due course <2003TL4523, 2003OL2319, 2003OL1225, 2000EJO1443, 1998JA1218, 1997T14355, 1996T13035, 1995JA11839>. Sometimes sulfonamides are formed as a result of amine deprotection <2003TL6099>. The major synthetic methods for sulfonamides are well documented in COFGT (1995) <1995COFGT(2)333> and only new methods or original modifications of known ones are reviewed here. In the 1990s the sulfonamide group has widely been used either as the end group <1998JA2690, 1998AG(E)3109, 1997TL4965, 1997TL3373> or as an anchor <2003TL4153, 2003OL105, 2001T6399, 1996TL1145> in the solid-phase synthesis of amines,

peptides, oligonucleotides, oligosaccharides, and other biologically active compounds. Efficiency of the *o*-nitrobenzylsulfonyl protecting group was shown to be comparable to that of the Fmoc group in solid-phase alkylation of secondary amines <1998JA2690, 1995TL6373>.

2.06.3.6.1 From reaction at sulfur(VI)

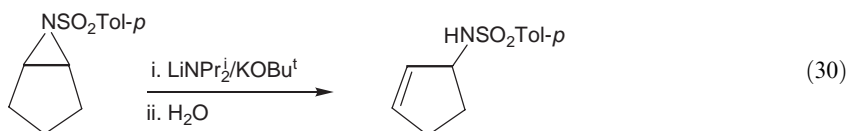
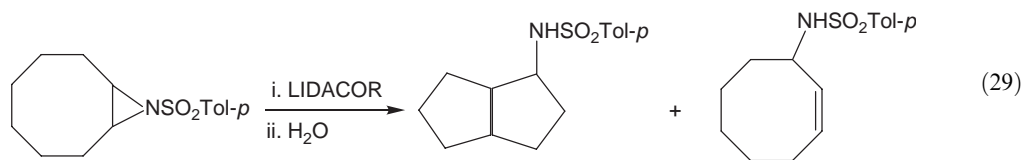
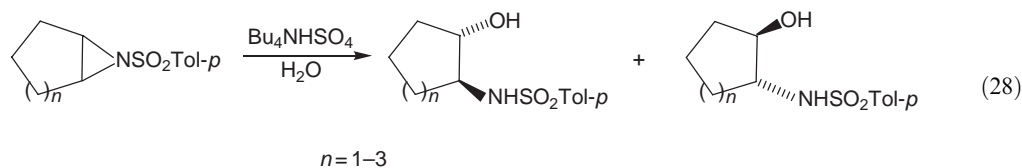
Reaction of sulfonyl chlorides with amines remains the method of choice for many studies. This well-known method was used as the last step of an original general total synthesis of sulfonamides starting with aliphatic or aromatic halides. Following halogen substitution by the trialkylsilylthio group catalyzed by $(\text{Ph}_3\text{P})_4\text{Pd}$, oxidation with $\text{KNO}_3/\text{SO}_2\text{Cl}_2$ gave the corresponding sulfenyl chlorides that reacted with a wide variety of amines including mono- and dialkylamines, morpholine, and piperazine <2003TL7821>. 1,3-Bis[(hydroxymethyl)amino]propan-2-ol reacts with excess phenylsulfonyl chloride to give γ -disulfonamides (73–85%) <2003TL7225>.

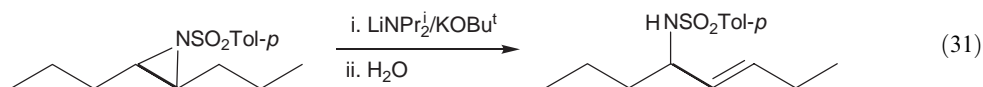
2.06.3.6.2 Other general methods

Arylation of *N*-alkylsulfonamides (54–90%) with iodo- or bromobenzene can be achieved using microwave irradiation and CuI catalysis <2003TL3385>.

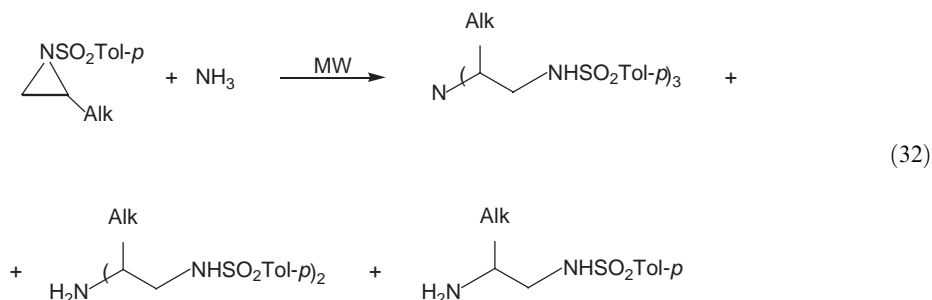
2.06.3.6.3 From *N*-sulfonylaziridines and other ring-opening reactions

A new method for monosubstituted sulfonamides is based on ring opening of *N*-sulfonylaziridines. Methods of synthesis of *N*-sulfonylaziridines have been described <2002T7153, 2002EJO3179, 2000TL7041, 2000TL7089, 1999T6387, 1998TL4715>. The nature and structure of products are determined by the reaction conditions. *N*-Tosylaziridines derived from cycloalkenes are hydrolyzed under the action of tetrabutylammonium bisulfate at 45–60 °C into stereoisomeric *trans*-2-(*N*-tosylamino)cycloalkanols in high yield (96–98%) (Equation (28)) <2003OBC1565>. The tetrabutylammonium bisulfate solution (10%) can be reused without decrease of the yield. Under superbasic conditions ($\text{LiBu}/\text{KOBU}^t$ or $\text{LiNP}^i_2/\text{KOBU}^t$) the hydrolysis of cyclooctene *N*-tosylaziridine proceeded either to formation of bicyclic sulfonamide (in pentane, 64%) or to a mixture of bicyclic sulfonamide and cyclooctene sulfonamide (in THF) with the corresponding ratio 80:20 at –20 °C and 45:55 at –50 °C (Equation (29)) <2002T7153>. Such superbasic conditions promoted the regio- and stereoselective prototropic process in the course of various *N*-tosylaziridine ring openings (Equations (30) and (31)) <2002T7153>.





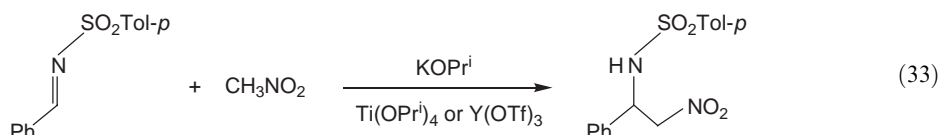
Butyllithium/(–)-sparteine system is also efficient for sulfamide aziridine opening [<2003TL6613>](#). 2-Alkyl-*N*-tosylaziridines react either with ammonia in methanol (Alk = Me) to give tris-(*N*-tosyl-*iso*-propyl)amine (70%) [<2002EJO3179, 1997TA2655>](#) or with ammonia and microwave irradiation (Alk = Prⁱ) to give a mixture of products (Equation (32)) [<2002EJO3179>](#).



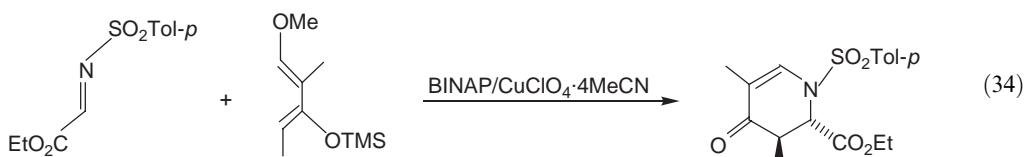
More examples of *N*-sulfonylaziridine ring opening by nucleophiles have been published [<2001TL1037, 2000OL4107>](#). Some alkaloids have been synthesized via rearrangement of *N*-tosylaziridine alcohols catalyzed by zinc bromide [<2003OL2319>](#). β -Aminoethylation of ketones and nitriles with *N*-tosylaziridines gave the corresponding products with yields varying from 24% to 91% [<2000EJO3337>](#). The majority of these processes are characterized by high regio- and stereocontrol. The organic fragments (Me or Ph) of Grignard reagents can play a decisive role in determining stereostructure of *N*-tosylaziridine ring-opening products [<2001HCA662>](#). 4-Unsubstituted *N*-alkyl- β -sultams react with methyl lithium or methylmagnesium bromide to give the corresponding vinylsulfonamides. Methyl lithium induces the formation of the (*E*)-isomers in high yield [<1998T5507>](#). *N*-Tosyl- and *N*-phenylsulfonylimidazolines can also be a source of mono-substituted sulfonamides using 40% HBr or 30% HCl [<1997JOC1799>](#). Some substituted *N*-tosylaziridines can be opened efficiently using magnesium in methanol [<1998JOC10006>](#). Alkene insertion into iodomethyl-*N*-tosylaziridine with the formation of iodomethyl-*N*-tosylpyrrolidine has been reported [<2001AC\(E\)3865>](#). Other examples of *N*-phenylsulfonylaziridines as a source of sulfonamides have been reported [<2003TL2677, 2001T6955, 2000BMCL2001>](#).

2.06.3.6.4 From sulfonylmines

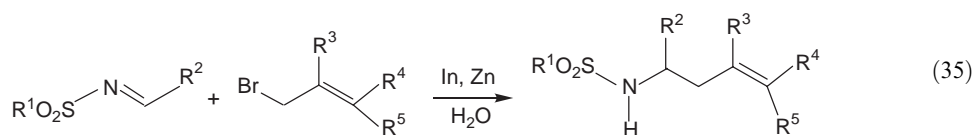
Sulfonylmines are good starting materials for the synthesis of various sulfonamides. Direct alkylation of *N*-sulfonylmines by alkyl iodides using zinc in the presence of water [<2000CC2059>](#), Et₃B in hexane/methylene chloride [<2000CC2059>](#), or Et₂Zn in toluene (without catalyst, or catalyzed by Cu(OTf)₂ which improves dramatically the stereoselectivity of the process) [<2000JA12055>](#) has been used efficiently to produce the corresponding arylsulfonamides. Nitromethylation (nitro-Mannich reaction) of *N*-tosylsulfonylmine has been carried out at room temperature under basic conditions and with Ti(OPrⁱ)₄ or Y(OTf)₃ (Equation (33)) [<2001TL4673>](#).



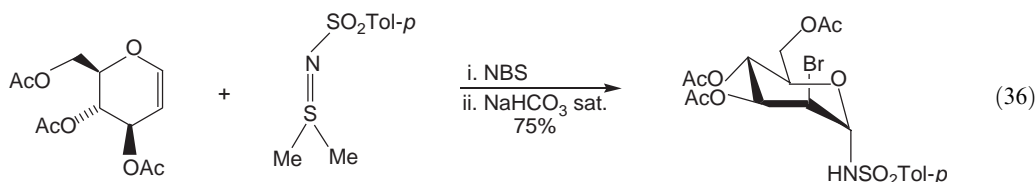
Lewis acids also catalyze cycloaddition of dienes to sulfonylmines. A wide variety of catalysts and pairs of coupling reagents giving products in low to good yields and poor to high stereoselectivity have been investigated [<1998AC\(E\)3121, 1997TA2619>](#). The highest enantioselectivity was achieved for *N*-tosylcarbonylmines and Danishefsky's diene initiated by complex catalysts including BINAP/CuClO₄·4MeCN, which favored *ee* stereoselectivity (Equation (34)) [<1998AC\(E\)3121>](#). The process was also carried out with solid supported chiral BINAP [<2000CEJ2435>](#).



Lithiated furan adds efficiently to sulfonimides in the presence of AlMe_3 <2001TL1433> or zinc chloride <2003T4939>. Benzaldehyde sulfonimides react with crotyl-, cinnamyl-, and γ -dimethylallyl bromides in water or water–THF solution with formation of unsaturated sulfonamides. Regioselectivity of the process was very high resulting in γ -allylation with no α -allylation observed. In water the *anti* isomers dominated, whereas in H_2O –THF *syn* forms prevailed (Equation (35)) <2001JOC3467, 2000JOC8589>. Efficient stereoselective crotylation of sulfonylimines can be achieved by the reaction of substituted *N*-tolylimines with (*E*)-crotylsilane catalyzed by a Lewis acid (TiCl_4 , SnCl_4 , $\text{BF}_3\cdot\text{OEt}_2$, and TMSOTf) <2000T10263>. Silylated sulfonamides have been synthesized (93%) by hydrosilylation of *N*-phenylarylsulfonimides in toluene under the action of $\text{B}(\text{C}_6\text{F}_5)_3$ <2000OL3921>.

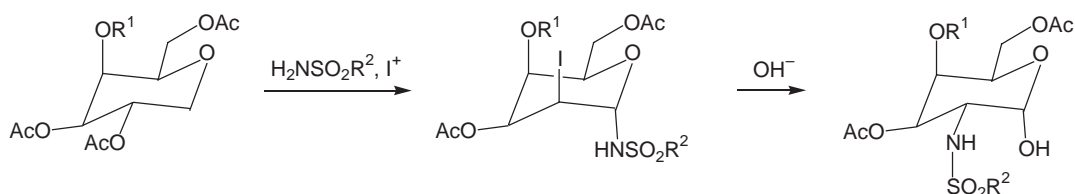


Stereoselective synthesis of brominated *N*-tosylaminosaccharides has been carried out by the reaction of triacetyl-D-glucal with dimethyl-*N*-tosylsulfonimine and NBS in methylene chloride at -15°C (Equation (36)) <2001SL851>.



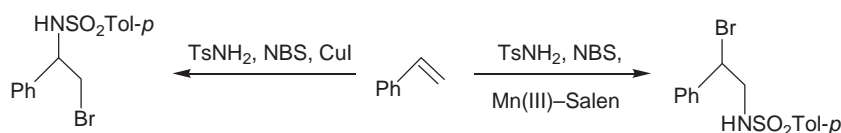
2.06.3.6.5 Other specific methods

N-Methylphenylsulfonamide is a product of hydrolysis of *N*-methyl-*S*-(1-nitroethyl)-*S*-phenylsulfoximine <2002JOC2859>. An original approach to a variety of secondary amines includes aminolysis of 2,4-dinitrobenzenesulfonyl chloride under mild basic conditions followed by *N*-alkylation using alcohol/ Ph_3P /DEAD or alcohol/ K_2CO_3 /DMF. Quick deprotection in *n*-propylamine and methylene chloride at 23°C gives the corresponding disubstituted amine <1997TL5831>. Synthesis of di- and trisaccharides involving the sulfonamidoglycosidation of an acylated carbohydrate as proposed by Ritzeler and co-workers <1997T1665> and Danishefsky and Roberge <1995PAC1647> has been applied fruitfully. This process is accompanied by iodination (iodinium-di-*sym*-collidine perchlorate) (Scheme 24).



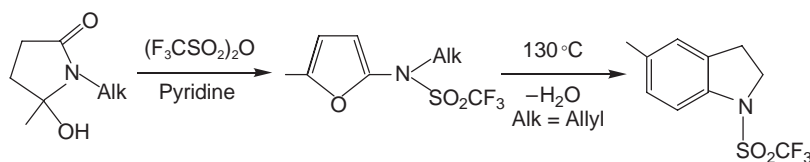
Scheme 24

A new method of alkene aminohalogenation is based on the reaction of alkenes with tosylamine and *N*-bromosuccinimide catalyzed by Cu(I), Cu(II), Mn(II), Mn(III), V(V), Fe(III), or Ni(II). Under similar conditions, styrene can form different sulfenylamido bromides using the catalysis of copper iodide or Mn(III)–salen (Scheme 25) <2003OL861>.



Scheme 25

Both mono- and dialkyltosylamides are formed in the reaction of methylenecyclopropenes with tosylamine initiated by $\text{Pd(PPh)}_4/\text{Pd(OAc)}_2$ in the presence of triphenylphosphine <2003OL1225>. The aminolysis–methylenecyclopropane ring-opening process is highly efficient (yields 62–100%). Catalytic amidation of acyclic and cyclic alkanes including *t*-alkanes by $\text{PhI=NSO}_2\text{Tol-}p$ catalyzed by ruthenium cyclic amines or bipyridine complexes gave the corresponding products with yields 81–93% <2000JOC7858>. Sulfonyltriazoles have been synthesized from sulfonyl azides and carboxyalkenes <2000JFC(104)195>. Triflic anhydride reacts with 5-hydroxy-5-alkylpyrrolidinones and pyridine to form *N*-alkyltrifluoromethylsulfonamidofurans (79% yield) <2003OL189>. Upon thermal dehydration at 130 °C, the *N*-allyl derivative is transformed into indoline (Scheme 26).



Scheme 26

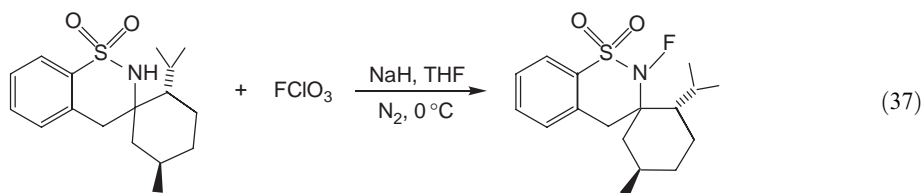
Various sultam derivatives have been investigated <2003OBC381, 1997TA2619> and the synthesis of macrocycles incorporating sulfonamide groups has been described <2003OBC2357>. Stereoselective self-coupling of benzotriazolylalkylsulfenamides with benzotriazole group elimination catalyzed by SmI_2 resulted in the formation of bissulfonamides $[\text{CH(Ar)NHS(O)}_2\text{C}_6\text{H}_4\text{Me-}p]_2$ (62–76%) <2003T8257>. Chiral rhodium (II, II) dimer complexes catalyze enantioselective intramolecular aziridination of *S*-arylsulfonamides in the presence of PhIO or PhI(OAc)_2 as oxidizing agents <2003TL5917>.

2.06.3.7 Sulfonamide Salts: $\text{R}^1\text{SO}_2\text{N}^+\text{R}_3^-$

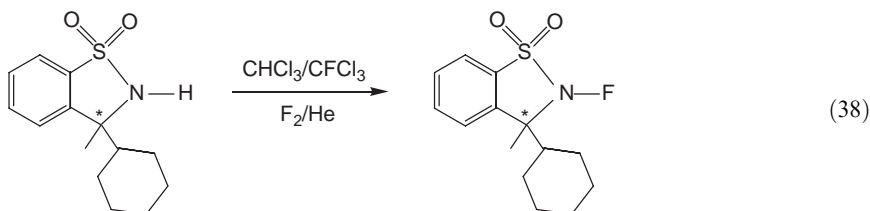
No developments have occurred since this topic was reviewed in COFGT (1995) <1995COFGT(2)333>.

2.06.3.8 *N*-Substituted Sulfonamides: $\text{R}^1\text{N(X)SO}_2\text{R}^2$

In the 1990s a number of novel and efficient electrophilic fluorinating agents based on *N*-fluorosulfonamides have been synthesized <2000JOC7583, 2000JFC(102)135, 1999JOC5708, 1998TL6135, 1998JOC2273, 1995JOC4730>. Takeuchi and co-workers <2000JOC7583, 1999JOC5708> have described several methods of sulfonamide fluorination. A tricyclic sulfonamide was fluorinated by perchloryl fluoride (FClO_3) under the action of NaH in THF (Equation (37)). The corresponding *N*-fluorosultams were diastereomerically pure products (44–81%).



Another approach to *N*-fluorosulfonamides has been achieved by fluorination of the corresponding sulfonamide with 15% F_2/He in the presence of potassium fluoride to scavenge hydrogen fluoride (Equation (38)) <1999JOC5708>.

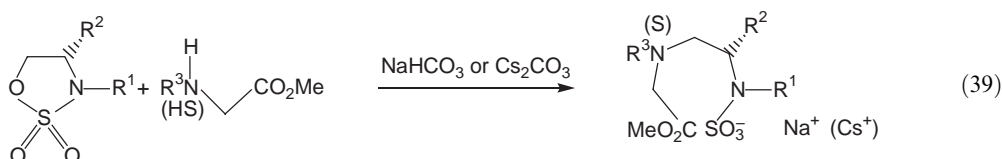


2.06.3.9 Sulfamic Acid and Derivatives Thereof: $R^1NHSO_3R^2$, $R^1NSO_3R^2$

The general synthetic methods used for the preparation of sulfamic acids were reviewed in COFGT (1995) <1995COFGT(2)333>.

2.06.3.9.1 Sulfamic acids: R^1NSO_3H

Ring opening of cyclic sulfamidates by acylamines or thiols results in the formation of sulfamic acid salts (Equation (39)) <2003OL811>. This process has been used in a synthesis of thiomorpholine and piperazine derivatives. Antibacterial agents <2000T5571> and oligosaccharide derivatives <2003OBC2253> are among recently described biologically active compounds containing sulfamic acids.



2.06.3.9.2 Sulfamate esters: $R^1NHSO_3R^2$, $R^1NSO_3R^2$

Cyclic derivatives of sulfamate esters have been reviewed recently by Melendez and Lubell <2003T2581>.

2.06.3.9.3 *N,N'*-Bisalkyl sulfamides: $R^1NHSO_2NHR^2$, $R^1NSO_2NR^2$

A recent example of the preparation of the title compounds <2003OL15> involves reaction of benzylalcohol with $ClSO_2NCO$ followed by amination with an amino ester in the presence of Et_3N . The product was anchored to a solid support.

2.06.3.9.4 Sulfamoyl halides: $R^1R^2NSO_2X$

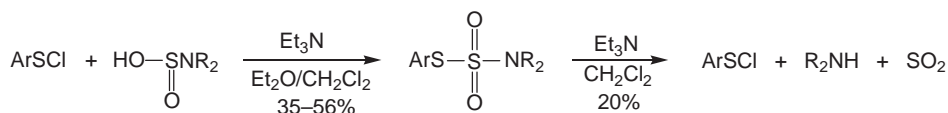
The synthetic approaches to sulfamoyl halides were reviewed in COFGT (1995) <1995COFGT(2)333>.

2.06.3.9.5 Other derivatives of sulfamic acids

These were reviewed in COFGT (1995) <1995COFGT(2)333>.

2.06.3.9.6 *N,N*-Dialkylthiosulfonamides: $R_2^1NSO_2SR^2$

Recently, Zik and co-workers <2000IZV1484> studied the synthesis of *N,N*-dialkylthiosulfonamides using the reaction of sulfenyl chlorides with *N,N*-dialkylsulfonic acids in the presence of Et_3N at $-20^\circ C$ to $-30^\circ C$ (Scheme 27). *N,N*-dialkylsulfonic acids also formed.



Scheme 27

2.06.4 SELENIUM AND TELLURIUM ANALOGS OF THIOHYDROXYLAMINES AND THEIR DERIVATIVES

2.06.4.1 Selenenamides: $R_2^1NSeR^2$

Peptide-substituted isoselenazolidines have been synthesized by oxidative cyclization of γ -amino-selenols using Bu^tOOH <1991BMC277>. Upon exposure to air, the products were transformed into aminodiselenides.

2.06.4.2 Aminoselenium(IV) Derivatives: R_2NSe^{IV}

The synthetic approaches to aminoselenium(IV) derivatives were reviewed in COFGT (1995) <1995COFGT(2)333>.

2.06.4.3 Seleninamides and Derivatives: $R_2^1NSe(O)R^2$

The synthetic approaches to seleninamides were reviewed in COFGT (1995) <1995COFGT(2)333>.

2.06.4.4 Selenonamides and Derivatives: $R_2^1NSeO_2R^2$

The synthetic approaches to selenonamides were reviewed in COFGT (1995) <1995COFGT(2)333>.

2.06.4.5 Tellureneamides and Derivatives: $R_2^1NTeR^2$

The N—Te bond was formed intramolecularly using NCS under oxidative conditions at $0^\circ C$ in methylene chloride and methanol followed by treatment with saturated aqueous $NaHCO_3$ <2003JA4918>. Another approach to tellureneamides is aminolysis of $Ph_2P(NSiMe_3)_2-Te(Cl)NPPH_2NSiMe_3 \cdot 0.50.5C_7H_8$ by $RNHLi$ in toluene at $-78^\circ C$ <1996IC9>.

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2.07

Alkylnitrogen Compounds: Compounds with N—N, N—P, N—As, N—Sb, N—Bi, N—Si, N—Ge, N—B, and N—Metal Functional Groups

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2.07.1 COMPOUNDS WITH AN N—N BOND (ALKYLHYDRAZINES AND RELATED FUNCTIONS)

The preparation of alkylhydrazines has been reviewed <1997KGS747, 1998ACR494, B-1999207-01, 2000ZOB51, 2001CSR205, 2001MI207-01, 2002JHC1> since the publication of COFGT (1995) <1995COFGT(2)371>, and three informative reviews <1964UK361, 1967HOU(10/2)1, 1967HOU(10/2)169> omitted from COFGT (1995) should also be noted.

2.07.1.1 Monoalkylhydrazines

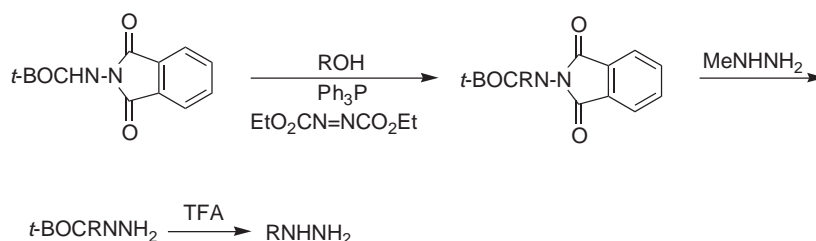
There is a detailed review especially devoted to the preparation and properties of monoalkylhydrazines <1964UK361>.

2.07.1.1.1 By alkylation

As was mentioned in COFGT (1995) <1995COFGT(2)371>, the direct alkylation of hydrazine is often difficult because of polyalkylation. A large excess of hydrazine and bulky alkyl groups facilitates direct monoalkylation. Alkyl halides, dialkyl sulfates, alkyl sulfonates, alcohols in the presence of phosphoric acid or hydrogen halides, oxiranes and aziridines, as well as activated alkenes (e.g., acrylonitrile and styrenes) are used for direct monoalkylation of hydrazine <1967HOU(10/2)1, 2001CSR205>. Dimethyl phosphite as an efficient agent for monomethylation of hydrazine has been described <2001MI207-02>.

A two-step procedure for the preparation of chiral hydrazines has been reported <1996WOP33163>. This involves monoalkylation of unsubstituted or monosubstituted hydrazines with chiral reagents followed by the separation of the diastereomers as salts of a chiral acid.

Protecting groups are widely used in monoalkylation of hydrazines. The hydrazine molecule can be mono-, di-, or triprotected, with phosphoryl, BOC, propyl-2-ide, and phthaloyl being among the most popular protecting groups <2001CSR205>. In particular, Mitsunobu alkylation with alcohol allowed the transformation of *N*-(BOC-amino)phthalhydrazide to *N*-alkyl derivatives, which were readily deprotected to give monoalkylhydrazines in high yields (Scheme 1) <2000JOC4370>.

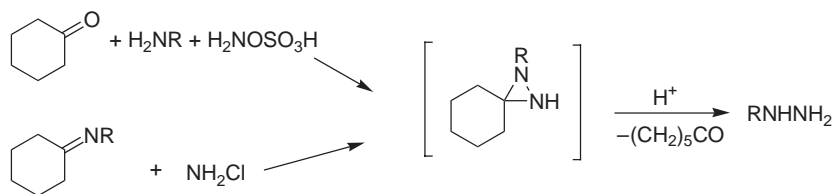
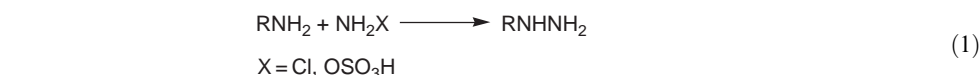


Scheme 1

An interesting case of using protonation for protection was published recently: *t*-butylhydrazine was prepared in high yield and highly selectively by reactions of hydrazine hydrohalides with methyl *t*-butyl ether in the presence of a hydrogen halide, which simultaneously cleaves the ether bond <1997EUP779274>.

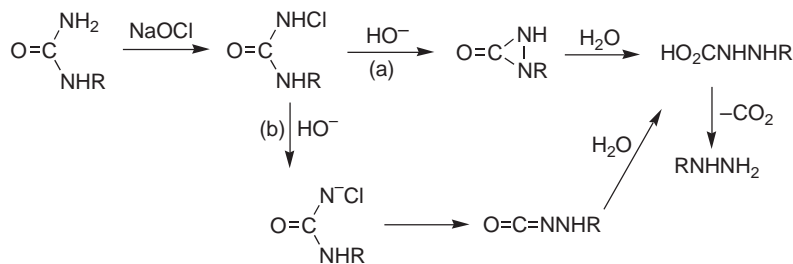
2.07.1.1.2 By *N*-amination

No new data on *N*-amination has been reported since the publication of COFGT (1995) <1995COFGT(2)371>. The main procedures can be summarized as follows: *N*-amination of amines is analogous to the Raschig synthesis of hydrazine, and chloramines and hydroxylamine-*O*-sulfonic acid (HOSA) are both convenient reagents for electrophilic amination (Equation (1)). The interaction of HOSA and an amine in the presence of a ketone and reaction of Schiff bases with chloramine both yield alkylhydrazines via diaziridines (Scheme 2).



Scheme 2

Intramolecular amination to give diaziridinones as intermediates may take place in the reactions of substituted ureas with NaOCl (Scheme 3, path (a)), while an alternative process (path (b)) is similar to Hofmann rearrangement of amides <1970JPR349, 2001CSR205>.



Scheme 3

2.07.1.1.3 By reduction of hydrazones and hydrazides

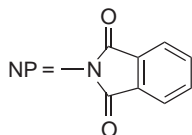
Hydrazones are easily reduced to give monoalkylhydrazines using either catalytic hydrogenation or agents such as diborane, sodium borohydride, sodium cyanoborohydride, and lithium aluminum hydride <1997WOP38973, 2001CSR205>. To prevent N—N bond cleavage on catalytic hydrogenation, the NH_2 function is usually protected by acyl or alkoxy carbonyl groups. A direct reduction of a hydrazide with lithium aluminum hydride can be used for monoalkylhydrazine preparation <2001CSR205>.

2.07.1.1.4 By miscellaneous methods

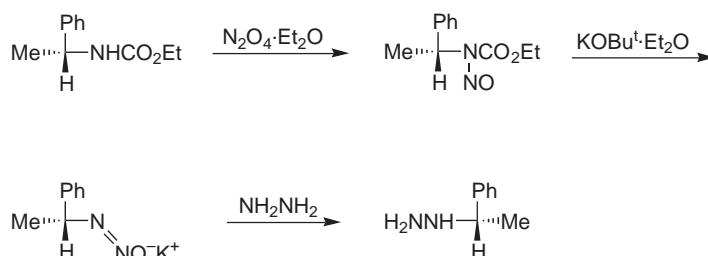
Sydnone, readily prepared from primary amines via *N*-nitroso α -amino acids, yield hydrazines on hydrolysis <1964UK361, 1955JA1843, 1957HCA918>. Addition of CH acids to azodicarboxylates followed by hydrolysis gives α -hydrazino acids. This reaction has been carried out with both achiral and chiral precursors.

Limited data have been reported on the reaction of Bu^tMgCl with Ph_2CN_2 to give the corresponding hydrazone, which on hydrolysis affords Bu^tNHNH_2 hydrochloride (~50%) <1958JOC1595>. β -Functionalized hydrazines can be prepared diastereoselectively by nucleophilic

cleavage of *N*-phthalimidoaziridines followed by hydrazinolysis (Scheme 4) <1985HCA220>. *N*-Phthalimidoaziridines are prepared by addition of phthalimidonitrene to an alkene <1970JCS(C)576, 1975HCA1995>. Heterochiral hydrazines can be prepared by the process shown in Scheme 5 <1975JOC1213>.



Scheme 4



Scheme 5

The classical hydrazine synthesis involving nitrosation of an amine cannot be used to prepare monoalkylhydrazines owing to deamination <1964UK361>. However, nitrosation of an alkyl urea followed by reduction and hydrolysis have been applied to the preparation of some alkylhydrazines <1964UK361, 1973OPP219>.

2.07.1.2 *N,N'*-Disubstituted Hydrazines

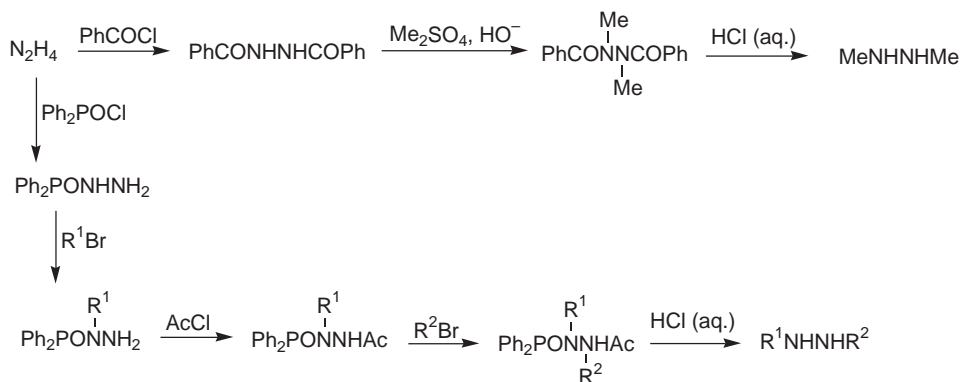
2.07.1.2.1 By alkylation

Since dialkylation occurs mainly on the monoalkylated nitrogen atom, the latter should be protected. To prevent dialkylation, primary *N*-atoms should also be protected. Among protecting groups, benzoyl, acetyl, formyl, carbamoyl, and phosphoryl groups are most useful. The synthesis can start from unsubstituted hydrazine to give either symmetrical or unsymmetrical *N,N'*-disubstituted hydrazines ([Scheme 6](#)) [<2001CSR205>](#).

Substituted 1-aryl-2-benzylhydrazines have been prepared using benzylation of *N'*-lithiated arylhydrazines <2001TL2937>. Intramolecular Se-induced alkylation of homoallylhydrazines leads to cyclic *N,N'*-substituted hydrazines, i.e., pyrazolidine derivatives <2001T10259>.

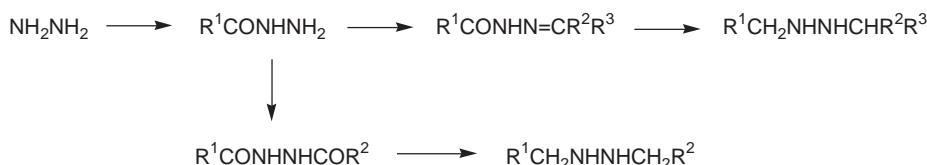
2.07.1.2.2 *By reduction of hydrazones and hydrazides*

Monoalkylhydrazones can be subjected to catalytic hydrogenation or reduced with diborane, NaBH_4 , NaBH_3CN , or lithium aluminum hydride (LAH) to give *N,N'*-disubstituted hydrazines [<1997WOP38973, 2001CSR205>](#). In particular, on reduction with NaBH_4 acetone phenylsemicarbazone and phenylthiosemicarbazone gave 2-isopropyl-1-carbamoyl- and -1-thiocarbamoylhydrazines, respectively [<1997ZOR1497>](#).



Scheme 6

LAH or diborane can be used to reduce hydrazides. However, 1-acyl-2-alkylhydrazines are rather difficult to obtain owing to the formation of isomers and it is more convenient to reduce either *N*-acylhydrazones or *N,N'*-diacylhydrazines (Scheme 7) <2001CSR205>.



Scheme 7

2.07.1.2.3 By reduction of azo compounds and azines

Catalytic hydrogenation and reduction with hydrazine or Raney nickel can also be used for preparation of *N,N'*-dialkylhydrazines, as described in COFGT (1995) <1995COFGT(2)371>. Recently, specific charge-transfer-induced photoreduction of azoalkanes by amines was described <1997JA6749>. As mentioned in COFGT (1995) <1995COFGT(2)371>, the reduction of azines has been accomplished in good yield with LAH.

2.07.1.2.4 By miscellaneous methods

Ring opening of diaziridines and diaziridinones can be used for the preparation of *N,N'*-dialkylhydrazines in a similar way to that used in the preparation of monoalkylhydrazines (Section 2.07.1.1.2). Diethyl azodicarboxylate and its relatives have been used in cycloaddition reactions; removal of the ester groups from the adducts yields hydrazines <1995COFGT(2)371>. α -Cyanohydrazines can be obtained from NaCN, ketones, and hydrazine <1995COFGT(2)371>.

2.07.1.3 *N,N*-Disubstituted Hydrazines

2.07.1.3.1 By alkylation

Direct alkylation of hydrazine usually leads to mixtures of products with direct alkylation occurring mainly on the already alkylated nitrogen atom (Section 2.07.1.2.1). Therefore,

simple alkylation of monoalkylhydrazines can be used for the preparation of *N,N*-disubstituted hydrazines <2001CSR205>. *N*-Aminosubstituted saturated heterocycles can be prepared by dialkylation of hydrazine by compounds of the formula $X-(CH_2)_nX'$, where X and X' are leaving groups ($n = 5, 6$). For example, pentane-1,5-diol ditosylate with hydrazine hydrate in methanol at 25–30 °C gives *N*-aminopiperidine (96% yield) <2003JAP183250>.

Michael addition can also be regarded as a method for alkylation of monoalkylhydrazines to give *N,N*-disubstituted hydrazines <1995COFGT(2)371>.

2.07.1.3.2 By reduction of *N*-nitrosoamines

Reduction of *N*-nitrosoamines is a general method of synthesis of *N,N*-dialkyl-, *N*-alkyl-*N*-aryl-, and *N,N*-diarylhydrazines. Zn and HOAc, Zn and ammonium carbonate in aqueous ammonia, zinc or aluminum amalgam, Na in ethanol or liquid ammonia, dithionite, $NaHSO_3$, LAH and other reductive agents, as well as electrochemical reduction can be successively used for the preparation of *N,N*-disubstituted hydrazines. An example is the synthesis of solid-phase bound *N,N*-dialkylhydrazines (as linkers and scavengers for carbonyl compounds) in which reduction of an *N*-nitrosoamine by diisobutylaluminum (DIBAL) is used <2001GEP10007704>. A novel procedure for the preparation of *N*-nitrosoamines based on the reaction of *N*-lithiated secondary amines with nitric oxide should be mentioned <2000SL1825>. The main drawback of this method is the mutagenic and carcinogenic activity of *N*-nitrosoamines <2001CSR205>.

2.07.1.3.3 By *N*-amination

N-Amination of dialkylamines by chloramines or HOSA is a useful preparation of *N,N*-dialkylhydrazines. In particular, the manufacture of *N,N*-dimethylhydrazine is based on Raschig amination of dimethylamine <2001CSR205>.

A recent electrophilic *N*-amination procedure consists of the interaction of *N*-protected oxaziridines with secondary amines (Scheme 8). 3-Aryloxaziridines ($R^3 = Ar$) were used initially <1997CEJ1691>, but oxaziridines with the strongly electron-withdrawing trichloromethyl substituent are more efficient <1998TL8845>. In principle, this reaction is also possible with primary amines, but side reactions with the aldehyde product often reduce yields. With secondary amines, the yields are usually high.



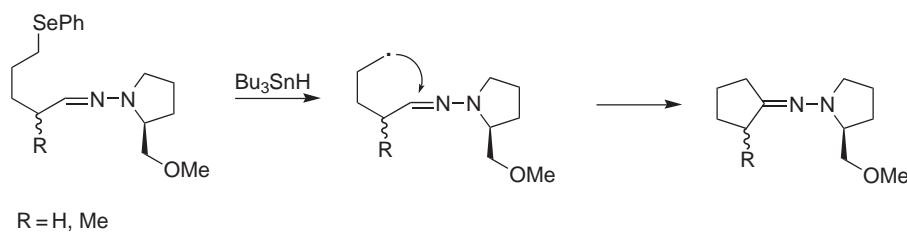
Scheme 8

2.07.1.3.4 By miscellaneous methods

For the preparation of *N,N*-dialkylhydrazines, reduction of *N*-acyl derivatives of monoalkylhydrazines with complex hydrides such as $NaBH_4$ or LAH and the action of strong alkali on quaternary hydrazinium salts <1995COFGT(2)371> should be mentioned.

Hydrazinolysis of *N*-phthalimidoaziridines (Section 2.07.1.1.4) leads to *N*-aminoaziridines <1995COFGT(2)371>.

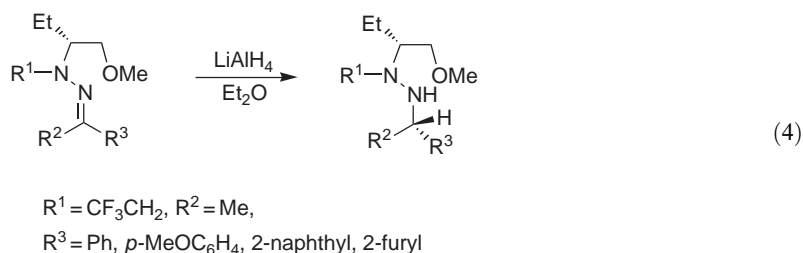
The action of hypochlorite or organic peroxides on ureas proceeds analogously to the synthesis of monoalkylhydrazines (Scheme 3). This reaction is of special interest, since the products formed by work-up with an alcohol instead of water (i.e., alkoxy carbonylhydrazines) can be used for the introduction of an additional alkoxy carbonyl substituent (Scheme 9) <2001CSR205>.



Scheme 11

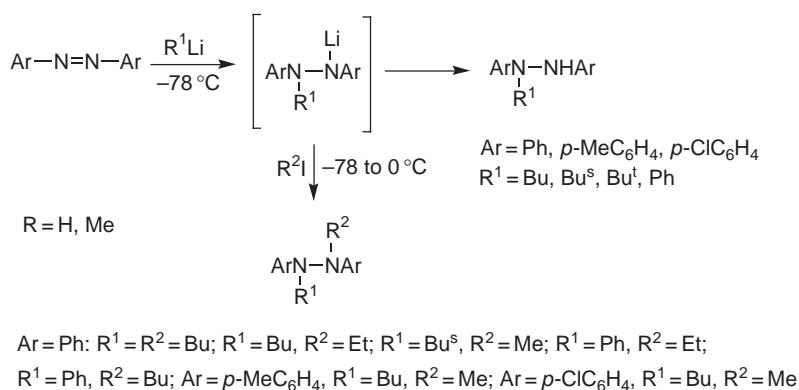
2.07.1.4.3 By reduction of hydrazones and hydrazides

Reduction of hydrazones and hydrazides can be considered together since there is little new information since the publication of COFGT (1995) <1995COFGT(2)371>. Acetone diisopropylhydrazone has been reduced with NaBH_3CN to afford triisopropylhydrazine <1995JA11434>. Diastereoselective LAH reduction of chiral ketone hydrazones derived from (*R*)-(-)-2-aminobutan-1-ol has been reported (Equation (4)) <2000TA1165>. It is of interest to note that while *N*-alkylhydrazones give a moderate diastereomeric excess, it is ~100% in the case of *N*-trifluoroethylhydrazones.



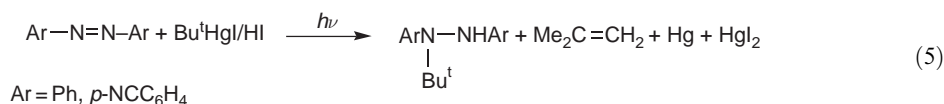
2.07.1.4.4 By miscellaneous methods

There is no new information concerning the reaction of organometallic reagents with *N*-nitrosoamines and diaziridinone ring-opening. Another approach, discussed in COFGT (1995), is addition of organolithium compounds to an $\text{N}=\text{N}$ bond and in this context a one-pot synthesis of tri- and tetrasubstituted hydrazines from azobenzenes should be noted (Scheme 12) <1995S651>.

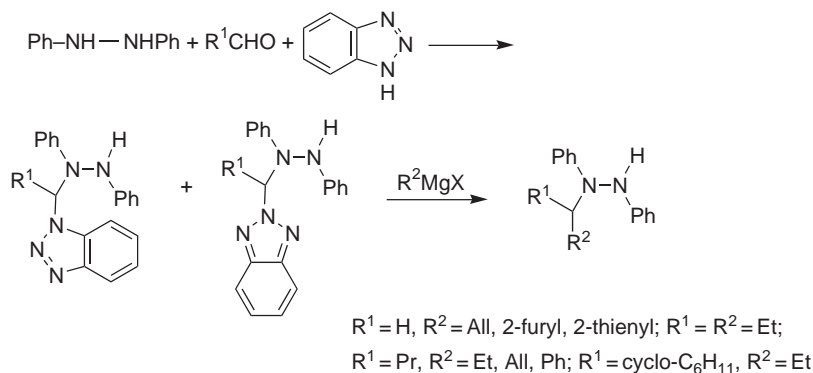


Scheme 12

Reductive *t*-butylation of aromatic azo compounds with *t*-butylmercury halides affords the corresponding trisubstituted hydrazines in high yields (90–97%) (Equation (5)) <1996JOC8988>.



Trisubstituted hydrazines have been prepared from *N,N'*-diphenylhydrazine, aldehydes, and benzotriazole via an equilibrium mixture of benzotriazol-1- and -2-yl-substituted hydrazines (Scheme 13) <1997JOC8210>.

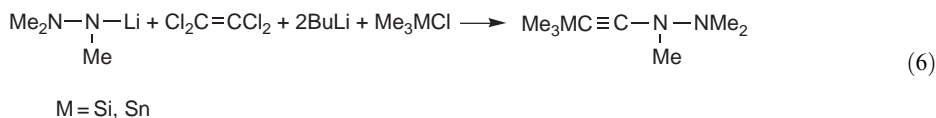


Scheme 13

2.07.1.5 Tetrasubstituted Hydrazines

2.07.1.5.1 By alkylation

The alkylation of *N*-lithium-substituted hydrazines instead of direct alkylation is rather popular now. This approach has been used in a one-pot synthesis of tetrasubstituted hydrazines from azobenzenes (Scheme 12) <1995S651>. *o*-Bromobenzoylation of *N*-lithio-*N,N,N*-trimethylhydrazine has also been reported <1998TL8481>. Related transformations are used in a straightforward synthesis of silylated and stannylated ynehydrazines (Equation (6)) <1997S293>.



Michael addition can be regarded as alkylation with activated alkenes. Besides reactions of di- and trisubstituted hydrazines with acrylic esters and acrylamide, mention should be made of the interaction of *N,N*-dimethylhydrazine with acrylonitrile catalyzed by $\text{Cu}(\text{OAc})_2$ to give *N',N'*-bis(β -cyanoethyl)-substituted hydrazines that are further transformed to *N,N*-dimethyl-*N',N'*-bis(γ -aminopropyl)hydrazines <1999ZPK1970>. Diisopropylhydrazine gives with cycloocta-1,4-dien-3-one, a Michael adduct which is transformed to 9-diisopropylamino-9-azabicyclo[3.3.1]nonane upon Wolff-Kishner reduction <1995JA11434>.

As mentioned in Section 2.07.1.4.1 (Scheme 10), hydrazino carbene metal complexes undergo acid-catalyzed intramolecular alkylation to give pyrazolidene carbenium complexes, which are tetrasubstituted cyclic hydrazines <1995JOM(490)229>.

2.07.1.5.2 By reduction and reductive alkylation of hydrazides and hydrazones

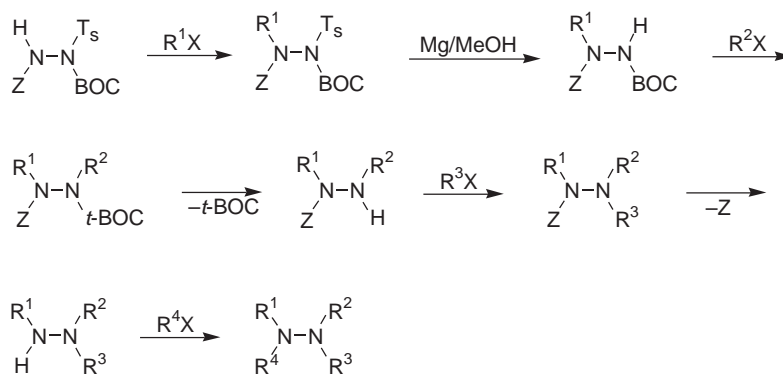
No new results concerning reduction of hydrazides with LAH or diborane and reductive alkylation of hydrazides and hydrazones (NaBH_3CN in MeCN in the presence of a carbonyl compound) have appeared since the publication of COFGT (1995) <1995COFGT(2)371> (see also <2001CSR205>).

2.07.1.5.3 By miscellaneous methods

No further advances have occurred concerning syntheses of tetrasubstituted hydrazines by cycloaddition reactions or by transformations of azo compounds and tetrazenes since the publication of COFGT (1995) <1995COFGT(2)371>.

Addition of isopropylmagnesium chloride to diisopropyl(isopropylimino)iminium hexafluorophosphate gives tetraisopropylhydrazine (26% yield) <1995JA11434>.

Specifically, triprotected hydrazines have been suggested as intermediates in the stepwise syntheses of various hydrazines without side reactions (Scheme 14) <1998ACR494, 2000JCS(P1)1405, 2000S1591, 2001CSR205>.



Scheme 14

2.07.1.6 Quaternary Hydrazinium Salts

Quaternary hydrazinium salts based on *N,N*-dimethylhydrazine have been reviewed <2001MI207-01>.

2.07.1.6.1 By alkylation

The alkylation of hydrazine hydrate, *N*-methyl-, and *N,N*-dimethylhydrazine with dimethyl carbonate leads to *N,N,N*-trimethylhydrazinium carbonate or bicarbonate, which on electrolysis using a cation-exchange membrane gives *N,N,N*-trimethylhydrazinium hydroxide <2000JAP07635>.

N,N-Dimethylhydrazine has been alkylated by C_{10-18} 1-chloroalkanes <1997RUP2074174, 1999ZPK1983> and 2-vinyloxyethyl chlorides <2000ZOR356> to give the corresponding *N*-alkyl-*N,N*-dimethylhydrazinium chlorides.

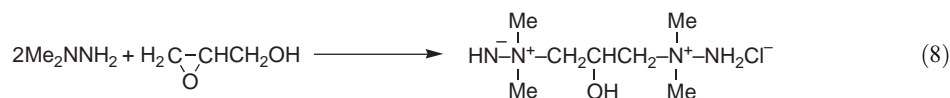
2.07.1.6.2 By miscellaneous methods

No further advances have occurred concerning syntheses of quaternary hydrazinium salts by *N*-amination or by Michael addition since the publication of COFGT (1995) <1995COFGT(2)371>. Quaternization of *N,N*-dimethylhydrazine with chloromethylated polystyrene, and the properties of the anion-exchange resins formed, have been described <2001ZPK1759>.

2.07.1.7 Other Alkylated Two-nitrogen Functions

2.07.1.7.1 Ammonium imides and amine-imines

Reaction of *N,N*-dimethylhydrazine with higher fatty acid esters and epichlorohydrin gives corresponding ammonium imides (Equation (7)) <1996UKZ(9-10)89>, whereas reaction of *N,N*-dimethylhydrazine (2 equiv.) with epichlorohydrin (1 equiv.) leads to unusual products containing fragments of amine-imine and ammonium salt (Equation (8)) <2000ZOR39>.

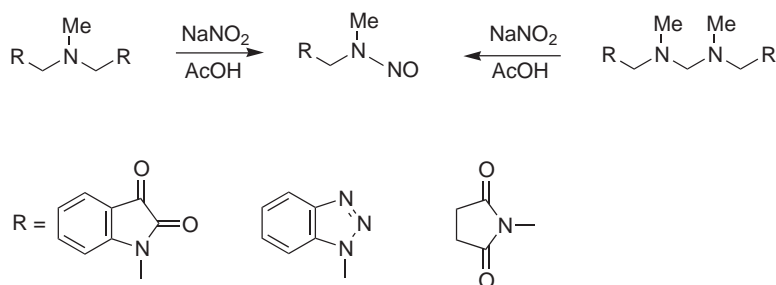


2.07.1.7.2 *N*-Nitrosoamines and *N*-thionitrosoamines

Secondary amines react with nitric oxide in the presence of oxygen to afford *N*-Nitrosoamines in good yields <1999CPB133>. Reaction of lithium amides with nitric oxide has been described as a convenient new methodology for the synthesis of *N*-nitrosoamines <2000SL1825>.

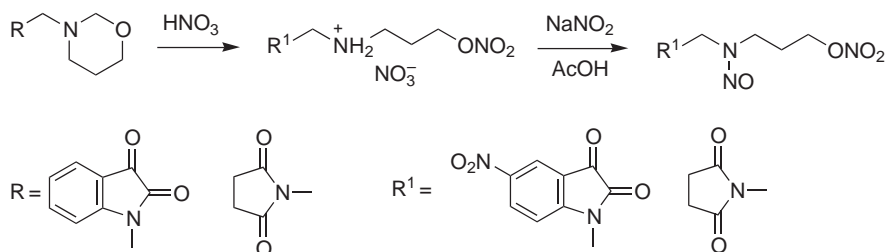
N-Nitrosoamines are almost the only products of reactions of secondary nitramines with tris(trimethylsilyl)silyl radicals generated from tris(trimethylsilyl)silane, whereas reaction of these nitramines with tributyltin radicals gives mostly the denitration products <1995JCR(S)328>.

The Mannich bases obtained from isatin, benzotriazole, or succinimide under the action of primary aliphatic amines and formaldehyde give the corresponding mixed *N*-nitrosoamines [HetCH₂N(NO)Alk] on nitrosative cleavage in the presence of sodium nitrite in acetic acid. The Mannich base with diisobutylamine fragment gives isobutyl nitrosoamine (Scheme 15) <2001IZV1553>.



Scheme 15

Dialkyl nitrosoamines bearing additional functionalities can be prepared using a two-step synthesis starting from tetrahydro-1,3-oxazine derivatives (Scheme 16) <2003IZV2110>.



Scheme 16

No further advances have occurred concerning the syntheses of *N*-thionitrosoamines since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.1.7.3 *N*-Nitroamines

The most common method for the preparation of *N*-nitroamines consists of direct nitration of an amine or amine derivative under the action of $\text{HNO}_3/\text{H}_2\text{SO}_4$ <1997IZV1061>, HNO_3 <1998IZV673>, or $\text{HNO}_3/\text{Ac}_2\text{O}$ <1997IZV1987>. For the preparation of *N*-nitroamines, some new nitrating agents have been reported including $\text{CF}_3\text{SO}_3\text{H}/\text{HNO}_3$ (nitration of *p*-nitrobenzyl-sulfonamides) <2002USP6417355>, N_2O_5 (for silylamines) <1996MI207-01, 1996MI207-02>, $(\text{CF}_3\text{SO}_2)_2\text{O}/\text{HNO}_3/\text{N}_2\text{O}_5$, or $(\text{CF}_3\text{CO}_2)_2\text{O}/\text{HNO}_3/\text{N}_2\text{O}_5$ (cleavage of secondary carboxamides) <1996MI207-03> and $\text{NO}_2^+\text{BF}_4^-$ (nitrolysis of urethanes) <1998IZV1162>.

Primary nitroamines give salts with amines, which can be used for their isolation, and are readily transformed back to the nitroamines by neutralization <2003GEP10132694>. Clathrate formation has also been described for isolation of nitroamines <2002WOP060881>.

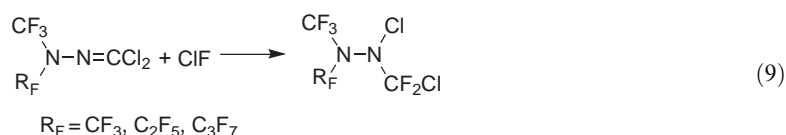
Previously unknown *N*-fluorinated polymethylenepolynitroamines were obtained by fluorination of polymethylenepolynitramines with F_2 in acetonitrile <1994IZV2174>.

2.07.1.7.4 Sulfinyldiazines (thionylhydrazines)

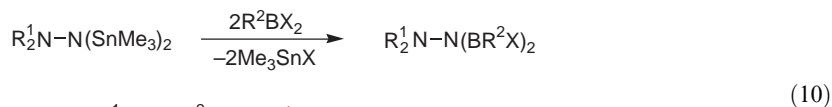
Sulfinyldiazines ($\text{R}^1\text{R}^2\text{NN}=\text{S}=\text{O}$) are usually made by the action of SOCl_2 on hydrazines either alone or in the presence of pyridine or triethylamine. An alternative method uses *trans*-thionylation, in which an aliphatic *N,N*-disubstituted hydrazine is treated with an aromatic sulfenylamine <1995COFGT(2)371>. No further advances have occurred concerning syntheses of sulfinyldiazines since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.1.7.5 Miscellaneous hydrazine derivatives

N-[Di(polyfluoroalkyl)amino]isocyanide dichlorides afford *N*-chlorohydrazines on addition of ClF (Equation (9)) <1995IC5049>.



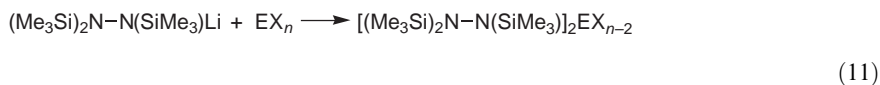
N,N-Dialkyl- and *N,N*-diphenyl-*N,N*-bis(trimethylstannyl)hydrazines react with alkylborondihalides to afford corresponding diboryldiazines (Equation (10)) <1999EJI1765>. Trisilylated hydrazines with a fourth N–E bond ($\text{E} = \text{B}, \text{C}, \text{P}, \text{Si}$) as well as tetrakis(trimethylsilyl)hydrazine have been obtained from lithium tris(trimethylsilyl)hydrazine and the reagents EX_n ($\text{X} = \text{F}, \text{Cl}, \text{Br}$) (Equation (11)) <1998IJC(A)626>.



$\text{X} = \text{Br}; \text{R}^1 = \text{Me}; \text{R}^2 = \text{Me}, \text{Pr}^i, \text{Bu}^t$

$\text{X} = \text{Cl}, \text{R}^1 = \text{R}^2 = \text{Me}$

$\text{X} = \text{Br}, \text{R}^1 = \text{Ph}, \text{R}^2 = \text{Me}, \text{Bu}^t$



$\text{E} = \text{B}, \text{X} = \text{F}, n = 3; \text{E} = \text{C}, \text{X} = \text{Br}, n = 4;$

$\text{E} = \text{Si}, \text{X} = \text{Cl}, n = 4; \text{E} = \text{P}, \text{X} = \text{Cl}, n = 5$

N',N'-bis(Trihydrosilyl)-*N,N*-dimethyl- and trimethyl(trimhydrosilyl)hydrazines have been prepared by reactions of SiH_3Br with the corresponding hydrazine in the presence of a base or with an *N*-lithiated hydrazine <1998CEJ692>. A synthesis of silyl-substituted hydrazines consists of the reaction of respective fluorides with monolithiated hydrazines <1996PS(108)121>. Reaction of *N,N*-dimethylhydrazine with a hydrosilane proceeds with evolution of hydrogen to give the corresponding *N'*-silylated hydrazine <1999IZV169>. (*N,N*-dimethylhydrazino)dimethylsilane and

bis(*N,N*-dimethylhydrazino)methylsilane react with alkenes in the presence of rhodium dicarbonylacetate as hydrosilylating agents to give *N'*-(trialkylsilyl)-*N,N*-dimethylhydrazines and dialkylbis(*N,N*-dimethylhydrazino)silanes, respectively <2002ZOB59>.

2.07.1.8 Alkylated Three-nitrogen Functions

2.07.1.8.1 Triazanes

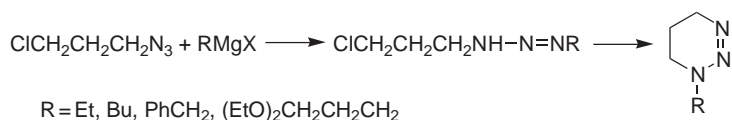
As described in COFGT (1995), triazanes, which contain a saturated chain of three nitrogen atoms (R_2NNRNR_2), are not stable in the absence of electron-withdrawing groups. Treatment of *N,N*-disubstituted hydrazines with a salt of HOSA or with chloramine yields stable triazanium salts quaternized on N^2 . No further advances have occurred concerning syntheses of triazanes since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.1.8.2 Triazines

Triazines have been reviewed <1995MI207-01, 2001OPP59, 2002AG(E)3338>. Alkylated triazines are usually made by the action of a Grignard or alkyllithium reagent on an alkyl azide. The same method can be used for the synthesis of “mixed” 1-aryl- and 1-heteroaryl-3-alkyltriazines <1994JOC5942>.

1-Aryl- and 1-heteroaryl-3,3-dialkyltriazines are usually made by the reaction of diazonium salts with secondary aliphatic amines <1994JA4227, 1995JA10662, 1996AG(E)297, 1996EJM735, 1999TL6353, 1999TL8347, 2001JOC3893, 2001JOC4973, 2002MI207-01>. High yields of triazines can be obtained by using solid arenediazonium salts <1997JPR256, 2001S2180>.

3-Chloropropyl azide reacts with Grignard reagents to give triazines which on attempted isolation by concentration undergo cyclization to give 1-alkyl-1,4,5,6-tetrahydro-1,2,3-triazines, which have the (*Z*)-configuration in contrast to open-chain (*E*)-triazines (Scheme 17) <1997JOC8660>.



Scheme 17

Triazines are acylated by BOC-protected amino acids in the presence of DCC, and deprotection of the acylation product is achieved by HCl in nitromethane <1998MI207-01>. Several methods for the syntheses of bis-triazines have also been reported <1998JOC7437, 2001OPP59>.

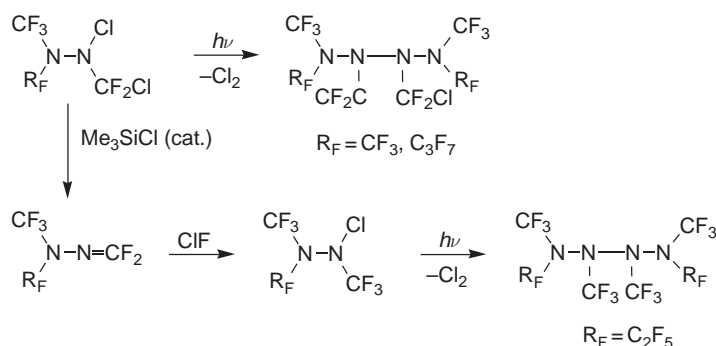
2.07.1.8.3 Nitrosohydrazines

Nitrosohydrazines ($RN(NO)NH_2$ and $R^1N(NO)NHR^2$) are prepared by the action of HOAc and $NaNO_2$ or alkyl nitrite on a hydrazine. Both types of nitrosohydrazine can be alkylated on the non-nitrosated nitrogen atom. No further advances have occurred concerning syntheses of nitrosohydrazines since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.1.9 Alkylated Four-nitrogen Functions

2.07.1.9.1 Tetrazanes and tetrazenes

Relatively few new works have appeared concerning syntheses of tetrazanes since the publication of COFGT (1995). However, information on tetrazanes, which are completely absent in COFGT (1995), has appeared. Synthesis of the previously unknown stable perfluorinated tetrazanes has been achieved using the method shown in Scheme 18 <1995AG(E)586, 1995IC5049>.



Scheme 18

The oxidation of hydrazines is normally used for the synthesis of tetrazines <2002ZN(B)365>. Gas-phase oxidation of methylhydrazine (He/O₂ mixture, 50 °C) is of interest, although it is not selective and gives a mixture containing methylene tetrazine H₂C=N—NH—N=NH in addition to the triazenes H₂C=N—N=NMe and HN=N—N=CH₂ <1999JCR(S)2218>.

2.07.1.9.2 Tetrazenium salts

Tetrazenes are quaternized in the usual way by alkyl halides. No further advances have occurred concerning syntheses of tetrazenium salts since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.1.9.3 N-Azidoamines

The dangerously explosive compound Me₂NN₃ has been made from Me₂NCl and sodium azide. No further advances have occurred concerning syntheses of *N*-azidoamines since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.1.9.4 Dinitrosohydrazines

The only example of a dinitrosohydrazine (PhCH₂N(NO)N(NO)CH₂Ph), prepared by the action of NaNO₂/H₂SO₄ on the corresponding hydrazine hydrochloride, is mentioned in COFGT (1995). No further advances have occurred concerning syntheses of dinitrosohydrazines since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.1.10 Alkylated Five-nitrogen Functions

1,4,4-Trimethyl-1-nitroso-2-tetrazene has been made by the action of N₂O₄ or N₂O₃ on the corresponding tetrazene. No further advances have occurred concerning syntheses of such compounds since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.2 COMPOUNDS WITH AN N—P BOND

This section corresponds to chapter 2.07.3 in COFGT (1995). This change, and the consequent renumbering of subsequent sections, has been made in order to correct an anomaly in COFGT (1995). The most widely used approach to N—P bond formation involves aminolysis of phosphorus halides and of alkoxy- or aryloxyphosphorus compounds.

2.07.2.1 Compounds Related to Phosphorous Acid, (HO)₃P

No further advances have occurred concerning syntheses of *N,N*-dialkylaminophosphinic dihalides and *N,N*-dialkylhalogenophosphoramidites, as well as those of thiophosphoramidites [$R_2^1NP(SR^2)(OR^3)$] and bis(dialkylamino)chlorophosphines since the publication of COFGT (1995) <1995COFGT(2)371>. Brief summaries of the main methods are given in the following sections.

2.07.2.1.1 *N,N*-Dialkylaminophosphinic dihalides, R_2NPX_2

N,N-Dialkylaminophosphinic dichlorides are usually synthesized by reaction of secondary amines with PCl_3 : primary amines give a mixture of products. Dialkylamino(difluoro)phosphines can be prepared by replacement of chlorine in the corresponding dichlorides using, for example, antimony trifluoride. The mixed halides such as Me_2NPFX ($X = Cl, Br$) can be obtained by reaction of dimethylamine with PFX_2 in the gas phase.

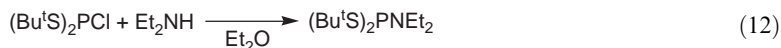
2.07.2.1.2 *N,N*-Dialkylhalogenophosphoramidites, $R_2^1NP(Hal)(OR^2)$

N,N-Dialkylchlorophosphoramidites can be prepared by the reaction of an alkoxydichlorophosphine with either a secondary amine, an *N*-trimethylsilyl derivative of the latter, or an *N*-lithiated amine. The chlorine atom in $(EtO)P(Cl)NMe_2$ may be exchanged for a fluorine atom by heating with KF in toluene.

2.07.2.1.3 *N,N*-Dialkylphosphoramidites, $(R^1O)_2PNR_2^2$, and their thio analogs, $(R^1S)_2PNR_2^2$

Preparation of *N,N*-dialkylphosphoramidites can be achieved by several routes: (i) treatment of a dialkylamino(dichloro)phosphine with an alcohol in the presence of a tertiary amine; (ii) reaction of a bis(dialkylamino)alkoxyphosphine with an alcohol (including nucleosides); and (iii) treatment of $(RO)_2PCl$ with a secondary amine in an inert solvent. No further advances have occurred concerning syntheses of such compounds since the publication of COFGT (1995) <1995COFGT(2)371>.

In a procedure similar to the latter method, a thio analog of *N,N*-dialkylphosphoramidites has been prepared (Equation (12)) <1999ZOB916>. An alternative procedure consists of reaction of the ethyl ester of phosphoramidochloridous acid with sodium butylthiolate <2000IZV1604>.



2.07.2.1.4 Thiophosphoramidites, $R_2^1NP(SR^2)(OR^3)$

Thiophosphoramidites which are useful intermediates in the synthesis of nucleoside phosphorodithioates can be obtained by reactions of *N,N*-dialkylaminophosphinic dihalides with sodium thiolates.

2.07.2.1.5 Bis(dialkylamino)chlorophosphines, $(R_2N)_2PCl$

Bis(dialkylamino)chlorophosphines are prepared either by the reaction of the appropriate amine (3 mol) in ether with PCl_3 at 0–10°C or by exothermic interaction of hexamethylphosphorus triamide with PCl_3 .

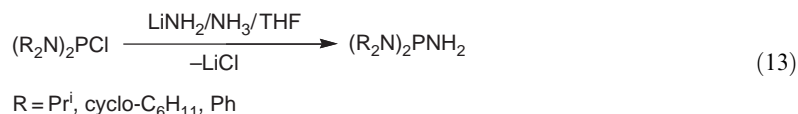
2.07.2.1.6 Alkoxy- or aryloxybis(dialkylamino)phosphines, $(R_2^I N)_2POR^2$, and their thio analogs, $(R^I N)_2POR^2$

Alkoxy- or aryloxybis(dialkylamino)phosphines are prepared by the reaction of phosphines ($ROPCl_2$) with secondary amines (4 mol) in ether or benzene. Another route is the treatment of bis(dialkylamino)chlorophosphines with alcohols or phenols. Finally, reaction of tris(dialkylamino)phosphines with a molar equivalent of an alcohol results in one amino group being replaced by an alkoxy group. No further advances have occurred concerning syntheses of such compounds since the publication of COFGT (1995) <1995COFGT(2)371>.

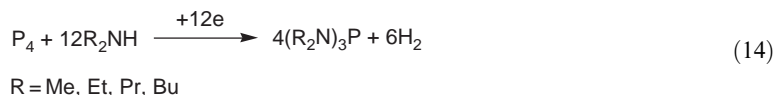
Reaction of 2-trimethylsilyloxy-1-(trimethylsilylthio)propene with bis(diethylamino) (chloro)-phosphine affords the corresponding bis(diethylamino)vinylthiophosphine <1994ZOB1488>. Heating $(Et_2N)_3P$ with mercaptoacetone (70 °C) gives $(Et_2N)_2PSCH_2Ac$ in almost quantitative yield <1994ZOB762>.

2.07.2.1.7 Tris(dialkylamino)phosphines, $(R_2N)_3P$

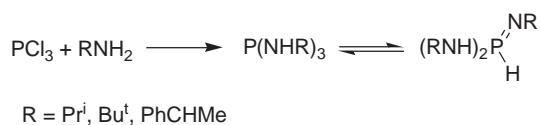
In COFGT (1995), two analogous procedures for the preparation of tris(dialkylamino)phosphines are mentioned. These are the reaction of PCl_3 with secondary amines or with their trimethylsilyl derivatives. A similar procedure is suggested for the preparation of *N,N,N*-hexakis(β -cyanoethyl)-phosphorus triamide, namely reaction of PCl_3 with excess bis(β -cyanoethyl)amine in the presence of tris(β -cyanoethyl)amine giving the target product in 80% yield <1995ROP105500>. Different methods have been used for syntheses of unsymmetrically substituted trisaminophosphines. Methyltrifluoroacetylaminobis(diisopropylamino)phosphine and bis(methyltrifluoroacetylaminodiisopropylaminophosphine were prepared by reactions of Pr_2NH with $CF_3C(O)N(Me)PCl$ or $[CF_3C(O)N(Me)]_2PCl$ (75% and 70% yields) <1997ZOB67>. Amino-bis(diorganylamino)phosphines were synthesized using the transformation shown in Equation (13) <1996CB911>.



An interesting electrochemical synthesis (Pt anode, steel cathode, undivided cell) of tris(dialkylamino)phosphines from white phosphorus and secondary amines has been reported (Equation (14)) <1995ZOB1663>.



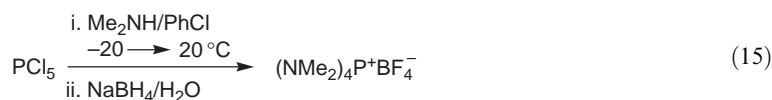
Primary amines and phosphorus trichloride give tris(alkylamino)phosphines, which are in tautomeric equilibrium with bis(alkylamino)imide, with the latter being the major form (Scheme 19) <2001ZOB691>.



Scheme 19

2.07.2.1.8 Tris(dialkylamino)phosphonium salts, $[(R_2N)_3PX]^+ Y^-$

Tris(alkylamino)methylphosphonium iodides $[(R_2N)_3PMe]^+ I^-$ have been prepared by the treatment of tris(alkylaminomethyl)phosphines with methyl iodide <2001ZOB691>. Hexaalkylphosphorus triamides react with CF_3Br to give tris(dialkylamino)trifluoromethylphosphonium bromides $[(CF_3P(NR_2)_3]^+ Br^-$ ($R = \text{Me}, \text{Et}, \text{Pr}$) <1995JFC(70)271>. Tetrakis(dimethylamino)phosphonium tetrafluoroborate is made from phosphorus pentachloride and dimethylamine (Equation (15)) <1994CB2435>.



2.07.2.2 Compounds Related to Phosphoric Acid, (HO)₃P(O)

As for the compounds of trivalent phosphorus discussed in Section 2.07.2.1, the majority of substances in this series are obtained by successive replacement of halide in P(O)X₃ with amines, alcohols, or phenols. The substitution of the lone pair on phosphorus by oxygen (or sulfur) leads to lower reactivity of the halide and more vigorous conditions are common in the formation of this class of compound.

2.07.2.2.1 *N,N*-Dialkylphosphoramidic dihalides, R₂NP(O)X₂

The treatment of POCl₃ with a secondary amine (1 mol) remains practically the only method for the synthesis of *N,N*-dialkylphosphoramidic dihalides. As an additional example to those given in COFGT (1995), the preparation of the dihalides R¹R²NP(O)X₂ (R¹ = Me; R² = CH₂CH₂X; X = Cl, Br, I) from POCl₃ and R¹R²NH·HX in the presence of Et₃N has been described <1995JMC2672, 1996S1227>.

Dialkylphosphoramidic difluorides can be obtained from the dichlorides by halogen exchange with KF. The mixed halides Et₂NP(O)FX (X = Cl, Br) can be prepared from P(O)FX₂. No further advances have occurred concerning the syntheses of such compounds since the publication of COFGT (1995) <1995COFGT(2)371>.

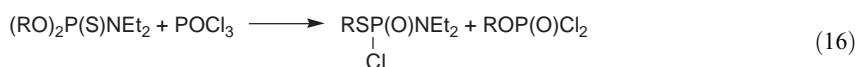
2.07.2.2.2 *N,N*-Dialkylhalogenophosphoramidates, R₂¹NP(O)Hal(OR²), and their thio analogs, R₂¹NP(O)Hal(SR²)

Reactions of R₂¹NP(O)Cl₂ with alcohols or phenols and addition reactions of diethyl *N,N*-dichlorophosphoramidate with activated alkenes have been presented in COFGT (1995) as useful procedures for the synthesis of corresponding amidophosphochloridates. The first of these reactions also gives good results for the preparation of *N,N*-dialkylhalogenophosphoramidates with functionalized R² used in the synthesis of 5-fluoro-2'-deoxyuridine phosphoramidate analogs <1995JMC2672>.

Alternative procedures are reaction of ROP(O)Cl₂ with 2 equiv. of a primary or secondary amine <1994JOC4402, 1996JOC3944> and the cleavage of one N—P bond in *N,N,N',N'*-tetraalkylphosphorodiamidates [(R₂¹N)₂P(O)OR²] by HCl gas <2000JFC(104)215>.

18-Crown-6 with KF is an effective reagent for the transformation of 4-methylphenyl dimethylphosphoramidochloride to the respective fluoride <1995PS(106)173>.

An interesting isomerization/chlorination reaction that allows preparation of *S*-alkyl (or *S*-alkenyl) *N,N*-dialkylchlorophosphorothioamidates [R₂¹NP(O)Hal(SR²)] from phosphorothioimidates has been described (Equation (16)) <1997MI207-01, 1999MI207-03>.

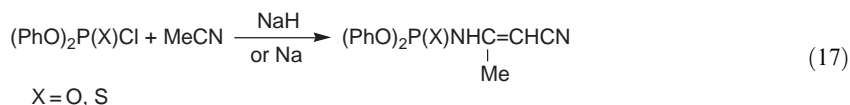


2.07.2.2.3 Phosphoramidates, (R¹O)₂P(O)NR₂², and their thio analogs

The reaction of (R¹O)₂P(O)Cl with primary or secondary amines is the most useful method for obtaining phosphoramidates. These reactions are carried out in the presence of a tertiary amine (usually Et₃N). Substituents include: (i) R² = 2-cyanoethyl, which can be further transformed to 3-aminopropyl by hydrogenation of the corresponding phosphoramidates <1999JMC3971>; (ii) R¹ = fluoroalkyl <2000JFC(104)215, 2002JFC(113)111>; and (iii) R¹ and R² = fluoroalkyls <2002PS(177)423>. The bromide (PhCH₂O)₂P(O)Br formed from tribenzylphosphite and bromine has been used without isolation for the synthesis of several *N*-substituted

O,O-dibenzylphosphoramidates <2001JOC7561>. Analogous reaction between $(R^1O)_2P(S)Cl$ and primary or secondary amines has been used for the synthesis of phosphorothioamidates <1996POL3725>. *O,S*-Dialkylphosphoramidothioates can be prepared from the respective chlorides and secondary amines <2000IZV1604>. The same approach can be used for the preparation of *O,S*-dialkylphosphoramidodithioates <1996PS(113)123>.

An unexpected reaction of diphenoxyphosphorylchloride and diphenoxythiophosphorylchloride with acetonitrile gives *N*-phosphorylated 3-aminocrotonitriles (Equation (17)) <2000PS(164)103>.



O,S-Dialkylphosphoramidodithioates have been obtained by treatment of the corresponding P(III) derivatives with sulfur <2000IZV1604>. Mercaptoacetone takes part in a reaction with $(AlkO)_2PNEt_2$ as sulfuration agent to give *O,O*-dialkylphosphorothioamidates $[(AlkO)_2P(S)NEt_2]$ with acetone being another product <1994ZOB762>.

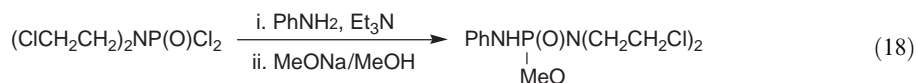
2.07.2.2.4 *N,N,N',N'*-Tetraalkylphosphorodiamidic halides or bis(dialkylamino)phosphoryl halides, $(R_2N)_2P(O)Hal$

Bis(dialkylamino)phosphorylchlorides can be prepared by reactions of $POCl_3$ with a dialkylamine (4 mol or 2 mol + base). The related fluorides can be obtained either by halogen replacement or by reacting amines with mixed dihalides such as $Et_2NP(O)BrF$. No further advances have occurred concerning syntheses of such compounds since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.2.2.5 *N,N,N',N'*-Tetraalkylphosphorodiamidates, $(R_2N)_2P(O)OR^2$

Only moderate yields of the diamidate esters are obtained when dialkylaminophosphorylchlorides are heated with sodium alkoxides. A better procedure is to treat the more reactive alkylphosphorodichloridates with a secondary amine.

Reaction conditions have been optimized for the preparation of an unsymmetrical diamidate ester with di(2-chloroethyl)amino and phenylamino substituents (Equation (18)) <1996S1227>.



Alkyl phosphoramidodithioates can be obtained by the treatment of the corresponding P(III) derivatives with sulfur <2000IZV1604>. No further advances have occurred concerning syntheses of such compounds since the publication of COFGT (1995) <1995COFGT(2)371>.

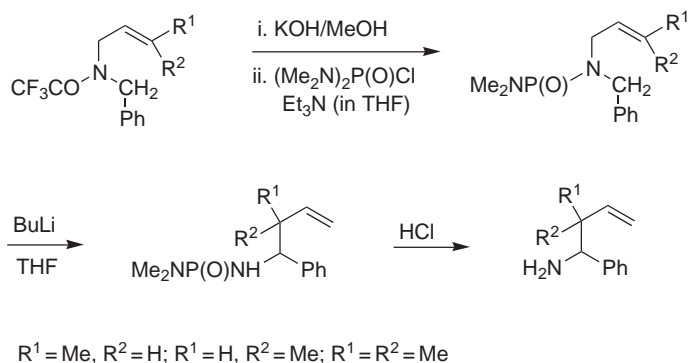
2.07.2.2.6 *Hexaalkylphosphoric triamides, $(R_2N)_3P(O)$, and hexaalkylthiophosphoric triamides, $(R_2N)_3P(S)$*

Symmetrical hexaalkyltriamides are conveniently prepared by reacting $POCl_3$ with at least 6 mol of primary or secondary amines. Thiophosphoric triamides can be similarly obtained from $P(S)Cl_3$. Unsymmetrical products can be obtained by treating $R_2NP(O)Cl_2$ with 2 mol of a secondary amine in the presence of a base or by reaction of phosphorodiamidic chlorides with amines.

Potassium peroxymonosulfate (oxone) is an efficient oxidant for the transformation of hexamethylphosphorous triamide to hexamethylphosphoric triamide (93% yield) <1999TL2637>. Hexaalkylthiophosphoric triamides can be obtained in 50–70% yields from white phosphorus, secondary amines, and carbon disulfide under electrochemical conditions <1995ZOB1663>. *N,N',N''*-Trialkylphosphorus triamides react with S_8 to give corresponding trialkylthiophosphoric triamides <2001ZOB691>.

As mentioned above (Section 2.07.2.1.6), heating $(\text{Et}_2\text{N})_3\text{P}$ with mercaptoacetone at 70°C gives $(\text{Et}_2\text{N})_2\text{PSCH}_2\text{Ac}$ in almost quantitative yield. However, at higher temperature (130°C) the same components form hexaethylthiophosphoric triamide (70–80% yield) with acetone evolution <1994ZOB762>.

N-Alkenyl-*N,N',N'',N'''*-pentamethylphosphoric triamides are obtained from POCl_3 by successive treatment with a 1-*R*-allylamine ($\text{R} = \text{Me, Et, Ph}$), Me_2NH , and BuLi followed by MeI <2003T2101>. For the synthesis of *N*-alkenyl-*N*-benzyl-*N',N'',N'''*-tetramethylphosphoric triamides, the corresponding *N*-alkenyl-*N*-benzyl(trifluoroacetamides) can be hydrolyzed (KOH/MeOH) and then treated with $(\text{Me}_2\text{N})_2\text{P}(\text{O})\text{Cl}$ (in THF in the presence of Et_3N). The phosphoramides undergo an aza[2,3]-sigmatropic rearrangement when treated with BuLi to give isomeric phosphoric triamides. The dimethylaminophosphoryl group can be removed to give unprotected primary amines (Scheme 20) <1997TL2491>.



Scheme 20

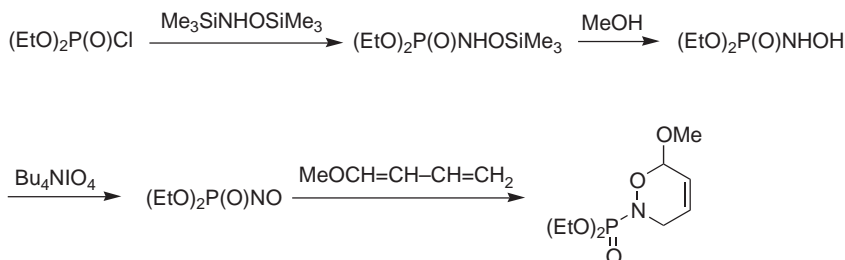
Various unsymmetrically substituted phosphoric triamides have been prepared by treating $(\text{ClCH}_2\text{CH}_2)_2\text{NP}(\text{O})\text{Cl}_2$ with a secondary or primary amine (2 mol) in the presence of triethylamine <1996S1227, 1999JCS(P2)2589>. Such phosphoramidate mustards are potential antitumor drugs or intermediates in their synthesis <1997MI207-02>.

2.07.2.2.7 Miscellaneous compounds containing an *N*–*P* bond

O-Ethylphosphoramidic acids with bulky *N*-substituents are prepared in 85–95% yield by alkaline hydrolysis of the corresponding chlorophosphoramidates followed by ion exchange using Amberlist- H^+ <1994JOC4402>.

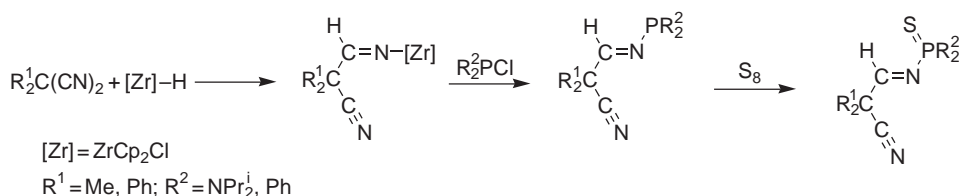
N-Substituted phosphoramidic acids including *N*-sulfonylphosphoramidic acids are prepared by hydrogenation of their dibenzylesters over Pd/C catalyst <2001JOC7561>.

P-Nitrosophosphate compounds can be synthesized via hydroxylamine derivatives and react as dienophiles (Scheme 21) <2000JOC8725>.



Scheme 21

Reactions of Schwartz's reagent (1 or 2 mol) with a *gem*-dinitrile give mono- or di-*N*-zirconated imine complexes, which are transformed to phosphorylated imines (Scheme 22) <2003EJO385>.



Scheme 22

2.07.3 COMPOUNDS WITH AN N—As, N—Sb, OR N—Bi BOND

2.07.3.1 Compounds Containing an N—As Bond

2.07.3.1.1 (Dialkylamino)dihaloarsines, $(\text{R}_2\text{N})\text{AsHal}_2$

(Dialkylamino)dihaloarsines are usually prepared by the replacement of one halogen atom in AsHal_3 by secondary or primary amines. Lithium *N*-(*t*-butyl)-*N*-(trimethylsilyl)amide reacts with arsenic trichloride to give the aminodichloroarsine <2000EJI165>. The treatment of silver *N,N*-dimesylamide with arsenic trichloride leads to (dimesylamino)dichloroarsine $[(\text{MeSO}_2)_2\text{NAsCl}_2]$ <1997PS(122)107>. No further advances have occurred concerning the syntheses of (dialkylamino)dihaloarsines by the reaction between a tris(dialkylamino)arsine, $\text{As}(\text{NMe}_2)_3$, and AsCl_3 or AsBr_3 since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.3.1.2 Bis(dialkylamino)haloarsines, $(\text{R}_2\text{N})_2\text{AsHal}$

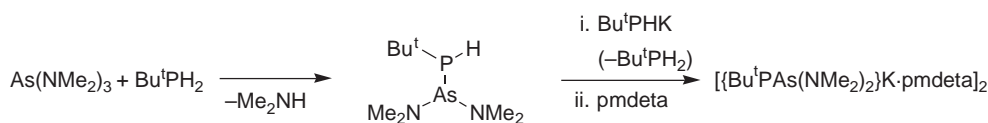
As described in COFGT (1995), bis(dialkylamino)chloroarsines can be prepared by the reaction between AsCl_3 , and an amine. Other routes are treatment of (dialkylamino)dihaloarsines with amine or reaction of a tris(dialkylamino)arsine with either HCl , PhCOCl , or PHCH_2Cl to give the chloro compound or with AsBr_3 to give the bromo derivative. Reactions of $(\text{Me}_2\text{Bu}^t\text{Si})_2\text{NLi}$ with AsCl_3 and of $(\text{Me}_3\text{Si})_2\text{NLi}$ with dichloro(2,2,6,6-tetramethylpiperidino)arsine gave the desired diaminochloroarsines <2000EJI477>. The treatment of silver *N,N*-dimesylamide with arsenic trichloride in appropriate ratio leads to $[(\text{MeSO}_2)_2\text{N}]_2\text{AsCl}$ <1997PS(122)107>. No further advances have occurred concerning the syntheses of bis(dialkylamino)haloarsines since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.3.1.3 Tris(dialkylamino)arsines, $(\text{R}_2\text{N})_3\text{As}$

Compounds of the type $(\text{R}_2\text{N})_3\text{As}$ have been made by the reaction of a dialkylamine with AsCl_3 or with a bis(dialkylamino)chloroarsine. *N*-Lithiated amines and aminostannanes have also been used with arsenic halides. Treatment of a secondary amine with tris(dimethylamino)arsine results in amine exchange. No further advances have occurred concerning the syntheses of tris(dialkylamino)arsines since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.3.1.4 Miscellaneous compounds containing an N—As bond

A complex containing both N—As and N—P bonds has been obtained by the reactions shown in Scheme 23 <1999CC739>.



pmdeta = pentamethyldiethylenetriamine

Scheme 23

2.07.3.2 Compounds Containing an N—Sb Bond

In COFGT (1995), the methods for synthesis of compounds containing an N—Sb bond are described as follows: (i) reaction of *N*-lithiated amines with SbCl_3 or SbBr_3 giving tris(dialkylamino)stibines or bis(dialkylamino)halostibines; (ii) reaction of (dimethylamino)trimethylstannane with SbF_3 giving $(\text{Me}_2\text{N})_3\text{Sb}$; and (iii) replacement of the ethoxy groups in F_2SbOEt and FSb(OEt)_2 by substituted amino groups leading to aminofluorostibines.

The treatment of bis(dimesyl)trimethylsilylamine with SbCl_3 gives $(\text{MeSO}_2)\text{NSbCl}_2$ <1997PS(122)107>. The reaction of $\text{Sb}(\text{NMe}_2)_3$ with 2,6-diisopropylaniline affords an unusual *cis* dimer $[(\text{Me}_2\text{N})\text{Sb}(\mu\text{-NDipp})]_2$ (Dipp = 2,6- $\text{Pr}^i_2\text{C}_6\text{H}_3$) <1998POL745>. No further advances have occurred concerning the syntheses of such compounds since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.3.3 Compounds Containing an N—Bi Bond

In COFGT (1995) only one example of the synthesis of compounds containing an N—Bi bond is described: the reaction of lithium methyl(trimethylsilyl)amide with BiBr_3 to give the bismuthine-triamine. A dimeric compound, $[\text{Bi}_2(\text{NBu}^t)_4]\text{Li}_2 \cdot 2\text{THF}$, containing the $[\text{Bi}_2(\text{NBu}^t)_4]^{2-}$ dianion has been reported <1996ICA(248)9>.

2.07.4 COMPOUNDS WITH AN N—METALLOID BOND

2.07.4.1 Compounds Containing an N—Si Bond

As in COFGT (1995), cyclic silazanes are considered to be heterocycles rather than functional groups. In the sections below, the expression “dialkylamino” should be taken to include both mono- and dialkylamino residues.

2.07.4.1.1 Dialkylaminosilanes, R_2NSiX_3

Dialkylaminosilanes are usually prepared by reaction of secondary and primary amines with SiCl_4 , SiF_4 , or trichlorosilanes, with only one halogen atom of the silylating agent being replaced by a diethylamino or piperidino groups.

Reactions of chloro(dimethyl)phenylsilane with primary amines have been used to obtain a series of alkylaminosilanes $[\text{Ph}(\text{Me})_2\text{SiNHR}]$ ($\text{R} = \text{Et}, \text{Pr}^i, \text{Bu}^t, \text{CH}_2\text{Ph}$) <1999MI207-02>.

Stable *N*-silylated *t*-butylcarbamates $\text{RN}(\text{SiX}_3)\text{CO}_2\text{Bu}^t$ ($\text{R} = \text{PhCH}_2, \text{Pr}$; $\text{SiX}_3 = \text{SiMe}_3, \text{SiPr}_3, \text{SiMe}_2\text{Bu}^t$) were prepared in high yields by treating *N*-*t*-BOC-protected primary amines with silyl triflates in dichloromethane in the presence of triethylamine <1997TL191>. A modified classical procedure including successive treatment of chlorosilanes with $\text{HC(OMe)}_3/\text{AlCl}_3$ and HNEt_2 made it possible to convert the methylchlorosilanes $\text{ClSiMe}_2\text{—SiClMe}_2$, $\text{Cl}_2\text{SiMe—SiCl}_2\text{Me}$ and methylchlorotrisilanes $\text{ClSiMe}_2\text{—SiClMe—SiClMe}_2$, $\text{Cl}_2\text{SiMe—SiClMe—SiCl}_2\text{Me}$ to diethylamino(methoxy)-substituted methylchlorooligosilanes <1998JOM(552)99>.

Other modifications of the synthesis of alkylaminosilanes from chlorosilanes include reaction of the latter with lithium amides and co-ammonolysis of two chlorosilanes. Thus, the hydridosilylamines $\text{ArR}^1\text{SiHNHR}^2$ ($\text{Ar} = 2\text{-Me}_2\text{NCH}_2\text{C}_6\text{H}_4$, 8-dimethylamino-1-naphthyl; $\text{R}^1 = \text{Me}, \text{Ph}$; $\text{R}^2 = \text{Bu}^t$ or

$R^1 = \text{Me}$, $R^2 = \text{SiMe}_3$) were prepared from the corresponding chlorosilanes (ArR^1SiHCl) either by reaction with the stoichiometric amount of Bu^tCNHLi or by co-ammonolysis in liquid NH_3 with Me_3SiCl in the molar ratio 1:3. Silylamides ($\text{ArR}^1\text{SiHNLiR}^2$) react with Me_3SiCl in THF to give the *N*-substitution products ($\text{ArR}^1\text{SiHNR}^2\text{SiMe}_3$) in good yield <1999ZAAC1532>.

Two new reactions were suggested for the synthesis of alkylaminosilanes but with aryl silanes as examples: (i) dehydrogenative silylation of primary and secondary amines to monoaminosilanes with triphenylsilane and (ii) hydrosilylation of imines to give mono- and diaminosilanes by using phenyl silane. Both reactions were catalyzed by ytterbium-imine complexes $[\text{Yb}(\eta^2\text{-Ph}_2\text{CNAr})\text{-(hmpa)}_n]$ <1999JOC3891>.

Structural modification of aminosilanes has been used for the preparation of new complex aminosilanes. Reaction of $(\text{Me}_3\text{Si})_2(\text{Me}_2\text{NMe}_2\text{Si})\text{CCl}$ with BuLi in THF at low temperature gives $\text{Li}\{\text{C}(\text{SiMe}_3)_2\text{SiMe}_2\text{NMe}_2(\text{THF})_2\}$, which is readily transformed by reactions with HgBr_2 , AlCl_3 , GaCl_3 , and SnCl_4 to $\text{Hg}\{\text{C}(\text{SiMe}_3)_2\text{SiMe}_2\text{NMe}_2\}_2$, $\text{Al}\{\text{C}(\text{SiMe}_3)_2\text{SiMe}_2\text{NMe}_2\}\text{Cl}_2$, $\text{Ga}\{\text{C}(\text{SiMe}_3)_2\text{SiMe}_2\text{NMe}_2\}\text{Cl}_2$, and $\text{Sn}\{\text{C}(\text{SiMe}_3)_2\text{SiMe}_2\text{NMe}_2\}\text{Cl}_3$, respectively. The treatment of the aluminum dichloride complex with LiPh gives $\text{Al}\{\text{C}(\text{SiMe}_3)_2\text{SiMe}_2\text{NMe}_2\}\text{Ph}_2$. Reaction of the initial lithium aminosilane with 1,2-diiodomethane results in the iodide $(\text{Me}_3\text{Si})_2(\text{Me}_2\text{NMe}_2\text{Si})\text{CI}$. It is of interest that, according to crystal structure determinations, there is intramolecular coordination of the N atom to the metal M with formation of a planar four-membered C-Si-N-M ring in all the compounds with $\text{M} = \text{Li}$, Al , Ga , and Sn (but not with Hg) <1999OM45>.

2.07.4.1.2 Bis(dialkylamino)silanes, $(R_2N)_2\text{SiX}_2$

As described in COFGT (1995) (chapter 2.07.5.1.2), by using the correct molar ratio of dialkylamine, it is possible to replace two of the chlorine atoms in SiCl_4 or HSiCl_3 with di- and monoalkylamino residues. At the same time, heating (diisopropylamino)trichlorosilane with diisopropylamine in benzene at 200°C in a sealed tube leads, because of steric hindrance, to the replacement of only one chlorine atom in low yield.

A mixture of trichloro(piperidino)silane and chlorotris(piperidino)silane on disproportionation (sealed tube, 260°C) gives dichlorobis(piperidino)silane.

Dehydrogenative silylation of primary and secondary amines with diphenyl and phenyl silanes, catalyzed by ytterbium-imine complexes <1999JOC3891>, gave diaminosilanes as major products. Whereas *n*- and *s*-alkylamines were readily silylated, *t*-alkylamines and aromatic amines exhibited lower reactivities. In attempted reductive cross-coupling of chlorobis(dialkylamino)silanes $[\text{ClSiH}(\text{NR}_2)_2]$ ($\text{R} = \text{Et}$, Pr^i) with ClSiMe_3 and Li , symmetrical coupling was preferred and afforded $(R_2N)_2\text{HSiSiH}(\text{NR}_2)_2$ <1998HAC311>.

The cationic Zr^{2+} complexes $\text{Me}_2\text{Si}(\text{N}^-\text{Bu}^t)_2\text{Zr}^+\text{R}_2$ ($\text{R} = \text{Cl}$, PhCH_2 , Bu^tCH_2) were synthesized from the amide $\text{Me}_2\text{Si}(\text{NLiBu}^t)_2$ by reaction of the latter with $\text{ZrCl}_4(\text{THF})_2$ followed by alkylation with PhCH_2Mg and $\text{Bu}^t\text{CH}_2\text{Li}$, respectively. Several analogous complexes having the same anion but other zirconium cations were obtained by alkyl substitution in Zr^+R_2 <1997OM5424>.

There is a substantial amount of new data concerning the synthesis of stable bis(dialkylamino)silylenes. Thus, bis(diisopropylamino)silylene, which is stable at room temperature, was generated by UV-irradiation of 3,3-bis(diisopropylamino)-1,2-bis(trimethylsilyl)-3-silacyclopentene and subsequently trapped by reaction with triethylvinylsilane or 2,3-dimethyl-1,3-butadiene. The disilene $(\text{Et}_2\text{N})_2\text{Si}:\text{SiMe}_2$ was generated by photolysis of 7,7-bis(diethylamino)-8,8-dimethyl-1-phenyl-7,8-disilabicyclo[2.2.2]octa-2,5-diene and subsequently trapped by Pr^iOH , Bu^tOH , or Et_2NH <1998JA9955>.

Dimethyl(isopropylamino)silyl chloride ($\text{Me}_2\text{Si}(\text{NPr}^i)_2\text{Cl}$) reacts with lithium metal to give symmetrical 1,2-bis(diisopropylamino)-1,1,2,2-tetramethyldisilane <1999HAC605>. 1,2-Disilane-diylbis(triflate) is a key intermediate for the facile preparation of open-chain and cyclic 1,1- and 1,2-diaminodisilanes. This bis(triflate) reacts with 2 equiv. of diethylamine to afford a mixture of the 1,2- and 1,1-isomers $(\text{Et}_2\text{NSiH}_2\text{SiH}_2\text{NET}_2)$ and $(\text{Et}_2\text{N})_2\text{SiHSiH}_3$, while with isopropylamine it gives the 1,2-isomer $(\text{Pr}^i_2\text{NSiH}_2\text{SiH}_2\text{NPr}^i_2)$ exclusively. Reaction of the triflate with 1 equiv. of a primary alkylamine affords 1,4-dialkyl-2,3,5,6-tetrasilapiperazines; bis(isopropylamino)silanes $[(\text{Pr}^i\text{NH})_2\text{SiR}_2]$ ($\text{R} = \text{Me}$, Ph) react with the triflate to give the corresponding 2-R-1,3-diisopropyl-2,4,5-trisilaimidazolidines <1997IC1758>.

Reduction of dichlorobis(diisopropylamino)silane by potassium metal in the presence of triethylsilane, alkenes, bis(trimethylsilyl)acetylene, as well as of toluene and benzene, leads, via intermediate bis(diisopropylamino)silylene, to respective bis(diisopropylamino)silanes bearing an

additional substituent on silicon or 1,1-bis(diisopropylamino)-2-(triethylsilyl)silacyclopropane (in the case of triethyl(vinyl)silane) and 1,1-bis(diisopropylamino)-2,3-bis(trimethylsilyl)silacycloprop-2-ene (in the case of bis(trimethylsilyl)acetylene) <1997BCJ253>.

2.07.4.1.3 Tris(dialkylamino)silanes, $(R_2N)_3SiX$

According to COFGT (1995), tris(alkylamino)silanes can be prepared by reactions of di(alkylamino)dichlorosilanes, $SiCl_4$, or trichlorosilanes with the corresponding amines. The reductive coupling of chlorotris(dialkylamino)silanes with $ClSiMe_3$ by the action of lithium in THF provides, for steric reasons, an easy access to unsymmetrical amino-substituted disilanes $[(R_2N)_3Si-SiMe_3]$ ($R_2N = Et_2N$, piperidino; morpholino). A similar cross-coupling between $(Et_2N)_3SiCl$ and $ClSiH(NEt_2)_2$ gives pentakis(diethylamino)disilane $[(Et_2N)_3SiSiH(NEt_2)_2]$ <1998HAC311>.

2.07.4.1.4 Tetrakis(dialkylamino)silanes, $(R_2N)_4Si$

As described in COFGT (1995), only tetrakis(dimethylamino)silane can be prepared by reactions of dimethylamine with $SiCl_4$ or dimethylamino-substituted chlorosilanes. Higher tetrakis(dialkylamino)silanes cannot be obtained because of steric hindrance and their preparation demands either drastic conditions or use of organometallic reagents such as Et_2NMgBr . No further advances have occurred concerning syntheses of tetrakis(dialkylamino)silanes since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.4.1.5 Miscellaneous compounds containing an N—Si bond

Aminotri- and aminotetrasilanes have been synthesized by using reductive cross-coupling (Li in THF) of either diaminodichlorosilanes or aminotrichlorosilanes with chlorotrimethylsilane <1999HAC605>.

Stable lithium hydrosilylamides $[Me_2SiH-N(Li)R]$ ($R = Bu^t, SiMe_3$) react with Me_3SnCl in THF to give $N-R$ -dimethylsilyl(trimethylstannyl)amines $[Me_2SiH-N(SnMe_3)R]$ <2000ZN(B)924>. Condensation reaction of $(Et_2N)_2MeSiSiMe(NEt_2)Cl$ with lithium in THF yields the hexakis(diethylamino)-substituted linear tetrasilane $Et_2N[SiMe(NEt_2)]_4NEt_2$ <1997JPR637>. Highly selective lithium metal-promoted cross-coupling reactions between 2 equiv. of Me_3SiCl or $(Et_2N)Me_2SiCl$ and aminodichloromonosilanes $[R(Et_2N)SiCl_2]$ ($R = Me, Et, Ph, Et_2N$) or 1 equiv. of Me_3SiCl , $(Et_2N)Me_2SiCl$, or $(Me_2N)_nR_{3-n}SiCl$ and aminochlorodisilanes $[(Et_2N)_nMe_{3-n}SiSiMe(NEt_2)Cl]$ ($n = 1, 2$) in THF at room temperature afford the corresponding symmetrical and unsymmetrical diamino- to pentaaminotrisilanes in high yields. A tetraaminotetrasilane was prepared by reductive homocoupling of $(Et_2N)Me_2SiSiMe(NEt_2)Cl$ <1997OM780>.

2.07.4.2 Compounds Containing an N—Ge Bond

Methods for the synthesis of compounds with an N—Ge bond resemble those used in the preparation of their silicon analogs. No further advances have occurred concerning syntheses of (alkylamino)germanes since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.4.3 Compounds Containing an N—B Bond

In the sections given below, which are the same as those used in COFGT (1995), the expression “dialkylamino” should be taken to include both mono- and dialkylamino residues.

2.07.4.3.1 Dialkylaminoboranes, R_2NBX_2

In COFGT (1995), the following routes for the preparation of dialkylaminoboranes were presented: (i) reactions of BCl_3 with dialkylamines, tris(dimethylamino)alane, or

dimethylamino(trimethyl)stannane; (ii) the reaction between HCl and tris(diethylamino)borane; and (iii) reactions of alkylamine–borane complexes with dialkylamines, the latter reactions proceeding with loss of hydrogen.

Dialkylamino(halo)boranes have been prepared by the reaction of dialkylamino(dihalo)boranes [Alk₂NBX₂ (X = Cl, Br)] with dialkylaminoboranes at 180 °C without a solvent <1999MI207-01>. Reduction of dialkylamino(dihalo)boranes by LAH in toluene can be used for the preparation of amino(dihydro)boranes <2000MI207-01>.

The *in situ* Rh-catalyzed addition of pinacolborane (HBpin, pin = 1,2-O₂C₂Me₄) to allylamine afforded products arising from hydroboration [RN(Bpin)CH₂CH₂CH₂Bpin, where R = H, Bpin] and hydrogenation [RN(Bpin)CH₂CH₂CH₃]. Hydroboration of allylimines [ArHC:NCH₂CH:CH₂] with catecholborane (HBcat) occurs initially at the more reactive imine bond to give borylamines [RCH₂N(Bcat)CH₂CH:CH₂]. Further reaction with HBcat gives varying amounts of hydroboration products [RCH₂N(Bcat)CH₂CH₂CH₂Bcat and RCH₂N(Bcat)CH₂CH(Bcat)CH₃] as well as the diboration product [RCH₂N(Bcat)CH₂CH(Bcat)₂], depending on the choice of catalyst <2001CJC1898>.

2.07.4.3.2 Bis(dialkylamino)boranes, (R₂N)₂BX

Tris(diethylamino)borane reacts with BCl₃ or BBr₃ at –80 °C to give chloro- or bromobis(diethylamino)borane; dialkylamines can be used with BCl₃ instead of boranes. An alternative route involves reaction of triphenyl borate with bis(dialkylamino)alane (the latter can be formed *in situ* from the dialkylamine) aluminum metal and H₂. Bis(dialkylamino)chloroboranes can be used as intermediates in syntheses of other bis(dialkylamino)boranes. No further advances have occurred concerning syntheses of bis(dialkylamino)boranes since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.4.3.3 Tris(dialkylamino)boranes, (R₂N)₃B

Dialkylamines (and primary amines) with BCl₃ give tris(dialkylamino)boranes. Unsymmetrically substituted compounds may be made by the reaction of an amine with a bis(dialkylamino)chloroborane. However, both of these reactions are subject to steric hindrance. Tris(dimethylamino)borane may be prepared in high yields by reaction of dimethylamino(trimethyl)stannane with trimethyl borate, BF₃ etherate or triethylamineborane. Tris(dialkylamino)boranes can be made by reaction of BF₃/alkylamine complexes with EtMgBr.

In different approaches the dimethylamino derivative is prepared by the reaction of LAH with trimethylamine hydrochloride followed by treatment with tributyl borate and the diethylamino compound by the hydrogenation of a mixture of triphenyl borate, aluminum, and diethylamine. Exchange reactions between alkylamino groups can be carried out: *s*-butylamine reacts with tris(isopropylamino)borane at 205 °C to give tris(*s*-butylamino)borane (75%) and this product can be converted into tris(methylamino)borane (40%).

No further advances have occurred concerning the syntheses of tris(dialkylamino)boranes since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.4.3.4 Miscellaneous compounds containing an N–B bond

Anions of the alkylaminosilanes Ph(Me)₂SiNHR react with trichloroborane or dichloro(phenyl)borane to give the corresponding (silylamino)boranes [Ph(CH₃)₂SiN(R)B(X)Cl (X = Cl, Ph)] <1999MI207-02>.

Reactions of metallated sulfur diimides [K–N=S=N–R (R = Bu^t, SiMe₃, PBu₃) and K–N=S=N–K] with various boron chlorides [R₂BCl, (R¹CH₂N)₂BCl and R¹R²NBCl₂] lead to the boryl-substituted sulfur diimides. The sulfur diimides (Et₂N)₂B–N=S=N–SiMe₃ and (PrⁱN)₂B–N=S=N–Bu^t react with hexachlorodisilane by cleavage of the Si–Si bond to give bis(amino)sulfanes in which the nitrogen atoms bear additional SiCl₃ substituents <1998PS(134/135)255>.

Lithiation of *N*-methylaziridine borane complex, followed by treatment with Bu₃SnCl, affords a mixture (98:2) of (*E*)- and (*Z*)-1-methyl-2-tributylstannylaziridinium 2-borates. Reaction of *N*-(2-*t*-butyldimethylsilyloxy)ethylaziridine with borane followed by lithiation (Bu^sLi) and electrophilic trapping afford (*E*)-aziridinium borates <1997JA6941>.

2.07.5 COMPOUNDS WITH AN N—METAL BOND

2.07.5.1 Compounds Containing an N—Alkali Metal Bond

2.07.5.1.1 Compounds containing an N—Li bond

As noted in COFGT (1995), substances of this type (e.g., LDA) have found extensive use in organic synthesis. The methods for preparation of these compounds have been discussed in detail in COFGT (1995). Here only selected new data are given concerning some alterations in procedures for preparation and contents of formulations of lithium alkylamides.

Ether-free compositions containing a lithium alkoxide which increases the solubility of a lithium alkylamide have been patented <1995USP5391824>. An improved method for the preparation of lithium alkylamides using bulk lithium metal has been described <1995WOP23803>. To prepare hydrocarbon solutions of lithium dialkylamides from lithium metal and dialkylamines free of amine electron carriers (e.g., styrene) have been suggested <1997WOP21714>. The solvent-free method for the preparation of lithium and other alkali metal dialkylamides using an electron carrier (e.g., α -methylstyrene) is of interest <2001USP6169203>. Also of note is the preparation of LDA as a crystalline solid by two successive vacuum sublimations <1998JA1718>.

2.07.5.1.2 Compounds containing an N—Na bond

According to COFGT (1995), compounds containing an N—Na bond have usually been made by the reaction of sodamide or sodium hydride with an amine. However, these substances can also be prepared by a solvent-free method from sodium metal and a dialkylamide using an electron carrier <2001USP6169203>. Similarly to lithium analogs, sodium diisopropyl- and cyclohexyl(isopropyl)-amides with TMEDA, $[\text{Pr}^i_2\text{Na}(\text{TMEDA})]_2$ or $[\text{CyPr}^i\text{Na}(\text{TMEDA})]_2$ form dimers that have a central planar (N—Na)₂ azametallocycle <1996JOM(518)85>.

2.07.5.1.3 Compounds containing an N—K bond

Only a few references can be added to the rather scarce data concerning syntheses of compounds containing an N—K bond that was presented in COFGT (1995). The solvent-free synthesis from potassium metal and a dialkylamide using an electron carrier should be mentioned with the same being also true for caesium dialkylamides <2001USP6169203>. Using ¹³C NMR, complexation has been observed between alkali metal hexamethyldisilylamides $[\text{MN}(\text{SiMe}_3)_2 \text{ (M = Li, Na K)}]$ and the stable carbenes 1,3-diisopropyl-3,4,5,6-tetrahydropyrimidin-2-ylidene, 1,3-diisopropyl-1,3-dihydropyrimidin-2-ylidene, and bis(diisopropylamino)methylidene. For the complex of the first of these carbenes with $\text{KN}(\text{SiMe}_3)_2$, X-ray diffraction data show it to be dimeric with the $\text{N}(\text{SiMe}_3)_2$ groups acting as bridging ligands <1999CC241>. Similar bimetallic complexes with THF have also been described <1991JA9671>.

2.07.5.2 Compounds Containing an N—Metal Bond (Not N—Alkali Metal)

The section in COFGT (1995) is mainly based on data from <B-1980MI207-01> and includes information concerning the methods used to make compounds with N—metal bond for the metals Be, Mg, Ca, V, Nb, Ta, Cr, Mo, W, Fe, Cu, Zn, Cd, Al, Ga, Sn, and U. Some additional data published after 1995 are presented below.

2.07.5.2.1 Compounds of alkaline-earth metals and zinc

Considerable interest in readily available dialkylaminomagnesium halides and bis(dialkylamino)-magnesium was stimulated by their unexpected ability to direct *ortho*-magnesiumation of functionalized derivatives of benzene <1989JA8016>, pyridine <1995LA1441, 1995JOC8414>, and indole <1996JCS(P1)2331> bearing carbamide, carbamoyl and sulfonyl substituents, as well as by their other unusual reactions <1995MI207-02, 1999TL4037, 2000H(53)1021, 2001CL602>. “Amide

Grignards” are usually prepared by the action of alkylmagnesium halides on secondary amines, preferably 2,2,6,6-tetramethylpiperidine <1989JA8016, 1995LA1441> or diisopropylamine <1996JCS(P1)2331, 2001CL602>. Magnesium bis(hexamethyldisilyl)amide has been electrogenerated from hexamethyldisilylazane in an undivided cell with a sacrificial Mg anode and used without isolation in regio- and stereoselective syntheses of silyl enol ethers <1996JOC5532>. Mixed lithium and magnesium amide compositions with good stability and solubility in hydrocarbons have been reported to be useful reagents <1994USP5320774>.

Calcium, strontium, and barium bis(hexamethyldisilyl)amides form complexes with stable carbenes (i.e., 1,3-dihydropyrimidin-2-ylidenes) <1997AG(E)2163>.

Bis(dialkylamino)zinc compounds $[\text{Zn}(\text{NR}_2)_2]$ and zinc alkyl(dialkylamides) $[\text{R}'\text{Zn}(\text{NR}_2)_2]$ have been prepared. The latter are volatile (vapor pressure ~ 5 torr at 0°C) making them potential zinc precursors in vapor deposition <1997POL3593>.

2.07.5.2.2 Compounds of group III metals

Several unassociated amide derivatives of aluminum and gallium have been obtained, namely, $\text{Mes}^*\text{Ga}(\text{Cl})\text{NHPH}\cdot 0.25(\text{hexane})$, $\text{Mes}^*2\text{GaNHPH}$, $\text{MesAl}[\text{N}(\text{SiMe}_3)_2]$, $\text{Mes}^*\text{Ga}(\text{NHPH})_2$, and $\text{ClGa}[\text{N}(\text{SiMe}_3)_2]_2$ ($\text{Mes}^* = 2,4,6\text{-Bu}_3\text{C}_6\text{H}_2$, $\text{Mes} = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2$) <1994OM2792>. Less sterically hindered compounds such as $\text{Al}(\text{NEt}_2)_3$ <1997IC1955>, $\text{Al}(\text{NPr}^1)_3$ <1994OM2792, 1997IC1955>, and $\text{Ga}[\text{N}(\text{SiMe}_3)_2]_3$ <1994OM2792> exist as dimers. Dimeric aluminum, gallium, and indium silylamides of the type $[\text{Me}_2\text{MN}(\text{R})\text{SiMe}_3]_2$ have been prepared from equimolar mixtures of Me_3M ($\text{M} = \text{Al}, \text{Ga}, \text{In}$) with the silylamines $\text{N}(\text{SiMe}_3)_3$, $\text{HN}(\text{SiMe}_3)_2$, $\text{MeN}(\text{SiMe}_3)_2$, $\text{Me}_2\text{NSiMe}_3$, and $\text{HN}(\text{Me})\text{SiMe}_3$ in benzene- d_6 and toluene- d_8 solutions. The *trans*-isomer is the major isomer according to variable temperature ^1H - and ^{13}C NMR spectroscopy. The molecular structure of *trans*- $[\text{Me}_2\text{InN}(\text{Me})\text{SiMe}_3]_2$ was determined by a single crystal X-ray diffraction study <1999JOM(585)266>.

2.07.5.2.3 Compounds of first row transition metals

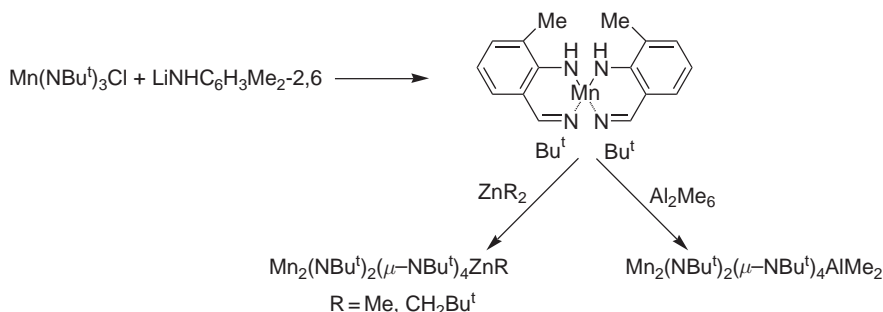
A series of *N*-substituted titanium amides have been prepared, their distinctive feature being the presence of a bulky alkyl (*t*-butyl, neopentyl, CMe_2Ph) and an *ortho*-substituted aryl group on nitrogen <1996OM3825>. A salt containing a titanium amide cation $\{[\text{Ti}(\text{NMe}_2)_3(\text{NC}_5\text{H}_5)_2]^+ [\text{BPh}_4]^- \}$ has been prepared and its crystal structure determined <1997JOM(531)115>.

The interaction of LDA with cyclopentadienyltitanium and -hafnium trichlorides ($\text{C}_5\text{R}_5\text{MCl}_3$, $\text{R} = \text{H}, \text{Me}$; $\text{M} = \text{Ti}, \text{Zr}$) leads to the products $\text{C}_5\text{R}_5\text{M}(\text{NPr}^1_2)\text{Cl}_2$ with $\text{M}-\text{N}$ bonds <1995JOM(497)17>. Zirconium and hafnium tetramethylamides as well as zirconium tetrapyrrolidide replace one of their amino ligands with 1,2-bis(indene-3-yl)ethane by loss of a secondary amine <1996OM4030>.

The paramagnetic *t*-butylimidovanadium(IV) complex $\text{Bu}^t\text{N}=\text{VCl}_2\cdot\text{DME}$ reacts with LiOR ($\text{R} = \text{Et}, \text{Pr}^1, \text{SiMe}_3$), LiOAr , or LiNR_2 ($\text{NR}_2 = \text{NBu}^t(\text{SiMe}_3)$, $\text{N}(\text{SiMe}_3)_2$) to form binuclear diamagnetic compounds of V(IV) $[(\mu\text{-NBu}^t)_2\text{V}_2(\text{OR})_4]$, $(\mu\text{-NBu}^t)_2\text{V}_2\text{Cl}_2(\text{OAr})_2$, $(\mu\text{-NBu}^t)_2\text{V}_2(\text{OAr})_4$, and $(\mu\text{-NBu}^t)_2\text{V}_2\text{Cl}_2(\text{NR}_2)_2$. Their analogs $[(\mu\text{-NBu}^t)_2\text{V}_2(\text{CH}_2\text{CMe}_3)_2(\text{OAr})_2]$, $(\mu\text{-NBu}^t)_2\text{V}_2\text{Me}_2(\text{NR}_2)_2$, $(\mu\text{-NBu}^t)_2\text{V}_2\text{Cl}_4$, and $\text{Bu}^t\text{N} = (\text{OAr})_3$ were also prepared <2000ZAAC(626)1665>. The reactions of $\text{Bu}^t\text{N}=\text{VCl}_2\cdot\text{DME}$ with Bu^tNHLi and MeLi afford the binuclear diamagnetic V(IV) compounds $(\mu\text{-NBu}^t)_2\text{V}_2\text{X}_4$ ($\text{X} = \text{NHBu}^t$ and Me). The syntheses of the binuclear compounds $(\mu\text{-NBu}^t)_2\text{V}_2(\text{NBu}^t)_2\text{Cl}_2$ and $(\mu\text{-O})\text{V}_2(\text{NBu}^t)_2\text{Cp}_2\text{Cl}_2$ have also been described <2001ZN(B)1100>.

Monomeric chromium tris(dialkylamides) [e.g., $\text{Cr}(\text{NPr}^1_2)_3$], readily available from CrCl_3 and lithium amides, on treatment with nitric oxide quantitatively give the nitrosyl compounds $\text{ON-Cr}(\text{NRR}')_3$, which are deoxygenated by the THF complex of trimesitylvandium to give chromium(VI) nitrido compounds $\text{N}\equiv\text{Cr}(\text{NRR}')_3$ <1995JA6613>.

Tris(*t*-butylimido) Mn(VII) chloride reacts with lithium *t*-butylamide to give a dimeric compound of Mn(VI) and a salt containing the Mn(VII) nitrido anion $[\text{Mn}(\text{N})(\text{NBu}^t)_3]^{2-}$ (Equation (19)). The interaction of the same chloride with lithium 2,6-dimethylphenylamide leads to a paramagnetic tetrahedral spiro compound of Mn(II), which affords bimetallic compounds on reactions with dialkylzinc or trimethylaluminum (Scheme 24) <1995JCS(D)205>. A bimetallic compound of the type $\text{Mn}[\mu\text{-NBu}^t)_2\text{AlMe}_2]_2$ has been obtained by the reaction between $[\text{Li}(\text{dme})]_2\text{Mn}(\text{NBu}^t)_4$ and Al_2Me_6 <1995JCS(D)205>.



Scheme 24

2.07.5.2.4 Compounds of transition metals of second and third rows

Tetrameric (pentamethylcyclopentadienyl)ruthenium chloride reacts with LDA to give an unusual binuclear $\text{Cp}^*\text{Ru}(\mu\text{-H})(\mu\text{-}\eta^3\text{-}\eta^1\text{-Pr}^i\text{NC(Me)CHH}_{\text{agostic}})\text{RuCp}^*$ complex <1995OM3188>.

The THF complex of cerium trichloride reacts with lithium dialkylamides to give cerium tris(dialkylamides) $\text{Ce}(\text{NR}_2)_3$ ($\text{R} = \text{Et}, \text{Pr}^i$) <1997AG(E)2480>. $\text{SmCl}_3(\text{THF})_3$ reacts with LDA to give a product characterized as a binuclear complex $(\text{Pr}_2\text{N})_2\text{SmCl}_3[\text{Li}(\text{TMEDA})_2]$ <1996IC1866>.

LDA reacts even with neodymium trichloride to form the “ate” complex $[(\text{Pr}_2\text{N})_2\text{Nd}(\mu\text{-NPr}^i)_2]_2\text{-Li}(\text{THF})$ as by-product: the main product $[\text{Nd}(\text{NPr}^i)_3(\text{THF})]$ on treatment with trimethylaluminum gives a bimetal complex $\{\text{Nd}[\text{NPr}^i][(\mu\text{-NPr}^i)(\mu\text{-Me})\text{AlMe}_2][(\mu\text{-Me}_2)\text{AlMe}_2]\}$ possessing agostic metal, interacting with all three ligand systems <1995IC5927>.

2.07.6 N-ALKYL COMPOUNDS OF THE TYPE $\text{RN}=\text{Y}$

2.07.6.1 Azo and Azoxy Compounds and Their Derivatives

2.07.6.1.1 Azo compounds

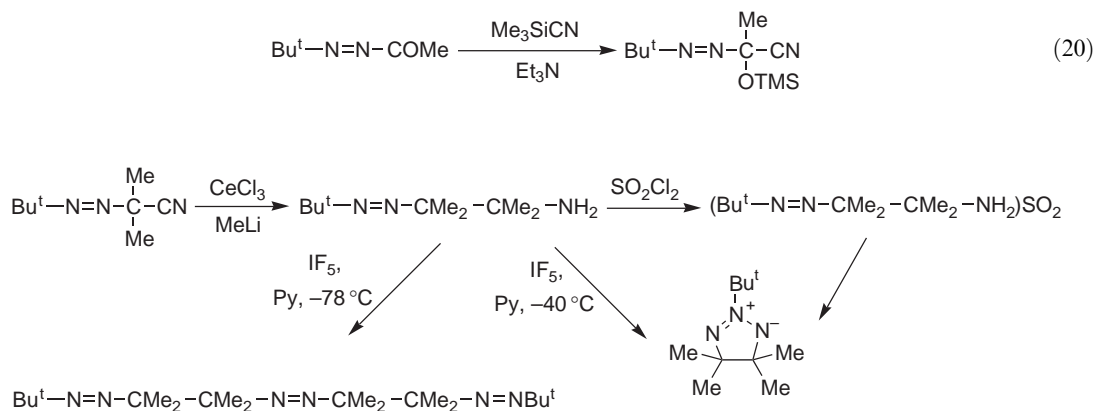
Many methods for the preparation of aliphatic azo compounds (diazenes) are known and have been described in COFGT (1995) <1995COFGT(2)371>. These include oxidation of N,N' -disubstituted hydrazines. Along with conventional use of HgO as an oxidant <1995JOC1897>, some new and modified oxidizing systems have been described including the solid-state system $\text{K}_3\text{Fe}(\text{CN})_6\text{-KOH}$ <2001MI207-03>, lead tetraacetate <1998JOC9763>, $\text{H}_2\text{O}_2\text{-Br}_2$ <2002RUP2177939>, and NBS in pyridine <1997MI207-03>. Oxidation of NH_2 groups attached to a tertiary carbon atom with IF_5 has also been used for the preparation of aliphatic azo compounds <2000JOC1016>.

Azo compounds have been synthesized by the reduction of N,N' -azoxydioxides with hexachlorodisilane <1996JOC7895> and by catalytic hydrogenation of ketazines <1996MI207-04>.

Trifluoronitrosomethane reacts with methanesulfonyldiazene in the presence of Na_2CO_3 in THF to give 1-trifluoromethyl-2-methylsulfonyldiazene <1997ZN(B)135>.

A vast number of publications are devoted to the preparation of 1,2-diazabuta-1,3-dienes (ethenyldiazenes) and their use in organic synthesis (see reviews <1995FES379, 1997SL1128, 2002MI207-02>). A synthesis of 1,2-diazabuta-1,3-dienes consists of 1,4-dehydrohalogenation of the appropriate hydrazones by EtNPr_2^i <1996JOC8921> and the same procedure has been used for the first preparation of polymer-bound diazabutadienes <1999TL9277>. The action of t -butyl hypochlorite on hydrazones leads to 2-substituted 1-(chloroalkyl)diazenes <1998S721>.

There are also some methods for transformations of diazene substituents and two are shown in Equation (20) <1998JOC9763> and Scheme 25 <2000JOC1016763>. The formation of a trisazoalkane and a cyclic azimine (Scheme 25) are of special interest.



Scheme 25

On UV irradiation, stable *trans*-dimethyldiazene equilibrates to a mixture (10:1) with the *cis*-isomer, which has been isolated in pure form <1995JOC1897>.

2.07.6.1.2 Azoxy compounds

The preparation of azoxy compounds has been reviewed <1993UK157> and carcinogenesis induced by these compounds has also been reviewed <2001MI207-04>.

As discussed in COFGT (1995), the oxidation of azo compounds with a peroxyacid or H_2O_2 is commonly used for the preparation of azoxy compounds. Partial oxidation of a bis-azo compound has been accomplished using *meta*-chloroperbenzoic acid (MCPBA) <1999JA6367>.

Reactions of alkyl- and allylhydroxylamines with nitrosating agents (e.g., NaNO_2 or BuONO) give the salts of alkyl(hydroxy)diazene 1-oxides, which can be further transformed to their tosylates or alkyl ethers by treatment with TsCl or AlkX <1998IZV1996, 1998IZV2262> as well as to bis[(1-alkyl-*NON*-azoxy)oxy]methanes and 1,2-bis[(1-alkyl-*NON*-azoxy)oxy]ethanes <1997IZV1486, 1998IZV2266, 1999IZV123>.

Reaction of *N,N*-dibromo-*t*-butylamine with ketoximes ($\text{R}_2\text{C}=\text{NOH}$) gives 1-bromoalkyl(cycloalkyl)-substituted 2-*t*-butyldiazene oxides <1994IZV176>, whereas aromatic nitroso compounds with the same reagent give 2-aryl-1-(*t*-butyl)diazene oxides <1999IZV2126>. Aromatic nitroso compounds react with $\text{NH}_4\text{Br}/\text{NBS}$ in acetonitrile to give 1-aryl-2-bromodiazene oxides, which with alkenes give aryl(2-bromoalkyl)diazene oxides <1995IZV917> and 2-alkenyl-1-aryldiazene oxides <1995IZV924>. Stable 1-aryldiazene oxides [$\text{ArN}(\text{O})=\text{NR}$ ($\text{R} = \text{Bu}^t$, CO_2Bu^t , CONH_2)] under the action of nitronium tetrafluoroborate in MeCN give 1-aryl-2-nitrodiazene oxides (45–91% yield) <1997IZV1081>. Fluoro(trifluoromethyl)diazene 2-oxide has been prepared by reaction of CF_3NO with tetrafluorohydrazine <2002IC6125>.

Addition of NO (2 mol) and sodium alkoxides to propenyl ketones followed by methylation with MeI gives 1-substituted 2-methoxydiazene oxides, which after removal of the acyl group yield 1-(2-alkoxymethyl)propyl 2-methoxydiazene oxides <1997ZOR173>.

The preparative electro-oxidation of anions of primary nitroamine salts [$\text{RNNO}_2^-\text{M}^+$ ($\text{R} = \text{Me}$, Et ; $\text{M} = \text{Bu}_4\text{N}$, Li , Na)] in the presence of nitrosobenzene gives diazene oxides [$\text{RN} = \text{N}(\text{O})\text{Ph}$] in moderate-to-good yield <2000IZV1427>.

2.07.6.1.3 *N,N'*-Azodioxides (nitroso dimers)

N,N'-Azodioxides exist as an equilibrium mixture of monomeric (azodioxide) and dimeric (nitroso dimer) forms. These compounds are usually prepared by oxidation of: (i) hydroxylamines by oxygen, using a cobalt naphthenate catalyst, or by bromine, (ii) azoxy compounds by MCPBA, and (iii) amines by H_2O_2 /tungstate. A series of primary amines including Bu^tNH_2 and several bicyclic and adamantyl amines have given azodioxides using MCPBA as the oxidant <1995JA10460>.

No further advances have occurred concerning the syntheses of such compounds since the publication of COFGT (1995) <1995COFGT(2)371>.

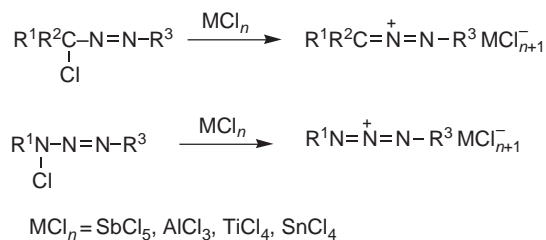
2.07.6.1.4 Azamines

Azamines (or azimines) are known to be only stable at -78°C <1995COFGT(2)371>. These compounds are prepared by the reaction of Bu^tOCl with highly hindered *N,N*-dialkylhydrazines. One example of a rather stable cyclic azamine was mentioned in Section 2.07.6.1.1 (Scheme 25) and was prepared in 85% yield from highly hindered alkyl(2-aminoalkyl)diazene under the action of IF_5 in pyridine <2000JOC1016763>.

No further advances have occurred concerning the syntheses of azamines since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.6.1.5 1-Aza- and 1,3-diaza-2-azoniaallene salts

Since 1992 many publications by Jochims and co-workers have described previously unknown 1-aza-2-azoniaallene salts <1992S710, 1993CB2519, 1993T9973, 1994CB541, 1994CB947, 1996S274, 1998S721, 2001PHA372> and 1,3-diaza-2-azoniaallene salts <1997S233, 1997T5755>, and their use in organic synthesis <1998JCS(P1)947>. Both types of salt are prepared by treatment of chlorinated precursors with Lewis acids (Scheme 26).



Scheme 26

2.07.6.2 Compounds Containing an $\text{N}=\text{P}$, $\text{N}=\text{As}$, $\text{N}=\text{Sb}$, or $\text{N}=\text{Bi}$ Bond

2.07.6.2.1 Compounds containing an $\text{N}=\text{P}$ bond

A review concerning preparation and chemical transformations of phosphazenes has been published <2002MI207-03>.

(i) Substances of the type $\text{RN}=\text{P}^+\text{Hal}^-$

These compounds were thought not to exist as monomers. However, it has now been shown that the ability to exist in monomeric form depends on the steric properties of the substituents R: with $\text{R} = 2,6\text{-diisopropylphenyl}$ and especially $2,4,6\text{-tri}(t\text{-butyl})\text{phenyl}$ the chlorides and triflates are stable as monomers <2002JA14012>.

(ii) Substances of the type $\text{RN}=\text{PNR}'_2$

Aminophosphazenes ($\text{RN}=\text{PNR}'_2$) can be obtained by the reaction between PBr_3 or PCl_3 and an amine or a *N*-lithiated amine. It is also possible to prepare them via an intermediate of the type $\text{R}^1\text{R}^2\text{NPCI}_2$. Similar methods can be used to make compounds of the type $\text{R}^1\text{N}=\text{PNR}^2\text{NR}^3\text{R}^4$. No further advances have occurred concerning the syntheses of compounds considered in this section since the publication of COFGT (1995) <1995COFGT(2)371>.

(iii) Substances of the type $RN=PHal_3$

Compounds of this type rapidly dimerize when R = alkyl but monomers can be isolated when the group is bulky, as in the case of the preparation of $PhSO_2N=PCl_3$ by a Kirsanov reaction between PCl_5 and $PhSO_2NH_2$ <2001JAP335590>. It is possible to convert the trichloro compounds to the tribromo derivatives by treatment with $TMS-Br$.

(iv) Substances of the type $RN=P(OR')_3$

Iminophosphates can be obtained by reaction of phosphates $[P(OR')_3]$ with R_2NCl or with $RNCl_2$. A variant of the Staudinger reaction has also been employed in which an azide reacts with a phosphite with loss of nitrogen. An alternative route to these compounds is reaction of the compounds $RN=PHal_3$ with alkali metal alkoxides <2001JAP335590>.

(v) Substances of the type $RN=P(NR'_2)_3$

Iminophosphoric triamides can be prepared by a number of methods. In a variant of the Staudinger reaction, an azide is allowed to react with $(Me_2N)_3P$. An alternative procedure adds an amine to one of the $P=NR$ bonds of the compounds $(RN=)_2PNR'_2$.

Reaction of N -aryliminotrichlorophosphoranes with pyrrolidine gives the corresponding N -arylimino(tripyrrolidino)phosphoranes <2000JCS(P1)2637>. Tris(*t*-butylamino) (trimethylsilylimino)phosphorane has been obtained by treatment of trichloro(trimethylsilylimino)phosphorane with lithium *t*-butylamide (3 mol) <2002CC2332>.

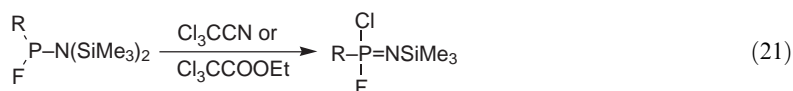
There are many syntheses of iminophosphoranes based on elimination reactions of tetraaminophosphonium salts. As an example, preparation of a series of iminophosphoranes which are very strong bases <1994CB2435, 1996LA1055> should be mentioned. On reactions of chlorotris(pyrrolidino)phosphonium chloride with ammonia or aromatic amines, the corresponding iminophosphoranes have been synthesized <2000JCS(P1)2637>.

(vi) Miscellaneous substances containing $N=P$ bonds

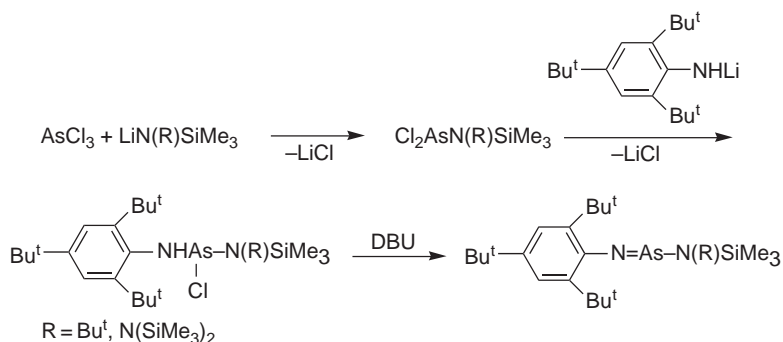
Several phosphorylated iminophosphoric triamides $[(RR'N)_3P=NP(O)(NRR'')_2]$ have been obtained by the reaction of $Cl_3P=NP(O)Cl_2$ with an amine <1994HAC349>.

Amidophosphonium isothiocyanates, such as $S=C=N-P^+(NMe_2)_3Cl^-$, react with electron-rich heterocycles (HetH), and enamines, in the presence of Et_3N to give N -thioacylated iminophosphoric triamides $[Het-C(S)-N=P(NMe_2)_3]$ <2002ZOB1791>.

Chlorofluoro(N -trimethylsilyl)imidophosphates have been prepared according to Equation (21) <1996IZV1295>.

2.07.6.2.2 Compounds containing an $N=As$ bond

Few publications have appeared concerning the preparation of compounds containing an $N=As$ bond since the publication of COFGT (1995) <1995COFGT(2)371>. However, the first examples of monomeric compounds with an $N=As$ bond have been published recently. Dehydrochlorination of [*t*-butyl(trimethylsilyl)amino]chloro[2,4,6-tris(*t*-butyl)phenylamino]arsine and [2,4,6-tris(*t*-butyl)phenylamino]chloro[2,4,6-tris(trimethylsilyl)hydrazino]arsine with DBU affords stable iminoarsines (Scheme 27) <2000EJI165>. Another compound of this type $[(Me_2Bu^tSi)_2N=As-SiMe_2Bu^t]$ was obtained by elimination of *t*-butyldimethylsilyl chloride from $[(Me_2Bu^tSi)_2N]_2AsCl$ by vacuum thermolysis <2000EJI477>.



Scheme 27

2.07.6.2.3 Compounds containing an N=Sb bond

As in the case of arsenic, the first monomeric antimony compounds with N=Sb bonds [$\text{Ar}_3\text{Sb}=\text{NSO}_2\text{CF}_3$ (Ar = *o*-tolyl and *o*-anisyl)] have been synthesized <2000IC1340>. For these syntheses two alternative routes were used: (i) Kirsanov-type reaction of Ar_3SbCl_2 with trifluoromethanesulfonamide in the presence of potassium *t*-butoxide or (ii) redox condensation of Ar_3Sb with the same sulfonamide in the presence of diethyl azodicarboxylate. It is important to note that attempts to prepare analogous compound with Ar=Ph failed. Bismuth analogs [$\text{Ar}_3\text{Bi}=\text{NTs}$] were prepared from Ar_3Bi and (tosyliminoiodo)benzene [$\text{TsN}=\text{I}-\text{Ph}$] <1996JCR(S)24>. No other advances have appeared concerning syntheses of such compounds since the publication of COFGT (1995) <1995COFGT(2)371>.

2.07.6.3 Compounds Containing an N=Si or N=B Bond

Hydridosilylamides [$\text{ArR}^1\text{SiHNLiR}^2$ (Ar = 8-dimethylamino-1-naphthyl; $\text{R}^1 = \text{Me, Ph}$; $\text{R}^2 = \text{Bu}^t$)], in contrast to the amides with Ar = 2-Me₂NCH₂C₆H₄, are unstable in hot xylene. They eliminate LiH to form the silanimines [$8\text{-Me}_2\text{NC}_{10}\text{H}_6\text{Si(R}^1)=\text{NBu}^t$] <1999ZAAC1532>.

The dehydrohalogenation of amino(chloro)(aryloxy)boranes [ArOB(Cl)NHBu^t (Ar = 2,6-Bu₂C₆H₃, 2,6-Ph₂C₆H₃)] with Bu^tLi at low temperature involves the intermediate formation of an aryloxy(imino)borane whose structure can be represented as $\text{ArO}-\text{B}=\text{N}-\text{Bu}^t \leftrightarrow \text{ArO}-\text{B}^-\equiv\text{N}^+-\text{Bu}^t$. However, the diazadiboretidines [ArOB:NBu^t]₂ are isolated as the ultimate products <2000OM5083>.

2.07.6.4 Compounds Containing an N=Metal Bond

The corresponding section in COFGT (1995) included only three references which were to tantalum and niobium compounds apparently containing an N=metal link. To these can be added the half-sandwich Nb(V) and Ta(V) complexes $\text{RN}=\text{M}(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)\text{Cl}_2$ <1999JOM(580)161>.

Paramagnetic *t*-butylimidovanadium(IV) complexes Bu^tN:VCl₂·DME, Bu^tN:VCl₂·2L (L = 1,4-dioxane, THF, PMe₃, PET₃, pyridine) and Bu^tN:VBr₂·DME have been prepared. Their structures can be formally regarded as having N=V double bonds although the free compounds were found by mass spectrometry to be the binuclear substances ($\mu\text{-NBu}^t$)₂V₂X₄ (X = Cl, Br) <2000ZAAC(626)1665>. In reactions of Bu^tN=VCl₂·DME with LiX (X = NR₂, OSiPh₃, SR, Cp), only the vanadium(V) compounds Bu^tN=VX₃ and Bu^tN=VCpCl₂, formed by disproportionation of the V(IV) precursors, could be isolated <2001ZN(B)1100>.

Tetrahedral osmium(VIII) tetrakis(*t*-butylamide) has been prepared and its structure determined in the gas phase by electron diffraction <1994JCS(D)1563>.

Having in mind metal-like properties of tellurium, several compounds with N=Te bonds prepared from tellurium tetrachloride and lithium *t*-butylamide have been reported <1995JA2359>.

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Biographical sketch

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2.08

Alkylphosphorus Compounds

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2.08.1 INTRODUCTION

Among the basic inorganic reagents that are used to introduce phosphorus into organic molecules, phosphorus halides still play the most important role. However, contrary to the earlier work, elemental phosphorus and phosphine (PH_3) have recently gained considerable attention. Apart from the inorganic reagents, numerous simple organo-phosphorus derivatives, usually commercially available, remain the starting materials of choice for the synthesis of structurally more sophisticated products. This chapter provides an update of the alkylphosphorus chemistry described in COFGT (1995) <1995COFGT(2)425> and covers the literature published since 1995.

2.08.2 ALKYLPHOSPHINES— RPH_2 , R_2PH , R_3P —AND SALTS THEREOF— $R_4P^+X^-$, etc.

Methods of synthesis of phosphines and phosphonium salts that were published in the years 1995–2000 have been comprehensively reviewed by Allen <1995MI1>. It should be mentioned here that most of the earlier approaches, have been used recently for the synthesis of new types of phosphines, e.g., air-stable, water-soluble, and multi-functional.

2.08.2.1 Primary Phosphines— RPH_2

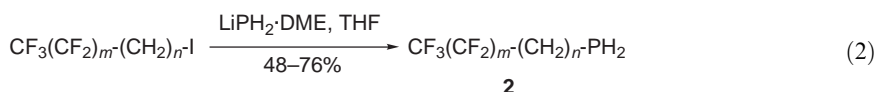
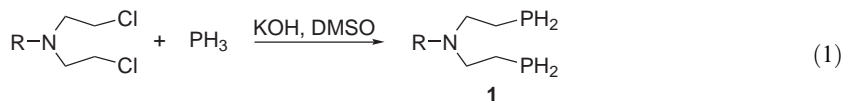
2.08.2.1.1 Primary phosphines from PH_4I and alkylating agents

This is the oldest method for the preparation of phosphines and has not been explored further recently.

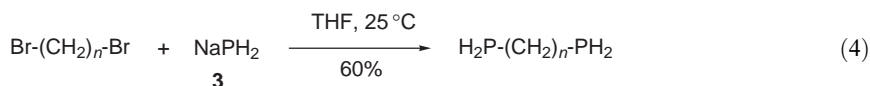
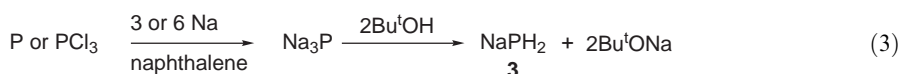
2.08.2.1.2 Primary phosphines from metallated phosphines

Earlier reports describe the reaction of monometallated phosphine with alkyl halides as a common route to primary phosphines. Among the metals used are sodium, potassium, lithium, calcium, and even aluminum in the form of a complex between $AlCl_3$ and PH_3 . Also, a variety of reaction conditions have been applied, including liquid ammonia and DMSO. Most of these approaches

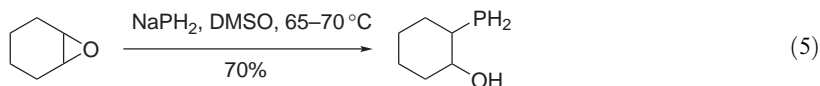
are still in use, although some modifications have been made, usually subject for patents. Thus, primary phosphines have been prepared from PH_3 and alkyl halides in an aqueous alkali/organic solvent system in the presence of phosphonium halides of the type $\text{Bu}_3(\text{C}_{16}\text{H}_{33})\text{P}^+\text{Br}^-$ as phase-transfer catalysts <2002JAP(K)2002255983> or in the presence of 18-crown-6 at 80°C <2001JAP(K)2001354683>. A similar methodology has also been used for the preparation of structurally more sophisticated primary phosphines, e.g., bis-(2-phosphinoethyl)-amines **1** (Equation (1)) <1998JOM(553)39> and fluoro phosphines **2** (Equation (2)) <2000EJI1975>.



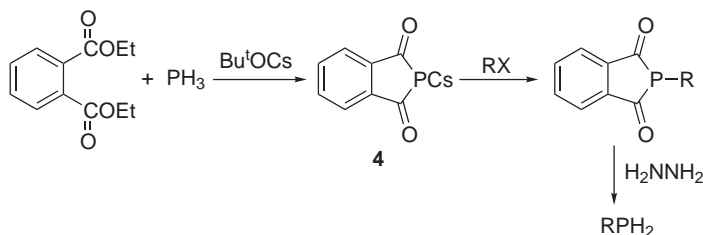
Metallated phosphine has also been generated from white or red phosphorus either by alkali metal hydroxides in DMSO or DMF, or by *t*-butanol-assisted fission of the P—P bonds with alkali metals in liquid ammonia <1995MC14, 1998IZV1695, 1996ZOR269>. Recently, liquid ammonia has been replaced by organic solvents (THF, DME) with naphthalene or phenanthrene as a metal-solubilizing additive and, besides elemental phosphorus, phosphorus trichloride has also been used as a phosphorus source (Equation (3)) <2000PS(162)39>. Sodium phosphide **3** thus formed, has been treated with alkyl halides or dihalides to give primary phosphines or diphosphines (Equation (4)).



When oxiranes are used as electrophiles, the corresponding 3-hydroxyalkylphosphines are formed <1997ZOB1907>. For less reactive cycloalkyl oxiranes DMSO has to be used as a solvent at elevated temperatures (Equation (5)) <2000S65>.



A masked metallated phosphine **4**, obtained from phosphine, diethyl phthalate, and alkali metal *t*-alkoxides <2001OM1705> has been used for the synthesis of primary alkylphosphines by a phospho-Gabriel route (Scheme 1) <2001MI091>.

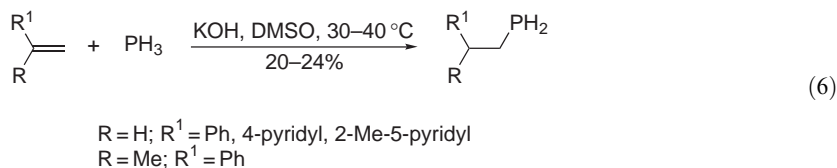


Scheme 1

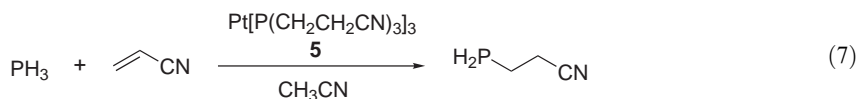
2.08.2.1.3 Primary phosphines by addition of P—H to unsaturated compounds

The addition of PH_3 to unsaturated compounds can be achieved by using acidic or basic catalysts or by performing the reaction under radical conditions. In recent years very little progress has been made in this area. Thus, addition of phosphine to alkenes in the presence of HF under high

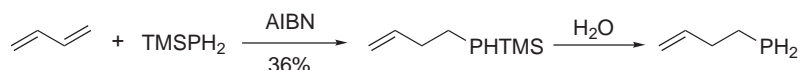
pressure is reported to give primary phosphines in 27% yield <1998JAP(K)10158284>. Similar yields have also been obtained in the addition of phosphine to alkenes having weak electrophilic double bonds, in the presence of strong bases (Equation (6)) <1995IZV1597, 1997ZOB70>.



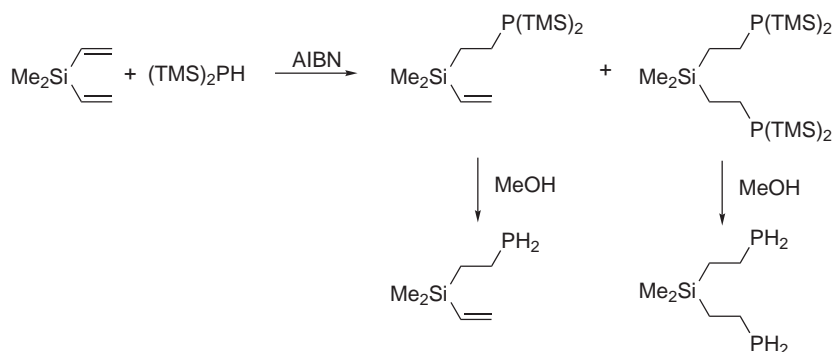
The Pt(0) complex **5** has been found to be the most efficient catalyst among several analogous complexes of other metals (Pd, Ni, Rh, Ir) for the addition of phosphine to acrylonitrile (Equation (7)) <1997JCS(D)4277>.



Another approach that has been reported involves application of trimethylsilylphosphine (Scheme 2) or bis(trimethylsilyl)phosphine (Scheme 3), which on radical addition to alkenes form secondary silylalkylphosphines or tertiary bis-silylalkylphosphines, respectively. Further methanolysis or hydrolysis lead to the parent primary phosphines <1997PS(123)141>.

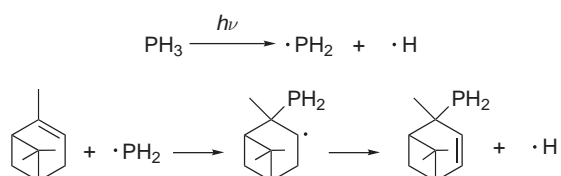


Scheme 2



Scheme 3

Phosphine reacts via a free-radical pathway with α -pinene or linaol to form products in which the double bond migrates to the adjacent position (Scheme 4) <1996IJC(B)611>.

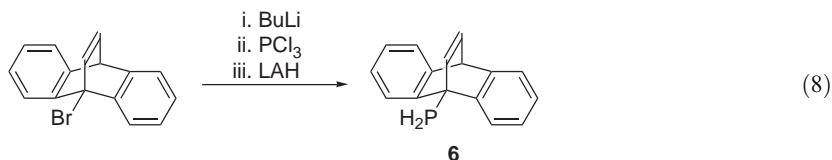


Scheme 4

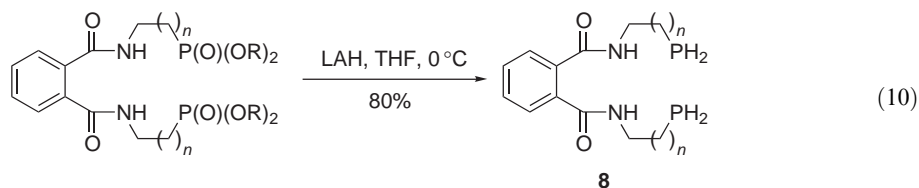
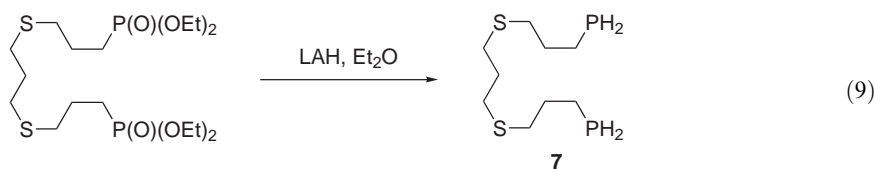
2.08.2.1.4 Primary phosphines by reduction of phosphonous and phosphonic compounds

Reductions of various types of phosphonous and phosphonic compounds with a wide range of reducing agents have always been one of the most used methods of synthesis of primary phosphines. Recently not only a large number of applications of this methodology are reported, particularly the synthesis of certain unusual or sophisticated primary phosphines, but also the development of the reducing agents and the conditions applied.

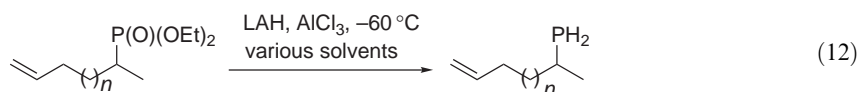
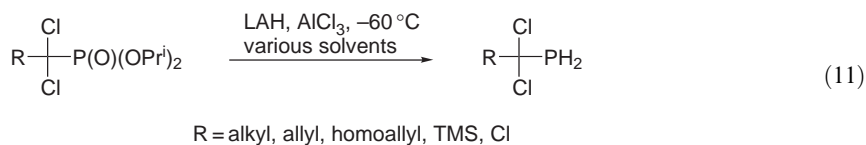
Thus, dihalophosphines are normally reduced using LAH in various solvents which gives many different types of phosphines, e.g., menthylphosphine <1997T4363>, bis-silylalkylphosphines <2002JOM(656)43>, *t*-alkylphosphines <2000ZOB1320, 1995JAP(K)07316171>, and a variety of allyl-type phosphines <1998JOC59>. A particularly interesting example is dibenzobarellene-phosphine **6**, an air-stable, crystalline compound (Equation (8)) <1999CC961>. Phosphonyl dihalides have also been used as substrates for this type of reduction <1995JAP(K)07285977>.



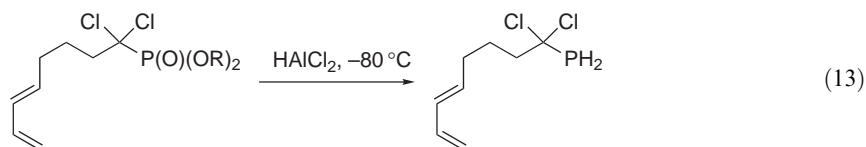
LAH has also been used as a reducing agent for phosphonites <1995ZN(B)1004> and phosphonates, both to obtain lower alkylphosphines <1997JOM(529)205, 1999JA4653> and differently substituted bis-phosphines <1998JCS(P1)1643>, e.g., **7** (Equation (9)) <1997MI444>, tris-phosphines, e.g., 1,3,5-[PH₂(CH₂)_n]₃C₆H₃, *n* = 2, 3, 4 <2001JOM(630)244> and a variety of air-stable mono-, bis- and tris-primary phosphines having different organic framework, e.g., an amido functionality **8** (Equation (10)) <2000MI431, 2000JA1554, 2000JOC676>.



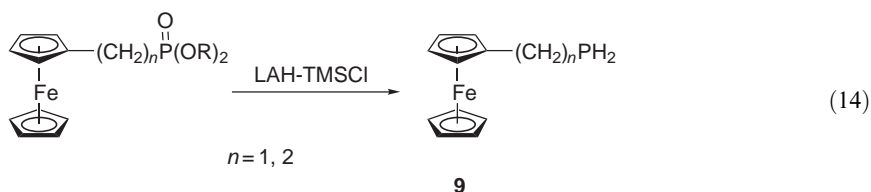
In turn, a modification in which a mixture of LAH and AlCl₃ is used as a reducing agent has made it possible to obtain ω -bromo- <1999AG(E)2020>, mono-, di-, and trichloroalkylphosphines (Equation (11)) <2001JOC7864, 2002CEJ4919> and variously substituted ω -alkenylphosphines (Equation (12)) <2000JA1824, 2001JA10221>.



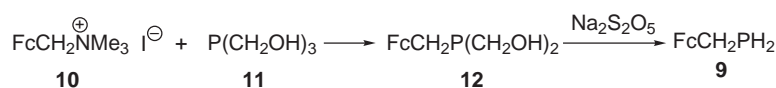
Similar results have been obtained using AlCl_2H as a reducing agent. The low temperatures of this reaction has enabled the preparation, for example, of a chlorodienylphosphine with retained configuration at the double bond (Equation (13)) <1996PS(109-110)461, 1998CC457>. Primary phosphines possessing triple bonds can also be obtained in this way <2000JA1824, 1999JA4653, 2002CEJ4919>.



A new reducing system, namely $\text{LAH-Me}_3\text{SiCl}$, has been used in the synthesis of a series of air-stable alkylphosphines bearing the ferrocenyl group **9** (Equation (14)) <2002JOM(656)120>.



Ferrocenylmethylphosphine (**9**, $n = 1$) was obtained earlier by the same group via a sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$) mediated elimination of formaldehyde from the corresponding bis(hydroxymethyl)phosphine **12** <1997CC31, 1999JCS(D)1785> which, in turn, was synthesized from ferrocenylmethylammonium iodide **10** and tris(hydroxymethyl)phosphine **11** (Scheme 5) <1996CC1551>.



Scheme 5

New reducing agents of another kind, namely the silanes PhSiH_3 or Ph_2SiH_2 in the presence of catalytic amounts of tris(pentafluorophenyl)borane, have been used for reduction of dialkyl phosphonates to primary phosphines. However, this methodology proved to be not very efficient with much better results being obtained in the synthesis of secondary phosphines (cf. Section 2.08.2.2.4.(ii)) <2002TL5569>.

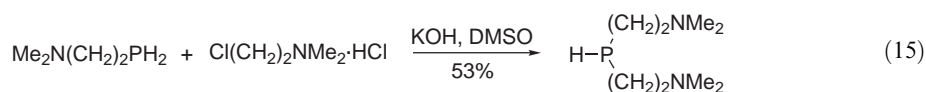
2.08.2.2 Secondary Phosphines— R_2PH and $\text{R}^1\text{R}^2\text{PH}$

In general, secondary phosphines have been synthesized in ways similar to primary phosphines. The main approaches involve alkylation of free phosphines or metallated phosphines, addition of P-H derivatives to unsaturated compounds, and reduction of organophosphorus derivatives having the P in a higher oxidation state as well as cleavage of the P-P and C-P bonds.

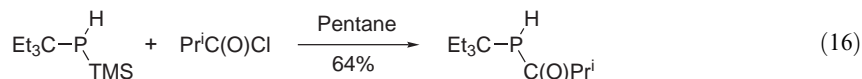
2.08.2.2.1 Secondary phosphines from phosphines and alkylating/aryllating agents

(i) Dialkylphosphines

Secondary phosphines have been obtained by the reaction of the corresponding primary phosphines with alkyl halides. They can be obtained either in the form of HX salts <2000BCJ705> or as free phosphines when the reaction is carried out in the presence of a base (Equation (15)) <1995CB275>.

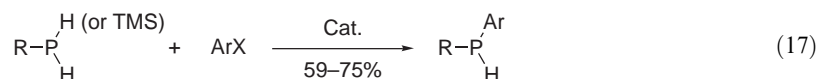


Synthesis of a secondary acylphosphine has been achieved by the reaction of a secondary silylphosphine with an acyl chloride (Equation (16)) <2000ZOB1320>.

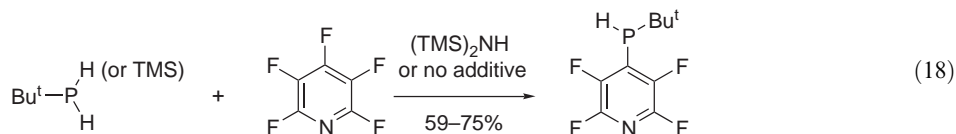


(ii) Alkylaryl- and alkylalkenylphosphines

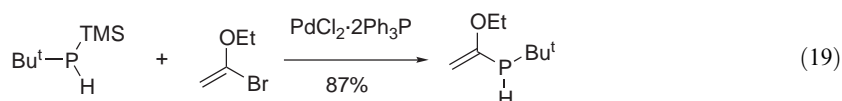
When primary alkylphosphines or secondary alkylsilylphosphines are treated with haloarenes, corresponding alkylarylphosphines are produced (Equation (17)). The reaction requires, however, the use of organometallic catalysts, such as $\text{Pd}(\text{PPh}_3)_2$ <2002JOM(653)167>, $\text{PdCl}_2(\text{PPh}_3)_2$ <1998ZOR559>, or *trans*-di(μ -acetato)-bis[*o*-(di-2-tolylphosphino)benzyl]dipalladium(II) <2002JOM(645)14>.



In contrast, a secondary silylphosphine (or a mixture of a primary phosphine with hexamethyldisilazane, $(\text{Me}_3\text{Si})_2\text{NH}$) reacts slowly with perfluoropyridine without catalyst to give the corresponding product in 65% yield (Equation (18)) <2000ZOR778>.



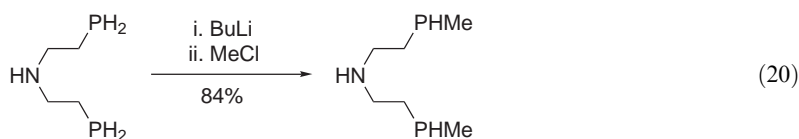
In a similar way, alkylalkenylphosphines can be obtained using vinyl halides as alkenylating agents (Equation (19)) <1995TL4121>.



2.08.2.2.2 Secondary phosphines from metallated phosphines

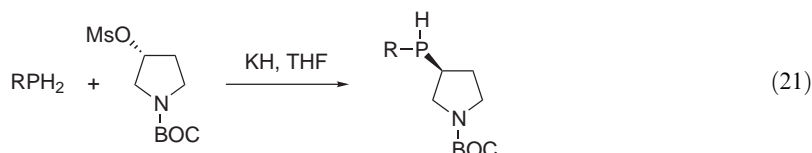
Two approaches to the synthesis of secondary alkyl phosphines, involving the metallated phosphine, have so far been described. These are: (i) reaction of dimetallated phosphine with alkylating agents, which leads to symmetrical dialkylphosphines, and (ii) alkylation of monometallated primary phosphines, which may produce either symmetrical or unsymmetrical secondary phosphines. Recently both methodologies have been extensively used for the preparation of a variety of secondary phosphines, particularly those bearing additional functional groups.

Thus, the first approach has been applied to the synthesis of symmetrical dialkyl phosphines starting from sodium phosphide **3** generated from elemental phosphorus or PCl_3 (cf. Section 2.08.2.1.2), which has been subsequently treated with butyllithium and alkyl halides <2000PS(162)39>. In the second approach, monometallated primary phosphines have been generated by the use of a variety of bases (sodium foil <2001JCS(D)1890>, potassium in liquid ammonia, butyllithium <2000JCS(D)1829>) and treatment with appropriate alkyl halides (Equation (20)) <1997CEJ1833, 1998JOM(553)39>.

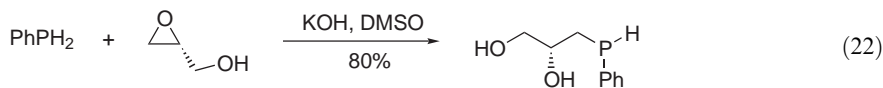


When ω -dihaloalkanes are applied as electrophiles, the corresponding alkyl- ω -haloalkylphosphines are formed in low yield and the main products are cyclic tertiary phosphines (vide infra) <1997T4363, 1997JPR/CZ482>.

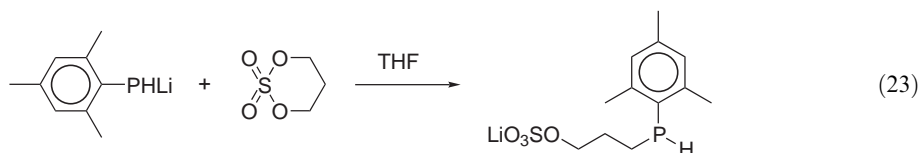
Metallated primary phosphines have also been alkylated with trimethylsulfonium iodide <1997ZOB252> or with an appropriate methanesulfonate (Equation (21)) <1997CB/RTC989>.



When oxiranes are used as electrophiles, the corresponding secondary β -hydroxyalkylphosphines are produced (Equation (22)) <2000EJI65, 2000EJI2167>, while thiiranes lead to secondary β -mercaptoalkylphosphines <2001EJI2587>.



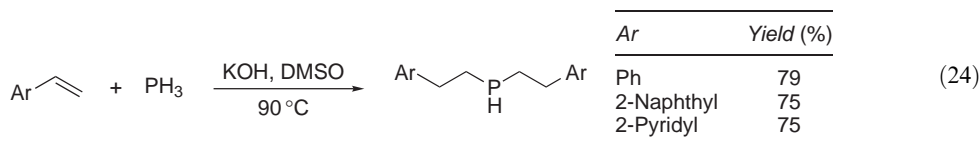
Reaction of monolithium mesityl phosphide with cyclic sulfates results in the formation of open-chain secondary phosphines with an ω -sulfate moiety (Equation (23)) <1997TL2947>.



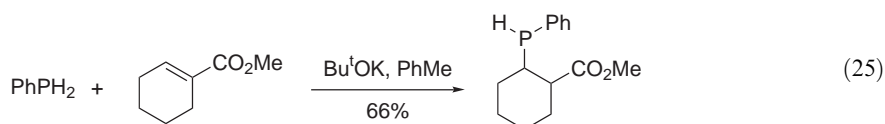
Metallated primary phosphine-boranes react with alkylating agents to give secondary phosphine-boranes in good yield <2002BCJ1359>.

2.08.2.2.3 Secondary phosphines by addition of P—H to unsaturated compounds

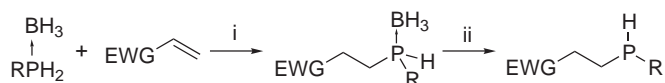
Phosphine generated in a mixture with hydrogen from elemental phosphorus in superbasic media <1994TL7647> adds smoothly to various alkenes. Although the reaction usually leads to a mixture of primary, secondary, and tertiary phosphines, carefully selected and strictly controlled conditions allow for the synthesis of desired secondary phosphines in high yield. Thus, the addition of PH_3 to arylalkenes gives the corresponding bis-(2-arylethyl)phosphines (75–79% yield) (Equation (24)) <1996ZOB56, 1998IZV1695, 2000ZOB43, 2002ZOB399>. In contrast, almost no addition of PH_3 to vinyl sulfoxides has been observed under similar conditions <1998ZOB1638>.



Michael-type addition of primary phosphines in the presence of bases (e.g., Equation (25)) results in the formation of the corresponding secondary β -alkoxycarbonylphosphines <2001EJI1251>.



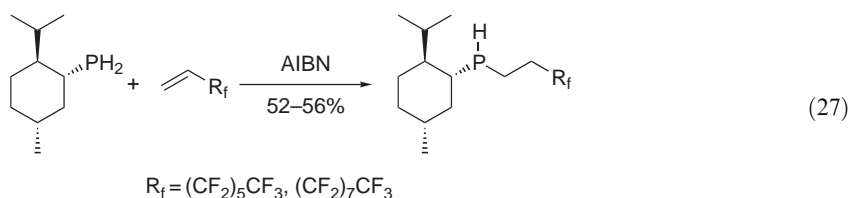
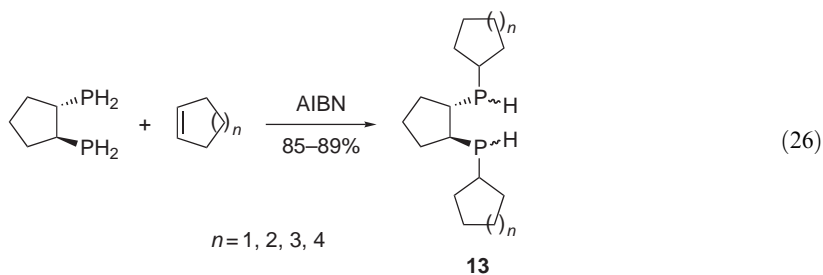
On the other hand, when the corresponding phosphine–borane complexes are used instead of free phosphines, the Michael-type addition takes place even in the absence of a base. However, the reactions require a much longer time (up to 30 days). Free phosphines can then be recovered from their BH_3 complexes by treatment with diethylamine (Scheme 6) <1997TL1923>.



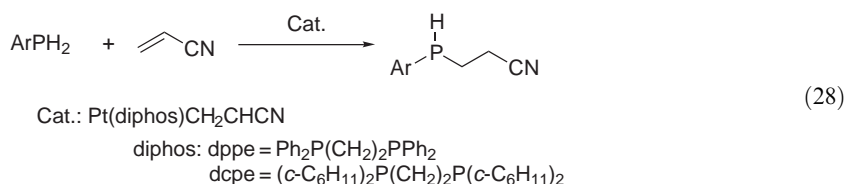
i. PhMe, 7–30 days, 40–75%; ii. Et_2NH
 R = Ph, Me; EWG = $(\text{MeO})_2\text{P(O)}$, CO_2Me

Scheme 6

The addition of primary phosphines to alkenes has been performed under free radical conditions, either by irradiation of the reaction mixture <1997CB/RTC1495> or using AIBN as an initiator <1997PS(123)141, 1998EJI597, 2002EJI2594>. It should be noted that the adducts **13** (Equation (26)) are formed as diastereomeric mixtures due to the presence of stereogenic phosphorus centers <1998EJI597>, as are the adducts of menthylphosphine and fluorinated terminal alkenes (Equation (27)) <1999TA2665>.

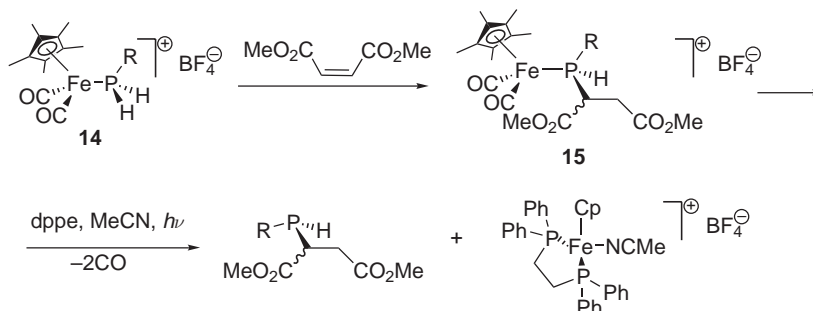


The addition of primary phosphines to acrylonitrile <1997JA5039, 1999OM5381> (cf. Equation (7), Section 2.08.2.1.3) and ethyl acrylate <1998CC49> is efficiently catalyzed by platinum complexes. The reaction shown in Equation (28) proceeds via a selective alkene insertion into a Pt–P bond.



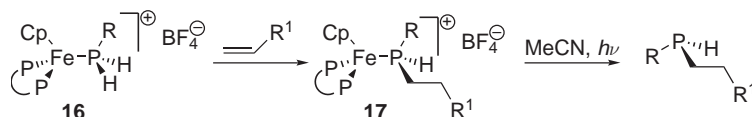
Bis-silylphosphines add to α,β -unsaturated carbonyl compounds either in a 1,2- or 1,4-fashion, depending on the structure and steric hindrance of the carbonyl substrates <1995ZOR179>.

Another approach has been presented by Malisch and co-workers (for a review see: <2002JOM(661)95>), who have used cationic primary phosphine iron complexes **14** in the synthesis of P-chiral secondary phosphines. Thus, addition of the complex **14** to pro-stereogenic alkenes (e.g., dimethyl maleate, Scheme 7) results in the formation of diastereomeric secondary phosphine complexes **15** in high yield and with a diastereomeric ratio up to 98:2. The phosphines are then released from the iron complexes **15** by a UV-light promoted ligand exchange.



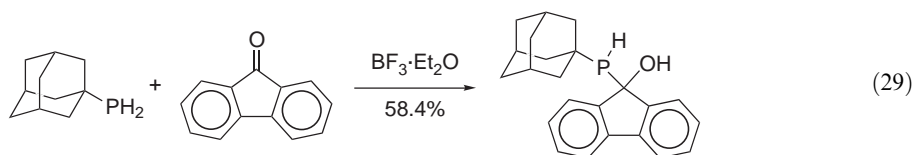
Scheme 7

When the CO groups in complexes **14** were replaced by enantiomerically pure diphosphine ligands (e.g., DIOP or CHIRAPHOS) and the new complexes **16** used for hydrophosphination of simple acrylic derivatives, the corresponding diastereomeric secondary phosphine complexes **17** were formed in good yield and with a diastereomeric ratio up to 85:15 (Scheme 8). The corresponding free phosphines were released as before. However, no information concerning optical activity and stereochemical stability of the chiral phosphines obtained has been reported <2002JOM(661)95> (for chiral, nonracemic secondary phosphines, see Section 2.08.2.2.5).

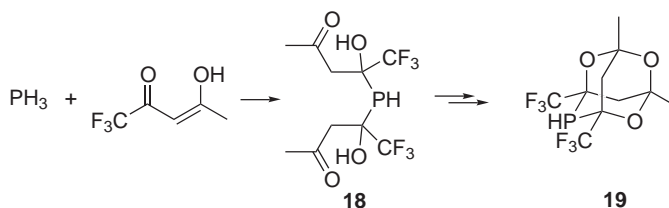


Scheme 8

Primary phosphines undergo addition to carbonyl compounds to give secondary α-hydroxy phosphines (Equation (29)) <1995PS(101)245>.



When phosphine is reacted with 1,1,1-trifluoropentane-2,4-dione, the product of a double addition **18** is initially formed and undergoes transformation into an interesting secondary cage phosphine **19** (Scheme 9) <1997CB/RTC1547>.

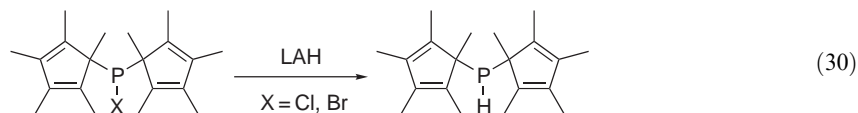


Scheme 9

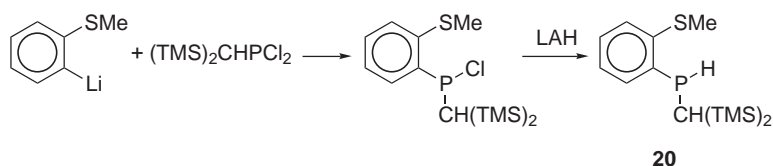
2.08.2.2.4 Secondary phosphines by reduction

(i) Reduction of halophosphines

The reduction of halophosphines has been accomplished using LAH as a reducing agent. Various types of secondary phosphines have been obtained in this way. Among the most interesting examples are bis(pentamethylcyclopentadienyl)phosphine formed by reduction of the corresponding chloro- or bromophosphines (Equation (30)) <1996PS(111)185, 1998EJI331> and a series of highly congested alkylarylphosphines <1996ZN(B)1183, 2002T5779>. The latter have sometimes been obtained in a protected form as borane complexes <2001HCA3519>.



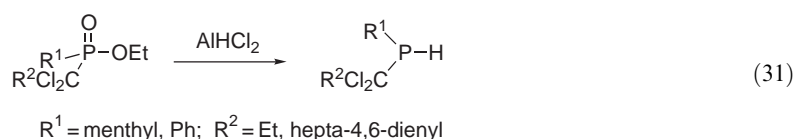
The thioanisole-functionalized secondary phosphine **20** has been prepared in 82% yield via the reaction of *o*-lithiated thioanisole with bis(trimethylsilyl)methyl-dichlorophosphine, followed by reduction with LAH in a one-pot procedure (Scheme 10) <2003OM302>.



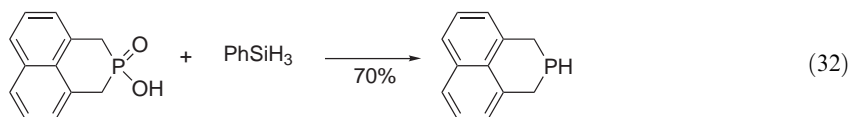
Scheme 10

(ii) Reduction of phosphinic and thiophosphinic compounds

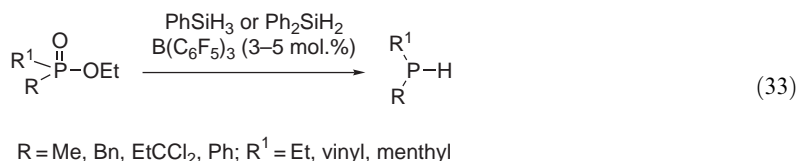
The reduction of phosphinic derivatives to secondary phosphines has been achieved mainly using two types of reducing agents: (i) various derivatives of LAH and (ii) silanes. Thus, di-1-adamantylphosphine has been obtained in 94% yield by reduction of di-1-adamantylphosphine chloride with either LAH or trichlorosilane (HSiCl_3) <1993PS(81)141, 1995PS(102)211>. In turn, AlHCl_2 has been used to reduce phosphinate esters bearing additional sensitive functional groups, e.g., a diene with a given configuration (cf. Section 2.08.2.1.4, Equation (13)) <1998CC457>, an alkynyl group <1995SL1168>, or halogen atoms in the α -position to phosphorus (Equation (31)) <1999PS(144)97>.



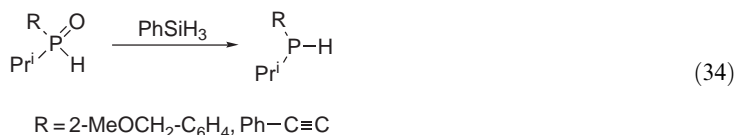
Phosphinic esters can also be reduced using an $\text{LAH}/\text{NaBH}_4/\text{CeCl}_3$ system which leads to the corresponding secondary phosphine-borane adducts. This reducing agent is, however, much less effective towards free phosphinic acids. In this case appropriate silanes (Ph_2SiH_2 or PhSiH_3) have been used <1998TL4291> and silanes are also used for cyclic phosphinic acids (Equation (32)) <2000EJO3497>.



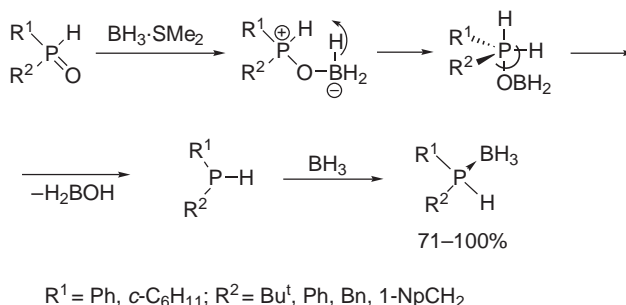
Phosphinic esters have also been effectively reduced to secondary phosphines by the above silanes in the presence of catalytic amounts of tris(pentafluorophenyl)borane (cf. Section 2.08.2.1.4) (Equation (33)) <2002TL5569>.



Phenylsilane (PhSiH₃) has also been used for the reduction of a secondary phosphine oxide (Equation (34)) <2002JOM(643)342>.

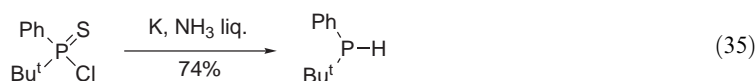


Secondary phosphine oxides have been expeditiously converted into secondary phosphine-boranes by treatment with excess of BH₃·SMe₂ in the presence of a small amount of water. The procedure is less efficient for substrates bearing sterically crowded substituents, because of the formation of phosphinous acid boranes as by-products. The reaction is believed to proceed via a pentacoordinate intermediate which undergoes ligand coupling (Scheme 11) <2003SL1012>.



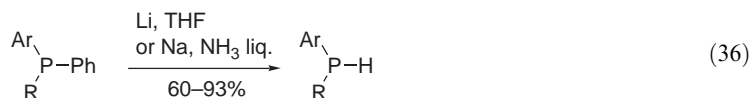
Scheme 11

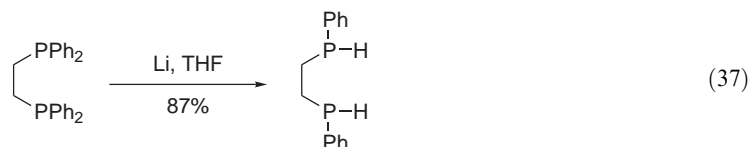
Thiophosphinic chlorides have been reduced to secondary phosphines using potassium in liquid ammonia (Equation (35)) <2002HAC330>.



(iii) Reductive cleavage of P–C bonds

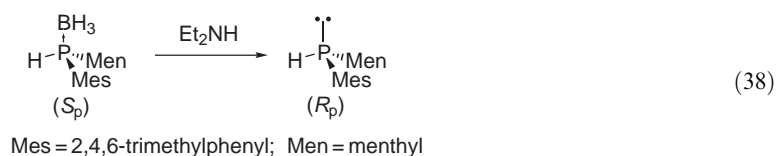
The treatment of a tertiary phosphine with an alkali metal results in the reductive cleavage of a P–C bond. In the case of alkylarylphosphines such a reaction usually leads to a mixture of products resulting from the cleavage of both the P–C_{alkyl} and P–C_{aryl} bonds. Detailed investigations indicate that the mechanism of P–C bond cleavage using lithium in THF involves a thermodynamic equilibrium between P–C_{alkyl} and P–C_{aryl} cleaved radicals and anions, followed by reaction and stabilization of these as lithium salts <2000JOC951>. Nevertheless, appropriately chosen conditions allow for the preparation of the required secondary phosphines, e.g., alkylarylphosphines (Equation (36)) <1997CB/RTC989, 1997JCS(D)2713, 2000JA1824, 2001JA10221> and 1,2-bis(phenylphosphino)ethane (Equation (37)) <2000JOC951>.



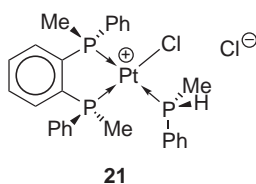


2.08.2.2.5 Chiral secondary phosphines

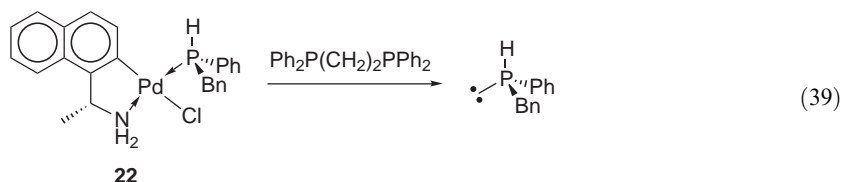
Only recently, some publications that deal with chiral, nonracemic secondary phosphines have appeared. This is undoubtedly due to the fact that these have turned out to be configurationally labile. Chiral secondary phosphines undergo an easy and rapid racemization (or epimerization in the case of diastereomeric structures) via a reversible protonation of the P-stereogenic center, which takes place even in the absence of external acids <1995IC384, 2000EJI1283>. This process may be substantially hampered by the addition of a proton scavenger, e.g., a trace of sodium acetylacetonate <1996IC3874>. However, to ensure full configurational stability of chiral secondary phosphines, it is necessary to transform them into certain complexes, which has been used in all attempts at the preparation of P-chiral, nonracemic species. The first attempt at the synthesis of a P-chiral secondary phosphine was made by Wild and co-workers <1996IC3874>. A diastereomeric mixture of menthylmesitylphosphine was transformed into its borane complex, from which the pure S_P diastereomer was isolated by crystallization. The free R_P phosphine was liberated using diethylamine (Equation (38)) and proved to be configurationally stable under the conditions applied.



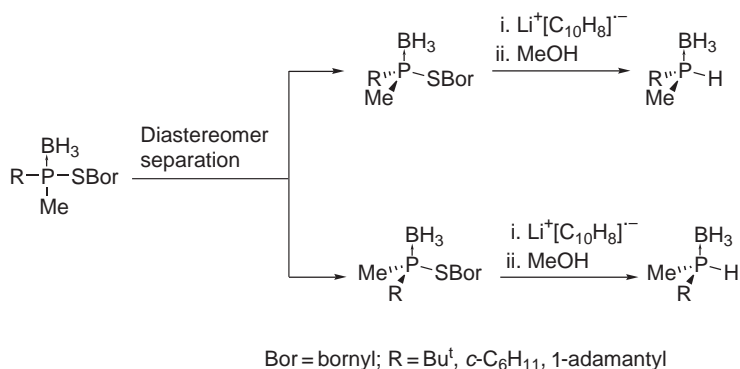
The same research group has accomplished the first resolution of a simple P-chiral secondary phosphine, namely methylphenylphosphine <1995IC384>, by recrystallizing a diastereomeric pair of a PF_6 salt of a complex: platinum-optically active bisphosphine-racemic methylphenylphosphine. The pure diastereomer **21** is stable in CH_2Cl_2 but epimerization at the secondary phosphine P-stereogenic center occurs rapidly in the presence of traces of chloride or water. Attempts to release the optically active secondary phosphine from the complex have been unsuccessful; the phosphine obtained has always been racemic.



In a similar way, chiral secondary phosphines have been resolved into enantiomers via their diastereomeric palladium complexes **22** <2000EJI1283>. In this case, however, benzylphenylphosphine which has been released from the diastereomeric complex (Equation (39)) proved to be configurationally stable in ether solution for 3 h. In contrast, methylphenylphosphine, obtained in the same way, underwent racemization within 5 min.

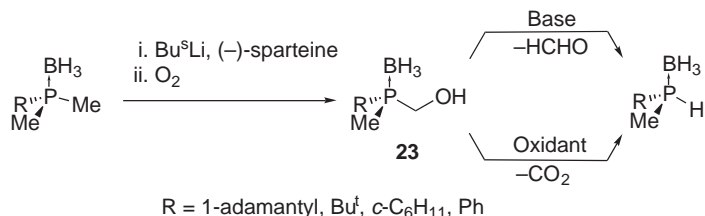


As phosphine-boranes have been found to provide reliable protection of the phosphine functionality under a wide range of conditions <1997S983, 1998S1391>, the synthesis of optically active secondary phosphines in the form of borane complexes is much easier and has been much more successful. Thus, Imamoto and co-workers <1991TL3371, 2000JOC1877> obtained a series of optically active secondary phosphine-boranes via reduction of diastereomerically pure tertiary derivatives, e.g., (menthyloxy)methylphenylphosphine-borane <1991TL3371>, bornylthio(methyl)-phosphine-boranes (Scheme 12) <2000JOC1877>, or (1*S*)-endo-2-bornyloxycarbonyl-(*t*-butyl)-methylphosphine-borane <2002BCJ1359>.

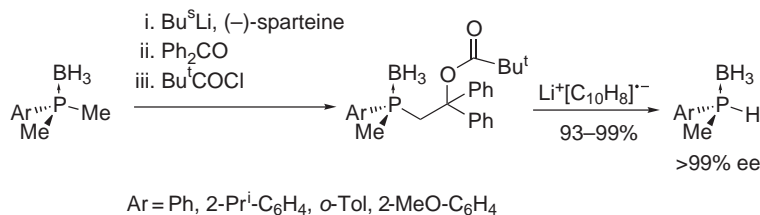


Scheme 12

Optically active secondary phosphine-boranes have also been obtained by a reductive degradation/elimination of appropriate enantiomerically pure precursors, e.g., hydroxymethyl derivatives **23** (Scheme 13) <2000JOC4185> or β -acyloxyethyl derivatives (Scheme 14) <2001JOC1514>.



Scheme 13



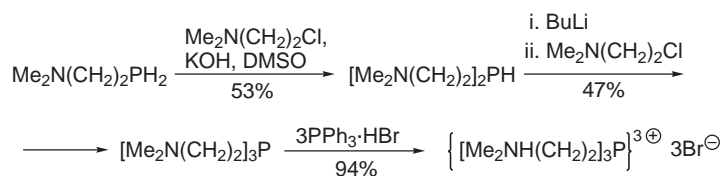
Scheme 14

2.08.2.3 Tertiary Phosphines—R₃P

2.08.2.3.1 Tertiary phosphines from phosphines and alkylating agents

This approach to tertiary phosphines closely resembles the analogous procedures used in the synthesis of primary and secondary phosphines. In contrast to those cases, however, the yields of tertiary phosphines are usually much higher, as there is no danger of a possible overalkylation.

Secondary phosphines react with *N*-(*t*-butoxycarbonyl)-3-iodo-L-alanine methyl ester in DMF using potassium carbonate as a base to afford phosphino derivatives of serine <2001ZAAC(627)1151>. Stepwise aminoalkylation of PH_3 with 2-chloroethyl-dimethylamine in the superbasic medium DMSO/KOH, followed by metalation of the secondary phosphine with BuLi and subsequent treatment with another equivalent of 2-chloroethyldimethylamine gives the basic tertiary phosphine. Protonation then affords the salt that is highly soluble in water (cf. Section 2.08.2.2.1.(i)) (Scheme 15) <1995CB275>. Similar monocationic amphiphilic tertiary phosphines have been reported <1995JOM(501)293>.

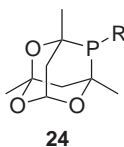


Scheme 15

Tertiary phosphines containing aminocarboxylic acid residues and water-soluble amphiphilic tertiary phosphines have also been prepared by the Mannich-based transformations of tertiary hydroxymethylphosphines <1999JA1658, 2002TL1299> and hydroxymethylphosphonium salts <2003JMOC(A)(195)47>, respectively.

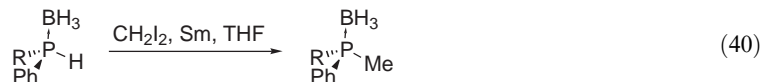
To the broad variety of bases that are used to remove the hydrogen halides formed during the reaction of phosphines with alkyl halides (*vide supra* and e.g., NaOH/MeOH <2000BCJ705>), caesium hydroxide has recently been added and proved to be highly advantageous <2003MI373, 2003TL8373>.

Alkylation or arylation of a trioxaphosphaadamantane leads to sterically hindered tertiary phosphadamantane phosphines **24** which are used as catalysts for palladium-catalyzed cross-coupling reactions <2003OL953>.



P-Acylphosphines [$\text{R}_2^1\text{P}-\text{C}(\text{O})\text{R}^2$], sometimes called “phosphomide ligands,” have been prepared by the reaction of either secondary phosphines with acyl chlorides in the presence of bases or silylphosphines with acyl chlorides <2003JOM(667)112>.

The use of borane as a protective group for the phosphine functionality has also found an application in the synthesis of tertiary phosphines <1998S1391>. In addition to a simple alkylation of $\text{P}-\text{BH}_3$ protected secondary phosphines described in 1990 <1990JA5244> and hydroxyalkylation (see Section 2.08.2.3.4.(ii)), a carbenoid insertion into the $\text{P}-\text{H}$ bond has been used to synthesize tertiary methylphosphines (Equation (40)) <1996CL705>.

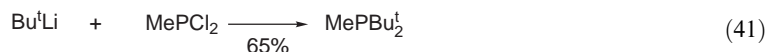


2.08.2.3.2 Tertiary phosphines from electrophilic phosphorus and organometallic reagents

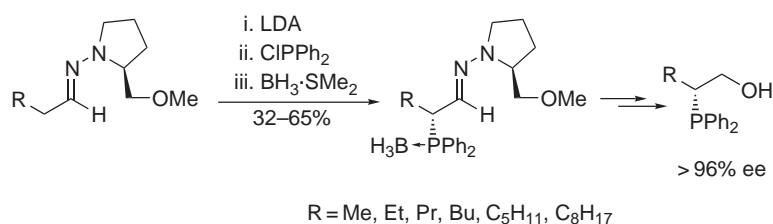
This is the most common approach used in the synthesis of tertiary phosphines. Depending on the starting electrophilic phosphorus derivative, it allows for the synthesis of symmetrical (R_3P), unsymmetrical ($\text{R}_2^1\text{R}^2\text{P}$), and fully asymmetric ($\text{R}^1\text{R}^2\text{R}^3\text{P}$) phosphines. Among organometallic reagents used in this reaction, alkylolithium and aryllithium as well as Grignard reagents play the most important role. In spite of many examples of syntheses of tertiary phosphines using this

methodology, no breakthrough has been achieved recently and most applications are based on the procedures that have been described previously <1995COFGT(2)425>. Therefore, only selected examples are presented here.

The reaction of phosphonous dichlorides <1996JOM(518)55> and phosphinous chlorides <1995AG1334, 1997TA2537> with alkylolithium reagents has been applied to the synthesis of long-chain or sterically hindered phosphines (Equation (41)), arylalkylphosphines <1995JOM(503)143, 1995OM5171>, and 1,3,5-*cis*-cyclohexanetriphosphine <1995CB719>. The same procedure has been used in the reaction of phosphinous chlorides or phosphonous dichlorides with aryllithium derivatives <1996CB1547, 2001OM648>.

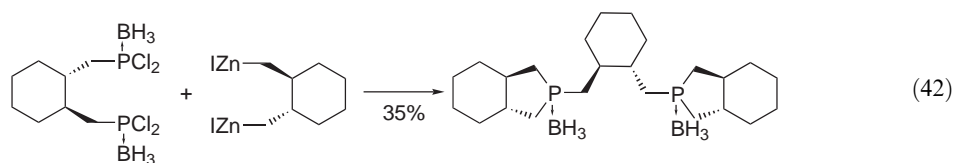


The reaction of methylphosphonous dichloride with excess of *n*-hexyl bromide in the presence of magnesium gives methyl(di-*n*-hexyl)phosphine in only 26% yield <2002JCS(D)1997>. Long-chain trialkylphosphines have been prepared by the subsequent treatment of the starting diethyl chlorophosphite [(EtO)₂PCl] with methylmagnesium bromide and long-chain *n*-alkyl bromides in the presence of magnesium <1997JA7670>. A sequential alkylation of chloroaminophosphines by Grignard and organolithium reagents allows for a highly efficient synthesis (chemical yield up to 99%) of unsymmetrical tertiary phosphines <1998CC149>. Triphenyl phosphite has also been used as the electrophilic substrate in the reaction with Grignard reagents for the synthesis of lower trialkylphosphines, e.g., trimethylphosphine <1997BMCL2893>. When the reaction of alkylmagnesium chlorides with dimethylphosphinous acid chloride is followed by the addition of BH₃·THF, the corresponding P-BH₃ protected phosphines are produced in moderate-to-good yield <2001MI118>. Reaction of phosphonous chlorides with deprotonated Enders' (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP), followed by *in situ* treatment with BH₃·SMe₂, leads to a diastereomeric mixture of P-BH₃-phosphine hydrazones, which after separation and subsequent transformations afford chiral β-hydroxy phosphines (Scheme 16) <1996SL796, 1997LA/RTC345>.

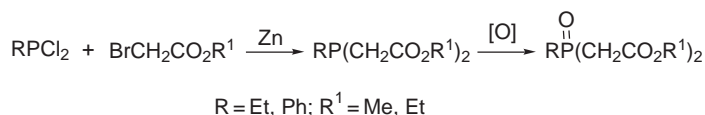


Scheme 16

P-Borane protected electrophilic phosphorus reagents have also been used as substrates in reactions with organometallic reagents. An elegant example of the synthesis of bis-phospholane derivatives is shown in Equation (42) <1997TA987>.

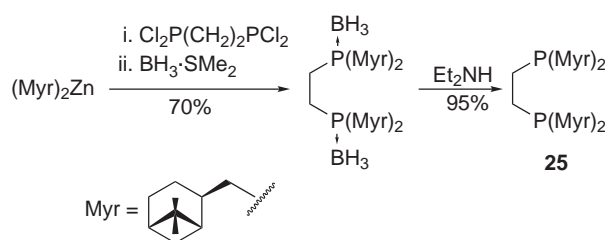


A zinc-mediated Reformatsky-type reaction of phosphonous dichlorides with alkyl bromoacetates has been applied to the synthesis of a series of di(alkoxycarbonylmethyl)phosphines, which were transformed *in situ* into the corresponding phosphine oxides (Scheme 17) <1995S144>.



Scheme 17

Coupling of diorganozinc reagents to chlorophosphines provides a synthesis of various functionalized phosphines (for a review see <1997CB/RTC1021>). As an example, the synthesis of compound **25**, a representative of a series of tetraterpenoid diphosphines, is shown in Scheme 18 <1995TL4591, 1996TL2209, 1997TA715>.

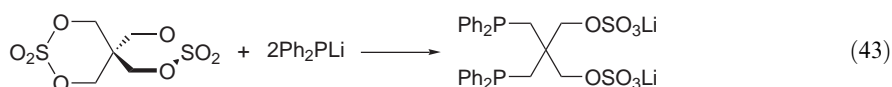


Scheme 18

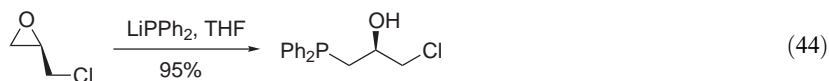
Zirconacyclopentanes react with mono- and dichlorophosphines to give the corresponding diphosphines or cyclic phosphines <1996TL3109, 1997CC1239>, including mono- and bicyclic phosphiranes <1998CC1177>.

2.08.2.3.3 Tertiary phosphines from metallated phosphines

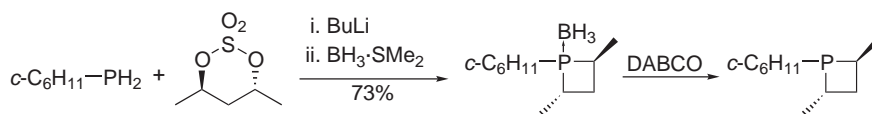
This methodology also allows for the synthesis of symmetrical, unsymmetrical and asymmetric phosphines, and in this way it resembles the methodology described in the two previous sections. As discussed in Sections 2.08.2.1.2 and 2.08.2.2.2, PH_3 , primary and secondary phosphines may be metallated by a broad range of reagents, e.g., alkali metals in various solvents, organometallic reagents, and strong bases in DMSO. Alkyl halides belong to the most commonly employed carbon electrophiles, giving rise to a variety of tertiary phosphines <1995ZOR794, 1996CC771>, including diphospha-macrocycles <1995PS(106)105>. Nevertheless, other electrophiles are often used as well (e.g., tosylates <1996TA885>, 1,4-ditosylates <1995TA1973, 1996TA397>, 1,3-dimesylates <2003TA2739>), particularly for the synthesis of phosphines bearing additional functional groups. Thus, metallated secondary phosphines (e.g., Ph_2PLi) react with cyclic sulfates to form amphiphilic or water-soluble ligands. The reaction has also been used for the synthesis of di-tertiary phosphines bearing two alkylene sulfate chains (Equation (43)) <1997CC2385>.



Enantiomerically pure β -hydroxyphosphines with a γ -chloro substituent are readily available starting from enantiopure epichlorohydrin by ring opening with LiPPh_2 (Equation (44)) <1996CB697>. The nucleophilic ring opening of appropriate epoxides is a key step in the synthesis of chiral phosphines based on carbohydrate systems <1995CL685, 1995JOC6226, 1995JOM(498)275>. Also oxetanes can be cleaved by LiPPh_2 to give γ -hydroxy phosphines <1995ZN(B)1045>, while thiirane under similar conditions gives the corresponding β -mercaptoethylphosphines <1995ZN(B)168>.



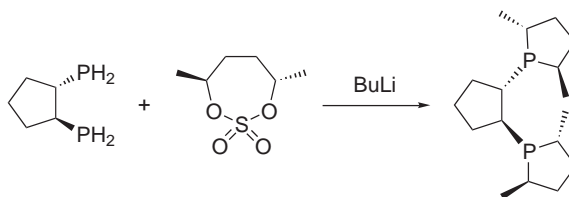
An interesting application of the methodology under discussion is the synthesis of phosphetanes (for a review see <2002CRV201>), particularly those having C_2 -symmetry, with stereogenic centers located on the C atoms adjacent to phosphorus. The reaction of dilithio phosphides, generated from primary phosphines by BuLi or LDA , with appropriately functionalized C_2 -diols, followed by *in situ* protection of the products with borane, gives corresponding phosphetane-boranes (e.g., Scheme 19) <1997T4363, 1997TL2947, 1999CEJ1160, 1999SL1975,



Scheme 19

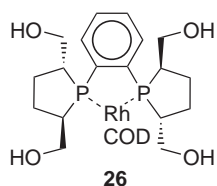
[2000AG\(E\)1981](#), [2000T95](#), [2001JOM\(624\)162](#), [2001S2095](#)>. The free phosphetanes are obtained after removal of the borane with DABCO in benzene. The phosphetane synthesis is compatible with both aryl- and alkylphosphines [<2000H905>](#).

A similar procedure has been applied to the synthesis of phosphiranes [<1996JOC7702>](#), phospholanes [<1996SL1211](#), [2001TA1159](#)>, and bis-phospholanes (e.g., [Scheme 20](#)) [<1999JOM\(585\)315](#), [2000CC1663](#), [2003OL1273](#)>; for an overview see [<2003EJI2733>](#).



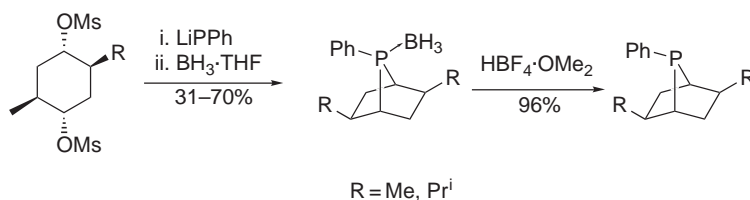
Scheme 20

The synthesis of the first water-soluble chiral tetrahydroxy diphosphine Rh(I) catalyst **26** has been accomplished by the reaction of tetralithio di-1,2-phosphidobenzene with appropriately protected tetraol sulfate [<1999TL7059>](#).



COD = cyclooctadiene

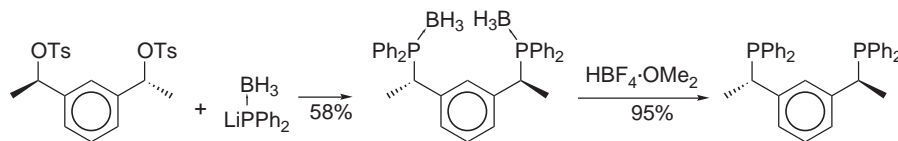
Finally, this approach has also been used in the synthesis of bicyclic phosphines ([Scheme 21](#)) [<1997JA3836>](#) and diphosphines [<1998AG\(E\)1100>](#).



Scheme 21

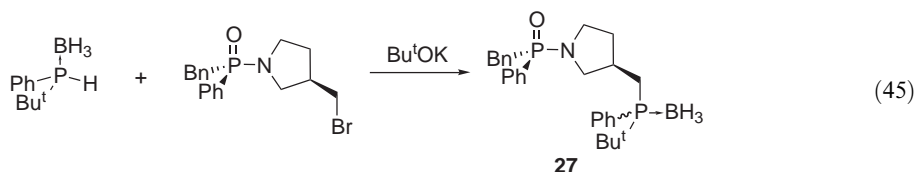
Lithium salts derived from the corresponding secondary phosphine *P*-boranes have also been found suitable for substitution reactions since they display sufficient nucleophilicity, being at the same time less basic than the borane-free counterparts [<1998S1391>](#). The latter is very advantageous, as many undesired base-catalyzed side reactions can be avoided. The first application of this approach was described in 1990 [<1990JA5244>](#). More recently, it has also been used for the synthesis of C_2 -symmetric diphosphines [<1994TL9319](#), [1994T6145](#), [1995T7655](#)>, among them

C₂-symmetric ligands with a cyclobutane backbone <1998TA1863>, starting either from the corresponding (*S,S*)-1,3- and 1,4-ditosylates, or for *meta* benzene derivatives from *m*-di(1-tosyloxyethyl)benzene (Scheme 22) <1997TL1725>.



Scheme 22

In a similar way, an interesting diastereomeric hybrid ligand **27** has been synthesized (Equation (45)) <1997T11577>.

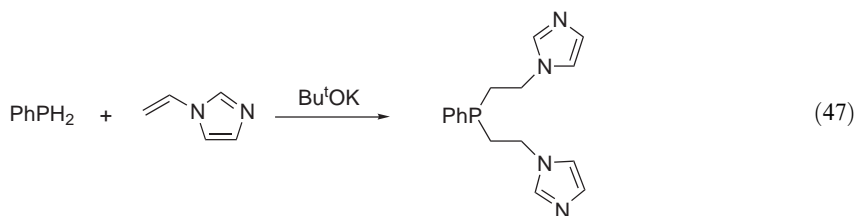
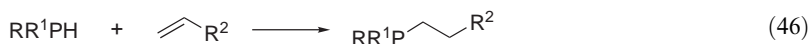


2.08.2.3.4 Tertiary phosphines by addition of P—H to unsaturated compounds

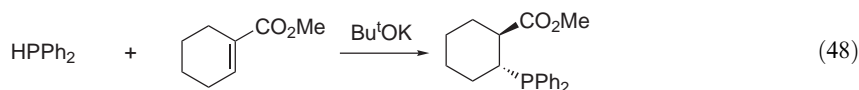
Like primary and secondary phosphines, tertiary phosphines can also be prepared by the addition of P—H containing substrates to a variety of unsaturated compounds. However, in the latter case the usefulness of the methodology and the yields of the products are higher, as no oversubstitution can take place.

(i) Addition to alkenes and alkynes

This addition reaction may be performed in four different ways: under acidic, basic or free-radical conditions or by using organometallic catalysts. The use of base catalysis is the most common way of performing the addition of P—H substrates to functionalized alkenes. Irrespective of the nature of substituents in the starting alkene, this reaction always leads to 2-substituted ethyl derivatives (anti-Markovnikov products) (Equation (46)). A variety of bases have been used to catalyze the addition. Thus, potassium *t*-butoxide in DMSO allows a smooth addition of Ph₂PH or (*c*-C₆H₁₁)₂PH to a large variety of functionalized alkenes (Equation (46); R² = Ph, SPh, SiPh₃, PPh₂, 2-pyridyl, 3-pyridyl) <2002TL5817>. It also catalyzes the reaction of primary phosphines and diphosphines with 1-vinylimidazole which results in the formation of the products of a double addition (Equation (47)) <2001JMOC(A)285>.

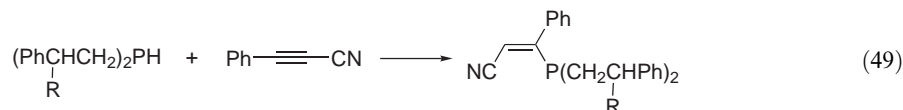


Michael-type addition of Ph₂PLi to *t*-butyl myrtenate <1995CC1845> or Ph₂PH or PhPH₂ to methyl 1-cyclohexenecarboxylate in the presence of Bu^tOK leads to the products in which the ester and phosphine moieties are in a *trans* position (Equation (48)). An analogous reaction has been performed using borane adducts of lithio phosphides instead of free phosphines; in this case the corresponding phosphine-boranes have been obtained <2001EJI1251>.

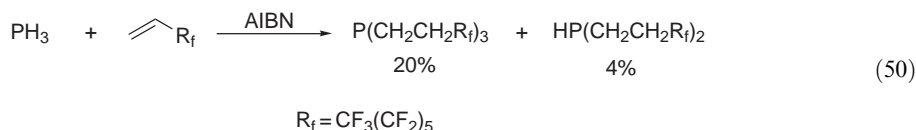


Reaction of KPH_2 , generated from potassium, red phosphorus and Bu^tOH in liquid ammonia, with styrene or heteroarylethenes gives tris-[2-aryl (or heteroaryl)-ethyl]phosphines in good yields <1997JGU650, 1997PS(126)125>. Nucleophilic addition of phosphine, generated from red or white phosphorus in superbasic suspension KOH-DMSO , to vinylpyridines gives the corresponding tris-(pyridylethyl)phosphines in yields up to 72% <1997ZOB70, 2000ZOB43, 2002ZOB399>. For the conditions allowing the synthesis of secondary phosphines under these conditions, see Section 2.08.2.2.3 (Equation (24)). Divinyl sulfone has been treated with secondary phosphines in KOH-dioxane to give bis-(2-phosphinoethyl) sulfones, which undergo an easy oxidation to the corresponding bis-(2-phosphinylethyl) sulfones <1998JOU1056>.

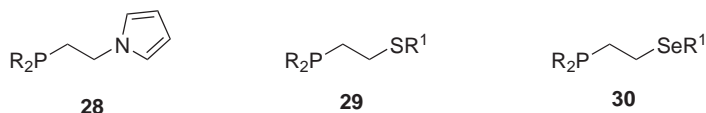
Primary and secondary phosphines react in a similar way with substituted alkynes to produce the corresponding alkenylphosphines (Equation (49)) <1999MC163, 2001JGU1907>.



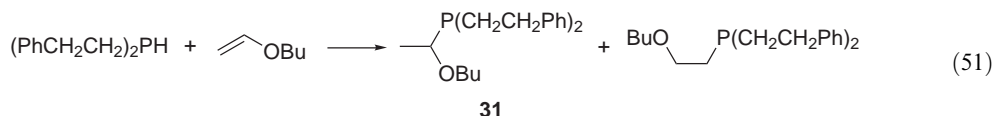
Free-radical conditions have been used with moderate success for the addition of phosphine to fluoro alkenes (Equation (50)) <1998JA3133>.



This approach has also proven to be suitable for the addition of secondary phosphines to *N*-vinylpyrroles <2003TL2629>, and vinyl sulfides and selenides <2002S2207>. In all these cases the reaction affords in high yield the corresponding anti-Markovnikov products, e.g., phosphines 28–30.



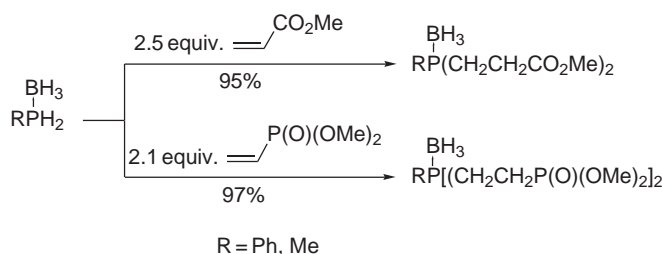
Vinyl ethers react with secondary phosphines in a similar way (AIBN as a catalyst, yield of the adducts around 67%). However, in the presence of TFA the regiochemistry is reversed and the Markovnikov product **31** prevails. Formation of the anti-Markovnikov adducts can be suppressed by adding hydroquinone to the reaction mixture (Equation (51)) <1997JGU58>.



The addition of phosphines to alkenes can also be catalyzed by organometallic complexes. When PH_3 is bubbled through a warm solution of ethyl acrylate in the presence of the platinum(0) complex with $\text{P}(\text{CH}_2\text{CH}_2\text{CO}_2\text{Et})_3$ (0.002 equiv.), the reaction proceeds smoothly and leads to the product in 97% yield (Equation (52)). No reaction is observed in the absence of the catalyst <1998CC49>. Nickel and palladium catalysts ($\text{Ni}[\text{P}(\text{OEt})_3]_4$ and $\text{Pd}(\text{MeCN})_2\text{Cl}_2$) have been found to effectively catalyze hydrophosphination of styrene (yields up to 100%) <2002OL761>. Methyl acrylate insertion into the P-H bonds of palladium(I)-coordinated secondary phosphines has also been accomplished <2000OM3062>. Ytterbium-imine complexes, e.g., $[\text{Yb}(\eta^2\text{-Ph}_2\text{CNPh})(\text{hmpa})_3]$, have also been used to catalyze hydrophosphination of alkynes and alkenes <2003JOC6554>.

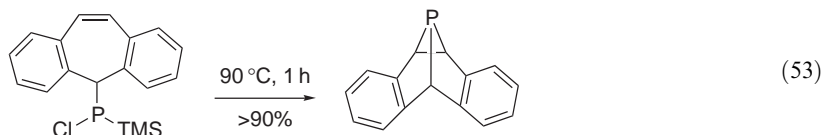


When a primary phosphine-borane is used instead of a free phosphine, the addition to activated alkenes proceeds without any catalyst. Moreover, depending on the proportions of the substrates used, the reaction can be stopped either at the stage of secondary phosphine-boranes (cf. [Scheme 6, Section 2.08.2.2.3](#)) or carried on to produce tertiary phosphine-boranes in high yield ([Scheme 23](#) <1997TL1923>). If terminal alkynes are subjected to hydrophosphination with secondary phosphine-boranes, vinylphosphine-boranes are produced. The regioselectivity of the reaction may be controlled by the choice of the activation process: thermal or metal catalyst activation <2003JOC7016>.



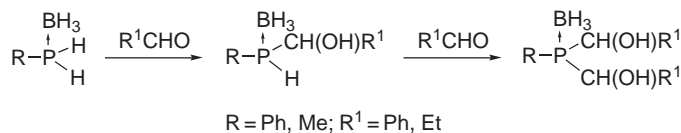
Scheme 23

A completely different approach has recently been used which involves a controlled thermolysis of a *P*-silyl-*P*-chlorophosphine and allows for the formation of dibenzo-1-phosphasemibullvalene ([Equation \(53\)](#)) <2003AG(E)3955>.



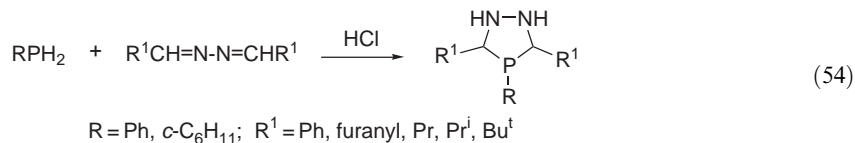
(ii) Addition to other unsaturated compounds

Secondary phosphines, e.g., Ph_2PH , undergo addition to aldehydes under neutral conditions to form the corresponding tertiary α -hydroxy phosphines <1995JOM(495)103>. Primary phosphine-boranes react smoothly with aldehydes but sluggishly with ketones. In the first step, the products of mono-addition are formed (secondary α -hydroxy phosphine-boranes), which are then transformed into bis-hydroxy phosphine-boranes when aldehydes are used in excess ([Scheme 24](#)) <1997JOM(529)205>.

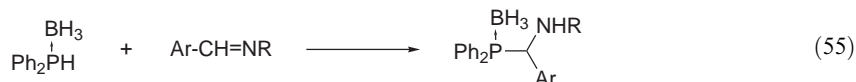


Scheme 24

Phosphines may also react with a C=N double bond. For example, a series of 3,4-diazaphospholindines has been synthesized by cyclization of primary phosphines with appropriate hydrazine derivatives in the presence of HCl as a catalyst ([Equation \(54\)](#)) <2001AG(E)3432>.



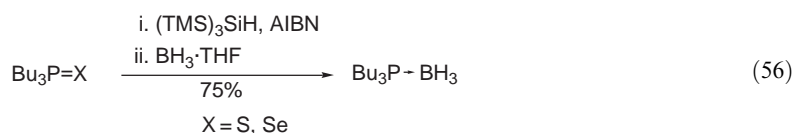
Addition of secondary phosphine-boranes to imines leads to mono-substituted α -amino phosphine-boranes (Equation (55)) <2000TL6143>.



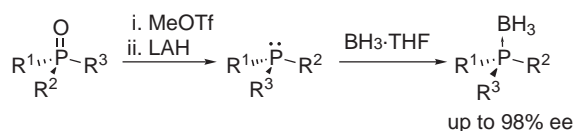
2.08.2.3.5 Tertiary phosphines by reduction

As in the case of primary and secondary phosphines, tertiary phosphines may also be obtained by reduction of the corresponding substrates containing phosphorus at a higher oxidation state. Among the reducing agents used are LAH and its derivatives, and various silanes and alkali metals in liquid ammonia. Stereochemistry and stereoselectivity of the reduction strongly depends on the reducing agent and the conditions of the reaction.

The reduction of tertiary phosphine oxides with trichlorosilane is a well-established method of generating phosphines <2002JOM(646)230>. Alane ($\text{AlH}_3 \cdot \text{THF}$) has been found to chemoselectively reduce phosphine oxides to phosphines in the presence of other functional groups, such as sulfides, sulfones, sulfoxides, nitroaryls, and epoxides <1999TL5267>. In turn, tertiary phosphine sulfides may be almost quantitatively reduced to tertiary phosphines by sodium in liquid ammonia <1998PS(133)79>. Cyclic phosphine sulfides have also been efficiently reduced to phosphines (yields up to 95%) using Raney nickel (for phospholane derivatives <2003AG(E)943>) or $\text{Si}_2\text{Cl}_2/\text{TMEDA}$ (in the case of bis-binaphthole derivatives <2003AG(E)3509>). When tertiary sulfides or selenides are treated with tris(trimethylsilyl)silane in the presence of AIBN, followed by the addition of $\text{BH}_3 \cdot \text{THF}$, tertiary phosphine-boranes are obtained in high yield (Equation (56)) <2000TL9899>.

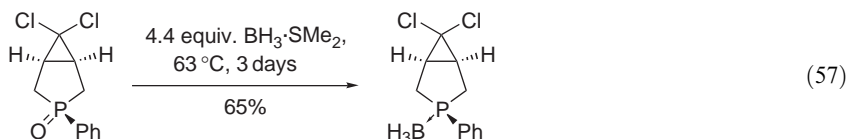


Various phosphine oxides have been efficiently reduced using methyl triflate as a methylating agent followed by LAH. The reaction has been found to proceed with virtually complete inversion of configuration at phosphorus. The phosphines obtained have been isolated as borane adducts (Scheme 25) <2001OL87>.



Scheme 25

Dimethyl sulfide-borane has been found suitable for a direct reduction of tertiary phosphine oxides to the corresponding phosphine-boranes. Monocyclic <2000JCS(P1)4451>, bi and tricyclic <2000T1> phosphine oxides have been used as substrates and the reduction has been found to be enhanced by ring strain <2001HAC161>. The reaction is stereospecific and proceeds with complete retention of configuration at phosphorus (Equation (57)).



Benzylphosphonium salts undergo reduction by LAH to give tertiary phosphines and toluene. When LiAlD_4 is used, variously deuterated toluene derivatives are obtained <1998CC1973>.

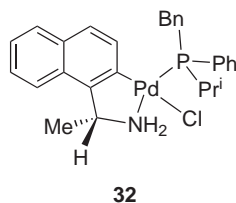
2.08.2.3.6 Chiral tertiary phosphines

Chiral tertiary phosphines have attracted interest due to their growing applicability as ligands in organometallic catalysts for a variety of reactions. Although a great majority of such chiral ligands owe their chirality to stereogenic centers located in the C framework, those possessing a stereogenic P are also becoming more common <2000CPB315, 2002EJO2535>. Because of the defined scope of this review, only phosphines that are chiral at P will be considered in this section. An exhaustive review of the methods of synthesis of P-chiral, non-racemic tertiary phosphines and their derivatives <1994CRV1375> and a review of asymmetric synthesis of various organophosphorus compounds <1998TA1279> have been published.

(i) Complexation method

This methodology involves application of transition metal complexes bearing enantiopure ligands. Their reaction with racemic phosphines leads to the formation of diastereomeric complexes, which may be separated by physical methods such as crystallization or column chromatography (cf. Section 2.08.2.2.5).

Racemic (2-chlorophenyl)(2-dimethylphosphinophenyl)methylphosphine has been resolved into enantiomers via fractional crystallization of internally diastereomeric Pd(II) complexes containing the racemic ligand and *ortho*-metallated (*S*)-dimethyl[1-(1-naphthyl)ethyl]amine <2001JCS(D)1890>. Similarly, benzylisopropylphenylphosphine has been resolved by means of an optically active metallocycle—diastereomers of the complex **32** have been separated by column chromatography <2000TA3335>.



In a similar way several other tertiary phosphines have been resolved, among others methylphenylvinylphosphine <1999TA1309>, *t*-butylmethylphenylphosphine <1995TA2747>, (*p*-bromophenyl)(*t*-butyl)phenylphosphine <1999TA1483>, and bicyclic heterofunctionalized phosphines <1996CC591, 1998TA2961>.

(ii) Phosphonium salt method

There have been no further developments in this area since the publication of COFGT (1995) <1995COFGT(2)425>.

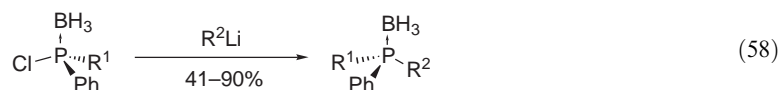
(iii) Phosphinate ester method

No reports concerning new applications of this methodology have appeared since the publication of COFGT (1995) <1995COFGT(2)425>.

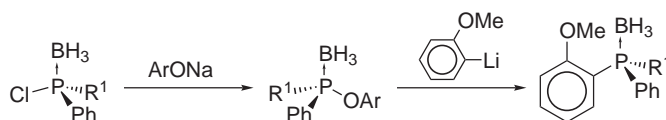
(iv) Phosphinite method

The phosphinite method is based on the application of chiral electrophilic phosphorus reagents which are transformed into optically active phosphines by reactions with C-nucleophiles. In earlier work, the role of the electrophilic reagents was played mainly by diastereomeric phosphinites bearing a chiral auxiliary <1996TA967>. Recently, substrates have been used in which the P is the sole stereogenic center <1997JOM(529)435> and this has become possible due to the

availability of optically active chlorophosphine-boranes (see [Section 2.08.3.1](#) <1997JOM(529)455>). Thus, a nonracemic chlorophosphine-borane reacts with alkyllithiums to give the corresponding optically active tertiary phosphines-boranes in high yield and high enantioselectivity ([Equation \(58\)](#) <2003JOC4293>).

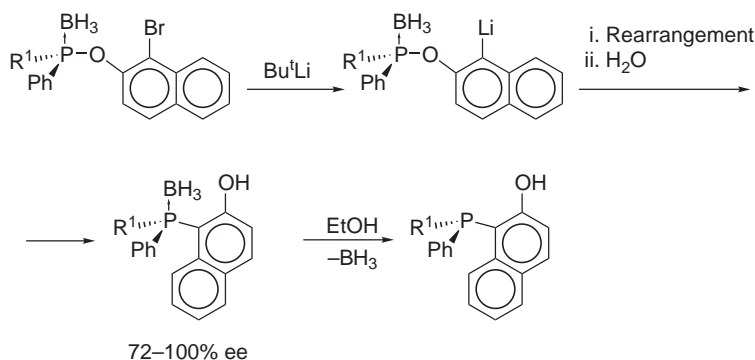


The chlorophosphine-borane can be transformed into a phosphinite-borane, which is then reacted with a C-nucleophile, e.g., [Scheme 26](#) <2000TA3939>.



Scheme 26

The C—P bond has also been formed in the *ortho*-Fries-like rearrangement of aryl phosphinite-boranes, which is known to proceed with complete retention of configuration at P ([Scheme 27](#) <2000TA3939>).



$\text{R}^1 = \text{Me}$, *o*-anisyl, *o*-Tol; the naphthyl moiety may be replaced by a phenyl group

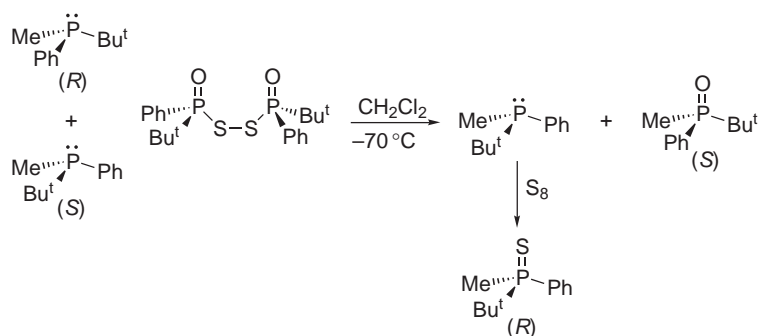
Scheme 27

(v) Reduction of phosphine oxides

Tertiary phosphine oxides are much easier to handle than the parent phosphines. Therefore, a procedure, which is quite frequently used, consists of the synthesis of optically active phosphine oxides followed by their stereoselective reduction to the corresponding phosphines. The stereochemistry of the reduction depends on the reducing agent used (cf. [Section 2.08.2.3.5](#)).

(vi) Kinetic resolution

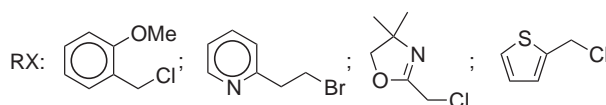
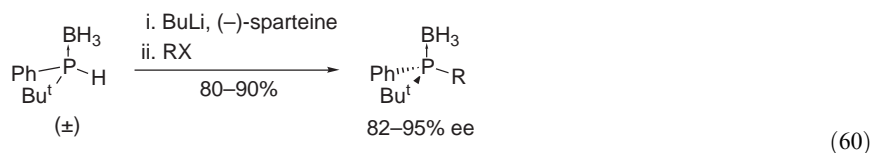
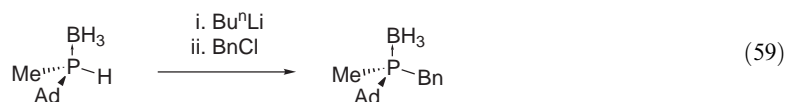
Treatment of racemic tertiary phosphines with enantiomerically pure bis-phosphoryl or bis-thiophosphoryl disulfides under kinetic resolution conditions (2:1 ratio) affords enantiomerically enriched tertiary phosphine oxides and sulfides ($\text{ee} \leq 39\%$) ([Scheme 28](#)). The free phosphines can be obtained by an appropriate reduction procedure <2001TL7841>.



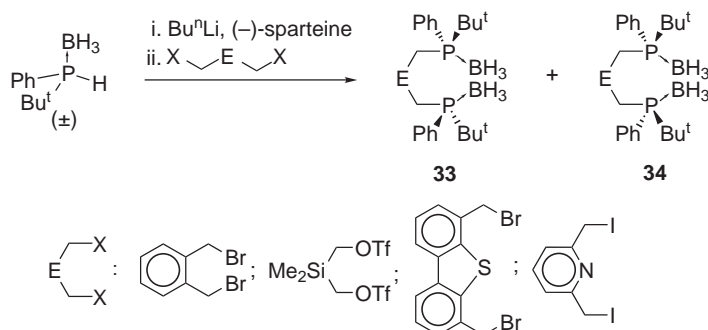
Scheme 28

(vii) *Alkylation/arylation of secondary phosphines*

Treatment of optically active secondary phosphine-boranes bearing a bulky alkyl and no aryl substituent with BuLi, followed by an alkylating agent, leads to optically active tertiary phosphines-boranes (ee \leq 99%) (Equation (59)) [<2000JOC1877>](#). It is noteworthy that the arylphosphine analogs undergo substantial racemization under similar conditions. Interestingly, this feature enables one to start from the racemic secondary phosphine-boranes of this kind, which treated with BuLi in the presence of (–)-sparteine and quenched with an electrophile to give, via a dynamic resolution process, optically active tertiary phosphine-boranes in yields up to 90% (ee \leq 95%) (Equation (60)).

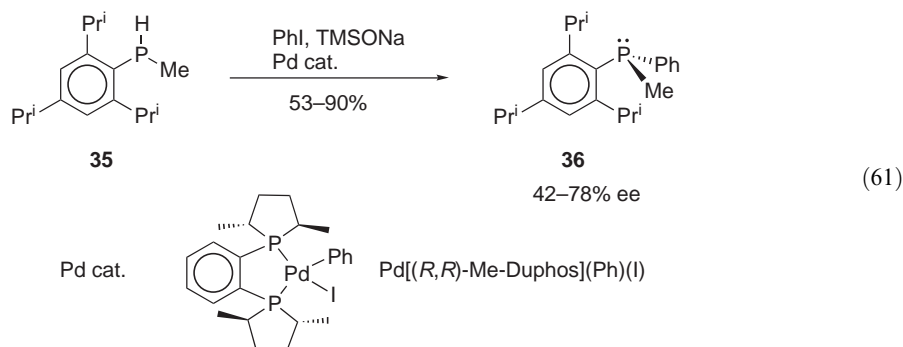


The use of bis-alkylating agents as electrophiles results in the formation of interesting bidentate ligands that are obtained with the dr **33:34** up to 23:1 and ee of **33** up to 99% (Scheme 29) [\[1998JA5116\]](#).



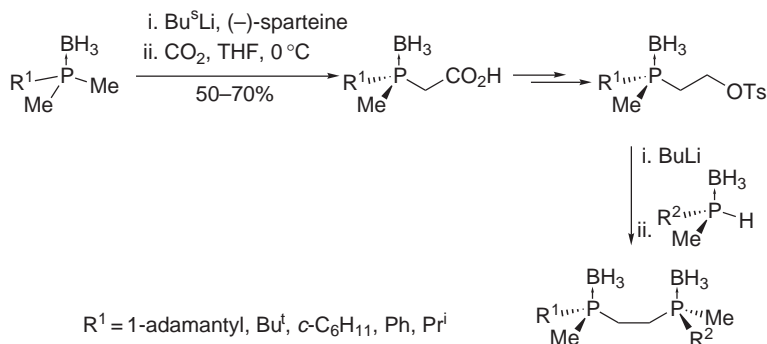
Scheme 29

For the same reason, the coupling of a racemic secondary phosphine **35** with iodobenzene or phenyl triflate in the presence of a chiral palladium catalyst results in the formation of an enantiomerically enriched tertiary phosphine **36** (Equation (61)) <2002JA13356>. In a similar way, platinum-catalyzed asymmetric hydrophosphination of activated alkenes using the catalyst precursor Pt[(*R,R*)-Me-Duphos](*trans*-stilbene) gives chiral phosphines with ee up to 27% <2000OM950>.



(viii) Asymmetric synthesis

Alkyl- or aryl(dimethyl)phosphine-boranes have been enantioselectively deprotonated by treatment with Bu^sLi in the presence of (–)-sparteine <1995JA9075, 1998JA1635> and treated with various electrophiles, e.g., ketones (Scheme 14) <1995JA9075>, oxygen (Scheme 13) <2000JOC4185>, or CO₂ (Scheme 30) <2002EJO2535> to give a variety of functionalized optically active tertiary mono- and bis-phosphine-boranes.

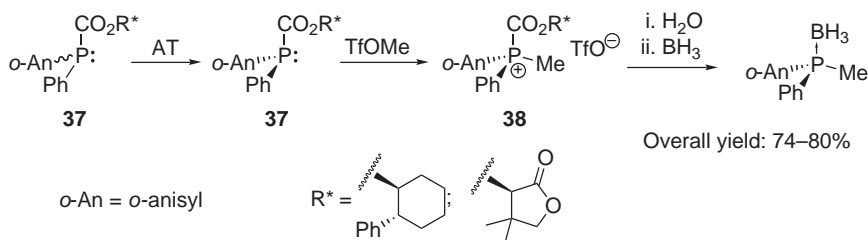


Scheme 30

Diastereoselective deprotonation of the phenyldimethylphosphine-borane complex, which bears an optically active boron moiety [BH(CN)(Ipc), Ipc = isopinocampheyl] followed by alkylation, leads to the corresponding diastereomeric products (de 47–74%) <1999JA1090>.

(ix) Asymmetric transformation

A diastereomeric mixture of *P*-alkoxycarbonylphosphines **37**, bearing a chiral alcohol moiety, has been subjected to crystallization which has produced an “asymmetric transformation of the second kind” (AT) resulting in the formation of virtually one diastereomer of the phosphine **37** (dr = 100:1). The latter can be transformed into the acylphosphonium salt **38**, from which *p*-anisyl(methyl)phenylphosphine-borane (PAMP-borane) can be obtained with ee exceeding 99.5% (Scheme 31) <1997JA9293>.



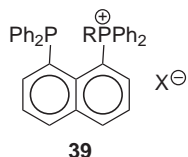
Scheme 31

2.08.2.4 Quaternary Alkylphosphonium Salts— $[\text{R}_4\text{P}]^+ \text{X}^-$

Several common strategies have been developed for the synthesis of quaternary alkylphosphonium salts. All of them are based on the nucleophilic attack of the tertiary phosphine lone pair on an electrophile. From among many examples described only those that involve formation of the products having at least one aliphatic C—P bond will be discussed.

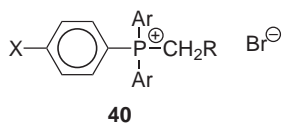
2.08.2.4.1 Quaternary alkylphosphonium salts from phosphines and alkylating agents

The usual method for the synthesis of quaternary phosphonium salts is alkylation of tertiary phosphines using organic halides. Since the publication of COFGT (1995) <1995COFGT(2)425>, this approach has been widely explored with the aim of preparing specific molecules. Simple alkylation of the appropriate tertiary phosphines has been used to synthesize azobenzenephosphonium salt chromophores <1998CEJ512>, α -fluorovinylphosphonium salts <2000JCS(P1)103>, P—C cage phosphonium salts <1996S87>, and porphyrin-containing cage octakis(phosphonium salts) <1995AG(E)2230>. Treatment of 2-phosphino-1,3-dithianes with methyl triflate gives the corresponding 2-dithianylmethylphosphonium salts <1995JOC5190, 1996JOC2995>. Alkylation of 1,8-bis(diphenylphosphino)naphthalene with methyl triflate in the presence of trifluoromethanesulfonic acid or with benzyl bromide results in the formation of the corresponding monophosphonium salts **39** <2001ZAAC(627)2589>.



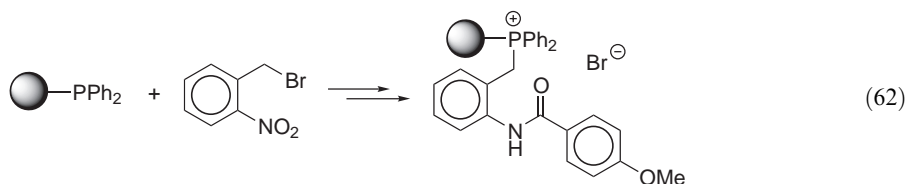
- i. R = Bn, X = Br
ii. R = Me, X = Ms

Water-soluble phosphonium salts **40** have been synthesized in a similar way and used as reagents in the Wittig reaction with carbonyl compounds performed in aqueous NaOH <1998TL7995, 2000JCS(P1)505>.

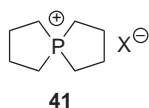


X = CO₂H, OH; Ar = Ph, *p*-HOC₆H₄; R = Ph, Pr

A phosphonium group has been used as a traceless linker for solid phase synthesis (Equation (62)) <1996TL7595>.

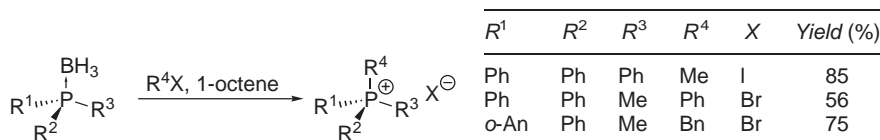


High-temperature alkylation of elemental phosphorus by 1,4-diiodobutane leads to spirocyclic tetraalkylphosphonium salts **41** <2002JA6126>.



As the reaction of tertiary phosphines with alkylating agents often requires harsh conditions, some innovations in the procedure have been made. Application of microwave radiation accelerates the reaction rate and allows shortening of the reaction time and the synthesis of a variety of phosphonium salts <2000TL1339>. In turn, high-energy ball-milling of triphenylphosphine with solid organic bromides without a solvent gives phosphonium salts in high yields (up to 99%). When α -bromoketones are used, no formation of *O*-alkylated Perkov-like by-products is observed <2002CC724>.

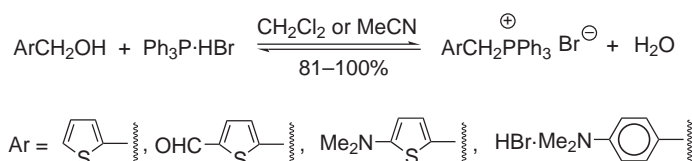
Phosphine-boranes may be transformed under mild conditions in the presence of an alkene into quaternary phosphonium salts by reaction with alkyl halides (Scheme 32) or aryl halides (using NiBr_2 as a catalyst). The reaction proceeds with complete retention of configuration at phosphorus <1997TL3405>.



Scheme 32

2.08.2.4.2 Quaternary alkylphosphonium salts from phosphines, alcohol, and hydrogen halides

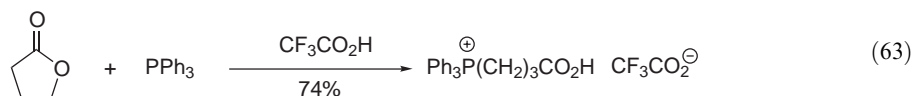
This methodology is based on the reaction of a phosphine with an organic halide that is formed *in situ* from the corresponding alcohol and hydrogen halide. It is particularly useful for alcohols that are easily transformed into the appropriate halides. Moreover, it also allows the use of phosphonium hydrohalides as substrates. In this way, new *P*-benzyl and *P*-thenyl phosphonium salts have been prepared from the parent alcohols and $\text{Ph}_3\text{P}\cdot\text{HBr}$. The water formed can be removed by azeotropic distillation (Scheme 33) <1996SC3091>. It should be added that a few air-stable, nonhygroscopic trialkylhydrogenphosphonium tetrafluoroborates ($[\text{HPR}_3]^+\text{BF}_4^-$) have been synthesized and used in some reactions instead of free phosphines <2001OL4295>.



Scheme 33

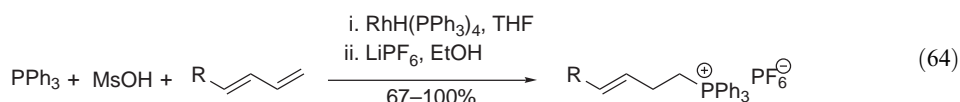
2.08.2.4.3 Quaternary alkylphosphonium salts from phosphines and cyclic compounds

Carboxy group containing phosphonium salts have been synthesized by a ring-opening nucleophilic addition of Ph_3P to lactones in the presence of acids (Equation (63)) <2001MI351>.



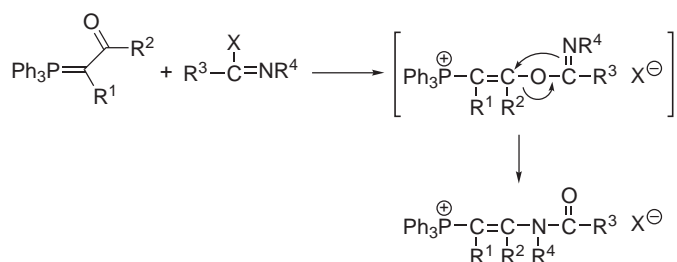
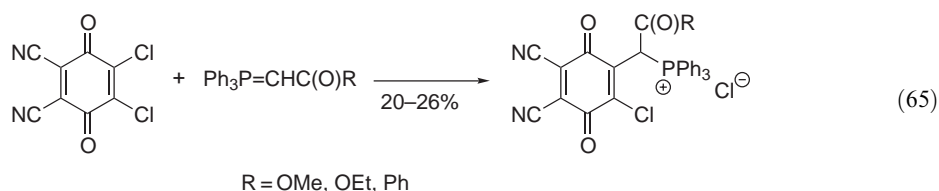
2.08.2.4.4 Quaternary alkylphosphonium salts from phosphines and unsaturated compounds

Rhodium-catalyzed addition of Ph_3P to (*E*)-1,3-dienes in the presence of trifluoromethanesulfonic acid gives (*E*)-3-alkenylphosphonium salts in the anti-Markovnikov mode. Interestingly, the corresponding (*Z*)-dienes react considerably more slowly, which makes it possible to separate diastereomeric mixtures of the dienes (Equation (64)) <2002CL272>.



2.08.2.4.5 Quaternary alkylphosphonium salts from ylides

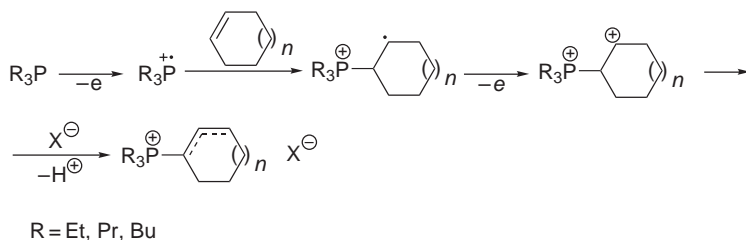
Treatment of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) with stabilized ylides gives phosphonium salts in low yield (Equation (65)) <1997T13945>. The treatment of similar ylides with imidoyl halides results in the formation of hitherto unknown β -(*N*-acylamino)vinylphosphonium salts in good yield (Scheme 34) <2002PS(177)2589>.



Scheme 34

2.08.2.4.6 Electrochemical synthesis of phosphonium salts

Electrochemical oxidation of aliphatic tertiary phosphines in the presence of cycloalkenes yields mixtures of isomeric cycloalkenylphosphonium salts (Scheme 35) <1999ZOB803>.

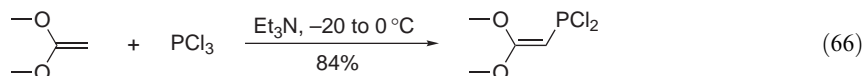


Scheme 35

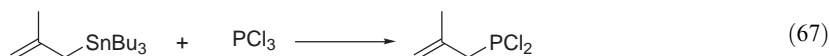
2.08.3 ALKYLPHOSPHORUS HALIDES

2.08.3.1 Alkylphosphorus Compounds with a P—Cl Bond— RPCl_2 and R_2PCl

The chlorophosphines are key substrates in the synthesis of a great variety of organophosphorus compounds (cf. Section 2.08.2.3.2). Among the most commonly used methods for their preparation are the reaction of PCl_3 with organometallic reagents, desulfurization of thionophosphoryl chlorides, chlorination of primary or secondary phosphines and splitting of P—N bonds by HCl. All these methods are well known <1995COFGT(2)425> and have been widely used recently for the synthesis of some chlorophosphines. Bu^iPCl_2 and Pr^iPCl_2 have been obtained (ca. 50% yield) from the reaction of the corresponding Grignard reagent with PCl_3 <1996CJC2167, 1996MI54>. In a similar way, 1-adamantylchlorophosphine has been prepared from 1-adamantylmagnesium bromide and PCl_3 <2000H905> and *t*-butyl(2-methylnaphthyl)phosphine from 2-methylnaphthylmagnesium bromide and Bu^iPCl_2 <2002JOC6539>. In turn, triptycenyldichlorophosphine can be obtained from bromotriptycene via its reaction with BuLi followed by PCl_3 <1996JPC10861>. The addition of PCl_3 to certain alkenes in the presence Et_3N results in the formation of the corresponding 1-alkenyldichlorophosphines (Equation (66)) <1996ZOR1657>.



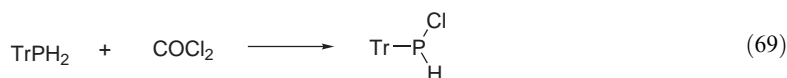
2-Alkenyldichlorophosphines have been obtained by the reaction of PCl_3 with the appropriate 2-alkenyltributylstannanes (Equation (67)) <1998JOC59>.



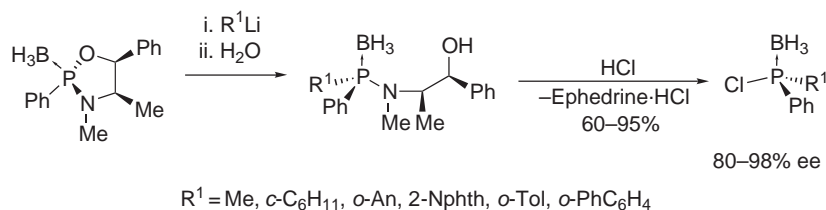
The desulfurization of thiophosphoryl mono- or dichlorides with thiophilic reagents, such as Bu_3P <1995CB581, 1996PS(115)273> or Ph_3P <1996PS(115)241> leads to mono- and dichlorophosphines (Equation (68)) <1996PS(115)241>.



Chlorination of primary and secondary phosphines has been achieved using various chlorinating agents. For example, phosgene allows the synthesis of di-1-adamantylchlorophosphine <1995PS(102)211> and chloro(triphenylmethyl)phosphine (Equation (69)) <1999ZAAC(625)1979>. Triphosgene has been used to obtain functionalized dichlorophosphines <1997TL2779> and bis-(dichlorophosphines) <1998EJI885>. Bis-(dichlorophosphines) are also produced in the reaction of primary bis-phosphines with trichloromethyl chloroformate <2000JOM(602)173> and by chlorination of bis-(phosphinous acids) with PCl_3 <1999S1776>. The P—Cl bond has also been formed by the treatment of *P*-silylphosphines with hexachloroethane <1997CB/RTC989>.



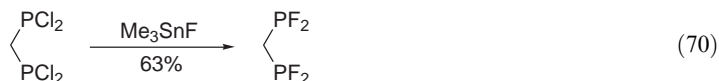
The treatment of aminophosphines with HCl to split the P—N bond has become a widely used method for the synthesis of chlorophosphines. It has been applied not only to the preparation of terpenoid mono- <1996TL2209> and dichlorophosphines <1997JOC297> and aryl-bis-(dichlorophosphines) <1997CB/RTC1485> from the corresponding mono- and diamino-phosphines but also to the preparation of optically active chlorophosphines. The latter have been obtained in the form of borane adducts starting from diastereomerically pure (+)-ephedrine-derived aminophosphine-boranes. The borane protection makes the chlorophosphines configurationally stable and allows their isolation in the optically active form <1997JOM(529)455, 2000TA3939, 2003JOC4293>: free chlorophosphines undergo rapid racemization <1995TA2369>. The substitution of the amino moiety by chloride proceeds with inversion of configuration at phosphorus (Scheme 36).



Scheme 36

2.08.3.2 Alkylphosphorus Compounds with a P—F, P—Br, and P—I Bond

Fluorophosphines have been synthesized from the corresponding chlorophosphines by chloride-fluoride exchange using various fluorine-containing reagents. Thus, trimethyltin fluoride converts methylenebis(dichlorophosphine) to methylenebis(difluorophosphine), a strongly pyrophoric and volatile material (Equation (70)) <1995ZN(B)1583>. In turn, a (diazaphosphol-4-yl)dichlorophosphine has been transformed into the corresponding difluorophosphine using NaF in the presence of 15-crown-5 in MeCN <1996PS(111)150>.

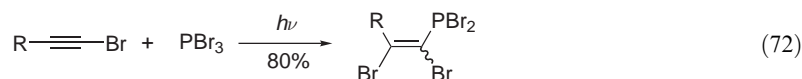


Racemic fluoro(*i*-propyl)phenylphosphine has been prepared by halogen exchange of the corresponding chlorophosphine with NaF in hot sulfolane and proved to be stable in benzene. It has been resolved into enantiomers using the method of metal complexation, via a second-order asymmetric transformation of diastereomeric complexes (for the structure of the complexes, cf. Section 2.08.2.2.5, Equation (39), formula **22** and Section 2.08.2.3.6.(i), formula **32**). However, the optically active fluorophosphine undergoes racemization in benzene within 6 h <1996IC1244>. Antimony trifluoride has also been used to convert dichlorophosphines to difluorophosphines <1997JST(413)371, 1998JST(449)255>.

Bromophosphines are usually obtained either from PBr₃, using transformations similar to those employing PCl₃, or by a chloride–bromide exchange in the starting chlorophosphines. Thus, 2-alkenyldibromophosphines are obtained from PBr₃ and 2-alkenyltributylstannanes (Equation (67)), <1998JOC59> and 1-alkenyldibromophosphines from the corresponding alkenes and PBr₃ in the presence of Et₃N (Equation (66)) <1996ZOR1657>. In turn, chloromethyldibromophosphine (Equation (71)) and bromo(alkyl)chloromethylphosphines can be synthesized by a halogen exchange in the corresponding chlorophosphines using MgBr₂ as the source of the bromide anion <1997ZN(B)883>.



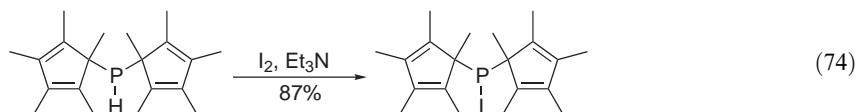
The photochemical addition of PBr₃ to alkynes or alkenes gives alkenyldibromophosphines (Equation (72)) and alkyldibromophosphines, respectively <1995ZOB1046, 1995ZOB1048>.



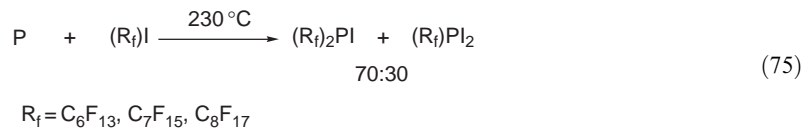
Iodophosphines are prepared from the corresponding chlorophosphines by a chloride–iodide exchange using NaI in toluene as the iodide anion source (Equation (73)) <1999CEJ385>.



An unusual secondary phosphine has been treated with iodine in the presence of Et₃N to give the corresponding iodophosphine (Equation (74)) <1997BSF1039>.



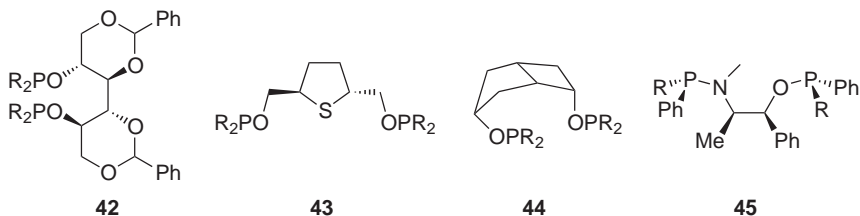
Perfluoroalkyl iodophosphines have been obtained in the reaction of red phosphorus with perfluoroalkyl iodides (Equation (75)) <2000IC1787>.



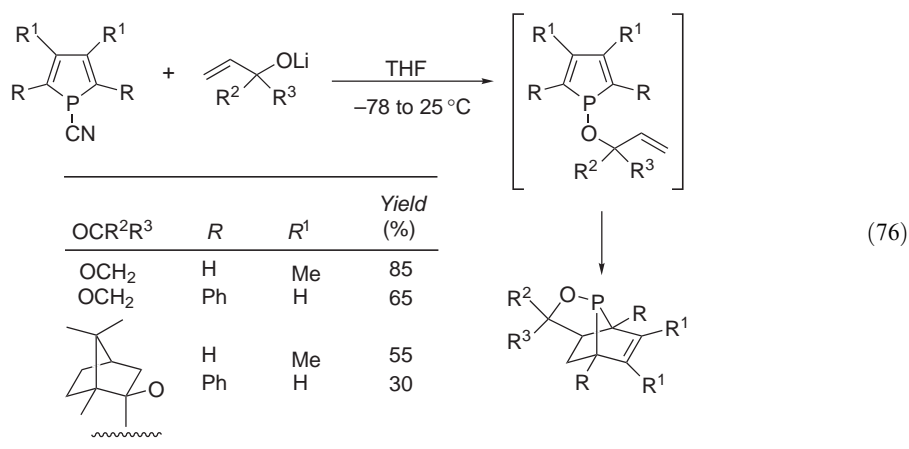
2.08.4 ALKYLPHOSPHORUS COMPOUNDS WITH A P–O BOND

2.08.4.1 Alkylphosphinous Acid Derivatives—RPHOH, R₂POH, etc.

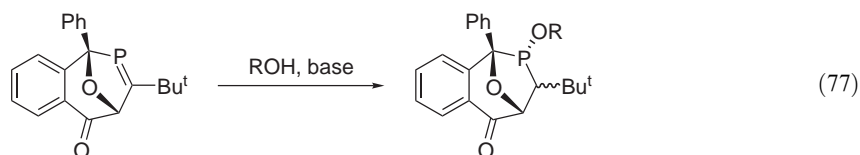
Since the publication of COFGT (1995) <1995COFGT(2)425>, most of the interest in this area has concentrated on the synthesis of new ligand systems for use in homogeneous catalysis. In most cases, the phosphinite or phosphonite centre is created using the well-known procedure involving reaction of an alcohol or phenol with a chlorophosphorus(III) precursor in the presence of base. An alternative approach is based on alcoholysis of aminophosphines. Using these methodologies, series of chiral phosphinites **42** <2000TL2867>, **43** <1998OM4976>, **44** <1999TA3341>, and aminophosphine-phosphinite systems **45** <1999TA4729> have been prepared.



Phospholes bearing an allyloxy substituent at phosphorus have been found to undergo an intramolecular Diels–Alder cycloaddition leading to tricyclic phosphinites (Equation (76)) <2002JOC5422>.

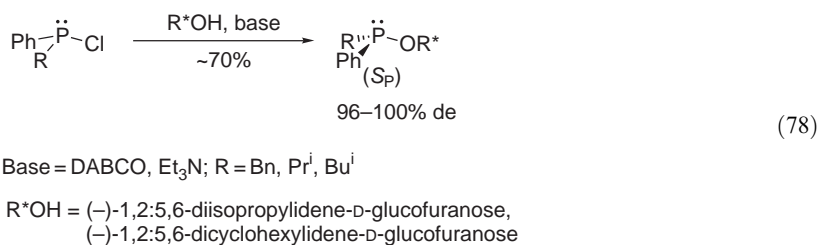


Phosphinites can also be prepared by addition of alcohols to phosphaaalkenes. Thus, chiral bicyclic phosphinites have been obtained as a mixture of diastereoisomers by base-promoted addition of alcohols to the P—C double bond of the bicyclic phosphaaalkene (Equation (77)) <2000EJO2219>.



A samarium carbenoid, generated from diiodomethane and samarium metal, undergoes insertion into the P—H bond of phenylphosphinous acid menthyl ester to give the corresponding phosphinite with retention of configuration at the phosphorus atom <1996CL705>.

The reaction of racemic nonsymmetrical chlorophosphines with (–)-1,2:5,6-disubstituted-*D*-glucofuranose proceeds with high stereoselectivity to give the P-chiral phosphinites (Equation (78)) <1996TA967>.

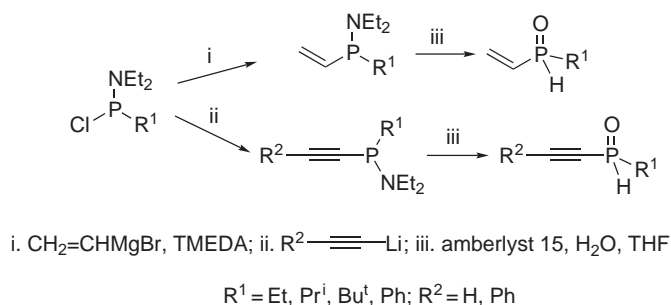


By alkylation of elemental yellow phosphorus with MeCl under phase-transfer conditions, methylphosphonous acid sodium salt can be prepared in 72% yield <2002PS(177)1757>.

Treatment of ethyl (diethoxyalkyl)phosphinates with Grignard or organolithium reagents gives protected primary phosphine oxides <1999SL1633>. These products, stable to chromatography or distillation, may be further converted into protected secondary phosphine oxides which can in turn be deprotected under acidic conditions yielding secondary phosphine oxides <1999SL1633, 1998SL283, 2002PS(177)1557>. Phosphinic acid chlorides and bromides have been found to easily undergo reduction with alkali metals (Li, Na, K) in NH₃ liq./THF and potassium naphthalene affording secondary phosphine oxides <2000PS(161)39>.

A general method for preparing secondary *P*-alkenyl- and *P*-alkynylphosphine oxides involves the condensation of the vinyl Grignard reagent or lithium acetylide with *P*-chloroaminophosphines followed by acidic hydrolysis of the corresponding vinyl- or ethynylaminophosphines on a solid acid (Amberlyst 15) (Scheme 37) <1995TL4421>.

Enantiopure secondary phosphine oxides have been obtained by a classical resolution using (*S*)-mandelic acid <2000JOC7561, 1999TA2757> and (*R*)-1,1'-binaphthalene-2,2'-diol <1999TA2757>, chiral HPLC <2003OL1503> or a three-step resolution procedure involving

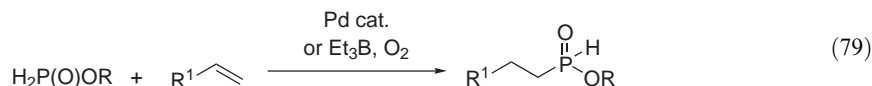


Scheme 37

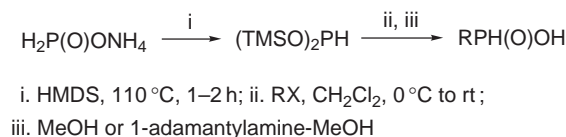
conversion of a racemic secondary phosphine oxide into phosphinothioic acid, followed by resolution with chiral amine and desulfurization by means of Raney nickel under ultrasound irradiation [<2000EJO3205>](#).

2.08.4.2 Alkylphosphonous Acid Derivatives— $\text{RP}(\text{OH})_2$, etc. Also Halides— $\text{RP}(\text{Hal})(\text{OH})$, etc.

Palladium-catalyzed hydrophosphinylation of alkenes with hypophosphorous acid, its salts, or esters constitutes an environmentally friendly route to alkylphosphonous acid derivatives (Equation (79)) [<2002JA9386>](#). Alkylphosphonous acid esters and salts have also been prepared in high yield by triethylborane-initiated radical addition of the corresponding hypophosphorous acid derivatives to alkenes (Equation (79)) [<2001JOC6745>](#). The reaction proceeds smoothly at room temperature under neutral conditions and tolerates a wide range of functional groups.



The reaction of alkyl halides with *in situ* generated bis(trimethylsilyl)phosphonite provides an alternative route to alkylphosphonous acids (Scheme 38) [<1994TL4223>](#).



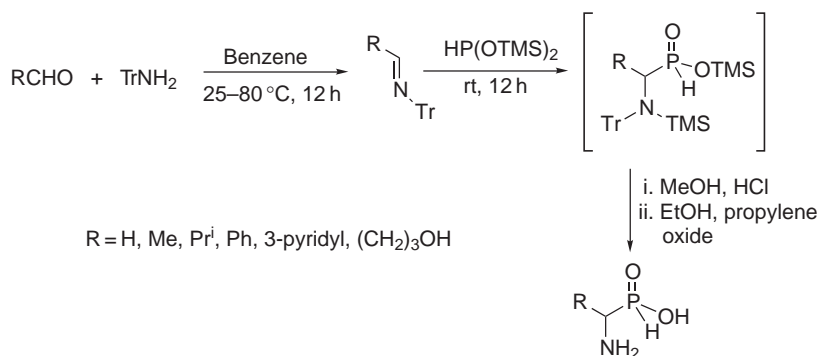
Scheme 38

A general method for the preparation of α -aminoalkylphosphonous acids consists of the addition of bis(trimethylsilyl)phosphonite to *N*-tritylalkanimines followed by deprotection of the corresponding bis(trimethylsilyl) *N*-tritylaminoalkylphosphites (Scheme 39) [<1994S23>](#).

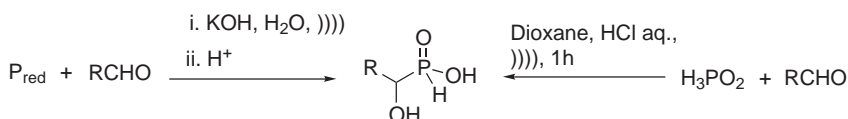
α -Hydroxyalkylphosphonous acids are readily available under sonication from hypophosphorous acid and aldehydes in the presence of catalytic amounts of hydrochloric acid as well as from red phosphorus and aldehydes in basic media (Scheme 40) [<1999EJO861>](#).

Functionalized alkylphosphonous acids and esters have been prepared starting from masked hypophosphorous acid synthons such as *O*-isobutyl 1-hydroxy-1-methylethylphosphinate [<1995TL9389>](#) and *O*-ethyl 1,1-diethoxyethylphosphinate [<1995TL9385>](#), respectively. Selective transformations performed at the P, followed by basic or acidic deprotection, gave the corresponding alkylphosphonous acids or phosphonites (Scheme 41).

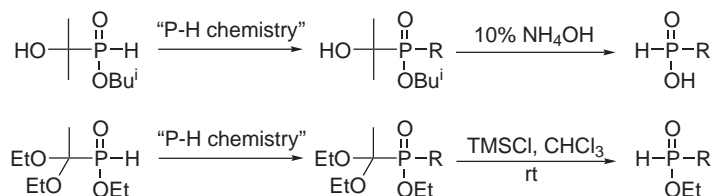
Orthosilicate-mediated esterification of phosphonous acids provides a simple route to phosphonous acid monoesters (Equation (80)) [<2000OL3341>](#). Esterification of phosphonous acids has also been accomplished using PyBOP/ Pr_2NEt [<1997BMCL505, 1995JOC5214>](#). Base-catalyzed alkylation of hypophosphorous acid isopropyl ester with primary alkyl halides affords the corresponding alkylphosphonous acid isopropyl esters in fair to excellent yields (Equation (81)) [<1996PS\(115\)255>](#).



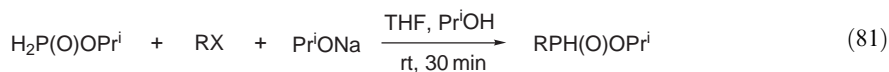
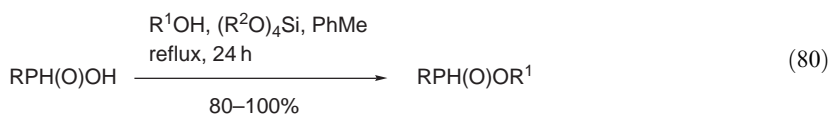
Scheme 39



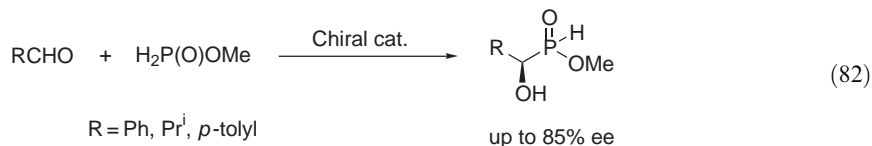
Scheme 40



Scheme 41



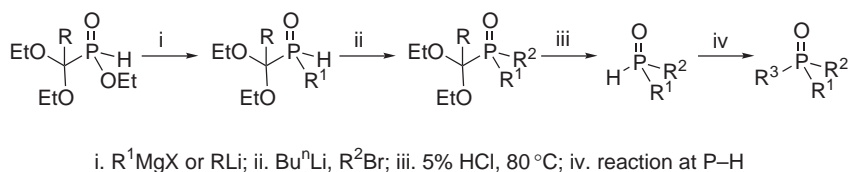
Enantiomerically enriched α -hydroxyalkylphosphonous acid methyl esters have been prepared by catalytic asymmetric hydrophosphinylation of aldehydes with hypophosphorous acid methyl ester in the presence of binaphthol-modified heterobimetallic complexes (Equation (82)) <1999T12125>.



2.08.4.3 Alkylphosphine Oxides—R₃PO

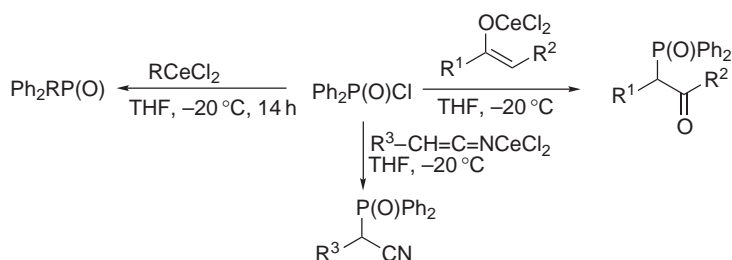
Protected primary phosphine oxides have been obtained by treatment of ethyl (1,1-diethoxyalkyl)-phosphinates with Grignard or organolithium reagents. Subsequent metallation and alkylation at P affords the protected secondary phosphine oxides which can be further elaborated into new

unsymmetrical secondary and tertiary phosphine oxides (Scheme 42) <1999SL1633, 2002PS(177)1557>. This approach has been used for the preparation of tertiary phosphine oxide-modified DNA <1998SL283>.



Scheme 42

The reaction of diphenylphosphinoyl chloride with organocerium reagents gives tertiary phosphine oxides in good-to-high yield <1999EJO2299>. When the reaction is extended to cerium enolates of ketones and nitriles, β -oxophosphine oxides and α -phosphinoylonitriles can be obtained (Scheme 43).



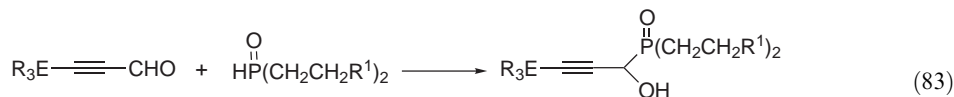
Scheme 43

Tertiary alkylphosphine oxides can be synthesized directly from phosphorus and primary alkyl halides <1998IZV1695> or alkenes <2000ZOB43>. Thus, tribenzylphosphine oxide has been prepared by treatment of red phosphorus with benzyl chloride in 50–60% aqueous KOH , dioxane under phase-transfer conditions in 75% yield <1998IZV1695>. A similar reaction of 2-chloro-5-(chloromethyl)thiophene with white phosphorus leads to tris[(5-chloro-2-thienyl)methyl]phosphine oxide in 56% yield <2001PS(175)163>.

Supercritical nitrous oxide has been used for oxidation of phosphines to the related phosphine oxides under mild conditions, allowing a simple isolation of products <1999OL583>.

The Bu^tOK -catalyzed addition of diphenylphosphine oxide to functionalized alkenes affords polyfunctional tertiary phosphine oxides <2002TL5817>. Functionalized tertiary phosphine oxides are also available by the addition of secondary phosphine oxides to carbonyl compounds, imines, and some alkenes, in an uncatalyzed process under neutral conditions in THF. The $P-H$ bond is activated by the presence of vinyl or phenylethynyl substituents at P <1998TL985>. Another route to tertiary phosphine oxides involves the alkylation of secondary phosphine oxides by quaternary ammonium salts <1999IZV390>.

Diorganovinylphosphine oxides have been prepared by heating secondary phosphine oxides with vinyl sulfoxides or divinyl sulfone in the presence of KOH <1997IZV1895>. α -Hydroxyalkylphosphine oxides have been synthesized by reacting dimethylphosphine oxides with aldehydes and ketones <1995PS(101)213>. In a similar way, 3-(trialkylsilyl)- and 3-(trialkylgermyl)-2-propynals as well as 2-propynal react with secondary phosphine oxides to give the corresponding tertiary α -hydroxyphosphine oxides in quantitative yield (Equation (83)) <2002JOM(659)172>.

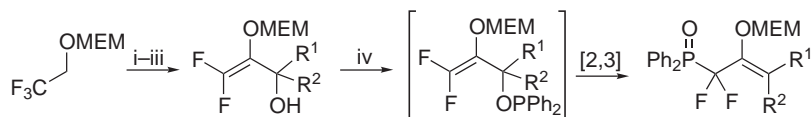


$E = \text{Si}, \text{Ge}$; $R = \text{Me}, \text{Et}$; $R^1 = \text{Ph}, 2\text{-pyridyl}$

N-Substituted (aminomethylene)diphenylphosphine oxides have been prepared by the reaction of diphenylphosphine oxide, paraformaldehyde, and a secondary amine under modified Mannich reaction conditions (Equation (84)) <1996ZOB692>.



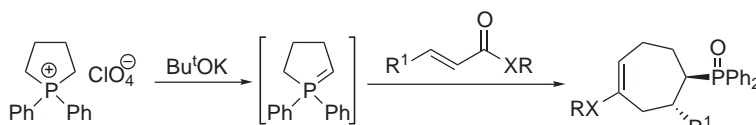
α,α -Difluoroalkylphosphine oxides are produced by the reaction of difluoroallylic alcohols with chlorodiphenylphosphine in the presence of triethylamine via a [2,3]-rearrangement of the transiently formed phosphinite ester (Scheme 44) <1996TL6403>.



i. LDA, HF, $-78\text{ }^\circ\text{C}$; ii. R^1COR^2 ; iii. NH_4Cl , MeOH; iv. $Ph_2P(O)Cl$, Et_3N , CH_2Cl_2

Scheme 44

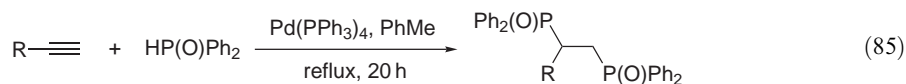
The tandem Michael addition–intramolecular Wittig reaction of a five-membered cyclic phosphonium ylide with α,β -unsaturated esters <1997JOC6627> and thioesters <1999JOC5988> proceeds with high stereoselectivity affording cycloheptenylphosphine oxide derivatives (Scheme 45).



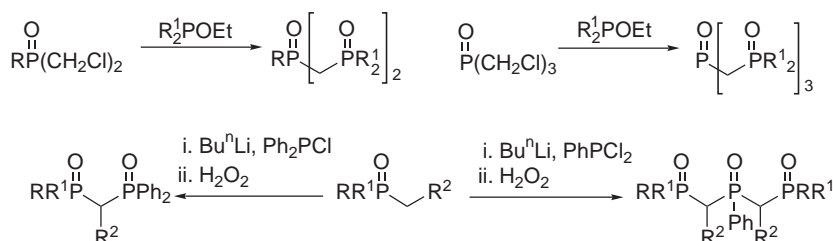
X = O, S

Scheme 45

Bisphosphine oxides have been synthesized in good yield via Pd-catalyzed bis-hydrophosphinylation reactions of terminal alkynes and diphenylphosphine oxide (Equation (85)) <2002TL3707>.

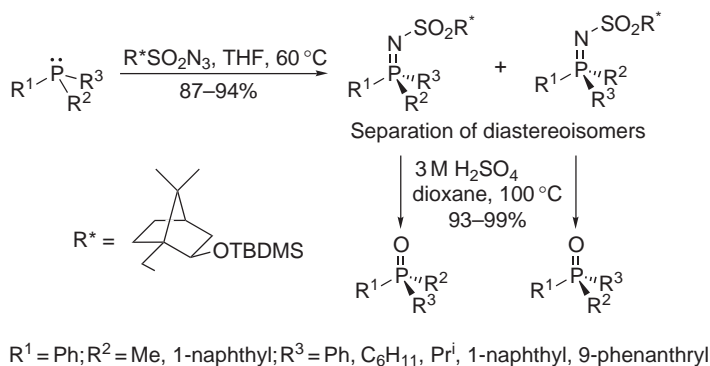


Polyphosphine oxides with the (O)PCP(O) skeleton can be obtained in good yield either by the Michaelis–Arbuzov reaction of chloromethylphosphine oxides and phosphorus(III) esters or by the reaction of the phosphine oxide α -carbanions with chlorophosphines followed by oxidation (Scheme 46) <1999EJO1561>.



Scheme 46

A general resolution procedure for the preparation of P-stereogenic phosphine oxides is given by the reaction of racemic chiral tertiary phosphines with optically pure (1*S*,2*R*)-*O*-(*t*-butyldimethylsilyl)isobornyl-10-sulfonyl azide, followed by separation of the diastereoisomeric phosphinimines and acid hydrolysis to liberate the resolved chiral phosphine oxides (Scheme 47) <1999OL2009, 2001JOC7478>.

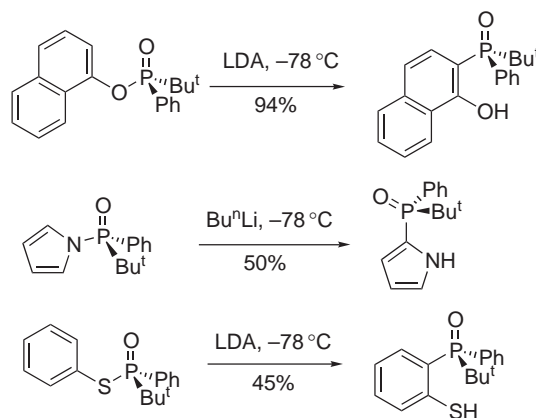


Scheme 47

A samarium carbenoid, generated from diiodomethane and samarium metal, reacts with chiral secondary phosphine oxides affording tertiary phosphine oxides with retention of configuration at P <1996CL705>.

Cyclic α -aminophosphine oxides have been obtained by catalytic asymmetric addition of diphenylphosphine oxide to cyclic imines. (*R*)-PrKB (PrKB: Pr = praseodymium, K = potassium, B = BINOL) turned out to be the most efficient catalyst giving ee up to 93% <1999TL2565>. Nucleophilic addition of the configurationally stable lithiated P-chiral *t*-butylphenylphosphine oxide to aldehydes and α,β -unsaturated carbonyl compounds gives functionalized tertiary P-chiral oxides in good yields and with diastereoselectivities ranging from 33% to >98% <1996TL4729>. The reaction of metallated chiral *tert*-butylphenylphosphine oxide with primary alkyl halides constitutes a simple route to chiral tertiary phosphine oxides <2000EJO3205>.

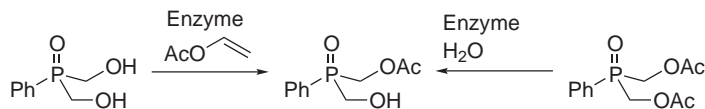
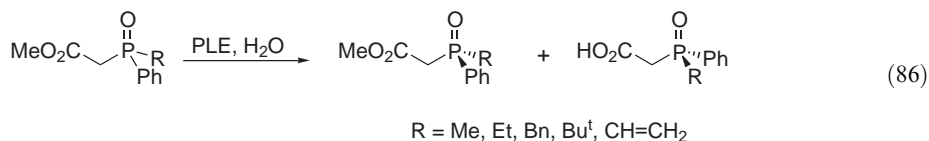
Upon treatment with LDA or alkyllithium, P-chiral phosphinates, phosphinoamidates, and phosphinothioates undergo clean, stereoselective rearrangement with retention of configuration at P to provide functionalized tertiary phosphine oxides in moderate-to-excellent yield (Scheme 48) <2001TL457>.



Scheme 48

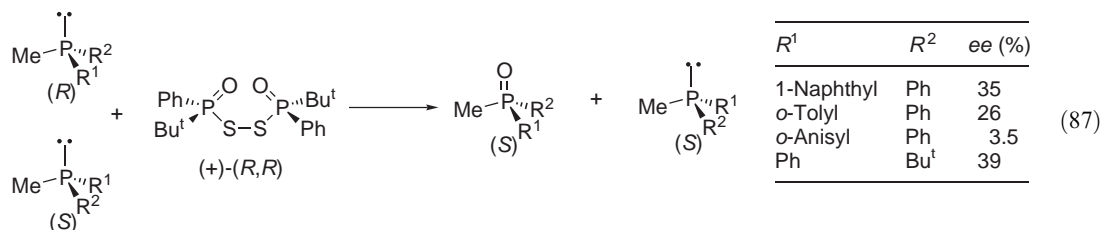
Non-racemic P-chiral phosphine oxides have also been prepared employing enzymatic methods. Thus, racemic phosphinoxyacetates have been resolved into enantiomers using pig liver esterase (PLE) under kinetic resolution conditions to give the corresponding P-chiral phosphinoxyacetic acids and unreacted esters with high enantiomeric purities (72–100% ee) (Equation (86))

<1994TL7081, 1998PJC564>. In turn, prochiral bis(hydroxymethyl)phenylphosphine oxide has been desymmetrized, using either a lipase-catalyzed acetylation or hydrolysis of the corresponding diacetyl derivative, to give a chiral monoacetate in yields up to 76% (and ee up to 79%) (Scheme 49) <2003TA3379>. PLE-mediated hydrolysis of bis(methoxycarbonylmethyl)phenylphosphine oxide leads to the corresponding monoacetate in 92% yield (72% ee) <2003TA3379>.



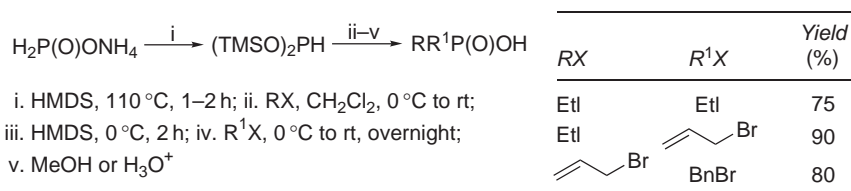
Scheme 49

Treatment of racemic P-stereogenic tertiary phosphines with enantiomerically pure (+)-(R,R)-bis(*t*-butylphenylphosphinoyl) disulfide under kinetic resolution conditions (2:1 ratio) gives the enantiomerically enriched tertiary phosphine oxides with the ee values up to 39% (Equation (87)) <2001TL7841>. In turn, 1-phenylphosphole derivatives of high enantiomeric purity are accessible by kinetic resolution of the corresponding racemates subjected to the enantioselective cycloaddition with enantiopure nitrones derived from tartaric acid <1994JOC1315>. Other methods, including stereoselective nucleophilic displacement at phosphorus <1994TL6343>, chirality transfer from sulfur to phosphorus <1996PS(109-110)573> as well as direct resolution of racemates by chromatography on chiral stationary phases <1995TA2017>, have also been successfully applied to the synthesis of P-chiral tertiary phosphine oxides.



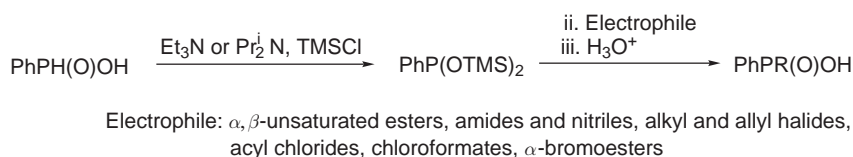
2.08.4.4 Alkylphosphinic Acid Derivatives— $\text{R}_2\text{P}(\text{O})\text{OH}$, etc. Also Halides— $\text{R}_2\text{P}(\text{O})\text{Hal}$, etc.

Symmetrical and unsymmetrical dialkylphosphinic acids have been prepared in a one-pot reaction from silyl phosphonites and alkyl halides (Scheme 50) <1994TL4223>. The same methodology has been applied to the synthesis of cyclic phosphinic acids from dihaloalkanes, ω -bromo-1,2-epoxides and ditriflates <1995JOC6076>.



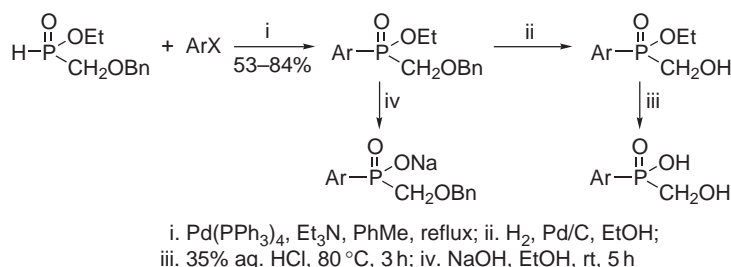
Scheme 50

The reaction of *in situ* generated bis(trimethylsilyl) phenylphosphonite with various electrophiles allows the synthesis of functionalized phenylphosphinic acid derivatives (Scheme 51) <1996TL1651>.



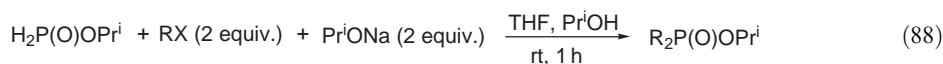
Scheme 51

Palladium-catalyzed arylation of benzyloxymethylphosphonous acid ethyl ester with aryl halides followed by hydrogenolysis of the benzyl protecting group and acidic hydrolysis of the ester function, constitutes a general route to aryl(hydroxymethyl)phosphinic acids (Scheme 52) <2003S2216>.

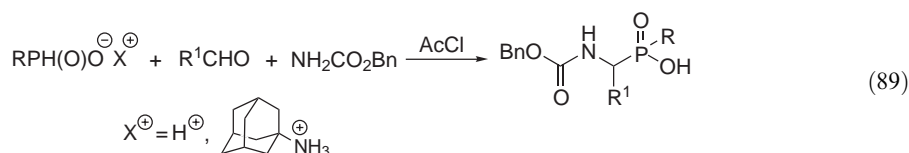


Scheme 52

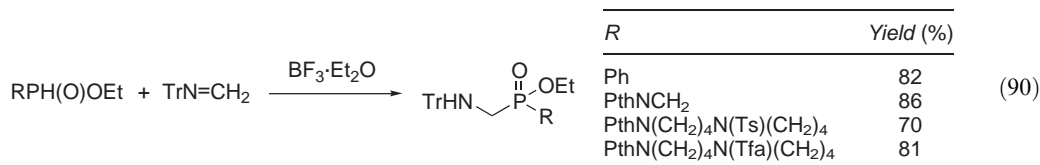
Base-catalyzed dialkylation of hypophosphorous acid isopropyl ester with alkyl halides affords the corresponding dialkylphosphinic acid isopropyl esters (Equation (88)) <1996PS(115)255>.



N-Protected α -aminoalkylphosphinic acids have been formed in the three-component condensation reaction of an alkylphosphonous acid (or its salt), an aldehyde and benzyl carbamate in acetyl chloride (Equation (89)) <1996TL4335>.

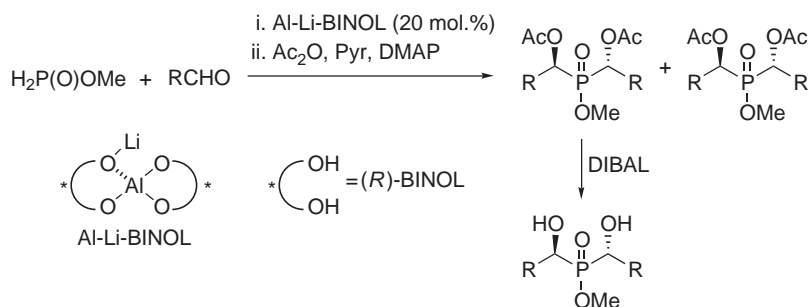


Trityl-protected α -aminoalkylphosphinates have been obtained by addition of phosphonous acid monoesters to tritylamine derived Schiff base in the presence of catalytic amount of BF₃ (Equation 90) <1998JOC502>.



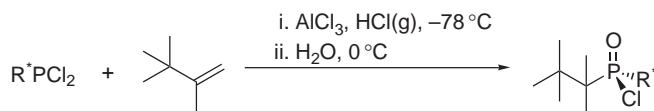
The straightforward synthesis of α, α' -dihydroxyphosphinates has been accomplished via the catalytic asymmetric hydrophosphinylation of aldehydes with methyl phosphinate albeit with low diastereoselectivities (Scheme 53) <1999T12125>.

1-Chloroalkyl phosphonochloridates upon treatment with Grignard reagents give 1-chloroalkylphosphinates <1996JCS(P1)2179>.



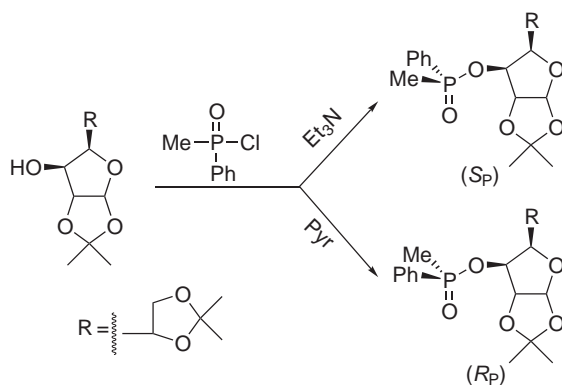
Scheme 53

P-Chiral phosphinic acid chlorides have been obtained by treatment of chiral dichlorophosphines with 2,3,3-trimethylbutene in the presence of AlCl_3 and gaseous HCl (Scheme 54) <1997JOC297>.



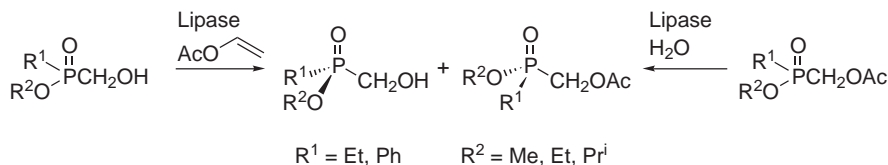
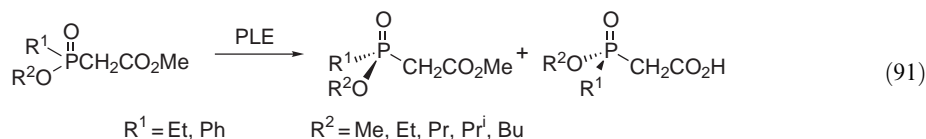
Scheme 54

P-Chiral phosphinates have been synthesized in excellent yield and with high diastereoselectivity by reacting phosphinyl chlorides with sugar-derived carbinols <1996TA3353, 1998TA1279, 1996TA967>. Either phosphinate diastereomer can be prepared by the appropriate choice of base and solvent <1996TA3353> (Scheme 55).



Scheme 55

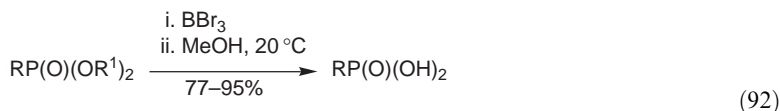
Enantiomerically enriched (50% ee) *t*-butylphenylphosphinoyl chloride has been obtained in the reaction of racemic *t*-butylphenylchlorophosphine with enantiopure (+)-(*R,R*)-bis(*t*-butylphenylphosphinoyl) disulfide under kinetic resolution conditions <2001TL7841>. When the same reaction is performed under dynamic kinetic resolution conditions in the presence of chloride ions, the phosphinoyl chloride (70% ee) has been obtained. Enzyme-promoted kinetic resolution of racemic, P-chiral phosphonylacetates gives the corresponding P-chiral phosphonylacetic acids and recovered esters in moderate to high enantiomeric purity (up to 95% ee) (Equation (91)) <1998TA2641>. Enantiomerically enriched P-chiral hydroxymethylphosphinates have been prepared by lipase-mediated acetylation of racemic P-chiral hydroxymethylphosphinates <1998TA3283, 2002TA735> and by hydrolysis of their *O*-acetyl derivatives conducted under kinetic resolution conditions (Scheme 56) <1998TA3283>.



Scheme 56

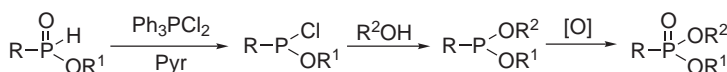
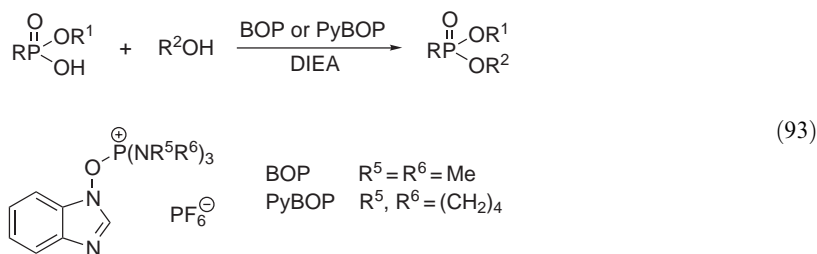
2.08.4.5 Alkylphosphonic Acid Derivatives— $\text{RP}(\text{O})(\text{OH})_2$, etc. Also Halides— $\text{RP}(\text{O})(\text{Hal})\text{OH}$, $\text{RP}(\text{O})(\text{Hal})_2$, etc.

Phosphonic acids are conveniently prepared by selective dealkylation of dialkyl phosphonates with boron tribromide followed by methanolysis (Equation (92)) <2001S553>. Me_3SiBr also efficiently and chemoselectively cleaves the isopropyl group in diisopropyl phosphonates if used in excess in dioxane at 60°C to give the corresponding monosodium salts of phosphonic acids after treatment with NaOH in methanol <1995TL6759>.



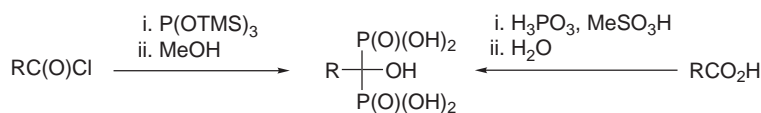
$\text{R} = \text{Me, Et, Bn, CH}_2\text{CN, CH}_2\text{OH, CH}_2\text{SMe, CH}_2\text{CO}_2\text{Et, CH}_2\text{CH}_2\text{Br, allyl, dodecyl, phthalimidomethyl}$
 $\text{R}^1 = \text{Me, Et, Pr}^i, \text{Bu}^t$

Mixed phosphonate diesters are readily formed from monoesters and appropriate alcohols using (1*H*-benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) or (1*H*-benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) as activating agents (Equation (93)) <1995JOC5214>. An alternative approach is based on a modified Mitsunobu coupling of a phosphonate monoester with an alcohol <1994JOC658>. Phosphonate diesters can also be prepared by a one-pot activation-coupling-oxidation procedure (Scheme 57) <1995JOC7390>. The key step in this process is the use of dichlorotriphenylphosphorane as activation reagent to generate the highly reactive phosphonochloridites. The transesterification of pinacol phosphonates in acidic methanol provides an efficient access to phosphonic acid mono methyl esters <2003JOC1459>.



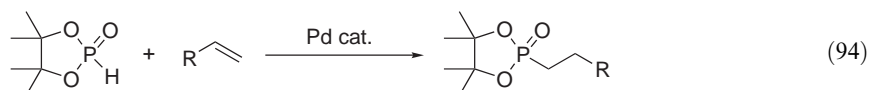
Scheme 57

The reaction of acyl chlorides with tris(trimethylsilyl) phosphite followed by the hydrolysis of the silyl esters leads to 1-hydroxymethylene-1,1-bisphosphonic acids ([Scheme 58](#)) [<2001TL8475>](#). The synthesis of these acids has also been achieved by treatment of carboxylic acids with phosphorous acid in MeSO_3H ([Scheme 58](#)) [<1995JOC8310>](#).



Scheme 58

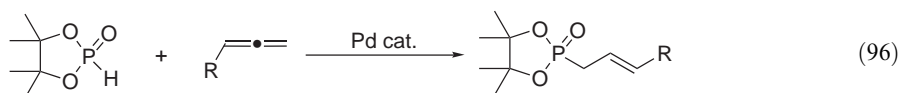
When 4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide is employed as a reactant, palladium-catalyzed addition to alkenes proceeds smoothly to afford the corresponding phosphonates in high yield ([Equation \(94\)](#)) [<2000JA5407>](#). Diethyl and dimethyl phosphite are totally unreactive under these conditions. Also, Wilkinson's complex catalyzes hydrophosphorylation of terminal alkenes with pinacol hydrogen phosphite [<2001OL4303>](#).



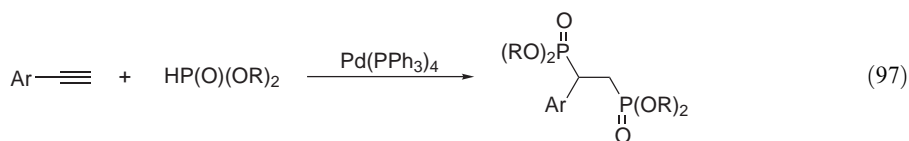
Organocerium compounds react with chlorophosphates to give phosphonates in good yield [<1999EJO2299>](#). An alternative approach is based on Cs_2CO_3 promoted reaction of dialkyl phosphites with alkyl halides ([Equation \(95\)](#)) [<2003TL8617>](#).



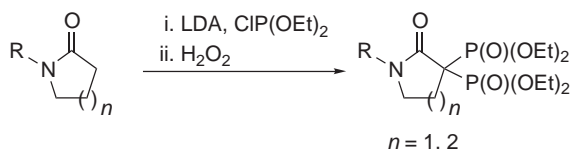
Palladium-catalyzed regio- and stereoselective hydrophosphorylation of allenes offers a convenient and clean route to allylphosphonates ([Equation \(96\)](#)) [<2000OM4196>](#).



1,2-Bis-phosphonates have been prepared via palladium-catalyzed bis-hydrophosphorylation reaction of electron-deficient terminal arylalkynes with dialkyl phosphites ([Equation \(97\)](#)) [<2000TL151>](#). Without electron-withdrawing functionalities on the aryl groups, alkenyl phosphonates are obtained.

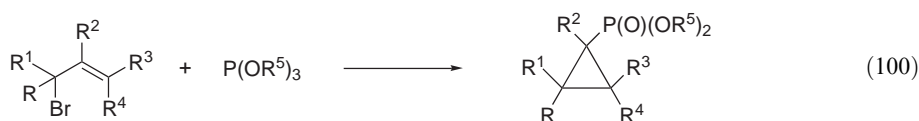
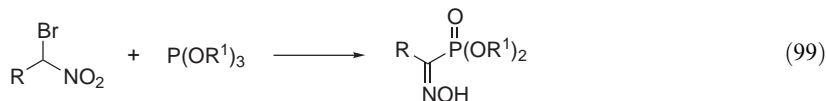
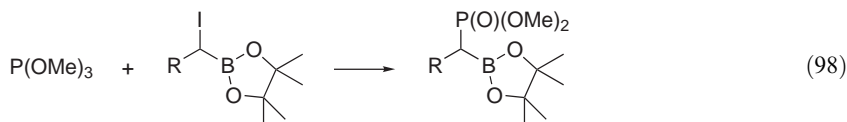


Geminal bis-phosphonates can be synthesized from different carbonyl compounds via reaction with a strong base and diethyl phosphorochloridite followed by oxidation ([Scheme 59](#)) [<2002TL8665>](#). The process gives moderate-to-good yield using *N*-alkyl lactams, but diverse results are obtained with other carbonyl compounds.



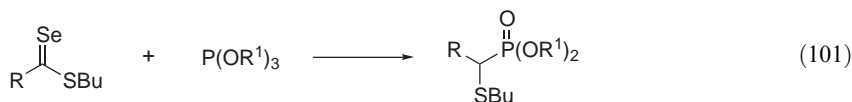
Scheme 59

The Michaelis–Arbuzov reaction continues to be widely employed in organic synthesis. Thus, the reaction of 1-iodoalkyl boronates with trimethyl phosphite has been employed for the synthesis of phosphonoboronates (Equation (98)) <1999TL3895>. *O,O*-Dialkyl-1-hydroxyiminoalkylphosphonates have been synthesized by the reaction of 1-bromo-1-nitroalkanes with trialkyl phosphites (Equation (99)) <1999JOC9272>. Cyclopropylphosphonates can be prepared by Michael-induced ring closure of trialkyl phosphates with γ -bromoalkylidene cyanoacetates or malonates (Equation (100)) <2002SL1089>.

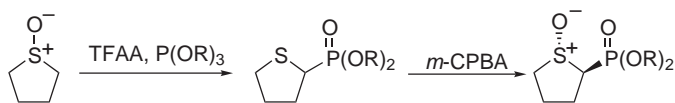


α -Substituted cyclic phosphonates [(OCH₂CMe₂CH₂O)P(O)CH(X)Ar; X = Cl, OMe, NMe₂, OTMS], which are useful precursors for Horner–Wadsworth–Emmons reactions, are readily prepared by treating (OCH₂CMe₂CH₂O)PX with an aromatic aldehyde <2001TL3219>.

α -(Trimethylsilyloxy)phosphonates can be synthesized in high yield from trialkyl phosphites, epoxides, and TMSCl in the presence of LiClO₄ <2003TL7933>. Dialkyl α -(alkylthio)phosphonates have been obtained as major products in the reaction of selenothiocarboxylic acid *S*-esters with trialkyl phosphites (Equation (101)) <1999CL105, 2000JCS(P1)917>. A similar reaction of diselenocarboxylic acid esters with trimethyl phosphite affords α -(alkylselenenyl)phosphonates in good yield.



2-Phosphonothiolanes can be prepared by the addition of trialkyl phosphite to a Pummerer intermediate generated from thiolane *S*-oxide (Scheme 60) <2001S1623>. Oxidation of these cyclic sulfides occur with total *trans*-stereoselectivity.

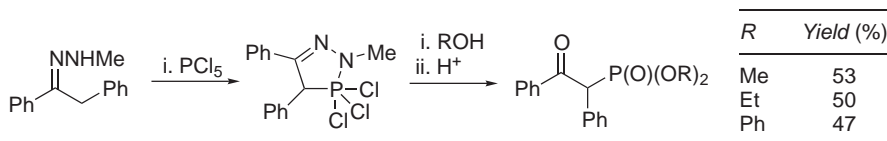


Scheme 60

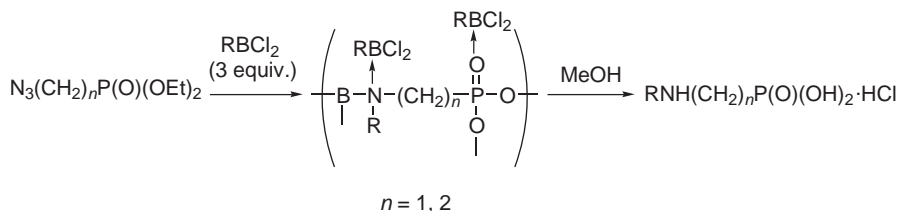
Tetramethylguanidine-catalyzed addition of dialkyl phosphates to α,β -unsaturated carbonyl compounds, aldehydes, ketones, and α,β -unsaturated nitriles constitutes a practical route to a variety of phosphonate synthons <1998TL7615>. The very mild conditions employed, together with the short reaction times, make the procedure highly versatile and tolerant to a range of functionalities.

Indirect phosphorylation of ketones has been accomplished through the reaction of a ketone methylhydrazone with PCl₅ followed by the reaction with an alcohol (Scheme 61) <1996G271>.

Halogen–metal exchange induced 1,3-phosphorus migration of 2-bromovinyl phosphates offers a route to β -ketophosphonates in moderate yield <1998JOC2613>. The HCl salts of *N*-alkyl/aryl- α - and β -aminophosphonic acids can be prepared by reductive alkylation of azidoalkyl phosphonates with organodichloroboranes (Scheme 62) <1999OL981>. The reaction is accompanied by simultaneous dealkylation of the phosphonates via polyborophosphonates.

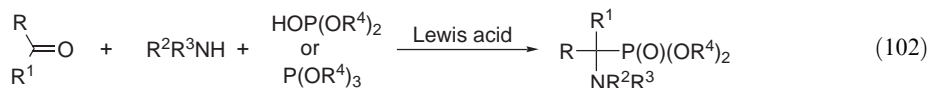


Scheme 61



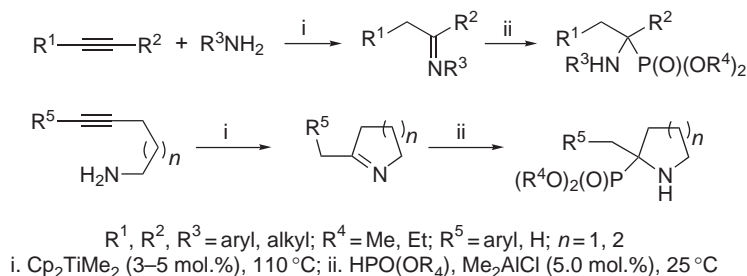
Scheme 62

A three-component coupling of carbonyl compounds, amines, and dialkyl or trialkyl phosphites is one of the most convenient methods for the synthesis of α -aminophosphonates (Equation (102)). Lewis acids are known to catalyze these reactions under mild conditions. A few one-pot procedures for α -aminophosphonate synthesis involve catalysis by LiClO_4 <1998TL6729, 2003T5329>, ZrCl_4 <2001S2277>, $\text{TaCl}_5\text{-SiO}_2$ <2001TL5561>, InCl_3 <1999OL1141>, lanthanide triflates <1998JOC4125> <2001CC1698>, scandium tris(dodecyl sulfate) <2000CC669> and montmorillonite KFS <2001SL1131>. An effective method for the synthesis of α -aminophosphonates is a solvent and catalyst-free variant of the three-component coupling reaction <2003SL505>.



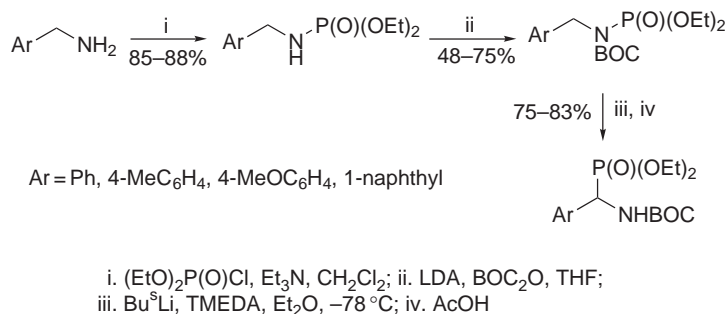
Pyrone, chromone, and coumarin derivatives of aminomethanephosphonic acid have been prepared in a one-step process by treatment of a mixture of heterocyclic aldehyde and amine with P(OTMS)_3 , and subsequent solvolysis of the formed silylated product with MeOH <2000SC1749>.

A highly flexible one-pot procedure for the synthesis of α,α -disubstituted- α -aminophosphonates is based on the reaction of disubstituted alkynes, primary amines, and diethyl or dimethyl phosphite <2002EJO457>. The reaction sequence involves Cp_2TiMe_2 -catalyzed hydroamination of the alkyne followed by addition of phosphorus nucleophile to the resulting imine. The application of intermolecular and intramolecular hydroamination reactions leads to the formation of both, cyclic and acyclic α -aminophosphonates (Scheme 63).



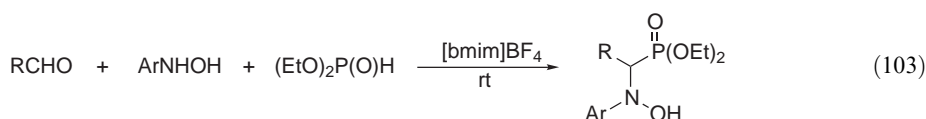
Scheme 63

N-Substituted α -aminophosphonates have been prepared by addition of diethyl phosphite to imines in the presence of catalytic amounts of CdI_2 <2002MI480>. Metallated *N*-protected *N*-arylmethyl phosphoramidates undergo phosphoramidate-aminophosphonates rearrangement to give the corresponding α -aminophosphonates in 75–83% yield (Scheme 64) <2000JOC6121>.



Scheme 64

(α -Hydroxyamino)phosphonates have been obtained in a one-pot operation by a three-component coupling reaction of aldehydes, hydroxylamines, and diethyl phosphite in ionic liquids under mild and neutral conditions (Equation (103)) <2003MI564>.



Base-catalyzed Michael-type addition of sodium diethyl phosphite to *N*-BOC imines, generated *in situ* by the action of NaH on α -amidoalkyl-*p*-tolyl sulfones, has been used in the synthesis of *N*-BOC- α -aminoalkanephosphonates (Scheme 65) <2002TL1079>.



Scheme 65

N-Trimethylsilyloxy- α -aminophosphonates are easily synthesized in high yield from aldehydes, phenylhydroxylamine and dimethyl trimethylsilyl phosphite in the presence of LiClO₄ <2001TL3629>.

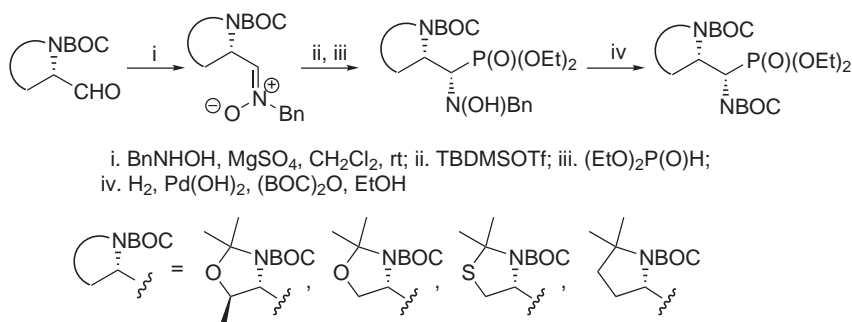
Enantiomerically enriched P-chiral *O*-methyl *O*-*p*-nitrophenyl alkanephosphonates have been prepared by the sequential addition of L-proline ethyl ester and *p*-nitrophenol to alkylphosphonic dichlorides followed by BF₃ catalyzed methanolysis of the formed phosphoroamidate <1998SL73>.

Optically active α -substituted- β -amidophosphonates have been obtained by a diastereoselective addition (up to 95% de) of diethyl phosphite to various chiral α,β -unsaturated carboxylic amides derived from chiral aminoalcohols <2001TL1025>.

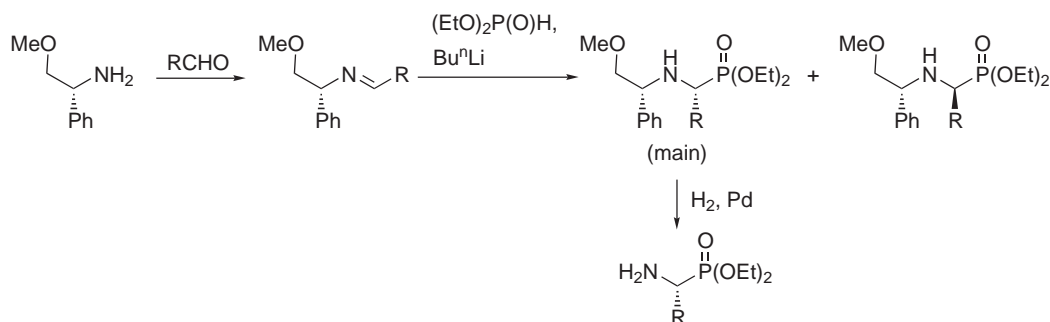
The nucleophilic addition of dialkyl phosphites to enantiopure nitrones, imines or sulfinimines appears to be the most general approach to the asymmetric synthesis of α -aminophosphonates. Thus, *t*-butyldimethylsilyl triflate-promoted diethyl phosphite addition to chiral *N*-benzyl nitrones derived from chiral α -alkoxy and α -(BOC-amino)aldehydes leads to optically active α -(hydroxyamino)phosphonates; the latter can be converted into the corresponding *N*-BOC-protected α -aminophosphonates by a conventional reductive process (Scheme 66) <2003EJO1904>.

An efficient protocol for the synthesis of highly enantioenriched α -aminophosphonates involves the addition of lithium diethyl phosphite to chiral chelating imines derived from (*R*)-(-)-1-amino-1-phenyl-2-methoxyethane followed by unmasking of the *N*-substituted α -aminophosphonates via hydrogenolysis (Scheme 67) <1995JA10879>.

Optically active α -aminophosphonates have also been prepared in one-pot procedures involving addition of trialkyl phosphites <2002TA2267, 2000TA2023, 2000EJO2153> or dialkyl phosphites <1998TL6729, 1998JOC4125, 1996TA21> to *in situ* generated chiral iminium intermediates.

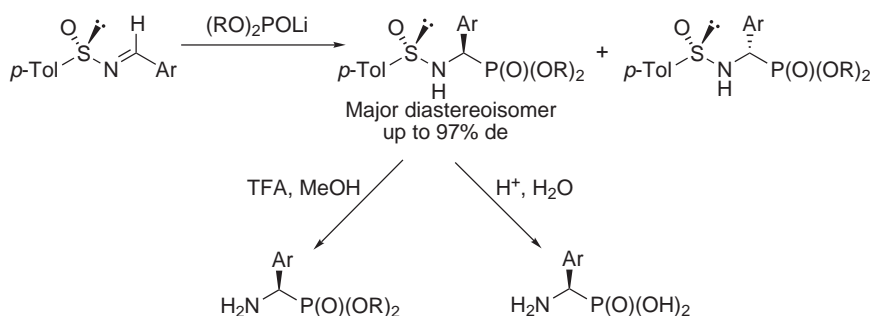


Scheme 66



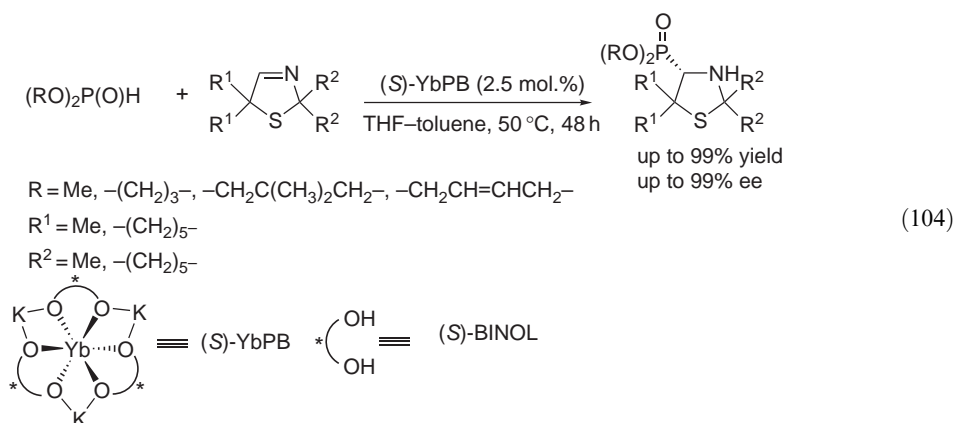
Scheme 67

Highly diastereoselective addition of dialkyl phosphite anions [<1997JOC7532, 1997TA3991>](#) or lithiated bis(dimethylamino)phosphine borane complex [<2002TA2571>](#) to enantiopure sulfonimines has been used in an asymmetric synthesis of α -aminophosphonates and the corresponding phosphonic acids ([Scheme 68](#)).

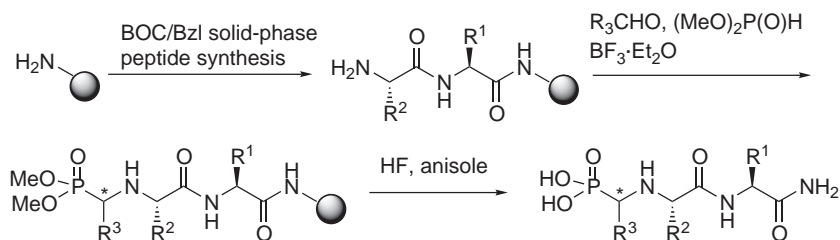


Scheme 68

Catalytic asymmetric hydrophosphonylation of imines using lanthanoid-potassium-BINOL heterobimetallic complexes (LnPB, Ln = lanthanoid metal) gives optically active α -aminophosphonates with modest-to-high enantiomeric excess [<1995JOC6656>](#). Employing this methodology to cyclic imines, the pharmacologically interesting 4-thiazolidinephosphonates have been synthesized with enantioselectivities of up to 99% ee when using (*S*)-YbPB as a catalyst ([Equation \(104\)](#)) [<2000JOC4818>](#).

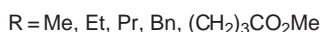
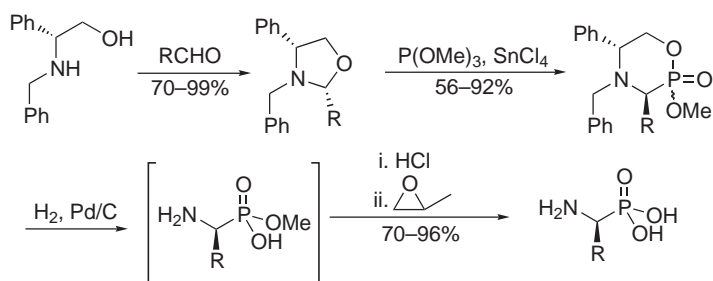


The formation of α -aminophosphonate functionalities on the amino terminus of peptides has been achieved utilizing solid-phase methodology (Scheme 69) <2002TL4103>. An inverse concept in which a polymer bound H-phosphonate reacts with imines in the presence of a Lewis acid to form an array of α -aminophosphonic acids has been presented by Zhang and Mjalli <1996TL5457>.



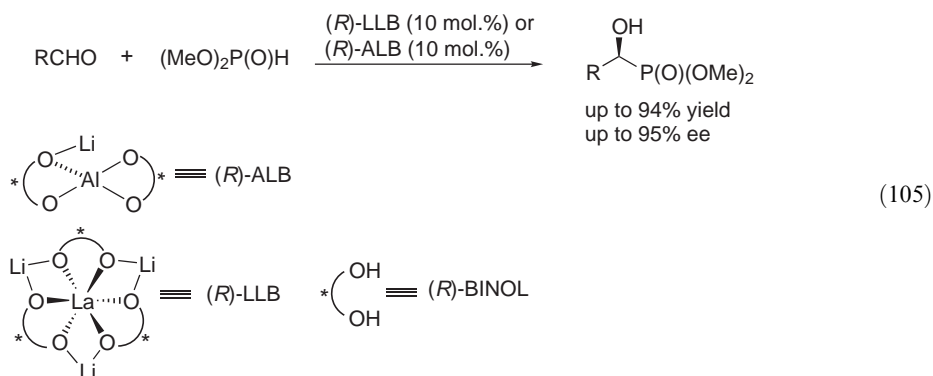
Scheme 69

Highly diastereoselective addition of trialkyl phosphites to various chiral oxazolidinones has been employed for the synthesis of chiral, nonracemic α -aminophosphonic acids <1996JOC3687>. Oxazaphosphorinanes thus obtained furnish the corresponding (*S*)- α -aminophosphonic acids in good overall yield and with high ee (77–97%) after simple deprotection (Scheme 70).

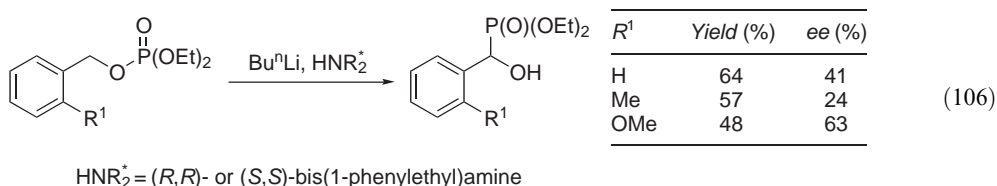


Scheme 70

Catalytic asymmetric hydrophosphonylation of aldehydes constitutes a simple and efficient route to enantiomerically enriched α -hydroxyphosphonates (Equation (105)) <1996JOC2926, 1997TL2717>. Using aromatic aldehydes and heterobimetallic multifunctional catalysts, such as (*R*)-LLB and (*R*)-ALB, the corresponding α -hydroxyphosphonates have been produced with up to 95% ee.

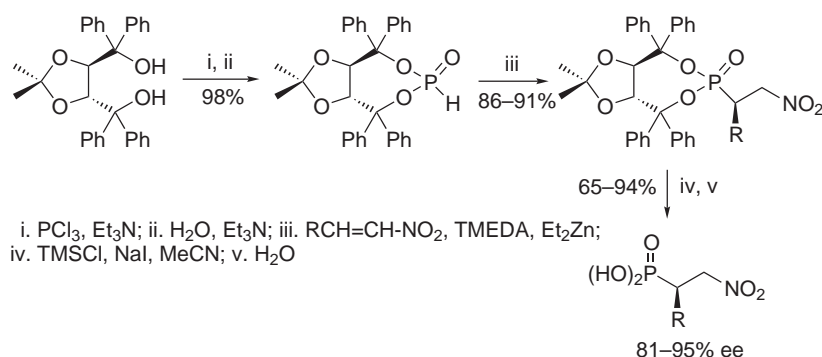


O,O-Dialkyl-*O*-benzyl phosphates have been isomerized to the corresponding nonracemic α -hydroxyphosphonates with modest ee upon treatment with chiral amides (Equation (106)) <1995CB823>. The origin of stereoselectivity is the enantioselective removal of benzylic hydrogen, yielding a carbanion of high configurational stability which quickly rearranges to an enantiomerically enriched phosphonate with retention of configuration.



Chiral α, β -dihydroxyphosphonates are easily prepared in generally good yields and with variable diastereoselectivity by the addition of trimethylsilyl diethyl phosphite to chiral α -silyloxy- or α -alkoxyaldehydes <1996TA3485>.

Optically active α -substituted- β -nitrophosphonic acids have been obtained, by the asymmetric Michael addition of the enantiomerically pure phosphite to nitroalkenes, followed by the removal of the chiral auxiliary (Scheme 71) <2000AG(E)4605>.

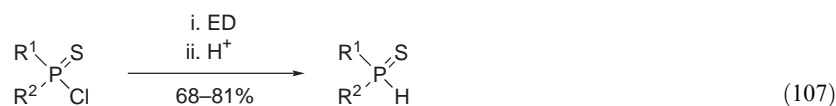


Scheme 71

2.08.5 ALKYLPHOSPHORUS COMPOUNDS WITH A P—S BOND

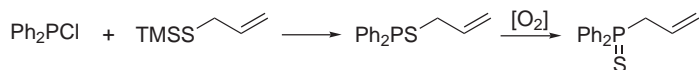
2.08.5.1 Alkylthiophosphinous Acid Derivatives— R_2PSH , etc.

The addition of elemental sulfur to secondary phosphines leads in high yields to thiophosphinous acids, which have been used as air-stable ligand precursors for the efficient nickel-catalyzed cross-coupling reactions <2002OM590>. Thiophosphinous acids are also conveniently synthesized by reduction of the corresponding thiophosphinic acid chlorides with alkali metals (Na, K) in liquid ammonia/THF or potassium anthracenide and potassium naphthalenide (Equation (107)) <2002HAC330>.



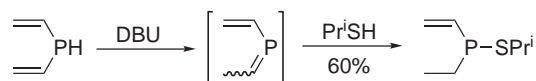
$\text{R}^1, \text{R}^2 = \text{Bu}^t, \text{Ph}$ $\text{ED} = \text{K}, \text{Na}, \text{potassium naphthalenide}$

Reaction of allyl trimethylsilyl sulfide with Ph_2PCl at -15°C gives *S*-allyl thiophosphinite, which under O_2 catalysis undergoes isomerization to the corresponding allylphosphine sulfide (Scheme 72) <1993IZV1441>.



Scheme 72

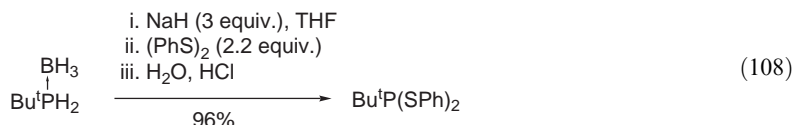
S-Alkyl dialkylthiophosphinites <1996IC6667> and *S*-alkyl alkyl(allyl)thiophosphinites <1996OM3466> have been obtained by thiol addition to transiently formed phosphalkenes and phosphadienes, respectively (Scheme 73).



Scheme 73

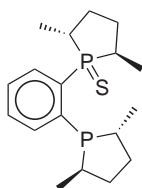
2.08.5.2 Alkylthiophosphonous Acid Derivatives— $\text{RP}(\text{SH})_2$, etc.

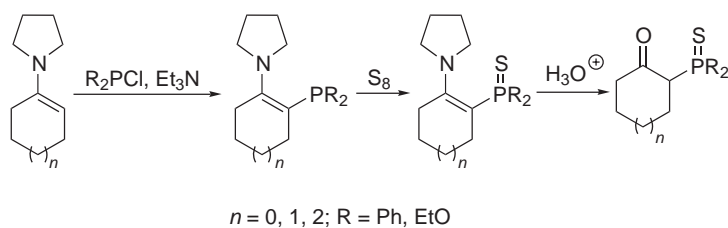
Alkylthiophosphonous acids and their derivatives are usually obtained by the appropriate introduction of a sulfur-containing moiety to tricoordinate phosphorus substrates, such as primary phosphines or P(III)-chlorides. Secondary *t*-butylphosphine-borane has also been used as a substrate in the reaction with diphenyl disulfide to give the *S,S*-diphenyl dithiophosphonite in high yield (Equation (108)) <2002BCJ1359>.



2.08.5.3 Alkylphosphine Sulfides— R_3PS , etc.

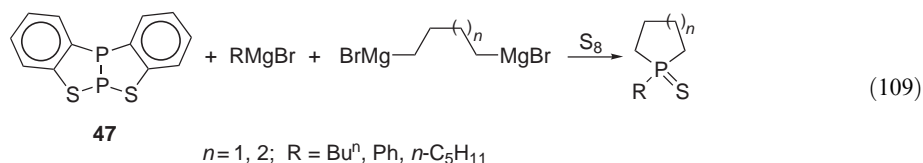
The most common method for preparation of phosphine sulfides is the addition of elemental sulfur to the corresponding phosphine. Among recent reports on this subject, the following deserve mentioning: synthesis of chiral diphosphine mono-sulfides, e.g., compound **46** obtained from (*R,R*)-Me-DUPHOS <2003TA705>, 2-alkoxyalkenylphosphine sulfides <1995ZOR651> and cycloalkyl- β -ketophosphine sulfides (Scheme 74) <1996PS(108)51>.



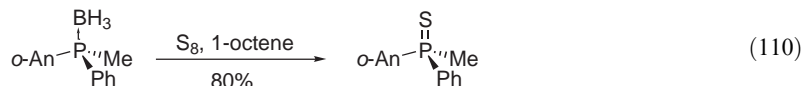


Scheme 74

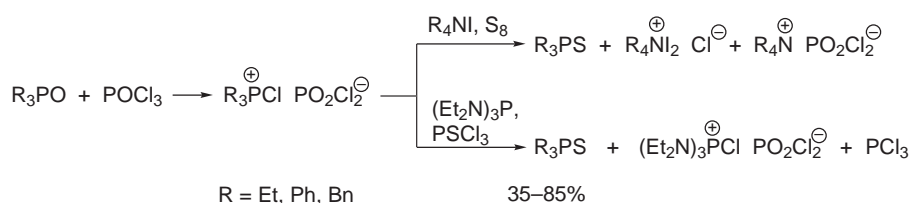
This approach also includes the addition of elemental sulfur to cyclic phosphines obtained from the reaction of benzothiadiphosphole **47** (serving as a source of phosphorus) with mono- and bis-Grignard reagents (Equation (109)) <2000SL1685, 2001S1938>.



Phosphine sulfides can also be obtained directly from the corresponding phosphine-boranes by the reaction with elemental sulfur in the presence of morpholine <1996MI331>, DABCO or 1-octene (Equation (110)) <2001TA1441>. This reaction proceeds with retention of configuration at phosphorus.

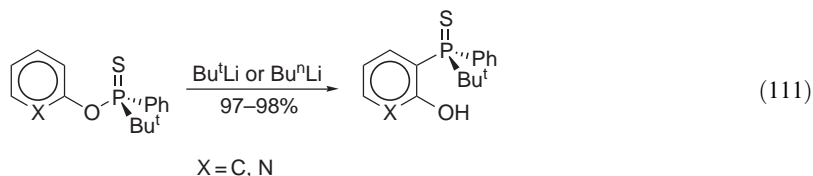


Phosphine oxides can easily be transformed to the corresponding phosphine sulfides by treatment with POCl_3 , followed by the addition of tetralkylammonium iodide and elemental sulfur or PSCl_3 (Scheme 75) <2002ZOB1751>.



Scheme 75

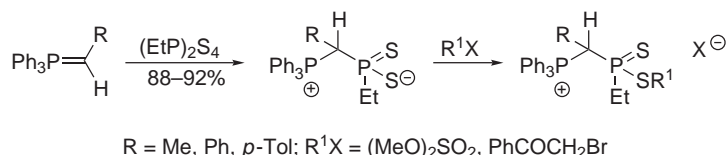
Optically active 2-hydroxyarylphosphine sulfides have been synthesized by a stereospecific base-induced [1,3]-intramolecular rearrangement of *O*-aryl thiophosphinates (Equation (111)) <2001TL457>.



Dialkylthiophosphinous acids (secondary phosphine sulfides) react with aldehydes in the presence of KOBu^t to give the corresponding tertiary α -hydroxyalkylphosphine sulfides <1995PS(101)213>. Aryldialkylphosphine sulfides have been prepared by reacting dialkylphosphine sulfides with aryl halides in the presence of $\text{Pd}(0)$ catalysts <1996EUP19960315>.

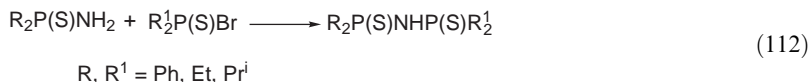
2.08.5.4 Alkylthiophosphinic Acid Derivatives— $R_2P(S)OH$, $R_2P(O)SH$, $R_2P(S)SH$, etc.

As in the case of phosphine sulfides, thiophosphinic and dithiophosphinic acids and their derivatives are synthesized mainly by the addition of sulfur to the corresponding phosphorus substrates of lower oxidation state. Some other approaches have also been used. Thus, alkoxyphosphine-boranes have been transformed to *O*-alkyl thiophosphinates by treatment with sulfur in the presence of 1-octene (cf. Section 2.08.5.3, Equation (110)) <2001TA1441>. In turn, zwitterionic 1-phosphonioalkyldithiophosphinates have been synthesized from the corresponding secondary ylidylphosphines by treatment with perthiophosphonic anhydride $[(EtP)_2S_4]$ (Scheme 76) <1998HAC433>.

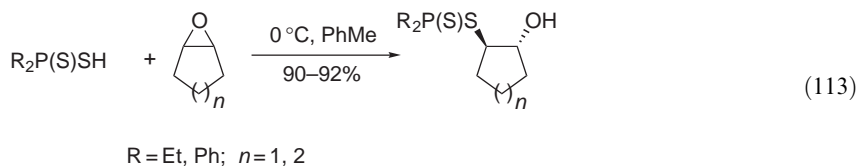


Scheme 76

Imido-bis(thiophosphinates) have been prepared from the corresponding thiophosphinic bromides and thiophosphinamides (Equation (112)) <1999POL707, 2001POL125>. Similarly, *N,N'*-bis(*P,P*-dialkylthiophosphinyl)diamines have been obtained in 40–60% yields from $R_2P(S)Br$ and alkylenediamines <1999JPR(341)182>.

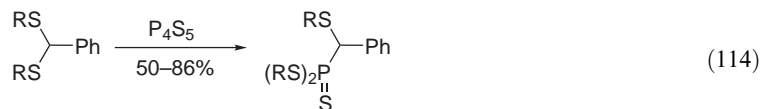


Dithiophosphinic (phosphinodithioic) acids react with epoxides to give the corresponding dithiophosphinates (phosphinodithioates) (Equation (113)) <2002TL7609>.

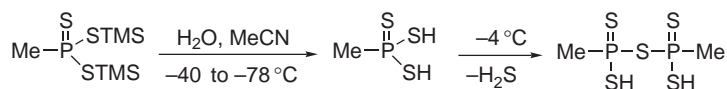


2.08.5.5 Alkylthiophosphonic Acid Derivatives— $RP(S)(OH)_2$, $RP(O)(SH)_2$, $RP(S)(OH)(SH)$, etc.

Tetraphosphorus pentasulfide $[P_4S_5]$ reacts with benzaldehyde dithioacetals to give *S,S*-dialkyl *S*-(alkylthio)benzyltrithiophosphonate, accompanied by sulfur and some other sulfur-rich by-products (Equation (114)) <1995PS(102)71, 1995ZOB520>.

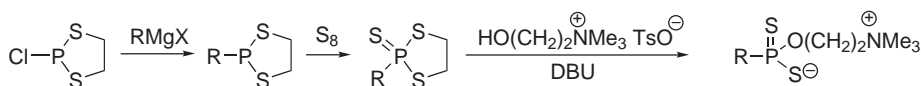


Methyltrithiophosphonic acid can be obtained by a careful hydrolysis of *S,S*-bis(trimethylsilyl) methyltrithiophosphonate. However, it undergoes decomposition at $-4^\circ C$ to give the corresponding thioanhydride (Scheme 77) <1996PS(116)133>.



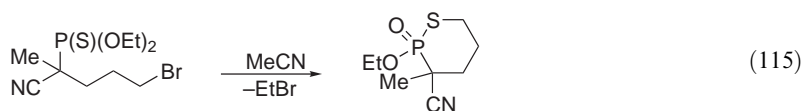
Scheme 77

A general procedure for the synthesis of *O*-esters of phosphonodithioic acids has been developed. This involves the reaction of Grignard reagents with 2-chloro-1,3,2-dithiaphospholane, followed by sulfurization with elemental sulfur and treatment of the resulting cyclic trithiophosphonate with alcohols in the presence of DBU (Scheme 78) <1994JOC7957>.



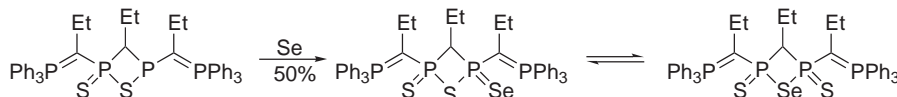
Scheme 78

The intramolecular cyclization of ω -halo- α -cyanoalkylthiophosphonates (intramolecular Pischchimuka-type rearrangement) results in the formation of cyclic thiophosphonates (Equation (115)) <2001ZOB393, 2002HAC1>.

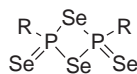


2.08.6 ALKYLPHOSPHORUS COMPOUNDS WITH A P—Se AND/OR A P—Te BOND

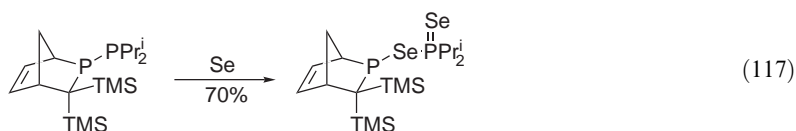
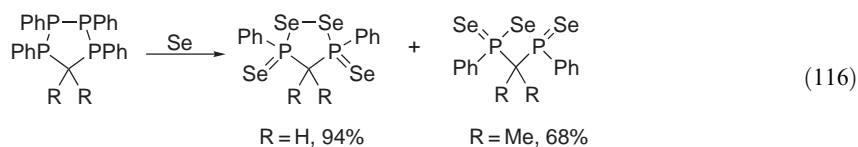
The addition of elemental selenium or tellurium to tricoordinated phosphorus substrates is the most commonly used method for the preparation of seleno- and tellurophosphorus compounds. This approach has also been applied to the synthesis of more sophisticated molecules, e.g., selenadiphosphetanes (Scheme 79) <1995CB1015> and diselenadiphosphetanes **48** <2001ZAAC(627)1269>.



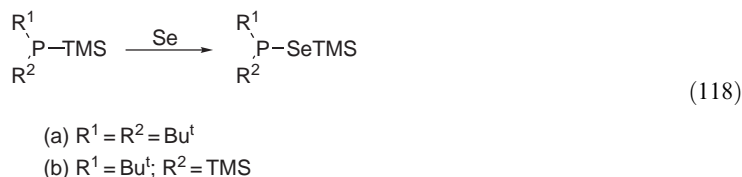
Scheme 79

**48**

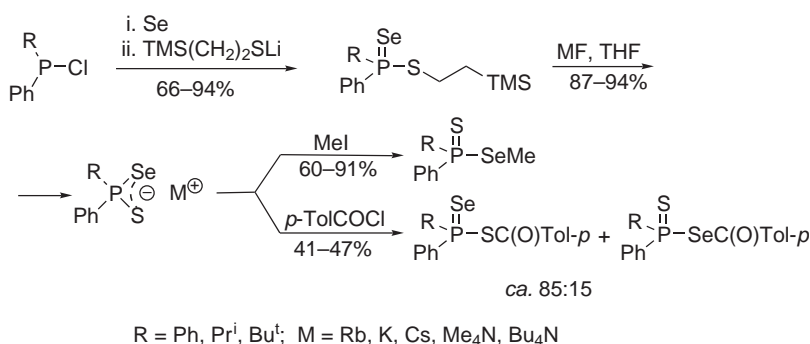
Oxidative addition of elemental selenium to cyclomonocarbatetraphosphines results in breaking of the P—P bonds with a concomitant P=Se and P—Se bond formation. This leads to five- and four-membered heterocycles, the ratio of which depends on the substituents R (Equation (116)) <2001CC2288>. Other P—P systems behave similarly, e.g., Equation (117) <1998ZAAC(624)1447>.



The treatment of trimethylsilylphosphines with selenium at low temperature leads unexpectedly to the insertion of selenium into the P—Si bond to give either *Se*-trimethylsilyl selenophosphinite (a) or *Se,Se'*-bis(trimethylsilyl) diselenophosphonite (b) in nearly quantitative yields (Equation (118)) <1997PS(124/125)505>. The insertion of selenium into the P—Li bond of lithiated secondary phosphines gives lithium selenophosphinites, which on treatment with additional selenium afford lithium diselenophosphinates <2002IC348>. Tertiary phosphine selenides can be efficiently obtained from the corresponding phosphine oxides using the same procedure as described for the P=O → P=S transformation and replacing sulfur with selenium in the last step (see Section 2.08.5.3, Scheme 75) <2002ZOB1751>.



Selenothiophosphonic acid salts have been synthesized according to the reaction sequence shown in Scheme 80. Their reaction with methyl iodide takes place at the selenium to give *Se*-methyl selenothiophosphinates in high yield. Acylation preferentially proceeds at the sulfur <2002CL914>.



Scheme 80

Diastereomerically pure *O*-nucleoside *Se*-methyl methaneselenophosphonates have been synthesized and their absolute configurations elucidated by X-ray crystallography <1998JOC5395>. Halogenoselenophosphonium salts are formed in the reaction of halogens or sulfonyl chloride with tertiary phosphine selenides, tris(dialkylamino)phosphine selenides, and selenophosphonates; their stability depends on the substituents on the phosphorus and the type of counterion (Equation (119)) <2002JCS(D)4471>.

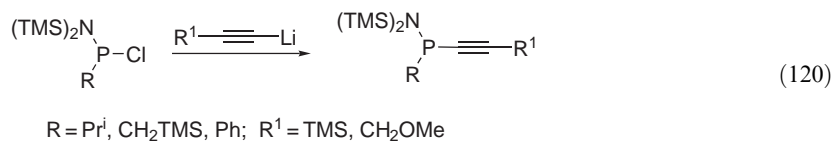


2.08.7 ALKYLPHOSPHORUS COMPOUNDS WITH A P—N BOND

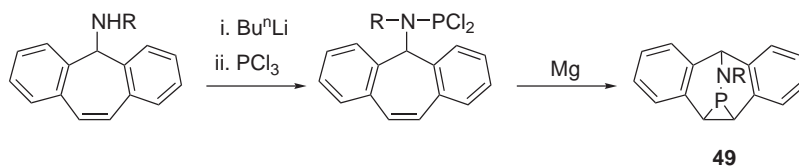
Most compounds possessing a P—N bond have been prepared by the reaction of the corresponding phosphorus halides with amines. Two other important approaches are the Kirsanov reaction and the Staudinger reaction. All these methodologies have been and continue to be widely used and some new strategies have been developed.

2.08.7.1 Amides of Alkylphosphinous Acid— R_2PNR^1

P-Acetylenic alkylphosphinous acid amides are readily prepared by a variant of the Wilburn method involving the reaction of mono-chlorophosphines with lithium acetylides (Equation (120)) <2002JOM(646)223>.

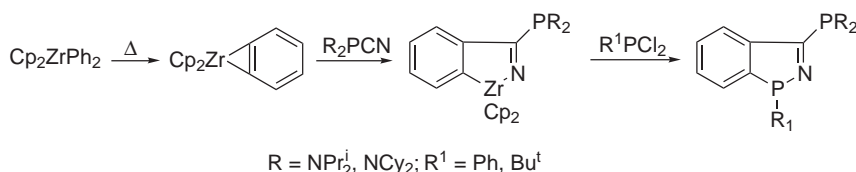


The tricyclic aminophosphines **49** have been prepared by intramolecular [2 + 1]-cycloaddition of an $\text{R}_2\text{N}-\text{P}$ unit to the C—C double bond of the central seven-membered ring of dibenzotropyliene (Scheme 81) <2000T143>.



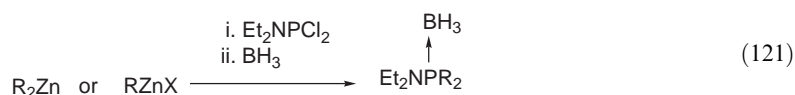
Scheme 81

1,2-Azaphosphindoles have been prepared by the thermolysis of benzynezirconocene in the presence of a cyanophosphine, followed by an exchange reaction involving the resulting azazirconacyclopentene and various dichlorophosphines (Scheme 82) <2000EJI417>.



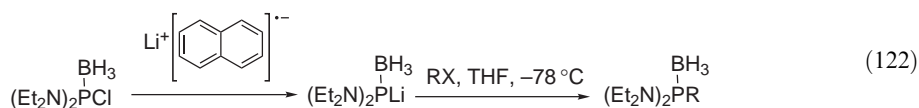
Scheme 82

Diethylaminodichlorophosphine reacts with various diorganozincs or organozinc halides to furnish, after protection with borane, air and water stable diethylaminodiorganophosphine-borane complexes in 70–80% yields (Equation (121)) <1996TL2209>.

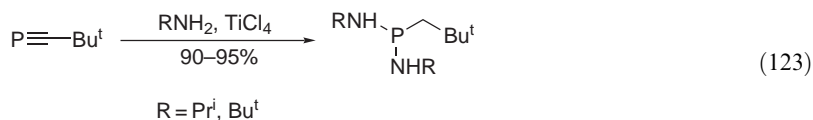


2.08.7.2 Amides of Alkylphosphonous Acid— $\text{RP}(\text{NR}^1)_2$

The reaction of lithiated bis(diethylamino)phosphine-borane complex with alkyl or aryl halides leads to aryl- or alkyldiaminophosphine-boranes (Equation (122)) <1996TL6099>.

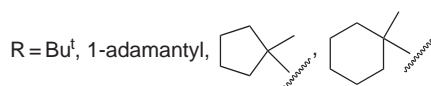
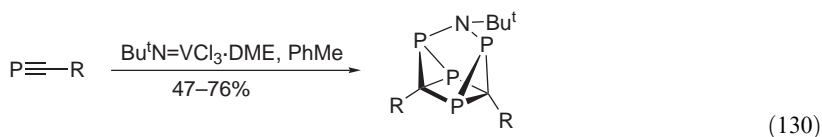
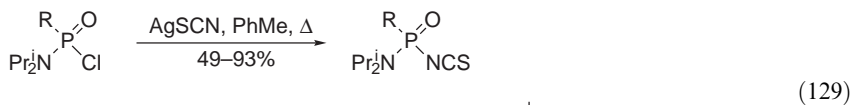
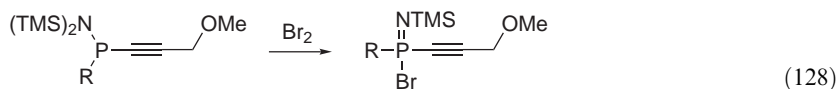


Treatment of *t*-butylphosphaacetylene with excess of a primary amine in the presence of a catalytic amount of TiCl_4 affords the corresponding bis(monoalkylamino)phosphine (Equation (123)) <2000CC2387>.

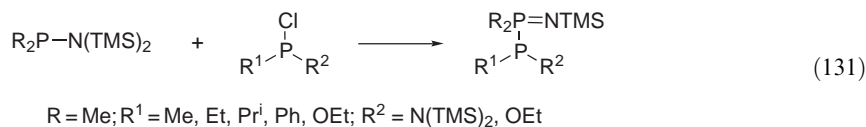




2.08.7.6 Other P—N Compounds

$$\begin{array}{ccc} \text{Et}_2\text{N}-\text{P}(\text{R})-\text{C}(\text{R}^1)_2 & \xrightarrow[\text{TMS}(\text{Bu}^t)\text{NCl}]{\text{Pr}_2^i\text{NCl or}} & \text{Et}_2\text{N}-\text{P}(\text{R})(\text{Cl})=\text{C}(\text{R}^1)_2 \end{array} \quad (127)$$


Chlorophosphines react with (silylamino)phosphines via a direct oxidative addition process to produce phosphino-phosphoranimes with the concomitant formation of a P—P bond (Equation (131)) <1996PS(109–110)625>.



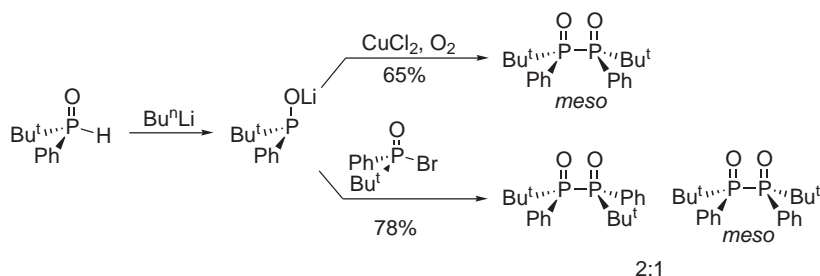
2.08.8 ALKYLPHOSPHORUS COMPOUNDS WITH A P—P, P—As, P—Sb, OR P—Bi BOND

2.08.8.1 Alkylphosphorus Compounds with a P—P Bond

The usual way of preparing compounds possessing a P—P bond is to react primary or secondary phosphines (or their oxides) with halogenophosphorus derivatives. This approach is applicable to the synthesis of both acyclic and cyclic compounds.

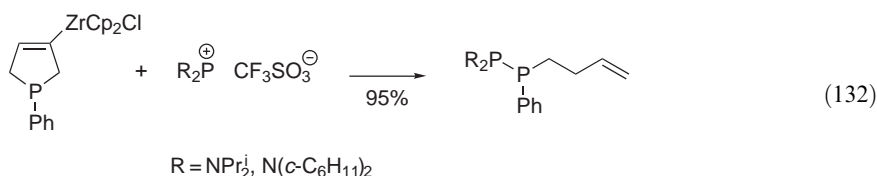
2.08.8.1.1 Acyclic compounds

Oxidative dimerization of enantiomerically pure lithium *t*-butylphenylphosphinite leads exclusively to the corresponding *meso* product. In contrast, nucleophilic substitution of the corresponding enantiomerically pure phosphinyl bromide with the same starting lithium phosphinite results in the formation of the enantiomerically pure diphosphine dioxide as a major product, together with the corresponding *meso* diastereomer. Both products can be readily separated by flash chromatography (Scheme 86) <1997CEJ2052>.



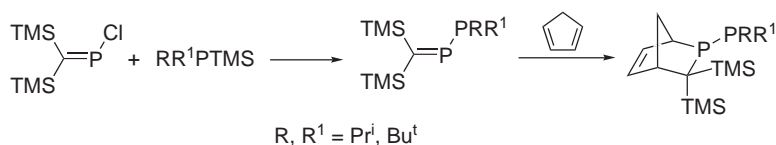
Scheme 86

β -Zirconated phospholene reacts with phosphonium salts to give homoallyl diphosphines (Equation (132)) <1996OM1208>.

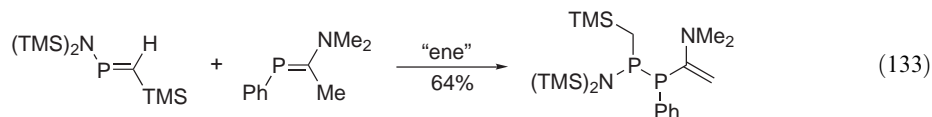


Methylidenechlorophosphine has been treated with dialkyl(trichlorosilyl)phosphines to give dialkylphosphinylphosphaalkenes, which are protected by a [2 + 4]-cycloaddition with cyclopentadiene (Scheme 87) <1998ZAAC(624)1447>.

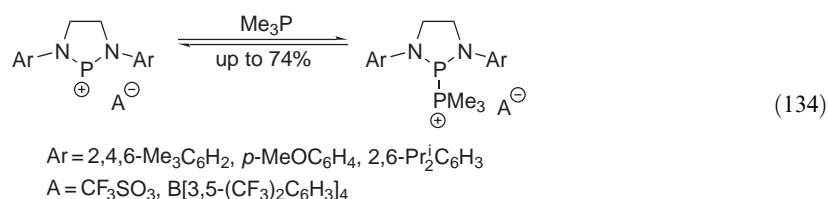
The phospho-ene reaction between methylidenephosphines as enophiles and C-aminophosphaalkenes possessing an allylic hydrogen atom proceeds by a P—P bond formation to furnish the corresponding functionalized diphosphines (Equation (133)) <1997JOC7605>.



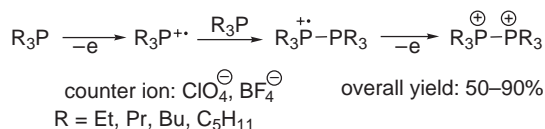
Scheme 87



Phosphinophosphenium adducts (P—P diphosphine monophosphonium salts) are formed in a reversible reaction of phosphonium cations with trimethylphosphine. The products can be isolated if excess Me_3P is used (Equation (134)) <2000OM4944>.

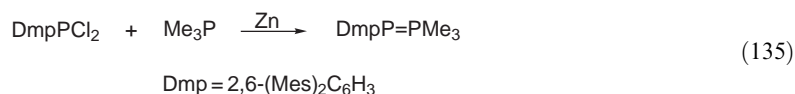


New types of P—P bond-containing compound, viz. hexaalkylbiphosphonium salts, have been obtained by electrochemical oxidation of trialkylphosphines in the presence of NaClO_4 or Et_4NBF_4 . The reaction proceeds via the anodic generation of radical cation (Scheme 88) <1996ZOB930>. Substituted diphosphaboretanes have been coupled by an irradiation-triggered free-radical process to form a new P—P bond <1996CB557>.



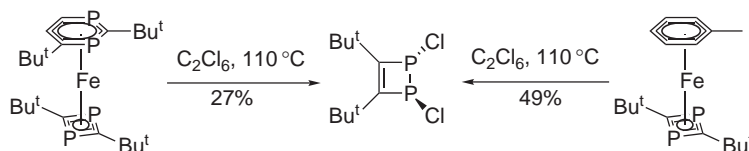
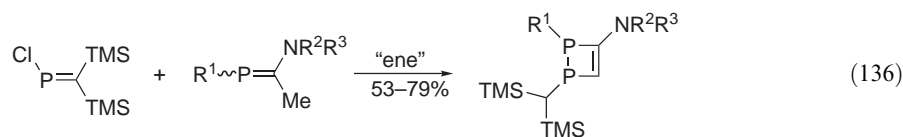
Scheme 88

Formation of P—P double bonds has been achieved by reaction of a sterically hindered dichlorophosphine with trimethylphosphine in the presence of zinc (Equation (135)) <2000JOM(608)12>.



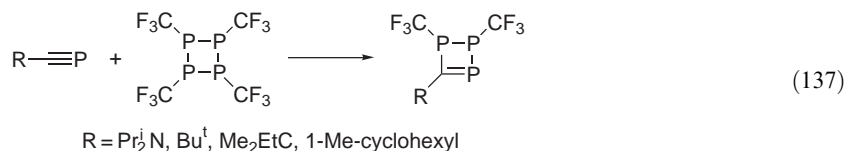
2.08.8.1.2 Cyclic polyphosphines

The phospho-ene reaction (cf. Section 2.08.8.1) can also be applied to the synthesis of cyclic P—P derivatives, viz. 1,2-diphosphetenes, provided that the enophile contains a leaving group, e.g., a chloro substituent (Equation (136)) <1997JOC7605>. In turn, a tandem Diels–Alder and ene reaction between phosphaaalkynes and dienes leads to more complex tricyclic products containing a diphosphirane ring <1995BSF652>. 1,2-Dichloro-1,2-diphosphetenes are also accessible by oxidative decomplexation of 1,3-diphosphete ligands of arene iron or cyclopentadienyl cobalt complexes by C_2Cl_6 (Scheme 89) <1996S265>.

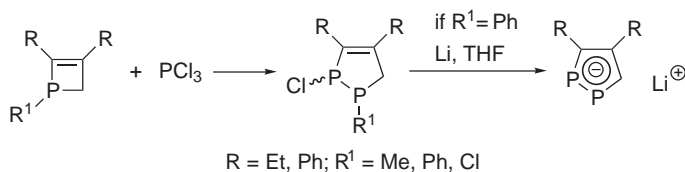


Scheme 89

1,2,3-Triphosphetenes are formed in reactions of phosphalkynes with the cyclotetraphosphine $(\text{PCF}_3)_4$ (Equation (137)) <1996CEJ208>.

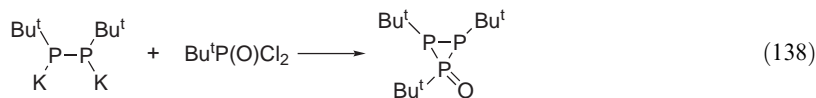


Dihydrophosphetes react with PCl_3 to give 1,2-diphosphacyclopent-3-enes. The products have been reduced by lithium in THF to yield 1,2-diphospholide anions which have been used to produce ferrocene analogs (Scheme 90) <1995AG(E)590>.

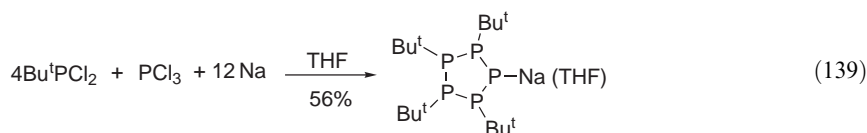


Scheme 90

The very unstable tris-*t*-butylcyclotriphosphine oxide (undergoes decomposition within 24 h at -30°C) has been synthesized by a [2 + 1]-cyclocondensation of dipotassium 1,2-diphosphide with phosphonous dichloride (Equation (138)) <1999ZN(B)1457>.



Sodium tetra-*t*-butylcyclopentaphosphanide has been obtained by reacting *t*-butyldichlorophosphine and sodium (Equation (139)). The product obtained is highly pyrophoric <2001AG(E)4217>.



2.08.8.2 Alkylphosphorus Compounds with a P—As, P—Sb, or P—Bi Bond

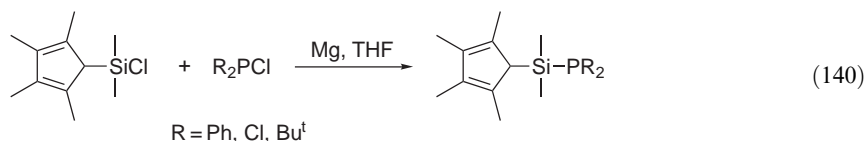
Practically no new advancements have been made in this field since the publication of COFGT (1995) <1995COFGT(2)425>. A number of publications dealing with the compounds that simultaneously contain phosphorus and arsenic, phosphorus and antimony, or phosphorus and bismuth usually refer to the complexes of the corresponding substrates. The only exception is the report on the synthesis of phosphastibetaines containing in their rings various numbers of phosphorus and antimony. However, the reaction has led to a mixture of products whose structures have not been unambiguously established <1999JOM(585)285>.

2.08.9 ALKYLPHOSPHORUS COMPOUNDS WITH A P—Si, P—Ge, P—Sn, OR P—Pb BOND

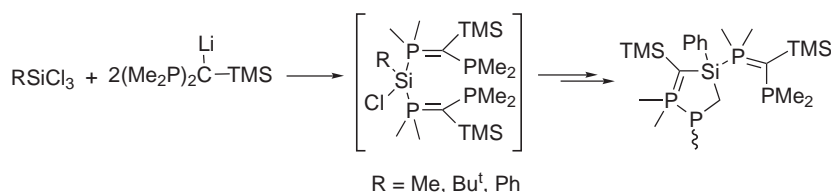
These classes of compounds are synthesized mainly using the reactions of phosphines or their derivatives (silylphosphines, metal phosphides, etc.) with the corresponding halogen-containing Si, Ge, or Sn derivatives. However, some other methods have also been applied.

2.08.9.1 Alkylphosphorus Compounds with a P—Si Bond

Chlorophosphines react with chlorosilanes in the presence of magnesium yielding the corresponding silylphosphines (e.g., Equation (140)) <1996ZAAC(622)1487>.

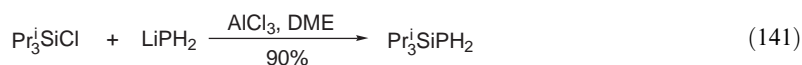


The ambident nature of phosphomethanides has been used to synthesize a variety of *P*-silyl phosphorus ylides. When trichlorosilanes are used, some new heterocycles are formed by multistep rearrangements (e.g., Scheme 91) <1995JOM(501)167>.

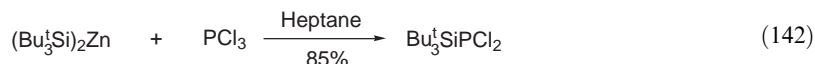


Scheme 91

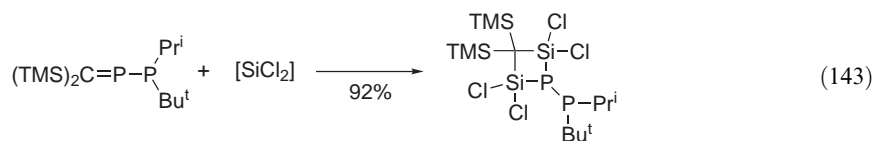
Chlorotrisisopropylsilane reacts with lithium phosphide in the presence of AlCl₃ to give primary triisopropylsilylphosphine (Equation (141)) <2000JA3952> together with secondary bis(trisopropylsilyl)phosphine. The latter is also formed when the reaction is carried out without AlCl₃ <1996JOM(513)213>.



Phosphorus trichloride reacts with zinc bis(tri-*t*-butyl silanide) to give dichloro(tris-*t*-butylsilyl)phosphine (Equation (142)) <2002ZN(B)1027>.



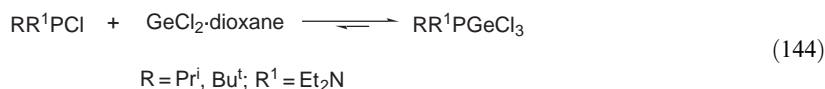
Dichlorosilylene, formed *in situ* from trichlorosilyltrimethylgermane, Me₃GeSiCl₃, has been trapped by a phosphalkene to form a disilaphosphetane (Equation (143)) <2002AG(E)3829>.



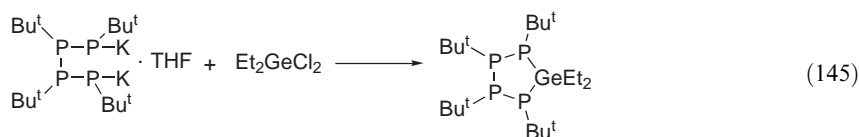
Trichlorosilylphosphines have been prepared in two ways: (i) by the reaction of chlorophosphines with trichlorosilane in the presence Et_3N <1996JOM(521)417> and (ii) by treating chlorophosphines with hexachlorodisilane <1995CB615>. The former method generally gives better yields and also allows the synthesis of bis(trichlorosilyl)phosphines, starting from the corresponding dichlorophosphines. More recently, trimethylsilylphosphines, trimethylgermylphosphines, and trimethylstannylphosphines have been used instead of chlorophosphines in the reaction with hexachlorodisilane <1999EJI1381>.

2.08.9.2 Alkylphosphorus Compounds with a P—Ge Bond

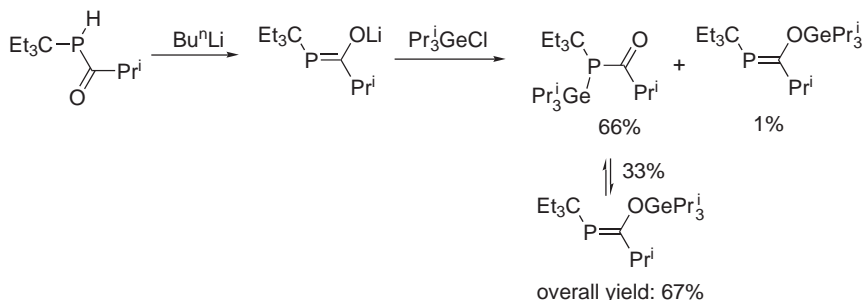
Chlorophosphines react with the dichlorogermylene-dioxane complex to give trichlorogermylphosphines; in some cases, the insertion reaction is incomplete (Equation (144)) <1997CB/RTC1619>.



The reaction of dipotassium tetra(*t*-butyl)tetraphosphide with dichloro(diethyl)germane leads to a five-membered GeP_4 ring system (Equation (145)) <1999ZAAC(625)699>.



The reaction of chloro(triisopropyl)germane with a lithiated secondary acylphosphine results in the formation of a tautomeric mixture of the products of *O*- and *P*-germylation (Scheme 92) <2000ZOB1237>.

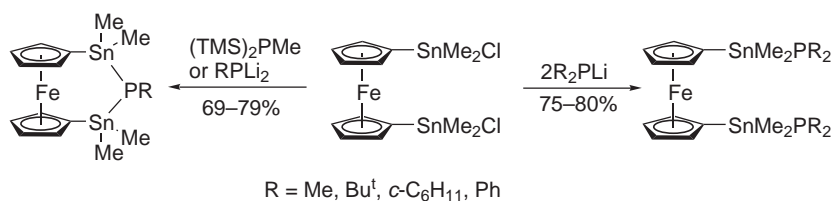


Scheme 92

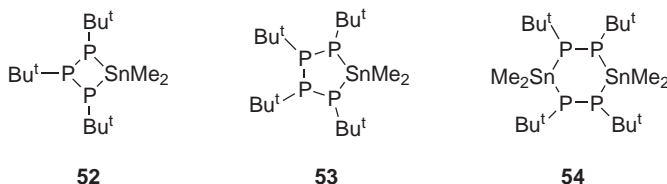
2.08.9.3 Alkylphosphorus Compounds with a P—Sn Bond

Trisubstituted stannyl halides react with alkali metal phosphides or trimethylsilylphosphines to produce stannylphosphines. This method has been used in the synthesis of ferrocenestannylphosphines and very interesting 1,3-distanna-2-phospha-[3]-ferrocenophanes (Scheme 93) <1999ZN(B)57>.

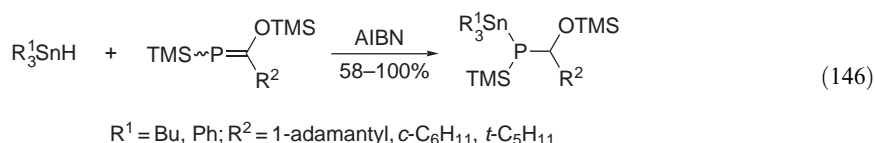
Dipotassium polyphosphino-diphosphides react with dihalo- and trihalostannanes to give a variety of four-, five- and six-membered cyclic compounds with one or two P—Sn bonds and several P—P bonds, depending on the substrates, e.g., compounds 52–54 <1995ZAAC(621)1358, 1996ZAAC(622)1167>.



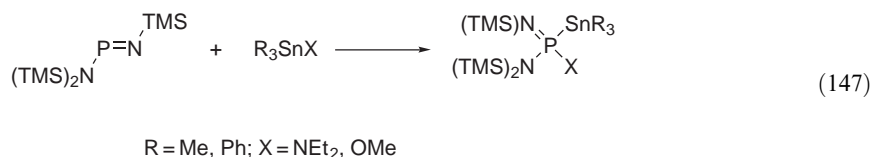
Scheme 93



The hydrostannylation of phosphalkenes leads to various products, depending on the structure of the phosphalkenes. For example, the Becker-type phosphalkene has proved to be suitable for the formation of the P—Sn bond-containing products (Equation (146)) <1997S455, 1998HAC453>.

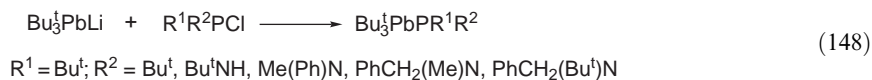


Aminoiminophosphines react with amino- or alkoxy-stannanes to yield the corresponding P—Sn derivatives (Equation (147)) <1996JOM(526)59>.



2.08.9.4 Alkylphosphorus Compounds with a P—Pb Bond

The reaction of (tri-*t*-butyl)plumbyllithium with chlorophosphines has been found to produce the corresponding plumbylphosphines, provided that the starting chlorophosphine contains at least one *t*-butyl substituent (Equation (148)) <2000ZN(B)939>.

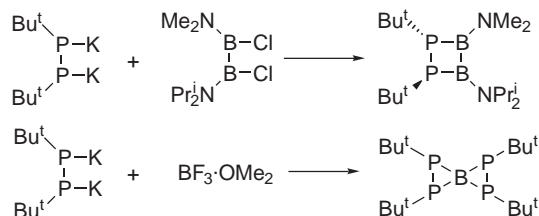


2.08.10 ALKYLPHOSPHORUS COMPOUNDS WITH A P—B, P—Al, P—Ga, P—In, OR P—M BOND

2.08.10.1 Alkylphosphorus Compounds with a P—B Bond

There is an increasing trend in synthetic applications of borane complexes of trivalent phosphorus compounds, as seen from the many references cited in the earlier sections of this chapter. At the same time, the number of new derivatives with a nondative covalent P—B bond is very limited.

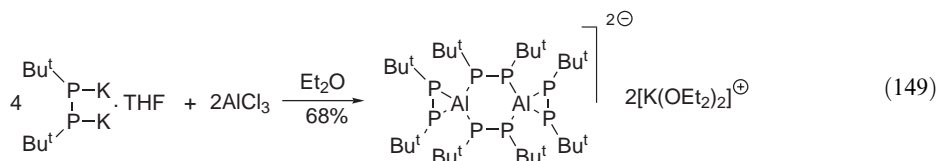
The cyclocondensation of dichlorodiboranes with dipotassium di(*t*-butylphosphide) gives 1,2-diphospha-3,4-diboretanes <1995ZAAC(621)1111>. When boron trifluoride is used instead, a spiro-product is formed (Scheme 94) <2001EJI1841>.



Scheme 94

2.08.10.2 Alkylphosphorus Compounds with a P—Al, P—Ga, or P—In Bond

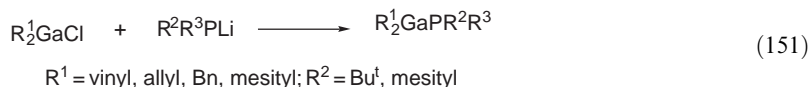
Dipotassium di(*t*-butylphosphide) reacts with AlCl_3 to give a dianionic aluminum–phosphorus tricyclic derivative (Equation (149)) <2001EJI1841>.



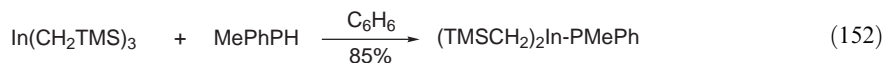
In turn, *P*-borane phosphides react with AlCl_3 in the presence of TMEDA or methyl *t*-butyl ether (MTBE) yielding an aluminate salt with four P—Al bonds (Equation (150)) <2003OM1463>.



Monomeric gallylphosphines (phosphinogallanes) have been synthesized from alkali metal phosphides and substituted gallium chlorides (Equation (151)) <1997IC5165, 1997CB/RTC663>.



The same method has been used for the synthesis of phosphinoindium derivatives <1997IC5165>. A series of phosphinoindium compounds, some of which are substituted with bulky groups, has been prepared in nearly quantitative yield by elimination reactions between the appropriate organoindium derivatives and phosphines (e.g., Equation (152)) <1995OM3448>.



To avoid the use of a free phosphine, a new procedure has been developed which allows its formation *in situ*. Thus, when chlorodiisopropylphosphine is added to $\text{KIn}(\text{CH}_2\text{CMe}_3)_3\text{H}$, the corresponding phosphinoindium product is obtained as a dimer. However, the yields are low and some other products are also formed <2001OM4896>.

2.08.10.3 Alkylphosphorus Compounds with a P—M Bond

Various methods have been used for the preparation of alkali metal phosphides (see the Sections dealing with the application of metallated phosphines in the synthesis of many kinds of organophosphorus compounds). Recently, some papers have appeared that are devoted to

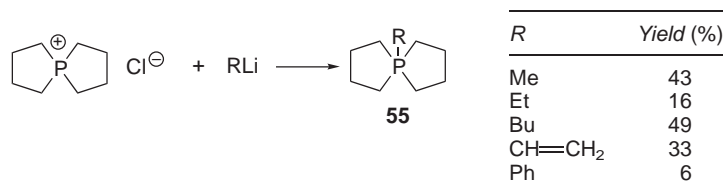
the determination of the molecular structures of the metal phosphides (obtained by well-known methods) and their complexes, e.g., Li phosphides <2002OM641, 2003OM1463>, K phosphides <1998CC1527, 1998MI221>, Na phosphides <1995CC47>, sterically demanding Na and K phosphides <1999JCS(D)1825>. Also, alkaline earth metal (Mg, Ca, Sr, Ba) phosphides have been synthesized and their structures elucidated <2002IC3886>.

2.08.11 PENTACOORDINATE ALKYLPHOSPHORUS COMPOUNDS (PHOSPHORANES)

An increasing trend towards the synthesis of new derivatives of pentacoordinated phosphorus has been observed. Their structure allows for an unlimited variability of substituents, which has resulted in a great number of publications devoted to this subject. Due to limited space, only selected characteristic examples are presented here.

2.08.11.1 Pentaalkylphosphoranes— R_5P

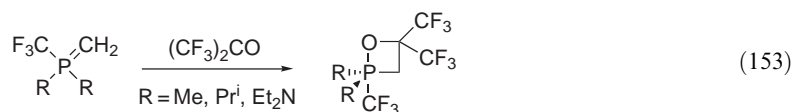
Investigations of the synthesis of spirocyclic phosphoranes **55** have been resumed and resulted in the preparation of a series of derivatives by a reaction between spirocyclic phosphonium salts and organolithium reagents (Scheme 95) <2002JA6126>.



Scheme 95

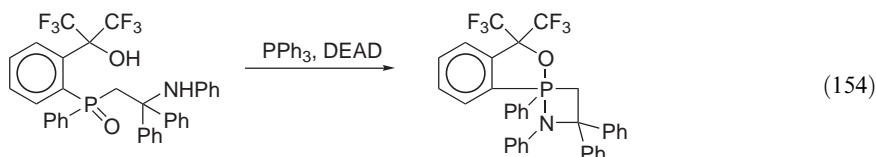
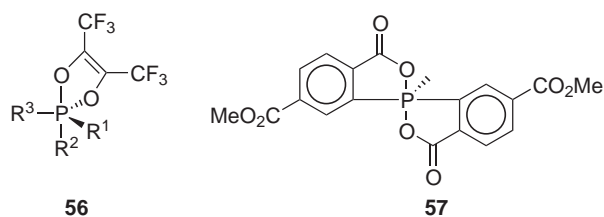
2.08.11.2 Tetraalkylphosphoranes— R_4PX

Phosphorus ylides have been trapped by use of hexafluoroacetone to give stable 1,2- $\lambda^5\sigma^5$ -oxaphosphetanes (Equation (153)) <1996HAC281, 2002HAC650>.



2.08.11.3 Trialkylphosphoranes— R_3PX_2

Difluorocarbene, generated from $(\text{CF}_3)_2\text{Cd}$, inserts smoothly into the P—F bonds of PF_5 to form $(\text{CF}_3)_3\text{PF}_2$ in 80% yield <1998ZN(B)1455>. Other difluorophosphoranes (R_3PF_2 ; R = Bu, NR^1_2) can be easily obtained from bromophosphonium bromides and zinc difluoride <1995JFC47>. Perfluorinated 2,3-pentanedione reacts with P(III) compounds to give 1,3,2- $\lambda^5\sigma^5$ -dioxaphosphenes **56** <1997PS(124/125)419>. Bis(*o*-carboxyaryl)methylphosphine oxides undergo spontaneous dehydration in acidic media to give spirodioxaphosphoranes (e.g., **57**) <1996PS(109/110)241>. The treatment of the appropriately substituted hydroxyamino phosphine oxides with the Mitsunobu reagent results in intramolecular cyclization and dehydration leading to 1,2- λ^5 -azaphosphetidines (Equation (154)) <1996AG(E)1096>.

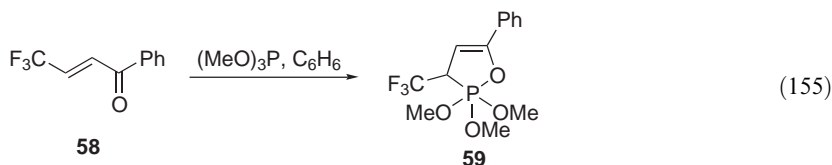


2.08.11.4 Dialkylphosphoranes— R_2PX_3

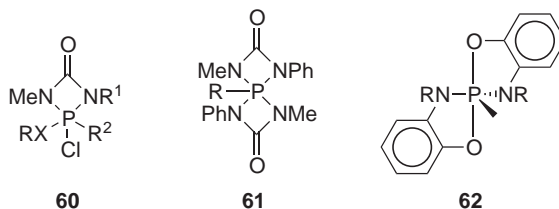
Air-stable trifluorophosphoranes $[Ph_3C(R)PF_3]$, $R = Bu^t$, Ph , NEt_2 have been obtained by the addition of Ph_3CF to the appropriate difluorophosphine RPF_2 [<1999ZAAC\(625\)1278>](#).

2.08.11.5 Monoalkylphosphoranes— RPX_4

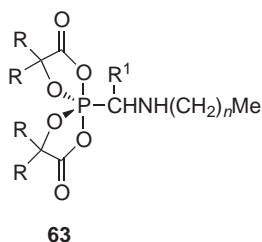
The reaction of the enone **58** with $(MeO)_3P$ in an aprotic medium affords trimethoxyphosphorane **59** as the sole product (Equation (155)) [<2000JFC73>](#).



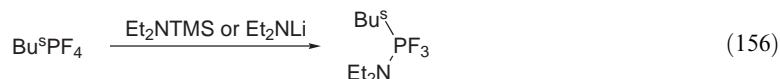
Methyldichlorophosphine reacts with HF (3 equiv.) to give $MePF_3H$, for which a distorted trigonal bipyramidal structure has been predicted on the basis of *ab initio* calculations [<2002ZAAC\(628\)1835>](#). When *N*-silyl-*N'*-arylthio- or *N'*-arylselenoureas are treated with dichlorophosphines, the corresponding 1,3,2 λ^5 -diazaphosphetidin-4-ones **60** are formed [<1995ZAAC\(621\)2001, 1996ZAAC\(622\)1250>](#). The corresponding spiro bicyclic phosphoranes **61** have been obtained from dichlorophosphines and *N,N'*-bis-trimethylsilylureas [<1997ZAAC\(623\)1325>](#). Other types of spirophosphoranes, e.g., compounds containing both N and O in the five-membered rings **62**, have also been synthesized [<2001BCJ1411>](#).



Chemical transformations of P(V) compounds provides access to a broad variety of new phosphoranes. For example, alkylation of tetraoxo P—H spirophosphoranes gives rise to a series of variously substituted phosphoranes [<1995ZOB1747, 1995ZOB1749, 1995ZOB1753>](#), while addition of the P—H bond to imines gives α -(aminoalkyl)spirophosphoranes **63** quantitatively and diastereoselectively [<2000EJO281>](#).

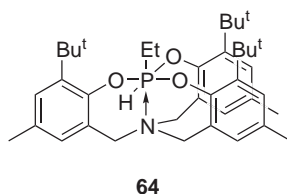


Acyclic fluorophosphoranes can be chemically transformed into other analogs (e.g., Equation (156)) <1998HAC659>.



2.08.12 HEXAVALENT ALKYLPHOSPHORUS COMPOUNDS

Reaction of EtPCl_2 with an appropriate hydroxyamine leads to the hexacoordinated phosphorane-phosphatrane **64** <2002JA7035>.



A variety of phosphorus(V)octaethylporphyrin derivatives have been synthesized; X-ray analysis has revealed that they are hexacoordinate hypervalent compounds <1995JA8287, 2001IC5553>.

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2.09

Alkylarsenic, -antimony, and -bismuth Compounds

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2.09.1 INTRODUCTION

Arsenic, antimony, and bismuth, a class of elements in group V of the periodic table and known as the pnictogens, have a colorful past from the ancient alchemists to Cadet's fuming arsenical liquid in 1760 <1760MI363>. A historic review of arsenic was written by Seyferth in 2001 <2001OM1488>. In the late nineteenth century, arsenic salts were used in green pigments, often used in wallpapers, which, when acted upon by fungi in damp houses, produced toxic trimethylarsine <2003NAT(423)688>. Today they are used in lasers.

The purpose of this chapter is to update the original COFGT (1995), chapter 2.09 <1995COFGT(2)479>. This update is organized in the same way as the original chapter and covers synthetic approaches to alkylpnictogens for the period 1995–2003. Other relevant reviews have appeared during this period. Reviews as well as books have been written on the chemistry of, and synthetic methods for, the pnictogens. A review of some of the chemistry of organoarsenic and -antimony compounds has been published by Jain <2001JIC224> and describes the preparation of precursors for chemical vapor deposition of group III–V semiconductors and their use as reagents in organic synthesis. There is also a description of RM(III), R₂M(III), and R₃M(V) (M = As, Sb) species that Jain has synthesized <2001JIC224>. *Organobismuth Chemistry* <B-2001MI001>, edited by Suzuki and Matano, describes well the chemistry of the Bi–C bond and compounds containing Bi(III) as well as Bi(V). The use of bismuth in organic transformations was also discussed <B-2001MI001>. A review has also been published by Wardell on group V metals in which arene complexes, tervalent compounds, and quinquivalent compounds were discussed <1996MI143>.

Arsenic, antimony, and bismuth are toxic and most compounds containing them are extremely harmful to health. The preparation, storage, and manipulation of these compounds should be done in an efficient fume hood and protective gloves should be worn at all times. Since most of these compounds are moisture- and oxygen-sensitive, an inert atmosphere, and anhydrous and oxygen-free solvents are normally required.

2.09.2 ALKYLARSINES, -STIBINES, AND -BISMUTHINES AND SALTS THEREOF, AND ARSORANES, STIBORANES, AND BISMUTHORANES

These alkylarsines, -stibines, and -bismuthines can be compared to the amines in reactivity. The newest use of arsenic here is the preparation of the chiral arsonium ylide **1** (Section 2.09.2.3.3).

2.09.2.1 Primary and Secondary Alkylarsine, -stibenes, and -bismuthines

2.09.2.1.1 Reduction of alkylarsenic, -antimony, and -bismuth halides

A newer method for producing primary stibines is the reaction of antimony trichloride with vinyltributylstannane or alkynyltributylstannane. Most of the dichlorostibines are unstable, even to purification. Reduction of chlorostibenes performed using Bu_3SnH with a radical inhibitor (hydroquinone, duroquinone, galvinoxyl) produced better results than did use of LAH, AlHCl_2 , and Bu_3SnH <1995IC1466>.

2.09.2.1.2 Reduction of alkylarsonic and -arsinic acids

The standard method for the reduction remains zinc (amalgam) in hydrochloric acid as described in COFGT (1995) <1995COFGT(2)479>.

2.09.2.1.3 Alkylation of arsine, primary alkylarsines, and metal derivatives thereof

The standard method for alkylation remains formation of the arsenide using metals and liquid ammonia and reaction with an alkyl halide as described in COFGT (1995) <1995COFGT(2)479>.

2.09.2.1.4 Other methods

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.2.2 Tertiary Alkylarsines, -stibines, and -bismuthines

The chemistry of trivinylarsine is little known. Monkowius and co-workers have reported work in this area <2003OM145>. Compounds of this type fall within the scope of Chapter 2.17.

2.09.2.2.1 Reduction of organometallics with arsenic, antimony, and bismuth halides

In an attempt to synthesize trialkyl group VA metal compounds without using ethers as the solvent, since the oxygen is a deleterious impurity, Shenai-Khatkhate and co-workers <2002EUP1247813> determined that group VA metal trihalides (AsX_3 , SbX_3 , BiX_3) reacted with a group IIIA compound of formula $\text{R}_n\text{MX}_{3-n}$ ($\text{M} = \text{B}, \text{Al}, \text{Ga}, \text{In}, \text{Tl}$) in a hydrocarbon solvent with the addition of a tertiary amine ($\text{NR}_1\text{R}_2\text{R}_3$) to produce extremely pure group VA alkyl compounds free of oxygenated impurities.

2.09.2.2.2 Reaction of organometallics with alkylarsenic, -antimony, and -bismuth halides

Only vinyl and allenyl derivatives have been reported and these are discussed in Chapter 2.17.

2.09.2.2.3 From aminoarsines, -stibines, and -bismuthines

A good precursor of tertiary alkylarsines is aminoarsine as described in COFGT (1995) <1995COFGT(2)479>.

2.09.2.2.4 Reactions of organometallics with other arsenic, antimony, and bismuth derivatives

Whilst lower aluminum alkyls ($C < 4$) will monoalkylate arsenic oxide, Grignard reagents remain the method of choice <1990IC3502> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.2.2.5 Alkylation of alkylarsenides and -stibides

Pure SbMe_3 , obtained by the method described in Section 2.09.2.2.7 was alkylated using excess bromoacetic acid forming $[\text{Me}_3\text{SbCH}_2\text{COOH}][\text{Br}]$. Subsequent elimination using Ag_2O in water produced the antimony analog of betaine, $\text{Me}_3\text{Sb}^+\text{CH}_2\text{COO}^-$ <2002APOC155>.

2.09.2.2.6 Miscellaneous methods

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.2.2.7 From pyrolysis of R_2SbX

Balázs and co-workers obtained pure SbMe_3 by heating Me_2SbBr at 160–180 °C with subsequent distillation from the MeSbBr_2 , which was also produced <2002APOC155>.

2.09.2.3 Alkylarsonium and -stibonium Salts

2.09.2.3.1 Alkylation of tertiary arsines and tertiary stibines

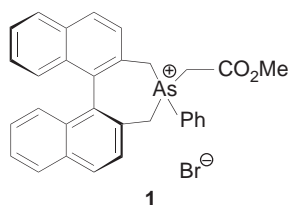
The most direct method of alkylation remains the reaction with an alkyl halide <1931JCS185> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.2.3.2 Alkylarsonium and -stibonium salts by other methods

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.2.3.3 Arsonium ylides

Despite the importance of the Wittig reaction, and the fact that numerous phosphorus-derived reagents do exist and ylides from Bu_3^+As and organic tellurides have been discovered to be catalytic, there was no catalytic asymmetric reaction of such ylides until 2002 when Dai and co-workers <2002TA2187> developed a chiral arsonium ylide **1**.



2.09.2.4 Alkylarsonanes and -stiboranes

2.09.2.4.1 Alkylarsonanes

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.2.4.2 Alkylstiborane

The standard preparation of alkylstiboranes remains the reaction of organometallic reagents and trialkylantimony dihalides as described in COFGT (1995) <1995COFGT(2)479>.

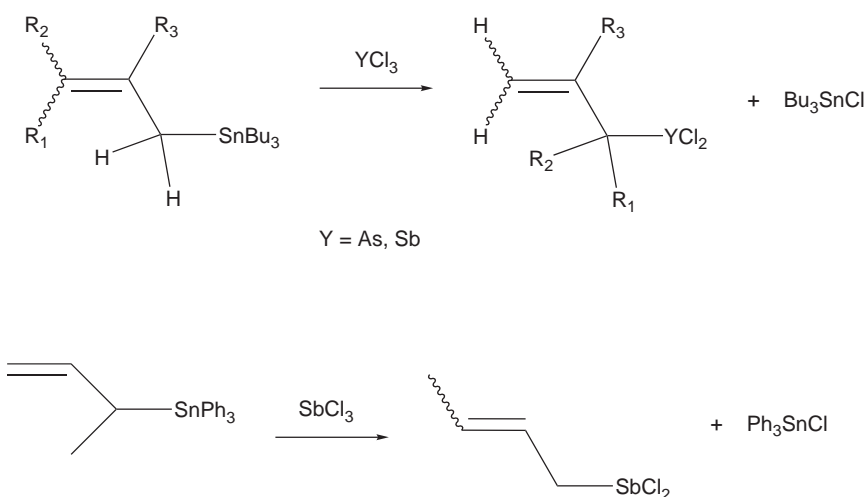
2.09.3 ALKYLARSINE HALIDES AND THEIR ANTIMONY AND BISMUTH ANALOGS

Work done in the late 1990s has demonstrated that triorganoantimony(V) dihalides R_3SbX_2 can be produced by the action of Br_2 or I_2 on tertiary stibines R_3Sb which are useful in the synthesis of diorganoantimony(III) halides R_2SbX and dihydroxides, or oxides, R_3SbO .

2.09.3.1 Alkylarsine Halides (R_2AsX , $RAsX_2$) and Their Antimony and Bismuth Analogs

2.09.3.1.1 Reaction of organometallics with arsenic, antimony, and bismuth trihalides

The reaction of allyl-substituted tributylstannanes with arsenic and antimony trichloride yielded only the α -substituted products, namely substituted dichlorostibines. However, (1-methyl-2-propenyl)triphenylstannane and antimony trichloride produced the γ -substituted products, which are the thermodynamic products (Scheme 1) <1998JOC59>.



Scheme 1

2.09.3.1.2 Pyrolysis of R_3EX_2 and R_2EX_3 ($E = As, Sb$)

Aonuma and co-workers observed that the step-wise pyrolysis of Me_3SbI_2 produced Me_2SbI and $MeSbI_2$ as mixtures <1997SM(86)1881>. See also Section 2.09.3.2.1.

2.09.3.1.3 Redistribution reaction

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.3.1.4 Reactions involving cleavage of As—, Sb—, and Bi—C bonds

A study on homolytic versus heterolytic bond cleavage was published in 1999 complete with *ab initio* MO calculations on C—As, C=As, and C≡As bonds <1999JPC(A)7087>.

2.09.3.1.5 Cleavage of As—As, Sb—Sb, and Bi—Bi bonds

The cleavage of (CF₃)₂AsAsMe₂ can be accomplished with Mn(CO)₅I forming (CO)₅MnAs(CF₃)₂ and Me₂AsI, which will react with the starting compound <2002ZAAC2523>.

2.09.3.1.6 Miscellaneous methods for alkylarsine halides

The reaction of I₂ with Me₄AsI, Me₃SbI, Me₂Et₂SbI, MeEt₃SbI, or Et₄SbI in the absence of solvent produces the respective arsonium/stibonium triiodide. However, Me₄SbI₃ is made from addition of I₂ to (Me₄Sb)₃I₈ in a reversible reaction. An additional method involves reaction of Me₄SbI in EtOH with I₂ in benzene <1997ZAAC1151>.

2.09.3.2 Arsenic(V) and Antimony(V) Halides—R₃EX₂, R₂EX₃ (E = As, Sb)

2.09.3.2.1 R₃AsX₂ and R₃SbX₂ (X = Cl, Br, I) by reaction of tertiary arsines and stibines with halogens

Triorganoantimony(V) dihalides R₃SbX₂ are produced by the action of Br₂ or I₂ upon tertiary stibines, R₃Sb. Their usefulness is in the synthesis of diorganoantimony(III) halides R₂SbX, produced upon thermal elimination of RX or for hydrolysis reactions which form dihydroxides, or oxides, R₃SbO <2002JOM(648)33>.

As for the structure of Me₃SbBr₂, a reinvestigation has determined that the structure is nonionic and possesses a high degree of symmetry (*D*_{3h}) <1996JOM(512)21>.

2.09.3.2.2 R₃AsF₂ and R₃SbF₂

Triorganoarsenic and -antimony difluorides are still produced from the reaction of other dihalides with silver fluoride or sodium fluoride <1968IC834> as well as oxidative fluorination of tertiary alkylarsines and -stibines using XeF₂ and IF₅ <1988JCS(D)451> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.3.2.3 R₂AsX₃ by reaction of R₂AsX with halogens

The standard method of producing triorganoarsenic dihalides is the reaction of halogens with dialkylhaloarsines as described in COFGT (1995) <1995COFGT(2)479>.

2.09.3.2.4 Miscellaneous methods

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.4 ALKYLARSENIC COMPOUNDS WITH AN As—O BOND, AND THE ANALOGOUS ANTIMONY AND BISMUTH COMPOUNDS

The newest achievements are that the Meyer reaction between a carbon electrophile and an arsenic(III) nucleophile can be used to create a C—As bond. Arsinolipids have also been synthesized in the late 1990s.

2.09.4.1 Alkylarsinous Acid Derivatives ($R_2^1\text{AsOAsR}_2^1$, $R_2^1\text{AsOR}^2$) and Their Analogous Antimony and Bismuth Compounds

2.09.4.1.1 Bisdialkylarsine oxides and their analogous antimony and bismuth compounds— $R_2\text{EOER}_2$ ($E = \text{As, Sb, Bi}$)

The standard method of preparing bisdialkylarsine and bisdialkylstibine oxides remains hydrolysis of the respective dialkylhaloarsines and -stibines <1970JA3969> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.4.1.2 Esters of arsinous acid ($R_2^1\text{AsOR}^2$) and their analogous antimony and bismuth compounds

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

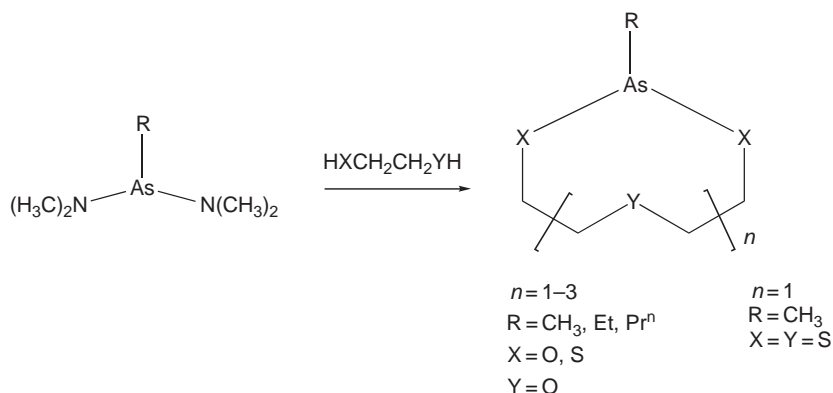
2.09.4.2 Alkylarsonous Acid Derivatives ($(\text{RAsO})_n$, $R^1\text{As}(\text{OR}^2)_X$) and Their Analogous Antimony and Bismuth Compounds

2.09.4.2.1 $(\text{RAsO})_n$ and $(\text{RSbO})_n$

The standard method of producing alkylarsaoxanes is hydrolysis of dihalo(alkyl)arsines <1903CR(137)925>, oxidation of primary arsines and cyclopolyarsines <1970JA3969> and reduction of arsonic acids <1919IEC817> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.4.2.2 Esters of alkylarsonous acids, $R^1\text{As}(\text{OR}^2)_2$, and their analogous antimony and bismuth compounds

$\text{RAs}[(\text{NCH}_3)_2]_2$ (Section 2.09.6.1.1) reacted with several diols producing esters of macrocyclic arsinous acid along with mixed thioalcohols (Scheme 2) <2000MI930>.



Scheme 2

2.09.4.3 $R^1As(OR^2)X$

2.09.4.3.1 *Reaction of $RAsX_2$ with an alcohol*

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.4.3.2 *Reaction of $R^1As(OR^2)_2$ with halogenating agents*

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.4.4 Alkylarsine and -stibene Oxides— R_3EO ($E = As, Sb$)

2.09.4.4.1 *Oxidation of tertiary alkylarsines and tertiary alkylstibines*

The chelate oxides of bis(trimethylantimony) (Me_3SbLI)₂O where ($I = 1, 2$; $L1 =$ acetylacetonate, $L2 =$ trifluoroacetylacetonate) and bis(triethylantimony) can be produced by a one-step oxidation of the corresponding trialkylantimony with *t*-butyl hydroperoxide in benzene at 20 °C in 79–85% yield in the presence of β -diketones <1995IZV154>.

2.09.4.4.2 *From R_3EX_2 ($E = As, Sb$)*

See Section 2.09.4.8.1.

2.09.4.5 Alkylarsonic Acids ($RAsO(OH)_2$) and Alkylarsinic Acids ($R_2AsO(OH)$)

2.09.4.5.1 *The Meyer reaction*

The Meyer reaction has been reviewed by Ioannou <2002PS(177)1>. It is used to create a C—As bond from a carbon electrophile reacting with an arsenic(III) nucleophile. Ioannou determined that electrophilic substrates and bulky As(III) nucleophiles, which were unable to achieve the correct S_N2 transition state, would not progress to a successful reaction. Aqueous solvents are also required for the reaction and solubilizing a lipophilic substrate can prove challenging. Conditions for optimal yields have also been reported <2002PS(177)1>.

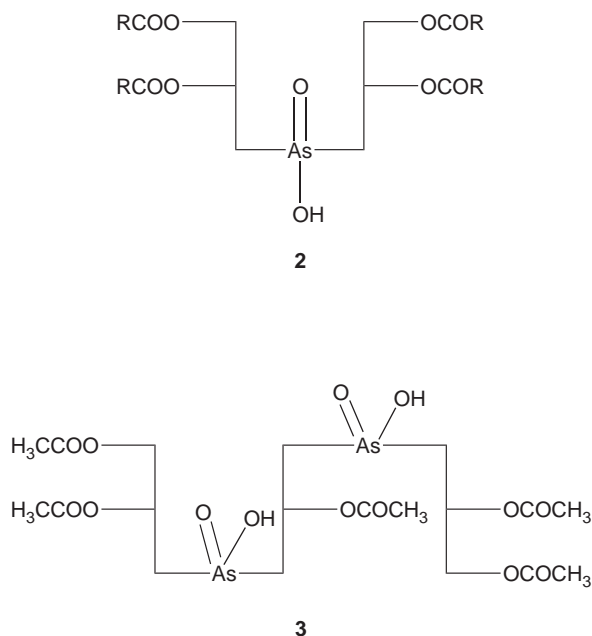
A study on the mechanism and kinetics of the Meyer reaction of sodium arsenite with chloroacetic acid indicated an S_N2 mechanism. The entropies and activation energies of the reactions were also reported <1999JGU1389>.

2.09.4.5.2 *Oxidation of various derivatives ($R_2AsX, RAsX_2$)*

The standard oxidants remain oxygen, selenium dioxide, and hydrogen peroxide as described in COFGT (1995) <1995COFGT(2)479>.

2.09.4.5.3 *Arsinolipids*

Kordalis and Ioannou have synthesized arsinolipids starting from arsenosobenzene and arsenosobenzene-*rac*-2,3-dihydroxypropane <2000APOC273>. The As—O bond is hydrolytically very unstable <1973B3932> and so the As—O bond is replaced with the stable As—C bond. The compounds produced are of the type shown in 2. Ioannou continued the synthesis of arsinolipids by producing a nonisosteric analog of the fully acylated cardiolipin (see 3) <2002MI7>.



2.09.4.6 Derivatives of Alkylantimony(V) Acids

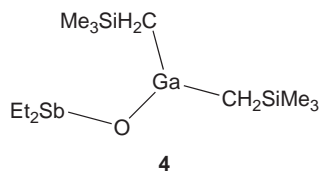
2.09.4.6.1 Oxidative hydrolysis of antimony(III) halides

Balázs and co-workers converted Me_2SbBr into $\text{Me}_3\text{Sb}(\text{OH})_2$ using bromoethylacetate forming $[\text{Me}_3\text{SbCH}_2\text{COOEt}][\text{Br}]$ that was hydrolyzed with Dowex[®]2 $[\text{OH}^-]$ or with KOH/water <2002APOC155>.

2.09.4.7 R_2SbOGa

2.09.4.7.1 Reaction of Sb_2R_4 with GaR_3 and O_2

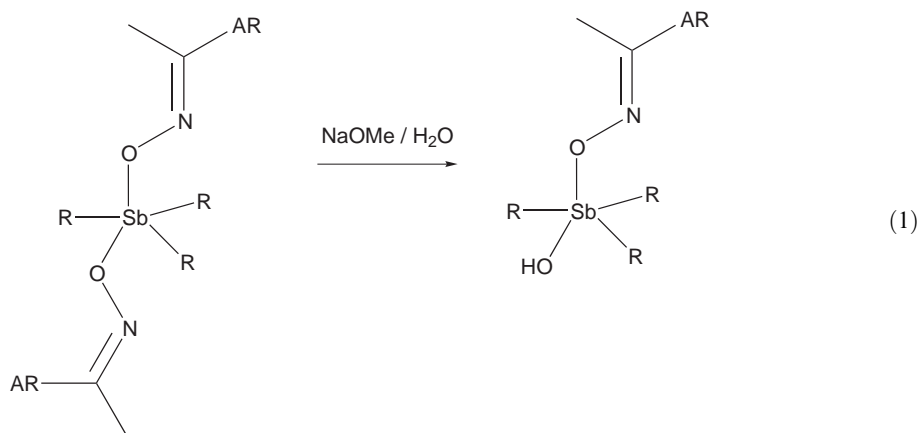
Bruenig and co-workers <1998ZAAC1965> reacted $(\text{Me}_3\text{SiCH}_2)_3\text{Ga}$ with Sb_2Et_4 and oxygen to produce $[(\text{Me}_3\text{SiCH}_2)_2\text{GaOSbEt}_2]$ (see **4**), which dimerized upon crystallization.



2.09.4.8 Oxime Formation

2.09.4.8.1 From R_3SbX_2 or $\text{R}_3\text{Sb}(\text{OH})_2$

The reaction of R_3SbBr_2 with 2 equiv. of $\text{NaON}=\text{C}(\text{Me})\text{Ar}$ produced the oxime $\text{R}_3\text{Sb}[\text{ON}=\text{C}(\text{Me})\text{Ar}]_2$ that, upon treatment with $\text{NaOMe}/\text{H}_2\text{O}$, underwent loss of one of the oximes producing $\text{R}_3\text{Sb}(\text{OH})[\text{ON}=\text{C}(\text{Me})\text{Ar}]$. The singly substituted bismuth could also be produced by using $\text{Pr}^i_3\text{Sb}(\text{OH})_2$ and 1 equiv. of the oxime acid, as opposed to the sodium salt (Equation (1)) <2002JOM(645)118>.



2.09.5 ALKYLARSENIC COMPOUNDS WITH AN As—S, As—Se, or As—Te BOND, AND THE ANTIMONY AND BISMUTH ANALOGS

Dickson and Heazle <1995JOM(493)189> observed that R_4Sb_2 , and Et_4As_2 when reacted with R_2Te_2 produced products having SbTe and AsTe bonds. Subsequent thermal degradation of $Et_2SbTeEt$ in a hydrogen stream (conventional metal organic chemical vapor deposition (MOCVD) conditions) produced a 1.6 Sb: 1 Te metal deposit.

A review of the chemistry of diorganothiophosphate (and phosphinate) derivatives, with arsenic, antimony, and bismuth, by Chauhan <1998CCR1> has described their synthesis and characterization.

2.09.5.1 Bis(dialkyl)arsines Chalcogenides ($R_2AsE'AsR_2$; $E' = S, Se, Te$) and Their Antimony and Bismuth Analogs

2.09.5.1.1 Reaction of dialkylhaloarsines and -stibines with metal sulfides

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.5.1.2 Insertion reaction of tetraalkyldipnicogens by a chalcogen element

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.5.2 Dialkyl(organochalcogeno)arsines ($R_2^1AsE'R_2$; $E' = S, Se, Te$) and Their Antimony and Bismuth Analogs

2.09.5.2.1 $R_2^1EE'R^2$ ($E = As, Sb, Bi$; $E' = S, Se, Te$) from exchange reaction between tetraalkyldipnicogens and diorganodichalcogenides

Dickson and Heazle observed that Et_4Sb_2 , Me_4Sb_2 , or Et_4As_2 when reacted with $Pr_2^1Te_2$ or Et_2Te_2 produced $Et_2SbTeEt$, $Me_2SbTeEt$, $Et_2SbTePr^1$, and $Et_2AsTeEt$ <1995JOM(493)189>. The products are light-sensitive and some could not be purified because of reverse dissociation or free-radical decomposition. The thermal degradation of $Et_2SbTeEt$ in a hydrogen stream (conventional MOCVD conditions) produced an Sb and Te metal deposit having a ratio of 1.6:1, respectively.

2.09.5.2.2 $R_2^1AsSR^2$ and $R_2^1AsSeR^2$ from reactions of R_2^1AsX with R^2SH and R^2SeH derivatives

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.5.2.3 $R_2^1AsSR^2$ and $R_2^1AsSeR^2$ from reactions of aminoarsines with RSH and $RSeH$

The standard method of producing organoarsenic compounds having As—S and As—Se bonds remains reacting aminoarsines with thiols <1975ZAAC202> and selenols <1972JOM(39)301> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.5.2.4 $R_2^1AsSR^2$ from reactions of $RP(S)S_2$ and $AsR^1OR_2^2$

1,3,2,4-dithiadiphosphetane-2,4-disulfides react with *N,N*-dialkylaminodiethylarsines to produce *S*-diethylarsenic(III)-aryl-*N,N*-dialkylamidodithiophosphonates in anhydrous benzene at 20 °C over 5–8 h <1999HAC670>.

2.09.5.3 Alkylthioarsonous Acid Anhydrides $(RAS)_n$ and Their Antimony Analogs $(RSbS)_n$

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.5.4 Alkyldiorganochalcogenoarsines $(R^1As(E'R^2)_2)$; $E' = S, Se, Te$ and Their Antimony and Bismuth Analogs

2.09.5.4.1 From alkyldihaloarsines, -stibines, and -bismuthines

The standard method of preparation is reacting alkyldihalo compounds with thiols and selenols or their salts <1987POL1593> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.5.4.2 From diamino- and dialkoxy-arsines, -stibines, and -bismuthines

$RAs[(NCH_3)_2]_2$ (Section 2.09.6.1.1) reacts with a thiol producing an ester of macrocyclic arsine-dithious acid along with a mixed thioalcohol (Scheme 2) <2000MI930>.

2.09.5.4.3 Other methods

Breunig and co-workers produced the novel ligand $MeSb(SSbMe_2)_2$ as a side product from the reaction of $Me_2SbSSbMe_2$ with 2 equiv. of norbornadienyl $Cr(CO)_4$ in the synthesis of *cyclo*- $[Me_2SbSSbMe_2Cr(CO)_4]_2$ <1999ZAAC2120>.

2.09.5.5 Tertiary Alkylarsine Sulfides and Selenides (R_3AsS, R_3AsSe) and Their Antimony Analogs

2.09.5.5.1 Reaction of tertiary alkylarsine and -stibines with chalcogens

The standard method of preparing tertiary alkylarsine sulfides and selenides is the reaction of trialkylarsines with sulfur and selenium <1980ZAAC183> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.5.5.2 Other methods

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.5.6 Other Alkylantimony(V) Derivatives with Sb—S and Sb—Se Bonds

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.6 ALKYLARSENIC COMPOUNDS WITH AN As—N BOND AND THE CORRESPONDING Sb—N AND Bi—N ANALOGS

Shi and Tu <1999JEM(28)43> have developed a kinetic model for the decomposition of tris(dimethylamino) arsine describing the surface pyrolysis of the arsine on a GaAs(100) surface where the substituted arsine only has As—N bonds and a moderate vapor pressure, potentially reducing the need for toxic gaseous arsine.

2.09.6.1 Aminoarsines ($R_2^1AsNR_2^2$, $R^1As(NR^2)_2$ and Their Analogous Antimony and Bismuth Compounds**2.09.6.1.1 Reaction of alkylarsenic, -antimony, and -bismuth halides with ammonia, amines, and metal amides**

The reaction of $RAsCl_2$ with $HN(CH_3)_2$ produces $RAs[(NCH_3)_2]$, which will further react with diols (Section 2.09.4.2.2) and thiols (Section 2.09.5.4.2) <2000MI930>.

2.09.6.1.2 Reaction of R_2NEX_2 , $(R_2N)_2EX$ ($E = As, Sb$) with organometallics

The standard method of preparing aminoarsines is the reaction of aminoarsenic halides, prepared from arsenic trihalides and amines with organometallic reagents as described in COFGT (1995) <1995COFGT(2)479>.

2.09.6.1.3 Other methods

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.6.1.4 Cleavage of As—N bonds

Nine aminoarsines [Me_2AsR ($R = NMe_2$, NPr_2^i , NPr_2^i , NBu_2^i , NBu_2^i , NC_4H_8 , NC_5H_{10} , NC_6H_{12} , and $N(C_2H_4)_2NMe$)] were cleaved by reaction with Me_2AlH or Bu_2AlH in C_6D_6 at room temperature. The relative rates of the reactions depended on the steric requirements of the alkyl groups on both the aluminum and nitrogen atoms. The majority of the reactions produced dimeric aminoalanes [Me_2AlR] $_2$ and [Bu_2AlR] $_2$ with Al—N bond formation. When the bulky Bu^i and Pr^i aminoarsines were used, Al—As bond formation was observed <1996OM2458>.

Shi and Tu <1999JEM(28)43> developed a kinetic model for the decomposition of tris(dimethylamino) arsine to describe the surface pyrolysis of the arsine on a GaAs(100) surface. The substituted arsine has no As—C bonds, only As—N bonds, and has a moderate vapor pressure. Hence it could reduce the need for the toxic, gaseous arsine. Their model reproduces behavior of data in the literature of the desorption products from a heated GaAs(100) surface heated within a vacuum chamber.

2.09.6.2 Other Compounds with As—N, Sb—N, and Bi—N Bonds

The standard method of preparing azidoarsines and azidostibines is the reaction of a metal azide with alkylhaloarsines and -stibines <1985ZN(B)1320> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.6.3 Arsenic(V) and Antimony(V) Compounds with As—N, Sb—N Bonds

The standard method of preparing iminotriorganoarsoranes remains treatment of aminotrialkylarsonium halides with potassium amide in liquid ammonia <1980CB2928> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.7 ALKYLARSENIC, -ANTIMONY, OR -BISMUTH COMPOUNDS WITH HETEROATOM BONDED TO P, As, Sb, OR Bi

Research in this area in the early years of the twenty-first century has focused on the formation of Zintl compounds, Sb_7^{3-} and As_7^{3-} , produced by heating [*cyclo*-(CyP)₄Sb]Na·Me₂NH·TMEDA]₂ and [*cyclo*-(BuⁿP)₃As]Li·TMEDA·THF], respectively.

2.09.7.1 Tetraalkyldiarsines, -distibines, and -dibismuthines—R₂EER₂ (E = As, Sb, Bi)

Sharma and co-workers <1997MI697> have discussed in detail the synthesis, general properties, and X-ray structures of distibines as well as cyclic and noncyclic polystibines. The reactions of compounds with an Sb—Sb bond are also presented.

2.09.7.1.1 Reduction of R₂EX (E = As, Sb, Bi) derivatives

The standard method of reducing dialkylhaloarsines is reaction with lithium, sodium, magnesium, mercury, or zinc, however, the choice of metal and solvent determines the product as described in COFGT (1995) <1995COFGT(2)479>.

2.09.7.1.2 From arsenic, antimony, and bismuth metal derivatives

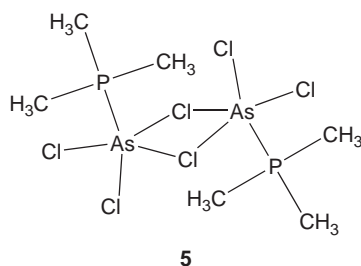
No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.7.1.3 Miscellaneous methods

(Difluoromethyl)triorganopnicogenium tetrachlorobismuthanes are produced in good yields from Bi(CF₃)₃/AlCl₃ and R₃As (R = Buⁿ, Et, NEt₂) derivatives. (Difluoromethyl)triorganopnicogenium bromides result from Zn(CF₃)Br·2CH₃CN and Et₃E (E = As, Sb) <1999JFC207>.

2.09.7.1.4 From AsX₃

The reaction of AsX₃ (X = Cl, Br, I) with 1 equiv. of ligands such as PMe₃, AsMe₃, and MeC(CH₂AsMe₂)₃ produces products of type AsX₃L. In the reaction with 2 equiv. of PMe₃, the product is AsX₃(PMe₃)₂. However, AsX₃ with AsMe₃ in a 1:1 or 1:2 ratio produced only AsX₃(AsMe₃). Upon crystallization AsCl₃(PMe₃) forms dimeric units of type **5** <2002JCS(D)1188>.



2.09.7.2 Polyalkylarsines ((RAs)_n) and Polyalkylstibenes ((RSb)_n)

2.09.7.2.1 Reduction of RAsX₂ and RSbX₂ derivatives

The reduction of Bu^IAsI₂ with equivalent amounts of Mg, Ca, Zn, Li, or CoCp₂ in THF at low temperatures produced (Bu^IAs)₄ in high yields. Further chemistry where (Bu^IAs)₄ is the starting material is discussed in [Section 2.09.9.2.10 <1997ZN\(B\)790>](#).

2.09.7.2.2 Reduction of alkylarsonic acid derivatives

The standard method of preparing polyalkylarsines is the reduction with hypophosphorous acid of alkylarsonic acids or salts [<1986OCS618>](#) as described in COFGT (1995) [<1995COFGT\(2\)479>](#).

2.09.7.2.3 Oxidation of primary alkylarsines

The standard method of oxidizing primary alkylarsines is the use of dibenzylmercury to produce polyarsines [<1986OCS618>](#) as described in COFGT (1995) [<1995COFGT\(2\)479>](#).

2.09.7.2.4 Miscellaneous methods

No further advances have occurred in this area since the publication of COFGT (1995) [<1995COFGT\(2\)479>](#).

2.09.7.3 Mixed Tetraalkyl Dipnicogens (R₂AsSbR₂, R₂SbBiR₂, etc.)

2.09.7.3.1 Exchange reaction

No further advances have occurred in this area since the publication of COFGT (1995) [<1995COFGT\(2\)479>](#).

2.09.7.3.2 Miscellaneous methods

No further advances have occurred in this area since the publication of COFGT (1995) [<1995COFGT\(2\)479>](#).

2.09.7.4 Zintl Compounds—As₇M₃, Sb₇M₃

2.09.7.4.1 Formation of Zintl compounds

The Zintl compounds Sb₇³⁻ and As₇³⁻ can be formed by heating [{*cyclo*-(CyP)₄Sb}-Na·Me₂NH·TMEDA]₂ and [{*cyclo*-(Bu^tP)₃As}Li·TMEDA·THF], respectively <2000JCS(D)479>. These precursors are described in Section 2.09.9.13 <1998CC2485>. Heating {[Sb(PCy)₃]₂-Li₆·6HNMe₂} at 30–40 °C also produced Zintl compounds with Sb₇³⁻ anions <1998SCI(281)1500>.

2.09.8 ALKYLARSENIC, -ANTIMONY, OR -BISMUTH COMPOUNDS WITH HETEROATOM BONDED TO A METALLOID

2.09.8.1 Compounds with the Heteroatom Bonded to Silicon

For formation of a mixed silylated arsenic or antimony, the lithium disilylarsenic or antimony can be reacted with a trialkylsilyl chloride at 0 °C <2002EJI3268>. Formation of silylated arsenics results from the reaction of Na₃As (generated from powdered arsenic and sodium in THF) with chlorodimethylcyclohexylsilane in refluxing THF producing As(SiMe₂Cy)₃ <2000POL1639>. Arsenic and antimony can also be silylated using the (Na/K)₃E form with TIPSCl in refluxing DME <2001ZAAC1414>.

2.09.8.2 Compounds with the Heteroatom Bonded to Germanium

The reaction of Me₃GeCl with (Me₃Si)₃Sb provides (Me₃Ge)₃Sb <1995PS(102)287>.

2.09.8.3 Compounds with the Heteroatom Bonded to Boron

Except for a six-membered As₂B₄ ring with aromatic substituents <1995ZAAC1933>, no further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.9 ALKYLARSENIC, -ANTIMONY, OR -BISMUTH COMPOUNDS WITH HETEROATOM BONDED TO A METAL

This section contains the majority of the material that is new since 1995, such as the development of AlSb films, arsenic's chelates with palladium, and complexes with tantalum. Also included are the formation of rings of Ga₂As₂ and In₂As₂, and products containing a Sb₂Na₂ ring.

2.09.9.1 Alkali Metal Derivatives of Arsenic, Antimony, and Bismuth Compounds

2.09.9.1.1 From primary and secondary arsines and stibines

The standard preparation of secondary alkylarsines and -stibines remains their treatment with organolithium reagents as described in COFGT (1995) <1995COFGT(2)479>.

2.09.9.1.2 From dialkylhaloarsines and -stibines

The standard preparation of metal derivatives remains the reaction of dialkylhaloarsines and -stibines with an alkali metal <1967CJC675> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.9.1.3 From tertiary alkylarsines, -stibines, and -bismuthines

Cyclo-(Bu^t₄Sb₄) upon reaction with potassium or sodium will form [Bu^t₄Sb₃]. However, if the reaction is prolonged, the previous product decomposes to [Bu^t₃Sb₂][−]. Breunig and co-workers <2002JOM(660)167> formed a complex with the reaction mixture and pentamethylenediamine, and the crystal structure indicated that the terminal antimony atoms of [Bu^t₂Sb—Sb—SbBu^t₂][−] acted as a bidentate chelating ligand to the sodium.

The reaction of SbPrⁱ₃ and [IrCl(C₂H₄)(PPrⁱ₃)₂] produced the mixed-ligand complex [IrCl(C₂H₄)(SbPrⁱ₃)(PPrⁱ₃)] which reacted with CO, H₂, or diphenylacetylene as well as diaryldiazomethanes (R₂CN₂) to produce four-coordinate iridium(I) carbenes [IrCl(=CR₂)(SbPrⁱ₃)(PPrⁱ₃)] in 60–70% yield <2002OM2369>.

Cyclo-(CH₃AsS)_{3,4} upon reaction with sodium formed Na₂(S)_n(CH₃As)_{n−1} in the same manner as the cyclic antimony reaction described above <1997OM5142>.

2.09.9.1.4 Miscellaneous methods

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

2.09.9.2 Other Main Group Metal Derivatives of Arsenic, Antimony, and Bismuth Compounds

2.09.9.2.1 From secondary alkylarsines

The standard preparation of these compounds [(Me₂AsMe₂)₃:M = Al, Ga, In] remains reacting Me₃M with Me₂AsH <1965JCS3241> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.9.2.2 From arsenide and stibide derivatives

The standard preparation of compounds having As—Ga, Sb—Ga, and Sb—In bonds is the reaction of arsenides and stibides with gallium and indium halides <1993JCS(D)1737> as described in COFGT (1995) <1995COFGT(2)479>.

2.09.9.2.3 Metathetical reaction

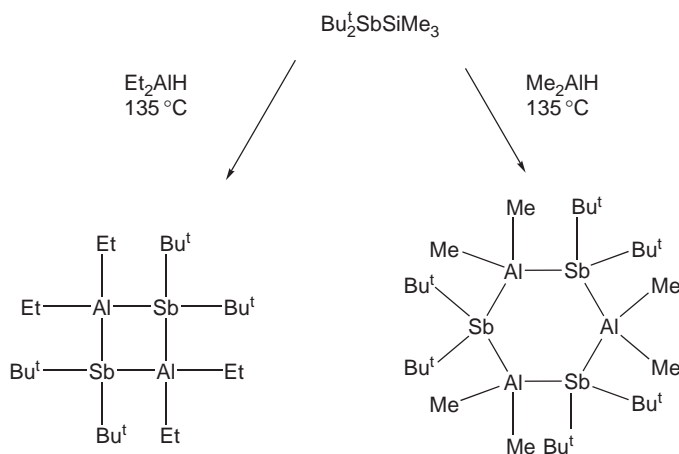
Carmalt and co-workers produced nickel pnictides utilizing a liquid-mediated metathetical reaction of metal dihalides with a sodium pnictide <2000POL829>.

2.09.9.2.4 From peralkylated arsino(phosphino)methanes

Peralkylated arsino(phosphino)methanes have been observed to form a chelate with palladium forming a bond between arsenic and palladium <2002JCS(D)2815>.

2.09.9.2.5 From R₂SbSiMe₃

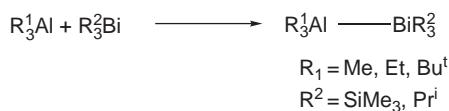
The need for AlSb films in MOCVD experiments <1999MI179> led to their formation from reactions between Bu^t₂SbSiMe₃ and diorganoaluminum hydrides. This produced all-alkyl-substituted Al—Sb ring compounds (Scheme 3) <2000OM699>.



Scheme 3

2.09.9.2.6 From R_3Bi with R_3Al

Reactions between trialkylalanes AlR_3 ($\text{R} = \text{Me}, \text{Et}, \text{Bu}^t$) and triorganylbismuthanes R_3Bi ($\text{R} = \text{Pr}^i, \text{SiMe}_3$) produced six trialkylalanes of the type $(\text{R}_3^1\text{Al}-\text{BiR}_3^2)$ (Scheme 4) <2001EJ12605>.



Scheme 4

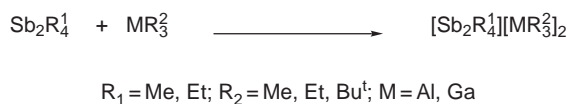
2.09.9.2.7 From dibismuthanes R_4Bi_2

Tetraethyldibismuthane Et_4Bi_2 was reacted with tri(*t*-butyl)alane and -gallane producing compounds of the type $[\text{Et}_4\text{Bi}_2][\text{MBu}_3]_2$ where $\text{M} = \text{Al}, \text{Ga}$ <2001AG(E)4222>. Both products were dibismuthane bisadducts.

2.09.9.2.8 From distibanes R_4Sb_2

(i) With aluminum and gallium

Tetraalkyldistibanes R_4Sb_2 react with trialkylalanes and -gallanes producing compounds of the type $[\text{R}_4^1\text{Sb}_2][\text{MR}_3^2]_2$ (Scheme 5) <2001OM2000>.



Scheme 5

(ii) With indium

Breunig and co-workers reacted Sb_2Me_4 with $(\text{MeSiCH}_2)_3\text{In}$ and obtained crystals of $(\text{MeSiCH}_2)_3\text{InSbMe}_2$ in which the indium was bound to the antimony <1998ZAAC1965>.

2.09.9.2.9 From As_4 or $(Bu^tAs)_4$

Mast and co-workers synthesized a $[(Cp''Ta)_2(\mu-\eta^4:\eta^4-As_8)]$ complex of tantalum and arsenic from $[Cp''Ta(CO)_4]$ ($Cp'' = C_5H_3Bu^t-1,3$) and As_4 or $(Bu^tAs)_4$ <1999ZAAC70>. The procedure for its preparation is discussed in Section 2.09.7.2.1.

2.09.9.2.10 From $[H_2]As(SiMe_3)_3$ or $Sb(SiMe_3)_3$

Thomas and co-workers prepared triel-pentel heterocycles $[Me_2InE(SiMe_3)_2]_x$ from the dehalosilylation reactions of Me_2InCl and $E(SiMe_3)_3$ ($E = As, x = 2$; $E = Sb, x = 3$) for 3 h at 90 °C in toluene <2002ZAAC235>.

Von Hänisch <2001ZAAC68> formed the cyclic $[GaCl(PBu^tMe)As(SiMe_3)]_2$ from $GaCl_3 \cdot P-Bu^tMe$ and $As(SiMe_3)_3$. The four-membered Ga_2As_2 ring formed has a three-coordinate arsenic atom. Wells and co-workers <1995OM2123> used $Ga(CH_2SiMe_3)_3$ in the reaction with $As(SiMe_3)_3$ to form $(Me_3SiCH_2)_3Ga \cdot As(SiMe_3)_3$.

Von Hänisch <2001ZAAC68> also formed cyclic $[Et_2InAs(SiMe_3)_2]_2$ from the reaction of $Et_2In \cdot PR_3$ ($R = Et, Pr^i$) with $H_2AsSiMe_3$ with the release of C_2H_6 and AsH_3 . The In_2As_2 ring contains a four-coordinate arsenic.

2.09.9.2.11 From silylated arsenic and antimony

Von Hänisch and co-workers reacted the mixed silylated compounds $Pr^i_3SiE(SiMe_3)_2$ ($E = As, Sb$), formed by the method described in Section 2.09.9.2.10, with the phosphane complex $[GaCl_3PPr^i_2Ph]$ in diisopropyl ether for one day producing $[GaCl(PPr^i_2Ph)(SbSiPr^i_3)]_2$ <2002EJI3268>. In the crystal structure the gallium and antimony form a four-membered planar Ga_2Sb_2 ring with the silyls and chlorine *trans* orientated. The arsenic showed no reactivity toward gallium chloride.

2.09.9.2.12 From $As(NMe_2)_3$ and $Sb(NMe_2)_3$

Beswick and co-workers <1998CC2485> formed $[(cyclo-CyP)_4Sb]Na \cdot Me_2NH \cdot TMEDA)_2$, having a central Sb_2Na_2 ring, from the reaction of $[Sb(NMe_2)_3]$ with $[CyPHNa]$ and $[CyPH_2]$ (1:1:1 equiv.). Also formed was $[(cyclo-Bu^tP)_3As]Li \cdot TMEDA \cdot THF$ from $[As(NMe_2)_3]$ with $[Bu^tPHLi]$ (1:3 equiv.) in TMEDA-THF. These molecules are precursors to the Zintl compounds discussed in Section 2.09.7.4.1.

2.09.9.3 Transition Metal Derivatives of Arsenic, Antimony, and Bismuth Compounds

2.09.9.3.1 Reaction of a transition metal complex anion with alkylarsenic, -antimony, and -bismuth halides

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)479>.

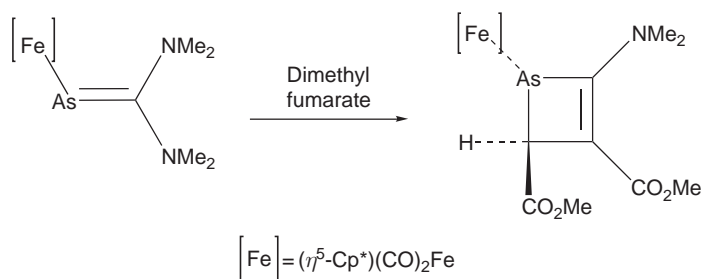
2.09.9.3.2 Miscellaneous methods

(i) Cr and W complexes

The reaction of *cyclo*-methylarsathiane, *cyclo*-(CH_3AsS)_{3,4} with group 6 metal carbonyls $M(CO)_6$ ($M = Cr, W$) in THF produced $[Cr(CO)_5-\eta^1-cyclo-(CH_3AsS)_4]$, $[Cr(CO)_3-\eta^3-cyclo-(CH_3AsS)_5]$, and $[W(CO)_3-\eta^3-cyclo-(CH_3AsS)_6]$. In all three complexes, the metal shows preference for arsenic over sulfur. Sulfur bonding results only when it is necessary to accommodate octahedral symmetry about the metal <1998OM726>.

(ii) Fe complexes

$\text{Me}_3\text{SiAs} = \text{C}(\text{NMe}_2)_2$ reacts with $(\eta^5\text{-Cp}^*)(\text{CO})_2\text{FeBr}$ to produce an arsaalkene which upon treatment with dimethyl fumarate produces a 1,2-dihydroarsete (Scheme 6) <1996CB223>.



Scheme 6

2.09.9.3.3 Metathetical reactions

Carmalt and co-workers produced cobalt pnictides utilizing a liquid-mediated metathetical reaction of transition-metal dihalides with a sodium pnictide. The ratio of Co to As and/or Sb in the products is the same as the ratio of the starting materials CoCl_2 , Na_3As , and Na_3Sb <2000POL829>.

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Biographical sketch



Margaret Brimble was born in Auckland, New Zealand and received her B.Sc. in 1982 and her M.Sc. (Hons) in 1983 from the University of Auckland. She was then awarded a Commonwealth Scholarship to study in the United Kingdom and received her Ph.D. in 1986 from the University of Southampton. She then took up her initial academic appointment at Massey University, New Zealand in 1986. In 1992, she was a visiting Professor at the University of California, Berkeley for 6 months and then moved to the University of Sydney in 1994. In 1999, she returned to New Zealand to take up the Chair in Organic and Medicinal Chemistry at the University of Auckland. She has been awarded the New Zealand Institute of Chemistry Easterfield Medal, the Royal Society of New Zealand Hamilton Prize and the Federation of Asian Chemical Societies Distinguished Young Chemist Award. Her scientific interests include the synthesis of polyether antibiotics containing bis-spiroacetal ring systems, the synthesis of pyranonaphthoquinone antibiotics, the synthesis of complex shellfish toxins, and the synthesis of peptidomimetics for the treatment of neurodegenerative disorders.



Mark Levi was born in Arkansas, USA. He studied at Harding University, where he obtained a B.S. in 1997 and at the University of Mississippi where he obtained his Ph.D. in 2002 under the direction of Professor R. F. Borne. He was appointed Postdoctoral Research Fellow for 2003 at the University of Auckland working with Professor Margaret Brimble. He was appointed Research Instructor in the Department of Pharmacology & Toxicology at the University of Arkansas for Medical Sciences in 2004. His scientific interests include drug design, parallel solution-phase and solid-phase chemistries, neurological agents and peptides.

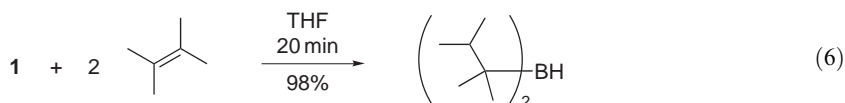
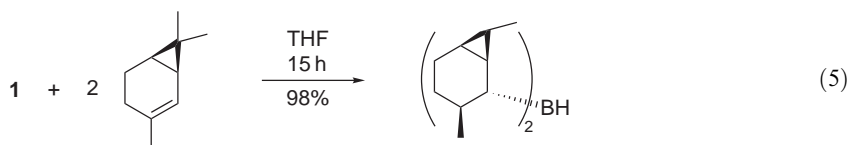
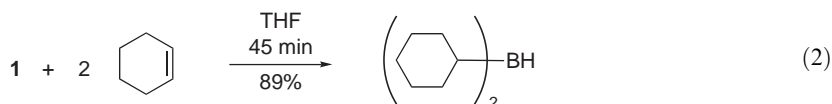
2.10

Alkylboron and -silicon Compounds

W. FRASER

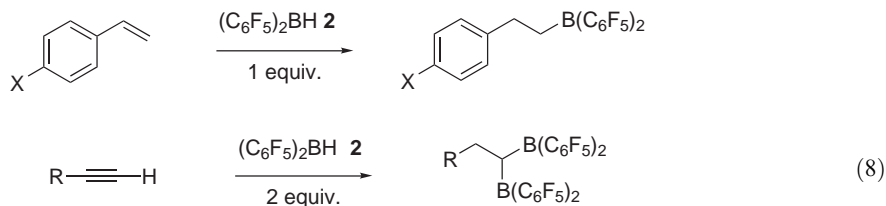
Aston University, Birmingham, UK

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(i) Monoalkylboranes by hydroboration

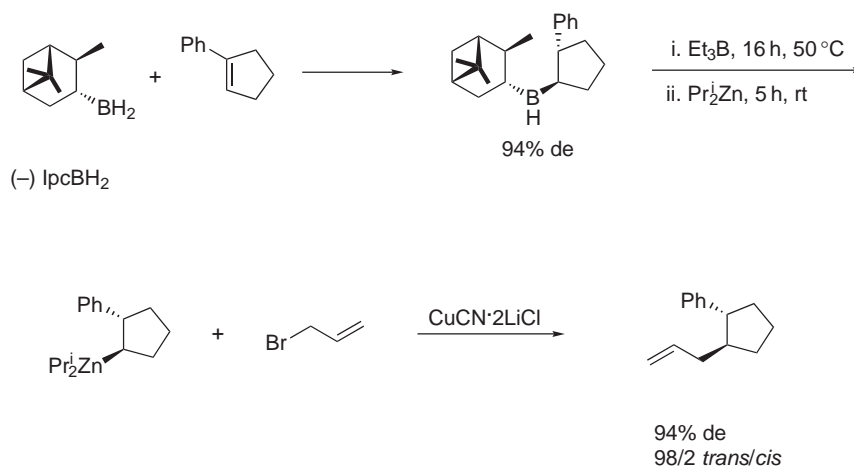
Dialkylborane reagents $\text{R}^1\text{R}^2\text{BH}$ are unable to hydroborate terminal alkynes without some degree of accompanying diboration. It is possible to form exclusively the 2-borylethylalkynes from styrenes, which are hydroborated using bis(pentafluorophenyl)borane **2** (Equation (7)) <1997CSR345>. Reaction of terminal alkynes with 2 equiv. of reagent **2** leads rapidly to bidentate Lewis acids through dihydroboration (Equation (8)). Silylamine borane reagents provide useful alternatives to the traditional reagents for hydroboration such as $\text{BH}_3\cdot\text{THF}$ and $\text{BH}_3\cdot\text{SMe}_2$ <B-2001MI026, 1998TL6119>. Use of the borane-silylamine complex $\text{BH}_3\cdot\text{Bu}^t\text{NHTMS}$ allows the controlled monohydroboration of thexylborane, which is isolated as its TMEDA complex <1998TL6123>.



(ii) Dialkylboranes by hydroboration

Monoisopinocampheylborane (IpcBH_2) is available enantiomerically pure and has been used for sometime with trisubstituted aliphatic alkenes to give the corresponding alcohols in high diastereomeric excesses <2000PAC1699>. Diastereomeric excesses improve further with trisubstituted alkenes bearing an aromatic ring. For example, hydroboration of 1-phenylcyclopentene with IpcBH_2 gives the borane product in 94% enantiomeric excess from which the mixed organic zinc reagent is formed by boryl exchange on the reaction with Pr^i_2Zn in THF (Scheme 1). Allylation

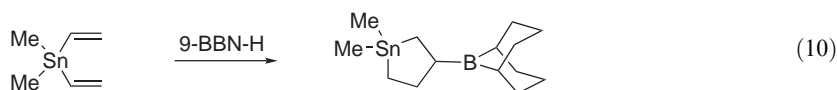
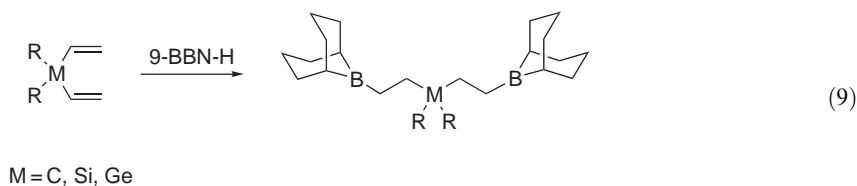
gives the final disubstituted cyclopentane with an excellent *trans*–*cis* product ratio. Recent applications of the B–Zn exchange reaction to the syntheses of new C–C bonds have recently been reviewed <2003JOM(680)136>.



Scheme 1

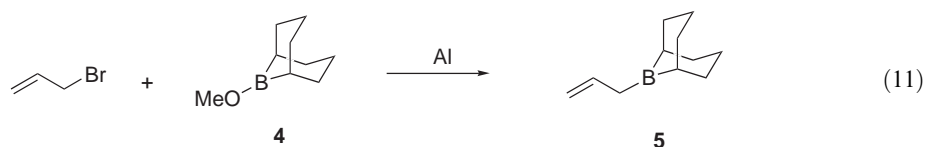
(iii) Trialkylboranes by hydroboration

Trialkylboranes are an important part of organic synthesis. The process of hydroboration of alkenes for the synthesis of trialkylboranes is well established <B-2001MI026, 1995COFGT(2)513>. The reaction of diisopinocampheylborane (Ipc₂BH) with *trans* and hindered alkenes such as trialkyl-substituted derivatives is slow and the enantioselectivity has been found to be poor. However, when a donor group is attached to the double bond, Ipc₂BH readily adds to the adjacent carbon as evidenced by asymmetric hydroboration of (*E*)- and (*Z*)-2-methoxy-2-butene at –25 °C, where product alcohols form after subsequent oxidation in high yield and diastereomeric excess <2000TA4831>. Stepwise hydroboration of two different alkenes is possible by reacting isopinocampheylidichloroborane (IpcBCl₂). The first alkene is hydroborated in the presence of trimethyl silane (Section 2.10.2.1.1) to give the product from mono-hydroboration cleanly <1996TL1763>. Addition of LiAlH₄ followed by the second alkene gives exclusively the trialkylborane. Unsymmetrical ketones may be produced by replacing boron by carbonyl in a one-pot procedure <1996TL1763>. A previously unknown process, which contrasts with the formation of 1,5-boryl adducts formed by the reaction of 9-BBN-H with divinyl derivatives of group 14 metalloids, has been reported (Equation (9)) <1998TL2511>. When 9-BBN-H is reacted with dimethyldivinylstannane, the stannacyclopentane is formed cleanly as the exclusive reaction product (Equation (10)).



2.10.1.1.2 Reaction of an organometallic compound with a haloborane, alkoxyborane, or dialkylaminoborane

The monomeric bis(pentafluorophenyl)chloroborane [(C₆F₅)₂BCl] **3** is a convenient starting material for preparing multigram quantities of the highly electrophilic bis(pentafluorophenyl)borane [(C₆F₅)₂BH] **2** <2002JFC1>. Dimethylchlorosilane, which also acts as the solvent, reacts with the chloroborane **3** to give [(C₆F₅)₂BH]₂ that precipitates quantitatively from solution as a microcrystalline powder <1995AG(E)809>. As a result of the high reactivity of the reagent **2** with even weakly coordinating donor solvents, traditional methods such as LiAlH₄ reduction in donor solvents (e.g., diethyl ether or THF) cannot be used <1997CSR345>. In aromatic solvents, detectable amounts of the monomer are observed and it is this propensity for dissociation that might explain the greater reactivity of the borane derivative **2** compared with other hydroborating reagents (Section 2.10.1.1.1). Bis(pentafluorophenyl)borane **2** may also be prepared directly in 69% yield from tris(pentafluorophenyl)borane (C₆F₅)₃B <1999EJO527> by heating with triethyl silane or alternatively in 62% yield by a three-step process where chloroborane **3** is converted to borane **2** with a choice of silane <1998OM5492>. *B*-Allyl-9-BBN derivative **5** (Section 2.10.1.11) may be readily prepared by reacting *B*-MeO-BBN **4** with allyl bromide in the presence of aluminum chips as activator <1999JOM(576)147> (Equation (11)). The related compound *B*-allyldiisocampheylborane is a fundamentally important compound that has been used extensively for enantioselective allylboration of many aldehydes and related substrates to give homoallylic alcohols, for example, in extremely high diastereomeric and enantiomeric excess <B-1997MI010, B-1997MI011, B-2001MI026, 1997TL2417, 1999TL1433, 2000TA4629, 2001JOM(624)239, 2003T5953>.



2.10.1.1.3 Miscellaneous methods

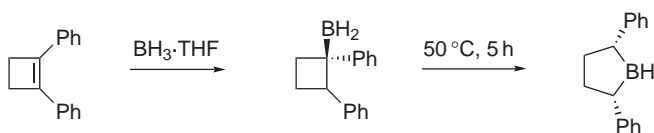
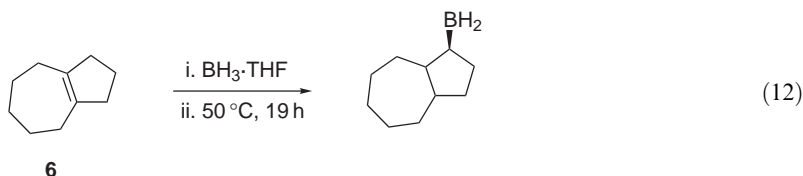
(i) Organoboranes by hydride reduction of chloroboranes or alkoxyboranes

The reduction of a chloroborane with a source of hydride is an integral part of the methods for synthesis of mixed di- and trialkylboranes <B-1996MI007>. The process is illustrated by the synthesis of *t*-1-decalone from 1-allyl-1-cyclohexene <1996JOC1906>. The novel asymmetric hydroborating 10-TMS-9-BBN-H is formed by hydride reduction of the corresponding *B*-9-MeO-BBN precursor using LiAlH₃(OEt) <B-2001MI026>.

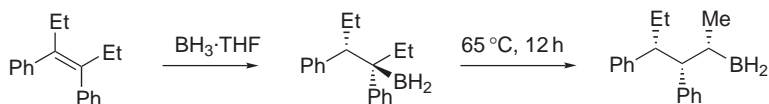
(ii) Organoboranes by equilibration (redistribution) and isomerization

Stereoselective thermal rearrangement of organoboranes is a valuable route to products that are obtained in good yield and in high enantiomeric excess <B-1997MI010, B-2001MI026>. Alkene **6** undergoes normal hydroboration followed by [1,2]-migration to the less sterically hindered secondary borane, which may then be oxidized by standard methods to the corresponding alcohol (Equation (12)) <2000PAC1699>. Hydroboration of 1,2-diphenylcyclobutene gives a tertiary borane that undergoes a remarkable new rearrangement to a five-membered boracycle, which on oxidation gives the *meso*-diol as a single diastereoisomer (Scheme 2) <1998AG(E)2460>. The tetrasubstituted alkene (*Z*)-1,2-diethyl-1,2-diphenylethene undergoes hydroboration with BH₃·THF followed by rearrangement in which only one diastereotopic proton migrates from carbon-to-boron (Scheme 3). Thus, diastereospecific formation of the primary borane is ensured and subsequent oxidative work-up or separate amination give the corresponding alcohol (80% yield, >99.5% de) or the benzyl-protected amine (82%, >99.5% de) <2000PAC1699>. *B*-alkylated derivatives of 9-BBN-H are often the reagents of choice for many important organoborane transformations such as Suzuki–Myaura coupling reactions <1995CRV2457> due to their greater Lewis acidity compared to the oxygenated analogs of the general formula R¹B(OR²)₂, and

the robustness of the 9-BBN spectator ligand. Organometallic routes provide access to *B*-9-alkyl-BBN derivatives that cannot be prepared by straightforward hydroboration. The typical reaction between *B*-MeO-9-BBN **4** and a Grignard or organolithium reagent does have some limitations. For example, some organolithium reagents form stable intermediate “ate” complexes that require a Lewis acid to convert to the *B*-9-alkyl-BBN products. With the exception of methyl Grignard reagents, others form “ate” complexes that decompose too quickly to give tetracoordinate borinate salts. These limitations can largely be overcome through the use of (TIPS)S-9-BBN **7**, which provides a versatile alternative to compound **4** (Scheme 4) <2000TL3537>.



Scheme 2



Scheme 3



R = CH₃, 73%
 R = CH₂CH₃, 57%
 R = Ph, 90%
 R = cyclopropyl, 68%
 R = CH₂CHCH₂, 60%
 R = CHCH₂, 25%
 R = CH₂CH₂CH₂CH₃, 82%
 R = CHCHCH₂CH₂CH₂CH₃, 73%

Scheme 4

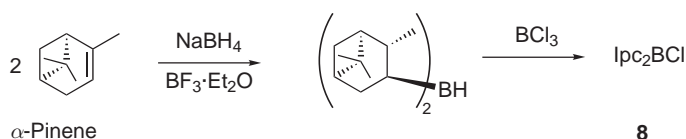
(iii) Organoboranes by alkylation α to boron

Stabilized dimesitylboron carbanions ($\text{Mes}_2\text{BCHR}^-\text{Li}^+$) react with aromatic aldehydes to form intermediates that may be oxidized at a low temperature to form predominantly *erythro*-1,2-diols <1996T1085>.

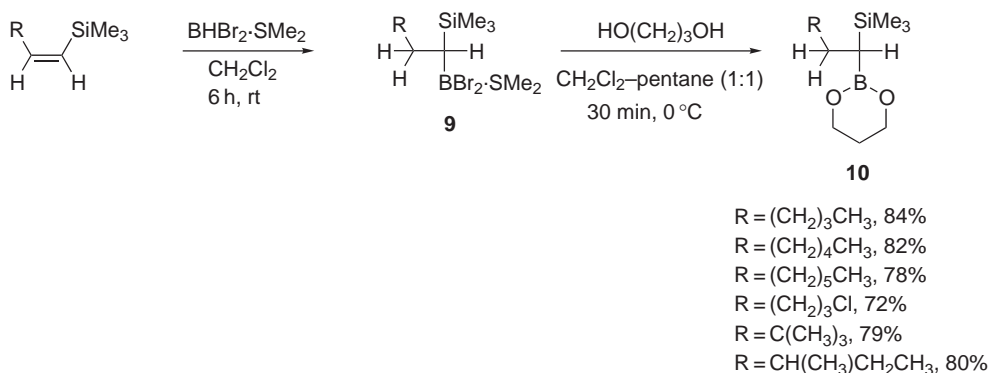
2.10.1.2 Alkylhaloboranes

2.10.1.2.1 Hydroboration of alkenes

Amongst their traditional roles, organoboron chlorides and bromides are valuable reagents for the alkylation of aromatic aldehydes as well as for the addition of aldehydes to alkenes, and dialkenylation of aldehydes <2003JOM(680)12>. The most direct preparation of alkylhaloboranes is by hydroboration of an alkene using dimethyl sulfide complexes of haloboranes such as BH_2Cl , BH_2Br , BHCl_2 , BBr_2 , or BHI_2 . Hydroboration of terminal alkenes using borane complexes with THF and BMS gives mixtures of regioisomers. Some exceptional chloroborane–Lewis base adducts, notably dioxane–monochloroborane, have been described as superior reagents for the selective hydroboration of alkynes <2001JOC5359>. A number of successful terphenyl-derived haloboranes have been described <B-2001MI026, 1996TL8345, 1996TL9021>. *B*-Chlorodiisopinocampheylborane **8** (Ipc_2BCl , DIP-chloride) has proven to be an excellent reagent for a range of synthetic applications <1996TA3527> including the asymmetric reduction of aralkyl ketones <1997TL2641, 2002JOC5315> and for the high stereoselection in aldol reactions (Section 2.10.1.3.5) <1997OR1, 2003TL5285>. A convenient method for the preparation of this reagent *in situ* <1997TL2641, 2000JA7218> that avoids the combined use of $\text{BH}_3\cdot\text{SMe}_2$ or $\text{BH}_2\text{Cl}\cdot\text{SMe}_2$, and is amenable to scale up, proceeds by the reaction of α -pinene with NaBH_4 and $\text{BF}_3\cdot\text{Et}_2\text{O}$ (Scheme 5). Chlorination of the resulting borane (Ipc_2BH) gives Ipc_2BCl **8**. Hydroboration of 1-trimethylsilylalkynes with dicyclohexylborane followed by protonolysis and work-up provides the corresponding 1-trimethylsilylalkenes that are starting materials for further hydroboration with $\text{BHBr}_2\cdot\text{SMe}_2$ to give the *gem*-dimetalloalkanes **9** (Scheme 6). Further reaction with 1,3-pentandiol gives good yields of the borinane products **10**, which are purified by high vacuum distillation <2003TL6833>.



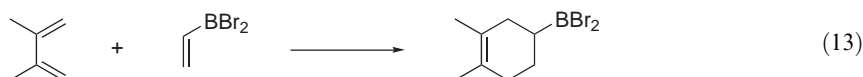
Scheme 5



Scheme 6

2.10.1.2.2 Miscellaneous methods

Diels–Alder cycloaddition of dienes with alkenyldihaloboranes, formed by the treatment of alkenyl or alkynyl silanes <1997JOM(544)157> or stannanes <1997JOC1955> with BCl_3 or BBr_3 , gives the cyclohexenylborane adducts (Equation (13)) from which the corresponding secondary alcohol is formed (74%) on oxidation.



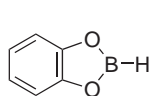
2.10.1.3 Alkyloxyboranes

2.10.1.3.1 Hydroboration of alkenes

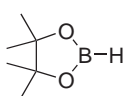
Catecholborane (1,2,3-benzodioxoborole) (catBH) **11** has stood out as a valuable and versatile reagent for the synthesis of alkyloxyboranes <1997T4957, 2000CC347>. It has high reactivity for various transition metal catalysts. However, it is less reactive than most other dialkylboranes and requires elevated temperatures to effect hydroboration of alkenes, but does so generally with high regioselectivity. The catecholborane products can be converted to the corresponding boronic acids, which have been used extensively in synthesis. The scope of most of the other boranes **12–19** has yet to be fully studied, but of these pinacolborane (pinBH) **12** and bis(pinacolate)borane (pin₂B₂) **13** are of particular note with the latter **13** finding important uses in catalytic borylation of unactivated alkanes and arenes by C–H bond activation <2003JOM(680)3> (Section 2.10.1.3.3). Pinacolborane **12** is an excellent alternative to catecholborane **11** from a practical point of view as it is a more stable, readily prepared, and durable hydroborating agent <B-1995MI002, B-2001MI025>. The durability of the pinacol *B*-alkyl and *B*-alkenyl boronate ester products of alkene and alkyne hydroboration are stable to moisture and chromatography and are therefore very convenient for organic synthesis.

Of the transition metal catalysts used to mediate hydroboration, Rh(I)- and Ir(I)-based catalysts are of particular interest <B-1999MI016, B-2001MI025>. Other transition metal catalysts such as Ti, Ni, and Sm have also yielded successes but are less frequently used. In addition to accelerating hydroboration reactions, the transition metal catalyst has a significant impact on each regio- and stereochemical outcome compared with the uncatalyzed additions of dialkylboranes <B-1999MI016, B-2001MI025>. As there has been no systematic study of the effects of borane agents, the best choice is still highly dependent upon the substrate and catalyst. For example, the time to complete hydroboration of cyclopentene using an Rh catalyst varies significantly depending on the borane agent used (Equation (14)) <1997CB363>. The hydroboration of styrene derivatives has been studied extensively <B-2001MI025>. With careful choice of metal catalyst and borane agent, attachment of boron to the terminal carbon or internal carbon of the alkene double bond can be controlled to give a single isomer of alkylborane product from which the alcohol is obtained by oxidative deborylation. When an aliphatic alkene is used instead of a styrene, neither the borane agents nor the metal catalyst alter the high terminal selectivity, whereas fluorinated alkanes mimic the behavior of styrenes <1996JA909, 1996TL3283>.

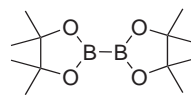
The outcomes of asymmetric hydroboration reactions using modified homochiral ligands have been documented <1995TA2593, 1997T4957>. For example, use of ligand **20** favors the formation of one enantiomer and ligand **21** favors the opposite enantiomer (Scheme 7). Oxidative deborylation gives the corresponding product alcohols with retention of configuration. The process of silaboration uses *B*-silyl-borate esters, particularly pinacol esters, to achieve addition of B–Si across a C–C double or triple bond, which has some interesting synthetic possibilities <1995OM3112, 2003JOM(680)43>. For example, silaboration product α -phenethyl- β -borylallyl-silane reacts sequentially with two different aldehydes followed by cationic cascade cyclization to give *t*-1,2-benzooxadecalin frameworks <2001CC1090>. Palladium- or platinum-catalyzed addition of a B–Si bond across a C–C triple bond gives high yields of the β -silylalkenylborane products <1996CC2777>. By contrast the use of nickel catalysts gives selectively 1-silyl-4-boryl-1,4-dienes via successive insertion of alkynes into the B–Si bond <1998OM5233>. With alkenes as substrates in place of alkynes, silylborolated products are obtained using a nickel catalyst <2003JOM(680)43>. The reaction yield and product stereochemistry are dependent upon the ligand of the catalyst used. For example, reaction of cyclohexadiene with *B*-(dimethylphenylsilyl)pinacolborane **22** gives a quantitative yield of the *cis*-isomer with phosphine ligand PCyPh₂ (Equation (15)). The conditions work well with cycloheptadiene as the substrate (Equation (16)). With PMePh₂ as ligand the yield and product stereochemistry are nearly as good but both suffer when either PMe₂Ph or PBu₃ are used as ligands. In the presence of PPh₃ or in the absence of a phosphine ligand, the reaction does not yield the product.



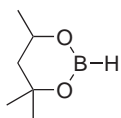
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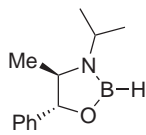
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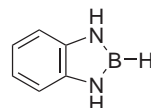
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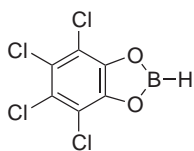
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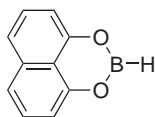
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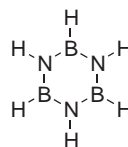
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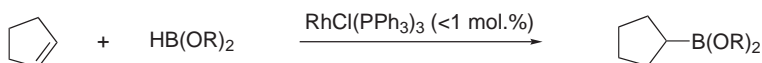
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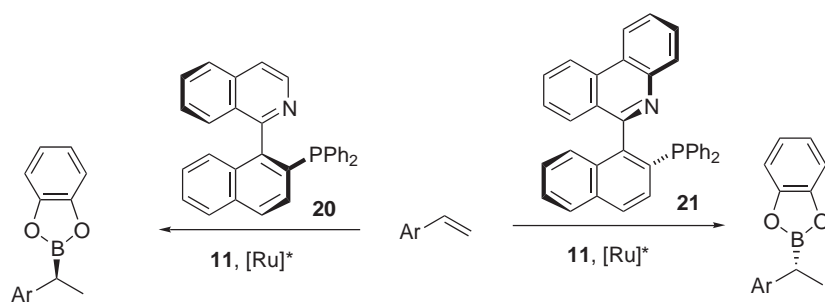


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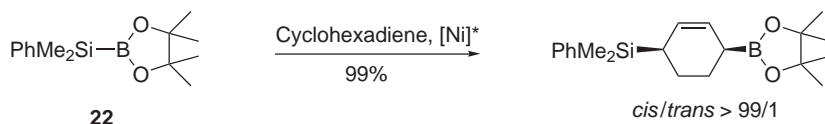


Borane	Time for >90% conversion
18	4 min
17	30 min
11	90 min
HB(OCH ₂ Ph) ₂	No reaction

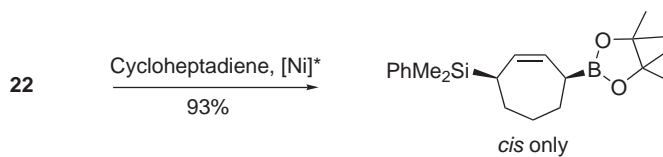
(14)



Scheme 7



(15)

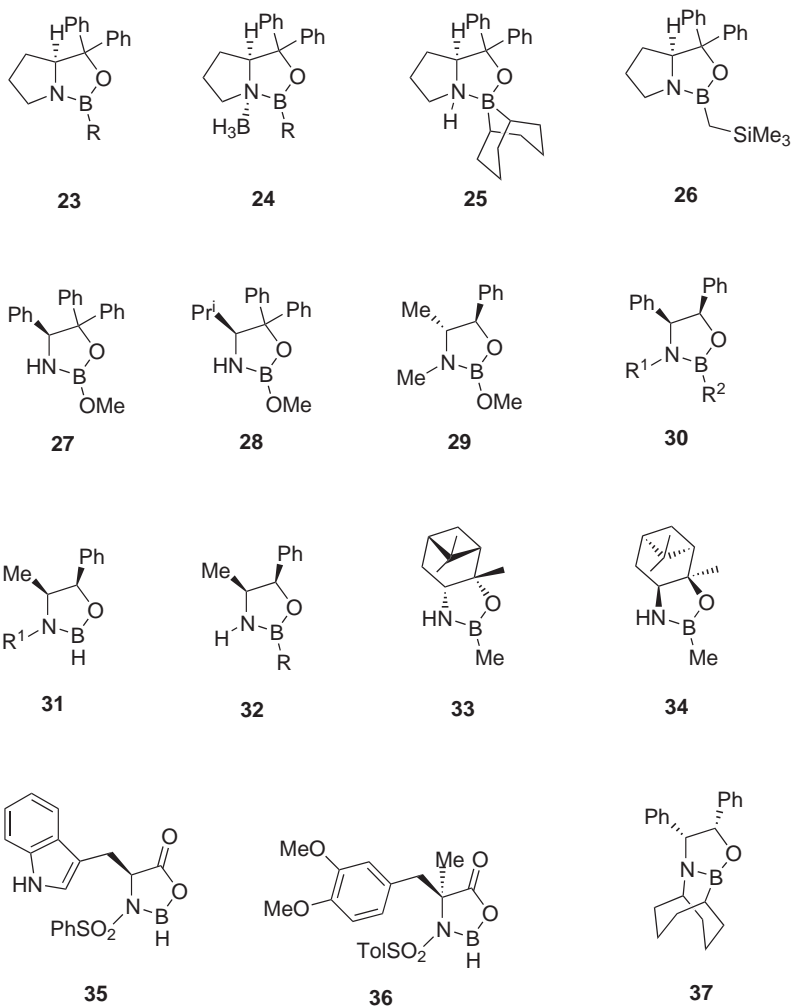


(16)

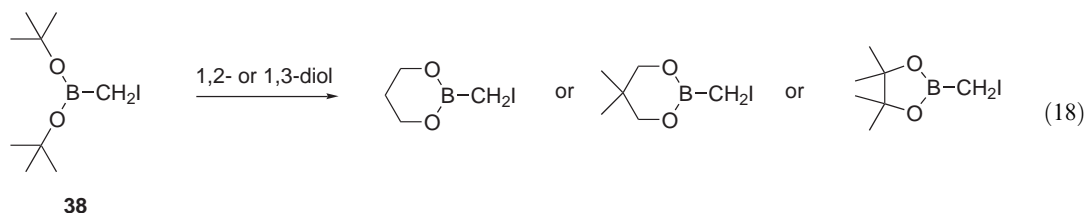
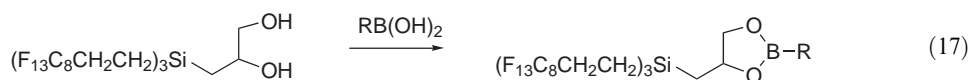
2.10.1.3.2 Reaction of alcohols with a borane derivative

Catecholborane **11** (Section 2.10.1.3.1) is also widely used as an alternative to borane and has been of prime importance in the development of synthetically valuable hydroboration processes <1998TL8479>. A new procedure has been described for its preparation that is both convenient and economical <2000OPRD550>. Tri-*O*-phenylene-bisborate is reacted with diborane in triglyme or tetraglyme at moderate temperature (70–80 °C). Catecholborane **11** can then be isolated by distillation. Borane–Lewis base compounds such as $\text{BH}_3 \cdot \text{SMe}_2$, $\text{BH}_3 \cdot \text{THF}$, or $\text{BH}_3 \cdot \text{NR}_3$ may be used in the process as alternatives to diborane, with or without solvent.

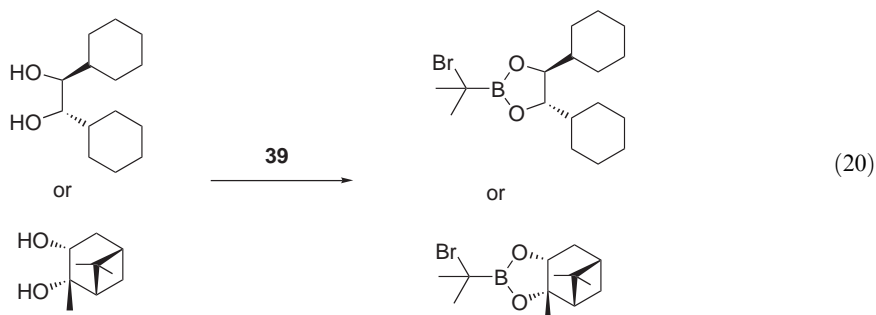
Oxaborolidines (oxazaborolidines) such as compound **23** and the analogs **24–37** are important compounds, which are used to catalyze the asymmetric reduction of prochiral ketones by borane <B-2000MI021, B-2001MI026, 1995T8363, 2002T1069>. These compounds may be prepared by the direct reaction between an aminoalcohol and a borane at an elevated temperature or by combining the aminoalcohol with the appropriate boronic acid with concomitant removal of water. New oxaborolidines **31**, formed from ephedrine ($\text{R}^1 = \text{Me}$) and norephedrine ($\text{R}^2 = \text{H}$), are converted to *B*-alkylated analogs **32** in one pot to give good to excellent yields of the oxaborolidine products <2003OL3447>. Oxaborolidine **37** and related analogs may be prepared by reacting 9-BBN-H with the corresponding azidoalcohol <2001ARKIVOC(4)43>. For optimum results the compounds must be kept dry, since partial hydrolysis of the oxaborolidine reagent results in lower product yields and enantioselectivities. If this is difficult then use of the boron complex **24** is an option. A new innovation that is successful for enantioselective reductions of prochiral ketones involves the generation of oxaborolidine **23** *in situ* at room temperature by the reaction between borane and (*S*)-5-phenylhydroxymethylpyrrolidin-2-one <2003T8411>. Examples of solid-supported oxaborolidine catalysts have been documented recently <2001T4637>.



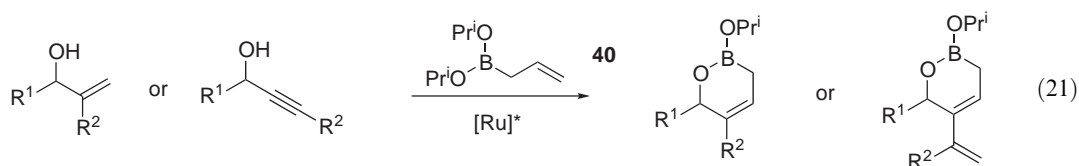
Arylboronic acids can be esterified successfully in high yield using the appropriate diol (Equation (17)) <2003T579>. Transesterification of an acyclic boronate triester with 1,2- or 1,3-diols provides a useful route to boronates <1998T10555, 1999JOM(581)51, 2000JOM(614-615)314>. For example, diisopropyl boronate **38** when reacted separately with 1,3-propanediol, 2,2-dimethylpropanediol, or pinacol gives the corresponding cyclic boronates (Equation (18)) <1997TL765>.



The cyclic boronate ester **39**, formed from 1,2-ethanediol, may be transesterified with other 1,2-diols to give alternative cyclic boronate ester products (Equations (19) and (20)) <2003JOM(680)100>. There are many examples of cyclic boronic esters that may be formed using the process of ring-closing metathesis <2002AG(E)152>.

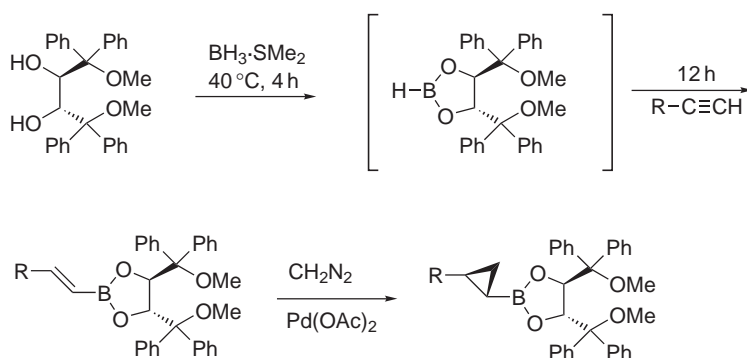


Transesterification of the unsaturated boronic ester **40** with allylic or propargylic alcohols gives the intermediate mixed boronic esters, that are trapped with Grubbs' catalyst <1997TL4757> to give annulated products (Equation (21)). Subsequent oxidation of the boronic ester products yields highly functionalized trisubstituted alkenes. A solid-supported version of the procedure using alkylsiloxane-linked beads has also proven successful <2001JCO312>.



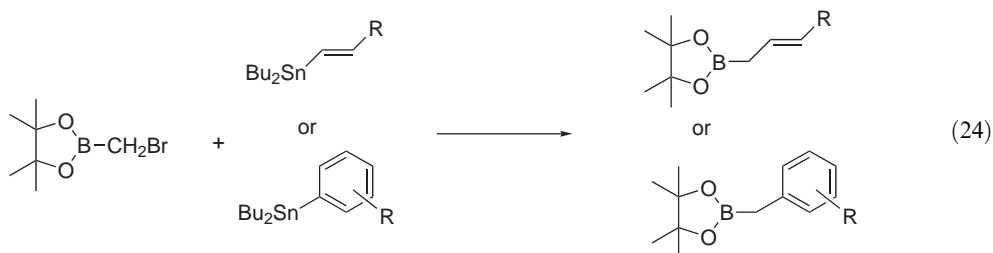
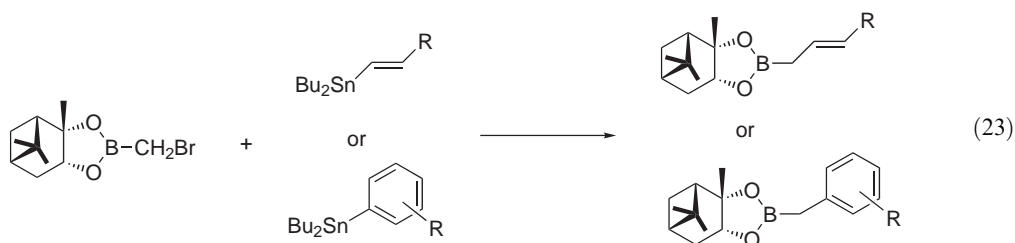
2.10.1.3.3 Reaction of an organometallic reagent with a borane derivative

Boronic esters are of wide applicability to organic synthesis <1998T10555>. Alkoxyboranes may undergo displacement reactions sequentially with organometallic reagents in a controlled manner as each subsequent displacement occurs less readily (Scheme 8). A recent example involves preparation of fluororous boronates in a one-pot procedure, first by reaction of the appropriate Grignard reagent with trimethyl borate ($\text{B}(\text{OMe})_3$) followed by transesterification with the fluororous pinacol **41** (Scheme 9) <2003T7879>.

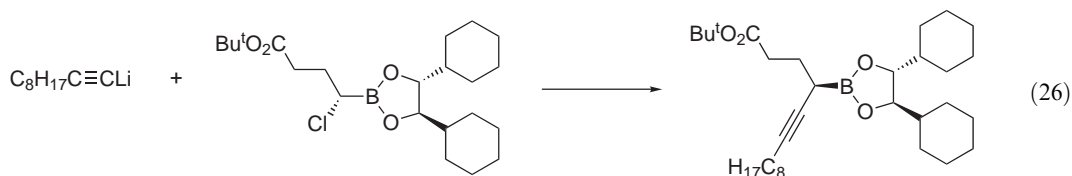
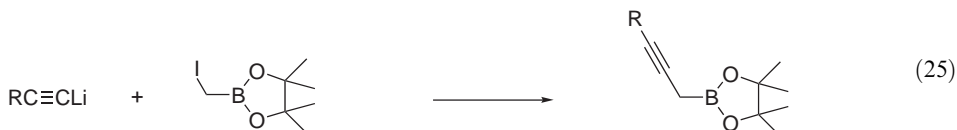


Scheme 11

The cyclopropanation process also works in a further novel way with dienyI boronate substrates to give synthetically useful *trans*-substituted 1-boranato-2-vinylcyclopropanes regioselectively [<2002TL2317>](#). Pinacol and pinanediol bromomethyl boronates react with aryl- and alkenylstannanes to give homologated benzylic and allylic boronate esters in moderate to good yields in a straightforward and reliable Pd-catalyzed coupling reaction (Equations (23) and (24)) [<1999TL5667>](#).

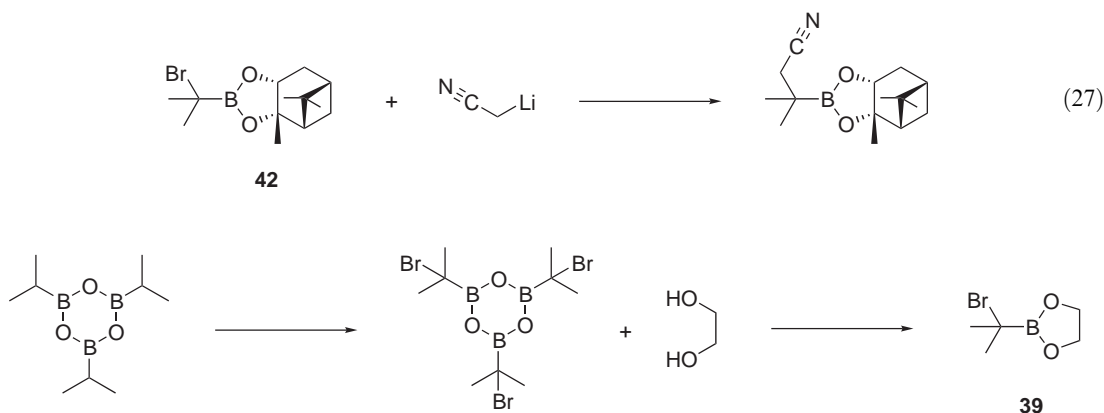


Propargylboronic esters can be prepared by reacting halomethylboronic esters with the appropriate alkynyllithium reagent (Equation (25)) [<1997TL765>](#). When a homochiral α -haloboronic ester is used, then the propargyl group may be attached with high stereoselectivity (Equation (26)) [<2000JOM\(614-615\)314>](#).



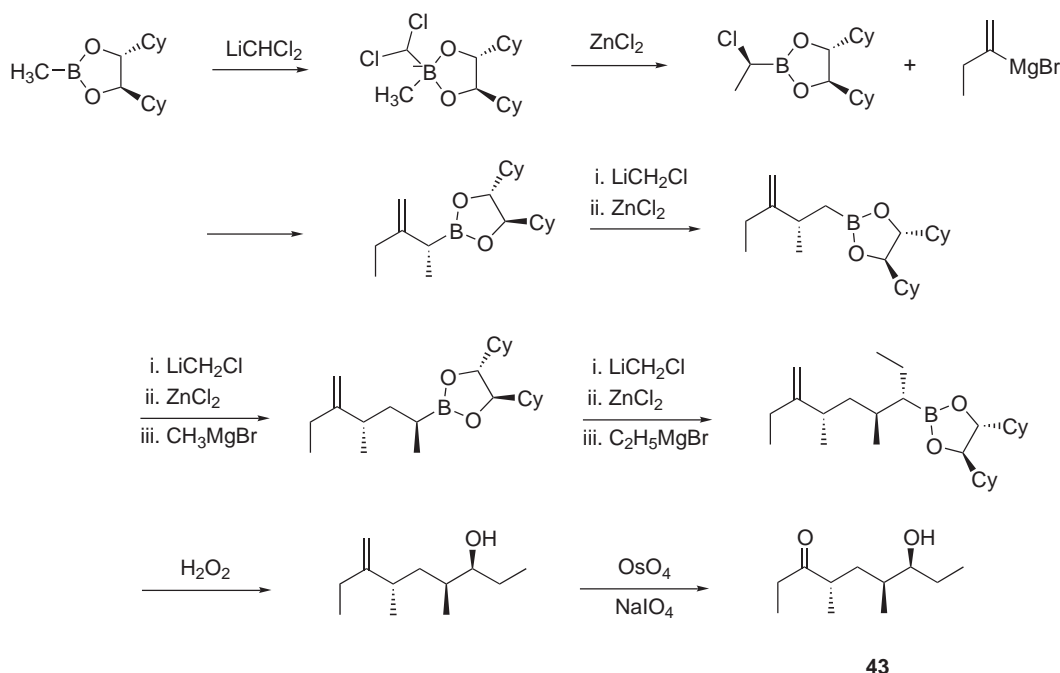
The α -bromoboronic ester **42** undergoes alkylation with lithioacetonitrile to give the tertiary product (Equation (27)) [<2003JOM\(680\)100>](#). The alkylation fails or gives dioxaborinane side-products with other bromoboronic ester substrates. As with other α -haloboronic esters, the

derivatives **39** cannot be prepared by direct α -bromination. A useful alternative exploits triisopropylboroxine, which is tribrominated quantitatively in the absence of solvent via a radical reaction that proceeds in normal fluorescent room light (Scheme 12) <2003JOM(680)100>.



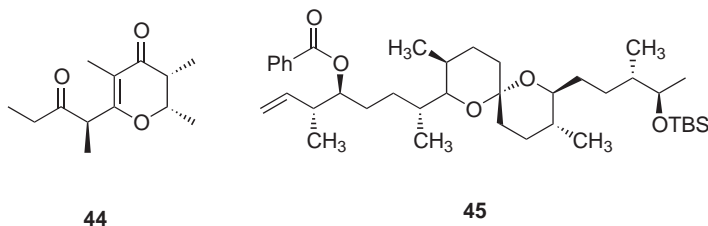
Scheme 12

Matteson's dihalomethylithium insertion methodology has been used frequently for the stereocontrolled construction of key fragments in organic syntheses <B-1995MI002, B-1997MI010, B-2001MI026, 1998T10555, 1999JA6355, 2000JOC6650, 2000JOM(614-615)314, 2003PAC1249>. The process involves reaction of dichloromethylithium with alkyl dialkoxyboranes to form the "ate" complex in which the carbon atom migrates to displace the first chlorine in a stereospecific fashion. The presence of zinc chloride is pivotal to the stereocontrol inherent in the process <B-1995MI002, 1998T10555>. The second chlorine atom may be displaced using an organometallic reagent and the elongation repeated a number of times to give *S*-alkyl chains of high stereochemical purity. The process is illustrated by the synthesis of serricornin **43** where the dihalomethylithium insertion procedure is performed four times sequentially (Scheme 13) <1998JOC4466>.

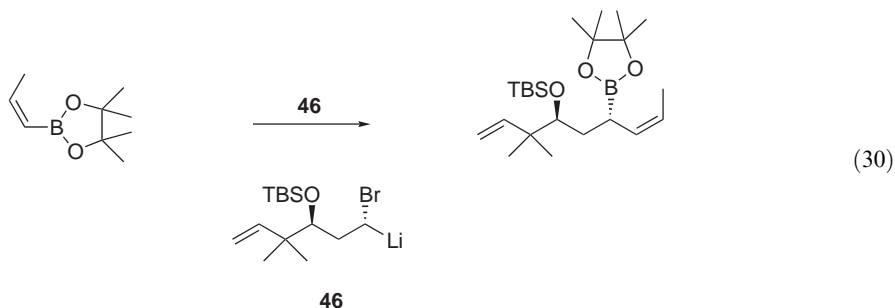
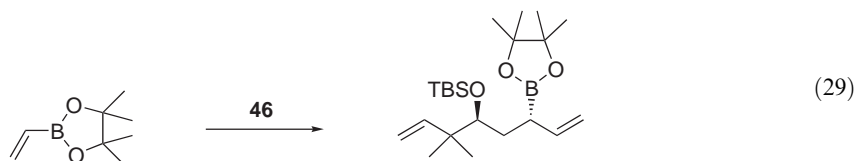
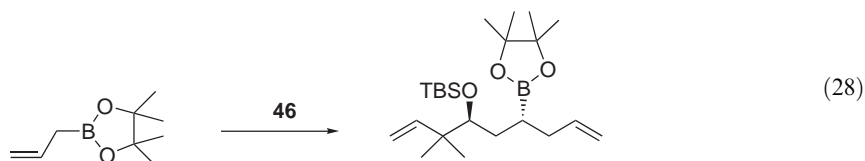


Scheme 13

Even though it is an apparently lengthy procedure to connect the four stereogenic centers (one in each chain extension step), the overall yield of product is high (35%) because of the high efficiency of each insertion. Other notable examples where these methods have been applied in total synthesis include stegobinone **44** <1996JA4560> and the major C1 to C21 fragment **45** of tautomycin <1996JOC3106>.



Allyl and vinyl boronates react with the stereochemically pure alkyllithium reagent **46** to give the homoallyl and allyl products (Equations (28)–(30)), which may be isolated. Oxidation with triethylamine-*N*-oxide gives the secondary alcohols, which are then reacted further with benzaldehyde to give addition products <1995TL4595>.

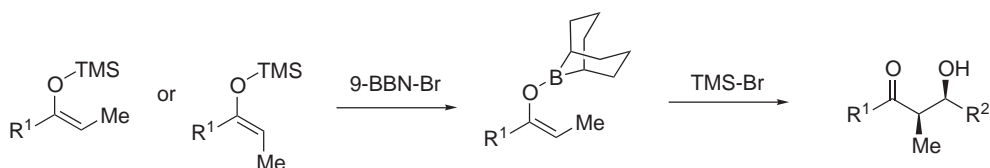


2.10.1.3.4 Reaction of an organoborane with an aldehyde or ketone

Asymmetric reduction of aldehydes and other carbonyl-containing substrates is a process that has been extensively studied <B-1996MI007, B-2000MI023, B-2001MI026, 1999JOC721, 2002JOC5315>. The intermediate borinates are normally converted to the product alcohols directly by oxidation.

Bis(pinacolato)diboron **13** undergoes Rh-catalyzed 1,4-addition reactions with α,β -unsaturated ketones, aldehydes, and other electron-deficient alkenes <2002TL2323>. The usual direct methods for enolization of ethyl ketones (R_2BOTf , Pr^i_2NEt) to their (*Z*)-enolates are ineffective for sterically hindered ketones (Section 2.10.1.3.5). Transmetalation of enoltrimethyl silanes of mixed double bond configuration using *B*-bromo-9-BBN gives the (*Z*)-boron enolate in which high levels of *syn* selectivity are supported during aldolization of sterically hindered ethyl ketones (Scheme 14) <1995TL9245>. Efficient synthesis of a series of *B*-iododialkyl- and *B*-alkyldiiodoboranes as their acetonitrile complexes can be achieved by treating the corresponding

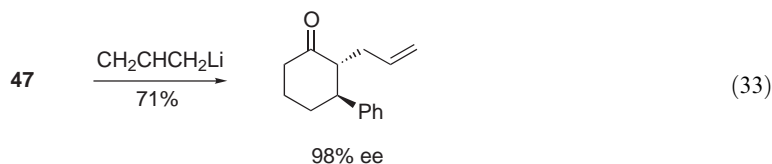
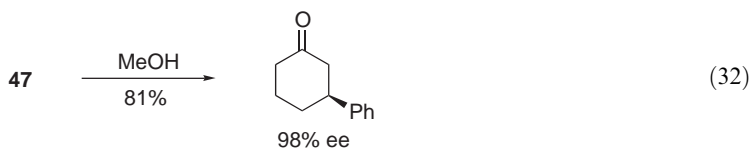
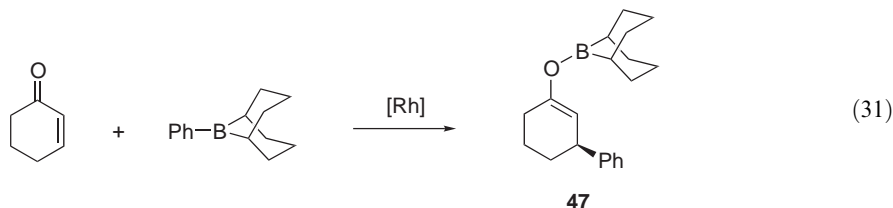
chloro- and bromoboranes with NaI or KI in acetonitrile. The *B*-(cyclohexyldiiodo)borane–acetonitrile complexes are then able to convert ethyl ketones to the (*Z*)-enolates, which give *syn*-aldol products exclusively and in high yield on aldolization with a series of aldehydes <2002HCA3027>.



Scheme 14

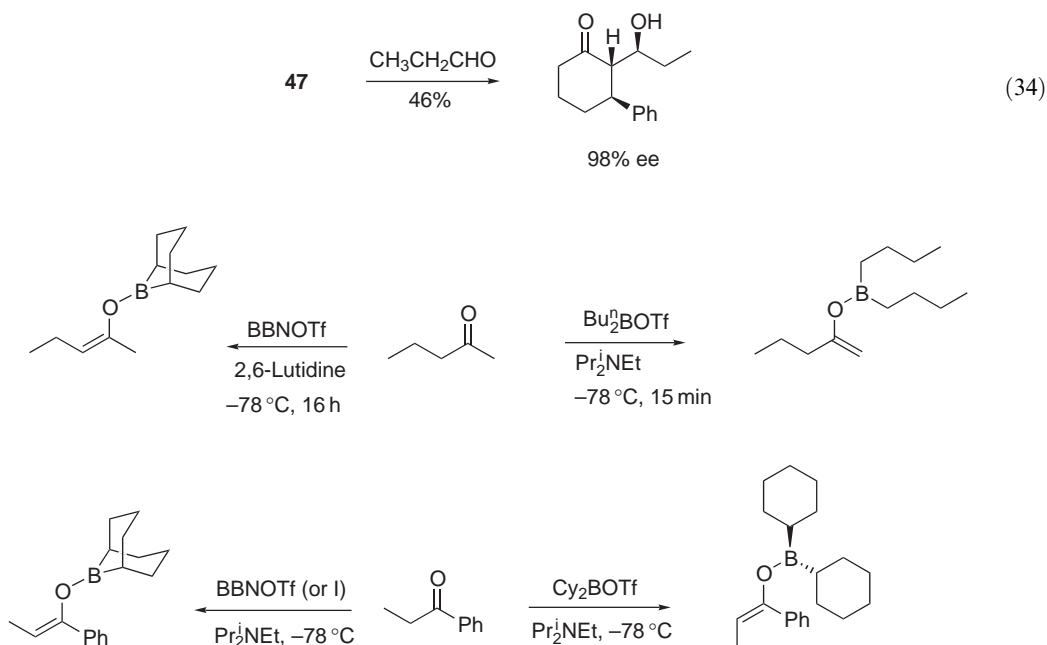
2.10.1.3.5 Miscellaneous methods

The aldol reaction is of great importance in organic synthesis <1996TL4911, 1999T8609, 2000AG(E)44, 2003JA10893>. It allows formation of a C—C bond with concomitant generation of two new stereocenters giving rise to four possible products: a pair of *syn*-stereoisomers and a pair of *anti*-stereoisomers. The selective formation of any one of these four stereoisomers constitutes an asymmetric process <B-1995MI002, B-1996MI004, B-1996MI005, B-2000MI023, 1995CRV2041, 1998CEJ1137, 1999CEJ1959, 2000AG(E)1352, 2002CEJ37>. Boron enol ethers (vinylxyboranes) remain central to the asymmetric aldol reaction although silylenol ethers are increasingly very effective <2002JCS(P1)447> (Section 2.10.2.3). There are many examples of asymmetric aldol reactions that employ such boron enolates <B-1995MI002, 1997OR1, 1999JCS(P1)1003, 2002TL4737, 2002OL391, 2002TL6005> with solid-supported variants now in evidence <1998T14999, 1998TL2655, 2002OL2473, 2003OL35>. The boron enol ethers that are generated are not usually isolated but used directly after the enolboration in the aldolization. One of the recent examples involves the generation of boron enolate **47** by Rh-catalyzed asymmetric 1,4-addition of *B*-aryl-9-BBN to 2-cyclohexenone to give a high yield of boron enolate (Equation (31)) from which the 2-substituted-3-phenylcyclohexanone products are obtained with perfect regio- and stereochemistry (Equations (32) and (33)) <2003JOC1901>.



When aldolization is performed using acetaldehyde, the aldol product is isolated in 46% yield but in 98% ee (Equation (34)). The first boron enolate-mediated, diastereoselective aldol reactions to be carried out in aqueous solution have been reported and involve the use of catalytic amounts of boronic acids as boron source <2002T8263>. Stereoselective synthesis of *syn,syn*-2-methyl-1,3-diols can be achieved through a one-pot aldol-reduction sequence if the aldolization procedure is concluded by reduction of the boron aldolate by LiBH₄ <2002TL6145>. The most successful

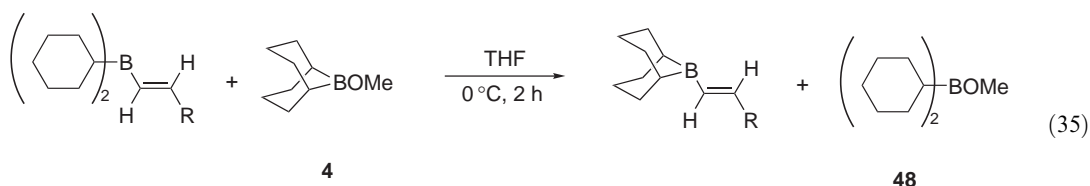
class of reagents for enaloboration is the combination of a dialkylboron triflate with a tertiary amine <1995COFGT(2)513, B-1995MI002, B-1996MI004, B-1996MI005, 1997OR1>. The correct choice can ensure complete regioselectivity in many cases (Scheme 15). The reaction conditions can be selected to control the geometry of the boron enol ether and a substantial amount of work has been carried out on subsequent reactions with aldehydes and ketones. If geometrically pure boron enol ethers can be generated in the enaloboration step then the subsequent aldolization proceeds with very high and predictable stereochemical outcome. Minor changes to the enaloboration step can play a very important role in favoring the stereochemistry (*E*) or (*Z*) at the double bond of the boron enol ether <2002TL6005> (Scheme 15).



Scheme 15

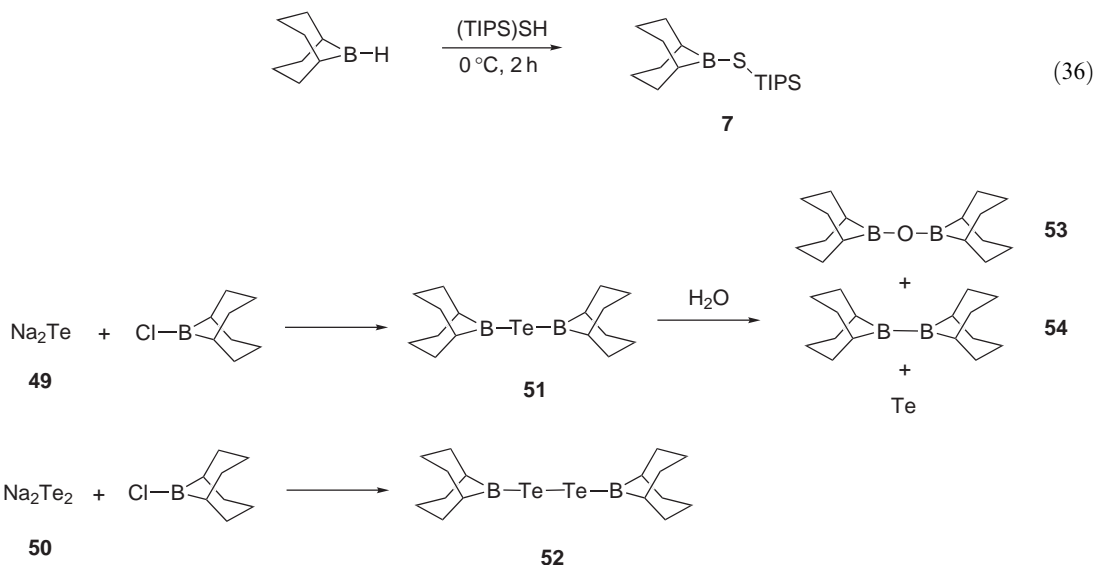
The optimum conditions of base and diborane source for a given target enolate have been well established for sometime <1997OR1>. Of particular value is the combination of dicyclohexylboron triflate (Cy_2BOTf) or iodide (Cy_2BI) as borane sources with diisopropylethylamine (Pr_2NEt) as the base. *B*-Iododialkyl and *B*-alkyldiiodoboranes have been recently studied in the context of enaloboration–aldolization of ethyl ketones (Section 2.10.1.3.4) <2002HCA3027>. *B,B*-Dihaloalkylboranes have been reported to convert ethylketones to their (*Z*)-enolates, predominantly, and provide essentially pure *syn*-diols when reacted with aldehydes <1997TL769> whereas *B,B*-dihaloterphenylboranes give the *syn*-diols stereoselectively <1997TA1379>. The enantioselectivities of aldol reactions between aldehydes and *B,B*-diisopinocampheyl borinates formed from methyl ketones depend on the steric requirements of the R group of the methyl ketone <1996TL4911>.

B-9-BBN-substituted alkenes, which are tricky to prepare from 1-alkynes by hydroboration directly using 9-BBN-H, are accessible by an exchange process whereby *B*-MeO-9-BBN **4** is converted to dicyclohexylmethoxyborane **48** with retention of configuration in the alkene (Equation (35)) <1998CC1225>.



2.10.1.4 Alkylboranes with a B—S, B—Se, or B—Te Bond

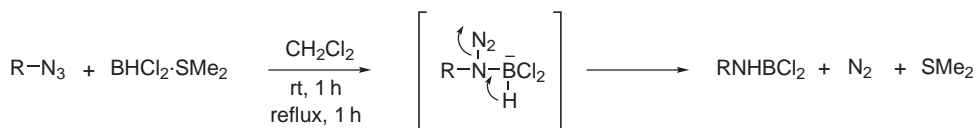
Compounds of this type may be formed by reaction between an aminoborane and a lithiated thiocatechol <2000NJC115>. *B*-(TIPS)S-9-BBN **7** with its covalent Si—S—B arrangement of atoms is a useful starting material for synthesis of *B*-alkylated-9-BBN derivatives <2000TL3537> via intermediate “ate” complexes (Section 2.10.1.1.3.2). It is readily prepared from 9-BBN-H and (TIPS)SH (Equation (36)) <1994TL3221>. Since the publication of COFGT (1995) <1995COFGT(2)513>, the first alkylborane compounds with a boron—tellurium bond have been described <1995CB87>. Sodium tellurides, **49** or **50**, formed by reacting tellurium with sodium triethylborane, react with *B*-chloro-9-BBN to form the respective tellurides **51** and **52** (Scheme 16). Reaction of telluride **51** with water produces boranes **53** and **54** together with elemental tellurium.



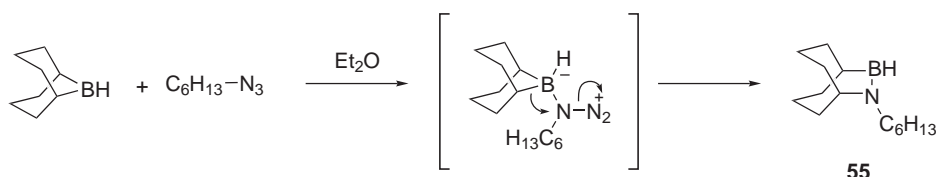
Scheme 16

2.10.1.5 Alkylaminoboranes and Related Compounds with a B—N Bond

The reduction of azides provides a useful route to primary amines in organic synthesis as attachment of the azide group can be carried out with regio- and stereochemical control <1995T12821>. Unlike catalytic hydrogenation and borohydride reduction, use of $\text{BHCl}_2\cdot\text{SMe}_2$ in noncoordinating solvents such as dichloromethane allows chemoselective reduction of alkyl azides, including tertiary azides, in the presence of C—C double bonds, esters, nitriles, and halides <1995TL7987>. Alternatively, chemoselective hydroboration of C—C double bonds in the presence of azides is achievable using $\text{BH}_3\cdot\text{THF}$ demonstrating the complementary use of these borane reagents <2002T10059>. Formation of a B—N bond, hydride migration, and elimination of N_2 gives the aminoborane products (Scheme 17). Subsequent reduction is achieved by hydrolysis and neutralization giving amine products in 75–95% isolated yields. Reaction of *n*-hexyl azide with 9-BBN-H, which is normally an excellent reducing reagent, failed to give hexylamine but instead gave the secondary amine **55** (Scheme 18).



Scheme 17



Scheme 18

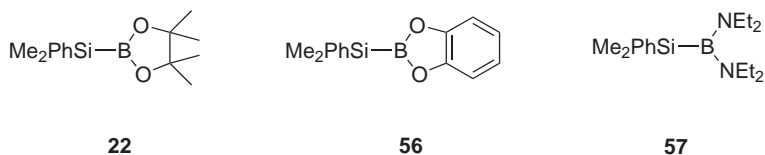
Bis(dialkylamino)cyanoboranes of the general formula $(R_2N)_2BCN$ are prepared by reacting boron trichloride with the appropriate secondary amine (2 equiv.) and TMSCN (1 equiv.) at room temperature <2002CC1392>. These cyanoborane products are highly efficient reagents for Strecker-type cyanation of aldehydes and ketones. Tetracoordinate amine-boranes may be formed by a variety of different methods that have recently been reviewed <1999T1197>. For example, reaction of an ammonium carbonate with lithium or sodium borohydride as borane source is a convenient method for synthesis of this class of compounds.

2.10.1.6 Alkylboranes with a B—P, B—As, B—Sb, or B—Bi Bond

Tetracoordinate phosphine-boranes may be formed by a variety of different methods that have recently been reviewed <1999T1197, 1999TL2283>. Boranophosphate nucleotides <2002MI581> have been prepared as have oligonucleotides with a boranophosphate backbone, which display interesting molecular recognition properties <1997TL4957, 1998TL3899>.

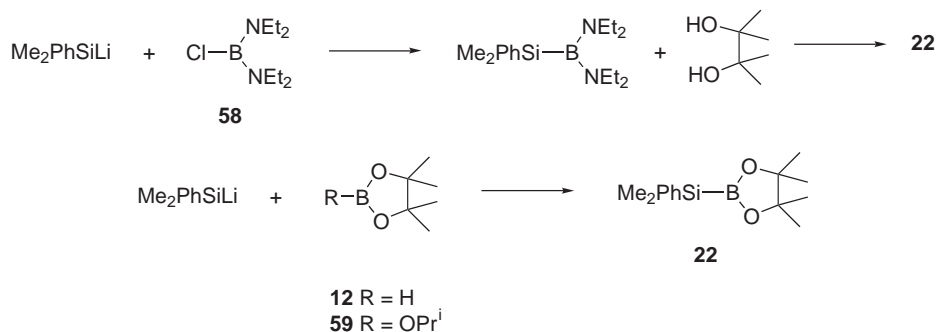
2.10.1.7 Alkylboranes with a B—Si Group

Alkoxyboranes such as (dimethylphenylsilyl)pinacol borane **22**, and the catechol **56** and bis(dimethylamino) **57** derivatives are an important class of compounds that have been used for stereocontrolled, transition metal-catalyzed silaboration of alkenes, alkynes, and allenes (Section 2.10.1.3.1).



Synthesis of alkoxyborane **22**, for example, is possible by two routes (Scheme 19) <1999T8787, 2000OM4647>.

Reaction of dimethylphenylsilyllithium with the chloroborane **58**, followed by displacement of the diethylamino groups by pinacol gives the alkoxyborane **22**. Alternatively, pinacol borane **12** or its *B*-isopropoxy derivative **59** is silylated to form compound **22**.



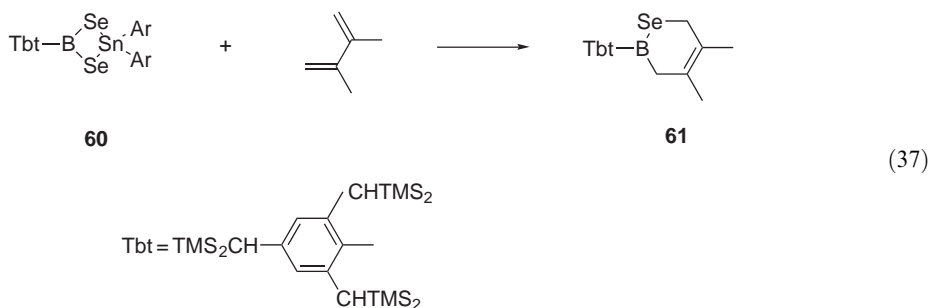
Scheme 19

2.10.1.8 Alkylboranes with a B—B Bond

The borylating agent bis(pinacolato)borane **13** is a valuable reagent that has been used for efficient and regiospecific reaction with unactivated C—H bonds to give functionalized alkanes (Section 2.10.1.3.1) <2003JOM(680)3>. The related bis(catecholato)borane has also been used in transition metal-catalyzed hydroborations of unsaturated C—C bonds <1997T4957>.

2.10.1.9 Alkylboranes with a B—Metalloid Bond (Other Than Si or B)

Because boron atoms prefer planar, tricoordinate geometry, small ring compounds that contain boron have a large ring strain and are therefore quite reactive. For example, 1,3,2,4-diselenastannaborene **60**, which contains a novel four-membered boracycle, undergoes reaction with 2,3-dimethyl-1,3-butadiene to give the six-membered selenaboracycle **61** (Equation (37)) <1998CC2495>.

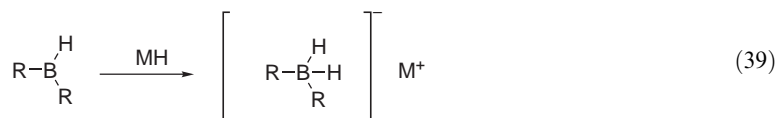
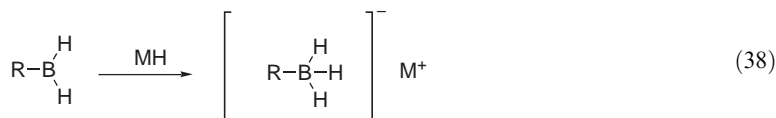


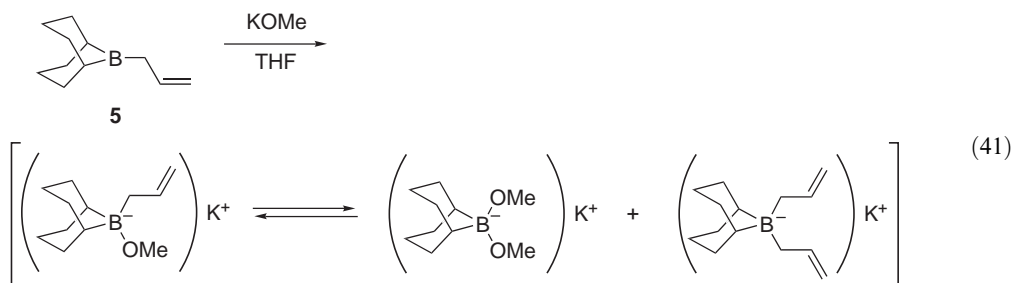
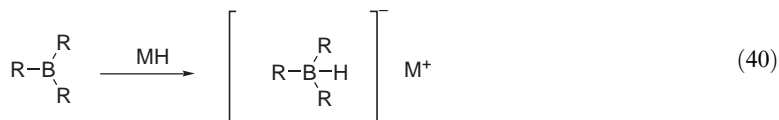
2.10.1.10 Alkylboranes with a B—Metal Bond

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)513>.

2.10.1.11 Alkylboranes with Boron Having a Coordination Higher Than 3

There are a number of commercially available, tetracoordinate hydroborates that are frequently used for hydride reductions in organic synthesis <B-1995MI001, B-1996MI007, 1995COFGT(2)513, 1998OR395, 1998TL8425, 2001TA2225>. They are formed by the reaction of an alkylborane with a hydride donor (Equations (38)–(40)) and although stable in solution for sometime, exposure to air can cause these reagents to decompose violently. The first trifluoromethyl- and pentafluoroethylboronic esters have recently been prepared via the tetracoordinated potassium and triethylammonium boronate salts (Scheme 10) (Section 2.10.1.3.3) <2003TL8273>. Reaction of *B*-allyl-9-BBN **5** with potassium methoxide gives a mixture of tetracoordinate alkyl borates of which the monoallyl borate predominates (Equation (41)) <1999JOM(576)147>. When this mixture is prepared *in situ* and reacted with aryl halides and triflates, good-to-excellent yields of allylated aryl products are obtained in Pd-catalyzed Suzuki–Miyaura cross-coupling reactions <1995CRV2457, 1998T263>.





2.10.2 ALKYL SILICON DERIVATIVES

The options for the synthesis and application of functionalized alkylsilicon compounds have increased considerably since the publication of COFGT (1995) <1995COFGT(2)513>. Most of the alkylsilicon compounds mentioned in this chapter are commercially available and procedures for the preparation of these and many others have been documented <B-1995MI001, B-1995MI002, B-1995MI003, B-1996MI006, B-1998MI014, B-1999MI016, B-1999MI019, B-1999MI020, B-2000MI021, B-2000MI022, B-2001MI024, B-2001MI025, B-2004MI028, 1995CRV1009, 1997CRV2063>.

Although they play more than just a spectator role in organic synthesis <1995CRV1293, 1998JCS(P1)2377>, organosilicon compounds are ubiquitous protective groups <B-1999MI019, 2001JCS(P1)2109>. Selective strategies for their introduction and removal <1996S1031> have been tabulated with new strategies and improvements being made all the time <1996CC2351, 1997TL1873, 1998TL327, 1998TL2495, 2000JCS(P1)2305, 2003TL4689>. The use of alkylsilicon compounds has advanced in several areas of organic synthesis including catalytic and stoichiometric asymmetric synthesis <B-1999MI019, B-2001MI025, 1998TL2711>. Organosilicon functionalized supports, including some that are recyclable <1997JOC6183>, find use in solid-supported synthesis of different classes of compounds including oligosaccharides <1995SCI202>, peptides <2001TL5629>, and oligonucleotides <1996USP5589586, 1997TL1651>. Organosilicon linkers, especially those that are traceless, find application in the construction of smaller molecules and combinatorial libraries <1997COS216, 1997JOC6102, 1998JCS(P1)3293, 1998T15385, 1998TL2711, 1999T4855, 2000CRV2091, 2000T515, 2001JA4356, 2003CRV893>. Polymer-supported, highly enantioenriched allyl silanes augment the plenty solution-phase techniques for asymmetric synthesis <2001JA4356>.

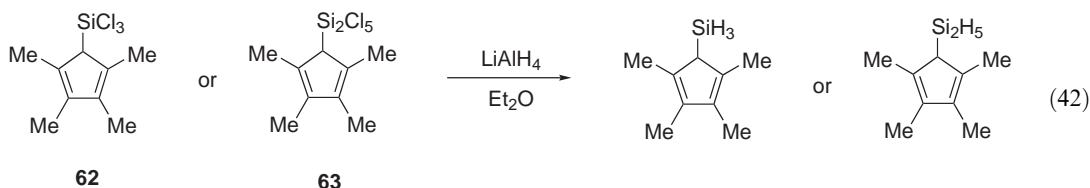
The ability of alkylsilicon groups to act as hydroxyl precursors has enhanced their usefulness and versatility in organic synthesis <1996T7599, 1997CRV2063>. Oxidative conversion of the Si—C bond to an Si—O bond occurs via rearrangements of the intermediate silyl peroxides. By combining the nucleophilicity of allyl silanes with the Si—C to Si—O annulation process, stereochemically defined cyclopentanol, oxetanes, and tetrahydrofurans with hydroxyl functionalization are accessible <2001T2635>.

2.10.2.1 Alkyl Silanes

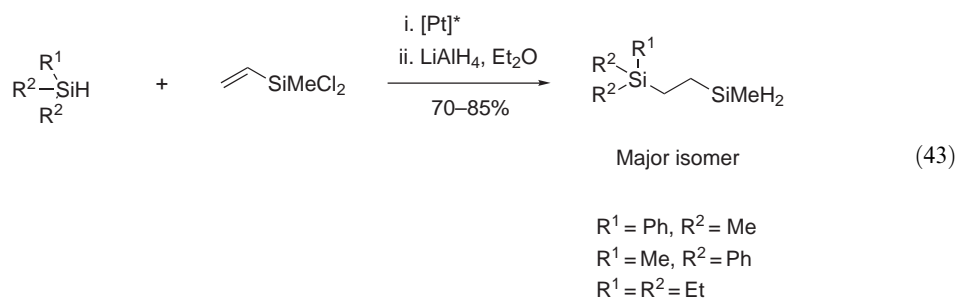
2.10.2.1.1 Hydridosilanes

Compounds that contain Si—H bonds (hydrosilanes) are prepared by the reaction of proton sources such as aqueous acids with compounds that contain a silicon–metal bond, e.g., metal silicides <B-1996MI006, B-2001MI024, 1995COFGT(2)513>. Although silane SiH₄ and its higher catenates Si₂H₆ and Si₃H₈ are of little significance in organic synthesis, the alkylhydridosilanes by contrast are of particular importance. Another main route to hydridosilanes that works well in the laboratory is reduction of the chlorosilane precursor using LiAlH₄, although it is still not possible to achieve selective reduction of di- and trichlorosilanes <B-1996MI006, B-2001MI024, 1995COFGT(2)513>.

[2000CC437](#)>. Lithium hydride provides an alternative hydride source for the reduction of reactive silanes such as allyltrichlorosilane that can polymerize in the presence of AlCl_3 formed from LiAlH_4 . Recently reported cyclopentadienyl trichlorosilanes and disilanes [62](#) and [63](#), for example, are reduced in diethyl ether, otherwise AlCl_3 -catalyzed redistribution occurs to release silane SiH_4 , which is extremely pyrophoric in air ([Equation \(42\)](#)) [<2001JOM\(620\)20>](#).



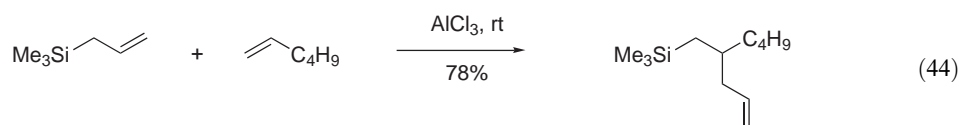
Hydrosilylation of allyldichloromethylsilane gives a mixture of major and minor isomers, which on hydride reduction gives a reasonably good yield of the hydridosilanes ([Equation \(43\)](#)).



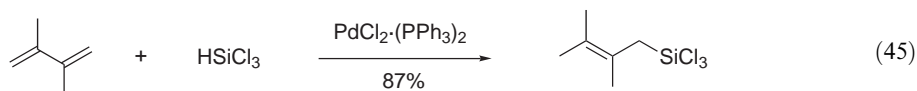
Alkyl hydridosilanes such as phenyl- (PhSiH_3), triethyl- (Et_3SiH), triphenyl- (Ph_3SiH), dimethylphenyl- (Me_2PhSiH), methyldiphenyl- (MePh_2SiH), *t*-butyldimethylsilane ($\text{Bu}^t\text{Me}_2\text{SiH}$), and *t*-butyldiphenylsilane ($\text{Bu}^t\text{Ph}_2\text{SiH}$) are of major importance in hydrosilylation and in ionic hydrogenation [<B-1999MI016, B-2001MI025, 1996AG\(E\)1968, 1997JA5499, 1998TL4627, 2000JOC3090, 2000T2779, 2001JOM\(624\)367, 2002T8247, 2003OL3085>](#). Of these, dimethylphenylsilane (Me_2PhSiH), which is a precursor to higher-order silylcyanocuprates ([Section 2.10.2.9](#)), is commercially available and inexpensive [<B-1995MI003>](#). This reagent has been used recently in the first examples of hydrosilylation that use a gold complex for regio- and chemoselective reduction of aldehydes and aldimines [<2000CC981>](#). As an alternative to hydrolytic cleavage of trityl-protected alcohols, use of Et_3SiH in the presence of a catalytic amount of TES- or TMS-triflate is effective and compatible with a variety of acid-sensitive functional groups [<2003OL153>](#). When Et_3SiH is used as reductant together with a transition metal, catalytic hydrosilylation of alkynes can be carried out at room temperature in water to give alkenes in high yield with good-to-high regio- and stereoselectivities [<2003CC1668>](#). Radical-based reducing agents are highlighted in a new review of the area [<B-2004MI028>](#). Among the reagents of proven synthetic utility as radical-based reducing agents are tris(trimethylsilyl)silane (TTMSS) ([Section 2.10.2.8.1](#)), tris(alkylthio)silanes, phenyl silane, diphenyl silane, triphenyl silane, and triethyl silane in the presence of thiols [<1995COFGT\(2\)513>](#). Silylated cyclohexadienes that may be prepared on a large scale have recently been used as radical hydrosilylating agents for nonactivated alkenes, alkynes, aldehydes, and ketones [<2002HCA3559>](#).

2.10.2.1.2 Tetraorganosilanes

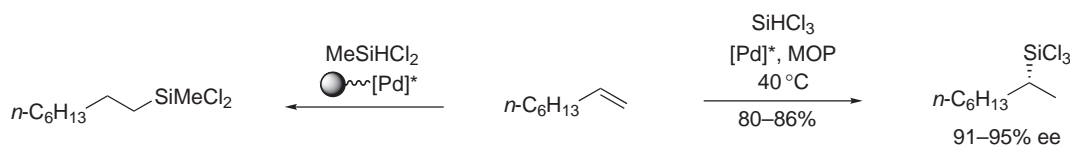
Several methods for the preparation of tetraorganosilanes exist [<B-1996MI006, B-1998MI014, B-2000MI022>](#). A novel aluminum chloride-catalyzed addition of allyltrimethyl silane to unactivated alkenes involves regiospecific attachment of the silyl group to the terminal carbon ([Equation \(44\)](#)) [<1995OM2361>](#).



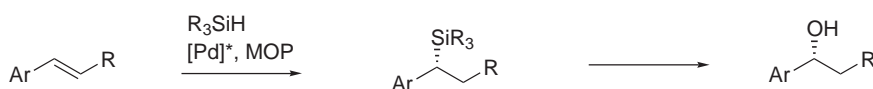
In the presence of trimethylsilyl chloride as activator a second molecule adds to give chain extension products formed from 1,5-hydride shift in a silylenium ion intermediate <1998OM2409>. Hydrosilylation of alkenes and alkynes can be achieved under a variety of conditions <2003CC1668>. Although the process may be initiated thermally using high pressures, it is more convenient to use catalysts such as radical initiators, Lewis acids, or transition metals <B-1999MI016, B-2001MI025, 1999JOM(582)70, 2001JCS(P1)1452>. For example, Pd-catalyzed hydrosilylation of 2,3-dimethylbutadiene gives the silylated product of terminal addition (Equation (45)) <2003T7879>.



One of the most commonly used catalysts is hexachloroplatinic acid $\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$ (Speier's catalyst). With simple alkenes, the catalyst promotes terminal addition of the silyl group <B-1999MI016, B-2001MI025>. A solid-supported variant of this solution method uses macroporous styrene-divinylbenzene-divinylbenzyl chloride resins that are aminated with benzyltrimethylethylenediamine ligands, and loaded with Pt using KPtCl_4 <2002JCS(P1)1523>. This solid-supported catalyst is less active compared with soluble Speier's catalyst but still displays good hydrosilylating activity, and is of practical value giving minimal levels of substrate isomerization to yield the terminal silylated product when reacted with 1-octene. Hydrosilylations may be carried out asymmetrically on 1-octene and other alkene substrates using Pd as catalyst in the presence of a monodentate phosphine ligand (MOP) to give the internal addition products in both high yield and enantiomeric excess (Scheme 20) <1995BCJ713>. Similarly, hydrosilylation of styrene derivatives allows internal attachment of the silyl substituent (Scheme 21). Chiral alcohols are obtained in high yield and with good enantiomeric excess on oxidation (Section 2.10.2.3) <1995CC1533, 1995JA9101>.

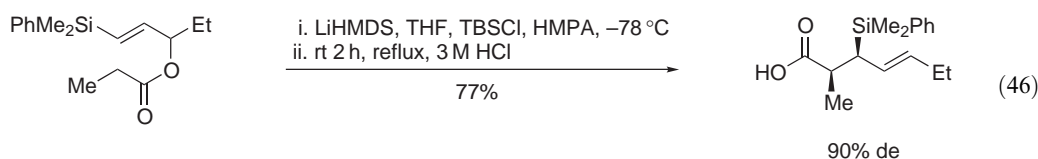


Scheme 20



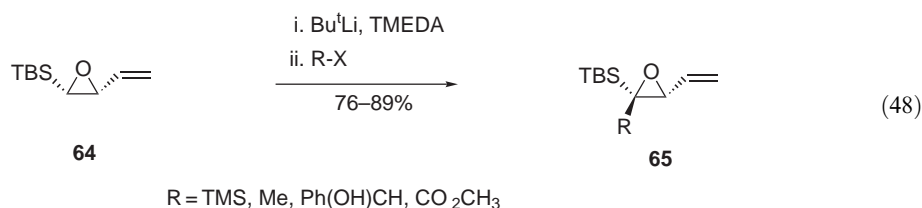
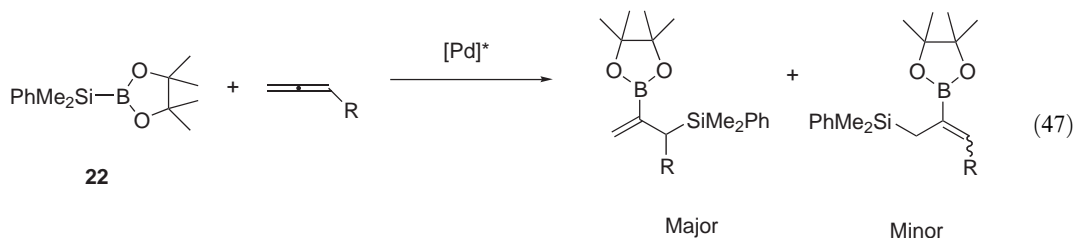
Scheme 21

Tetraorganosilanes can be formed in good yield and diastereomeric excess by Claisen rearrangement of vinyl and allyl silanes (Equation (46)) <1995T12821, 2003OBC4005>.



Silylboration of allenes has recently been described whereby Pd complexes catalyze the regioselective addition of (dimethylphenylsilyl)pinacol borane **22** to allenes in good yield <2003JOM4(680)43>. Regioselectivities and yields depend upon the metal catalyst used, the electron-withdrawing properties, and the pattern of substituents at the allene (Equation (47)); fluorinated alkyl groups give single isomers. Subsequent replacement of the boryl group selectively using iodobenzenes gives 2-phenylallylsilanes by a Miyaura–Suzuki coupling process <1995CRV2457>. Lithiation of the vinyloxirane **64** followed by C–C bond formation with

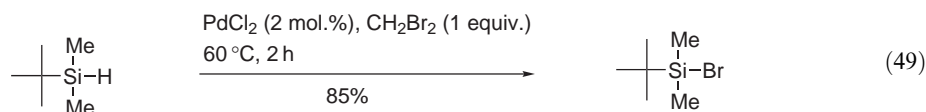
electrophiles gives new silylated vinyloxiranes **65** with retention of configuration (Equation (48)) <2003T9759>. The formation of five- and six-membered alkylsilicon heterocycles is a lively area that has been recently reviewed. Lower-coordinate silicon reagents (silylenes) are often employed for their synthesis <1998JCS(P1)2209, 1999JCS(P1)81>.



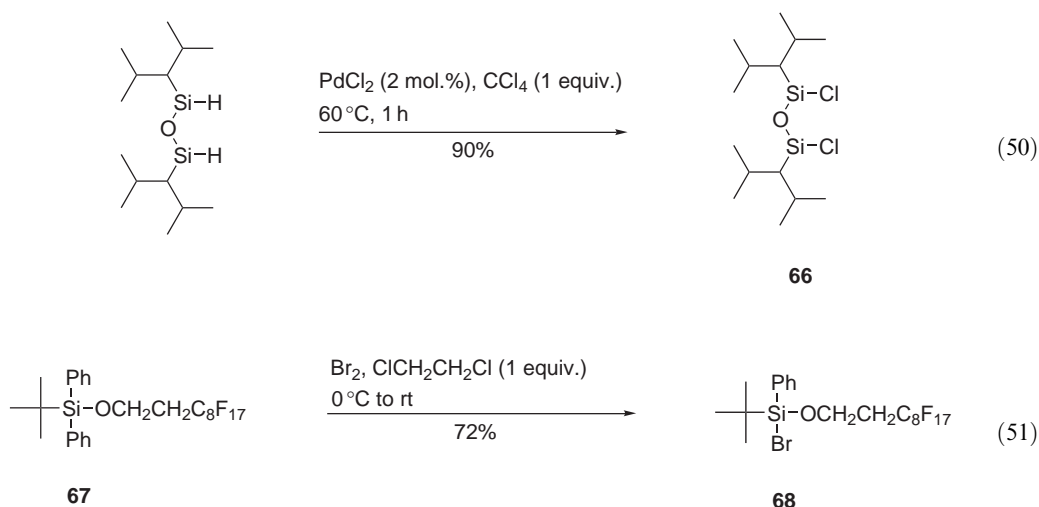
2.10.2.2 Alkylsilyl Halides

Dichlorodimethyl silane is produced industrially on a large scale as raw material for the preparation of a number of organodisilanes. Direct synthesis of organodichlorosilanes may be achieved using a copper catalyst by the reaction of metallic silicon and hydrogen chloride with an alkene or an alkyne, or alternatively by the reaction of metallic silicon with an alkyl chloride <2001JCS(D)71>. For example, metallic silicon is converted to dichlorodimethyl silane in 36% yield and 47% selectivity when reacted with HCl and ethylene in the presence of copper(I) chloride as catalyst. When isopropyl chloride is used together with metallic silicon and Cu(I)Cl, dichlorodiisopropyl silane is formed with high selectivity (85%) and silicon conversion (86%).

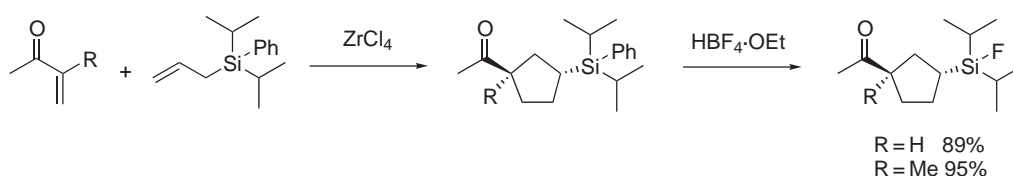
Catalytic asymmetric reduction of styrenes using Pd-MOP complexes and trichlorosilane gives high yields of the alkyl trichlorosilane products with high regio- and stereoselectivities <2001JOC1441>. Oxidation of these products provides a general and effective route to enantioenriched chiral alcohols. Alkyl silanes provide useful starting materials for the preparation of the corresponding alkylsilyl halides. For example, *t*-butyldimethylsilyl bromide can be prepared in good yield by the treatment of *t*-butyldimethylsilane with dibromoethane in the presence of a catalytic amount of PdCl₂ (Equation (49)) <1999TL1197>.



A similar procedure is very successful for the preparation of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane **66**, which is a reagent that is used extensively for the simultaneous protection of 5'- and 3'-hydroxyl groups in nucleoside and carbohydrate chemistry (Section 2.10.2.3). Treatment of 1,1,3,3-tetraisopropyldisiloxane with a catalytic amount of PdCl₂ in CCl₄ <1999TL1197> or with HCl gas in the presence of Pd on charcoal <2001EP1114824, 2002EP1173446> provides the product **66** (Equation (50)). Phosphonium chloride-catalyzed dehydrohalogenative Si—C bond coupling between alkyl chlorides (even when unactivated) and trichlorosilane or methyl-dichlorosilane provides good-to-high yields of alkyltrichloro- or alkyl-dichloromethylsilanes <2001JA5584>. Formation of the alkylsilyl fluoride is the outcome of fluoride-mediated deprotection of the corresponding silyl ether. The *t*-butyldiphenylsiloxane **67** undergoes brominolysis to give a good yield of the silyl halide **68**, which is employed as a fluorous protecting group (Section 2.10.2.3) for alcohols (Equation (51)) <1999TL5667>.

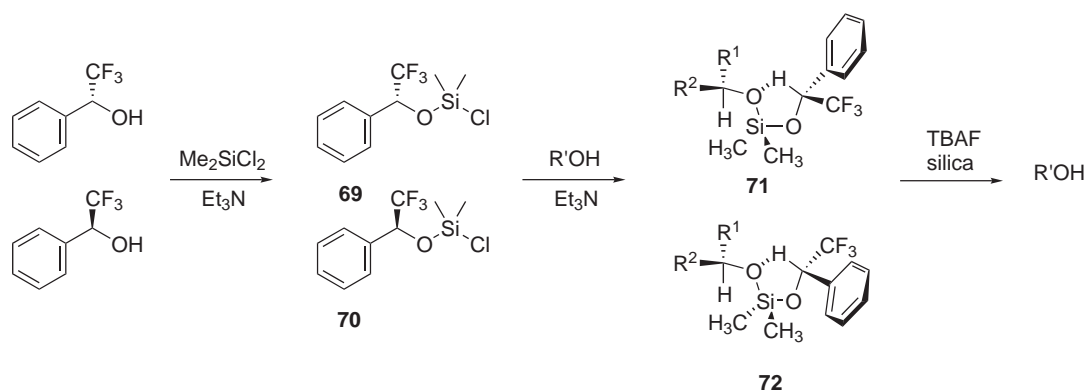


Use of the dimethylphenylsilyl (DMPS) and its derivatives as directing groups and masked hydroxyl groups is of great importance to organic synthesis and there exists a variety of different conditions for their installation and conversion to OH [<1996T7599, 1997CRV2063, 1998JCS\(P1\)2645, 1998JCS\(P1\)2651, 1998JCS\(P1\)2663, 1998JCS\(P1\)2673, 1998JCS\(P1\)2679, 1998JCS\(P1\)2687, 1998JCS\(P1\)2711, 1998JCS\(P1\)2733>](#). Alternatives to the DMPS group include triphenyl, dimethyltrityl, and triisopropyl silane [<2001T2635>](#). Where a two-step sequence is employed, protodesilylation using KF as the nucleophile gives initially the silyl fluoride, which may be isolated. Subsequent oxidation of the silyl fluoride gives the alcohol. It is more common to combine the two steps in a one-pot procedure without isolation of the silyl fluoride. The alkyldiisopropylfluorosilyl group Pr_2FSiR can be cleaved oxidatively under Tamao conditions [<1996T7599>](#) to give a hydroxyl group [<1998JCS\(P1\)3655>](#). Also with its bulky substituents, the reagent allyldiisopropylphenylsilane acts as a useful 2-hydroxy-1,3-dipole equivalent to give stereochemically defined cyclopentanes on ZrCl_4 -promoted [3 + 2]-cyclization with α,β -unsaturated ketones (Scheme 22) [<1998JCS\(P1\)2121>](#). Protodesilylation gives silyl fluorides that can be isolated in high yield. The corresponding secondary alcohols are formed after the follow-up oxidation step.



Scheme 22

A new set of alkylsilyl chloride reagents has been described for determining absolute stereochemistry and enantiomeric purity of secondary alcohols by proton NMR analysis [<2003OL1745>](#). Dichlorodimethyl silane is reacted separately with (*R*)- and (*S*)- α -(trifluoromethyl)benzyl alcohols to give chiral chlorosilanes **69** and **70**, which then react smoothly and quickly with mild base to give separately the silyl ethers (*R*)- and (*S*)-PhTFE **71** and **72** (Scheme 23). According to the general conformational model for the derivatives **71** and **72**, protons that show a $(\delta(R) - \delta(S))$ value <0 occupy the R^1 position and protons with $(\delta(R) - \delta(S))$ value >0 occupy R^2 . This silicon-based reagent approach is suited to elimination-prone and sterically hindered alcohols that are unsuccessful for ester formation in the advanced Mosher method. It allows straightforward derivatization and efficient recovery of the chiral alcohol using silica-bound TBAF.



Scheme 23

TMS iodide is one of the most reactive silylating agents (Section 2.10.2.3). Its synthetic potential as a strong electrophile, reductant, and Lewis acid has been more fully exploited in recent years <1995T11043, 1997TL6945, 2000BMCL2311, 2003TL4129>. It can be conveniently prepared from the cheaper TMS chloride *in situ* by mixing with sodium iodide in the presence of silica chloride <2002TL7139>.

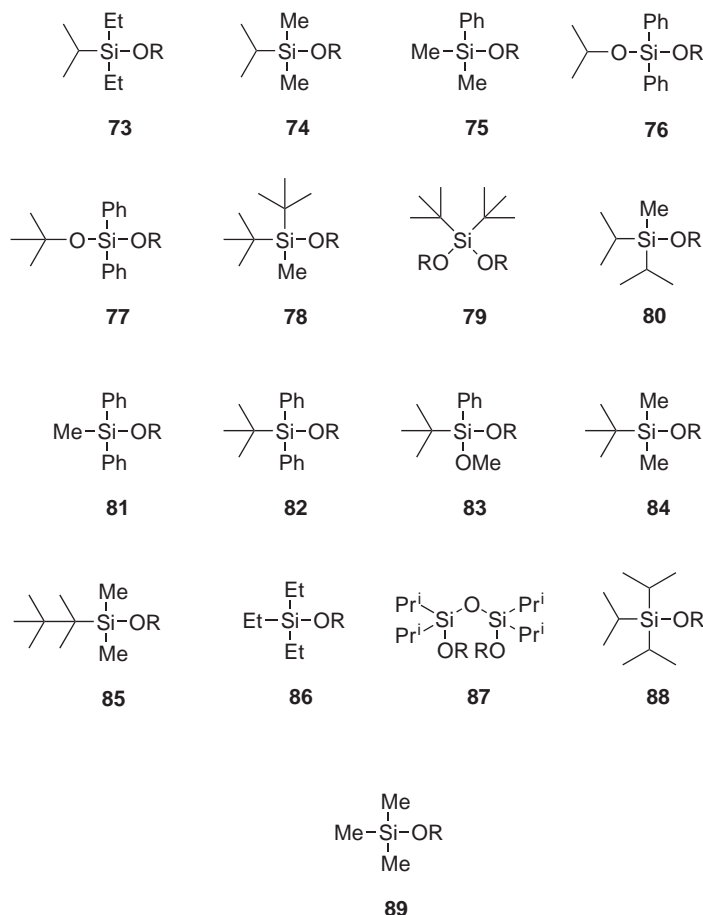
2.10.2.3 Alkylsiloxanes

Alkylsiloxanes play more than just a spectator role in organic synthesis. Silyl ether protecting groups are of such central importance to organic synthesis, especially to the synthesis of stereochemically complex natural products, that it is virtually impossible to undertake any major synthesis without their inclusion <B-1996MI008, B-1997MI013, B-2003MI027, 2003JA14294>. Silyl ethers may be formed by a variety of different methods that include reaction of an alcohol <B-1999MI017, B-1999MI018, B-1999MI019>, phenol <1998TL2495, 2003TL8819>, binaphthol <2000CC1029>, or carboxylic acid <2000PS71, 1998TL3349> with an electrophilic silylating agent, or by metal-catalyzed reduction of carbonyl compounds, which can often be achieved asymmetrically with high enantioselectivity <B-1999MI016, B-2000MI023, B-2001MI025>. Oxygen forms a stronger bond with silicon than any other element except fluorine with the Si—O and Si—F bond energies being 467 and 594 kJ mol⁻¹, respectively. Despite its strength the Si—O bond is readily broken hydrolytically or by fluoride ion, for which there are many and various convenient sources <B-1995MI001, B-1995MI003, B-1999MI019, 1995ACA31, 1996S1031, 1996T7599>. Desilylation of alkynes, for example, can be achieved using potassium fluoride in the absence of solvents and in good-to-excellent yields with microwave irradiation reducing the desilylation time from several hours to one minute <2001ARKIVOC(4)5>.

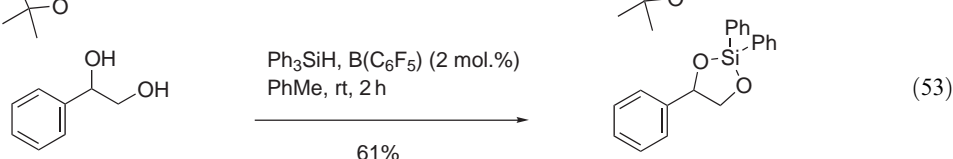
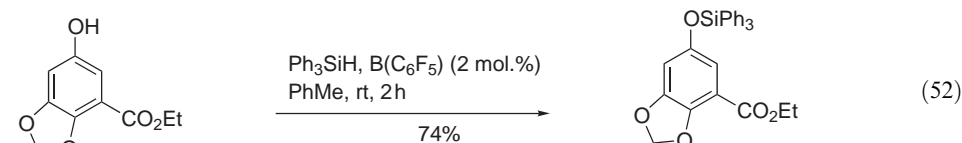
Recent advances in the fluoride ion-mediated reactions of silanes containing bonds to other elements as well as oxygen has recently been reviewed <2001MI315>. The different substitution patterns available at silicon offers differing levels of protection and the stability profiles of the wide range of such silyl ethers has been tabulated <B-1995MI003>. Many protocols have been established for selective protection and deprotection in the presence of other functional groups and two reference sources are of particular note <B-1999MI019, 1996S1031>. Further innovations in the installation and removal of silyl ether-protecting groups including new applications have been carefully and periodically reviewed <1995COS315, 1996AG(E)2056, 1996COS397, 1997COS454, 1998JCS(P1)4005, 1999JCS(P1)1589, 2000JCS(P1)2495, 2001JCS(P1)2109>. Several new methods have been reported that facilitate selective cleavage of silyl ethers by a variety of methods: hydrolytically, catalytically, photolytically, or by a metal, decaborane, or a halide <1996TL509, 1997TL495, 1997TL6997, 1998SL209, 1998TL327, 1998TL2495, 1998TL2989, 1998TL5249, 1999TL1985, 2000JCS(P1)2305, 2001T2109, 2002JCS(P1)1223, 2002OL2141, 2003TL2777, 2002TL4729, 2003SC4005, 2003SC4043, 2003SL694, 2003TL4689, 2003TL8819>.

The following trialkylsilyl groups are representative of those that have found uses in organic synthesis: diethylisopropylsilyl (DEIPS) **73**, dimethylisopropylsilyl (DMIPS) **74**, dimethylphenylsilyl (DMPS) **75**, diphenylisopropoxysilyl (DPIPS) **76**, diphenyl-*t*-butoxysilyl (DPTBS) **77**,

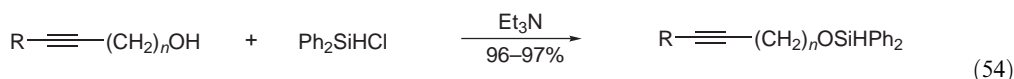
di-*t*-butylmethoxysilyl (DTBMS) **78**, di-*t*-butylsilylene (DTBS) **79**, methyldiisopropylsilyl (MDIPS) **80**, methyldiphenylsilyl (MDPS) **81**, *t*-butyldiphenylsilyl (TBDPS) **82**, *t*-butylmethoxyphenylsilyl (TBMPS) **83**, *t*-butyldimethylsilyl (TBS) **84**, hexyldimethylsilyl (TDS) **85**, triethylsilyl (TES) **86**, 1,1,3,3-tetra-isopropylidisiloxane (TIPDS) **87**, triisopropylsilyl (TIPS) **88**, and trimethylsilyl (TMS) **89** <B-1995MI003, B-1999MI019, 1996S1031>.



The most convenient precursors to alkyl silyl ethers and esters include chlorosilanes, alkylsilazanes, and silyl trifluoromethanesulfonates <B-1995MI003, B-1997MI012, 1996CB733>. The TBDPS group is the one silyl-protecting group for which the trifluoromethanesulfonate procedure is not an option <1995COS315>. Attempts to prepare the TBDPS triflate by standard methods result in protodesilylation of its aromatic rings. However, the rate of silylation using TBDPS chloride may be increased in the presence of silver nitrate. Direct reaction of hydrosilanes and disilanes with alcohols, catalyzed by transition metals, presents a valuable alternative to use of the more expensive chlorosilanes and trifluoromethanesulfonates <B-2000MI022>. The dehydrogenative silylation of alcohols using a silane such as Et_3SiH or Ph_3SiH in the presence of small amounts of tris(pentafluorophenyl)borane (Section 2.10.1.1.2) <2000JOC3090> as Lewis acid is a very effective alternative method to the use of silyl halides and triflates (Equation (52)) <1999JOC4887>. The method has general applicability as hindered silanes such as Bn_3SiH , Pr^i_3SiH , $\text{Bu}^t\text{Me}_2\text{SiH}$, and PhMe_2SiH are also able to participate in the reaction and the method also facilitates conversion of 1,2- and 1,3-diols to their cyclic silylene derivatives (Equation (53)). Alkenes, alkynes, alkyl halides, nitro compounds, methyl and benzyl ethers, esters, and lactones all remain intact under conditions that are effective for silyl protection of primary, secondary, tertiary, and phenolic hydroxyl groups.

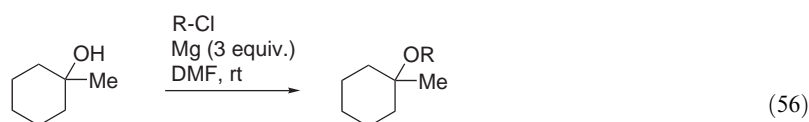
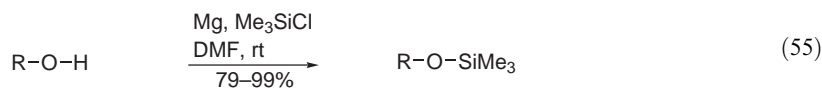


Alkynyloxyhydrosilanes that have been silylformylated for use in cross-coupling reactions <1995CRV2457> are prepared in excellent yield from the alkynyl alcohol and diisopropylchlorosilane (Equation (54)) <1995JA4419, 1995JA6797, 2003JOC5153>.



R = H, Me; $n = 1, 2$

Protection using TMS, however transient or temporary, remains the most important of all the different trialkylsilyl protecting groups <2003OL2303, 2003OL2367, 2003TL8513>. TMS ethers are themselves useful reagents for formation of further alkyl and aryl ether derivatives on replacement of the silyl group <2003SL1877, 2003TL7837>. TMS chloride is the oldest reagent for the silylation of alcohols. It has relatively poor silylating ability on its own but can silylate many functional groups in the presence of base such as triethylamine or other tertiary amine. The use of dipolar, aprotic solvents increases the reactivity of the TMS chloride when used in combination with triethylamine, whereas triethylamine hydrochloride can be filtered off on work-up of reactions carried out in inert, apolar solvents. TMS chloride may be conveniently activated in the presence of magnesium turnings to form TMS ethers of primary and secondary alcohols (Equation (55)) <2000SL1025>. Sterically hindered alcohols are also successfully silylated and the method is compatible with carbonyl and halogen groups (Equation (56)).

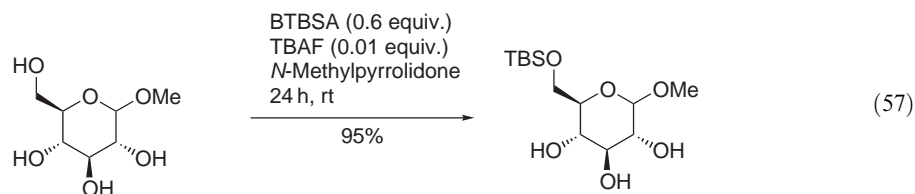


R = SiMe₃ 85%
R = SiPhMe₂ 97%

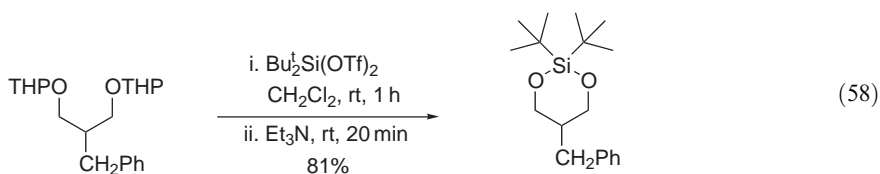
TMS iodide (Section 2.10.2.2), which is one of the most reactive silylating agents, can be conveniently prepared from the cheaper TMS chloride *in situ* by mixing with sodium iodide in the presence of silica chloride <2002TL7139>. Bis(trimethylsilyl)acetamide (BSA) and bis(trimethylsilyl)urea (BSU) are powerful silylating agents, delivering TMS protection to a variety of substrates <B-1995MI003, 1998S357>.

TBS and TIPS ethers have been well established for a number of years <B-1999MI019, 1995CRV1009>. Although they offer robust protection, they can be removed easily and selectively <1996S1031>. The increased protection conferred by the steric bulk of TBS, TIPS, and analogs hampers formation of such silyl ethers in the first place. This is rarely an issue, however, as there are many methods for their successful formation. Both primary and secondary alcohols can be converted readily under mild conditions to their TBS and TIPS ethers using the chlorosilane and imidazole in DMF <1995COFGT(2)513, B-1999MI019, 1995CRV1009, 1997CC1601>. Selective protection of alcohols and phenols using TIPS chloride and imidazole can be assisted using microwave irradiation <2000T7503, 2001T9225>. Silylating reagent

N,O-bis(*t*-butyldimethylsilyl)triflate (BTBSA) can be used efficiently to convert primary, secondary, and even tertiary alcohols directly to their TBS ethers when in the presence of catalytic amounts of TBAF or other source of fluoride <1996CB733>. The procedure allows selective protection of primary hydroxyl groups over secondary and even secondary in the presence of tertiary hydroxyl groups (Equation (57)) <1996TL605>.



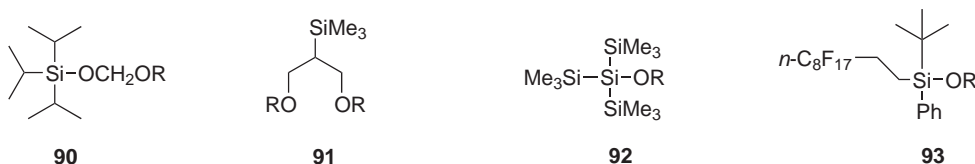
This otherwise very useful strategy is unsuccessful for the protection of 1,2-diols due to the migration of the TBS group caused by the basic fluoride employed. *N*-Trimethylsilylpyridinium triflate and analogs (Section 2.10.2.6) are powerful silylating agents for the preparation of silylated alcohols and carboxylic acids, and also for the formation of enol silanes. For example, complete silylation of glucose can be achieved and the persilylated product isolated without aqueous work-up; the product mixture is simply diluted with pentane to precipitate the pyridinium triflate and the product solution filtered to give the pure silyl ether <1997S744>. A variety of difunctionalized silanes and disiloxanes has been devised for the protection of 1,2-, 1,3-, and 1,4-diols and as linker groups in solid-supported synthesis <B-1995MI003, B-1999MI019, 1997TL1651, 2000CRV2091>. THP ethers are converted to the corresponding cyclic silyl ethers in one step by reaction with alkyl trifluoromethylsulfonates followed by triethylamine (Equation (58)) <1996SL523>.

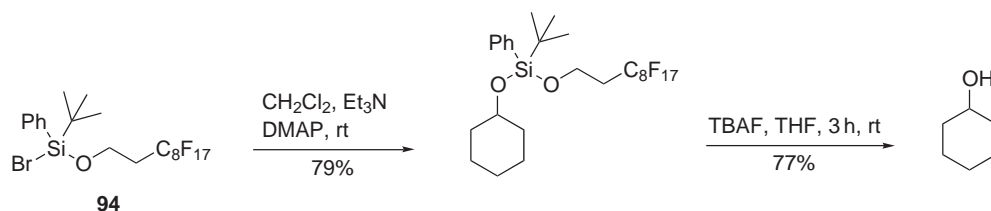


Solid-supported synthesis of oligoribonucleotides requires protection for the 2'-OH hydroxyl group, a role fulfilled traditionally by the TBS ether **84** <2002TL795>. A new protecting group, triisopropylsilyloxymethyl (TOM) **90**, has recently been introduced to provide a useful and practical alternative to TBS <1997USP5986084, 2001HCA3773, 2003MI1733>. Use of TOM allows high coupling efficiencies during solid-supported synthesis due to its lowered steric hindrance, which also facilitates the successful use of mild deprotection conditions.

A new carbonyl protecting group, cyclo-SEM **91**, converts ketones and aldehydes to their respective acetals and hemiacetals at room temperature using dry dichloromethane in the presence of 3 or 4 Å molecular sieves <1997TL1873>. Removal of the cyclo-SEM protective group can be achieved successfully using LiBF₄ in THF at 65 °C where conventional ketone acetal groups in the same substrate remain intact.

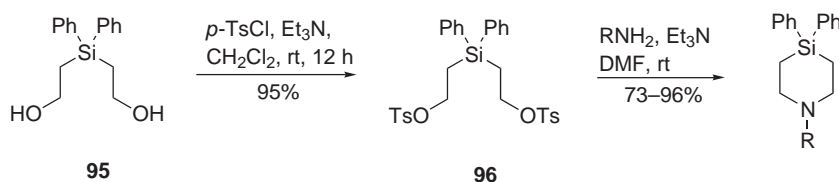
The tris(trimethylsilyl)silyl ether (TTMSS) **92** may be used as a photolabile protecting group for primary and secondary alcohols <1997TL6997>. Steric bulk precludes use of ether **92** for the protection of tertiary alcohols. The protecting group is introduced by reacting tris(trimethylsilyl)silane, Chatgililoglu's reagent (Section 2.10.2.8.1), with CCl₄ in DMAP to give a 1.2 M solution of the chloride, which is reacted with the appropriate alcohol. Fluorous *t*-butylphenyl-1*H*,1*H*,2*H*,2*H*-heptafluorodecyloxysilyl (BPFOS) ether **93** has been developed as a protecting group for alcohols that allows their purification by solvent extraction or by solid-phase extraction with reversed phase fluorosilica gel <1999TL5667>. The protecting group is introduced using the reagent *t*-butylphenyl-1*H*,1*H*,2*H*,2*H*-heptafluorodecyloxysilyl bromide **94** (Scheme 24).





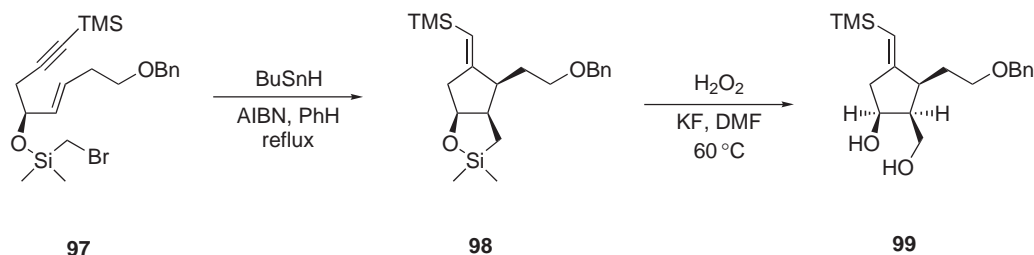
Scheme 24

The BPFOS reagent **94** has also been used very recently to attach a fluorosilyl ether tag to the anomeric carbon of sugar acceptors allowing rapid synthesis of oligosaccharides by fluorosilyl solid-phase extraction [\[2003CC2930\]](#). The hydrolytic stability of the linker is highly dependent upon the substituents attached at silicon. When methyl substituents replace the phenyl and *t*-butyl groups, this alternative ether linkage becomes susceptible to the methoxide-catalyzed deacylation conditions used in disaccharide synthesis. A new silyl-protecting group for primary amines is provided by diphenylsilyldiethylene (DPSide) **95**. The diol **95** is converted to the ditosylate **96** giving the reagent, which is treated with the appropriate amine to give the protected product (Scheme 25) [\[1999TL5333\]](#). Removal of the DPSide protecting group can be achieved efficiently using TBAF–CsF in 1:1 ratio.



Scheme 25

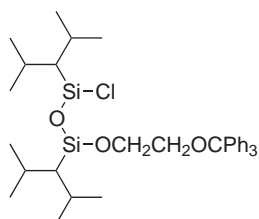
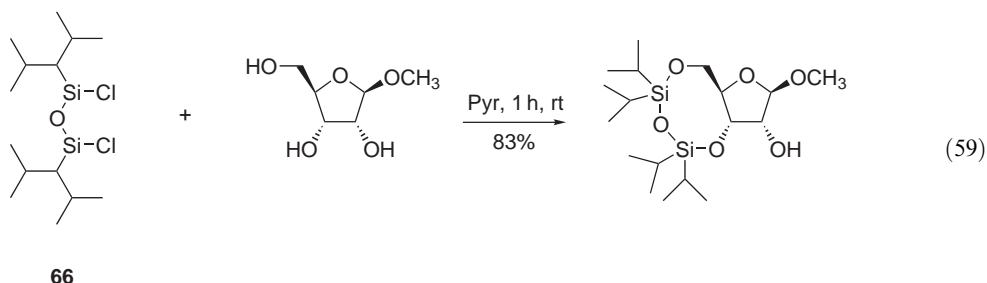
Bromomethyldimethylsilyl ethers that are prepared from allylic or homoallylic alcohols have been used increasingly in organic synthesis [\[1996T7599, 1997CRV2063\]](#). They undergo radical-induced cyclization and give overall *anti* addition of a hydrogen and hydroxymethyl group to an alkene when the procedure is concluded with oxidative cleavage of the Si–C bond [\[1999JSC\(P1\)697\]](#). The bromomethyldimethylsilyl ether **97**, for example, undergoes radical-induced cyclization to the bicyclic product **98** with the TMS-substituted acetylene function acting as the radical trap. Oxidative cleavage of the Si–C bond gives the 1,3-diol product **99** (Scheme 26) [\[1998TL5367\]](#).



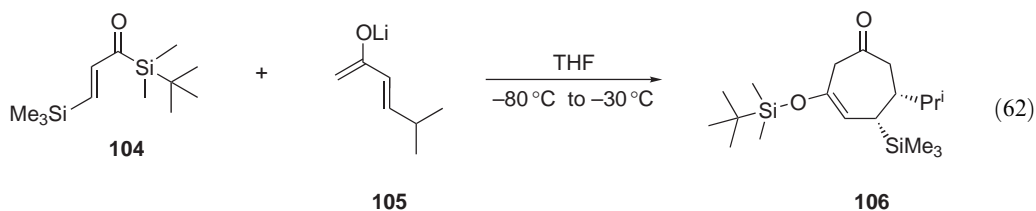
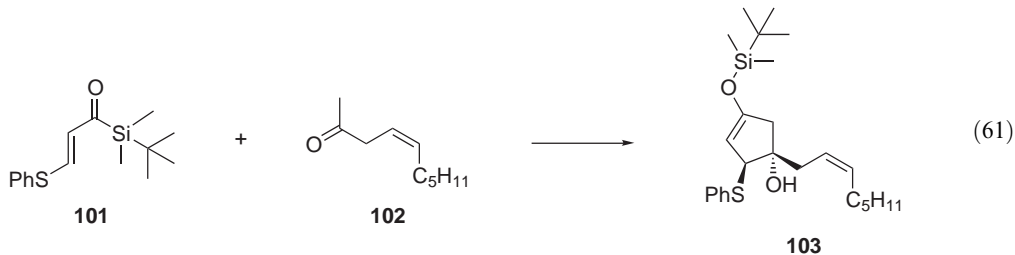
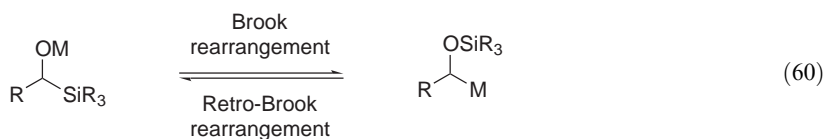
Scheme 26

1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (TIDPS) **87** (Section 2.10.2.2) is used extensively in carbohydrate chemistry [\[B-1996MI009, B-1998MI015\]](#), natural product chemistry [\[B-1997MI013\]](#), and for the simultaneous protection of 5' and 3' hydroxyl groups of nucleosides [\[B-1999MI019, 1996S1031, 2003TL5065\]](#). The TIDPS protective group is installed giving good yields of protected ribonucleosides with O2' available for subsequent transformation (Equation (59)). Highly selective detachment of TIDPS from O5' is possible to leave its remaining bond to

O3' intact under conditions that are also successful for the selective removal of the TBS protection from the O5' position of perisilylated ribonucleosides <2000JCS(P1)2305>. The derivative 1-chloro-1,1,3,3-tetraisopropyl-3-((2-triphenylmethoxy)ethoxy)disiloxane (TES) **100**, generated from **66** *in situ*, has been used to derivatize the O5' position of ribonucleotides to give a fluoride-labile alternative to the acid-labile dimethoxytrityl protection normally used <1998TL2989>.

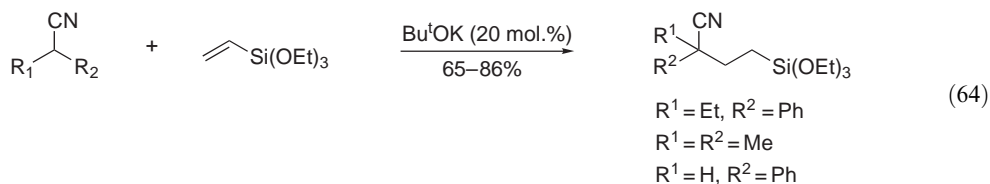
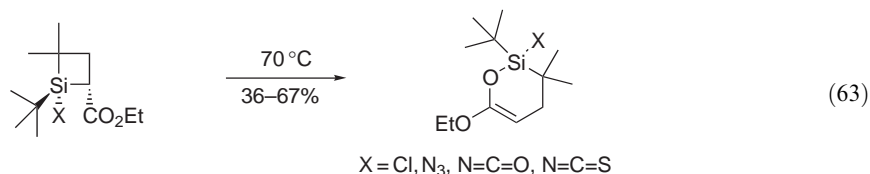
**100**

Brook rearrangement is the process of formation of an alkoxy silane by 1,2-anionic migration of a silyl group from a carbon to an oxygen atom (Equation (60)) <B-2000M1022, 2001T2065>. It is the key tandem bond-forming process that allows the acryloylsilane **101**, for example, to react with the lithium ketone enolate **102** to form the functionalized, TBS-protected cyclopentenol **103** (Equation (61)) <1997SL255>. Migration of the TBS group from carbon to oxygen follows on from initial attack on the acrylate carbonyl by the enolate. The reaction of lithium ketone enolate **105** with ketone **104** giving TBS-protected cycloheptenone **106** is an intriguing process with the likely involvement of an aldol reaction, a Brook rearrangement, a cyclization to the conjugate base of 1,2-dialkenyl-1,2-cyclopropanediol monosilyl ether and concluded by Cope rearrangement (Equation (62)) <1995JA6400>.

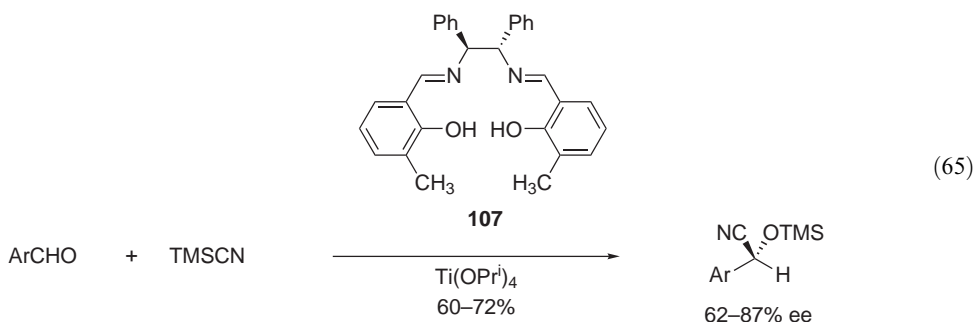


Similar approaches to other fused-ring systems <2001T2065, 2000OL1903> and a number of [1,3]- and [1,4]-silyl migrations have been documented <2001T2065>. Enantioselective α -silyl amino acid synthesis by retro-aza-Brook rearrangement has been reported recently <2003OL4677>.

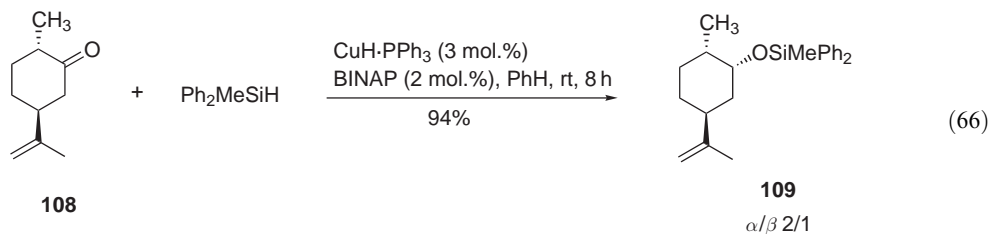
Silacyclobutanes, formed from photolysis of α -diazoacetates, undergo an interesting thermally promoted [1,3] carbon-to-oxygen ring expansion to yield cyclohexadienes (Equation (63)) <2000CC437>. These products are then converted to straight-chain dialkylhydrosilanes on reduction with LiAlH_4 . Reaction between secondary nitriles and triethoxyvinyl silanes in the presence of catalytic amounts of Bu^tOK in DMSO leads smoothly to the addition products (Equation (64)) <2001CC745>.



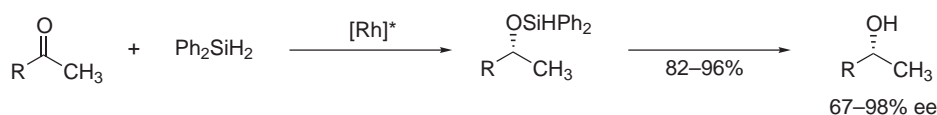
Asymmetric silylcyanation of aldehydes <1995TL405, 1996SL337, 1997T14327, 2003TA3937> and ketones <2002SL793, 2002SL1353> can be achieved in good yield and enantiomeric excess using Ti(IV) complexes in combination with salen **107** <1998T4319> or related ligands. For example, arylaldehydes give the (*R*)-TMS ethers that are hydrolyzed to the cyanohydrins (Equation (65)) <2003ARKIVOC(2)21>. Enantioselective silylcyanation of aldehydes has recently been performed in ionic liquids <1999CRV2071, 2002ACA75> using salen complexes of vanadium <2003TL6813>.



Catalytic hydrosilylation of carbonyl compounds provides alkylsiloxanes that can be hydrolyzed to give alcohols. The reaction can be performed asymmetrically with careful design and combination of metal catalyst and ligand to provide high yields and enantiomeric excesses of alkylsiloxane products from which chiral alcohols may be derived. It is an area that has been studied extensively with many successes documented <B-1999MI016, B-2001MI025, 1998OR395, 2000JCS(P1)275, 2001JCS(P1)1729, 2003T4959>. Copper-catalyzed hydrosilylations feature among the most recent examples of this type of reaction <2001JA12917, 2003OL3085>. For example, reduction of compound **108** to its diphenylmethylsilyl ether **109** is achieved cleanly and in high yield to give a mixture of diastereoisomers in which the α -isomer is favored via axial attack of the silyl-copper complex (Equation (66)) <2001JOM(624)367>.



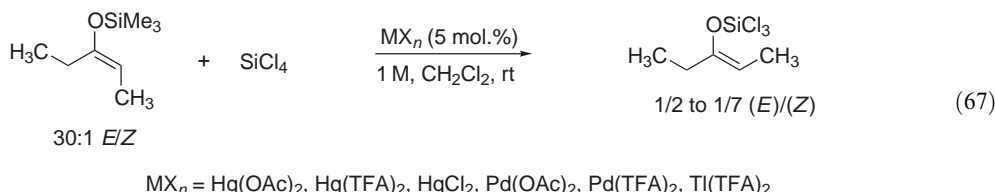
Hydrosilylation of a broad range of substrates that include alkyl, aryl, and dialkyl ketones can be achieved in high yield with good-to-high enantioselectivities using axially chiral rhodium-*N*-heterocyclic carbene (Rh-NHC) prepared from 1,1'-binaphthalenyl-2,2'-diamine (BINAM) (Scheme 27) <2003CC2916>.



Scheme 27

Hydrolysis of the intermediate silyl ethers by standard methods gives the chiral alcohols. New, optically active organoantimony (BINASb) and bismuth (BINABi) ligands have been described and used in conjunction with an Rh catalyst that encourage asymmetric hydrosilylation of aryl methyl ketones to give products with moderate enantiomeric excess where the traditional BINAP ligand fails <2003T4959>.

Trichlorosilyl enol ethers represent a new class of aldol reagents <1996JA7404, 1997JA2333, 1999JA4982, 2000ACR432>. Their chiral phosphoramidate-promoted reaction with aryl aldehydes provides aldol products with very respectable diastereo- and enantioselectivities whereas only modest selectivities are achievable with unsaturated and aliphatic aldehydes <2003JOC5045>. The configuration of the enolate, (*E*) versus (*Z*), has important consequences for the *anti* versus *syn* relationship of the substituents at C1 and C2 in the aldolization products formed by the enolate. Careful choice of conditions can be used to effect isomerization of silyl enolates that begin as a mixture of (*E*)/(*Z*) isomers in up to 30:1 ratio, to produce mixtures where the corresponding (*E*)/(*Z*) isomers are from 1:2 to 1:7 in ratio (Equation (67)) <2003JOC5045>.



2.10.2.4 Alkylsilathianes

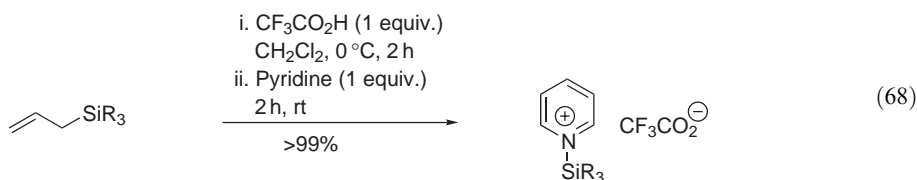
The normal preparative routes to alkylsilathianes involve reaction of a halosilane with a metal thiolate <B-2000MI022, 1995TL3731>. Use of trimethylsilylacetylene in the presence of elemental sulfur and butyllithium gives alkynyl silyl sulfides <1997S942>. Carbonyl sulfide reacts with organosilanes at 60–85 °C in the presence of a radical initiator to give the corresponding silanethiols <2001TL763>. Silathiols prepared in this manner include: Ph_3SiSH , $\alpha\text{-NpPhSiSH}$, $(o\text{-MeC}_6\text{H}_4)_2\text{SiSH}$, MePhSiSH , $\text{Bu}^t\text{Ph}_2\text{SiSH}$, Pr^i_3SiSH , $\text{Bu}^t\text{OPh}_2\text{SiSH}$, $(\text{Bu}^t\text{O})_2\text{PhSiSH}$, and $\text{Ph}_2\text{Si}(\text{SH})_2$.

2.10.2.5 Alkylsilicon Compounds with an Si—Se and/or Si—Te Bond

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)513>.

2.10.2.6 Alkylsilazanes

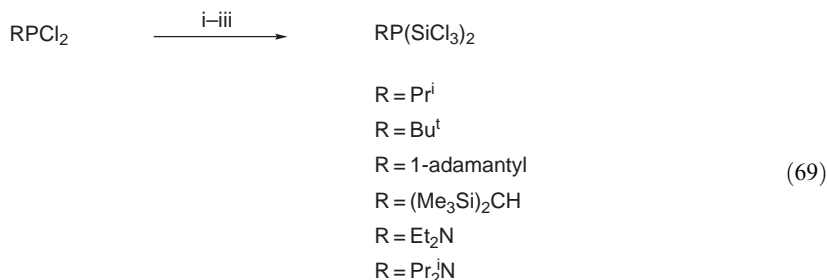
N-Silylpyridinium triflates are powerful silylating agents (Section 2.10.2.3). The appropriate allyl silane is treated with triflic acid then pyridine to give quantitative yields of the silylpyridinium triflates as crystalline solids that are stable under an inert atmosphere indefinitely (Equation (68)) <1997S744>.



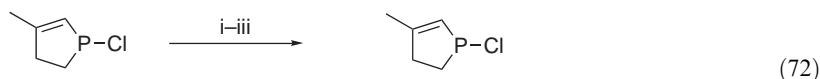
Alternatively, they may be conveniently prepared *in situ* immediately prior to use. Formation of alkylsilazane derivatives may be achieved by direct reaction of a primary amine with the appropriate chlorosilane <2000TL3285>. *N*-Silylaldimines react with *N*-chloroacetyl derivatives of chiral oxazolidinones to give stereochemically enriched β -lactam products <2000EJO2379>. Commercially available 1,2-bis(chlorodimethylsilyl)ethane continues to find use for the conversion of primary amines to their cyclic “stabase” derivatives <1996AG(E)1968, 1997JA5499>.

2.10.2.7 Alkylsilicon Compounds with an Si—P, Si—As, Si—Sb, or Si—Bi Bond

Transition metal-catalyzed dehydrogenative SH/HP coupling of alkyl silanes and alkyl phosphanes in the absence of solvent gives quantitative yields of Si—P bonded adducts <1998JA12988>. Bis(trichlorosilyl)phosphanes $\text{RP}(\text{SiCl}_3)_2$ are formed from Benkeser reactions between alkyl dichlorophosphanes RPCl_2 and 2 equiv. of trichlorosilane in the presence of triethylamine (Equation (69)) <1996JOM(521)417>. Trichlorosilyl phosphanes are formed when 1 equiv. of trichlorosilane is used (Equations (70)–(72)). Most of the products may be purified successfully by vacuum distillation.



i. HSiCl_3 (2 equiv.); ii. Et_3N ; iii. hexane, 0–20 °C, 24 h

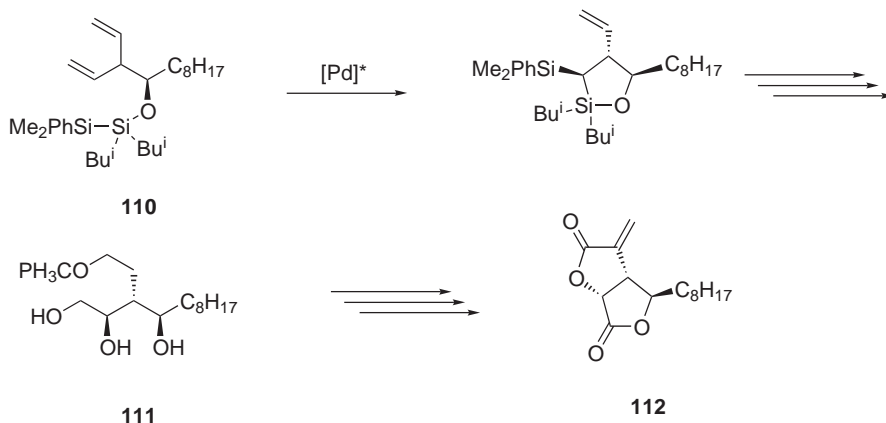


i. HSiCl_3 ; ii. Et_3N ; iii. hexane, 0–20 °C, 24 h

2.10.2.8 Alkylsilicon Compounds with an Si—Metalloid Bond

2.10.2.8.1 Compounds with Si—Si bonds

The use of alkylsilicon compounds with Si—Si bonds in organic synthesis has continued in momentum <B-2000MI022, B-2004MI028, 1998JCS(D)1925>. During bissilylation of alkene **110**, stereocontrolled formation of one of four possible isomers is controlled by the palladium-isocyanide catalyst (Scheme 28). Several steps conclude the synthesis of (–)-aveaceolide **112** via triol **111** <1995JA9608, 1996TL8887>.



Scheme 28

Chatgililoglu's reagent, tris(trimethylsilyl)silane (TTMSS), is prepared in 30% by the reaction of trichlorosilane with lithium metal and trimethylsilyl chloride [<1995COFGT\(2\)513>](#). The role of TTMSS as a radical reducing agent and that of other organosilanes in organic synthesis has been recently reviewed [<B-2004MI028>](#). The reagent is similar in efficiency to tributyltin hydride as a free-radical-based reducing agent toward a wide variety of substrates that include halides, ketones, selenides, and xanthates [<B-2000MI022, 1995CRV1229>](#) and recently for reduction of phosphine sulfides and selenides to phosphines in good yield [<2000TL9899>](#). The reagent has also been used as a mediator in the formation of C—C bonds, for example, in radical cascade macrocyclization [<1997TL3647>](#) and radical carbonylation [<1996AG\(E\)1050, 1996CRV177, 1997JOM\(548\)105, 1997T14615, 2003OBC4262>](#). Although use of phenyl silane gave superior product yields, TTMSS did promote the cyclization of bromoaldehydes to secondary alcohols employing the aldehyde carbonyl as the radical trap [<1998TL7267>](#). Use of TTMSS, where tributyl- and triphenyltin hydride both failed in a pivotal C—C bond forming step, ensured the success of the shortest total synthesis of the antimalaria drug (+)-artemisinin to date [<2003ARKIVOC\(3\)125>](#). Allyl tris(trimethylsilyl)silanes that are used in radical allylation processes [<1996TL6387>](#) are prepared in high yield by reacting allyl phenyl sulfides with TTMSS, whereas allyl phenyl sulfones react slower to give moderate yields [<1996TL6383>](#).

2.10.2.8.2 Compounds with Si—Ge bonds

No further advances have occurred in this area since the publication of COFGT (1995) [<1995COFGT\(2\)513>](#).

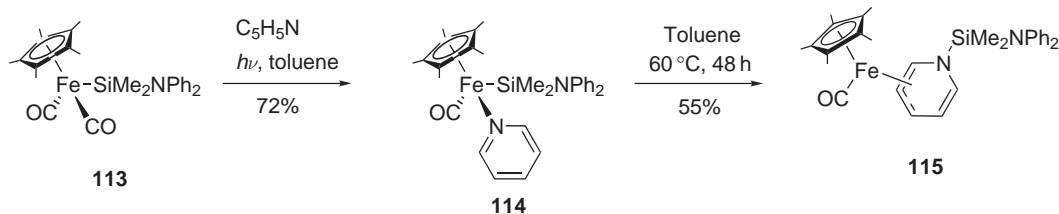
2.10.2.8.3 Compounds with Si—B bonds

Compounds of this type may be formed by direct reaction of the appropriate trialkylsilyllithium reagent with a chloroborane [<1995OM3112>](#).

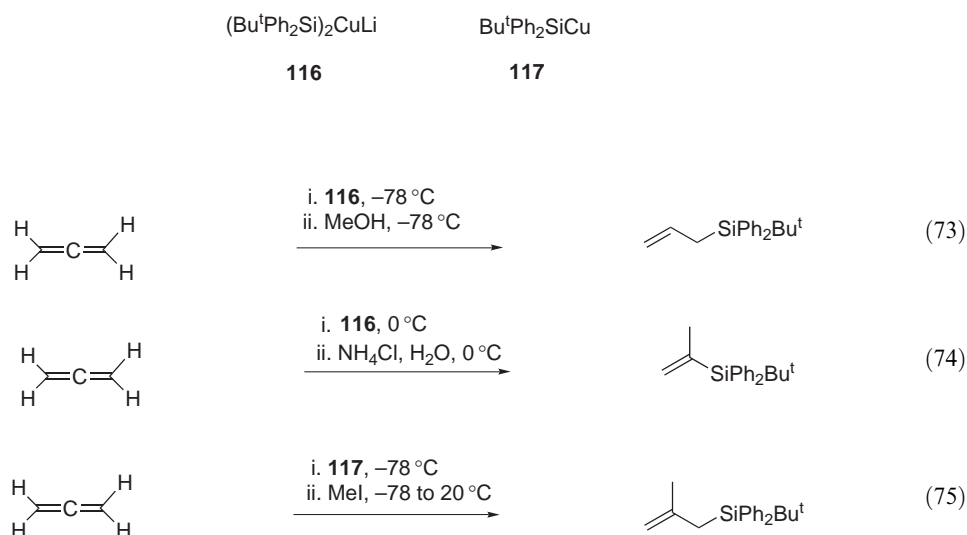
2.10.2.9 Alkylsilicon Compounds with an Si—Metal Bond

Commercially available trimethyl(tributylstannyl)silane ($\text{Me}_3\text{SiSnBu}_3$) facilitates formation of acyl silanes from Pd-catalyzed coupling with acid chlorides. Both aryl- and alkylacylsilanes can be prepared with this reagent, whereas hexamethyldisilane ($\text{Me}_3\text{SiSiMe}_3$) fails in the alkyl series [<1999TL3113>](#). With its Fe—Si bond [<2003JCS\(D\)1114>](#), iron complex **113** reacts with pyridine to form crystals of complex **114**, which on heating produces insertion product **115** in a process that may prompt development of metal-catalyzed hydrosilylation of aromatic ring systems (Scheme 29) [<2003CC2744>](#). Use of silylcuprate **116** and the new silylcopper reagent **117** provides complementary

methods of regiocontrol in the *t*-butyldiphenylsilylcupration of allene <2003T5855> (Equations (73)–(75)). The silylcopper reagent **117** is generated and used *in situ* by mixing equimolar amounts of *t*-butyldiphenylsilyllithium and copper (I) cyanide in THF <2003T5855>.



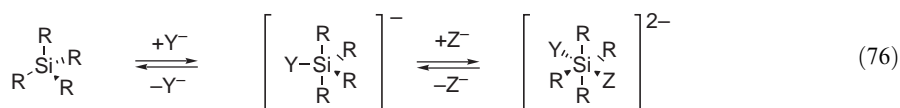
Scheme 29



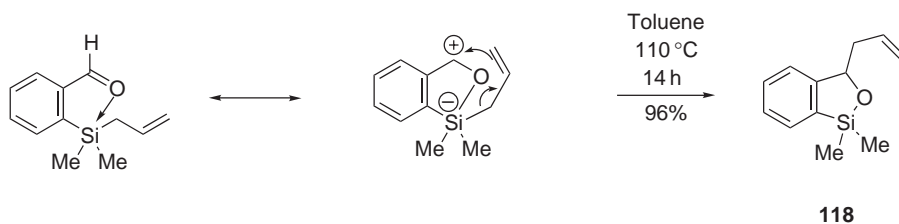
Phenyldimethylsilylcuprate $[(\text{Me}_2\text{PhSi})_2\text{CuLi}]$ undergoes conjugate addition with homochiral α,β -unsaturated ketones <2003OBC3989> and esters <2003OBC4017> with typically high levels of stereocontrol. Vinyl silanes that are attached to the bulky *t*-butyldiphenylsilyl group may be substituted for electrophiles. The value of this hindered group compared to TMS (Section 2.10.2.3) or DMPS (Section 2.10.2.3) is in the possibility to heat with acids without protodesilylation <1995JCS(P1)1525>. Hydrido(trialkylsilyl)silyllithium compounds may be prepared by a sila-metalation route <2002JA11604>.

2.10.2.10 Alkylsilicon Compounds with Silicon Having a Coordination Higher Than 4

The preparation, structure, and reactivity of pentacoordinate silicon compounds and those with higher coordination <2002SC3733> are areas of continued extensive study <B-1999MI020, 1999CL1139, 1996CRV927, 2000PAC1655, 2001JOC7159, 2003JOM(687)190, 2003JOM(686)202>. The pentacoordinate silicon atom exists in reactive intermediates during transformation of tetracoordinate silicon to hexacoordinate, and in isolable compounds offering a unique reaction site in organic synthesis (Equation (76)).

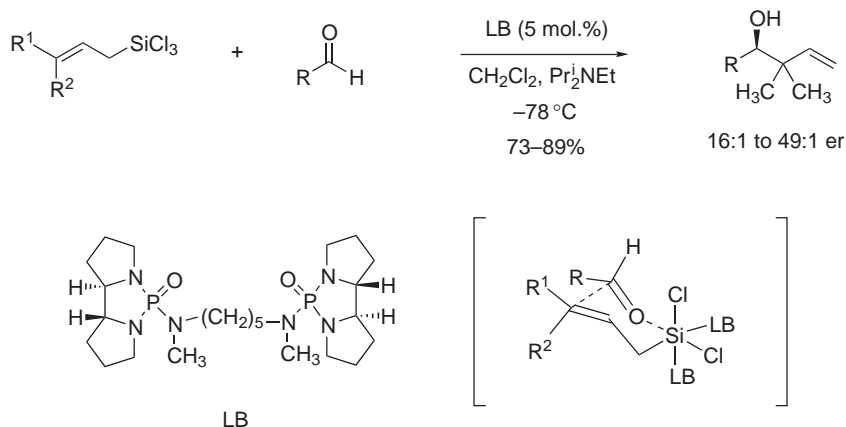


A new synthesis of benzo[1,2]oxazoles involves an unprecedented allylic transposition that takes place with the likely involvement of a pentavalent silicon intermediate [<2004CC122>](#) (Scheme 30). Desilylation of compound **118** with TBAF yields the homoallylic alcohol, whereas treatment with KF/H₂O₂ (Tamao conditions) gives the corresponding *o*-hydroxy derivative.



Scheme 30

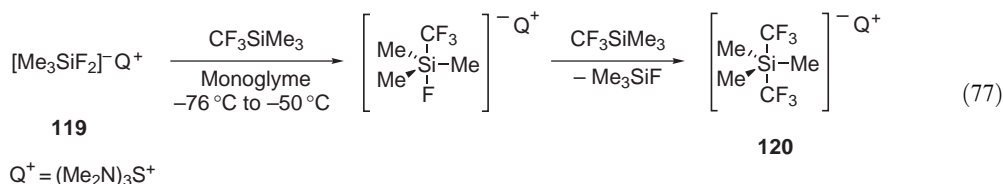
Hexa-, hepta-, and the very rare octacoordinate alkylsilicon compounds have each been documented [<B-1999MI020>](#). Hepta- and octacoordinate silicon compounds have octahedral or bicapped tetrahedral geometries that show fluxional behavior in solution and possess different reactivities compared with their lower coordinate analogs. A useful new reaction is the catalytic, chiral Lewis base promoted allylation of aldehydes [<2003CC167>](#). With careful design of catalyst, the synthetically very useful homoallylic alcohol products form with excellent enantioselectivities in a reaction process that features hexacoordinate silicon in a transition state that is more stringent than that of the alternative Lewis acid promoted allylation process (Scheme 31) [<1995CRV1293>](#).



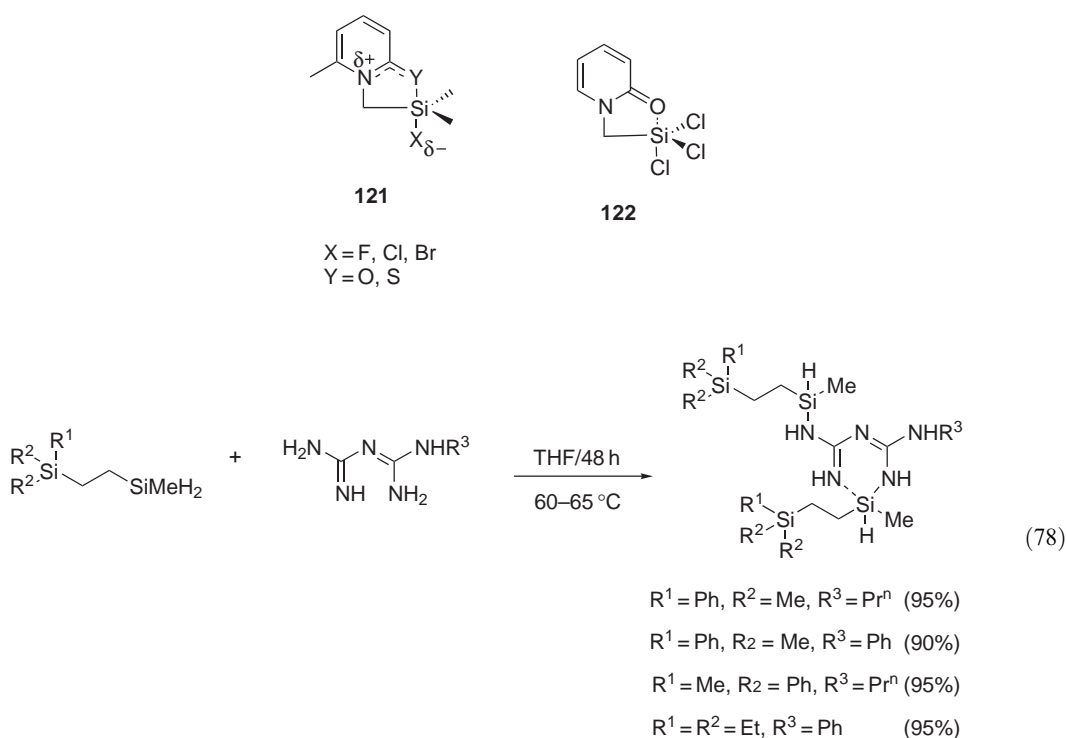
Scheme 31

Although Lewis base catalysis currently lags behind Lewis acid approaches to allylation and aldol reactions [<2000ACR432>](#) (Sections 2.10.1.3.5 and 2.10.2.3), the search for new Lewis base reagents that support higher yields and enantiomeric excesses continues to gain momentum. The first use of a chiral sulfoxide as a Lewis base promoter of the allylation of aryl aldehydes by allyltrimethylsilane drives investigation into new systems based around pyridyl sulfoxides and sulfonamides [<2003CC2712>](#). Allylation of aldehydes and reactive ketones using allyltrimethoxysilane and CdF₂-terpyridine complex in aqueous solution gives good yields of homoallylic alcohols although the detailed mechanism or any involvement by hypercoordinate silicon remains to be established [<2003CC676>](#). Of the isolable alkylsilicon compounds with coordination higher than 4, it is the pentacoordinated derivatives that are of most importance in organic synthesis [<B-1999MI020, B-2000MI022>](#). The enhanced reactivity of pentacoordinate silicon compounds in nucleophilic substitutions has been demonstrated experimentally. They react with alkali metal alkoxides, Grignard, alkyllithium, and reducing reagents to give the corresponding tetracoordinate silicon products in good yields. For example, [PhMeSiF₃][−] [K, 18-c-6]⁺ reacts two orders of magnitude

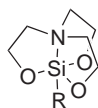
faster than PhMeSiF_2 with hindered Grignard reagents such as Bu^tMgBr and Pr^iMgBr <B-1999MI020>. Trifluoromethylation of organic compounds can be achieved by nucleophilic, electrophilic, radical, and carbene processes <2003CC8726>. Ruppert's reagent, (trifluoromethyl)-trimethyl silane (CF_3SiMe_3), is one of the most useful for anionic trifluoromethylation of organic and organometallic electrophiles <1995TL7761, 1996COS151, 1997CRV757, 2000T7613>. It has been used to form the first isolated pentacoordinate silicon compound **120** with five Si—C bonds to separate substituents <1999CC1017>. Addition of CF_3SiMe_3 to a suspension of compound **119** produces siliconate **120**, which has been characterized structurally by X-ray crystallographic analysis (Equation (77)).



Formation of pentavalent silicon has been proven to occur in the Peterson olefination reaction <B-1999MI020, 2001T2065>. Good control of the configuration ((*E*) versus (*Z*)) at the resulting double bond is possible <2003JOC7979>, but the stereochemical outcome of the olefination is highly dependent upon the combination of base and solvent used in the reaction <1999JA6816>. The recently prepared halodimethylsilylmethyl derivatives of 2-thiopyridones **121** have been studied by ^{13}C and ^{29}Si NMR and show much weaker pentacoordination compared with the pyridone analog **122** <2000JCS(P2)1059>. The attachment of groups at silicon that have increased electronegativity improves the pentacoordination achievable. Pyridone derivative **122** and its analogs with substituents in the pyridine ring possess an Si—O bond that is almost fully formed <2000JOM(606)125>. Novel pentacoordinate silanes containing a chelated Si—N—C—N—C—N ring have been prepared using biguanide ligands (Equation (78)). At elevated temperature, in the absence of catalyst, silanes undergo SiH/NH dehydrocoupling with biguanides to form pentacoordinate chelates that are isolated in high yield as hygroscopic, low-melting solids that decompose thermally above 100°C <2003JOM(687)190>.



Many silatrane derivatives **123**, some with significant biological activity, have been synthesized <B-1999MI020, B-2000MI022, 2003ARKIVOC(8)125>. Depending on the electronegativity of the substituent to which silicon is directly attached, the transannular bond to nitrogen varies between 0.234 to 0.202 nm. Recently reported 1-ferrocenecarboxysilatrane shows Si—N bond distances near 0.206 nm that are shorter than those of 1-alkyl or alkoxysilatrane but closer to those of 1-halosilatrane <2003JOM(678)90>. Although it is the higher coordinate alkylsilicon compounds that are of most significance to organic synthesis, stable, isolable dialkylsilylenes and related compounds that have a silicon coordination of less than four have now been documented <1998JA1639, 1999JA886, 1999JA9722, 2000PAC2333>.



R = halogen, alkyl, aryl

123

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Biographical sketch

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2.11

Alkyl Metals

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2.11.1 INTRODUCTION

The importance of alkyl metal derivatives lies in their great value as nucleophiles in C—C bond-forming reactions. This role places alkyl metals at the heart of synthetic organic chemistry and drives continuing development in the area. A thorough review of the preparation of alkyl metal derivatives was given in COFGT (1995) <1995COFGT(2)549>. The aim of this work is to provide an overview of developments occurring since the appearance of COFGT (1995) and to focus specifically on the synthesis of bonds between metals and sp^3 -hybridized carbons.

2.11.2 ALKYL GROUP 1 METAL DERIVATIVES

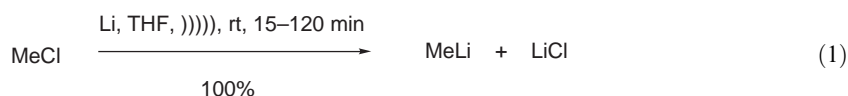
Alkyl lithium derivatives have continued to be of great importance in organic and organometallic chemistry. The extensive literature describing their preparation has been comprehensively reviewed <1995COFGT(2)549>. Recent reviews cover, amongst other topics, stability and control of configuration during preparation of alkyl lithiums <2002AG(E)716, 1996ACR552>, heteroatom-stabilized and heteroatom-directed lithiation <2000TCC113, 2002ACR226>, and lithiated epoxides <2002S1625>.

2.11.2.1 Alkyl lithium Derivatives

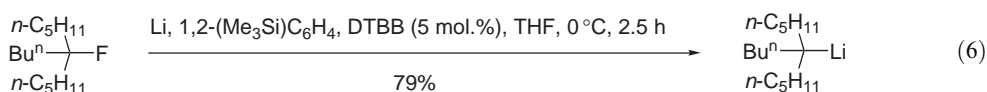
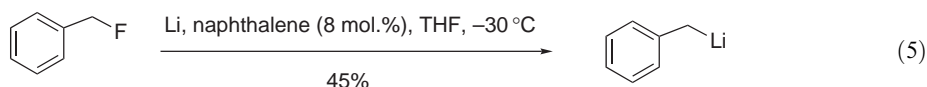
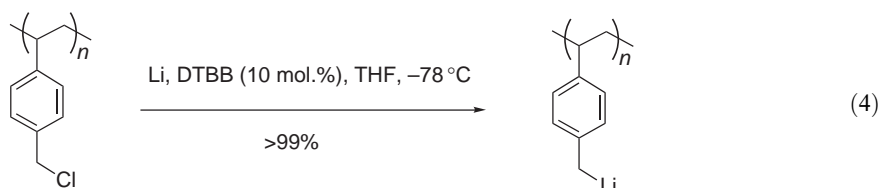
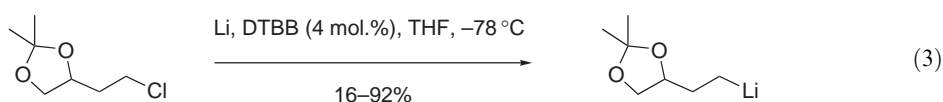
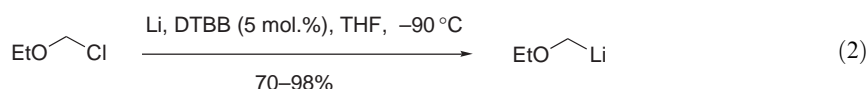
2.11.2.1.1 Preparation by halogen–metal exchange

(i) From alkyl halides

Reaction of alkyl halides with lithium metal is the most direct method of forming alkyl lithiums. The reaction is applicable to primary, secondary, and tertiary halides, with the order of reactivity being $I > Br > Cl \gg F$. Suitable conditions involve the use of ether or hydrocarbon solvents and lithium metal containing 1–2% of sodium. Sonication can be beneficial (Equation (1)) <1995SL459>.

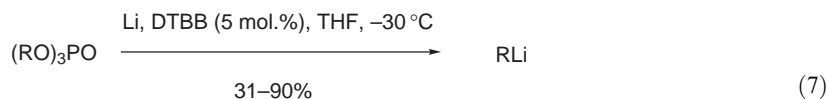


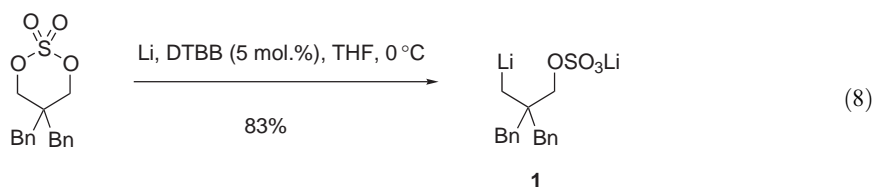
Very active lithium can be obtained by mixing the metal with certain arenes in THF as solvent, naphthalene and 4,4'-di-*t*-butylbiphenyl (DTBB) being the most frequently used. Lithium arene radical anions are formed which undergo lithium–halogen exchange with alkyl halides, in particular alkyl chlorides, under very mild conditions. Stoichiometric or catalytic quantities of arenes can be used in these processes, the catalytic version having advantages of shorter reaction times and greater ease of product isolation and purification (Equations (2)–(4)) <1996T1643, 1996T8333, 2003T1909>. The method can be used to induce reaction of lithium metal with allylic and benzylic fluorides in Barbier-type reactions, Wurtz-type coupling products being obtained in the absence of an electrophile to trap the alkyllithium products (Equation (5)) <2001JOM(624)53>. More general fluorine–lithium metal exchange can be induced by addition of silanes, such as 1,2-bis(trimethylsilyl)benzene (Equation (6)) <2003T1237>. However, the resulting alkyllithiums cannot be trapped by electrophiles and tend to abstract protons. Arene-catalyzed lithiation reactions have been reviewed by Yus <1996CSR155>.



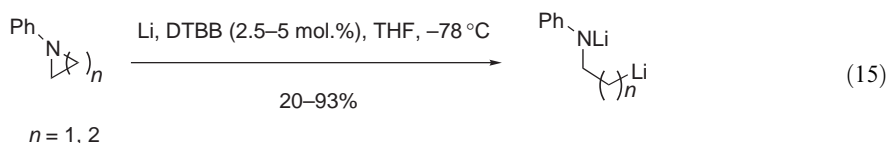
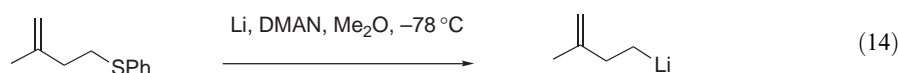
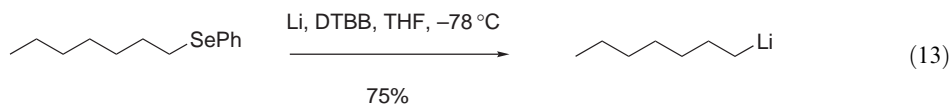
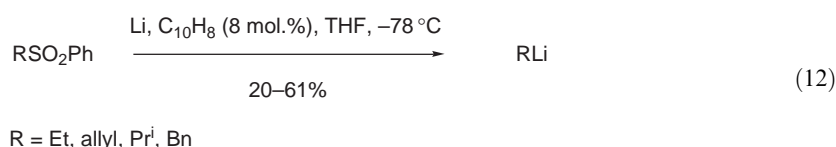
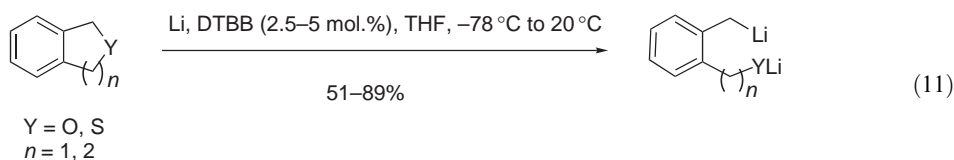
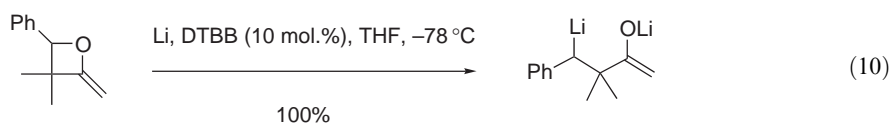
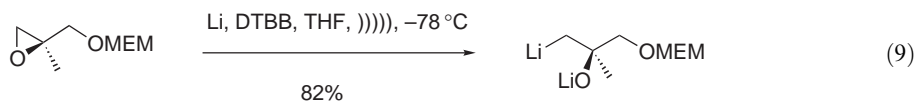
(ii) From other leaving groups

Alkyllithiums can be prepared by arene-catalyzed lithiation of the corresponding dialkyl sulfates; similar conversions have been reported using trialkyl phosphates (Equation (7)) <1994T8551>. Reaction of cyclic sulfate derivatives of 1,3-diols generates γ -lithiated sulfates **1** (Equation (8)), which undergo subsequent intramolecular cyclization to give cyclopropanes <1995T11445>.





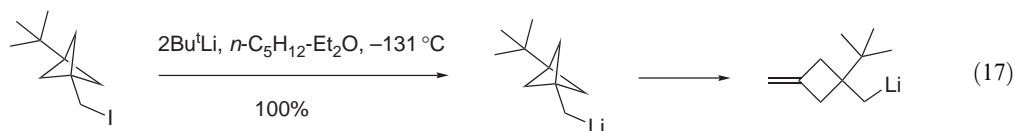
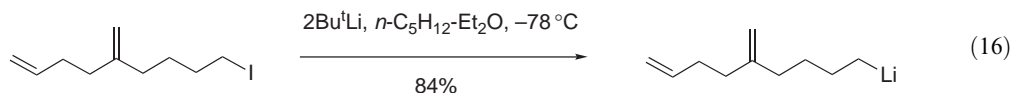
Cleavage of ethers by lithium metal to give alkyllithiums and alkoxides can be used to prepare certain alkyllithiums, such as benzylolithium derivatives [<1994SC591>](#). Use of lithium–arene complexes is more generally useful, especially for cleavage of cyclic ethers, including epoxides ([Equation \(9\)](#)) [<2000T1081>](#), oxetanes ([Equation \(10\)](#)) [<2000TL1855>](#), phthalans, isochromans, and their thioether analogs ([Equation \(11\)](#)) [<1996CSR155, 1996JOC1859, 2003T1909>](#). Lithium–arene complex cleavage of phenyl thioethers, phenyl sulfones ([Equation \(12\)](#)) [<1995T2699>](#), and alkyl phenyl selenides ([Equation \(13\)](#)) [<1995TL8111>](#) constitute versatile methods of preparing alkyllithiums. Dimethyl ether can be used in place of THF for the low-temperature generation of lithium-1-(dimethylamino)naphthalene (DMAN) complexes in the cleavage of phenyl thioethers ([Equation \(14\)](#)) [<2001JA3478>](#). Lithium arene complexes can also be used to cleave cyclic *N*-phenylamines ([Equation \(15\)](#)) [<1996CSR155>](#).



2.11.2.1.2 Preparation by halogen–metal interconversion

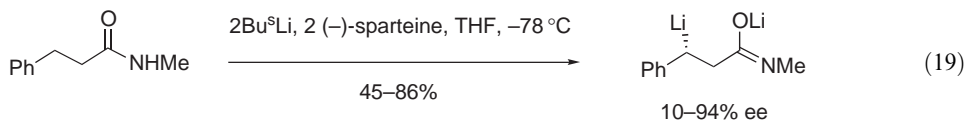
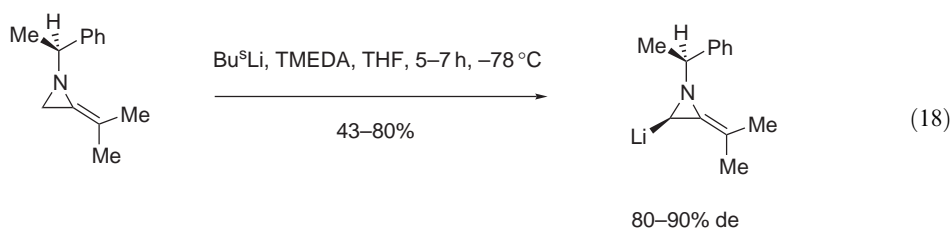
Reaction between organic halides and strong lithium bases such as *n*-butyl- or *t*-butyllithium, also known as the Wittig–Gilman reaction, is most useful for the preparation of aryl- or vinylolithium derivatives (see Chapter 2.19) but can also be useful for the preparation of certain alkyllithiums.

Good results can be obtained using alkyl iodides as substrates and pentane/diethyl ether mixtures as solvent. The reaction by-product, *t*-butyl iodide, is destroyed in the presence of a second equivalent of *t*-butyllithium (Equation (16)) <1999TL5433>. Use of cyclobutylmethyl iodides as substrates in this process gives cyclobutylmethylolithiums, which undergo subsequent ring opening to give 4-pentenylolithiums (Equation (17)) <1995JOC297>.



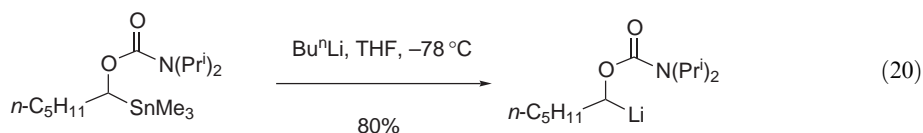
2.11.2.1.3 Preparation by deprotonation

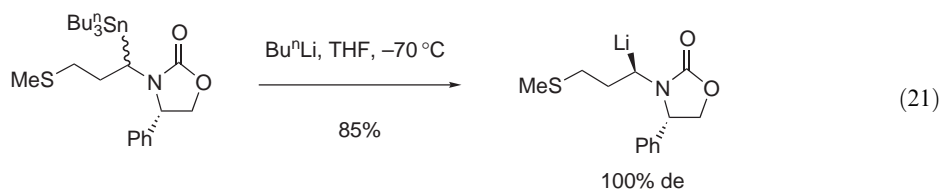
In general, alkanes are not sufficiently acidic to allow direct deprotonation by lithium bases. However, carbon–hydrogen bonds activated by conjugation, heteroatom electron-withdrawal, or intramolecular heteroatom assistance can often be successfully deprotonated to give alkylolithiums. The process can be enhanced by the use of coordinating tertiary amine additives, such as tetramethylethylenediamine (TMEDA) (Equation (18)) <2003CC1344>. Use of chiral additives, such as (–)-sparteine, allows for enantioselective alkylolithium preparation (Equation (19)) <1996JOC4542>.



2.11.2.1.4 Preparation from other alkyl metals: transmetalation

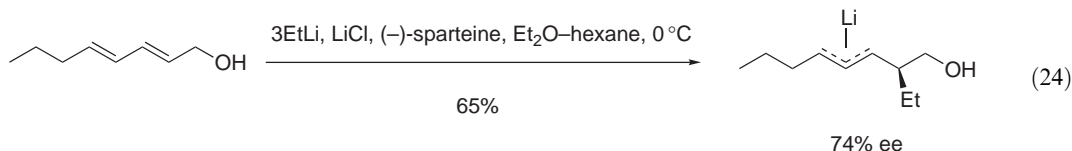
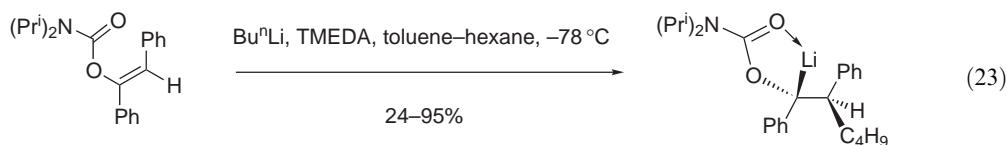
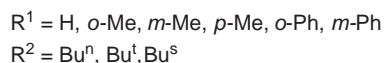
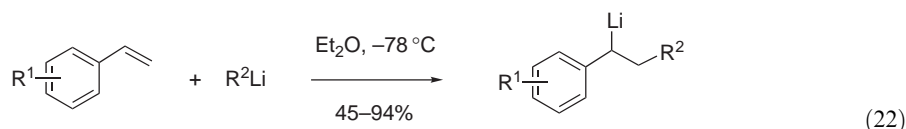
Tin–lithium exchange has been used to generate functionalized alkylolithiums, such as α -oxygen-, nitrogen-, or halo-bearing derivatives (Equation (20)) <1998TL9617> or β -keto derivatives, which would be difficult to obtain by other routes. Chiral auxiliaries can be used to control configuration at the lithiated carbon (Equation (21)) <1997TL7547>. Metal–lithium exchange with metals other than tin is not widely used.



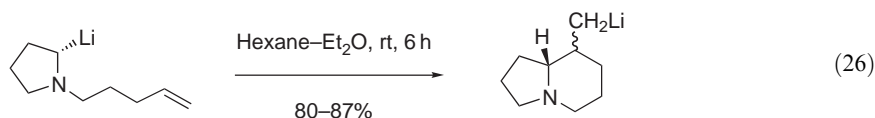
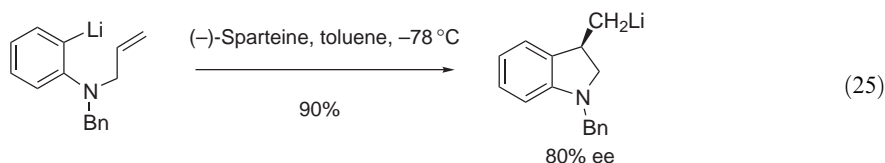


2.11.2.1.5 Addition to C—C double bonds: carbolithiation

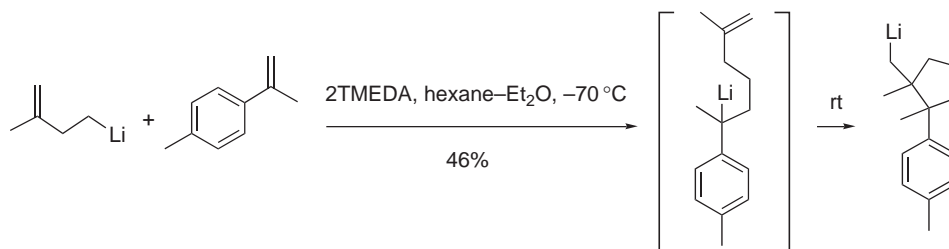
Addition of organolithium reagents to C—C double bonds, also known as alkene carbolithiation, is attractive as a two-component preparation of alkyl lithium derivatives. Anionic oligomerization is the dominant process undergone by alkenes in the presence of organolithiums, and this has been widely exploited in polymer synthesis. A variety of approaches allow oligomerization to be suppressed, giving synthetically viable alkene carbolithiation processes. Carbolithiation of styrene was found to be most successful using diethyl ether as solvent, use of THF resulting in polymerization (Equation (22)) <2000JCS(P1)1109>. Carbolithiation products can be stabilized against oligomerization by intramolecular heteroatom coordination (Equation (23)) <2002S381>. Addition of TMEDA or similar coordinating reagents can be used to increase reactivity of organolithiums toward inert alkenes, and use of (–)-sparteine allows some degree of enantioselectivity in certain cases (Equation (24)) <2000TL6575>.



Intramolecular carbolithiation has received considerable attention as a route to lithiated cycloalkanes. 5-Hexenyllithium derivatives undergo specifically 5-*exo-trig* cyclizations to give (lithiomethyl)cyclopentanes. Use of (–)-sparteine as an additive provides an enantioselective process (Equation (25)) <2000JA6789>. 6-*Exo-trig* intramolecular carbolithiation has also been reported (Equation (26)) <2000CC1569>.



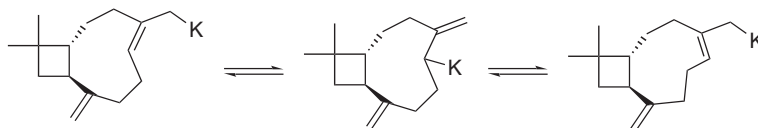
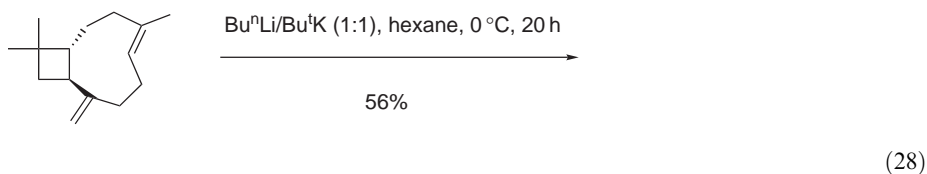
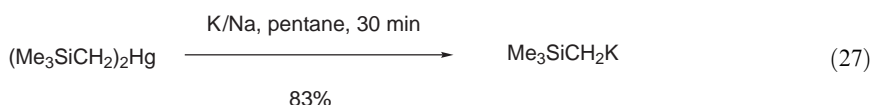
Tandem carbolithiation reactions have been used to obtain cyclopentane- and bicyclopentane-containing targets. For example, tandem inter- and intramolecular carbolithiation were employed in the synthesis of the natural product cuparene (Scheme 1) <2001JA3478>.



Scheme 1

2.11.2.2 Alkylsodium, Alkylpotassium, and Other Derivatives

Alkylsodium and alkylpotassium derivatives are less stable than their alkyllithium counterparts, and their chemistry is not explored thoroughly. Historically, transmetalation of organomercury compounds has been the most useful route to these compounds (Equation (27)) <1981JOM(220)277>. 1:1 Mixtures of *n*-butyllithium and potassium *t*-butoxide provide strongly basic conditions for the generation of alkylpotassiums by deprotonation (Equation (28)) <1998TL4031>. Alkylrubidium and -caesium compounds have been obtained from dialkylmercury derivatives, and by ether cleavage, but there has been little recent work on the preparation of these alkyl metals.

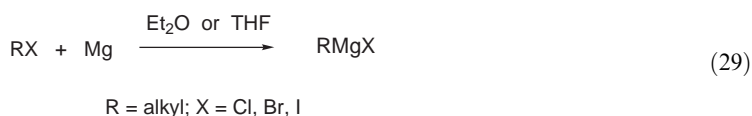


2.11.3 ALKYL GROUP 2 METAL DERIVATIVES

2.11.3.1 Alkylmagnesium Derivatives

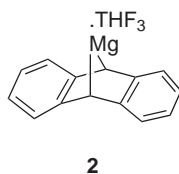
2.11.3.1.1 Preparation by oxidative addition: the Grignard reaction

Reaction of organic halides with magnesium turnings, better known as the Grignard reaction, is the most widely used method for preparing alkylmagnesium compounds. Alkyl chlorides, bromides, and iodides are the most suitable substrates, and diethyl ether and THF the most suitable solvents (Equation (29)).



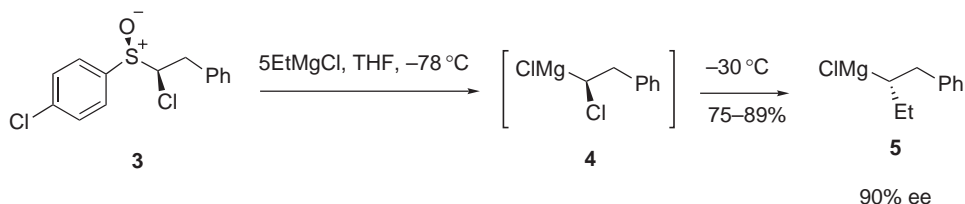
Activation of the magnesium surface is often necessary for successful Grignard reactions. A common practice is the use of small quantities of iodine or 1,2-dibromoethane as activating additives, which induce initiation of the reaction. Diisobutylaluminum hydride has been used to activate magnesium turnings for the manufacture of alkylmagnesium halides <2002OPRD906>. Sonication has been found to be a very effective method of activation. Primary and secondary alkyl chlorides can be converted into alkylmagnesium chloride in toluene containing small quantities of diethyl ether or THF with ultrasound assistance <1996JOM(523)133>. Effective activation can also be achieved by stirring magnesium particles without solvent under an inert atmosphere. Photomicrographic observation of magnesium surfaces during Grignard reactions with and without activation has shown that the reaction proceeds at discrete initiation sites on the magnesium surfaces. Addition of iodine increases the density of reactive sites on the magnesium surfaces, while sonication does not appear to affect the magnesium surfaces directly <1996JOC1059>. Highly reactive forms of magnesium can be used to achieve Grignard reaction of substrates, which are inert under the conditions described above, or which tend to give rise to side reactions, in particular Wurtz coupling. A slurry of finely powdered magnesium can be obtained by condensation of magnesium vapor into diethyl ether or THF. Highly reactive magnesium, known as Rieke magnesium, can be obtained by reduction of magnesium chloride with potassium in THF. Rieke magnesium is sufficiently reactive to induce Grignard reaction of alkyl fluorides, and for the preparation of unstable alkylmagnesium halides at low temperatures.

Magnesium reacts with anthracene in THF to form Mg(anthracene) (THF)₃ complex **2**. Complex **2** decomposes in solvents other than THF to give an activated form of magnesium, which can be used to metallate allylic, benzylic, and propargylic halides. Polymer- <1995JOM(502)35> and silica-supported <1995OM584> derivatives of complex **2** have been reported to effect benzylic metallation in THF.



In solution, alkylmagnesium halides exist in equilibrium with dialkylmagnesiums and magnesium halides; this phenomenon is known as the Schlenk equilibrium. Strongly coordinating solvents, such as dioxane or TMEDA, can precipitate magnesium halides and drive the formation of dialkylmagnesiums. Precipitation of magnesium halides from solutions of alkylmagnesium halides in toluene containing small quantities of diethyl ether results in the formation of highly soluble complexes, $xR_2Mg \cdot yMgX_2 \cdot zEt_2O$ <1997MGMC1>.

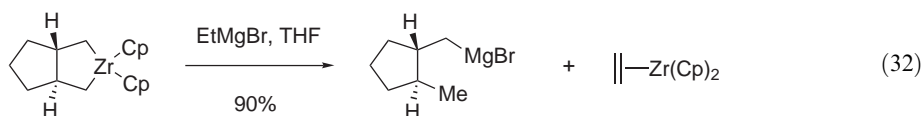
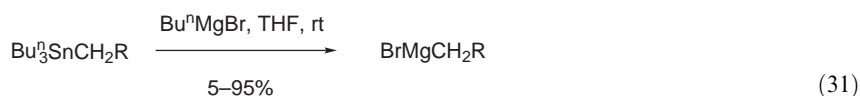
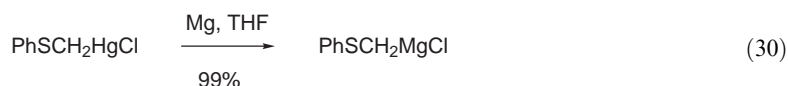
Highly activated magnesium is sufficiently reactive to induce cleavage of ethers, but the reaction has generally not been useful to synthesize alkylmagnesiums. Benzylmagnesium species can be prepared effectively by cleavage of benzyl methyl ethers using the Mg(anthracene) (THF)₃ complex **2**. A configurationally stable alkylmagnesium **5** has been prepared by the cleavage of α -chlorosulfoxide **3** by ethylmagnesium chloride, followed by further *in situ* reaction of the resultant α -chloro Grignard derivative **4** (Scheme 2) <2000AG(E)3072>.



Scheme 2

2.11.3.1.2 Preparation by transmetallation

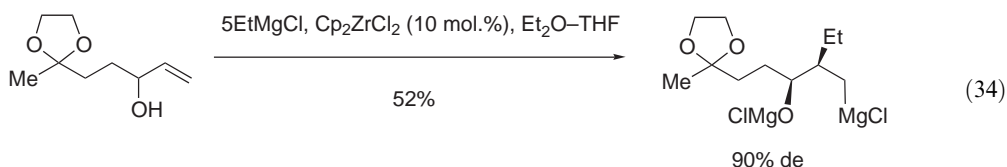
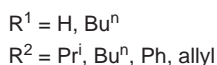
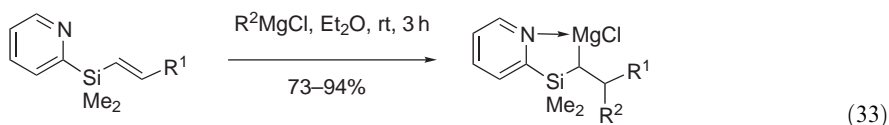
Preparation of certain functionalized alkylmagnesiums by transmetallation from the corresponding alkylmercury or alkyltin derivatives has been reported. Thiomethylmagnesium chlorides have been obtained by transmetallation of thiomethylmercury chloride complexes (Equation (30)) <2001ZAAC2408>, while sulfur- and phosphorus-functionalized alkylmagnesium halides were obtained by transmetallation of the corresponding tributyltin derivatives (Equation (31)) <2002JOM(655)111>. Zirconabicyclo[3.3.0]octanes undergo transmetallation to give monocyclic alkylmagnesiums when treated with ethylmagnesium bromide (Equation (32)) <1998ICA8>. Magnesium dibromide has been used to prepare alkylmagnesiums by transmetallation of alkyl-lithiums <2001JA30>.

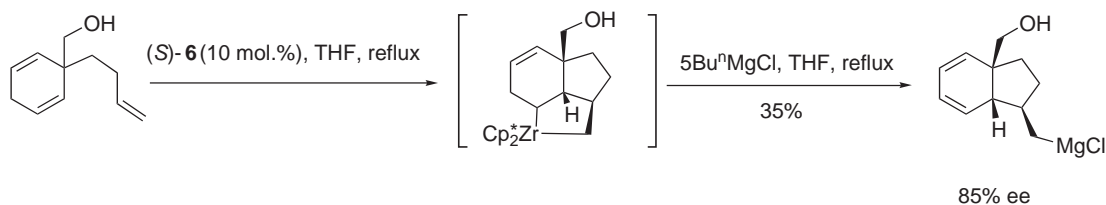


2.11.3.1.3 Addition to C—C double bonds

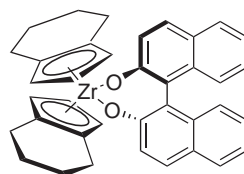
(i) Carbomagnesation

Grignard reagents are less reactive toward alkenes than alkylolithiums; consequently activating conditions are required for successful carbomagnesation. This can be provided by high pressures and temperatures, or by heteroatom coordination (Equation (33)) <2001AG(E)2337>. Carbomagnesation is very effectively catalyzed by organozirconium species (Equation (34)) <1997JA10302>. Use of nonconjugated diene substrates in these reactions can give *in situ* zirconacycle formation, followed by Grignard transmetallation (Scheme 3). Use of a chiral nonracemic catalyst, e.g., complex **6**, provides some enantioselectivity <2003TL3797>.





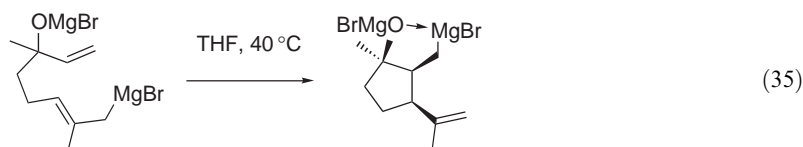
Scheme 3

Cp₂^{*}ZrBINOL

6

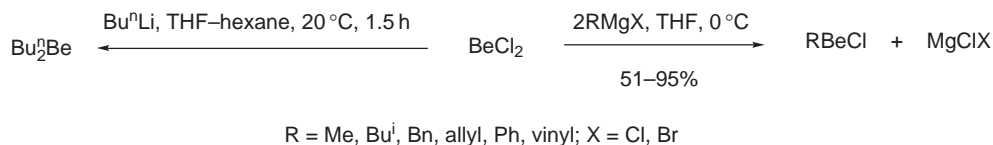
(ii) *The magnesio-ene reaction*

Carbomagnesation of alkenes using allylic Grignards proceeds with γ -regioselectivity: the magnesio-ene reaction. The intramolecular version of this reaction is of considerable synthetic utility. The reaction generally requires heating of a preformed allylic Grignard. Presence of coordinating alkoxy-functionality provides a diastereoselective process (Equation (35)) <2001JA30>.



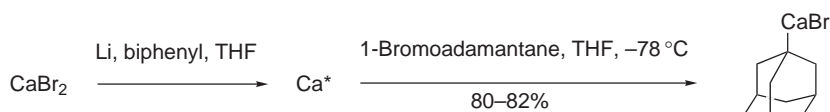
2.11.3.2 Other Derivatives

Organoberyllium, -calcium, -strontium, and -barium derivatives have been much less utilized than the corresponding magnesium derivatives. Alkylberyllium derivatives can be obtained by halogen-metal exchange between alkylolithiums or Grignard reagents with beryllium dichloride. These can be obtained as salt-free R₂Be species by distillation, or as RBeCl species as components of salt mixtures (Scheme 4) <1997TL6295>. Alkylberyllium derivatives can also be obtained by reaction of dialkylmercury compounds with beryllium metal, and by reaction of trialkylboron derivatives with diethylberyllium.



Scheme 4

Reduction of CaBr₂ with lithium biphenylide gives a highly reactive form of calcium, which reacts with alkyl halides to give alkylcalcium halides (Scheme 5) <1995OS147>. Alkylbarium derivatives can be obtained similarly from BaI₂.



Scheme 5

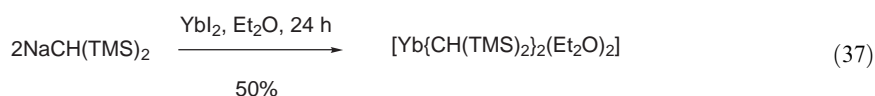
2.11.4 ALKYL TRANSITION METAL DERIVATIVES

2.11.4.1 Alkylscandium, -yttrium, -lutetium, and -lanthanide Derivatives

In general, the most stable oxidation state for lanthanides is (III), although some form relatively stable derivatives with oxidation state (II).

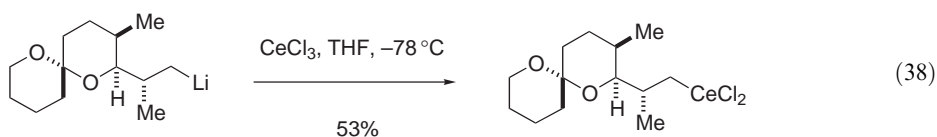
2.11.4.1.1 *M(II)* derivatives

Powdered lanthanide metals react with alkyl iodides in Grignard-like reactions in THF as solvent, giving alkyl metal iodides RLnX [<1995COFGT\(2\)549>](#). This process is most successful for those lanthanides with relatively stable *M*(II) oxidation states, notably Eu and Yb ([Equation \(36\)](#)) [<2002JOM\(647\)21>](#). Metal activation may be necessary, for example, by addition of CH_2I_2 . RLnX can also be obtained by exchange reactions with other alkyl metals and LnX_2 salts. Exchange reactions can also be used to obtain dialkyl metals ([Equation \(37\)](#)) [<1995AG\(E\)2466>](#).

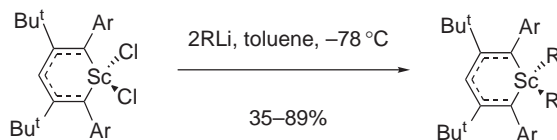


2.11.4.1.2 *M(III)* derivatives

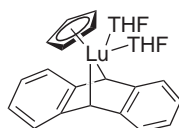
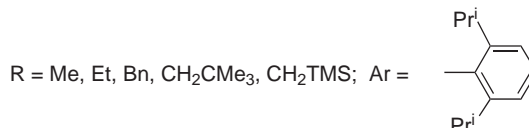
Monoalkylated derivatives, the most important for synthetic applications, can be obtained by reaction of organometallics and anhydrous lanthanide salts. Alkylolithiums are the most widely used organometallics for this purpose ([Equation \(38\)](#)) [<1998JA2523>](#). Monoalkyl *Sm*(III) derivatives can be prepared by oxidative addition of alkyl iodides and bromides to SmI_2 ([Equation \(39\)](#)) [<1997TL3171>](#). Dialkylated derivatives can be obtained through the use of stabilizing ligands ([Equation \(40\)](#)) [<2001OM2533>](#). Various lanthanide complexes can be formed from anthracene dianion. Reaction with cyclopentadienyllutetium chloride complexes gives lutetium—anthracene addition complexes, e.g., **7** [<2002JOM\(647\)21>](#). Trialkyl lanthanides are the least stable derivatives and their chemistry is the least well explored.



$\text{RX} = n\text{-C}_7\text{H}_{15}\text{I}, \text{CH}_3\text{CHBr}(\text{CH}_2)_4\text{CH}_3, n\text{-C}_6\text{H}_{13}\text{I},$
 $n\text{-C}_{10}\text{H}_{21}\text{Br}, n\text{-C}_6\text{H}_{13}\text{I}, \text{BnBr}, n\text{-C}_{10}\text{H}_{21}\text{Br}$



(40)



7

2.11.4.2 Alkyltitanium, -zirconium, and -hafnium Derivatives

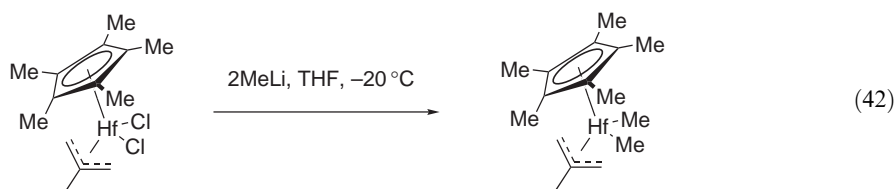
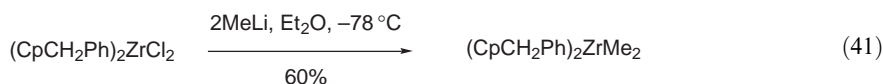
Alkyl derivatives of these metals are in oxidation states (II), (III), and (IV), the last being the most stable.

2.11.4.2.1 *M(II) and M(III) derivatives*

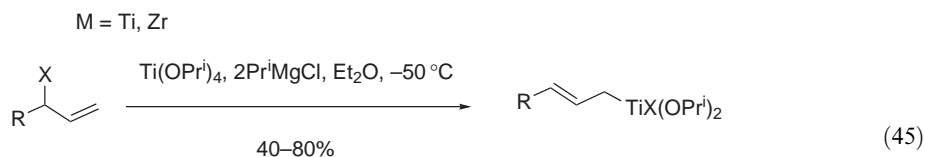
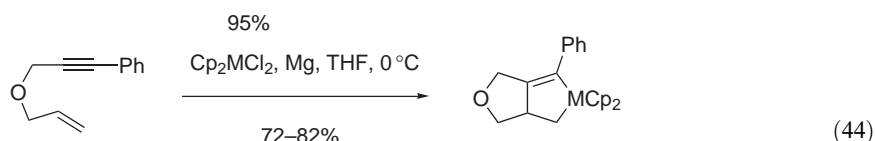
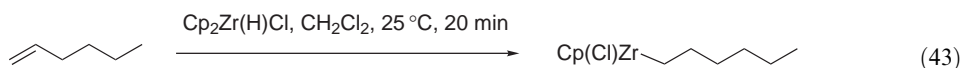
M(II) derivatives containing alkyl metal bonds are rare. M(III) derivatives are more common, especially for Ti. RMCP₂ complexes can be obtained by reaction of alkylolithiums with (Cp₂MCl)₂ (M = Ti, Zr, Hf), although this is successful only with bulky alkyl groups. M(III) derivatives can also be obtained by reduction of M(IV) derivatives using alkylolithiums or alkylmagnesium compounds, e.g., Cp₂TiBn can be obtained from Cp₂TiCl₂ by treatment with a twofold excess of benzylolithium.

2.11.4.2.2 *M(IV) derivatives*

Reaction of anhydrous metal salts MX₄ (M = Ti, Zr, Hf) with organometallic reagents gives mono-, di-, tri-, or tetraalkyl derivatives depending on the reaction stoichiometry. Alkylolithium and Grignard reagents have been most extensively used in these processes. Commonly used MX₄ salts include MCl₄ and Cp₂MCl₂ (M = Ti, Zr, Hf). Reactions are usually carried out in diethyl ether (Equation (41)) <1999JCS(D)43> or THF (Equation (42)) <1997JOM(543)237> as solvent.



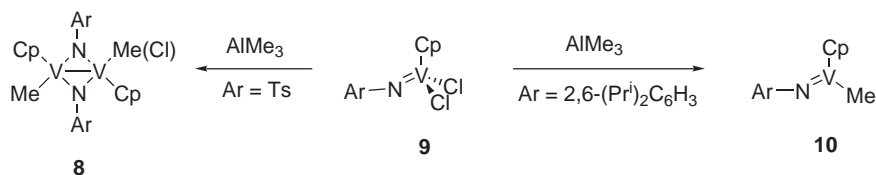
Zirconocene hydrides such as Schwartz's reagent ($\text{Cp}_2\text{Zr(H)Cl}$) and related derivatives react with alkenes to give alkylzirconium compounds by hydrozirconation. This reaction generally proceeds under mild conditions and gives primary alkylzirconium derivatives regioselectively (Equation (43)) <1999TL8411>. Bicyclic metallocycles can be obtained by the intramolecular reductive coupling of dienes and enynes with low-valent derivatives, generated *in situ* from Cp_2MCl_2 ($\text{M} = \text{Ti}, \text{Zr}$) and metal or alkyl metal reductants (Equation (44)) <1996TL9059>. This has become a valuable method for the preparation of carbocycles and heterocycles. Allyltitanium(IV) derivatives can be obtained by reaction of allylic halides, carbonates, or phosphates with $(\eta^2\text{-propene})\text{Ti}(\text{OPr}^i)_2$, generated *in situ* from $\text{Ti}(\text{OPr}^i)_4$ and 2 equiv. of Pr^iMgBr (Equation (45)) <2002TL4373>.



R = alkyl; X = halide, alkyl carbonate, dialkyl phosphate

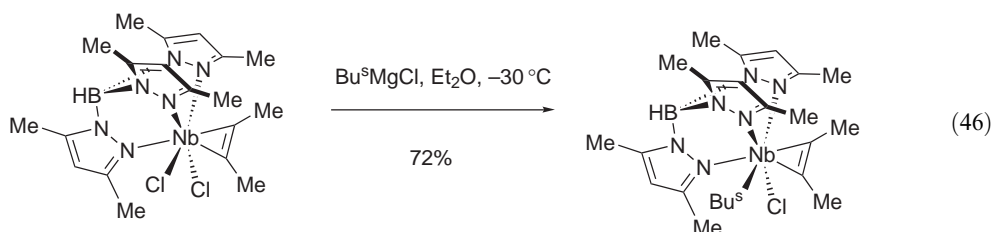
2.11.4.3 Alkylvanadium, -niobium, and -tantalum Derivatives

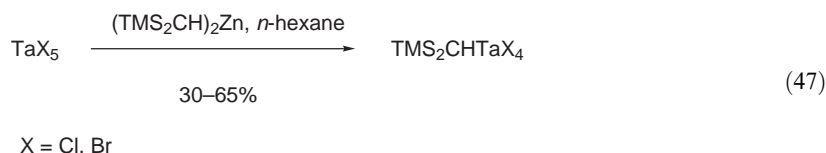
The M(II) and M(III) derivatives are relatively unstable. M(IV) derivatives can be prepared by transmetalation from derivatives such as $(\text{Et}_2\text{N})_3\text{VCl}$ or Cp_2MCl_2 ($\text{M} = \text{V}, \text{Nb}, \text{Ta}$) using organolithium or other organometallic reagents, giving $(\text{Et}_2\text{N})_3\text{VR}$ or Cp_2MR_2 derivatives, respectively. Reaction of the imidovanadium dichlorides **9** with AlMe_3 gives the methylvanadium(IV) derivatives **8** or **10**, depending on the nature of the imido *N*-substituent (Scheme 6) <1995JOM(497)161>.



Scheme 6

Alkyl M(V) derivatives are the most widely reported. Transmetalation of metal chloride complexes using alkyl lithium or Grignard reagents is the most general method. Use of bulky ligands stabilizes products and avoids side reactions (Equation (46)) <2001JA6000>. Treatment of MX_5 ($\text{M} = \text{Nb}, \text{Ta}$; $\text{X} = \text{Cl}, \text{Br}$) with dialkylzinc reagents gives alkylated M(V) halides (Equation (47)) <1999OM832>, the di- or trialkylated species are usually obtained.



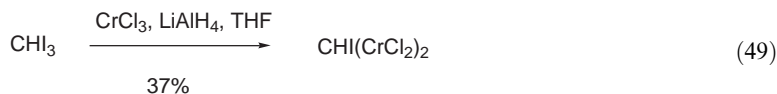
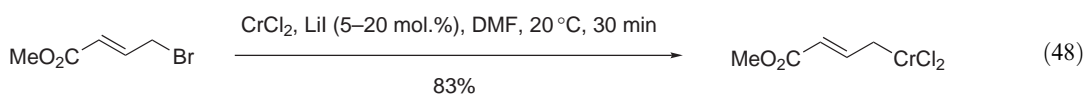


2.11.4.4 Alkylchromium, -molybdenum, and -tungsten Derivatives

The organometallic chemistry of these elements is dominated by alkylchromium(III) derivatives, which have considerable utility as nucleophiles for organic synthesis.

2.11.4.4.1 Cr(III) derivatives

A variety of alkylchromium(III) derivatives $[\text{RCrCl}_2(\text{THF})_n]$; $\text{R} = \text{alkyl}$, $n = 0\text{--}3$ can be obtained by transmetalation of alkylolithium, alkylmagnesium, or alkylaluminum compounds with CrCl_3 or $\text{CrCl}_3(\text{THF})_3$ complex. Alternatively, alkylchromium(III) derivatives can be obtained by the oxidative addition of Cr(II) species to alkyl halides (Equation (48)) <1997SL731>. Use of CrCl_2 doped with catalytic amounts of Ni(II) provides a reliable methodology for these transformations. As CrCl_2 is air sensitive and hygroscopic, *in situ* generation by reduction of CrCl_3 can be preferable; LiAlH_4 , Zn , $\text{Na}(\text{Hg})$, or Mn have been used as reducing agents. $\text{CrCl}_2(\text{THF})_n$ [$n = 0\text{--}2$] can be prepared from CrCl_3 and metallic Cr powder <1995COFGT(2)549>. Allyl, benzyl, and propargyl halides, and α -halosulfides have been used as substrates for this process. Oxidative addition of Cr(II) to alkyl halides other than allyl and benzyl can be hampered by competing $\text{S}_{\text{N}}2$ substitutions by chloride ion. This difficulty can be overcome by the trapping of alkyl radicals by catalytic quantities of cobalt complexes, such as vitamin B₁₂ or Co-phthalocyanine, allowing formation of functionalized alkylchromium derivatives from alkyl halides or alkyl tosylates. Use of geminal diiodoalkanes in Cr(II) oxidative additions generates geminal dichromium derivatives (Equation (49)) <1998TL803>. The preparation and use of organochromium(III) derivatives has been reviewed <1999CRV991>.



2.11.4.4.2 Other derivatives

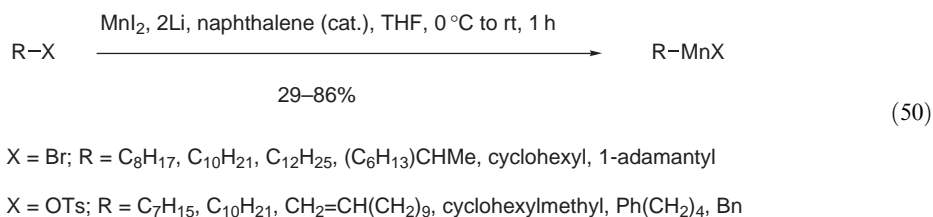
Few alkyl metal complexes involving group 6 metals in M^0 oxidation states are reported. Alkyl M(II) complexes can be obtained by transmetalation from alkylolithium derivatives, by alkylation of anionic complexes, or by decarbonylation of acyl metal complexes <1995COFGT(2)549>. Alkylmolybdenum(III) and alkyltungsten(III) derivatives can be prepared by reductive transmetalation and generally possess dimeric structures. Tetraalkylchromium(IV) complexes may be obtained by treatment of CrCl_3 with alkylolithium or alkylmagnesium reagents followed by oxidation, or by direct transmetalation of a Cr(IV) salt. Treatment of WCl_6 with alkylzinc, alkyltin, alkylmercury, or alkylboron reagents give monoalkylated W(VI) derivatives. Reaction with AlMe_3 gives Me_6W . Metal oxo complexes can be obtained by transmetalation, e.g., derivatives RWCl_3 and R_2LMoO_2 can be prepared using suitable organometallics from WOCl_4 and LMoO_2Br_2 , respectively.

2.11.4.5 Alkylmanganese Derivatives

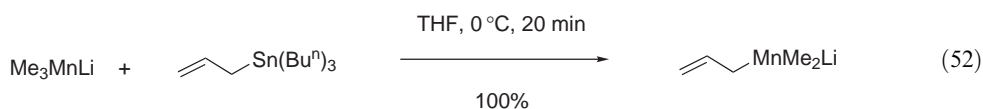
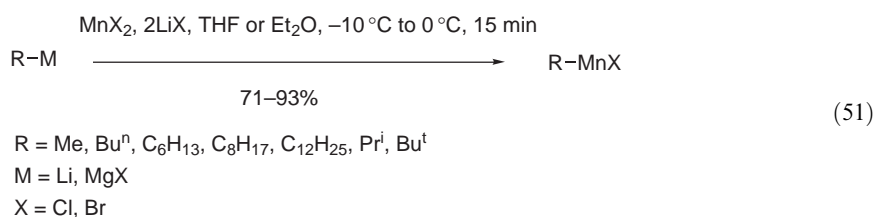
Alkylmanganese derivatives of oxidation state (I)–(IV) are known. However, the majority of reports concern the most synthetically useful alkylmanganese(II) derivatives.

2.11.4.5.1 Mn(II) derivatives

Alkylmanganese(II) derivatives can be obtained by oxidative addition to alkyl halides or sulfonates, or by transmetallation reactions. Elemental manganese is relatively unreactive and undergoes only oxidative addition to allylic halides. A reactive form of manganese, obtained by reduction of manganese halides with 2 equiv. of lithium metal and a catalytic quantity of naphthalene, is suitable for direct oxidative addition to primary, secondary, and tertiary alkylbromides and primary alkyl tosylates (Equation (50)) <1996TL2197, 1999TL4931>. 2-Phenylpyridine has been reported as a more readily extractable alternative to naphthalene in such processes <1999TL6407>. Treatment of Li_2MnCl_4 with activated magnesium in THF produces a black suspension of manganese, which oxidatively adds to allyl halides and α -iodocarbonyl compounds <2001T8807>.



Transmetallation can be used to prepare derivatives of formula RMnX , R_2Mn , or R_3MnM (R = alkyl, M = MgX or Li), depending on the reaction stoichiometry. Anhydrous manganese dichloride or diiodide can be used as substrates for these processes, but better results are achieved using ether-soluble manganate complexes MnX_4Li_2 (prepared *in situ* from MnX_2 and 2LiX, X = Cl or Br) (Equation (51)) <1995TL6449, 1998TL849>. R_3MnM derivatives react with activated alkyl halides, such as α -iodophenylmethyl sulfides, to give nucleophilic alkylmanganese derivatives of uncertain structure <2000OM4941>. These reactions also proceed with allyl ethers, resulting in *O*-allyl bond cleavage giving nucleophilic allylmanganese derivatives <1999TL6613>. Similar allylmanganese(II) complexes can also be obtained by transmetallation with allyl tributyltin (Equation (52)) <1997TL9019>.



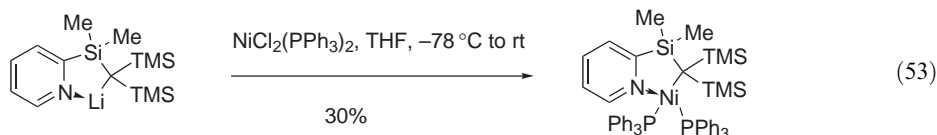
2.11.4.5.2 Other derivatives

Alkylmanganese(I) derivatives can be obtained by reaction of $\text{NaMn}(\text{CO})_5$ with alkyl halides, or with acyl chlorides followed by decarbonylation. Alternatively, transmetallation from $\text{BrMn}(\text{CO})_5$ using alkyllithium, alkylmagnesium, or alkylmercury reagents can be employed. Alkylmanganese(III) and alkylmanganese(IV) derivatives are obtained by oxidation of lower oxidation state complexes.

2.11.4.6 Alkyliron, -cobalt, and -nickel Derivatives

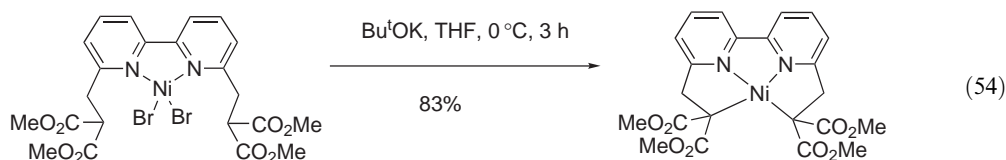
2.11.4.6.1 *M(0)* and *M(I)* derivatives

Alkyl derivatives containing *M*(0) to *M*(IV) are known. The oxidation state (0) is known only for iron and nickel. Alkyliron (0) derivatives can be obtained by treatment of disodium tetracarbonyl ferrate (Collman's reagent) with alkyl halides or tosylates. Alkylcobalt(I) derivatives can be obtained by alkylation of anionic complexes such as $\text{Co}(\text{PPh}_3)^-$, or by hydrometallation of alkenes with $\text{HCo}(\text{CO})_4$. Preparation of an alkylnickel(I) complex has been reported (Equation (53)) <2000CC693>.



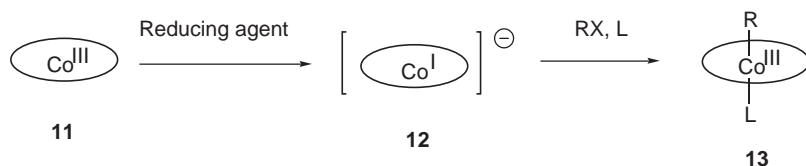
2.11.4.6.2 *M(II)* derivatives

Alkyliron(II) derivatives can be obtained by alkylation of the complex $\text{CpFe}(\text{CO})_2^-$ (or Fp^-). Alkylmetal(II) derivatives of iron, cobalt, and nickel can be obtained by transmetalation from appropriate metal (II) salts, usually chlorides. Mono- to tetraalkylated derivatives can be obtained: RMX , R_2M , R_3MLi , R_4MLi_2 (R = alkyl; M = Fe, Co) <1996AG(E)386>. Stabilized complexes can be obtained by use of ligands such as cyclopentadienylides and phosphines. A stable alkylnickel(II) complex featuring a functionalized bipyridyl ligand has been reported (Equation (54)) <2002ARK40>. Alkyliron(II) compounds can also be obtained by π - to σ -isomerization of alkene ligands, which occurs with concomitant addition of nucleophiles giving (α - or β -functionalized)alkyliron(II) derivatives <1995COFGT(2)549>.



2.11.4.6.3 *M(III)* and *M(IV)* derivatives

Coenzyme B_{12} is a naturally occurring alkylcobalt(III) porphyrin complex, while alkyliron(III) complexes are implicated in several metabolic processes. The biochemical significance of these compounds has stimulated considerable research activity, and several *M*(III) complexes of both metals have been prepared by the general methods of transmetalation, oxidative addition, or hydrometallation. Alkylcobalt(III) porphyrin complexes **13** were obtained by alkylation of the *in situ* generated anionic cobalt(I) complexes **12** (Scheme 7) <2000IC1518, 1997JA1648>.



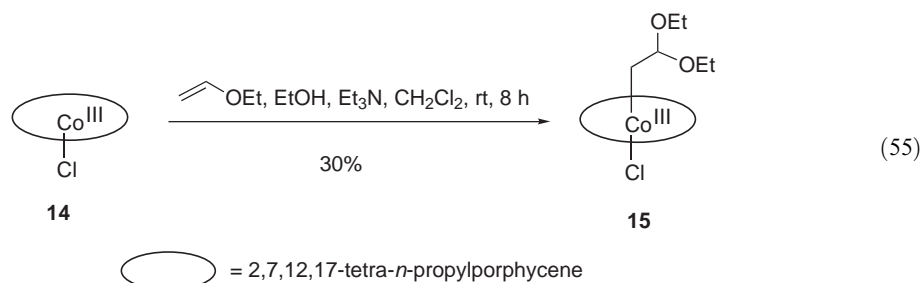
Reducing agents = NaBH_4 , $\text{Na}(\text{Hg})$

RX = MeI , Me_2SO_4 , EtI , PrI ; L = pyridine, PEt_3 , H_2O

= octaethylporphyrin, *t*-octaethylchlorin, *ttt*-octaethylisobacteriochlorin, (difluoroboryl)dimethylglyoximate

Scheme 7

Addition of vinyl ether to cobalt(III) complex **14** in the presence of ethanol gave the (β,β -dialkoxy)alkylcobalt(III) complex **15** (Equation (55)) <2001OM3074>. The alkyl metal (IV) derivatives of this group are labile to reduction, hindering their preparation.

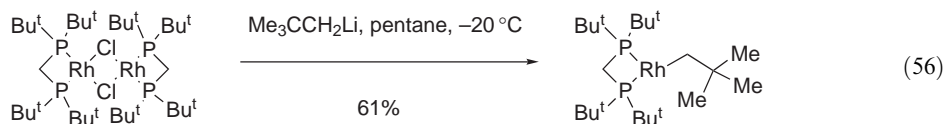


2.11.4.7 Alkylruthenium, -rhodium, -palladium, -rhenium, -osmium, -iridium, and -platinum Derivatives

Alkyl derivatives of these metals in oxidation states of (I)–(VII) are known.

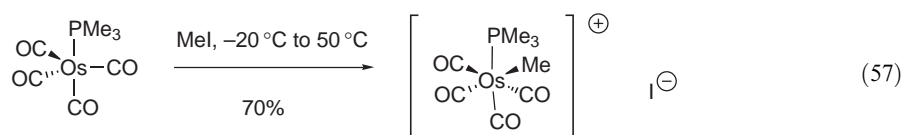
2.11.4.7.1 *M*(I) derivatives

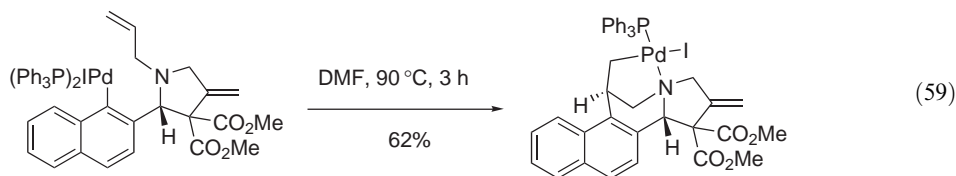
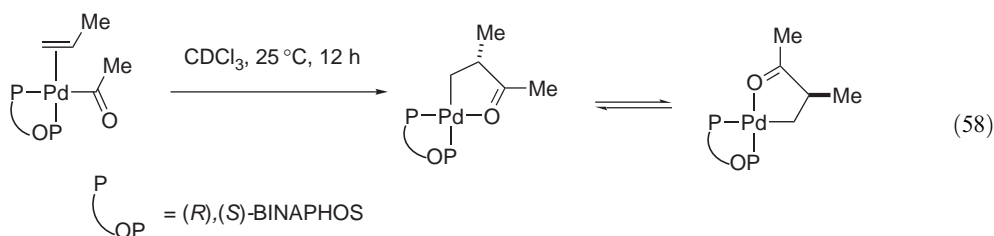
Alkylrhodium(I) and alkyliridium(I) phosphine complexes can be prepared by transmetalation of *M*(I) chloride complexes. Alkylated derivatives can be obtained by treatment of anionic complexes $\text{Re}(\text{CO})_5^-$ or $\text{Os}(\text{CO})_4^{2-}$ with alkyl halides. A neutral three-coordinate alkylrhodium(I) complex has been obtained (Equation (56)) <2001AG(E)781>.



2.11.4.7.2 *M*(II) derivatives

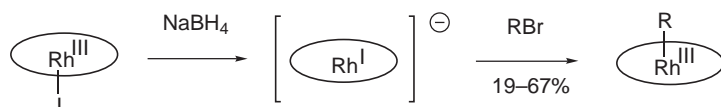
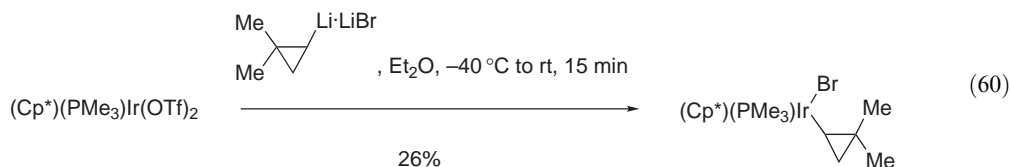
Alkylpalladium(II) and alkylplatinum(II) complexes have been prepared by transmetalation. Stabilizing ligands such as phosphines, phosphites, arsines, nitriles, or pyridines are required to prevent decomposition into alkenes and alkanes. Transmetalation of L_2OsCl_2 complexes can be used to obtain alkyl-osmium(II) derivatives. Palladium or platinum complexes bearing bulky ligands can undergo *o*-metallation reactions, with the formation of alkyl metal bonds. Anion osmium(II) and ruthenium(II) complexes can react with alkyl halides to give alkyl-metal (II) complexes. A variety of osmium (0), ruthenium (0), palladium (0), and platinum (0) species undergo oxidation addition reactions with alkyl halides to give alkyl metal(II) derivatives (Equation (57)) <1997JCS(D)1759>. Alkene π -complexes of ruthenium, palladium, osmium, and platinum undergo π - to σ -isomerization to give σ -bond alkyl complexes, often with concomitant nucleophilic addition or group insertion (Equation (58)) <2000OM2031>. Such processes are often important steps in the catalytic cycle of organopalladium-mediated coupling reactions, and some σ -bonded alkylpalladium(II) complexes have been obtained as a consequence of interrupted Heck reactions (Equation (59)) <2001AG(E)1439, 2003CC272>.





2.11.4.7.3 *M(III) derivatives*

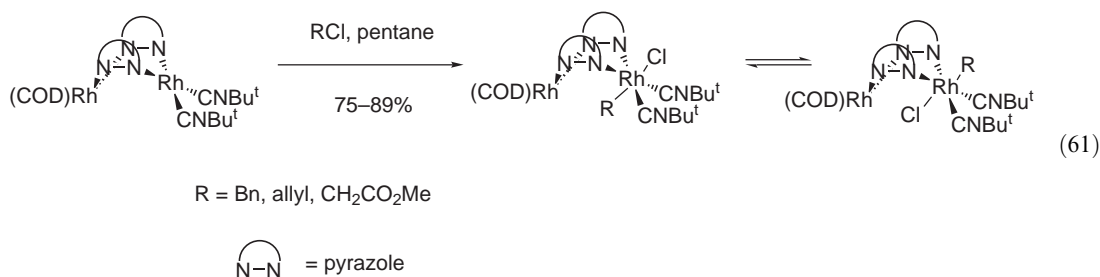
Alkyl metal(III) derivatives of rhenium, rhodium, and iridium can be prepared by similar methods to those suitable for metal(II) derivatives, i.e., by transmetalation (Equation (60)) <1998OM3574>, alkylation (Scheme 8) <2001TL4187>, or oxidative addition (Equation (61)) <2000OM4968>.



RBr = 3,5-dimethoxybenzyl bromide, poly(benzyl ether) dendritic bromides

= tetramesitylporphyrin

Scheme 8

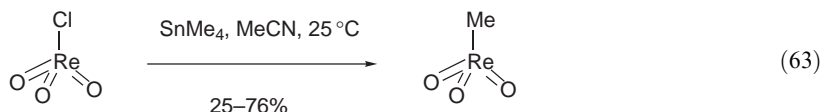
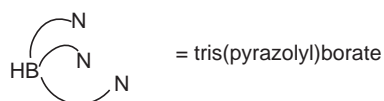
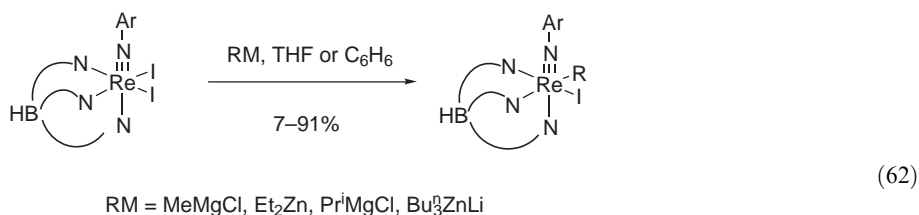


2.11.4.7.4 M(IV) derivatives

Alkylplatinum derivatives are the most significant in the M(IV) oxidation state. These can be prepared by transmetallation of PtCl_4L_2 or CpPtCl_3 complexes. Alkylrhenium(IV) complexes of formula R_{12}Re_4 can also be obtained by transmetallation. Alkylplatinum(II) complexes undergo oxidative addition of halogens or alkyl halides to give M(IV) derivatives. Platinum(IV) metallocyclobutanes can be obtained by oxidative addition of cyclopropane to platinum(II) salts.

2.11.4.7.5 M(V), M(VI), and M(VII) derivatives

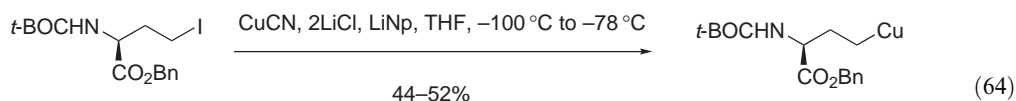
With the exception of the iridium(V) complex Cp^*IrMe_4 , alkyl derivatives in these oxidation states are known only for rhenium. Alkylrhenium(V) and (VII) derivatives can be obtained by transmetallation reactions (Equations (62) <1999OM3715> and (63)) <1997AG(E)2652>.



2.11.5 ALKYL COPPER, -SILVER, AND -GOLD DERIVATIVES

2.11.5.1 Alkylcopper Derivatives

Alkylcopper reagents are significant due to their usefulness in synthesis. Derivatives of formula RCu , R_2CuM (low-order cuprates), and R_3CuM_2 (higher-order cuprates) are known; all are of M(I) oxidation state. Preparation by halogen-metal exchange requires the use of activated metal, for example, as obtained by reduction of Cu(I) salts in the methods developed by Rieke <1997T1925>. For example, lithium naphthalene reduction of copper iodide in the presence of tributyl or triphenyl phosphine, lithium naphthalenide reduction of soluble $\text{CuCN} \cdot 2\text{LiX}$ ($\text{X} = \text{Cl}, \text{Br}$) complexes, or the reduction of 2-thienylcyanocuprates (Equation (64)) <1998JCS(P1)1903>. The majority of alkylcopper derivatives reported have been prepared by transmetallation reactions, usually involving alkyllithium or alkylmagnesium reagents.



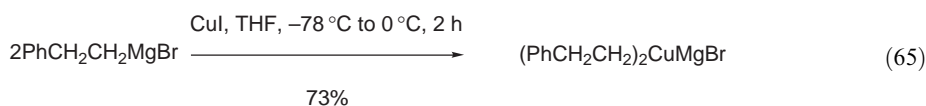
LiNp = Lithium naphthalenide

2.11.5.1.1 Monoalkylcopper derivatives

Monoalkylcopper derivatives are generally thermally sensitive and have been known to explode on attempted isolation. They are usually prepared at low temperatures and used immediately. These are best prepared by reaction of 1 equiv. of alkyllithium reagent with a copper(I) salt. Monoalkylcopper derivatives can also be obtained by treatment of copper(II) salts with 2 equiv. of alkyl metal reagent, the first equivalent inducing reduction to Cu(I). However, this method is not useful for preparing monoalkylcopper derivatives for synthetic applications.

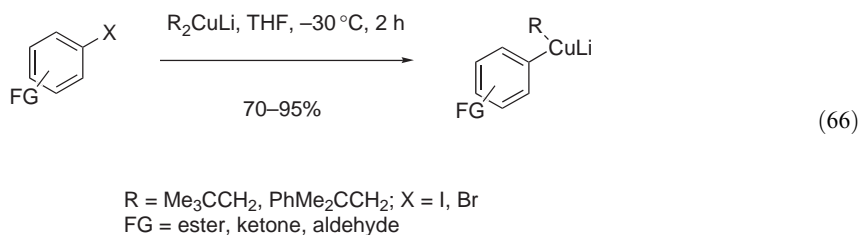
2.11.5.1.2 Homocuprates

The low-order cuprates R^1R^2CuM are the most widely exploited alkylcopper derivatives in organic synthesis. The homocuprates are those in which $R^1 = R^2 = \text{alkyl}$. These derivatives are more stable than the monoalkylcoppers and can be prepared by treatment of copper(I) salts with 2 equiv. of an alkyllithium or alkylmagnesium reagent (Equation (65)) <2002TL7499>. Homocuprates bearing chloro, amido, cyano, or alkoxy functionality can be obtained by transmetallation with alkylsamarium(III) or dialkylzinc reagents. A one-pot hydrozirconation–transmetallation procedure allows the preparation of alkylcuprates from alkenes via the intermediacy of alkylzirconium species.



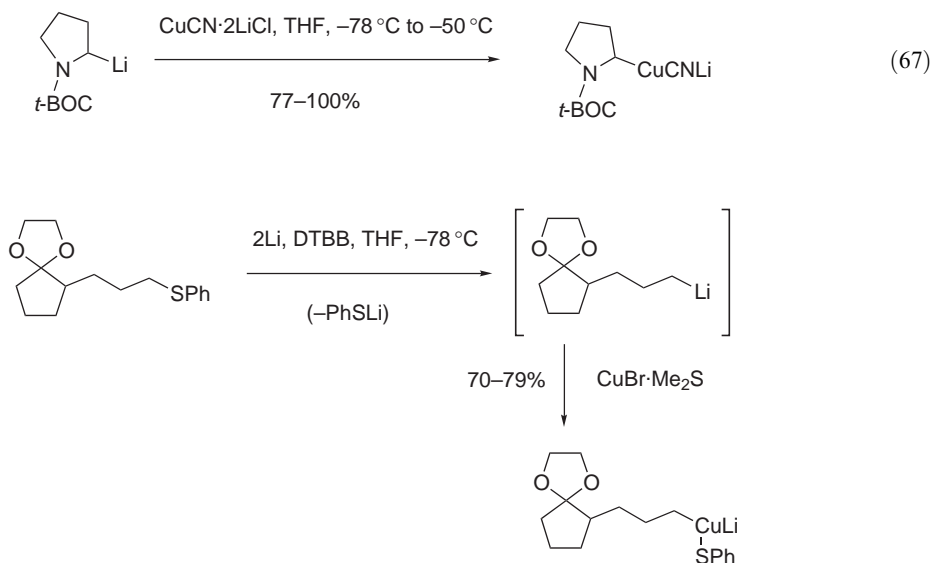
2.11.5.1.3 Mixed cuprates

Mixed dialkylcuprates can be obtained by sequential addition of different organometallic reagents to copper(I) salts. The most synthetically important mixed cuprates are those on which one group is tightly bound and is not transferable, for example alkynyl or 2-thienyl groups. Mixed alkylalkynyl cuprates are therefore reagents for the selective transfer of the alkyl groups <1995COFGT(2)549>. Mixed arylalkyl cuprates bearing sterically hindered alkyl groups have been prepared as reagents for the transfer of functionalized aryl groups (Equation (66)) <2002AG(E)3263>.



2.11.5.1.4 Heterocuprates

Heterocuprates contain one alkylcopper bond and one other ligand bonded to copper by a heteroatom (not halide), which is not transferred in subsequent nucleophilic attacks. Cyanide ion is accepted into this category and the cyanocuprates are the most important heterocuprates due to their stability and synthetic utility. The cyanocuprates are prepared by treatment of alkyllithium derivatives with copper cyanide, solubilized by addition of 2 equiv. of lithium chloride (Equation (67)) <2003T1083>. Other cuprate heteroligands include bulky alkoxides and thioalkoxides. Alkylthiophenoxide heterocuprates can be generated from alkyllithiums produced by cleavage of alkylphenyl sulfides (Scheme 9) <1997T17607>.



Scheme 9

2.11.5.1.5 Higher-order cuprates

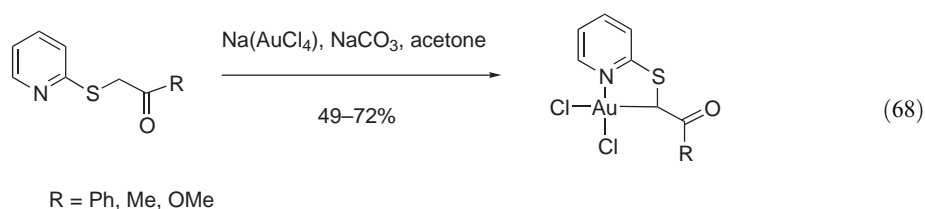
Reaction of 2equiv. of an alkyl lithium reagent with copper cyanide gives the stable dianionic complexes $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$. These are synthetically useful reagents for the transfer of tertiary alkyl groups and for reactions with hindered electrophiles. Nontransferable ligands, such as 2-thienyl groups, can be used for alkyl group economy [<1995COFGT\(2\)549>](#).

2.11.5.2 Alkylsilver Derivatives

Alkylsilver derivatives suffer from great thermal and photosensitivity and are of limited synthetic application. Methods for their preparation are the same as those for alkylcopper derivatives; however, the products tend to decompose above -50°C or above -10°C if stabilized by lithium bromide.

2.11.5.3 Alkylgold Derivatives

Alkylgold derivatives are known in the M(I) and M(III) oxidation states. Monoalkylgold derivatives decompose to precipitate metallic gold unless stabilized as phosphine complexes, in which form they can be prepared by transmetallation of gold(I) chloride phosphine complexes. Monoalkylated gold(III) complexes, in which the C—Au bond is contained in a metallocycle, can be obtained ([Equation\(68\)](#)) [<1999OM753>](#). Dialkylgold(III) halides can be prepared by the reaction of Grignard reagents with gold trichloride pyridine complex or digold hexabromide. Trialkylgold derivatives are unstable except as square planar complexes with phosphine or arsine ligands. These can be obtained by transmetallation of gold(III) halides or by alkylation of dialkylaurates.

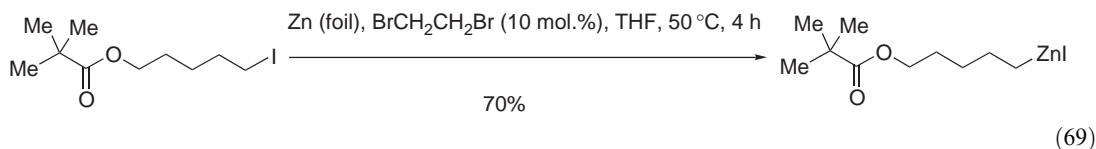


2.11.6 ALKYLZINC, -CADMIUM, AND -MERCURY DERIVATIVES

Alkylzinc, -cadmium, and -mercury compounds have been historically important, with dimethyl- and diethylzinc being the first alkyl metal compounds prepared, and alkylzinc and -mercury being essential reagents for the preparation of other alkyl metals. Alkylzinc, -cadmium, and -mercury derivatives are less reactive than their magnesium analogs, and their preparation is tolerant of a wide variety of functionality. This has led to a revival of interest in the preparation and use in the synthesis of alkylzinc compounds in particular.

2.11.6.1 Preparation by Oxidative Addition

The most extensively used method of preparing alkylzinc derivatives has been by the Grignard-like oxidative addition reactions. Only alkyl iodides, or allylic or benzylic bromides react with unactivated zinc metal. The activity of the metal can be increased by chemical activation (e.g., by addition of 1,2-dibromoethane), addition of catalytic amounts of alkali metal iodides or the use of *N,N'*-dimethylpropylene urea as solvent (Equation (69)) <2000T4197>. Reduction of ZnCl_2 with lithium naphthalenide gives a form of active zinc, which reacts instantaneously at room temperature with alkyl iodides and with alkyl bromides at room temperature over several hours. The process is tolerant of nitrile, ester, ketone, and chloride functionality <1997T1925>. Similar reduction of cadmium chloride can be used for the preparation of alkylcadmium derivatives. Zinc–copper couple reacts with functionalized alkyl iodides to give alkylzinc derivatives under mild conditions.



2.11.6.2 Preparation by Halogen–Metal Interconversion

Certain primary alkyl halides react with diethylzinc to give mixed alkylzinc species which, upon removal of diethylzinc under vacuum, are converted into homogeneous dialkylzinc derivatives. The reaction can be catalyzed by transition metal complexes: catalysis with copper(I) iodide gives dialkylzinc derivatives and catalysis with palladium complexes gives alkylzinc halides.

2.11.6.3 Preparation by Transmetallation

Transmetallation is the most general method for the preparation of mono- and dialkylated zinc, cadmium, and mercury derivatives. Alkylolithium, -magnesium, -mercury, or -aluminum reagents are best for the preparation of alkylzinc derivatives. Alkylolithium or alkylmagnesium reagents are best for preparation of dialkylcadmium derivatives. Alkyl- or dialkylmercury compounds can be prepared using alkylolithium or alkylmagnesium reagents <1995COFGT(2)549>. Organozincates of formula R_3ZnM and R_4ZnM_2 can also be prepared (Scheme 10) <1998JA4934>.

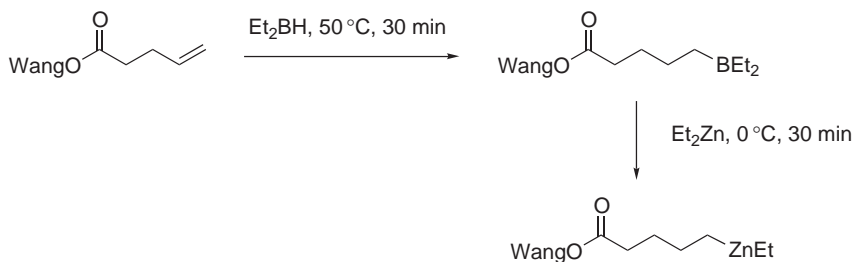


Scheme 10

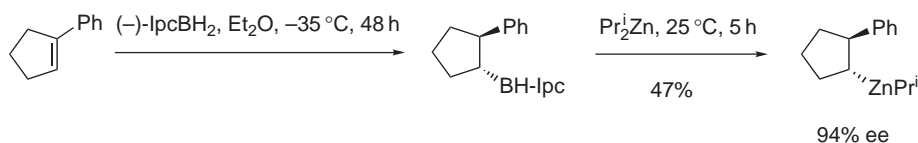
Hydrometallation–transmetalation, in particular boron-to-zinc alkyl transfer, has received considerable attention as a method for one-pot preparation of alkyl- and dialkylzinc derivatives from alkenes (Scheme 11) <2002JOC79>. A solid-supported dialkylzinc derivative has been obtained in this manner (Scheme 12) <2000CC1401>. Use of chiral nonracemic organoboranes allows for enantioselective formation of chiral dialkylzinc derivatives (Scheme 13) <1998SL1438>. Formal one-step hydrozincation of terminal alkenes can be achieved by the use of nickel catalysis (Equation (70)) <1996JOC7473>.



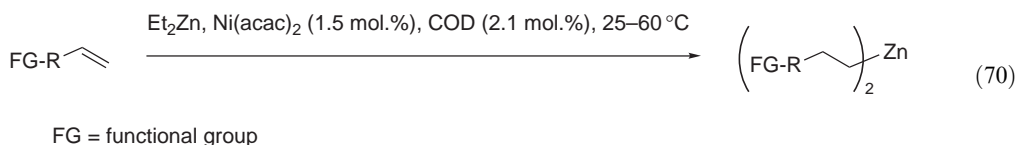
Scheme 11



Scheme 12



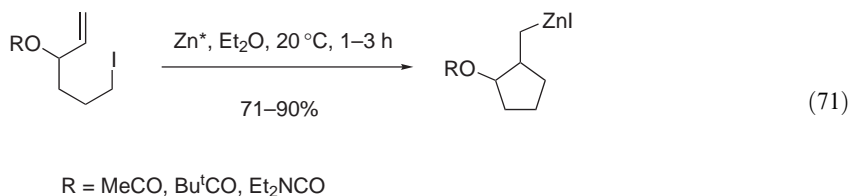
Scheme 13



2.11.6.4 Addition to C—C Double Bonds

2.11.6.4.1 Carbozincation

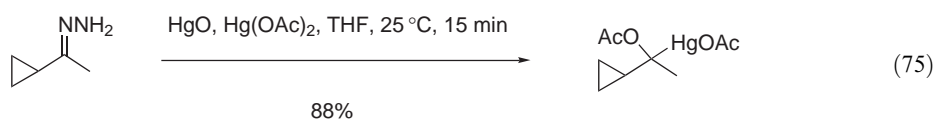
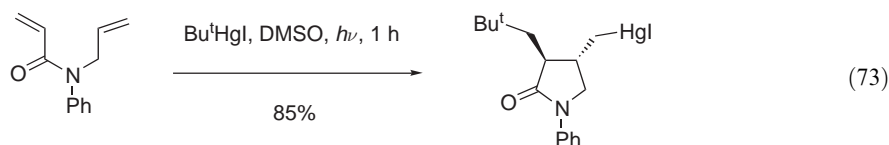
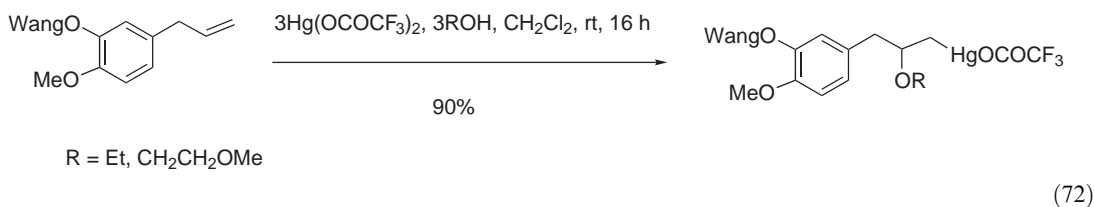
Alkylzinc derivatives can undergo intramolecular carbometallation reactions in a manner similar to alkyllithium derivatives, but with greater tolerance for functional groups (Equation (71)) <1997T1925>.



2.11.6.4.2 Mercuration

Addition of mercury salts to alkenes is well established and forms the basis of a general method for the preparation of alcohols. The C—Hg bonds formed are stable to hydrolysis, but can be reduced. Polymer-tethered (Wang resin) alkylmercury derivatives have been prepared in this way (Equation (72)) <2001TL8383>. Photostimulated addition of *t*-butylmercury halides to 1,6-dienes gives alkylmercury-functionalized cyclopentanes and heterocyclopentanes (Equation (73))

<1996JA9831>. Alkylmercury bonds can also be formed by addition to carbene-like intermediates, e.g., derived from diazoalkanes (Equations (74) <1996TL7307> and (75)) <2002JCS(P1)227>.



2.11.6.5 Miscellaneous Methods

Alkylcadmium and alkylmercury derivatives have been obtained electrochemically, by anodic transmetallation of alkylmagnesium and alkylaluminum derivatives and by cathodic oxidative addition of alkyl bromides. Alkylmercury derivatives have been obtained by photochemical decomposition of mercury carboxylates, and by thermal decomposition of alkyl sulfinic acids. Alkyl-1,1-bis(zinc) derivatives have been used for the preparation of α -chloroalkylzinc halides by reaction with benzenesulfonyl chloride. β -Alkoxy-functionalized alkyl-1,1-bis(zinc) species can be converted into cyclopropylzinc halides <1995COFGT(2)549>.

2.11.7 ALKYLALUMINUM, -GALLIUM, -INDIUM, AND -THALLIUM DERIVATIVES

2.11.7.1 Alkylaluminum Derivatives

Alkylaluminum derivatives have extensive application in organic synthesis. The most general methods for their preparation are very well established <1995COFGT(2)549> and are summarized below.

2.11.7.1.1 Preparation by oxidative addition

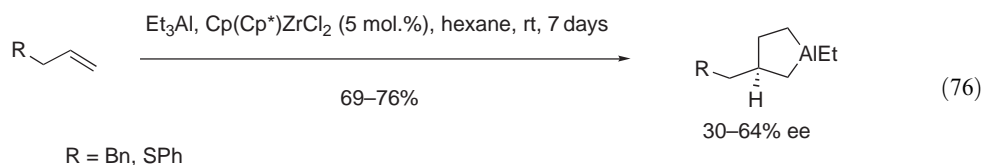
Alkylaluminum sesquichlorides, $R_3Al_2X_3$, can be prepared by reaction of primary alkyl iodides or bromides with activated aluminum turnings. Additives or sonication can be used to achieve activation. Alkylaluminum sesquichlorides can be converted into alkylaluminum dichlorides by treatment with aluminum trichloride, or into trialkylaluminum derivatives by treatment with alkyl metal reagents. Alkylaluminum sesquichlorides can be dehalogenated by reaction with sodium metal to give trialkylaluminum derivatives. Trialkylaluminum etherate complexes may be prepared from alkyl iodides by reaction with Al—Mg alloy in diethyl ether.

2.11.7.1.2 Preparation by transmetallation

Trialkylaluminum etherate complexes can be prepared by transmetallation of aluminum trichloride with alkyllithium or alkylmagnesium reagents in diethyl ether as solvent. Treatment of dialkylaluminum derivatives with alkyllithium reagents gives mixed trialkylaluminum derivatives. Alkyl-mercury reagents can be used in these processes, provided the products are not labile to heat.

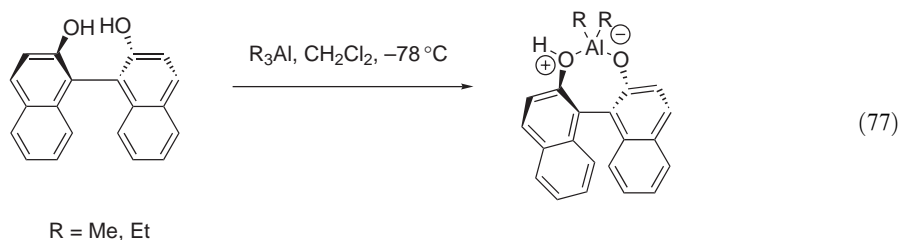
2.11.7.1.3 Addition to C—C double bonds

Hydroalumination and carboalumination of alkenes are important C—Al bond-forming processes. AlH_3 reacts with various alkenes to give trialkylaluminum derivatives. Reaction with LiAlH_4 gives tetraalkyl aluminate complexes LiAlR_4 . Dialkylaluminum hydrides, notably diisobutylaluminum hydride, are also efficient hydroalumination reagents. These reactions proceed under milder condition with titanium or zirconium catalysts. Metallocycles can be obtained by hydrometallation of dienes. Carboalumination reactions usually require titanium or zirconium catalysts. Organozirconium-catalyzed addition of triethylaluminum to alkenes gives alumina-cyclopentanes <1995T4333>. Use of asymmetric catalysts provides a degree of enantioselection (Equation (76)) <1997TL2335>. Dehydroalumination often occurs, the outcome of the overall process being alkylation of an alkene.



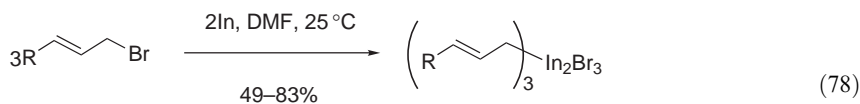
2.11.7.1.4 Disproportionation and ligand exchange

Dialkylaluminum chlorides can be obtained by reaction of trialkylaluminum derivatives with aluminum chloride, zinc chloride, or carbon tetrachloride. The fluoride analogs can be obtained by reaction with ZnF_2 . Dialkylaluminum hydrides can be prepared by reaction between trialkylaluminums and AlH_3 . Dialkylaluminum cyanides, alkoxides, thioalkoxides, or thiocyanates can be prepared from di- or trialkyl derivatives (Equation (77)) <1996TL4795>.

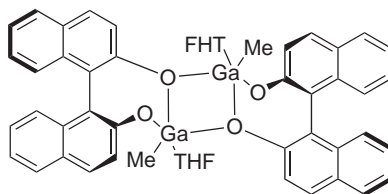


2.11.7.2 Alkylgallium and -indium Derivatives

Most of the preparative methods suitable for obtaining alkylgallium and -indium derivatives are similar to those used for obtaining alkylaluminum derivatives. Metallic indium reacts with alkyl bromides or iodides to give the alkylindium sesquihalides $\text{R}_3\text{In}_2\text{X}_3$. This process is effective for general alkyl halides, but is less so for allyl halides unless polar aprotic solvents are used (Equation (78)) <1995SL1087>. Further treatment of these with KBr or KI gives the dialkylindium halides. An attractive feature is that nucleophilic organoindium reagents can also be generated *in situ* in aqueous media. This works particularly well in organoindium-mediated Barbier-type nucleophilic addition to carbonyl compounds. Mono-, di-, tri-, and tetraalkylated derivatives of indium and gallium can be obtained by transmetallation from InCl_3 or GaCl_3 . GaMe_3 reacts with BINOL at 105°C to give a dimeric complex retaining an Me-Ga bond **16** <2001OM2338>.



R = H, Me, Prⁿ, Ph, PhCH=CH,



16

2.11.7.3 Alkylthallium Derivatives

While mono- and dialkylthalliums are highly unstable, dialkylthallium halides are amongst the most stable organometallics. They can be prepared by transmetallation or by addition to alkenes. Transmetallation can be performed using alkylmagnesium, -zinc, or -aluminum reagents. Addition of thallium(III) salts to alkenes in protic solvents leads to β -alkoxy alkylthallium derivatives. Generation of these species *in situ*, followed by removal of the thallium group by reduction, elimination, or reaction with nucleophiles, has been widely exploited synthetically.

2.11.8 ALKYL TIN AND -LEAD DERIVATIVES

2.11.8.1 Alkyltin Derivatives

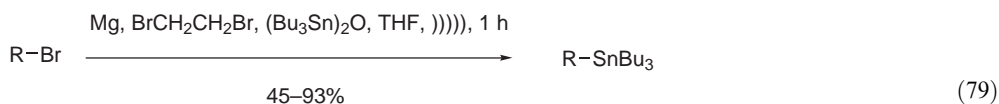
Work on alkyltin derivatives has been driven by their many applications in synthesis. Mono-, di-, tri-, and tetraalkyltin derivatives are known.

2.11.8.1.1 Preparation by transmetallation

Symmetrical tetraalkyltin derivatives can be prepared from tin tetrachloride by transmetallation. Grignard reagents are often used for this purpose. Alkylaluminum reagents give better results for bulkier alkyl groups. Alkylsodium reagents, generated *in situ* by reaction of alkyl chlorides with sodium, can also be used. Mono-, di-, or trialkyltin chloride derivatives can be obtained by reaction of the tetraalkyl derivatives with tin tetrachloride. Platinum(II) or palladium(II) catalysis facilitates this process <2001CC1840>. The trialkyltin chloride derivatives can be reduced by metal hydrides to give trialkyltin hydrides. Mixed tetraalkyltin derivatives can be obtained from the alkyltin chlorides by reaction with alkyl lithium, alkylsodium, or Grignard reagents.

2.11.8.1.2 Preparation by oxidative addition

Reaction of alkyl halides with tin powder or tin oxide gives dialkyltin dihalides. Reaction of alkyl halides with tin dichloride can be used to prepare alkyltin trichlorides. Mixed tetraalkylstannanes can be obtained by the sonochemical reaction of alkyl bromides, magnesium powder, 1,2-dibromoethane, and bis(tributyltin)oxide (Equation (79)) <1997T859>.

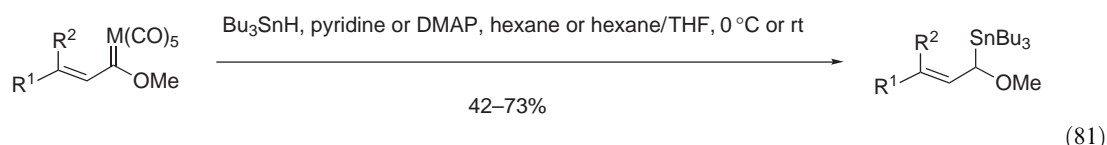
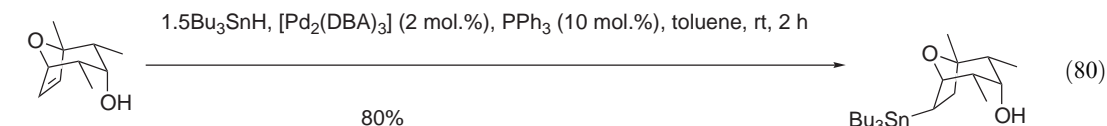


R = Bn, allyl, PhCH₂CH₂, cyclohexyl, 2-butyl, Cl(CH₂)₆, (CH₂)₃CN, (CH₂)₄OAc, (CH₂)₅CO₂Et

2.11.8.1.3 Preparation of R₃^ISnR²

Metallostannanes R₃^ISnM (M = Li, MgX, Na, K) react with primary and secondary alkyl halides or tosylates to give mixed tetraalkyltin derivatives. The metallostannanes can be obtained by deprotonation of trialkyltin hydrides using lithium diisopropylamide, Grignard reagents, or metal hydrides; or by halogen-metal exchange from R₃^ISnCl (for M = Li, Na); or by cleavage of hexaalkylditin compounds with metal (Li, Na) or alkyl lithium reagents. Mixed tetraalkylstannanes of formula R₃^ISnR² or R₂^ISnR₂² can be obtained by reaction of primary alkyl iodides with R₃^ISnCl or R₂^ISnCl₂ in co-solvent-aqueous ammonium chloride media containing zinc dust <2000JOM(612)78>. Certain metallostannanes, in particular trimethylstannyl lithium, undergo conjugate addition to α,β-unsaturated carbonyl compounds. More reactive nucleophiles can be obtained by addition of copper salts.

Di- and trialkyltin hydrides add to C=C double bonds in hydrostannylation reactions. The reaction is mediated by free-radical initiators, photolysis, or by palladium catalysis (Equation (80)) <1996AG(E)1329>. Chromium and tungsten vinyl carbene complexes also undergo hydrostannylation (Equation (81)) <1995TL1007>.



R¹ = Me, R² = H, M = W

R¹ = Ph, R² = H, M = W

R¹ = Me, R² = Me, M = Cr

R¹ = OMe, R² = Ph, M = Cr

2.11.8.2 Alkyllead Derivatives

Alkyllead derivatives are generally less useful in synthesis than their tin analogs due to their increased toxicity and thermal lability. Industrial-scale manufacture of tetraalkyllead derivatives involve catalyzed reactions of alkyl halides with sodium-lead alloy. Tetraalkyllead derivatives can be obtained by transmetallation from lead tetraacetate using organolithium or Grignard reagents.

2.11.9 ALKYL ACTINIDE DERIVATIVES

No significant developments have taken place in this area since the publication of COFGT (1995) <1995COFGT(2)549>.

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2.12

Vinyl and Aryl Halides

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2.12.1 GENERAL METHODS FOR HALIDES

Since the publication of COFGT (1995) <1995COFGT(2)605>, there has been considerable interest in the synthesis of vinyl halides, particularly fluorides, bromides, and iodides. This is a consequence of the plethora of natural products and compounds of biological interest possessing one or more alkenyl groups, usually as one geometrical isomer. Thus, the preparation of single geometrical isomers of vinyl bromides and iodides has become important because these compounds are frequently used as substrates for cross-coupling reactions (e.g., Suzuki and Stille reactions) yielding alkenes, dienes, or higher homologs with a defined stereochemistry around each alkenyl bond. The isosteric replacement of hydrogen by fluorine is a common theme in the synthesis of analogs of biologically active compounds because of the modification of the compound's biological properties as a consequence of this substitution. Hence, the preparation of vinyl fluorides has also attracted interest.

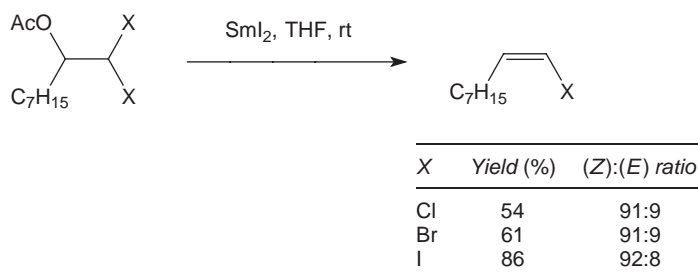
In COFGT(1995) <1995COFGT(2)605>, the sections relating to the preparation of aryl fluorides, chlorides, bromides, and iodides were each subdivided into five subsections. These subsections considered the synthesis of aryl halides: (i) by electrophilic substitution, (ii) from aryl metallic species, (iii) by halogen exchange and related reactions, (iv) from aryl diazonium salts, and (v) by miscellaneous methods. In this chapter the subsection which considers the preparation of aryl halides by electrophilic substitution has been retained and all other synthetic routes to these compounds have been considered in a miscellaneous methods subsection to reflect the proportion of literature available since 1995.

The synthesis of organic halides has been reviewed by Christie <1998JCS(P1)1577, 1999JCS(P1)737>.

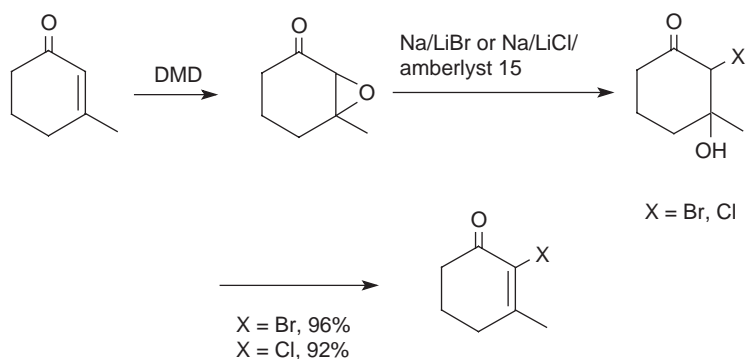
2.12.1.1 Vinyl Halides

2.12.1.1.1 Vinyl halides by elimination reactions

The samarium iodide-mediated β -elimination of *O*-acetyl-dihalo alcohols has given access to (*Z*)-vinyl halides as depicted in Equation (1) <1999AG(E)2384>. α,β -Unsaturated enones have been chlorinated and brominated at the α -position when treated with dimethyldioxirane (DMD) and then an appropriate metal halide and amberlyst 15 as illustrated in Scheme 1 <1999TL5889>. The reaction intermediates are epoxides and halohydrins with the vinyl chloride and bromide products formed by elimination of water from the halohydrins. For the 10 examples reported, yields were excellent (88–96%).



(1)



Scheme 1

2.12.1.1.2 Vinyl halides from alkynes

Disubstituted alkynes and either acrolein or methyl vinyl ketone reacted in the presence of either lithium chloride or lithium bromide and a catalytic quantity of palladium acetate to give either vinyl chlorides or vinyl bromides (Equation (2), Table 1) <1996CC535>. Yields were generally good (55–85%) and the (*Z*)-isomer predominated.

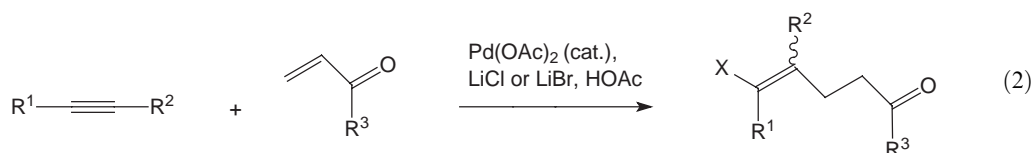
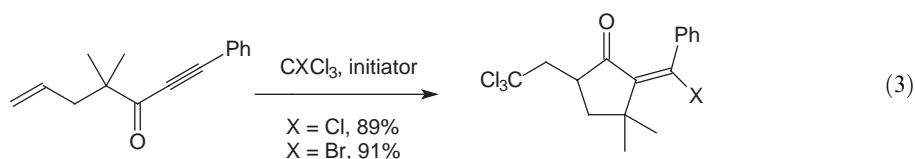


Table 1 Vinyl halides from alkynes (Equation (2)) etc

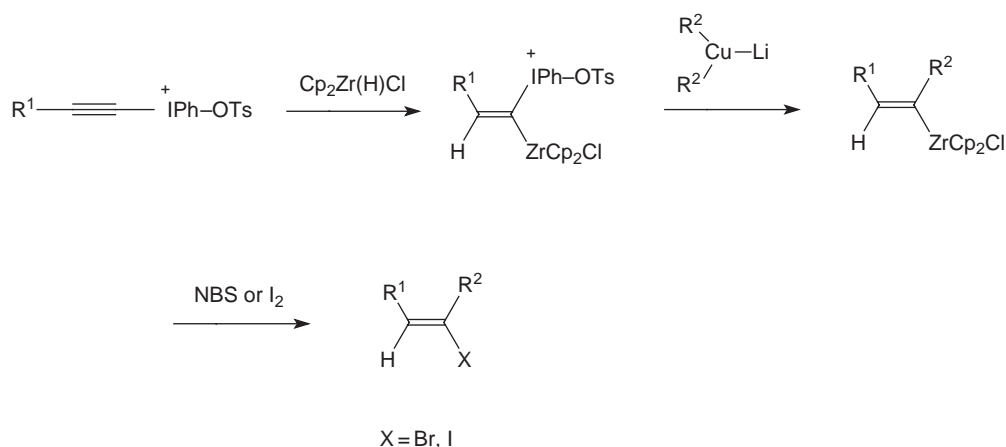
R^1	R^2	R^3	X	Yield (%)	(<i>Z</i>):(<i>E</i>) ratio
H	CO ₂ Me	H	Br	79	>97:3
Ph	H	H	Br	75	93:7
Me	CO ₂ Bn	Me	Cl	75	95:5
Ph	H	H	Cl	77	95:5

(*E*)-Haloalkylidene cyclopentanone derivatives have been prepared by a radical cyclization process as shown in Equation (3) <1997TL2919>. 2,2'-Azobisisobutyronitrile (AIBN) was used as the initiator for the preparation of the vinyl bromides but the slower carbon tetrachloride additions required dibenzoyl peroxide. For the nine examples reported the yields were good (60–91%).



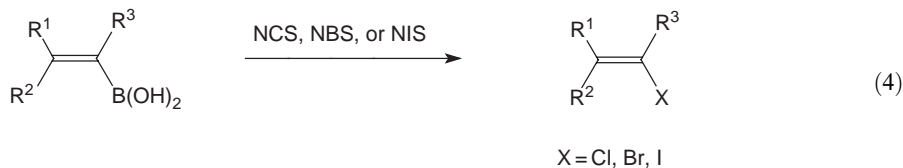
2.12.1.1.3 Vinyl halides from vinyl metallic species

Vinyl bromides and iodides have been synthesized in three steps from alkynyl(phenyl)iodonium salts as depicted in Scheme 2 and Table 2. *Syn*-addition of CpZr(H)Cl to alkynyl(phenyl)iodonium salts followed by sequential replacement of the iodonium moiety with an alkyl group and the zirconium substituent with a halogen gave the (*E*)-haloalkenes <1999JCS(P1)673>.

**Scheme 2****Table 2** Vinyl halides from carbonyl compounds (Scheme 2)

<i>Ar</i>	<i>R</i> ¹	<i>R</i> ²	<i>X</i>	<i>Base</i>	<i>Yield (%)</i>	<i>(E):(Z) ratio</i>
Ph	Ph	Me	Cl	NaH	65	75:25
Ph	Ph	Ph	Cl	NaH	85	
Ph	-(CH ₂) ₅ -		Cl	NaH	65	
4-MePh	Ph	H	Br	K ₂ CO ₃	52	30:70

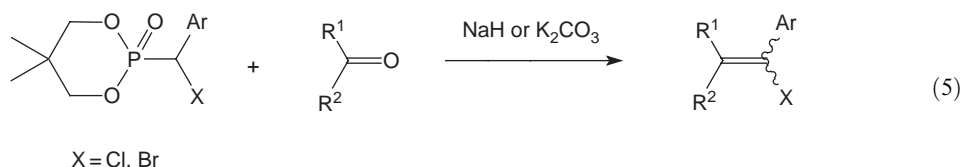
Alkenylboronic acids have been reacted with *N*-chloro-, *N*-bromo-, and *N*-iodosuccinimides (NISs) giving vinyl halides in good yield (Equation (4), Table 3) <1996TL567>. The boronic acid substituent is replaced with retention of stereochemistry in these reactions.

**Table 3** Vinyl halides from vinyl boronic acids (Equation (4))

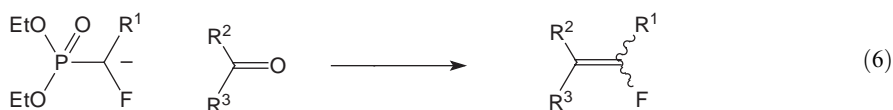
<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>X</i>	<i>Yield (%)</i>
Ph	H	Me	Cl	77
Ph	H	Me	Br	84
Ph	H	Me	I	83
H	Ph	H	Br	81
Bu ⁿ	H	H	I	73
Bu ⁿ	Br	H	Cl	76
Bu ⁿ	Br	H	I	71

2.12.1.1.4 Vinyl halides from carbonyl compounds

Cyclic phosphonates have been reacted with carbonyl compounds in the presence of a base to yield vinyl chlorides and bromides in moderate to good yields <1997TL2183, 1998T14315> (Equation (5), Table 4). The stereoselectivity of the reaction is generally not good and a mixture of (*E*)- and (*Z*)-vinyl halides is obtained. Sodium hydride is a satisfactory base for the formation of vinyl chlorides but this base gave only alkynyl products with α -bromophosphonates. In order to produce vinyl bromides, the weaker base, potassium carbonate was used. A wide variety of vinyl fluorides has been produced from anions derived from α -fluorophosphonates and carbonyl compounds as depicted in Equation (6) and Table 5 <1996TL629, 1997CC1489, 1998PS135, 1998TL4437, 2001MI681>.


Table 4 Vinyl halides from carbonyl compounds (Equation (5))

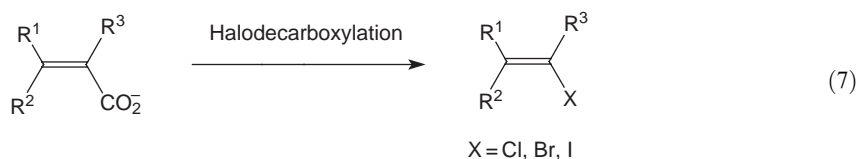
<i>Ar</i>	<i>R</i> ¹	<i>R</i> ²	<i>X</i>	<i>Base</i>	<i>Yield (%)</i>	<i>(E):(Z) ratio</i>
Ph	Ph	Me	Cl	NaH	65	75:25
Ph	Ph	Ph	Cl	NaH	85	
Ph	-(CH ₂) ₅ -		Cl	NaH	65	
4-MePh	Ph	H	Br	K ₂ CO ₃	52	30:70


Table 5 Vinyl fluorides from carbonyl compounds (Equation (6))

<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>Yield (%)</i>	<i>(E):(Z) ratio</i>	<i>References</i>
CO ₂ Et		H	> 70	90:10	<1998TL4437>
CO ₂ Et	C ₂ F ₅	H	42	80:20	<1998PS135>
CO ₂ Et		H	91	0:100	<1997CC1489>
CO ₂ Et	TBSOCH ₂	TBSOCH ₂	89		<2001MI681>
CO ₂ Et	Me	CO ₂ Et	65	45:55	<1996TL629>
Ph	C ₂ F ₅	H	38	1:99	<1998PS135>
Ph	Ph	H	71	46:54	<1996TL629>
Ph	Ph	Ph	48		<1996TL629>

2.12.1.1.5 Vinyl halides by miscellaneous methods

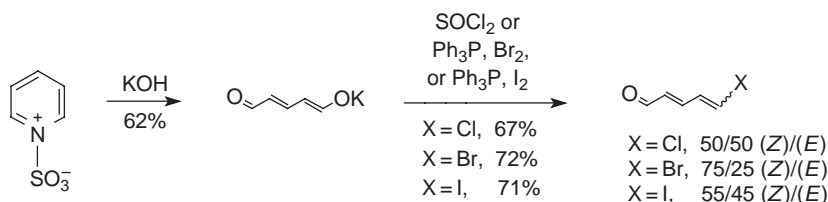
The halodecarboxylation of alkenyl carboxylates as depicted in Equation (7) (the Hunsdiecker reaction) has proved to be a popular method for the preparation of vinyl halides. The majority of examples studied have been on alkenyl carboxylates with *R*¹ = aryl and *R*² = *R*³ = hydrogen (Table 6). The (*E*)-vinyl halide is formed as the predominant geometrical isomer and yields are generally good. The halogen source is usually an *N*-halosuccinimide <1996TL2623, 1998TL699, 2000T1369, 1997JOC199, 2000OM1464, 2000SL1439>, bromine <1998CL1271>, sodium halide in the presence of oxone™ <2001SL105>, sodium halide in the presence of ceric ammonium nitrate (CAN) <2001TL9253>, or potassium bromide in the presence of hydrogen peroxide and Na₂MoO₄ <2001CC1916>.

**Table 6** Halodecarboxylation of alkenyl carboxylates (Equation (7))

R^1	R^2	R^3	Conditions	Yield (%)	(E):(Z) ratio	References
Ph	H	H	NBS	55	> 97:3	<1997JOC199>
Ph	H	H	NCS	61	> 97:3	<1997JOC199>
4-MeOPh	H	Me	NCS	93	1:1	<2000T1369>
4-MeOPh	H	Me	NBS	96	> 97:3	<2000T1369>
4-MeOPh	H	Me	NIS	73	89:11	<2000T1369>

NIS = *N*-iodosuccinimide.

The 5-halogenopentadienals shown in Scheme 3 have been prepared in two steps from 1-pyridinium sulfonate <1995CC563>. The overall yields were good and mixtures of geometrical isomers were obtained.

**Scheme 3**

2.12.1.2 Aryl Halides

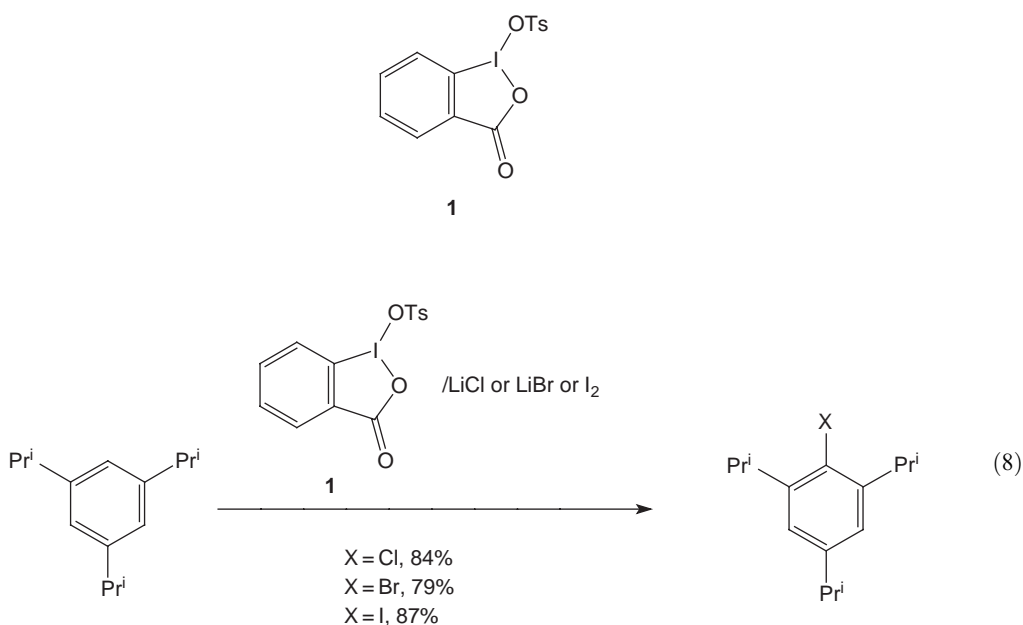
2.12.1.2.1 Aryl halides by electrophilic aromatic substitution

The preparation of aryl halides by electrophilic aromatic substitution reactions continues to be one of the most important methods for the synthesis of this class of compounds. Both the regioselectivity and the rate of electrophilic substitution are highly dependent upon the nature of ring substituents and this was discussed in COFGT(1995) <1995COFGT(2)605>. The halogenation of aromatic compounds over zeolite catalysts has been reviewed <1996AC25>.

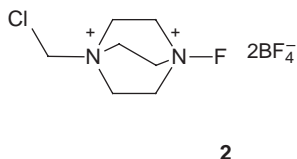
An environmentally benign chlorination and bromination procedure, which uses a hydrohalic acid in the presence of hydrogen peroxide has been developed for the halogenation of a range of aromatic amines, hydrocarbons, and naphthols <2003TL4085>. Thus, 4-nitroaniline gave 2,6-dibromo-4-nitroaniline in 95% yield when treated with a mixture of 3.0 equivalents of 49% aqueous HBr and 2.0 equivalents of 30% aqueous hydrogen peroxide in methanol at 0 °C for 8 h. With HCl as the halogen source, 2,6-dichloro-4-nitroaniline was produced in 87% yield after heating the mixture at reflux for 15 h. The chlorination and bromination of other aniline derivatives also gave good yields of halogenated products. Aromatic ethers can also be halogenated in good yield using HBr or HCl, using either aqueous hydrogen peroxide or aqueous *t*-butyl hydroperoxide as the oxidant <1998TL6349>. Aniline derivatives have been successfully chlorinated and brominated, using either KCl or KBr as the halogen source and sodium perborate as the oxidant in the presence of sodium tungstate as a catalyst

<1998SC3225>. Thus, acetanilide gave 4-bromoacetanilide (92% yield) and 4-chloroacetanilide (86% yield) using this methodology. Moist kaolin has been used as a catalyst for the chlorination of a range of aromatic ethers in good yield with good regioselectivity <1998JCR(S)662>. Sodium chlorite (NaClO_2) was used as the chlorinating reagent in the presence of a catalytic quantity of $\text{Mn}(\text{acac})_3$. For example, chlorination of anisole gave a mixture of 4-chloroanisole (94%) and 2-chloroanisole (5%). By adding sodium bromide to the reaction mixture, brominated ethers could be obtained along with only minor amounts (<4%) of chlorinated products. Bromination of anisole using this procedure yielded a mixture of 4-bromoanisole (98% yield) and 2-bromoanisole (1% yield) and no chlorinated products.

Alkyl-substituted benzene derivatives have been chlorinated and brominated using either LiCl or LiBr as the halogen source in the presence of 1-(*p*-toluenesulfonyloxy)-1,2-benziodoxol-3(1*H*)-one **1** as an oxidant (Equation (8)) <1998SL286>. When KF was examined as the halogen source, the reaction failed and no fluorinated products were obtained. Iodination could be achieved using iodine in the presence of compound **1**. Diiodination could also be carried out when compound **1** was used in excess: 1,3,5-trimethylbenzene was diiodinated in 99% yield when 2.4 equiv. of reagent **1** were used.

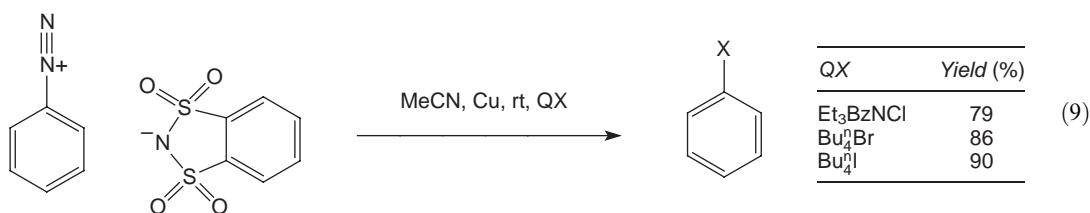


Selectfluor™ **2** in combination with either KCl or KBr in acetonitrile at room temperature has been used to chlorinate and brominate a range of aromatic systems that are generally electron rich. Mixtures of products were often obtained but in some cases single products were obtained, e.g., 1,4-dimethoxybenzene gave only 2-chloro and 2-bromo-1,4-dimethoxybenzene <2002JOC4487>.



2.12.1.2.2 Aryl halides by miscellaneous methods

The halodediazoniations of dry arenediazonium *o*-benzenedisulfonimides by quaternary ammonium halides (QX) has been developed as a procedure for the synthesis of aryl chlorides, bromides, and iodides (Equation (9)) <1999JOC3448>. In optimized conditions the yields were good to excellent (61–94%) for 60 reactions. The reactions could be carried out at room temperature in dry acetonitrile, usually in the presence of copper powder.



Arylboronic acids reacted with either *N*-bromo or *N*-iodosuccinimide to give aryl bromides (seven examples, 19–82%) or aryl iodides (13 examples, 25–90%), respectively [<1998SL141>](#). In these reactions, which were carried out in acetonitrile either at room temperature or at reflux, the boronic acid group was replaced by the halogen.

2.12.2 FLUORIDES

Electrophilic fluorination has been reviewed [<1999T12431>](#).

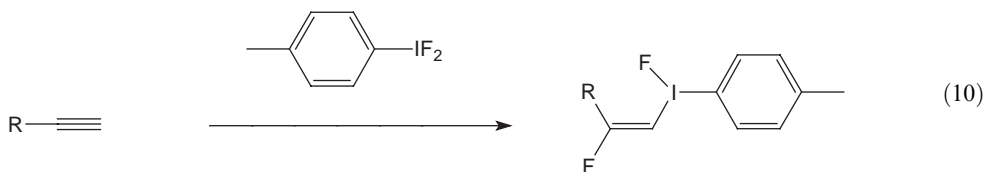
2.12.2.1 Vinyl Fluorides

2.12.2.1.1 Vinyl fluorides by elimination reactions

The synthesis of vinyl fluorides by elimination reactions has been satisfactorily covered in COFGT (1995) [<1995COFGT\(2\)605>](#).

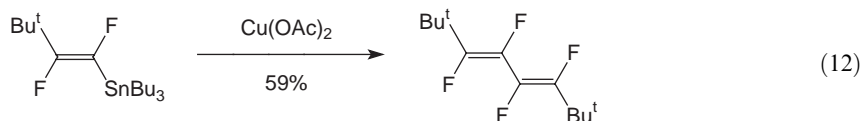
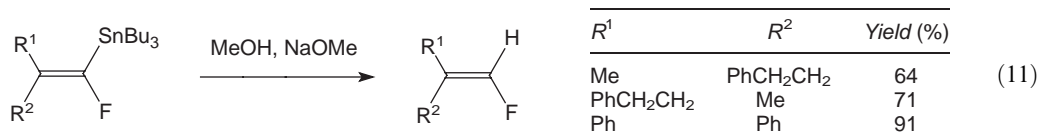
2.12.2.1.2 Vinyl fluorides from alkynes

Monosubstituted alkynes have been reacted with *p*-iodotoluene difluoride yielding (*E*)-(2-fluoro-1-enyl) (*p*-tolyl)iodonium fluorides as shown in [Equation \(10\)](#). The R-group is generally a long chain alkyl substituent and the (*p*-tolyl)iodonium moiety is generally replaced in a second reaction. Thus, it can be replaced by: (i) iodine (CuI, KI, dimethylformamide (DMF)) giving 1-fluoro-2-iodoalkenes [<1998CC965, 2002JCS\(P1\)384>](#) in good yield, (ii) a methyl ester by reaction with carbon monoxide and methanol in the presence of a palladium catalyst in moderate yield [<1999TL7815>](#), and (iii) alkenyl groups in Heck and Stille-type reactions giving fluorinated dienes in moderate yields [<2001JCS\(P1\)2283, 2000TL3887>](#).



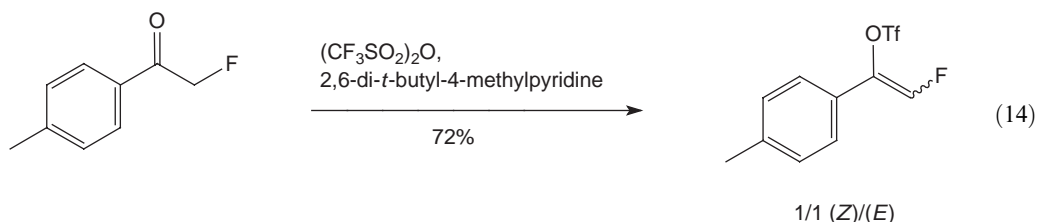
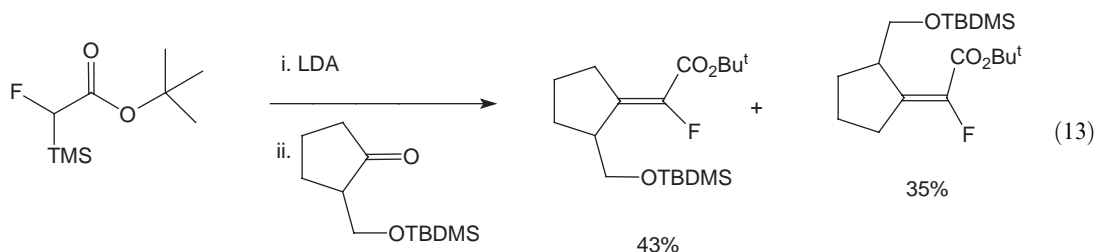
2.12.2.1.3 Vinyl fluorides from vinyl metallic species

The tributylstannyl group in (fluorovinyl)stannanes can be replaced stereospecifically by hydrogen yielding vinyl fluorides as illustrated by [Equation \(11\)](#) [<1996T45>](#). The tributylstannyl group in (fluorovinyl)stannanes can also be replaced by other groups giving access to vinyl fluorides as exemplified by Stille cross-coupling reactions with aryl iodides [<1995JOC6608, 1997TL7673, 1997TL7677, 1999JOC3476, 2002OL1483>](#). 1,2-Difluorovinylstannanes can also undergo homocoupling in the presence of Cu(OAc)₂ yielding fluorinated dienes as the major products ([Equation \(12\)](#)) [<1999IJ109>](#).

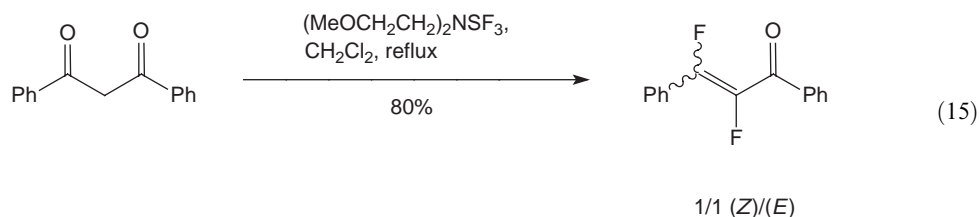


2.12.2.1.4 Vinyl fluorides from carbonyl compounds

In a study of fluorine containing dipeptide isosteres, an inhibitors of dipeptidyl peptidase IV (CD26), the Peterson alkenylation procedure has been used to prepare vinyl fluorides (Equation (13)) <1996T291>. The Wadsworth–Horner–Emmons reaction of α -fluorophosphonates and carbonyl compounds has also been used to construct other vinyl fluoride containing molecules <1996TL629, 1997CC1489, 1998PS135, 1998TL4437, 2003TL6231> and the anion of ethyl fluoroacetate has been reacted with an aldehyde yielding a vinyl fluoride <1995JOC3107>. α -Fluoroketones and triflic anhydride in the presence of 2,6-di-*t*-butyl-4-methylpyridine gave fluoroenol triflates in moderate-to-good yields for the six examples reported (Equation (14)) <1997TL49>.



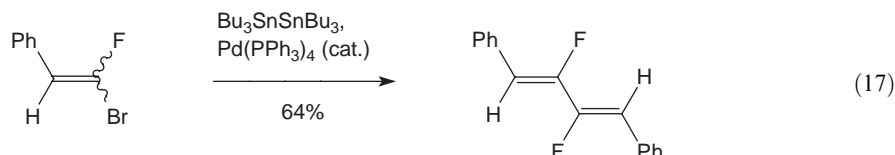
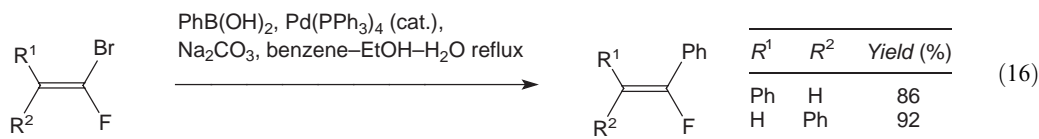
β -Diketones, as exemplified by dibenzoylmethane, reacted with Deoxo-Fluor[®] [($\text{MeOCH}_2\text{CH}_2$)₂NSF₃] in the presence of a catalytic quantity of hydrogen fluoride giving difluoroalkenones as a mixture of geometrical isomers (Equation (15)) <2001JOC6263>.



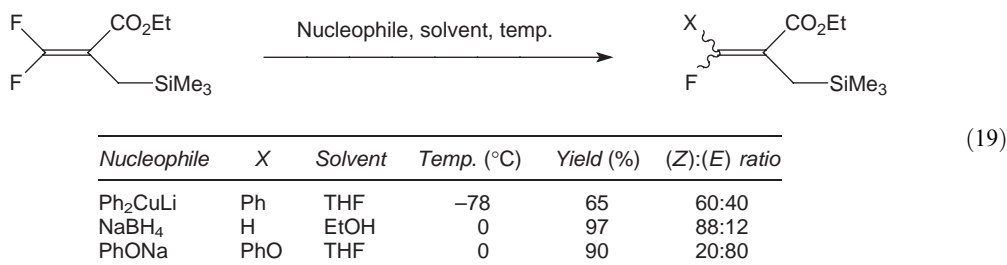
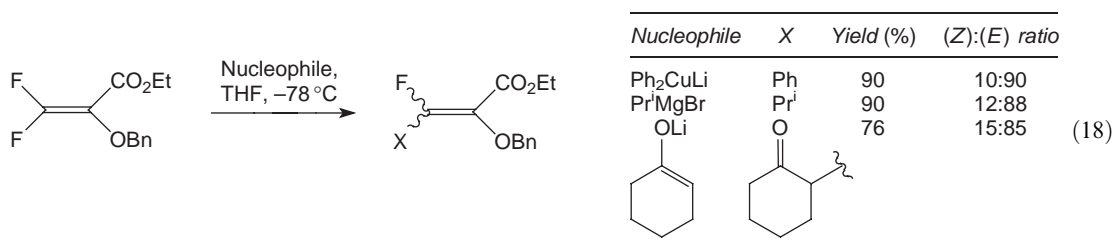
2.12.2.1.5 Vinyl fluorides by miscellaneous methods

1-Bromo-1-fluoroalkenes participate in Suzuki and Stille cross-coupling reactions with aryl boronic acids and organostannanes giving vinyl fluorides in good yield (Equation (16)) <2000JFC(101)285,

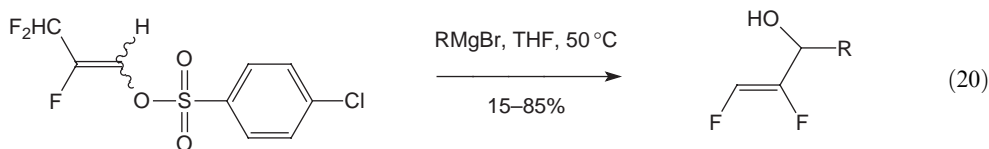
1999TL827>. Fluorinated dienes have been prepared from an (*E*)/(*Z*)-mixture of 1-bromo-1-fluorostyrenes and $\text{Bu}_3\text{SnSnBu}_3$ and a palladium catalyst as illustrated by Equation (17) <2002TL4565>.



One of the fluorine atoms in substituted ethyl 3,3-difluoropropenoate derivatives can be replaced by a suitable nucleophile yielding vinyl fluorides, generally in excellent yields, as illustrated by Equation (18) <1995CC1969> and Equation (19) <2000JOC627>.



The (*Z*)-difluorallylic alcohols shown in Equation (20) have been prepared by treating enol sulfonates with Grignard reagents <1998TL1913>. Aryl Grignard reagents generally gave moderate-to-good yields of isolated products but yields with benzylmagnesium chloride and *n*-hexylmagnesium chloride were poor (15% and 30%, respectively).



The sodium salt of dimethyl fluoromalonate reacted with α,β -unsaturated ketones and esters yielding fluorinated acrylic esters as shown in Equation (21) and Table 7 <1998JOC7525>. Yields were variable (0–94%) and the (*Z*)-isomer predominated and was often formed exclusively.

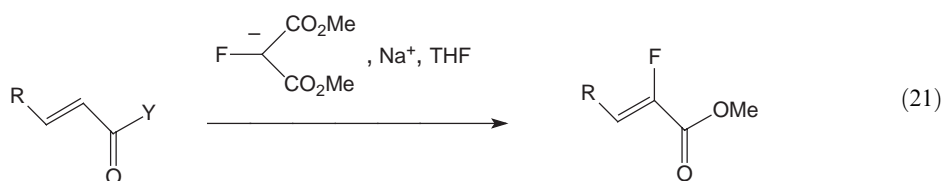
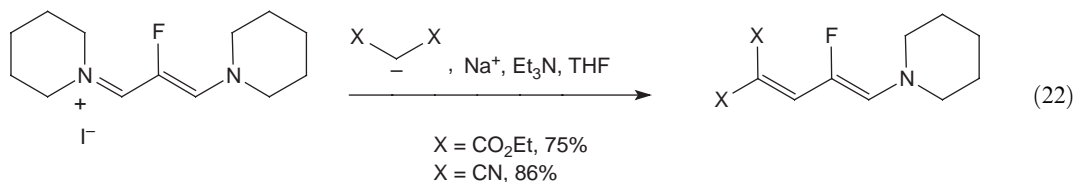


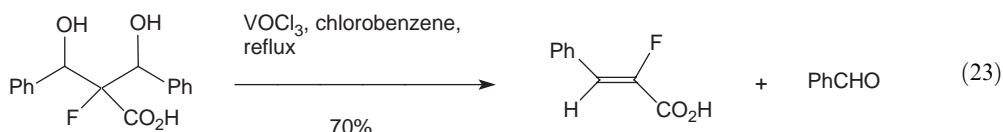
Table 7 Fluorinated acrylic esters (Equation (21))

R	Y	Yield (%)
Et	Bu ^t	71
Ph	Bu ^t	30
Me	OMe	57
Ph	OMe	82

The β -fluorovinamidinium salt depicted in Equation (22) reacted with the anions of activated methylene compounds yielding fluorinated dienaminones or dienaminonitriles <1998TL4355>. The anions derived from diethyl malonate and malononitrile are illustrative examples.



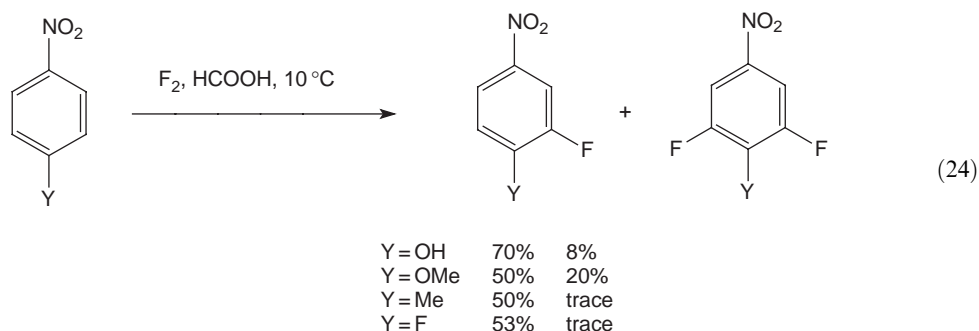
β,β -Dihydroxy carboxylic acids reacted with VOCl_3 in boiling chlorobenzene giving α -fluoro- α,β -unsaturated acids in moderate-to-good yield (Equation (23)) <1998TL4865>. This reaction involves a fragmentation process giving an aldehyde as a co-product. Esters of carboxylic acids reacted similarly.



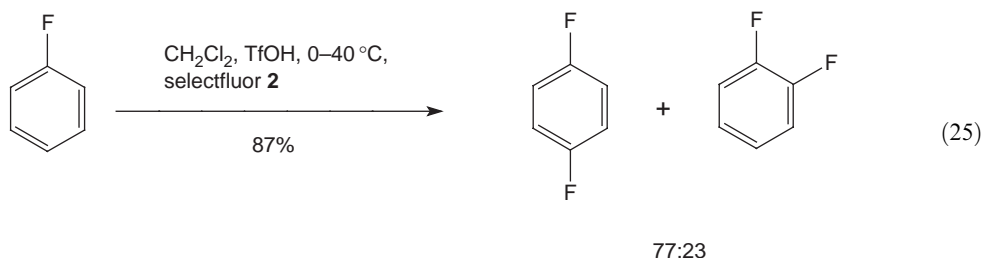
2.12.2.2 Aryl Fluorides

2.12.2.2.1 Aryl fluorides by electrophilic aromatic substitution

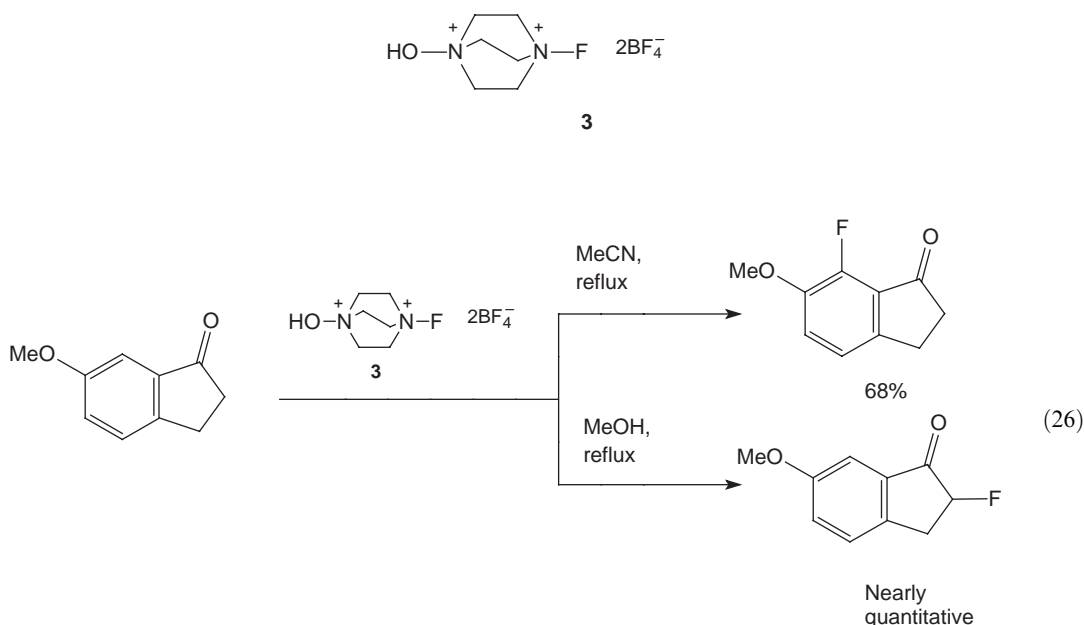
The fluorination of 1,4-disubstituted benzene derivatives has been achieved using elemental fluorine in acidic media as illustrated by the reaction shown in Equation (24) <1995CC17, 2000JFC(102)169>. The mono-fluorinated product was obtained as the major product accompanied by minor quantities of the difluorinated compound. Yields of the monofluorinated compounds were generally moderate. In addition to the 4-substituted nitro compounds depicted in Equation (24), the fluorination of 4-substituted phenols, anisoles, and benzonitriles was also studied. The fluorination of benzene, toluene, phenol, and benzoic acid by elemental fluorine diluted in nitrogen has been studied under a range of conditions. Monofluorinated products were generally formed in accordance with the mechanism for electrophilic substitution <1995JFC(70)175>.



The electrophilic fluorination of aromatic compounds has also been achieved in good-to-excellent yields using selectfluor™ **2** in the presence of trifluoromethanesulfonic acid (Equation (25)) <1999IJ207>. No reaction took place in the absence of the acid. Benzene, toluene, anisole, and halobenzenes could be successfully fluorinated using this methodology but the deactivated aromatic systems, nitrobenzene, and α,α,α -trifluorotoluene, were both unreactive. In the cases where regioisomers could be formed, the *para*-substituted product usually predominated but *ortho*-substituted compounds were also formed in significant yields.

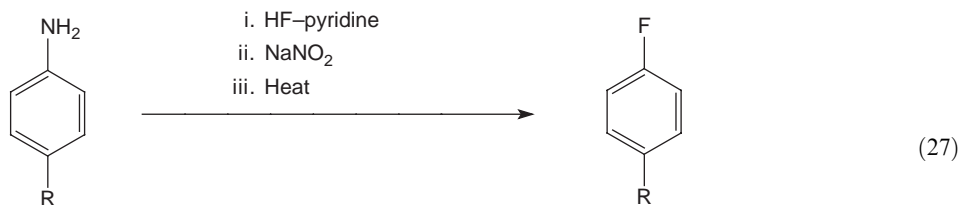


The site-selectivity of fluorination can be affected by the choice of reaction solvent. The reaction of aryl alkyl ketones with AccuFluor™ **3** in methanol gave the corresponding α -fluoroketone whereas the aromatic ring was fluorinated when acetonitrile was used as the reaction solvent (Equation (26)) <2000CC1323>. This observation was attributed to the higher enol content in methanol.



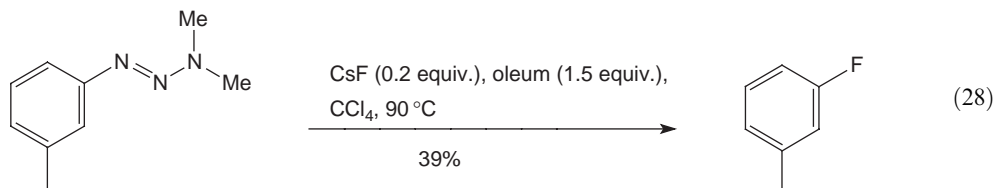
2.12.2.2.2 Aryl fluorides by miscellaneous methods

A “one-pot” deaminative fluorination of aniline derivatives has been described, in which the aniline derivatives are first diazotized and then treated with a HF–pyridine mixture <1996T23>. The HF mole fraction in the HF–pyridine mixture was important and best yields were obtained when the HF mole fraction was 0.86. Yields of aryl fluorides using this methodology were generally excellent (Equation (27)), and in the case of diazonium salts that were difficult to decompose thermally to the corresponding aryl fluorides, this transformation could be induced photochemically at lower temperatures.

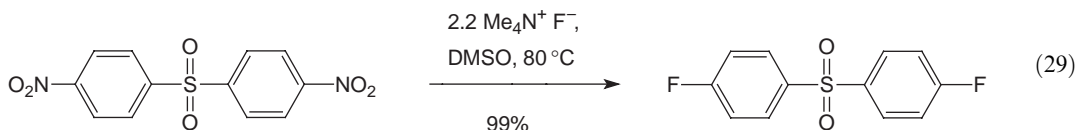


R = H, Me, Cl, NO₂, all 99%

1-Aryl-3,3-dialkyltriazines (which are readily available from the reaction of aryldiazonium chlorides with secondary amines) have been decomposed in the presence of strong nonnucleophilic acids and substoichiometric quantities of fluoride anions yielding aryl fluorides in low-to-moderate yields (Equation (28)) <2001JFC(107)321, 2001JFC(107)329>. These conditions have been developed to allow the preparation of relatively short-lived ¹⁸F-containing isotopes ($t_{1/2}$ = 110 min) for medical imaging using positron emission tomography (PET).



Aryl fluorides are often prepared from other aryl halides by halogen exchange and this reaction has been reviewed <1999CSR225, 2003MI13>. *p*-Haloacetophenones can be converted into the corresponding *p*-[¹⁸F]fluoroacetophenones by treatment with [¹⁸F] fluoride <1995CL835>. The nitro groups in dinitrodiphenyl sulphones have been replaced by fluorine by treatment with tetramethylammonium fluoride as illustrated by the reaction shown in Equation (29) <1995JFC(70)201>.



2.12.3 CHLORIDES

2.12.3.1 Vinyl Chlorides

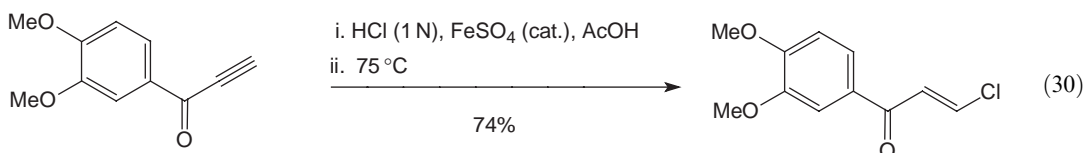
2.12.3.1.1 Vinyl chlorides by elimination reactions

The formation of vinyl chlorides by elimination reactions has been discussed in Section 2.12.1.1.1.

2.12.3.1.2 Vinyl chlorides from alkynes

Examples of the synthesis of vinyl chlorides from alkynes have been given in Section 2.12.1.1.2.

The reaction of aromatic acetylenic ketones with aqueous HCl in the presence of a catalytic quantity of FeSO₄ gave β -chlorovinyl ketones as a mixture of geometrical isomers, which isomerized almost exclusively to the (*E*)-isomer upon heating (Equation (30)) <2000TL4709>.



The ruthenium catalyzed reaction of alkynes and vinyl ketones has given vinyl chlorides in good yields (Equation (31) and Table 8) <1999JA1988>. In this reaction, the (*E*)-alkene geometry predominated and slightly better (*E*):(*Z*) ratios could be obtained when tetramethyl ammonium chloride was substituted for ammonium chloride.

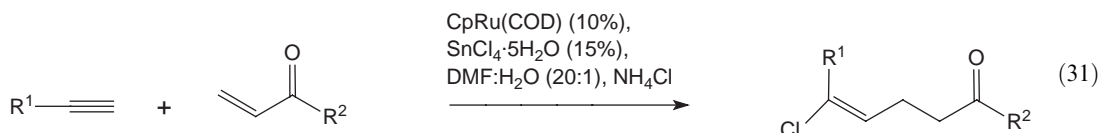


Table 8 Vinyl chlorides from vinyl ketones and alkenes
(Equation (31))

R^1	R^2	Yield (%)	(<i>E</i>):(<i>Z</i>) ratio
<i>n</i> -C ₆ H ₁₃	Me	72	6.0:1
<i>n</i> -C ₆ H ₁₃	Cyclohexyl	74	6.1:1
NC(CH ₂) ₃	Me	83	8.8:1
NC(CH ₂) ₃	Cyclohexyl	78	7.7:1
AcO(CH ₂) ₄	Me	75	7.0:1
HO(CH ₂) ₆	Me	61	6.4:1

The rhodium catalyzed chloroesterification of monosubstituted alkynes with methyl chloroformate has been reported to give vinyl chlorides in good yields (Equation (32) and Table 9) <1998JA12365>. The (*Z*)-vinyl chloride was obtained as the major product from these reactions and was sometimes formed exclusively.

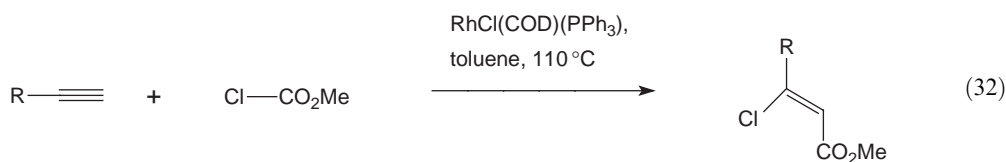


Table 9 Chloroesterification of alkynes
(Equation (32))

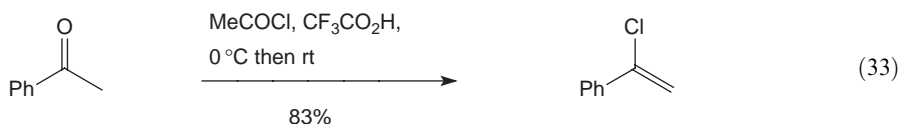
R	Yield (%)	(<i>Z</i>):(<i>E</i>) ratio
Me ₃ C	61	100:0
Cl(CH ₂) ₃	91	94:6
CN(CH ₂) ₃	82	94:6
Bn	73	97:3
Ph	79	100:0

2.12.3.1.3 Vinyl chlorides from vinyl metallic species

The synthesis of vinyl chlorides from vinyl metallic species has been considered in Section 1.12.1.1.3.

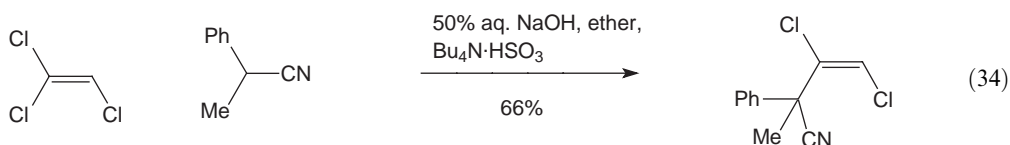
2.12.3.1.4 Vinyl chlorides from carbonyl compounds

The transformation of carbonyl compounds into vinyl chlorides has been discussed in Section 1.12.1.1.4. Vinyl chlorides have been prepared by treating ketones with acetyl chloride in acidic solution as illustrated by the reaction depicted in Equation (33) <1998TL59>. In cases where isomers could be formed, the (*Z*)-isomer is produced. For the five examples reported, yields were excellent.

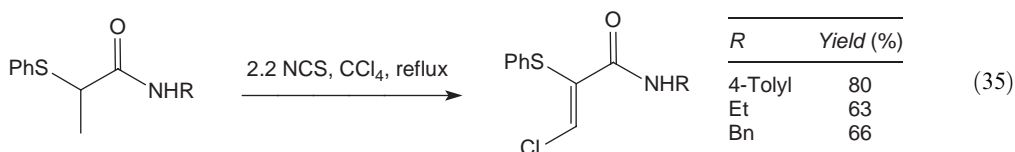


2.12.3.1.5 Vinyl chlorides by miscellaneous methods

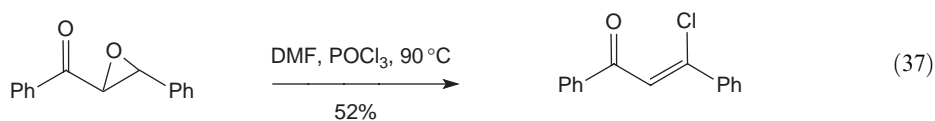
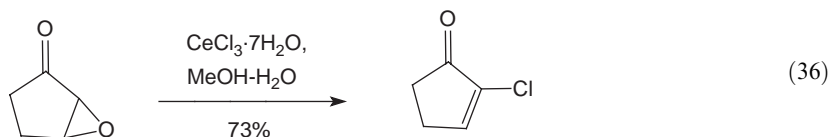
The preparation of vinyl chlorides by miscellaneous methods has been considered in Section 1.12.1.1.5. A vinyl chloride synthesis in which one of the chlorine atoms in *cis*- or *trans*-1,2-dichloroethene can be replaced in a transition metal catalyzed cross-coupling reaction with a Grignard reagent has been reviewed <2000S1499>. The reaction of 1,1,2-trichloroethene and the anions of nitriles gave 1-substituted-1,2-dichloroalkenes as illustrated by the transformation shown in Equation (34) <1998S962>.



Reaction of the 2-phenylthio secondary amides shown in Equation (35) with 2.2 equiv. of *N*-chlorosuccinimide (NCS) gave (*Z*)-acrylamide derivatives in moderate-to-good yields <1995TL467>.



Epoxy ketones have been used as precursors to vinyl chlorides. Thus, cyclic α,β -epoxy ketones reacted with cerium(III) chloride heptahydrate yielding cyclic α,β -chloroenones as illustrated in Equation (36) <1999TL5893>. For the seven examples reported, yields were in the range 40–88%. Chalcone epoxides gave vinyl chlorides when treated with the Vilsmeier reagent (Equation (37)) <1995TL7287>.



2.12.3.2 Aryl Chlorides

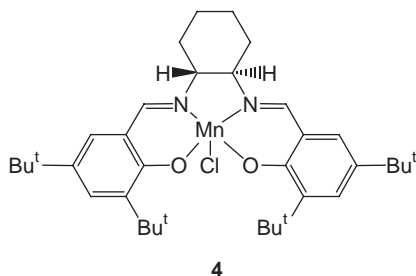
2.12.3.2.1 Aryl chlorides by electrophilic aromatic substitution

Several examples of electrophilic chlorination reactions that use either HCl or KCl in the presence of an appropriate oxidizing agent have already been discussed in the context of general methods

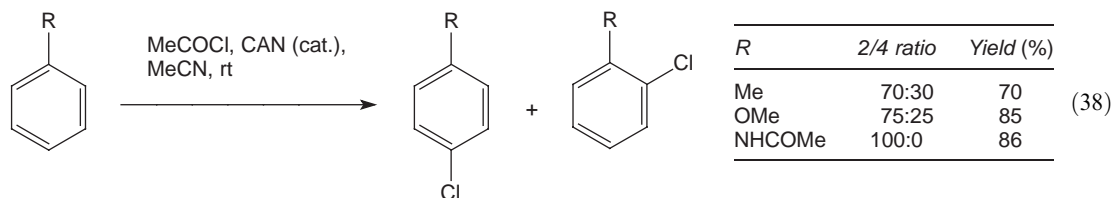
for halides (Section 1.12.1.2.1). KCl and oxone™ have also been used for the electrophilic chlorination of toluene, acetanilide, and phenol in acetonitrile at room temperature <2002SC279>. High conversions were achieved under these conditions and mixtures of *ortho*- and *para*-substituted products were obtained, for example chlorination of toluene gave a 70:30 ratio of 4-chlorotoluene and 2-chlorotoluene. Chlorobenzene, nitrobenzene, and benzoic acid were unreactive even when the reactions were carried out at 80 °C. Aromatic compounds have been chlorinated in good yield under mild conditions using a mixture of tin tetrachloride and lead tetraacetate in dichloromethane <1996T8863>. For example, toluene gave a 45:55 ratio of 4-chlorotoluene and 2-chlorotoluene in 80% yield. Bromobenzene and iodobenzene could also be chlorinated giving 4-bromochlorobenzene and 4-chloriodobenzene in yields of 56% and 58%, respectively.

t-Butyl hypochlorite in the presence of zeolites has been used as an efficient system for the monochlorination of a wide variety of mono- and di-substituted aromatic substrates under mild conditions <1999GC83>. The best system was generally *t*-butyl hypochlorite with HNaX in acetonitrile, which allowed high yielding (75–100%) monochlorinations of benzene, alkylbenzenes, anisole, chlorobenzene, and bromobenzene. Mixtures of *ortho*- and *para*-substituted products were obtained with the best selectivity being obtained for *t*-butylbenzene (*para:ortho* = 98:2) and the worst for anisole and toluene (*para:ortho* = 82:12 for both compounds).

Sodium chlorite has been used as a chlorinating reagent on several occasions. Thus, in combination with trichloroacetic acid (which generates chlorous acid, HOClO, *in situ*) benzene gave chlorobenzene in low yield (20%) and mesitylene underwent monochlorination in 95% yield <1999M1493>. Toluene, however, gave a mixture of 4-chlorotoluene (50%), 2-chlorotoluene (30%), and benzyl chloride (20%). In combination with the (salen)manganese(III) complex **4** and moist alumina, sodium chlorite has been used to chlorinate alkyl phenyl ethers in good yield with excellent *para*-regioselectivity in dichloromethane at room temperature <1997CJC1905>. Mesitylene also underwent monochlorination under these conditions but *o*-, *m*-, and *p*-xylenes were unreactive. Manganese(III) acetylacetonate, moist alumina, and sodium chlorite have also been used for the chlorination of alkyl phenyl ethers with high *para*-selectivity <1997JCS(P1)3081>.

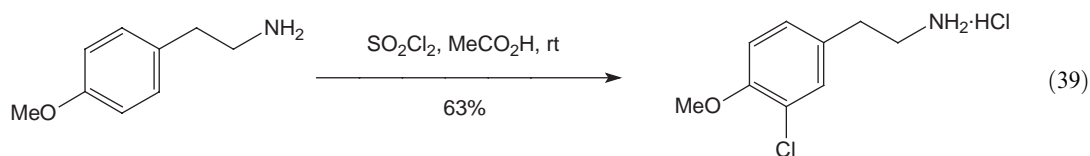


Aryl chlorides have been produced from the reaction of substituted benzene derivatives and acetyl chloride in the presence of a catalytic quantity of ceric ammonium nitrate (CAN) (Equation (38)) <2003SL221>. The reaction proceeds in acetonitrile at room temperature but is restricted to activated substrates. Acetyl chloride in combination with manganese(III) acetate has also been used for the chlorination of activated substrates and this reaction is significantly accelerated when performed under sonication <1996JCR(S)164>.

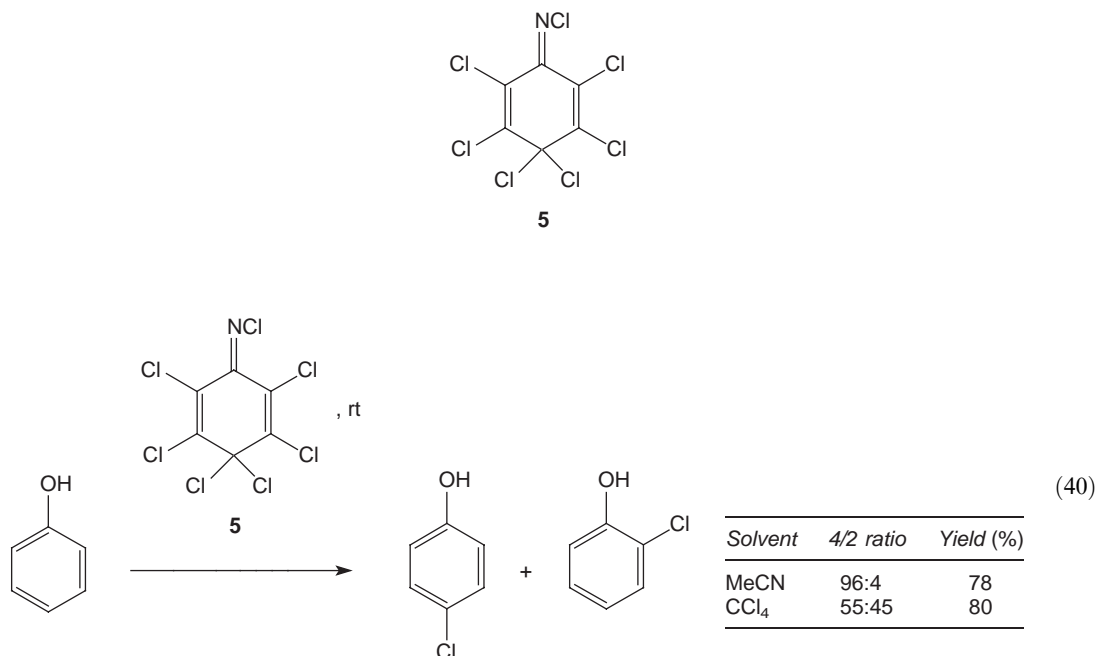


Sulfuryl chloride has often been used as a chlorinating agent for electron-rich aromatic compounds and its use has been extended to include the chlorination of aryl alkylamines, without need for protection of the amine group (Equation (39)) <2001TL3247>. For the five examples

reported, yields were good (60–80%). Merrifield resin bound *o*-cresol underwent chlorination with sulfonyl chloride giving *para:ortho* ratios in excess of 50:1 <2002T8059>.



Phenol and *o*-cresol have both been chlorinated by *N*-chloro-2,3,4,4,5,6-hexachlorocyclohexa-2,5-dienylamine **5** in a reaction in which the *ortho/para* selectivity was solvent dependent, as illustrated for the chlorination of phenol in (Equation (40)) <2002SC735>.



2.12.3.2.2 Aryl chlorides by miscellaneous methods

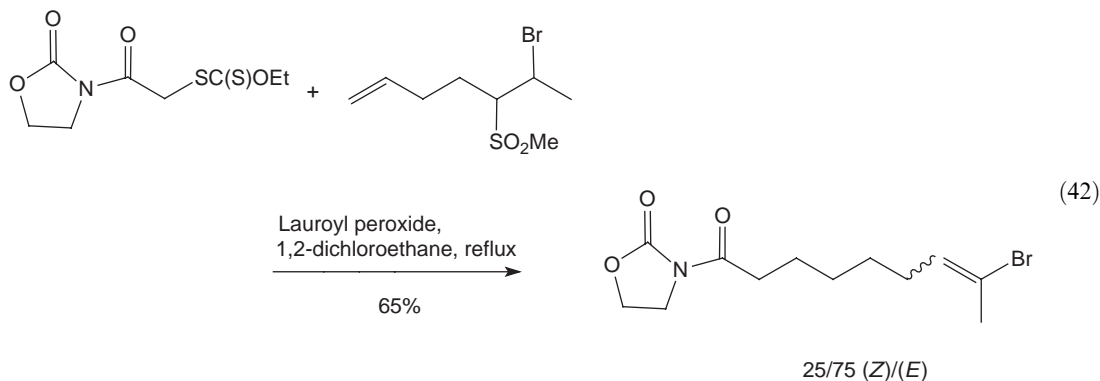
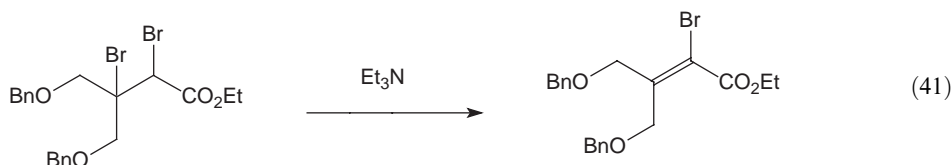
Arenediazonium tetrachlorocuprates ($\text{ArN}_2^+ \text{CuCl}_4^{2-}$) have been decomposed in dimethyl sulfoxide (DMSO) yielding chloroarenes in excellent yields for the nine examples reported <1998TL9567>.

2.12.4 BROMIDES

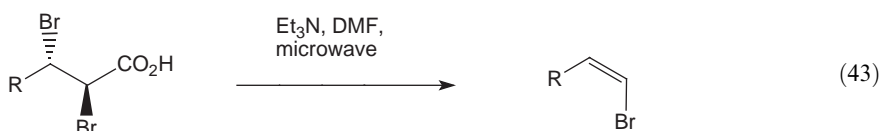
2.12.4.1 Vinyl Bromides

2.12.4.1.1 Vinyl bromides by elimination reactions

Treatment of a 1,2-dibromoalkane (Equation (41)) with triethylamine gave a vinyl bromide <2001MI681>. 1,2-Dibromoalkanes have been reacted with $\text{KF}/\text{Al}_2\text{O}_3$ under microwave irradiation to give vinyl bromides, generally as mixtures of (*Z*)- and (*E*)-geometrical isomers. Yields, however, were only estimated by proton NMR spectroscopy <1998TL4035>. An example of the formation of a vinyl bromide involving a radical elimination has been reported (Equation (42)) <2003CC778>.

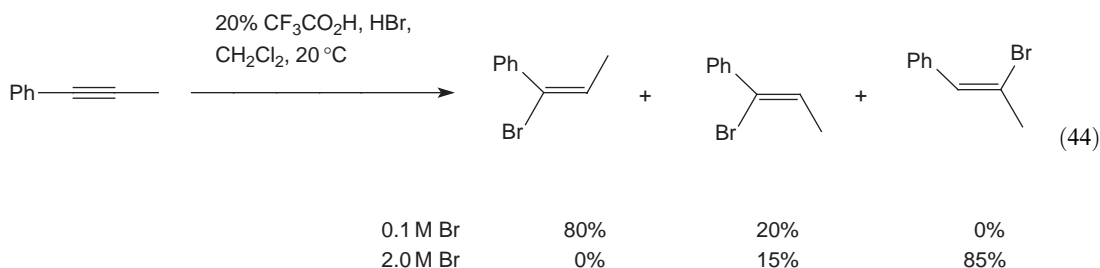


Anti-2,3-dibromoalkanoic acids gave (*Z*)-vinyl bromides in excellent yields and stereoselectivities when subjected to microwave irradiation in DMF in the presence of triethylamine (Equation (43)) <2001TL3893>. When R = Ph, the yield was 95% with the (*Z*):(*E*) ratio greater than 99:1. Other aryl derivatives gave similar yields and selectivities. When R = cyclohexyl, the yield was lower (82%) but the (*Z*):(*E*) ratio was reported to be greater than 99.9:0.1. The corresponding (*E*)-vinyl bromides could be prepared from the *syn*-2,3-dibromoalkanoic acids. *Anti*-1-aryl-2,3-dibromoalkanoic acids also gave (*Z*)-vinyl bromides in excellent yields in a similar reaction without microwave irradiation <1999SC4179>.

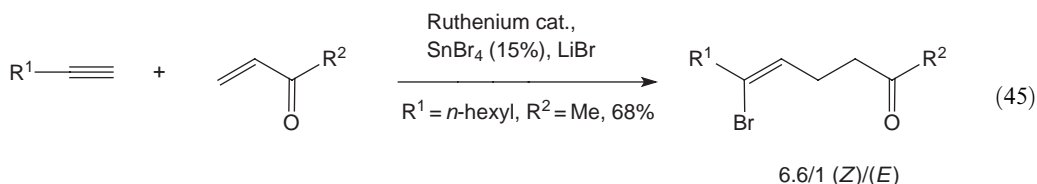


2.12.4.1.2 Vinyl bromides from alkynes

1-Phenylprop-1-yne gave a mixture of vinyl bromides when reacted with HBr in 20% trifluoroacetic acid in dichloromethane. The ratio of the products depended upon the concentration of the bromide ion; at low bromide concentrations, the Markovnikov products were formed whereas at high bromide ion concentrations the anti-Markovnikov product predominated (Equation (44)) <2003OBC2148, 2003OBC2152>.

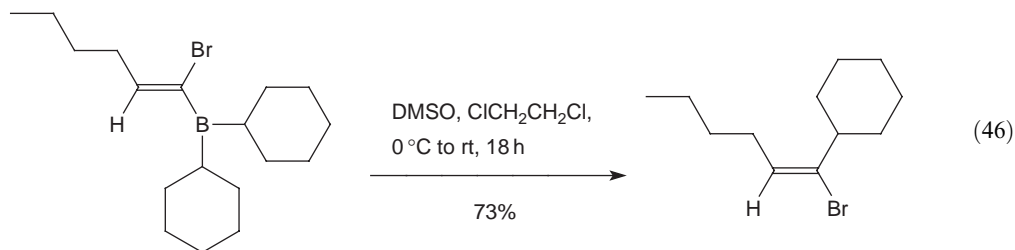


Mono-substituted alkynes and vinyl ketones reacted in the presence of a ruthenium catalyst, 15% SnBr₄, and 1.5 equiv. of lithium bromide to yield vinyl bromides (Equation (45)) <2000AG(E)360>. Nine examples were reported (64–92% yield) with the (*Z*)-isomer as the major product. With the corresponding reaction that produced vinyl chlorides, the opposite stereoselectivity was observed i.e., the (*E*)-isomer predominated (see Section 2.12.3.1.2).



2.12.4.1.3 Vinyl bromides from vinyl metallic species

(Z)-1-Bromoalk-1-enylboranes, which are readily prepared by hydroboration of 1-bromoalk-1-ynes, gave (*E*)-alkenyl bromides with excellent stereoselectivity when treated with DMSO (Equation (46)) <1999CC627>. In the nine examples reported, yields were in the range 28–73% and the isomeric purity was given as greater than 99%. (*Z*)-1-Bromoalk-1-enylboranes also reacted with either *N*-bromosuccinimide (NBS), *N*-bromoacetamide, or NCS in DMF yielding (*E*)-alkenyl bromides in good yield and excellent stereoselectivity <2000TL2595>. The synthesis of vinyl halides from vinyl boronic acids has been discussed in Section 2.12.1.1.3. Vinyl boronic acids have also yielded a mixture of (*Z*)- and (*E*)-vinyl bromides when treated with bromine and alumina <1995JOM(487)35>.

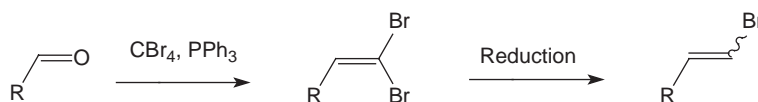


2.12.4.1.4 Vinyl bromides from carbonyl compounds

The synthesis of vinyl bromides from carbonyl compounds has been discussed in Section 2.12.1.1.4. Acetyl bromide can replace acetyl chloride in the reaction shown in Equation (33) (Section 2.12.3.1.4) and this gives access to vinyl bromides.

(i) Vinyl bromides by miscellaneous methods

1,1-Dibromoalkenes are readily available from the reaction of aldehydes with a mixture of triphenylphosphine and carbon tetrabromide. Consequently, several methods have been developed for the reduction of 1,1-dibromoalkenes to give vinyl bromides (Scheme 4).



Scheme 4

The reduction of 1,1-dibromoalkenes using tributyltin hydride in the presence of a palladium catalyst (Equation (47) and Table 10) has been extensively investigated by Uenishi and co-workers <1996TL6759, 1996JOC5716, 1998JOC8965, 1998AG(E)320, 2000T3493>. This reaction generally proceeds in good yield with excellent (*Z*)-stereoselectivity. This methodology has been used in the stereoselective synthesis of unsaturated, very long chain, fatty acid derivatives <1999TL4041>.

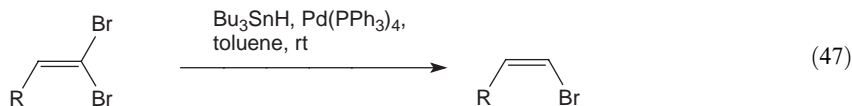


Table 10 Synthesis of vinyl bromides from 1,1-dibromoalkenes (Equation (47))

<i>R</i>	Yield (%)	References
Ph	76	<1998JOC8965>
4-Dimethylaminophenyl	90	<1998JOC8965>
PhCH ₂ CH ₂	79	<1998JOC8965>
Cyclohexyl	77	<1998JOC8965>
CH ₃ O ₂ C(CH ₂) ₁₃	83	<1999TL4041>

1,1-Dibromo-1,3-dienes and 1,3,5-trienes are also reduced with Bu₃SnH in the presence of a palladium catalyst in good yields (Equation (48) and Table 11) as are conjugated alkenylalkynes (Equation (49)) <1998JOC8965>. Unsymmetrical 2,2-disubstituted-1,1-dibromoalkenes are also reduced under similar conditions but the yields are low to moderate and there is a significant loss of stereoselectivity (Equation (50)) <1998JOC8965>.

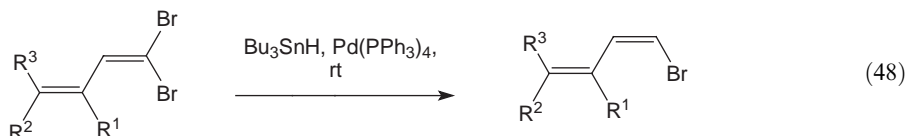
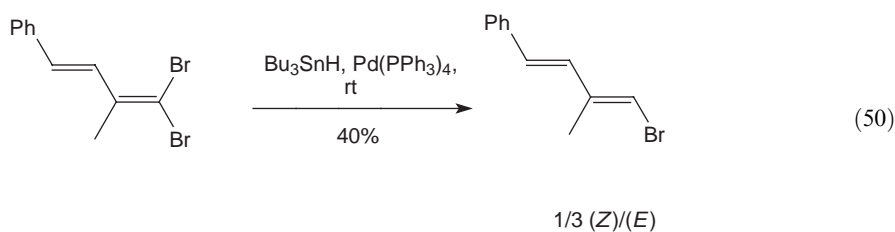
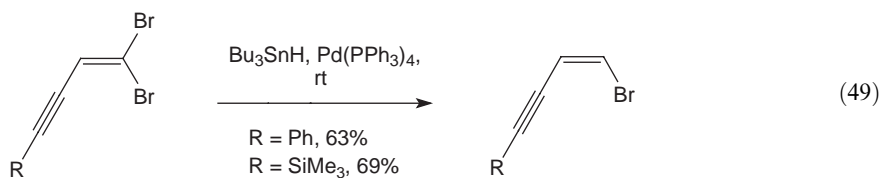


Table 11 Reduction of conjugated 1,1-dibromo-1, 3-dienes (Equation (48))

<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	Yield (%)	References
H	PhCH ₂ CH ₂	H	82	<1998JOC8965>
	(CH ₂) ₄	H	90	<1998JOC8965>
H		Me	86	<1998AG(E)320>



1,1-Dibromoalkenes have been reduced using a mixture of a dialkyl phosphonate and a base, with <2002T1491> or without microwave irradiation <1999SL1124, 2000TL3215>, yielding predominantly (*E*)-vinyl bromides (Equation (51) and Table 12).

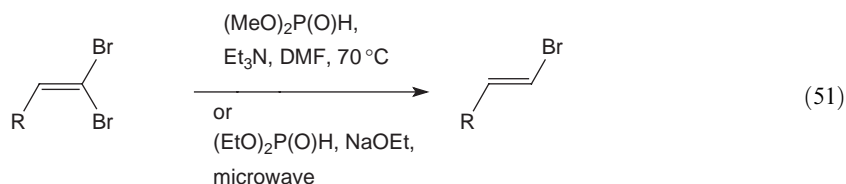


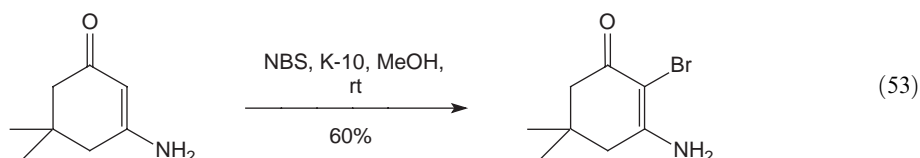
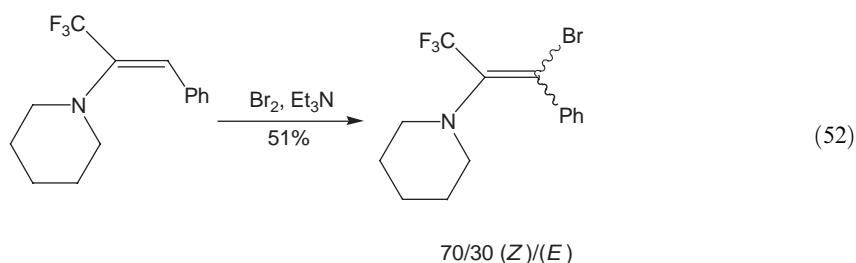
Table 12 Reduction of 1,1-dibromoalkenes with dialkyl phosphites (Equation (51))

<i>R</i>	Conditions ^a	Yield (%)	(<i>E</i>):(<i>Z</i>) ratio	References
Ph	A	67	100:0	<2000TL3215>
(<i>E</i>)-PhCH=CH-	A	87	68:32	<2000TL3215>
(<i>E</i>)-PhCH=CH-	B	92	73:27	<2002T1491>
Cyclohexyl	A	8	82:18	<2000TL3215>
Cyclohexyl	A	67	68:32	<2002T1491>
CH ₃ (CH ₂) ₆	A	22	80:20	<2000TL3215>

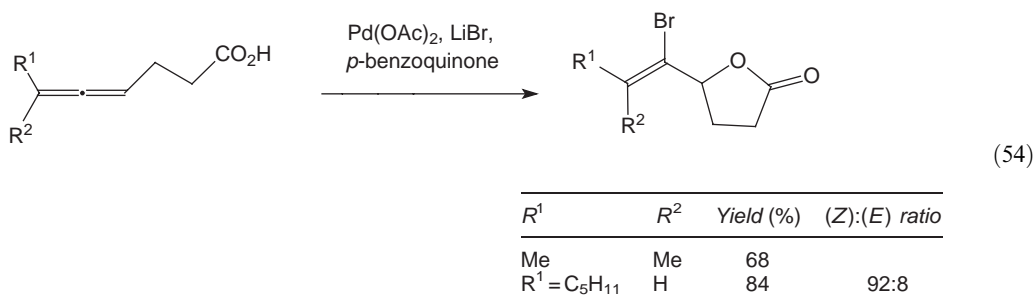
^a A, (MeO)₂P(O)H, Et₃N, DMF, 70 °C; B, (EtO)₂P(O)H, EtONa, microwave.

A small number of 2-aryl-1,1-dibromoalkenes have been reduced using isopropylmagnesium chloride in the presence of a catalytic quantity of Fe(acac)₃ yielding (*E*)-2-aryl-1-bromoethenes in good yield <2001JOM(653)131>. This reaction failed with 2-alkyl-1,1-dibromoalkenes. 2-Aryl-1,1-dibromoalkenes have also been reduced with indium in ethanol giving predominantly the (*E*)-2-aryl-1-bromoethenes in good yield (70–95%) for the 13 examples reported <2001JOC4102>.

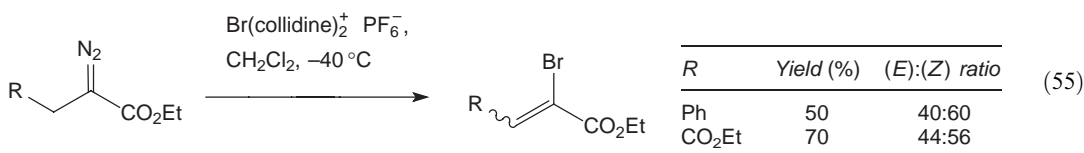
Trifluoromethylated enamines reacted with bromine in the presence of triethylamine to give vinyl bromides (Equation (52)) <2000S838>. For the five examples reported, yields were 51–95% and the (*Z*):(*E*) ratios were between 90:10 and 70:30. 1-Ethoxy-1-trifluoromethylated alkene derivatives similarly gave vinyl bromides <1998S288> in good yield with the (*Z*)-isomer predominating. Enaminones gave vinyl bromides when treated with NBS in the presence of K-10 montmorillonite as illustrated in Equation (53) <2001S1935>.



Allenic acids underwent a palladium catalyzed oxidative cyclization in the presence of lithium bromide and *p*-benzoquinone to give vinyl bromides (Equation (54)) <1998TL3601>.



Diazo-compounds have been converted into vinyl bromides as shown in Equation (55) <1999SC3705>.

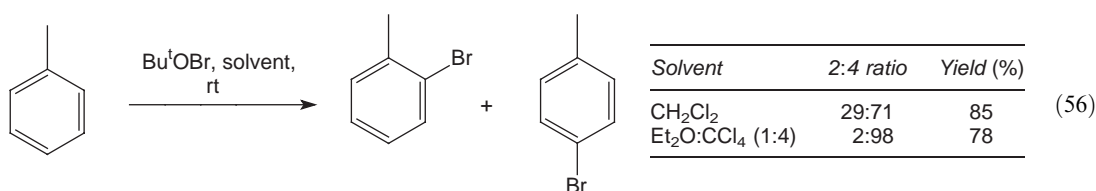


2.12.4.2 Aryl Bromides

2.12.4.2.1 Aryl bromides by electrophilic aromatic substitution

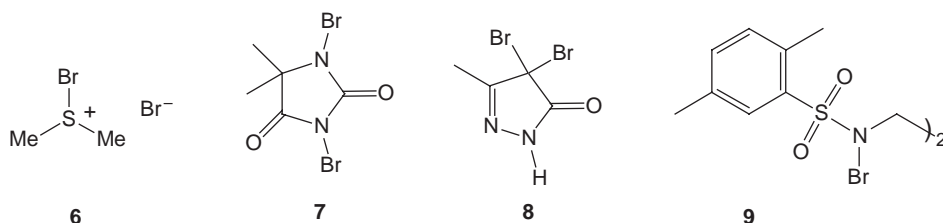
The preparation of aryl bromides by oxidation of HBr or KBr in the presence of arenes has already been discussed in some detail in Section 2.12.1.2.1. Additionally, treatment of arenes with a mixture of LiBr and CAN in acetonitrile at room temperature has been used to synthesize aryl bromides from electron-rich arenes <2001TL6941>. Representative substrates include toluene, which gave a 3:7 mixture of *o/p*-bromotoluene in 70% overall yield, and anisole, which gave 4-bromoanisole exclusively in 99% yield. The bromination of electron-rich arenes using a mixture of KBr and hydrogen peroxide in acetic acid at room temperature has been achieved in the presence of a shape selective zeolite catalyst (HZSM-5) in good yield <2000SC3669>. NBS in acetone with 1 M HCl catalysis has been used to brominate activated aromatic compounds in excellent yields <2000SC2091>. Aniline derivatives have been brominated by KBr in the presence of sodium perborate in good yield <2000TL2083>. Surfactants <1996T2465> and β -cyclodextrin <1996T3487> have been used to control the *ortho/para* ratio in the bromination of anilines.

Toluene has been brominated in the presence of a HNaX zeolite using *t*-butyl hypobromite at room temperature (Equation (56)) <2000JCS(P1)2745>. The *ortho/para*-selectivity was found to be solvent dependent; in dichloromethane a 29:71 mixture of 2-bromotoluene and 4-bromotoluene was obtained in 85% overall yield (as determined by quantitative gas chromatography), whereas in an ether–carbon tetrachloride mixture (1:4), the ratio of brominated products was 2:98 in favor of the *para*-substituted product. Similarly, in other mixed solvent systems that contained ether as one of the solvents, the proportion of 4-bromotoluene produced was over 94%. Bromination of toluene using bromine in the presence of a range of zeolites was also studied giving, in general, high yields of 4-bromotoluene <1996CC467, 2000JCS(P1)2745>. The liquid phase bromination of chlorobenzene, toluene, and xylenes over a zeolite H-beta catalyst with either bromine or NBS gave mixtures of *ortho/para*-substituted products in addition to benzylic brominated products in appropriate cases <1999JMOC(A)241>. The bromination of phenols and some aniline derivatives with bromine in the presence of a heterogeneous catalyst system composed of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ /cetylammmonium bromide occurred at room temperature in dichloromethane giving good yields of *para*-substituted products <2003JMOC(A)289>.

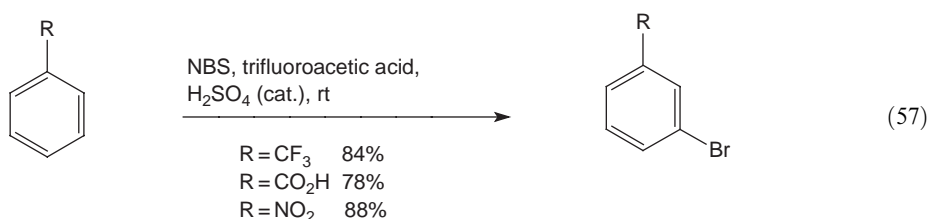


Bromodimethylsulfonium bromide **6**, which can be generated *in situ* from dimethyl sulfoxide and aqueous hydrobromic acid, has been shown to be a mild and selective reagent for the bromination of electron-rich aromatic compounds (mainly phenol, anisole, and aniline derivatives) in good yields <1997JOC4321>. Unactivated arenes such as benzene and toluene did not react with this reagent.

1,3-Dibromo-5,5-dimethylhydantoin **7** has also been developed as a mild brominating agent for electron-rich aromatic systems <1997TL4415>. Toluene was inert to this reagent, but compound **7** in combination with trimethylsilyltrifluoromethane sulfonate (TMSOTf) yielded a 1.4:1 mixture of 2-bromotoluene and 4-bromotoluene in 80% overall yield. 4,4-Dibromo-3-methylpyrazol-5-one **8** similarly brominated phenol and aniline derivatives in good yield in acetic acid at room temperature <1997TL4865>. The *N*-brominated sulfonamide reagent **9** brominated anisole in 80% yield and benzene in 59% yield in carbon tetrachloride at reflux <1999SC4079>. Toluene, however, gave only benzylic bromination with this reagent. Pyridinium hydrobromide perbromide brominated alkyl aryl ethers in good yield in aqueous polar solvents <1998SC499>. Zinc dibromide supported on mesoporous silica or acid activated montmorillonite has been shown to be an efficient catalyst for the bromination of activated and moderately activated arenes (bromobenzene, chlorobenzene, toluene, ethylbenzene, and *t*-butylbenzene) with good-to-excellent *para/ortho*-selectivity <1997CC1203>.



NBS in the solid state brominated phenol and aniline derivatives in moderate-to-good yield <2000JCS(P2)1113>. Deactivated aromatic benzene derivatives have been successfully brominated in good yield with NBS when trifluoroacetic acid was used as the solvent and a catalytic quantity of sulfuric acid was present (Equation (57)) <1999SL1245>.



2.12.4.2.2 Aryl bromides by miscellaneous methods

The preparation of aryl bromides by miscellaneous methods has been covered satisfactorily in COFGT(1995) <1995COFGT(2)605>.

2.12.5 IODIDES

2.12.5.1 Vinyl Iodides

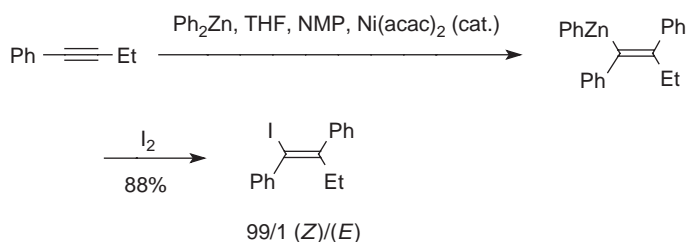
2.12.5.1.1 Vinyl iodides by elimination reactions

The preparation of vinyl iodides by elimination reactions has been mentioned in Section 2.12.1.1.1.

2.12.5.1.2 Vinyl iodides from alkynes

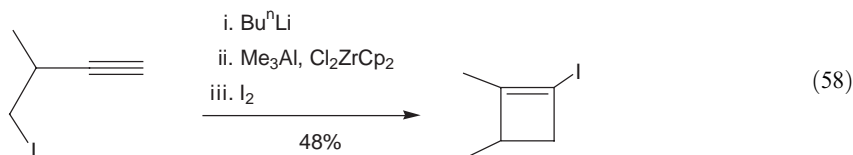
There are several routes to vinyl iodides, which commence from alkynes and an organo-metallic reagent that involve vinyl metallic intermediates which are not isolated. These vinyl metallic intermediates are then quenched with iodine yielding vinyl halides. Such reactions can formally be classed under [Section 2.12.5.1.3](#) (vinyl iodides from vinyl metallic species) but, in order to be consistent with COFGT (1995), [<1995COFGT\(2\)605>](#) these reactions are considered here because alkynes are used as starting materials and the vinyl metallic intermediates are not isolated.

The addition of diphenylzinc to 1-phenyl-1-butyne in the presence of a nickel catalyst followed by treatment of the vinylzinc intermediate with iodine gave the (*Z*)-vinyl iodide shown in [Scheme 5](#) in good yield [<1998T1299>](#). The corresponding (*E*)-isomer could also be prepared in 71% yield by addition of diethylzinc to diphenylacetylene in the presence of $\text{Ni}(\text{acac})_2$ as a catalyst.

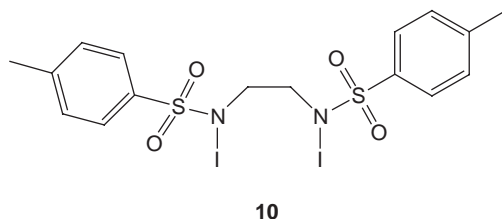


Scheme 5

1-Iodocyclobutenes have been prepared from 4-iodo-1-alkynes as illustrated by [Equation \(58\)](#) [<1997TL1149>](#). This reaction involves a vinylaluminum intermediate and similar chemistry has been used to prepare an acyclic vinyl iodide as part of a synthetic study toward the synthesis of the macrolide antibiotic, concanamycin A [<1998TL6003>](#).

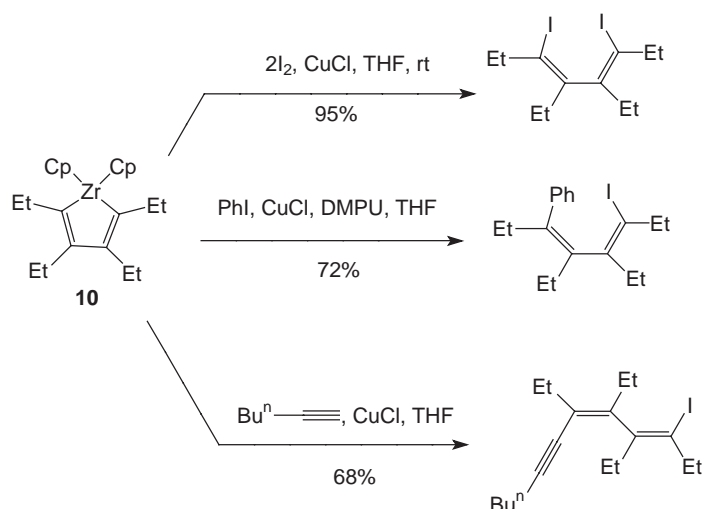


Zirconacyclopentadienes **10**, which are readily prepared from two alkynes, have given iodo-dienes, diiododienes, and iododienynes as illustrated by the reactions shown in [Scheme 6](#) [<1997TL4099, 1998T715>](#).

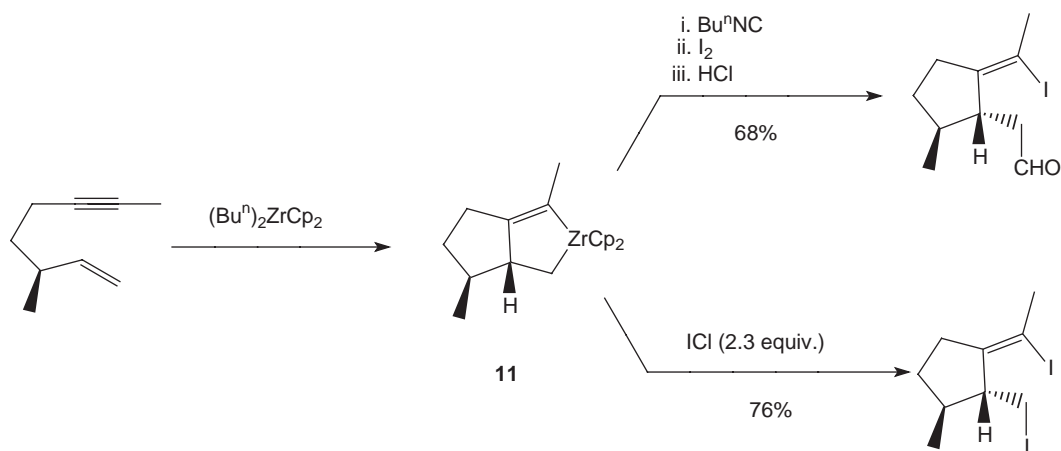


Bicyclization of enynes followed by further transformations of the resulting metallocycle intermediate **11** has given access to vinyl iodides as illustrated by the reactions shown in [Scheme 7](#) [<1997JOC1922>](#).

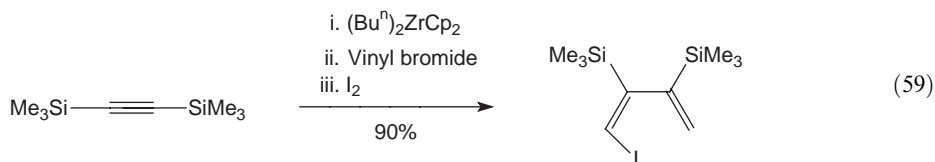
In an unusual reaction, which involves a skeletal rearrangement, bis(trimethylsilyl)acetylene and vinyl bromide were used to construct the vinyl iodide shown in [Equation \(59\)](#) [<1997JA4561>](#).



Scheme 6



Scheme 7

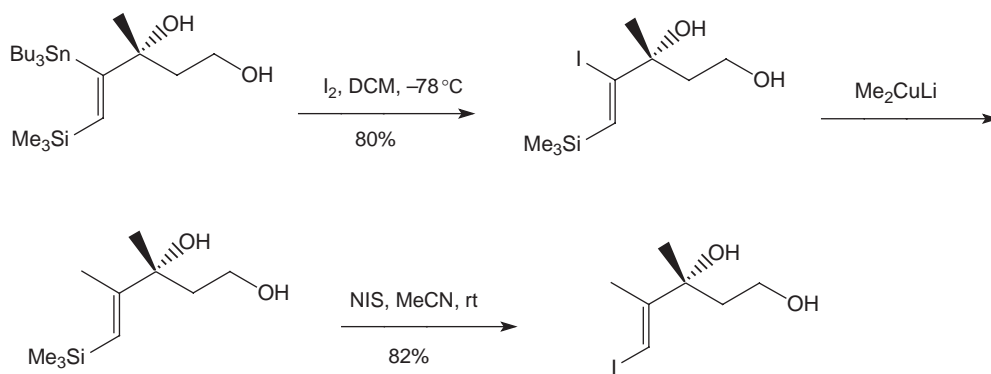


(59)

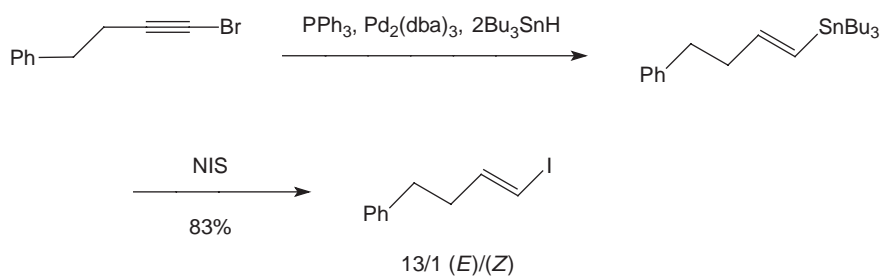
2.12.5.1.3 Vinyl iodides from vinyl metallic species

The trimethylsilyl or tributylstannyl group in vinyl silanes <1996TL8647> and vinylstannanes, respectively, can be replaced with retention of stereochemistry by iodine yielding vinyl iodides. Both of these reactions have been carried out (Scheme 8) as part of a study toward the synthesis of the marine macrolide amphidinolide B <1998SL540>. A similar replacement of a tributylstannyl group has been adopted in the synthesis of 9-*cis*-retinoic acid <1999TL8287>. A range of (*E*)-vinyl iodides have been prepared in good yield from the corresponding vinylstannanes which were generated *in situ* from 1-bromoalkynes (Scheme 9) <1996JCS(P1)2417>.

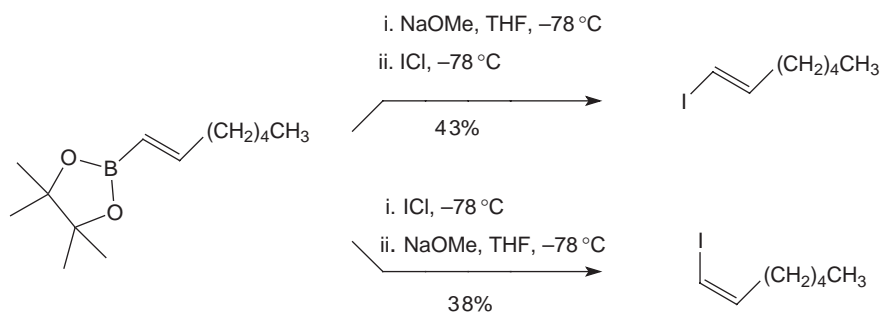
Alkenyl boronate systems gave (*Z*)-vinyl iodides when reacted with iodine monochloride followed by sodium methoxide (Scheme 10) <1995TL3929>. When the order of addition of these two reagents was reversed, the (*E*)-vinyl iodides were produced. (*Z*)- and (*E*)-1-Iodo-1,3-dienes could also be prepared using a similar procedure.



Scheme 8

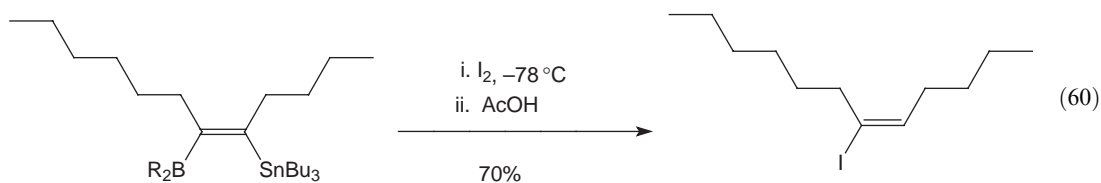


Scheme 9



Scheme 10

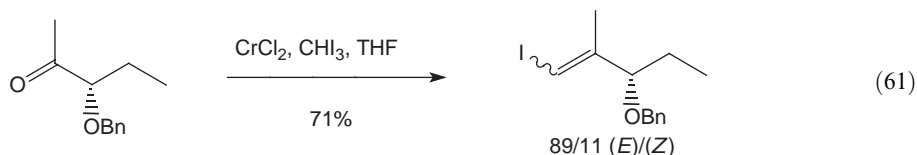
Sequential replacement of the tin and boron substituents in [2-(tributyltin)alkenyl]dialkylboranes gave (*E*)-alkenyl iodides as shown in Equation (60) [<1996JOC1857>](#). In the five examples reported, yields were moderate to good (41–70%).



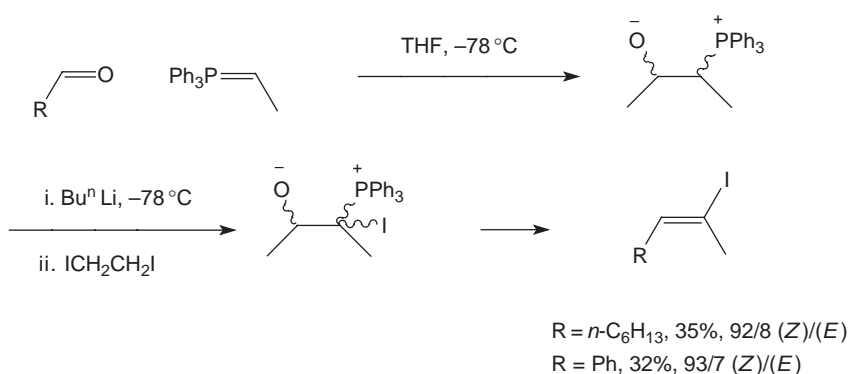
2.12.5.1.4 Vinyl iodides from carbonyl compounds

The reaction of ketones with a mixture of chromium(II) chloride and iodoform as illustrated in Equation (61) continues to attract interest as a method of preparing vinyl iodides

<2002JOM(653)229, 1997TL7333>. The reaction shown in Equation (61) was used in the total synthesis of the alkaloids pumilotoxins A and B. Aldehydes also participate in this reaction <1997TL5937, 1999SL1268> in moderate-to-good yields generally giving mixtures of geometrical isomers with the (*E*)-isomer predominating. Chromium(II) chloride can also be used in catalytic quantities when zinc metal is used to recycle the chromium <1999SL1268>.



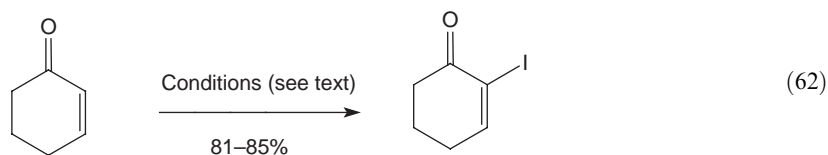
Vinyl iodides have been prepared from phosphoranes and aldehydes using the reaction sequence shown in Scheme 11 <1995JCS(P1)1331> but yields are only poor to moderate.



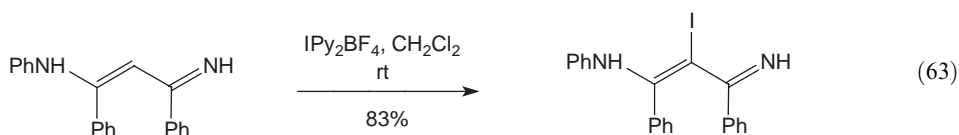
Scheme 11

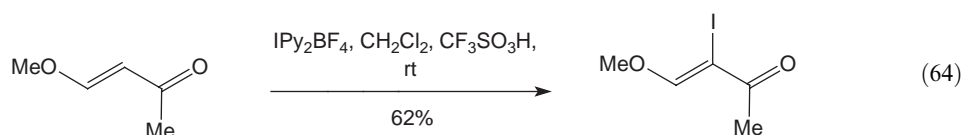
2.12.5.1.5 Vinyl iodides by miscellaneous methods

Cyclic α,β -unsaturated enones have been iodinated at the α -position as shown in Equation (62) for the iodination of cyclohexen-2-one. One method uses iodine in the presence of bis(tetra-*n*-butylammonium) peroxydisulfate in acetonitrile <1997CC1355> and another method treats the enone first with trimethylsilyl azide and then with iodine in pyridine <1995TL6927>. The yields from these two methods were 85% and 81%, respectively.

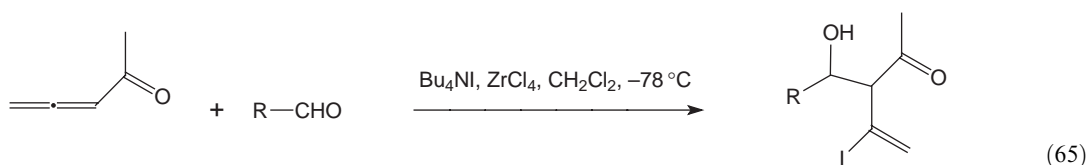


1-Hetero-1,3-dienes reacted with bis(pyridine)iodonium(III) tetrafluoroborate under mild conditions giving vinyl iodides in good yield (Equations (63) and (64)) <1995TL5257>. 1-Oxa-1,3-dienes were less reactive than their aza-analogs and hence triflic acid was added to promote the reaction.





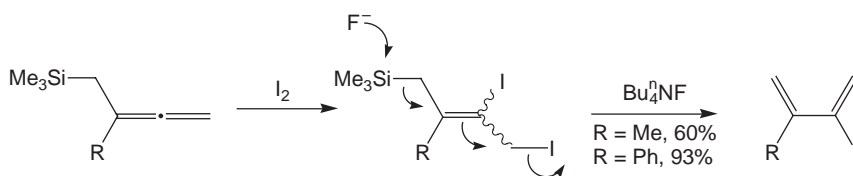
The zirconium tetrachloride-mediated tandem nucleophilic addition-aldol reaction of 3,4-pentadien-2-one, iodide, and aldehydes yielded a series of vinyl iodides in moderate-to-good yields as illustrated in Equation (65) <1997TL4831>.



R = Prⁿ, 64%, *syn:anti* 40:60

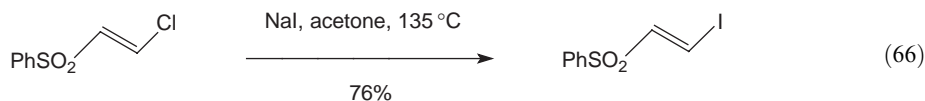
R = Ph, 71%, *syn:anti* 29:71

1-Trimethylsilyl-2,3-butadienes have given 2-iodo-1,3-butadienes in good yield when treated successively with iodine and fluoride (Scheme 12) <1998TL43>.



Scheme 12

A Finkelstein reaction under forcing conditions has been used to convert the (*E*)- α -chlorovinyl phenylsulfone shown in Equation (66) into its corresponding vinyl iodide <1998TL8089>.



2.12.5.2 Aryl Iodides

2.12.5.2.1 Aryl iodides by electrophilic aromatic substitution

The iodination of arenes using iodine in combination with an oxidant has been extensively studied. The products obtained from these reactions are in accord with an electrophilic substitution mechanism and are generally produced in good-to-excellent yields. Thus, iodine and compound **1** (see Section 2.12.1.2.1) have been used to iodinate 1,3,5-trialkylbenzenes <1998SL286>. Electron-rich arenes have been iodinated by iodine/urea–hydrogen peroxide addition compound <2002MI867>, iodine/nitrogen dioxide <1997TL6225>, iodine/silica supported ferric nitrate nonahydrate (silfen) <2002TL9457>, iodine/*t*-butylammonium peroxydisulfate

<1999TL6051>, iodine/mercury(II) oxide <1995SI1273>, iodine/selectfluor™ **2** <1997TL6305, 2002SI1513>, iodine (or *N*-iodosuccinimide)/xenon difluoride <1998JFC(88)37>, and iodine/lead tetraacetate <1995S926>. When an excess of iodine and oxidant are used, it is often possible to obtain diiodinated products. Iodination of methylated anisoles with a mixture of iodine, periodic acid, acetic acid, and sulfuric acid gave the expected mono- and diiodinations in the aromatic ring, but additionally iododemethylation and/or aryl methyl oxidations were observed <1995JOC7953>.

Iodination of electron-rich arenes has also been carried out with *N*-iodosaccharin <2000SL544>, *N*-iodosuccinimide <1996TL4081, 2002TL5047>, the *N*-iodosulphonamide **10** <2003TL7529>, iodine monochloride in the presence of a ferrocenium catalyst <2000TL9383>, bis(*sym*-collidine)iodine(I) hexafluorophosphate <1995TL8217>, and polymer bound benzyltriethylammonium dichloroiodate or tetrachloroiodate <1997MI281>.

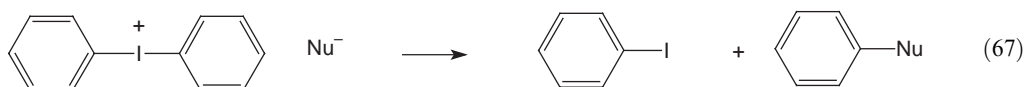
Electron-deficient arenes can also be successfully iodinated with iodine in combination with a suitable oxidant. Examples include the iodination of nitrobenzene and benzoic acid, which gave 3-iodonitrobenzene (70% yield) and 3-iodobenzoic acid (80% yield), respectively with iodine and *n*-butyltriphenylphosphonium peroxodisulfate in acetonitrile at reflux <2003SC1319>. Mixtures of iodine/chromium(VI) oxide <1997BCJ1665>, iodine/sodium periodate <2000BCJ951>, iodine/sodium iodate <2000BCJ951>, all in a solution of acetic and sulfuric acids have similarly been used to iodinate a range of electron-rich and electron-deficient aromatic compounds. Iodine in the presence of fluorine and sulfuric acid has been successfully used to iodinate a range of electron-deficient arenes in good yield. For example, both nitrobenzene and benzotrifluoride underwent *m*-iodination in 70% and 83% yields, respectively <1995CC19>.

N-Iodosuccinimide in sulfuric acid has been used to synthesize 3-iodonitrobenzene from nitrobenzene (79% yield) <2001JOU1503>. A mixture of iodine monochloride and silver sulfate in sulfuric acid similarly iodinated nitrobenzene in 74% yield <1999S748> as did tetramethyl ammonium dichloroiodate <2002JOC8622>. This latter reagent system also iodinated a range of other electron-rich and electron-deficient arenes.

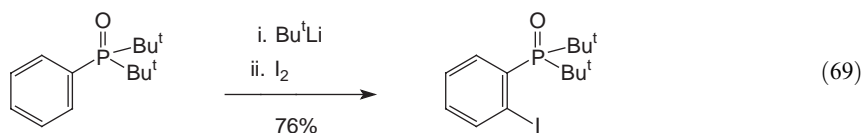
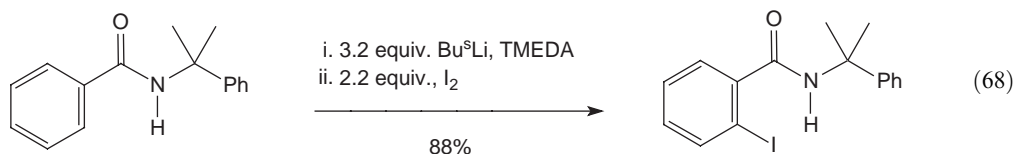
2.12.5.2.2 Aryl iodides by miscellaneous methods

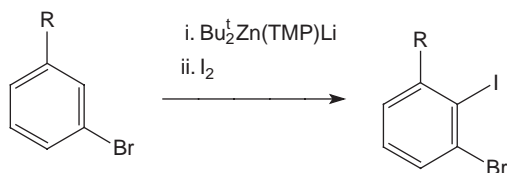
Treatment of aromatic amines with a mixture of nitrogen dioxide and sodium iodide in acetonitrile at -20°C gave aryl iodides in moderate-to-good yields <1998TL4533>.

The reaction of diaryliodonium salts, and their cyclic analogs, with nucleophiles yielding aryl iodides as depicted by the general reaction shown in Equation (67) has been reviewed <2000CSR315>.



Directed *o*-metallation continues to be an important method for the preparation of aryl iodides as illustrated by the examples shown in Equation (68) <1999OL1183>, Equation (69) <1998SL422> and Equation (70) <2002JA8514>. 2,2,2-Trifluoro-1-iodoethane has been used as a source of iodine to quench directed *o*-metallation reactions <1999TL6671>.





TMP = 2,2,6,6-tetramethylpiperidyl

R	Yield (%)
CN	96
OMe	95
Cl	77
F	93
CO ₂ Et	37 ^a

^aEthyl 3-bromo-6-iodobenzoate (55%) also formed.

(70)

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Biographical sketch

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2.13

Alkenyl and Aryl Chalcogenides: Oxygen-based Functional Groups

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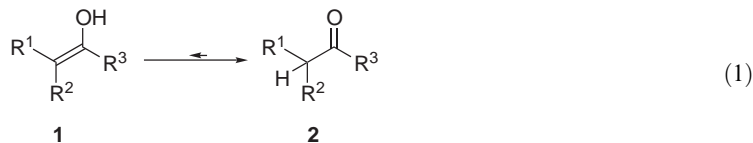
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2.13.1 OXYGEN-BASED FUNCTIONAL GROUPS ATTACHED TO AN sp^2 CARBON

2.13.1.1 Enols and Phenols: ROH

An enol is a tautomeric form of a carbonyl compound that is substituted at the α -position with at least one hydrogen (Equation (1)). For a majority of ketones and aldehydes in solution phase the equilibrium between the parent carbonyl compound **2** and enol **1** strongly favors **2**, such that under standard preparative laboratory conditions it is rarely possible to detect the enol **1** using analytical techniques available to the organic chemist. Nevertheless, many useful synthetic transformations of

enols have been developed because there is a small but kinetically significant concentration of species **1** in solution under a wide variety of reaction conditions. By changing the nature of the substituents R^1 , R^2 , and R^3 of carbonyl compound **2**, the overall stability of the corresponding enol can be modified. Substantial stabilization of the enol tautomer is realized by the presence of an electron-withdrawing group, especially carbonyls and nitriles. These enols derived from 1,3-dicarbonyl systems are treated in Chapter 1.19. Those enols that do not contain electron-withdrawing groups as stabilizing groups have been termed “simple enols” by Hart <1979CRV515> and are the subject of this section.



2.13.1.1.1 Enols

(i) Simple aliphatic enols

Simple aliphatic enols are short-lived species that typically are prepared by thermolytic, photochemical, hydrolytic, or metal-catalyzed isomerization procedures <1995COFGT(2)635> and then utilized immediately after generation.

(a) *By thermolysis.* The thermal retrocycloaddition of cyclobutanol was investigated under high vacuum at variable temperatures (950–1450 K) and the mechanism of formation of ethenol and ethene was determined to proceed via a biradical process (Equation (2)) <1996IJ249>, which is in agreement with earlier results published by Back <1982CJC2537>.

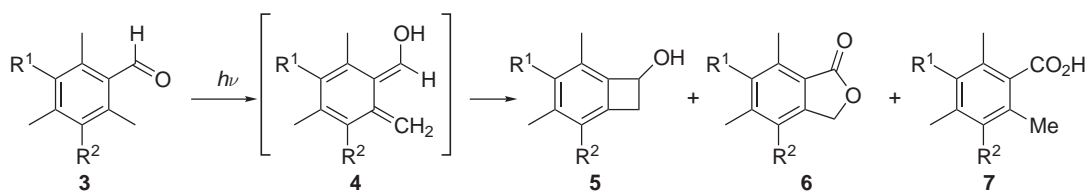


(b) *By photolysis.* The photoisomerization of *o*-alkyl aromatic aldehydes **3** is known to proceed via γ -hydrogen abstraction to furnish enols **4**, which react to give benzocyclobutanols **5**, lactones **6**, benzoic acids **7**, and dimeric and polymeric materials as products (Scheme 1) <1974CC514>. When this reaction is conducted in solution (typically in an alcoholic solvent under an atmosphere of oxygen) the intermediate enols are rapidly consumed and cannot be directly detected. Photoisomerization of these aldehydes in the solid state under an inert atmosphere also results in enol formation, but as the enols **4** remain immobilized in the crystal lattice the monomeric benzocyclobutanol products are favored and are isolated in improved yields over solution phase chemistry <2001JOC7013, 2003JOC3446>. When the starting aldehydes contain functional groups that can stabilize the incipient enol, a distinctive color change is observed on irradiation that is consistent with formation of the enol. The lifetime of these highly-colored enols ranges from several minutes to hours, allowing for their characterization by infrared (IR) and ultraviolet (UV)/vis spectroscopy.

(c) *Hydrolysis of O-substituted enol ethers.* The protonation of silyl enol ethers is a direct method for the preparation of enols from well-defined starting materials. Protodesilylation of *t*-butyldimethylsilyl enol ethers **8a**, **8b** using a mixture of acid and tetra-*n*-butylammonium fluoride (TBAF) results in generation of enols **9a**, **9b**, which were utilized as substrates for investigation of the stereochemistry of the ketonization reaction (Scheme 2) <2002JOC9216>.

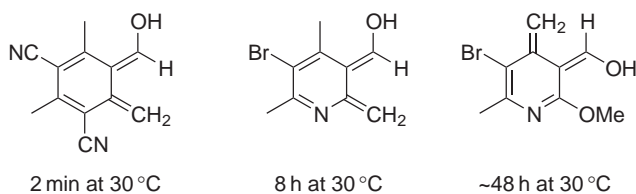
(d) *Isomerization of allylic alcohols.* The transition metal-catalyzed isomerization of an allylic alcohol (or protected version thereof) to the corresponding carbonyl derivative generally proceeds through an enol intermediate (Scheme 3), and with the judicious choice of metal catalyst it is sometimes possible to isolate the intermediate enol. This reaction has been the focus of a review by Bouwman and co-workers <2002JOM(650)1>. For optimum enol–keto selectivity, the use of a rhodium-based catalyst is required. With other metals, the rate of ketonization of the intermediate enols equals or exceeds the rate of enol formation, precluding isolation of the enol.

(e) *Miscellaneous methods.* The conjugate addition of thiobenzoic acid to benzylacrolein **10** at -18°C for 7 days results in formation of (*Z*)-enol **11** which is stable as a solution in CH_2Cl_2 at low temperature <1997TA3363>. When a chiral proton source is added to a solution of enol **11**, the ketonization reaction proceeds to give enantioenriched aldehyde **12** in up to 71% ee (enantiomeric excess) (Scheme 4). The conjugate addition reaction is also reported to proceed with thiolactic acid, but no other nucleophiles were utilized in this study.

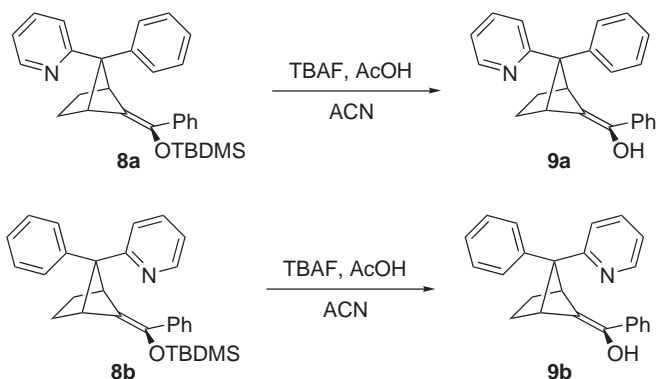


$R^1 = \text{H}, R^2 = \text{CN}, h\nu, \text{PhH}/\text{O}_2$	0%	25%	0%
$R^1, R^2 = \text{H}, h\nu, \text{Pr}^i\text{OH}/\text{O}_2$	33%	0%	14%
$R^1, R^2 = \text{H}, h\nu, \text{solid state}$	90%	0%	0%
$R^1, R^2 = \text{CN}, h\nu, \text{solid state}$	90%	0%	0%

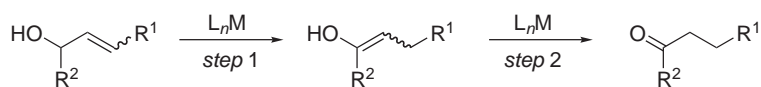
Long-lived enols:



Scheme 1

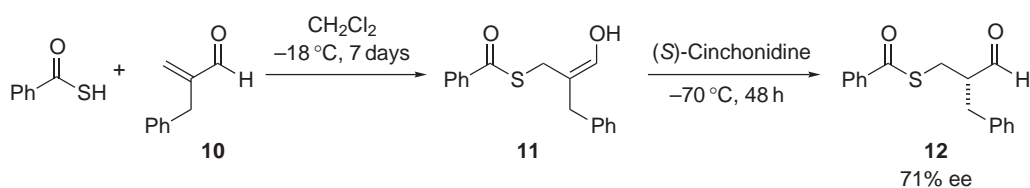


Scheme 2



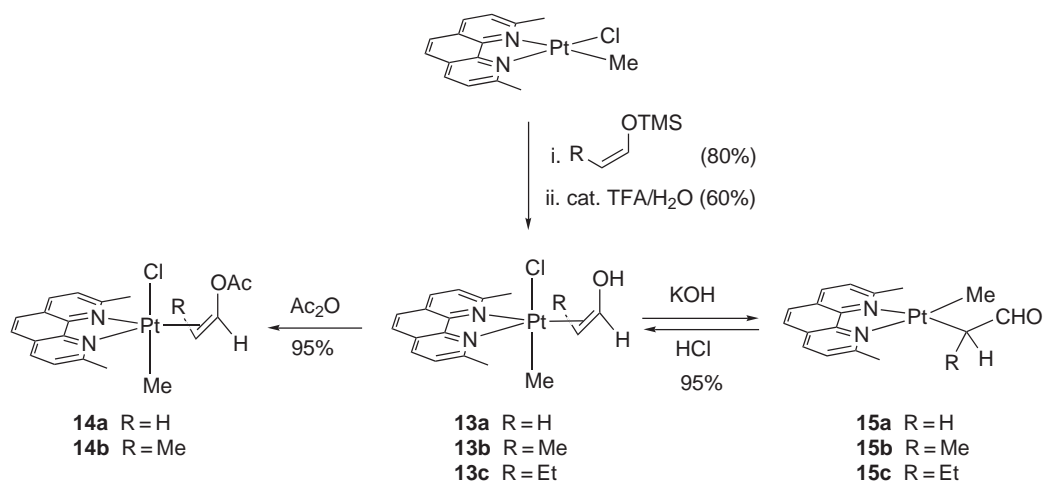
step 2 \geq step 1 for M = Cr, Mo, Fe, Ru, Os, Co, Ir, Ni, Pd
 step 1 \geq step 2 for M = Rh

Scheme 3



Scheme 4

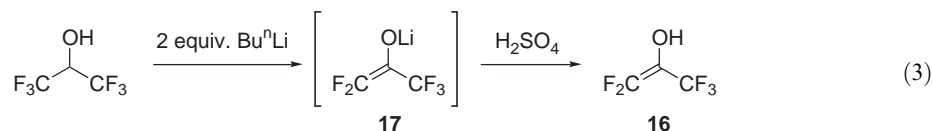
An alternative approach to generating and isolating reactive intermediates such as enols is to form a complex between the intermediate and a transition metal capable of stabilizing the species of interest. For enols, two accounts have appeared that describe the formation, isolation, and characterization of stable complexes of Pt(II) with ethenol **13a** <1997ICA(264)231>, 1-propenol **13b**, and 1-butenol **13c** <2001JOM(622)242>. These compounds are prepared by complexation of the parent silyl enol ether derivatives of enols $\text{RHC}=\text{CHOH}$ ($\text{R} = \text{H}, \text{Me}, \text{Et}$) with coordinatively unsaturated platinum(II) complex $\text{PtClMe}(\text{dmphen})$ ($\text{dmphen} = 2,9\text{-dimethyl-1,10-phenanthroline}$) followed by hydrolysis of the trimethylsilyl ether with water (Scheme 5). X-ray crystallography of the resulting Pt(II)–enol complexes reveals that the ligands adopt a trigonal bipyramidal arrangement around the metal center with the dmphen and enol ligands occupying the equatorial positions. With disubstituted enols, only the (*Z*)-isomers are detected in the isolated complexes. These enols undergo chemoselective reactions while remaining coordinated to the metal, including acylation with Ac_2O to give **14** and carbamate formation by reaction with an isocyanate. Interestingly, when complexes **13** are treated with KOH , deprotonation of the enol is followed by loss of halide and formation of square-planar complex $\text{PtMe}(\text{dmphen})(\text{CRCHO})$ **15** reflecting the change in binding mode of the enol ligand from η^2 to η^1 as the enolate is generated. Regeneration of the enol is accomplished by exposing complex **15** to aqueous acid.



Scheme 5

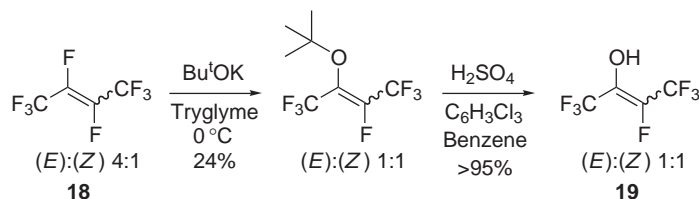
(ii) Fluorinated simple enols

The unique properties of highly fluorinated simple enols have resulted in continued interest through the late 1990s, in their synthesis and exploration of their chemistry. For example, while 1-propen-2-ol (the enol of acetone) exists in only a miniscule concentration ($4.7 \times 10^{-7}\%$) at ambient temperature <1990JA4862>, the corresponding perfluorinated enol **16** is an isolable and distillable liquid. A synthesis of enol **16** has been reported by Lindner and Lemal <1997JA3259> that utilizes the less costly and less toxic hexafluoroisopropanol as starting material (Equation (3)). Metallation of hexafluoroisopropanol with two equivalents of *n*-butyllithium results in formation of lithium enolate **17**, which is protonated with conc. H_2SO_4 in tetrahydrofuran (THF) to provide **16** in good yield.

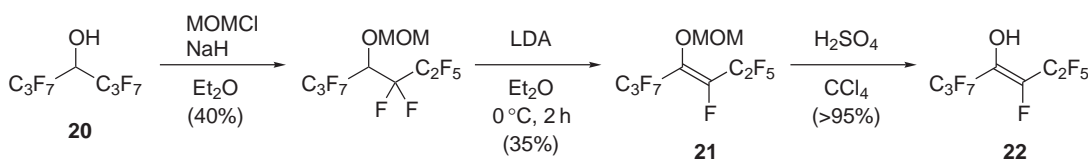


Longer-chain and cyclic perfluorinated enols are prepared in a similar manner, but as the stability of these enols is highly dependent on the structure, the optimized conditions for one substrate may not be applicable for the synthesis of others. For example, the synthesis of the enol of perfluoro-2-butanone **19** starts with addition of *t*-butoxide to perfluoro-2-butene **18** followed by ionization of the resulting *t*-butyl alkenyl ether with H_2SO_4 in trichlorobenzene containing benzene as a cation

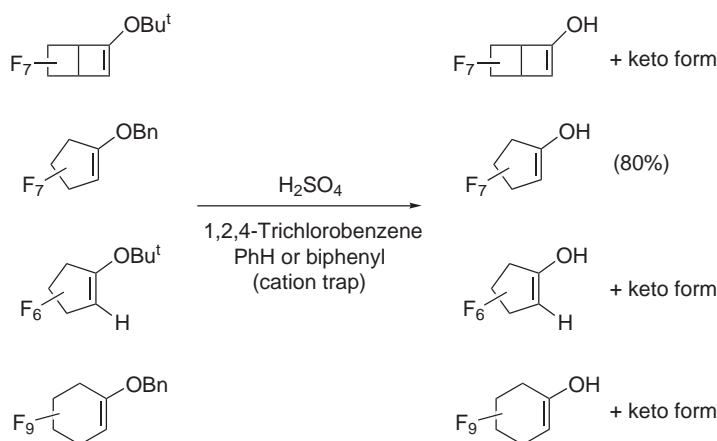
trap (Scheme 6). For the 7-carbon enol analog, perfluoro-4-heptanol **20** is protected as its methoxymethyl (MOM) ether and then treated with lithium diisopropylamide (LDA) to promote dehydrofluorination to provide the protected enol **21** (4:1 ratio of separable *E*:*Z* isomers). Protonolysis of the MOM ether with sulfuric acid results in formation of the desired enol **22** with retention of alkene geometry (Scheme 7). A variety of cyclic perfluorinated enols are also prepared by protonolysis of the corresponding benzyl and *tert*-butyl enol ethers <1996JA2556> (Scheme 8).



Scheme 6

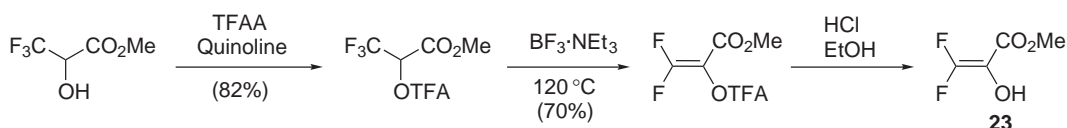


Scheme 7

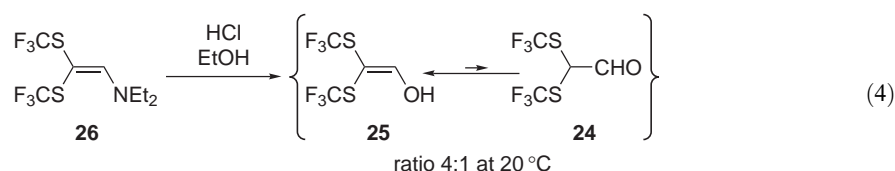


Scheme 8

More functionalized fluorinated enol ethers have also been prepared and characterized (Scheme 9). Fluorinated methyl lactate was utilized as the starting material for the three-step synthesis of enol **23**, which is a stable crystalline solid. This compound exhibits reactivity patterns that are characteristic of both fluorinated enols and of acrylates, including alkene halogenation, base-catalyzed self-condensation, and conjugate addition reactions <1995SL1269>. An attempt to prepare 2,2-bis(trifluoromethylthio)acetaldehyde **24** by protonolysis of *N,N*-diethylaminoethene derivative **26** with conc. HCl resulted in formation of a 4:1 mixture of products identified as the enol **25** and keto **24** forms in 77% yield (Equation (4)) <1998JOC319>.



Scheme 9



The relative stability of cyclic and acyclic perfluorinated simple enols has been evaluated [<1997JA3259, 1997JA3267>](#) on the basis of experimental observations and calculations. The ratio of equilibrium constants for enol–keto tautomerization for a series of enols are shown in [Figure 1](#). In general, there is a much greater tendency for perfluorinated cyclic ketones to exist as mixtures of keto and enol forms or entirely as the enol form in nonpolar solvents. In contrast, the enol forms of acyclic perfluorinated ketones (other than that of perfluoroacetone) rapidly convert to the more stable keto forms under equilibrating conditions. These results are in agreement with calculations which indicate that perfluoro acyclic enols are destabilized relative to their keto tautomers, unlike cyclic perfluorinated systems where ketones are destabilized relative to their enol forms.

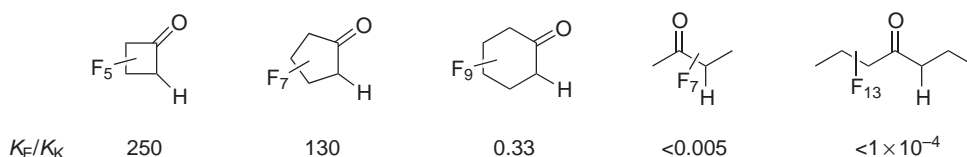
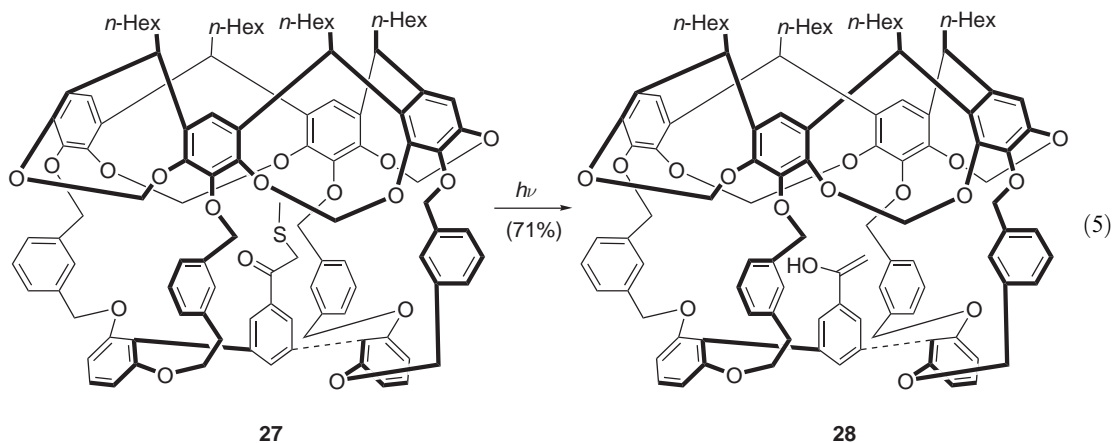
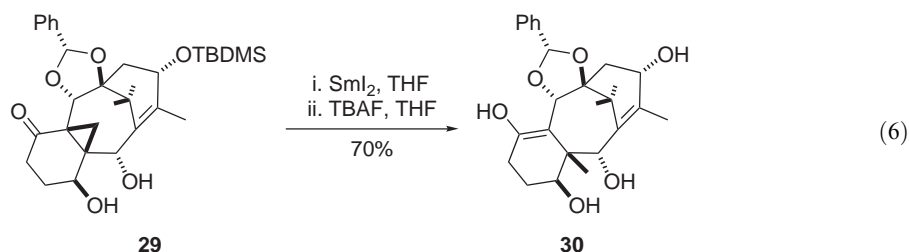


Figure 1

(iii) Sterically congested stable enols

The preparation and isolation of most simple enols is a challenging exercise, as great care is required to minimize tautomerization to the more stable carbonyl compound. In certain cases, however, enols prepared in very hindered steric environments show great kinetic stability that allows for their isolation, purification, and characterization. Okazaki and co-workers have published a very elegant demonstration of this principle in the synthesis of endohedral thiomethyl ketone **27** [<1997JA3195>](#), which on irradiation undergoes a Norrish-type II photocleavage of the α -thiomethyl ketone [<1970JA6082>](#). The resulting endohedral monosubstituted enol **28** was isolated in 71% yield after column chromatography and fully characterized by nuclear magnetic resonance (NMR), IR, and mass spectrometry (MS) ([Equation \(5\)](#)). The steric shielding of the enol functionality in **28** is responsible for its remarkable kinetic stability, as the enol **28** is stable in aprotic solvents at ambient temperature but undergoes slow ketonization over 3 days in the presence of trifluoroacetic acid (TFA). Steric effects are also responsible for the diminished reactivity of enol **30**, which is prepared by a SmI_2 -mediated reduction of α -cyclopropyl ketone **29** and is an isolated intermediate in Kuwajima's total synthesis of taxol ([Equation \(6\)](#)) [<2000JA3811>](#). This enol was tautomerized to a single diastereomeric ketone in a subsequent step.

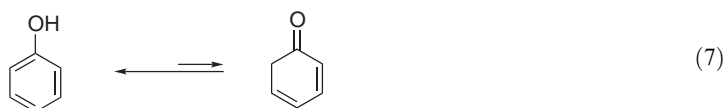




The rate of enol tautomerization can also be affected by electronic effects conferred by the choice of substituents on the enolic alkene. Placing bulky aromatic substituents on enol **1** gives a series of special enols known as Fuson's enols which are as stable as, or more stable than, their carbonyl tautomers. Their synthesis and properties have been broadly explored since the middle of the twentieth century. The reader is directed to COFGT (1995) <1995COFGT(2)635> for a comprehensive overview of methods for preparing Fuson's enols.

2.13.1.1.2 Phenols

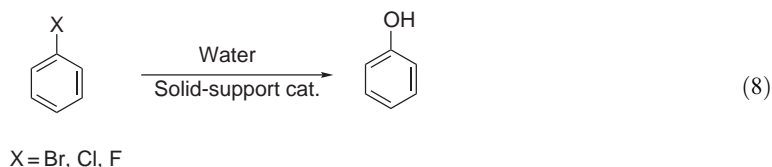
Phenols can be regarded as a class of special enols, stabilized by the aromaticity of the benzene ring. Owing to this stabilization, phenols exist in the enol form rather than the keto form (Equation (7)). The syntheses and reactions of monohydric phenols have been reviewed previously <1995COFGT(2)635, B-1996MI002>. In general, phenols are prepared by elaboration of aromatic substrates, aromatization of alicyclic substrates, and annulation of acyclic fragments. Although no fundamentally new methodologies have been introduced in the synthesis of phenolic compounds, a number of new and improved methods emerged in the decade 1993–2003 that exploit transition metal catalysis. The advancement in the synthesis of phenolic compounds in that decade will be the focus of this section.

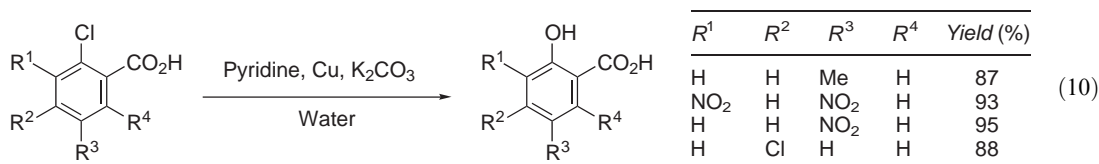
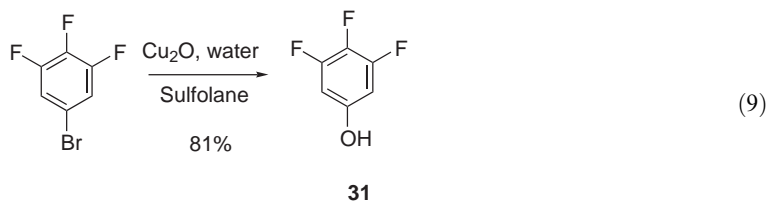


(i) From aromatic substrates

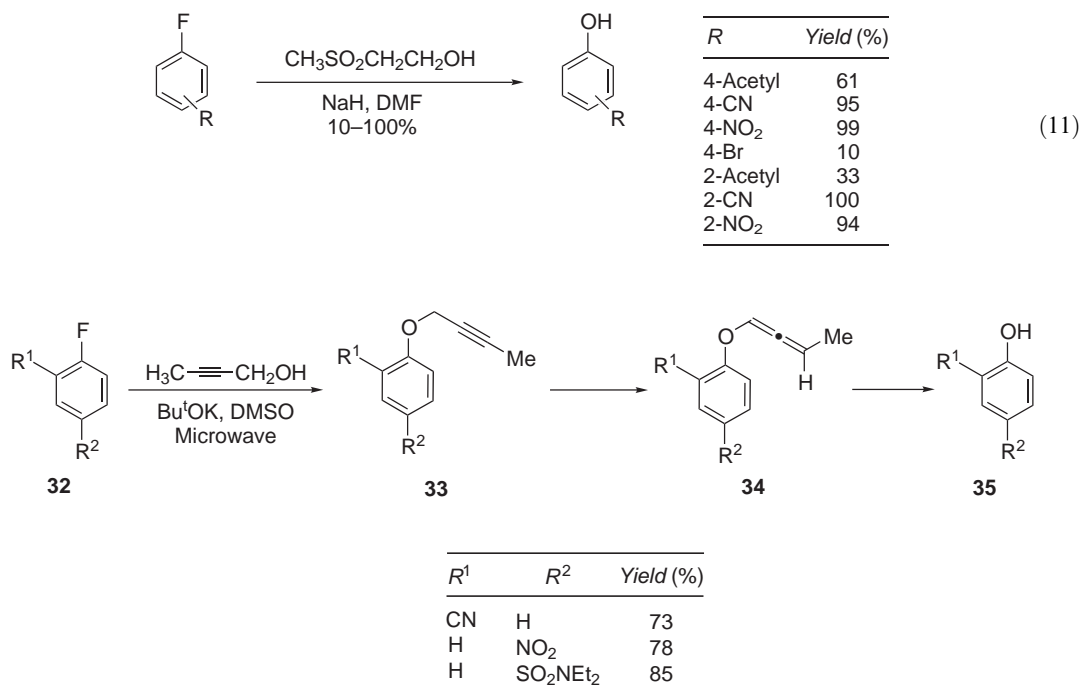
Many reactions have been developed to allow manipulation of an existing aromatic ring for the introduction of the hydroxyl group. This process can often be achieved in a regioselective or regiospecific fashion by taking advantage of the properties of the existing substituents on the benzene ring.

(a) *Aromatic nucleophilic substitution.* Aryl halides are common substrates for the aromatic nucleophilic substitution of water. The hydrolysis can be promoted by solid-support catalysts such as mordenite and zeolite–copper (Equation (8)) <1994MI1981, 1999RJOC246>. Another effective method for the synthesis of phenols from aryl halides is the Ullmann–Goldberg reaction, which employs copper metal or copper salts as a catalyst. Good chemoselectivity is observed in the conversion of 3,4,5-trifluorophenyl bromide to phenol **31** (Equation (9)) <2000JAP(K)2000154159>. The Ullmann–Goldberg reaction has been carried out under relatively mild conditions in pyridine and water (Equation (10)) <2002SC2055>.





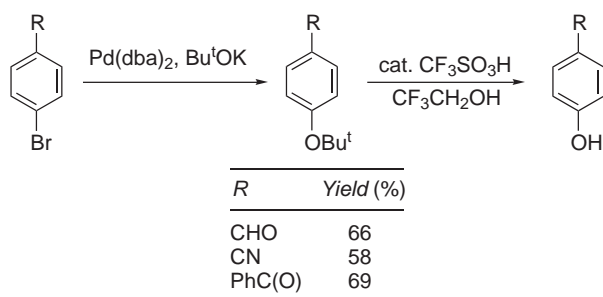
When activated by electron-withdrawing groups and under suitable reaction conditions, aryl fluorides can also be converted into phenols. For example, 2-cyanophenol was prepared in quantitative yield from 2-cyano-1-fluorobenzene via a mild one-pot procedure using commercially available 2-(methylsulfonyl)ethanol as a hydroxyl surrogate. Other aryl fluorides activated at the *ortho* or *para* position also work well for the reaction (Equation (11)) <2002TL3585>. Under microwave irradiation, a variety of aryl fluorides **32** react rapidly with 2-butyne-1-ol in the presence of potassium *t*-butoxide in dimethyl sulfoxide (DMSO) to give propargylic ethers **33**, which isomerize *in situ* to the corresponding allenyl ethers **34** and hydrolyze upon work-up to give phenols **35** in good yields (Scheme 10) <2002SC1401>.



Scheme 10

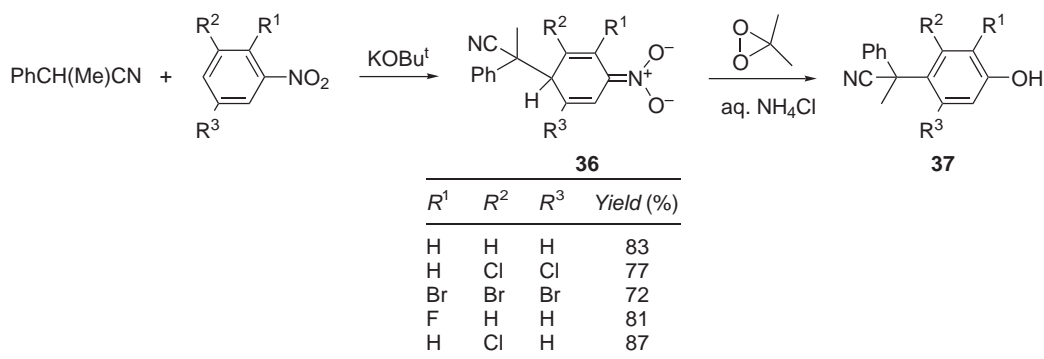
Aryl bromides can be displaced with *t*-butoxide in the presence of catalytic palladium to give *t*-butyl phenyl ethers, which on subsequent hydrolysis provides phenols in 58–69% yield (Scheme 11). This approach, however, is limited to activated aryl bromides <1996JA13109>.

Anilines can be readily converted via diazotization into diazonium salts, which hydrolyze to give phenols. This chemistry has been discussed in detail in several reviews <1995COFGT(2)635, 2001JA5651, 1994S1406>.



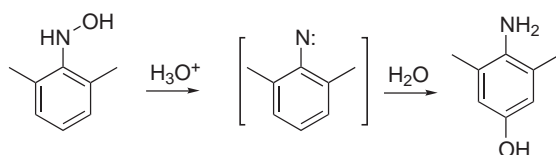
Scheme 11

When appropriately activated, an aryl nitro group can be easily displaced. For instance, 3-nitrophenol is obtained in 53% yield when 1,3-dinitrobenzene was treated with sodium hydroxide in dimethylimidazolidinone [<1995JAP\(K\)07165676>](#), and similarly 4-nitronaphthol is obtained from 1,4-dinitronaphthlene in 89% yield upon treatment with sodium hydroxide in water [<1987JMC906>](#). Less strenuous hydrolysis conditions can be utilized when base-sensitive functional groups are present. When 2,3-dicyanonitrobenzene is treated with sodium acetate in *N*-methyl-2-pyrrolidone (NMP), clean nitro group displacement occurs without affecting the nitriles; subsequent acetate cleavage gives 2,3-dicyanophenol in 52% yield [<1997BCJ2693>](#). Adam and co-workers [<1998JOC4390>](#) have reported that oxidation of Meisenheimer complexes **36** with dimethyldioxirane provides phenols **37** directly from nitroarenes. Cyclohexadienones are the likely intermediates of the reaction, although the details of the oxidation mechanism remain unclear (Scheme 12).

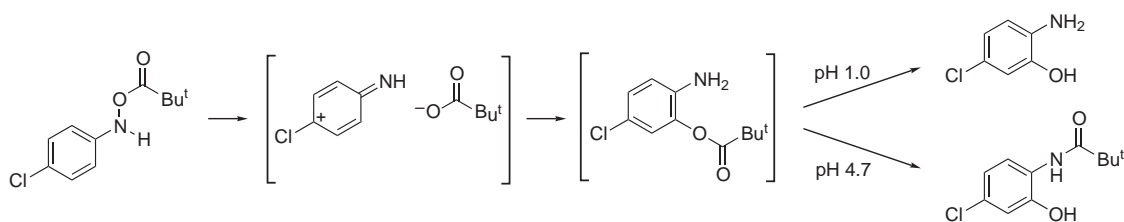


Scheme 12

Upon exposure to aqueous acid, *N*-arylhydroxylamines undergo Bamberger rearrangement to provide *p*-aminophenols (Scheme 13) [<1995COFGT\(2\)635, 1987JA2824>](#). When the *para* position is blocked, *o*-aminophenols can be obtained as shown in Scheme 14 [<1988JOC4762, 1991JOC2925>](#).



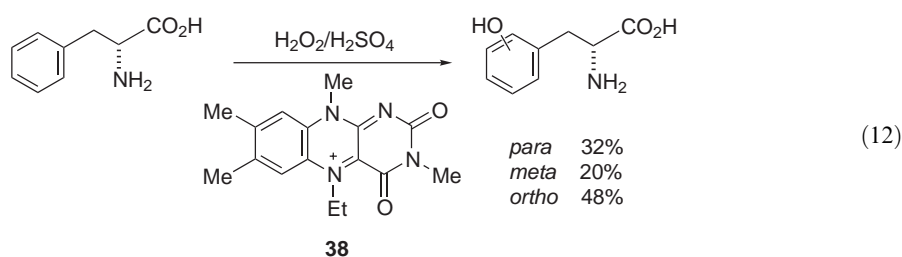
Scheme 13



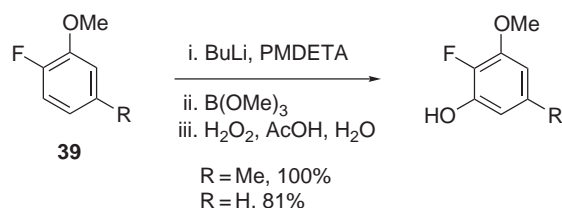
Scheme 14

(b) *Electrophilic hydroxylation of arenes.* There have been numerous efforts directed toward finding more economical industrial syntheses of phenol. Research has been focused on the catalytic electrophilic hydroxylation of benzene. For example, copper(I) salts in combination with metallocenes [<1995JAP\(K\)07223984>](#) and a system composed of cupric nitrate and H_2O_2 [<2000OPP373>](#) were found to be effective systems for the reaction. With $\text{K}_7[\text{NiV}_{13}\text{O}_{38}] \cdot 16\text{H}_2\text{O}$ as the catalyst, the hydroxylation was observed to occur under very mild reaction conditions (aq. H_2O_2 , 25°C , 112 h) [<2002JAP\(K\)2002241333>](#). 1- or 2-Naphthols can be obtained similarly by oxidation, although the yields are moderate ($<45\%$) [<2002JMOC\(A\)115, 1991JOC6148>](#). Solid-support catalysts have also been investigated extensively for this transformation. There are several patented procedures for the synthesis of phenol from benzene using a palladium-infused membrane [<2003MI140>](#), zeolites, and a resin-supported iron(III) complex [<2000MI16>](#) as the catalyst.

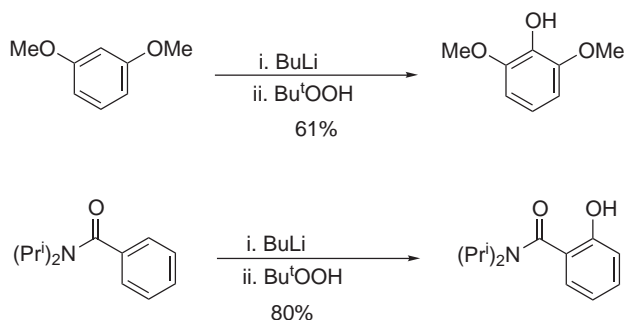
It has been reported that an oxidation with H_2O_2 catalyzed by flavin **38** is superior to other oxidation procedures for hydroxylation of phenylalanine (Equation (12)) [<1994T6759>](#). The flavin-initiated chain reaction gives rise to a mixture of three hydroxylated derivatives of phenylalanine efficiently with no degradation in enantiopurity.



(c) *Oxidation of metallated arenes.* Many arenes can be metallated regioselectively in a directed manner, and oxidation of the resulting metallated species is a popular method for the preparation of highly functionalized phenols. Frequently, the initial metallated species is transmetallated to a boronate, which is oxidatively cleaved with hydrogen peroxide to give the corresponding phenols in high yield [<1995COFGT\(2\)635>](#). For example, fluorine-directed metallation of arene **39** in the presence of *N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDETA) followed by transmetallation to boron and *in situ* oxidation with peroxide results in the *o*-fluorophenol in good yield (Scheme 15) [<2002JCB329>](#). *t*-Butyl hydroperoxide is also effective for the oxidation (Scheme 16) [<1996BSF15>](#).

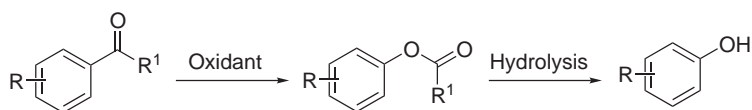


Scheme 15



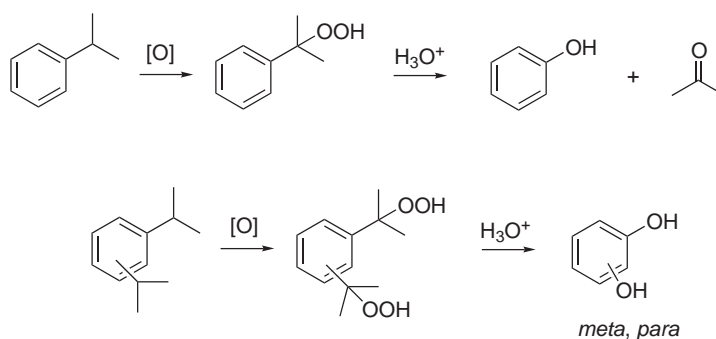
Scheme 16

(d) *Baeyer–Villiger oxidation of acyl arenes.* Many reviews on the Baeyer–Villiger oxidation have been published including those by Renz and Meunier <1999EJO737>, Chiu <1995COFGT(2)635>, and Krow <1993OR(43)251>. The Baeyer–Villiger oxidation remains a popular method for the conversion of aryl aldehydes and ketones to the corresponding aryl esters. Subsequent hydrolysis of the resulting esters gives the corresponding phenols in high yields (Scheme 17) <2002BMCL2345, 2002S1857, 2002TA1799>. Because of ease of handling and improved safety, the use of 30% hydrogen peroxide with catalytic SeO_2 <1995SC2121> and urea–hydrogen peroxide <1999OL189> have been developed as alternatives, to peracids for Baeyer–Villiger and Dakin reactions.



Scheme 17

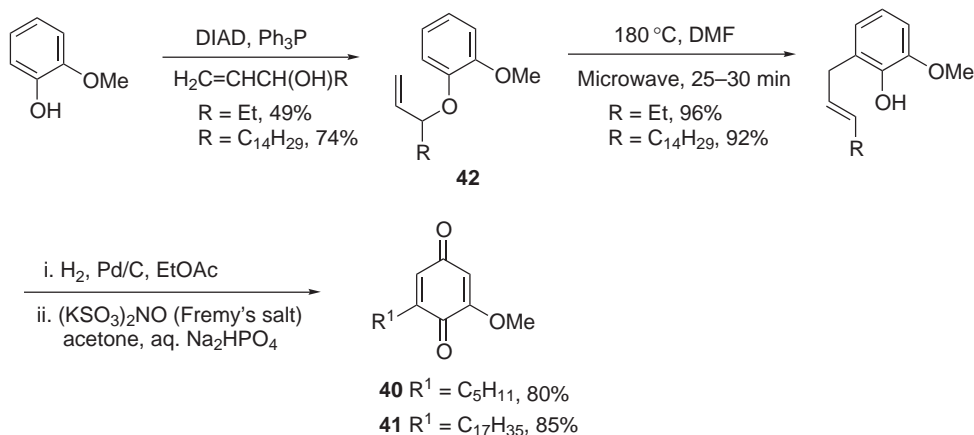
(e) *Benzylic hydroperoxide rearrangement.* Although there are several industrial processes for phenol production, the predominant route, in the early 2000s, is via the oxidation of cumene as it is still the most cost effective method to date (Scheme 18) <1998MI42>. Much of the worldwide cumene output (14 million metric tons in 2001) goes into the production of phenol to supply the 6.0 million metric ton global phenol market <2002CEN42>. Hydroquinone, resorcinol, and 2,6-naphthalenediol are prepared similarly by rearrangement of diisopropylbenzene dihydroperoxides or 2,6-diisopropylnaphthlene hydroperoxides on a sulfonated ion-exchange resin such as Nafion (Scheme 18) <1992CP1304755, 1999MI2765871>.



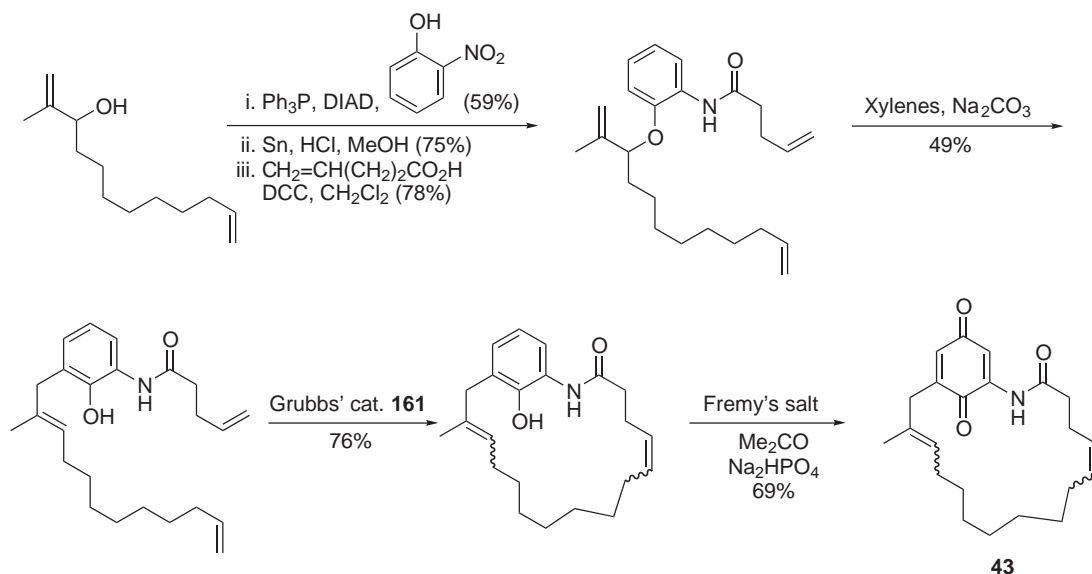
Scheme 18

(f) *Claisen rearrangement.* The aromatic Claisen rearrangement offers a convenient entry to highly functionalized phenols. For example, the naturally occurring benzoquinones primin **40** and pallasone **41** are synthesized by a simple protocol involving microwave-accelerated Claisen rearrangement of allyl ethers **42**, followed by hydrogenation of the side-chain alkene and

oxidation to the quinone (Scheme 19). This strategy has been extended to the synthesis of naturally occurring benzoquinones including an ansa-bridged derivative **43** related to the ansamycin antibiotics (Scheme 20) <2002SL1874>. The Claisen rearrangement can also be used to prepare substituted *o*-hydroxybenzaldehydes. The synthesis involves allylation of a phenol, Claisen rearrangement, alkene isomerization, and finally an OsO₄/NaIO₄ oxidative cleavage to give 2-hydroxybenzaldehydes **44** (Scheme 21) <1997SC4235>.



Scheme 19

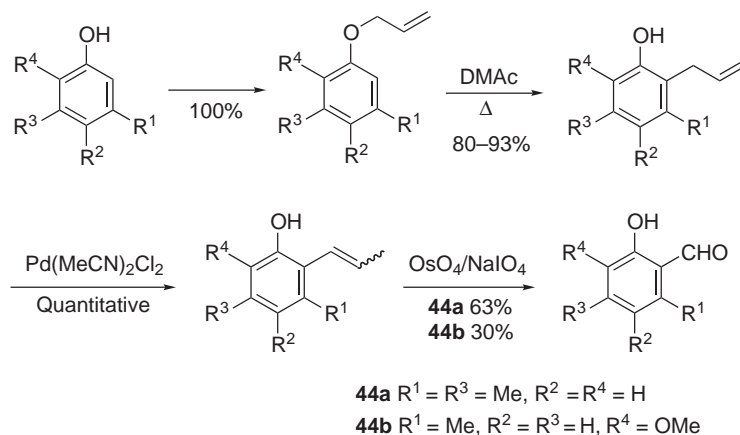


Scheme 20

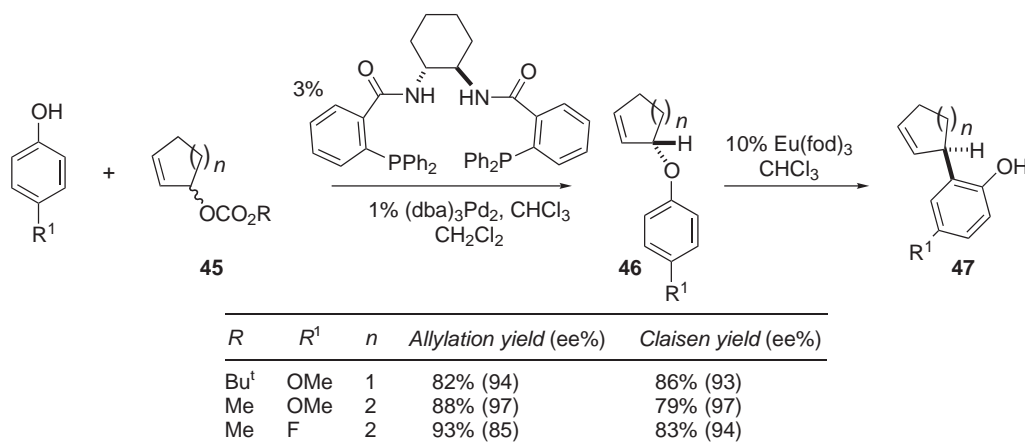
The aromatic Claisen rearrangement has also been utilized to prepare enantio-enriched α -alkylphenols. The asymmetric *O*-alkylation of phenols with allyl carbonate **45** gives allyl aryl ethers **46** in high enantiomeric excess. These compounds undergo stereospecific aromatic Claisen rearrangement under mild reaction conditions (50 °C) in the presence of europium complex Eu(fod)₃ to give phenols **47** in good yields (Scheme 22) <1998JA815>.

(g) *The Fries rearrangement.* The tandem Friedel–Crafts acylation/Baeyer–Villiger oxidation sequence provides access to wide range of substituted phenyl esters. On heating with a Lewis acid, these phenyl esters undergo the Fries rearrangement (migration of the carbonyl from oxygen to carbon on the aromatic ring) to give, predominantly, the *o*-acyl phenols in high yields <1995COFGT(2)635>. AlCl₃, TiCl₄, BF₃, CH₃SO₃H, anhydrous HF, and boric acid are frequently utilized Lewis acids to effect the Fries rearrangement. H₃PW₁₂O₄₀ has also been found to

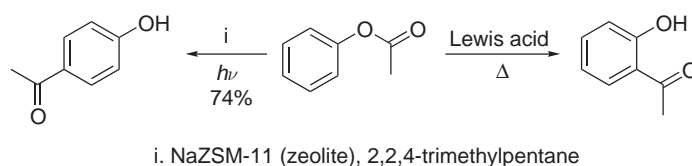
be an efficient and environmentally benign catalyst for the Fries rearrangement of phenyl acetate in both homogeneous and heterogeneous liquid phase systems <2002CC1178>. Hafnium trifluoromethanesulfonate ($\text{Hf}(\text{OTf})_4$) is also an efficient catalyst for the Fries rearrangement and for direct acylation of phenol and naphthol derivatives <1996TL2053>. Solid acid catalysts such as a silica–zirconium-based acid have also been used <2002MI7>. The Fries rearrangement using solid acid catalysts, particularly zeolitic and mesoporous molecular sieves is the topic of a review <B-2001MI004>. Under UV irradiation, *p*-acyl phenols are obtained as the major product in the Fries rearrangement (Scheme 23) <1996JA9428>.



Scheme 21

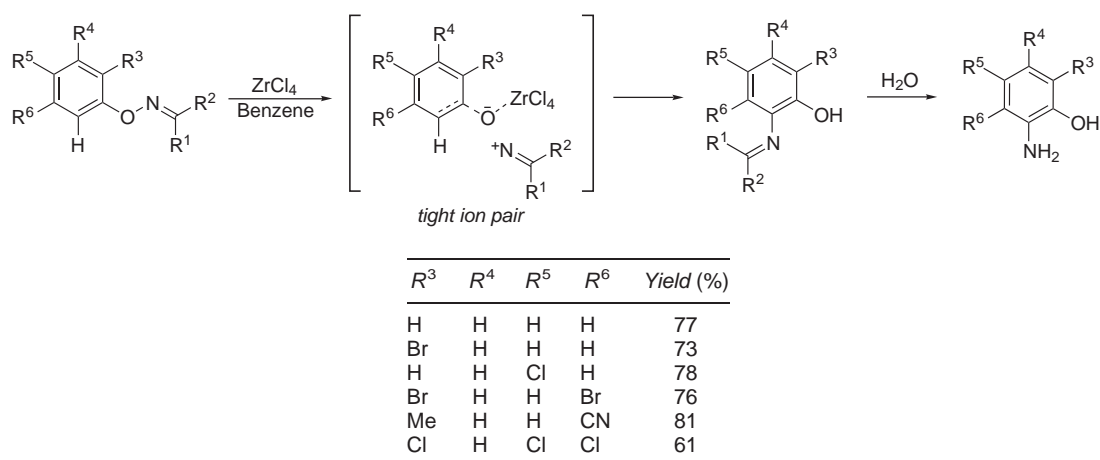


Scheme 22



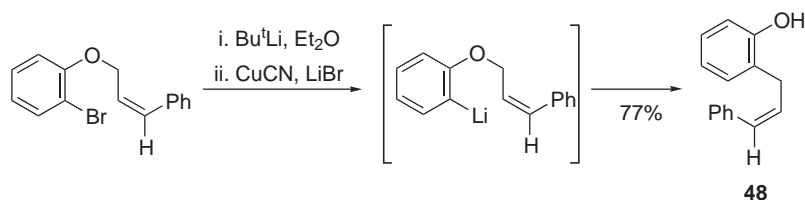
Scheme 23

(*h*) *Ketoxime rearrangement*. The ZrCl_4 -mediated decomposition of *O*-arylketoximes in benzene leads to regioselective intramolecular migration of the imino group from phenolic oxygen to the *ortho* position of the arene ring via electron-deficient nitrogen intermediates under Beckmann conditions (Scheme 24) <2001TL2337>.

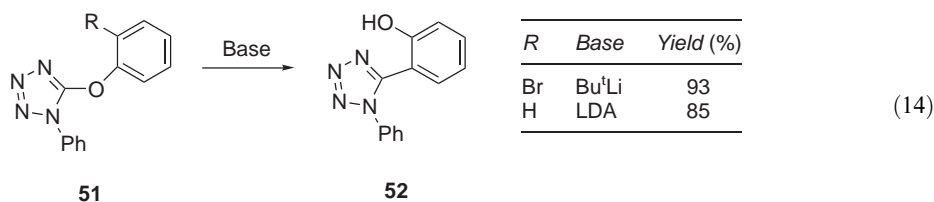
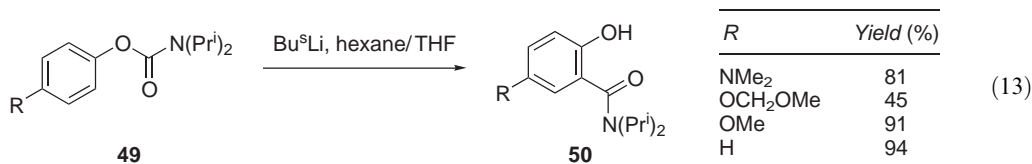


Scheme 24

(i) *Carbanion rearrangement*. 2-Lithiated phenol derivatives, generated by either *o*-directed lithiation or transmetalation, undergo carbanion rearrangement to provide phenols substituted at the *ortho* position by the group previously bound to the phenolic oxygen. The rearrangement occurs regioselectively. For example, the copper-induced isomerization of 2-lithiophenyl ethers gives phenol **48** in 77% yield with no degradation of alkene geometry (Scheme 25) <1997TL6103>. Phenyl carbamates **49** undergo *ortho*-lithiation with Bu^sLi , and the resulting aryllithium rearranges to give 2-hydroxybenzamides **50** in good-to-excellent yields (Equation (13)) <2000JCS(P1)3232, 2001CJC1736>. Phenyltetrazoles **51** are readily *ortho*-lithiated to give aryllithiums that rearrange to give tetrazolyl-substituted phenols **52** (Equation (14)) <1998JOC3753>.

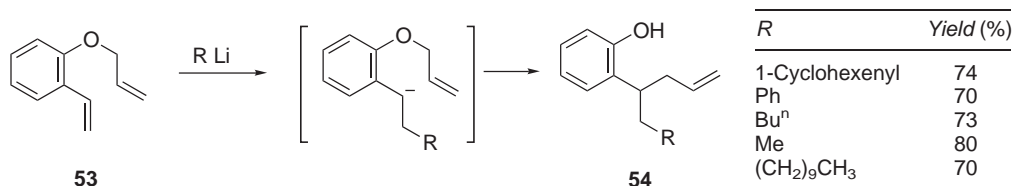


Scheme 25



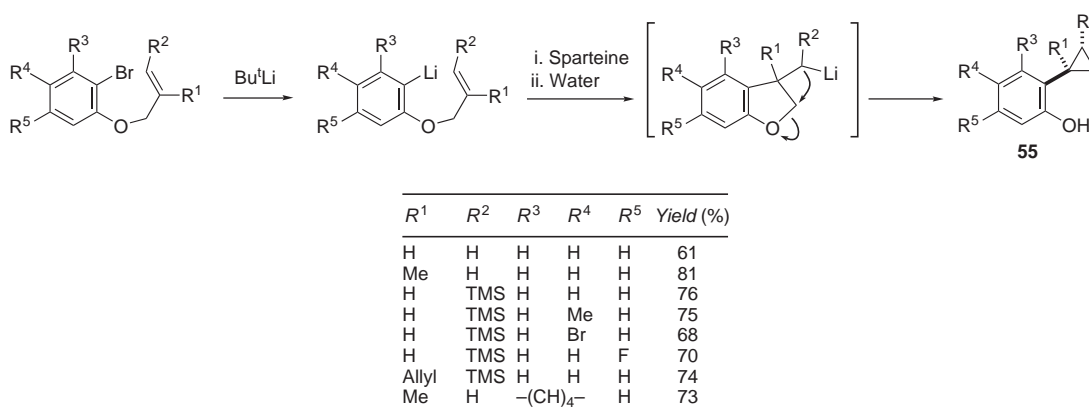
The carbanion rearrangement is not limited to aryllithiums. Allyl groups in an aryl allyl ether can migrate to an adjacent benzylic anion. A range of styrene derivatives **53** undergo

carbolithiation-trapping reactions in diethyl ether at -78 to -25°C resulting in 2-substituted phenols **54** in good yields (Scheme 26) <2000JCS(P1)1109>. In this reaction, the organolithium reagent must be adequately reactive to add to styrene but the resulting lithiated intermediate has to be sufficiently stabilized to minimize styrene oligomerization. Since the solvent influences the reactivity of organolithiums to a great extent, the choice of solvent is critical to this reaction. Diethyl ether seems to be the optimum solvent for this reaction, as hexane gives no reaction and THF leads to rapid polymerization even at -78°C .



Scheme 26

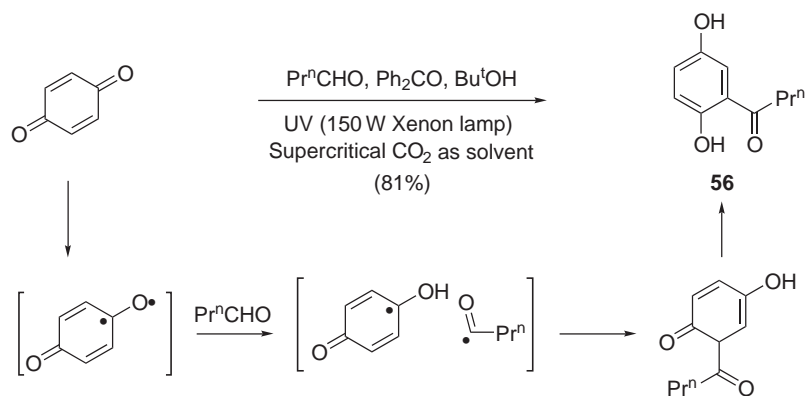
The carbanion rearrangement approach has been further elaborated by Barluenga and co-workers for the synthesis of chiral cyclopropyl phenol derivatives (Scheme 27) <2002OL2225>. Lithiation of α -bromophenyl ethers gives intermediate allyl 2-lithioaryl ethers, which undergo a tandem carbolithiation/ γ -elimination in Et₂O/tetramethylethylenediamine [1,2-bis(dimethylamino)ethane] (TMEDA) to afford cyclopropylphenols **55**. The use of (–)-sparteine as a chiral ligand instead of TMEDA results in formation of the phenol **55** in up to 81% ee with a typical yield of $\sim 70\%$. This approach can also be applied to cyclopropyl- β -naphthol systems.



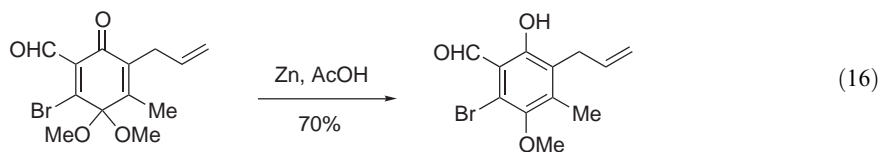
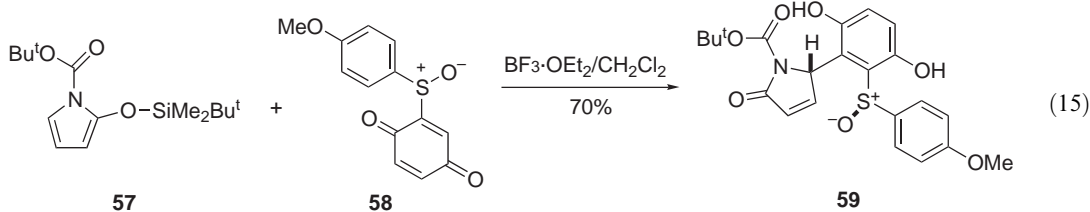
Scheme 27

(j) *Reduction of quinones.* Quinones can be transformed in high yields to hydroquinones by a variety of reducing agents. In addition to the reagents previously discussed by Chiu <1995COFGT(2)635>, hydrogen <2002JOC4635>, Na₂(S₂O₄)₂ <2002TL6929>, and hypophosphorous acid <1993MI407> have all been employed for the reduction of quinones. Pacut and co-workers <2001TL1415> have reported a photo-induced addition of aldehydes to quinones (Scheme 28) for the synthesis of 2-acyl-1,4-hydroquinones **56**. Similar results are observed when enones are employed in this reaction.

Diastereoselective Michael addition of pyrrole **57** to quinone **58** gives substituted hydroquinone **59** in 70% yield (Equation (15)) <2002JOC5638>. Reduction of quinone ketals is another viable approach to phenols (Equation (16)) <2002CC2380>.



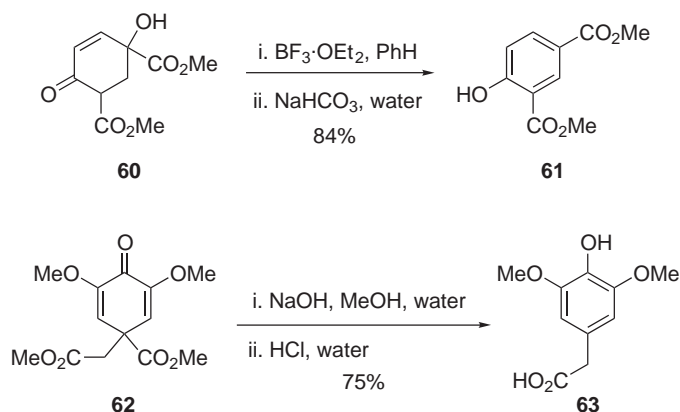
Scheme 28



(ii) Aromatization of cyclic aliphatic substrates

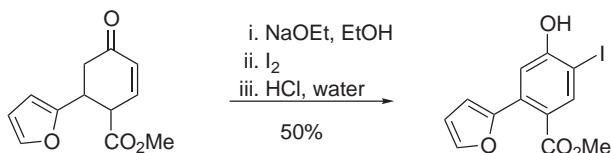
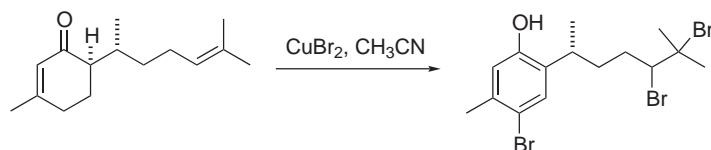
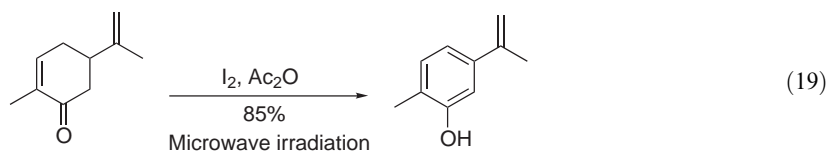
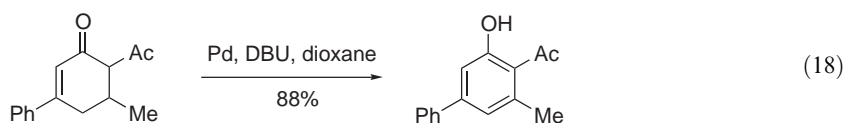
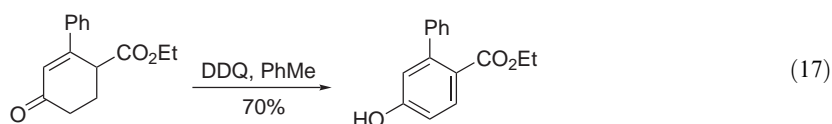
Cyclic aliphatic substrates with a certain degree of unsaturation can undergo aromatization to the corresponding phenols. The subject has previously been reviewed by Chiu <1995COFGT(2)635> and Tyman <B-1996MI002>.

(a) Aromatization of cyclohexanones, cyclohexenones, and cyclohexadienones. For appropriately substituted compounds, aromatization occurs readily through simple elimination. For example, $\text{BF}_3 \cdot \text{OEt}_2$ promotes the aromatization of hydroxycyclohexenone **60** by dehydration to give phenol **61** <1997JOC4088>. Cyclohexadienone carboxylate **62** undergoes decarboxylation under basic conditions and aromatizes to give phenol **63** in 75% yield (Scheme 29) <2001SC455>.

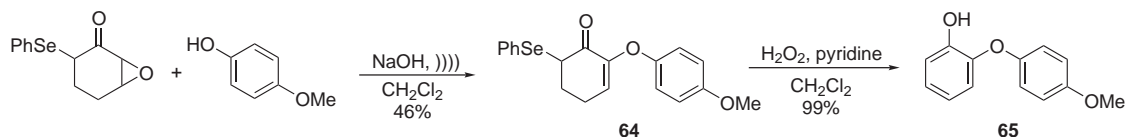
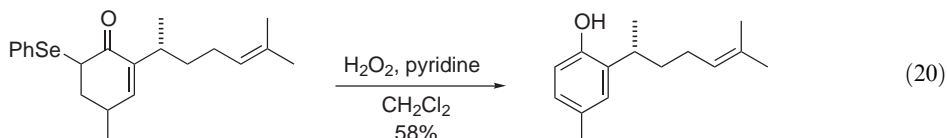


Scheme 29

More frequently, the aromatization involves an oxidative process using reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Equation (17)) <1952JCS(A)5040, 2001WOP0114314> and palladium(0) (Equation (18)) <1995JAP(K)07252183, 2002T5927>. A halogenation/dehydrohalogenation sequence is also effective for the aromatization of partially unsaturated cyclohexanol derivatives (Equation (19)) <1995COFGT(2)635, 1999JCR(S)404, 2001T1689>, but the reaction can result in additional undesired halogenation of reactive alkenes and aromatic rings as shown in Scheme 30. This complication can be circumvented by α -selenylation of a carbonyl precursor followed by oxidation and *syn* elimination of the selenoxide (Equation (20)). For example, the 6-phenylselenenylcyclohex-2-enone derivative **64** can be readily converted into phenol **65** by oxidation with hydrogen peroxide (Scheme 31) <2000OL473, 2002JCS(P1)895>.



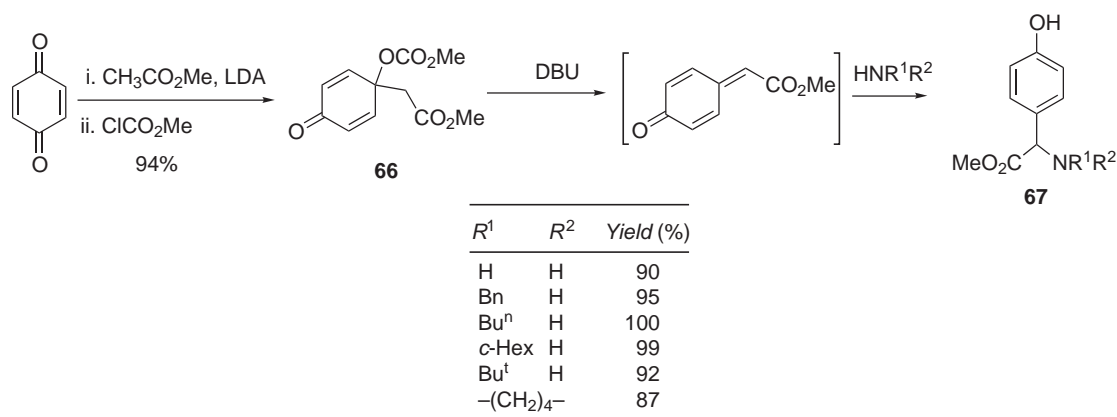
Scheme 30



Scheme 31

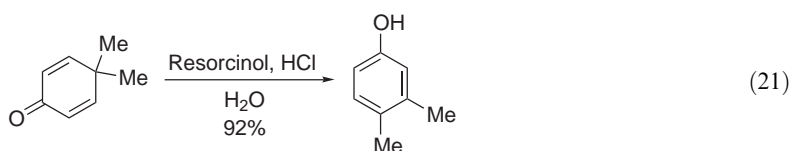
p-Benzoquinones are useful precursors to highly functionalized phenols. For instance, 1,2-addition of methyl lithioacetate to *p*-benzoquinone and subsequent quenching with methyl chloroformate gives dienone **66**. Elimination of carbonate followed by conjugate addition of an amine to the

exocyclic alkene gives amino acid derivatives **67** in excellent yields (Scheme 32). Diastereomerically enriched *p*-hydroxyphenylglycine derivatives can be prepared using this methodology by employing chiral acetate ester enolates in the initial 1,2-addition reaction <2000OL473>.

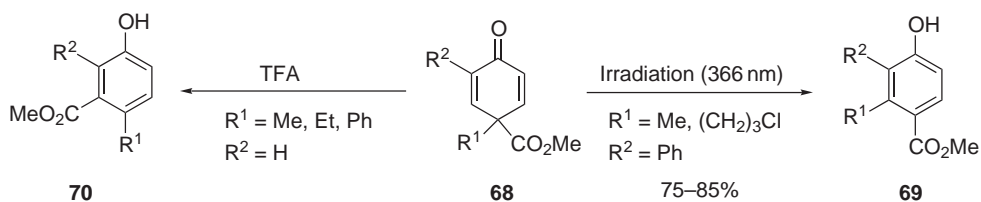


Scheme 32

(b) *Dienone-phenol rearrangement*. Photochemical, acid-catalyzed, and base-catalyzed dienone-phenol rearrangements are important methods for the preparation of highly functionalized phenols. The subject has been reviewed previously <1991COS(3)803, 1995COFGT(2)635>. The reaction is most frequently catalyzed by TFA, although many other acids are equally effective in inducing the rearrangement. For example, 4,4-dimethyl-2,5-cyclohexadienone is treated with resorcinol/HCl to give 3,4-dimethylphenol in high yield (Equation (21)) <1998JOC636>.



Photochemical rearrangement can afford phenols that are otherwise difficult to obtain by standard synthetic methods. On irradiation (366 nm), cyclohexadienones **68** undergo rearrangement to give tetrasubstituted phenols **69** that result from migration of the alkyl rather than the carbomethoxy group <2001OL1177>. Under acid-catalyzed conditions, the carboalkoxy group migrates preferentially to give phenol **70** as the only product (Scheme 33) <1974JA2121>.



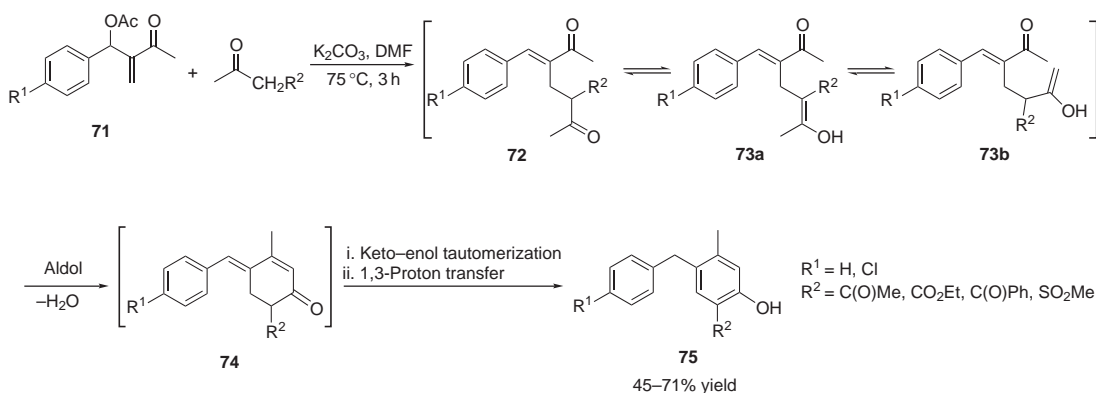
Scheme 33

(iii) *Annulation of acyclic fragments*

Over the period 1960–2003 many annulation methods have been developed that allow the preparation of a large number of ring systems from a wide variety of starting materials. The strategy has proven to be invaluable in the syntheses of phenols in simple systems and in complex natural products. The construction of the aromatic systems requires elegant design and consideration of multiple factors, including the location of new carbon-carbon bonds in the ring, any side-chain stereochemistry, and any additional latent functionality for future elaboration or additional ring-forming processes. In general, annulation reactions based on the Michael addition

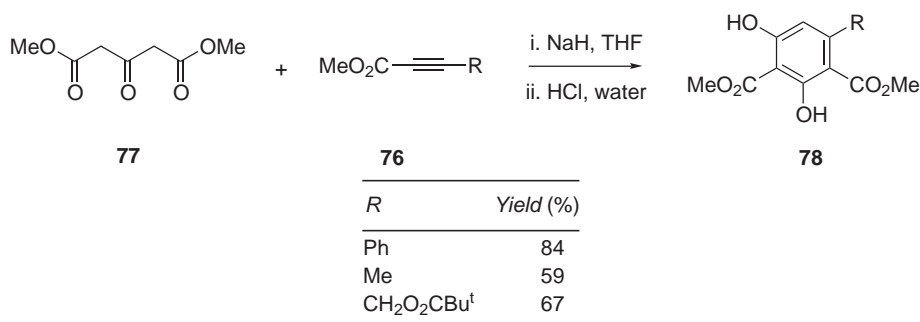
have been used extensively and tend to be quite successful. Aldol, Claisen, Dieckmann, and Diels–Alder reactions have also been frequently employed for the synthesis of phenols. Readers are advised to consult COFGT (1995) <1995COFGT(2)635> and reviews by Bamfield and Gordon <1984CSR441> as most of the developments in this area occurred before 1995.

(a) *[3 + 3]-Annulation.* The [3 + 3]-annulation is one of the most common approaches to the synthesis of phenols and has been previously discussed in detail in COFGT (1995) <1995COFGT(2)635>. A typical sequence involves the reaction of a ketone or 1,3-diketone containing acidic α - and α' -methylenes with an α,β -unsaturated carbonyl compound. For example, enone **71** reacts with aliphatic 1,3-diketones in the presence of potassium carbonate to give *o*-hydroxyacetophenones **75** (Scheme 34) <2002TL6597>. The mechanism is believed to follow an S_N2' pathway to give the allylic substituted intermediate **72** that exists as a tautomeric keto–enol **72** \rightleftharpoons **73a** \rightleftharpoons **73b** mixture. Subsequent intramolecular aldol condensation of enol **73b** affords **74**, and rapid tautomerization and proton transfer gives phenol **75**. Other active methylene compounds such as ethyl acetoacetate, methanesulfonylacetone, and 1-benzoylacetone are good substrates for the reaction.



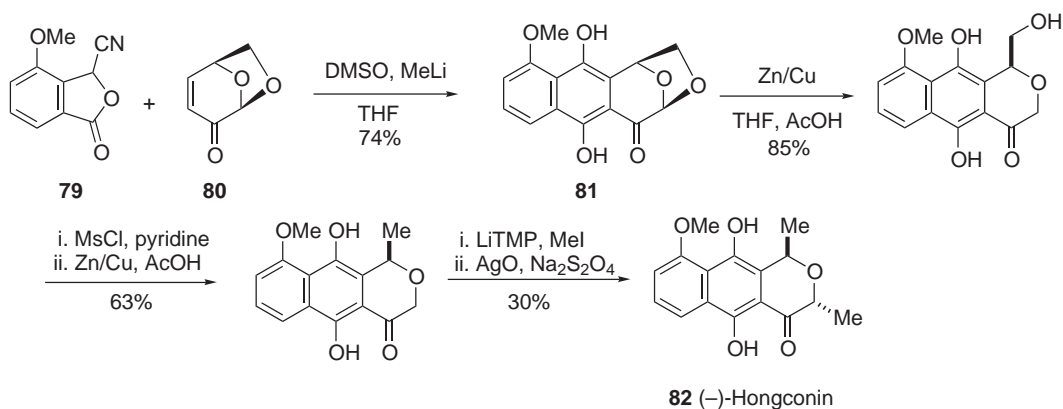
Scheme 34

Other α,β -unsaturated compounds can serve as substrates for the [3 + 3]-annulation. In a one-pot process, dicarboxylate **77** reacts with alkyne **76** to give resorcinols **78** with regiocontrol at the 3/5 positions via a Michael addition–Dieckman cyclization sequence (Scheme 35) <1998SC1525, 1998SC3461>.



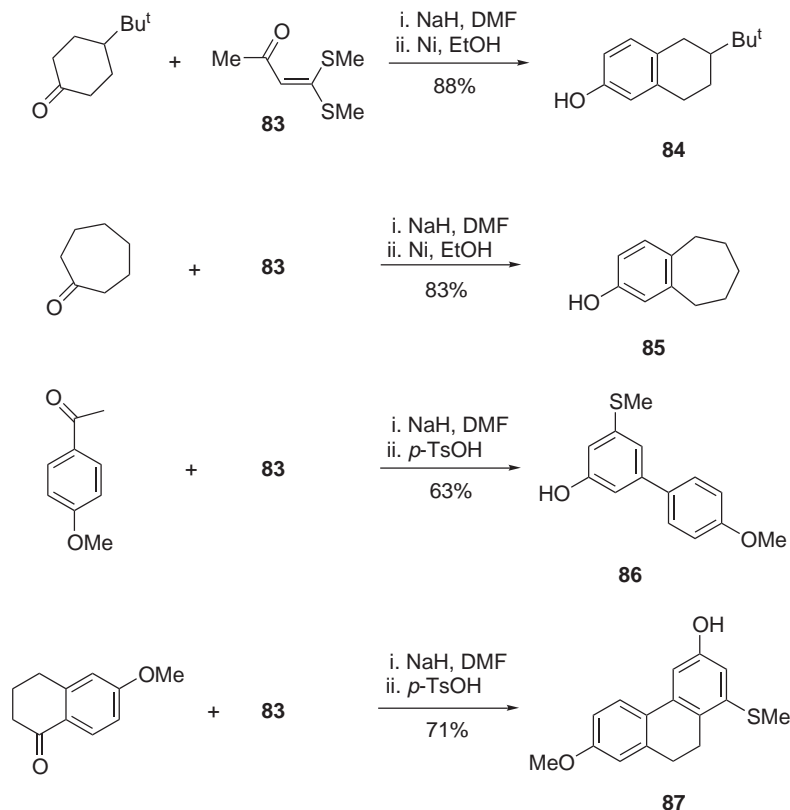
Scheme 35

(b) *[4 + 2]-Annulation.* The [4 + 2]-annulation is one of the most widely used approaches for the construction of aromatic compounds. The reaction typically involves a Michael addition to a α,β -unsaturated ketone followed by a Robinson-type annulation. For example, 3*H*-isobenzofuran-1-one **79** undergoes a carbanion Michael addition to levoglucosenone **80** to provide the naphthalene-1,4-diol intermediate **81**, which is a key intermediate in the total synthesis of (–)-hongconin **82** (Scheme 36) <1996JOC459>.



Scheme 36

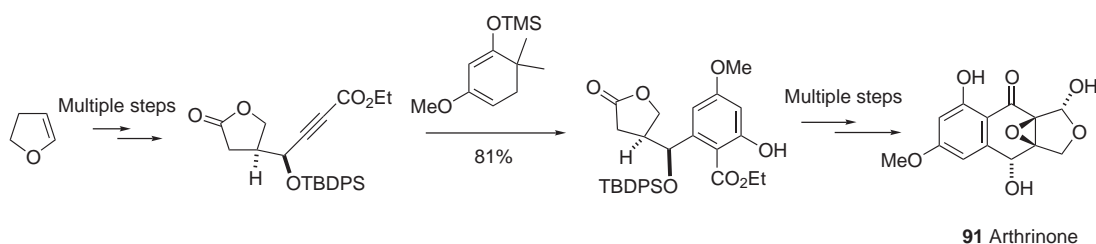
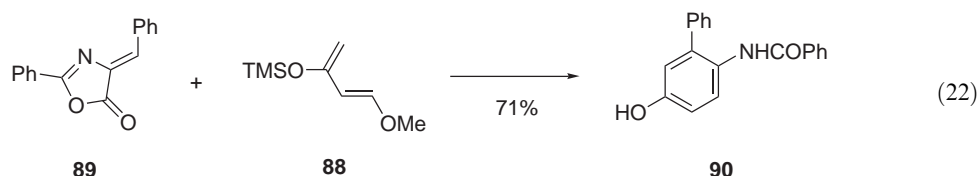
Similarly, Barun and co-workers [<2002JOC5398>](#) have described a [4 + 2] cycloaromatization of 4,4-bis(methylthio)-3-buten-2-one **83** with active methylene ketones (Scheme 37). The reaction involves a base-induced [4 + 2]-cycloaddition of ketone **83** with a variety of cyclic and acyclic methylene ketones. An appropriate choice of ketone allows synthesis of dihydroindans, tetrahydronaphthalenes **84**, their higher homologs **85**, biphenyls **86**, dihydro/octahydrophenanthrenes **87**, anthracene, and heteroannulated analogs in high yields with regiocontrol of the phenolic functionality.



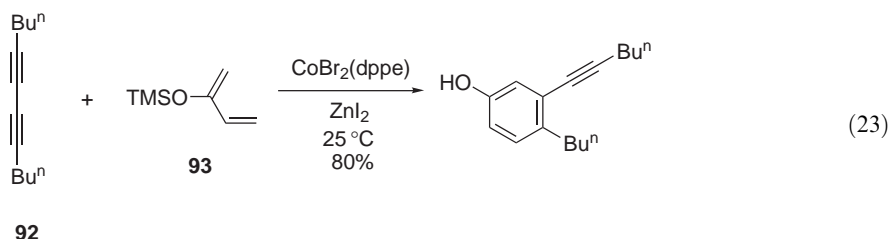
Scheme 37

(c) [4 + 2]-Cycloaddition. The use of [4 + 2]-cycloaddition reactions (the Diels–Alder reaction) to access substituted phenols has been previously reviewed [<1981ACR400, 1995COFGT\(2\)635>](#). Danishefsky's diene **88** and similar functionalized dienes are versatile and

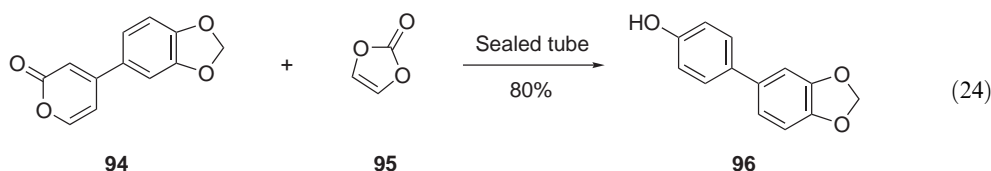
highly reactive substrates in this reaction. For example, reaction of diene **88** with oxazolone **89** affords 4-amino-3-phenylphenol **90** in 71% yield (Equation (22)) <1995S671>. The Diels–Alder reaction is often utilized in the total synthesis of natural products, as illustrated by (±)-arthrinone **91** and related compounds (Scheme 38) <2000TL10013>. The reaction can be catalyzed by Fe-, Co-, Ti-, and Ni-derived Lewis acids <1996CRV49>. When the dienophile is highly activated, the cycloaddition occurs under rather mild conditions. For example, reaction of 1,3-diyne **92** with 1,3-diene **93** occurs readily at room temperature (rt) in the presence of a cobalt(II) catalyst (Equation (23)) <2002S686>.



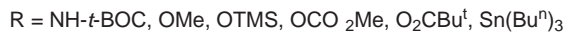
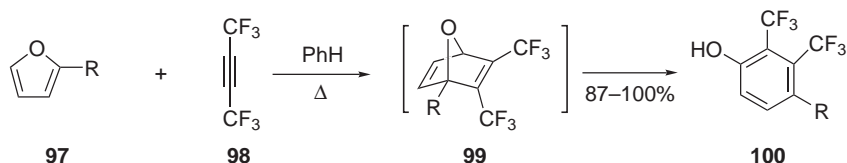
Scheme 38



α -Pyrones are versatile dienes in Diels–Alder reactions <1995COFGT(2)635>. In addition to being substrates in normal electron-demand cycloadditions, α -pyrones undergo inverse electron-demand Diels–Alder reactions with electron-rich dienophiles. For example, the Diels–Alder reaction of 4-aryl-pyrone **94** with vinylene carbonate **95** affords substituted 4-arylphenol **96** (Equation (24)) <2000TL7583>.

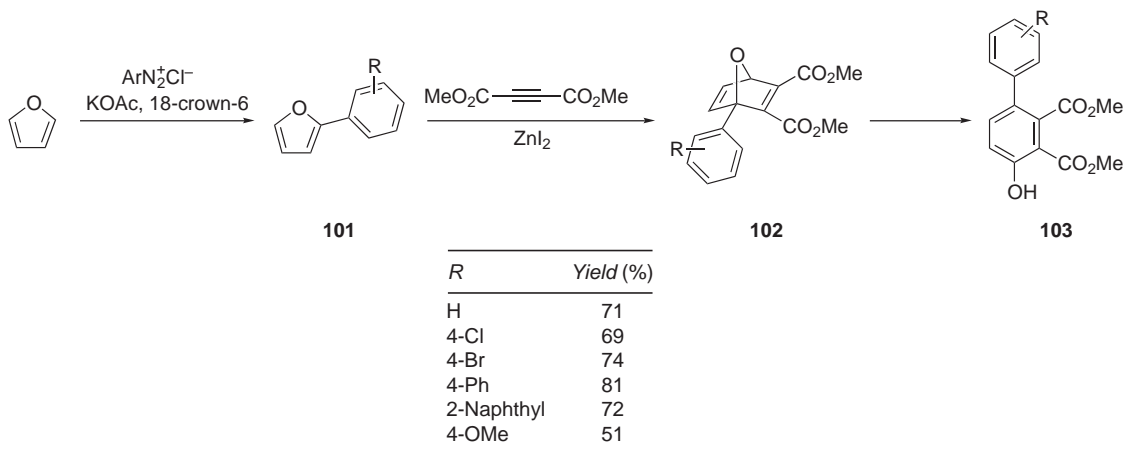


Furans undergo Diels–Alder reactions with benzyne and 1-sulfonyllallene <1995COFGT(2)635>. With an electron-donating heteroatom substituent at C-2, furan **97** reacts with hexafluoro-2-butyne **98** to give a cycloadduct **99** that undergoes regiospecific opening of the 7-oxa bridge producing a 4-heterosubstituted 2,3-di(trifluoromethyl)phenol **100** in a single step (Scheme 39) <1997S631>. As the resulting phenol can be readily manipulated, the method provides an entry to a variety of 1,4-disubstituted 2,3-di(trifluoromethyl)benzenes <2000OL3345>.



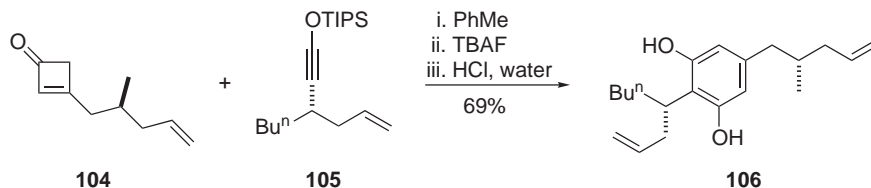
Scheme 39

2-Arylfurans **101**, prepared by coupling diazotized anilines with furan, react with but-2-ynedioic acid dimethyl ester in the presence of a Lewis acid to afford Diels–Alder adducts **102** (Scheme 40). A subsequent spontaneous or acid-induced β -elimination leads to polysubstituted phenylphenols **103** <1997S631>.



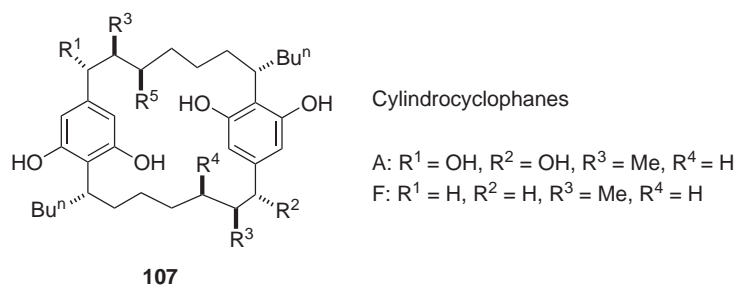
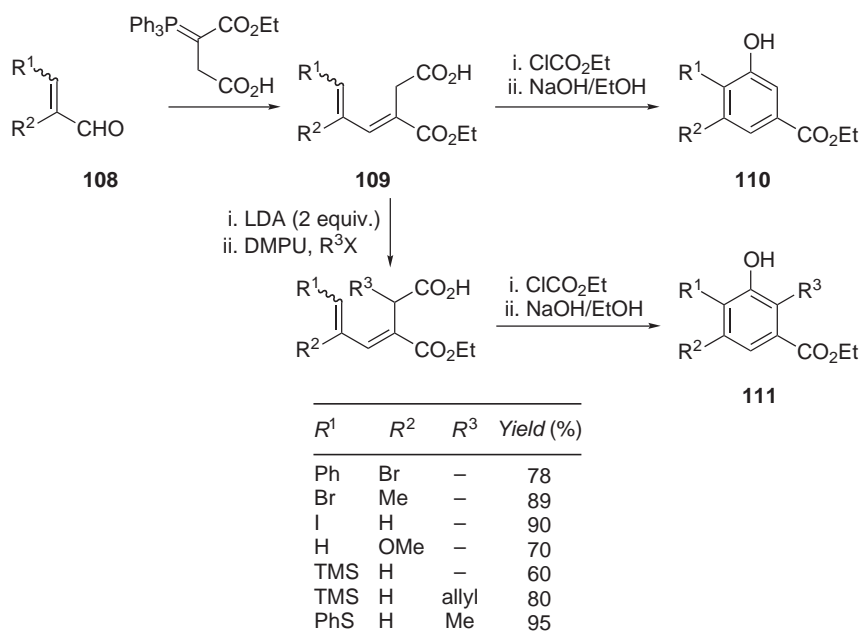
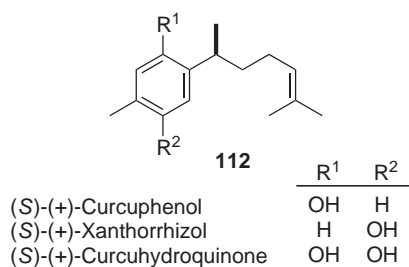
Scheme 40

(d) *[4 + 2]-Annulation of alkenyl ketenes.* The coupling of alkenyl ketenes with alkynes has been utilized in the synthesis of highly functionalized phenols <1995COFGT(2)635>. This method is particularly useful for the preparation of resorcinols and their derivatives. For example, the Danheiser annulation of cyclobutenone **104** with siloxyalkyne **105** gives resorcinol **106** in 69% yield (Scheme 41) <1984JOC1672>. This strategy has been elegantly adopted by Smith and co-workers <2001JA5925> in their total synthesis of (–)-cylindrocyclophanes A and F **107** (Figure 2).

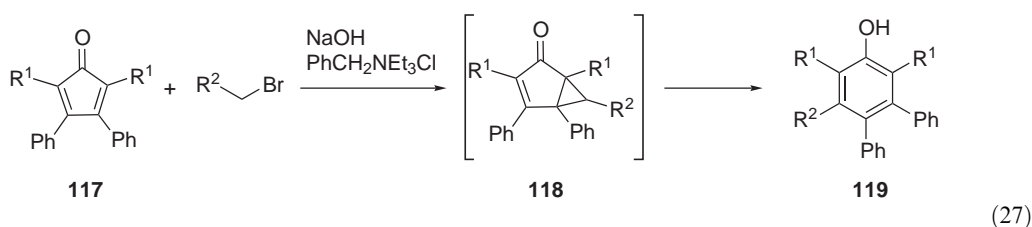
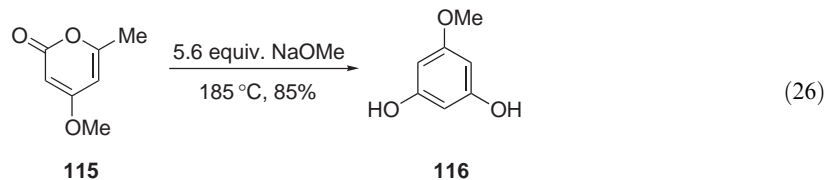
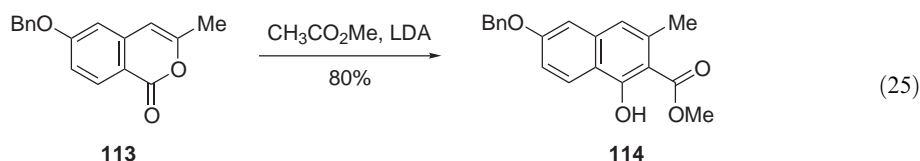


Scheme 41

(e) *[3 + 2 + 1]-Annulations.* Serra and co-workers <2001JOC7883> have described a regioselective synthesis of heterosubstituted phenols from 3-alkoxycarbonyl-3,5-dienoic acids (Scheme 42). α,β -Unsaturated aldehydes **108** undergo Wittig condensation to give (ethoxycarbonyl)hexadienoic acids **109**, which cyclize upon treatment with ClCO₂Et or trifluoroacetic anhydride (TFAA) in the presence of triethylamine to give phenols **110**. Alkylation of intermediate **109** allows the preparation of 2,4,5-trisubstituted 3-hydroxybenzoic acid derivatives **111**. The strategy is also used for the synthesis of naturally occurring phenolic sesquiterpenes such as (S)-(+)-curcuphenol **112a**, (S)-(+)-xanthorhizol **112b**, and (S)-(+)-curcuhydroquinone **112c** (Figure 3) <2002OL2241>.

**Figure 2****Scheme 42****Figure 3**

(f) *[1 + 5]-Annulations*. Reaction of isobenzopyranones **113** with the lithium enolate of methyl acetate regioselectively affords 1-hydroxy-2-carboxynaphthoates **114** in 80% yield (Equation (25)) <1978JHC1535, 2002OL2241>. Reaction of α -pyrone **115** in a melt with excess sodium methoxide gives an excellent yield of phloroglucinol methyl ether **116** (Equation (26)) <2002JA5926>. Tetrasubstituted cyclopentadienones **117** undergo base-induced cycloaddition with α -halogenated ketones, esters, and sulfones in the presence of benzyltriethylammonium chloride to provide pentasubstituted phenols **119** from ring expansion of the intermediate bicyclohexenone **118** (Equation (27)) <1995SC2561>.



R^1	R^2	Yield (%)
Ph	C(O)Ph	50
Ph	CO ₂ Et	60
Me	CO ₂ Et	60
Ph	<i>p</i> -Tol	80
Me	<i>p</i> -Tol	70

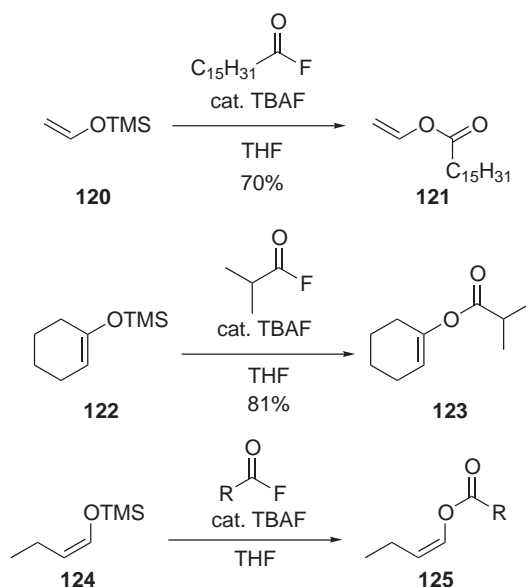
2.13.1.2 Alkenyl and Aryl Ethers

2.13.1.2.1 Alkenyl ethers and esters

Alkenyl ethers and esters are useful synthetic intermediates that have been traditionally prepared from their parent carbonyl compounds by alkylation/acylation of intermediate enolates, by 1,2-elimination reactions of substituted esters or ethers, or by alkenylation reactions <1995COFGT(2)635>. In the 1990s and early 2000s, the strong interest of the synthetic organic chemistry community in the synthesis of polycyclic ether natural products (exemplified by brevetoxin and halichondrin B) <2002T1779, 2002MI986, 1996AG(E)589> and the rapidly expanding field of oligosaccharide chemistry has spurred the development of additional methods for the preparation of enol ethers and glycals <1996AG(E)1380>.

(i) *O*-Alkylation/acylation of enols, enolates, and other enol derivatives

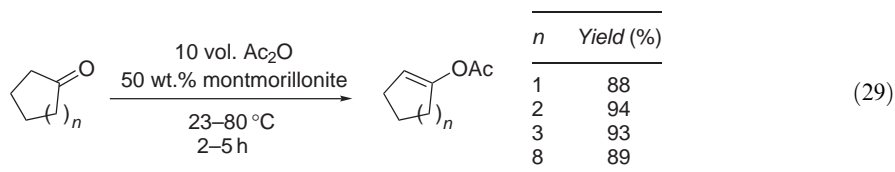
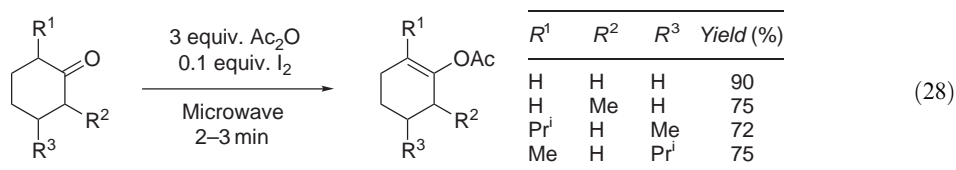
The *O*-alkylation or acylation of enolates, which are typically prepared by treatment of carbonyl compounds, enol esters, or enol silanes with strong base, is a versatile method for the synthesis of enol ethers and enol esters <1995COFGT(2)635>. For certain substrates, including saturated aldehydes, the synthesis of enol derivatives via this method can be difficult due to competing self-condensation reactions, even when the electrophile is present as the aldehyde is deprotonated. An alternative method for the synthesis of enol esters of reactive carbonyl compounds has been reported by Limat and Schlosser <1995T5799>. Treatment of stable silyl enol ethers **120**, **122**, and **124** with catalytic TBAF (2%) in THF in the presence of the corresponding acyl fluoride derivative furnishes enol esters **121**, **123**, and **125** in good yields with retention of the enol silane geometry (Scheme 43). The experimental conditions for this transformation are much less demanding than the corresponding enolate chemistry and the reactions proceed in higher yields without requiring additives like hexamethylphosphoramide (HMPA) to promote *O*-acylation versus *C*-acylation.



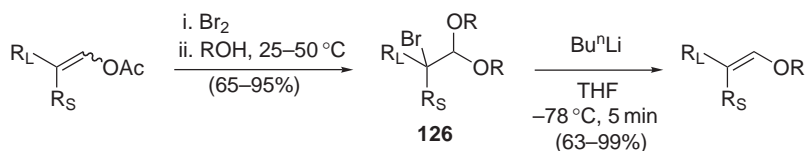
R	Yield (%)	Yield from Li-enolate (%)
Me	82	61
Et	77	52
Hexyl	82	43
Ph	85	31

Scheme 43

Two different reports of improved operational procedures for the acid-catalyzed enol esterification reaction have been reported. Under microwave irradiation, Sarma and co-workers <1999JCR(S)404> determined that enol acetates are efficiently formed from cyclohexanones with excess acetic anhydride in the presence of catalytic (10%) iodine (Equation (28)). Similarly, the reaction between cyclic ketones and acetic anhydride in the presence of montmorillonite KSF clay as catalyst results in the formation of enol acetates in good yields <2002SC3181>. Microwave irradiation substantially accelerates the process (Equation (29)).



Enol esters can be converted into enol ethers by a three-step sequence involving bromination of the enol ester, conversion of the intermediate α -bromo ether to an acetal **126**, and finally, halogen-metal exchange followed by alkoxide elimination as shown in Scheme 44 <2000TL4579>. A range of disubstituted and some trisubstituted enol ethers are formed in good yield with excellent (*E*):(*Z*) alkene selectivity from *anti*-elimination of the lowest energy rotamer of the incipient alkene.

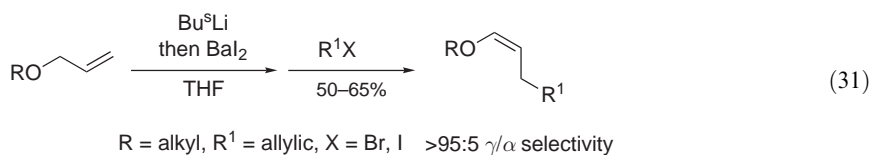
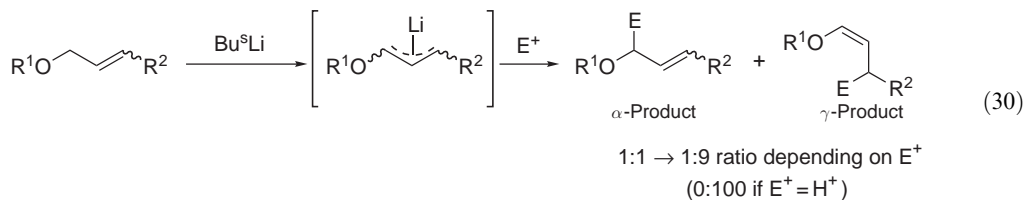


R_L	R_S	ROH	Overall yield (%)	(<i>E</i>):(<i>Z</i>)
Bu^n	H	MeOH	92	96:4
<i>n</i> -octyl	H	MeOH	71	97:3
Ph	H	EtOH	95	98:2
Ph	H	Pr^iOH	54	99:1
Ph	Me	MeOH	60	93:7

Scheme 44

(ii) Isomerization of allyl ethers

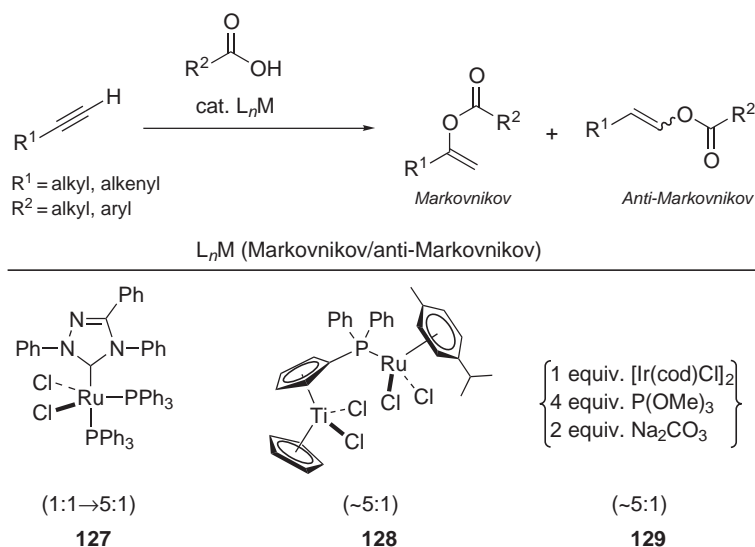
Treatment of allyl ethers with strong base (e.g., Bu^sLi in THF [<1974JA5560>](#)) results in formation of an allylic anion which preferentially protonates at the γ -position to give (*Z*)-enol ethers in good yield ([Equation \(30\)](#)). Alkylation of these lithiohomoenolates is not as selective, however, and the ratio of γ - to α -alkylation products has been shown to vary from 9:1 to 1:1 depending on the choice of electrophile and the identity of the alkyl ether. Improvement in the yield and selectivity of the alkylation reaction has been accomplished by transmetallating the initially formed lithium homoenolate to a barium homoenolate, which facilitates γ -selective alkylation and formation of (*Z*)-alkenyl ethers in good yield and high selectivity ([Equation \(31\)](#)) [<2000TL337>](#).



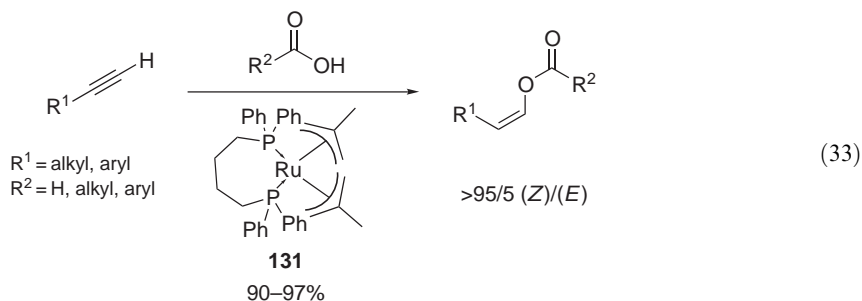
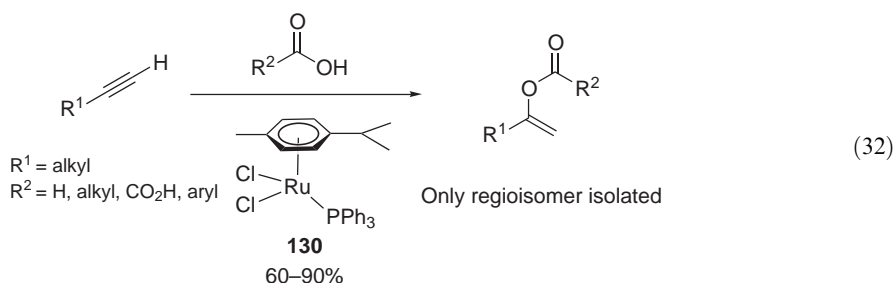
(iii) From alkynes

The transition metal-catalyzed addition of carboxylic acids to alkynes generally proceeds to give moderate-to-good yields of enol esters with Markovnikov regioselectivity when acyclic enol esters are formed. Several new catalysts for this transformation have been reported to be effective, including ruthenium(II) carbene complex **127** [<2003JMOC\(A\)39>](#), heterobimetallic Ru—Ti catalyst **128** [<2003ICA289>](#) and the iridium–phosphite complex **129**, which also catalyzes the ester exchange reaction between vinyl acetate and carboxylic acids ([Scheme 45](#)) [<2003TL103>](#).

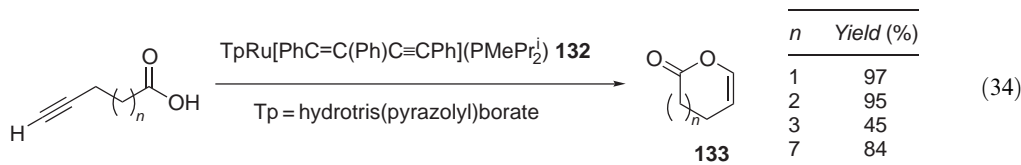
Bruneau and Dixneuf found that higher regioselectivity can be obtained in either Markovnikov or anti-Markovnikov sense by tuning the ligands on Ru(II) based catalysts. Highly Markovnikov-selective products are obtained with (arene)RuCl₂(PPh₃) complex **130** ([Equation \(32\)](#)), while the use of Ru(dppb) complex **131** promotes formation of anti-Markovnikov products with high regioselectivity and (*Z*)-alkene geometry ([Equation \(33\)](#)) [<1997CC507>](#).

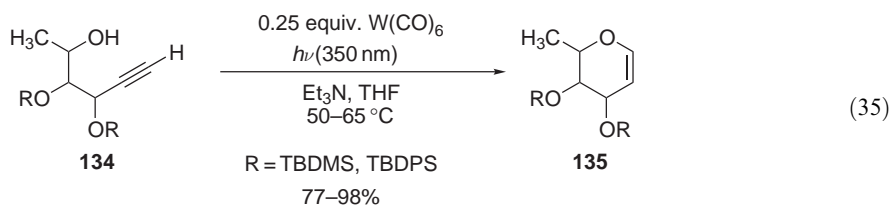


Scheme 45



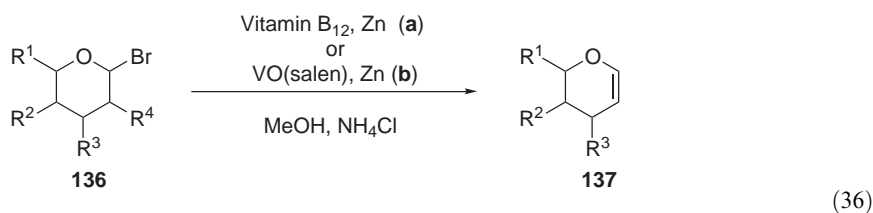
Similar regioselection is observed in the preparation of dienol diesters under otherwise identical conditions [<1999JCR\(S\)1247>](#). When the insertion reaction is intramolecular it is also possible to obtain both Markovnikov and anti-Markovnikov regioisomers. Ruthenium catalyst **132** efficiently catalyzes the formation of *endo*-enol lactones **133**, including macrocyclic enol lactones, in a highly regioselective manner (Equation (34)) [<2001CC2324>](#). A catalyst derived from $\text{W}(\text{CO})_6$ and Et_3N has also been reported to be effective for the alkynol cycloisomerization reaction of functionalized γ -hydroxyalkynes **134** to glycals **135** [<2000JA4304>](#) (Equation (35)). *Endo* selectivity of the enol ether products is maintained only when oxygen is strictly excluded from the reaction.





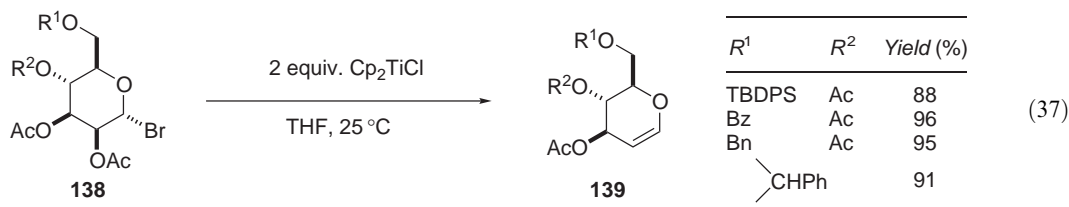
(iv) *By elimination of substituted alkyl ethers and esters*

Synthesis of enol ethers by 1,2-elimination processes remains one of the most direct methods for accessing this functionality. With the interest in oligosaccharide chemistry in the decade 1993–2003 there has been an increased need for flexible syntheses of glycals **137**. A direct method for introducing the alkene functionality in **137** is the Fischer–Zach synthesis, which involves a 1,2-elimination of acylated glycosyl halides **136**. This transformation is usually conducted with zinc dust in acetic acid and works well for pyranose-derived substrates that do not contain acid sensitive functional groups. One of the problems with this reaction is that the work-up is complicated by the need to neutralize all acetic acid with bicarbonate washes. Procedures have been devised that proceed under neutral conditions and utilize transition metal catalysts to accelerate the glycal synthesis. Vitamin B-12 [<1999JOC1424>](#), which is a source of cobalt(III), and VO(salen) [<2002AJC83>](#) have been utilized with zinc as terminal reductant in a NH₄Cl/MeOH solvent system to give glycals in good-to-excellent yields ([Equation \(36\)](#)).



<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>R</i> ⁴	Reductant	Yield (%)
CH ₂ OAc	OAc	OAc	OAc	a	94
CH ₂ OAc	OAc	OAc	OAc	b	91
H	OAc	OAc	OAc	b	69
Me	OAc	OAc	OAc	b	64

Other reductants have also been employed to facilitate this transformation. The trivalent titanocene complex (Cp₂TiCl)₂ is an efficient one-electron reducing agent that has been employed in the synthesis of glycals **139** by the reductive elimination of glycosyl bromides **138** [<1996TL4357, 2000T2103>](#). Silyl ethers, acetals, and other ester protecting groups are stable under the reaction conditions ([Equation \(37\)](#)). Similar results are obtained when utilizing Cp₂TiCl₂ and Mn powder to generate Cp₂TiCl *in situ* [<1999TL6087>](#) in a process which is more experimentally forgiving than utilizing the sensitive titanocene chloride dimer directly.

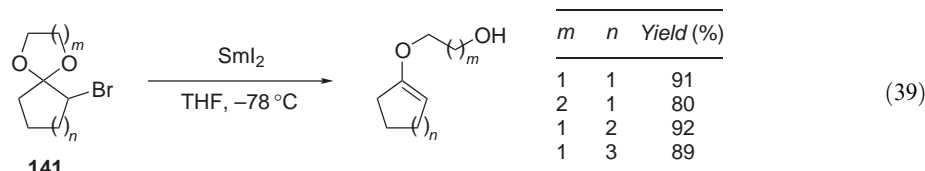
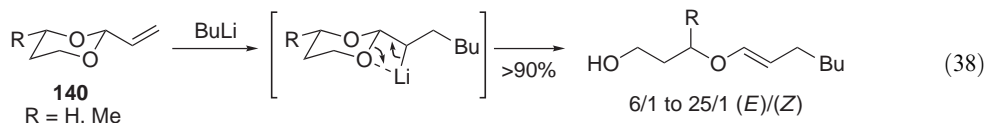


<i>R</i> ¹	<i>R</i> ²	Yield (%)
TBDPS	Ac	88
Bz	Ac	96
Bn	Ac	95
CHPh		91

(v) *From acetals*

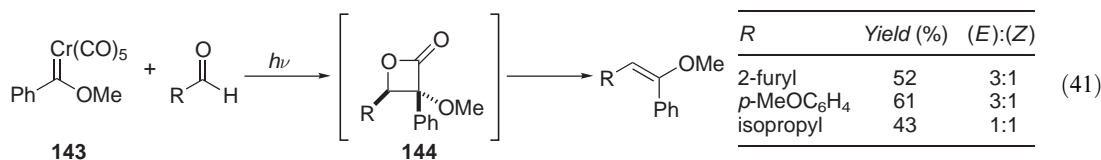
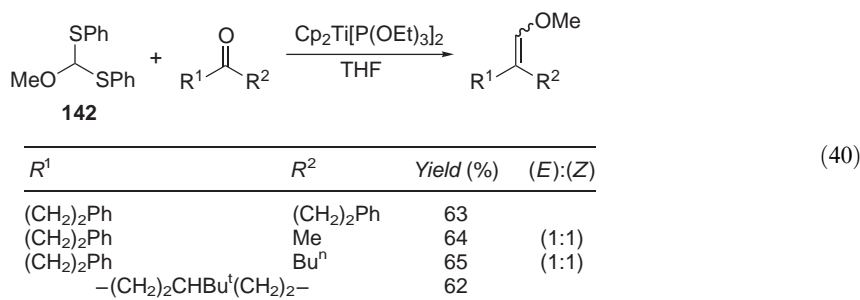
The synthesis of enol ethers from acetals under basic conditions involves the elimination of an alkoxide ion, which limits this procedure to substrates that can tolerate exposure to strong base. Bailey and Zarcone have studied the addition of organolithium reagents to α,β-unsaturated

dioxane acetals <2002CHIR163>. The reaction proceeds by initial regioselective addition of the organolithium reagent to the alkene in compound **140** (likely via a Li—O coordinated species) followed by *syn*-elimination of lithium alkoxide to give (*E*)-alkenes with high geometric selectivity (Equation (38)). Enol ethers are obtained from α -bromo dioxane and dioxolane acetals **141** by treatment with SmI₂ (Equation (39)) <2001TL3729>. Dienyl and trienyl enol ethers can be prepared in a similar manner by 1,4- or 1,6-elimination reactions of the appropriately functionalized acetals <1996CC1295, 1998TL2335>.



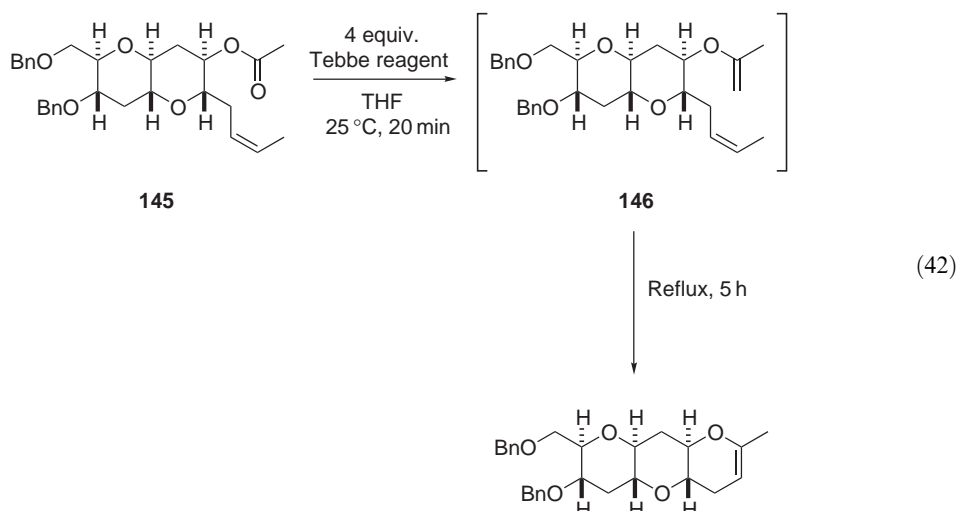
(vi) *By alkenylation of aldehydes and ketones*

The methylenation of aldehydes and ketones with α -oxygenated anions of phosphorus-containing reagents is a powerful method for the synthesis of enol ethers <1995COFGT(2)635>. A variation on this method has been reported that utilizes low-valent titanocene carbenes prepared from dithioorthoformates **142** and Cp₂Ti[P(OEt)₃]₂ for the homologation of ketones (Equation (40)) <1998TL2153>. Chromium carbenes **143** react with electron-rich aldehydes to give β -lactones **144** as intermediates that decarboxylate under the reaction conditions to provide enol ethers in good yields with modest (*E*)-alkene selectivity (Equation (41)) <2003JOC6056>.

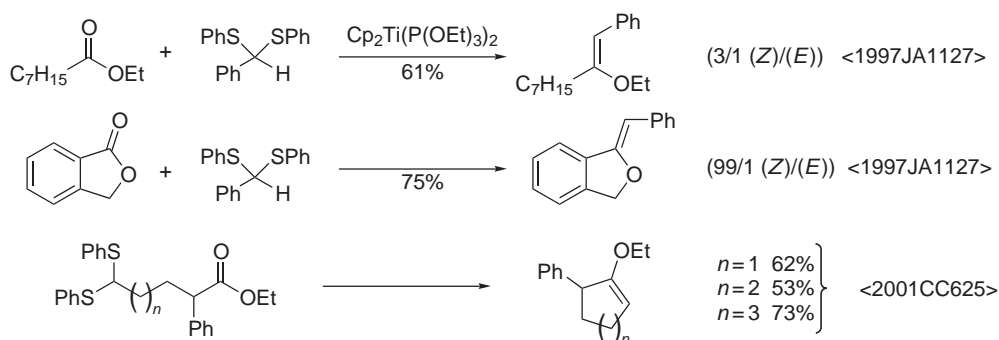


(vii) *By alkenylation of esters, lactones, and other carboxylic acid derivatives*

Alkenylation of carboxylic acid derivatives using the Tebbe reagent is a well-precedented method for the synthesis of alkenyl ethers where the carbonyl group has been homologated by a methylene. A significant advance in the utility of the Tebbe reagent has been reported by Nicolaou and co-workers <1996JA1565> in the synthesis of cyclic enol ethers from alkenyl esters (Equation (42)). In this reaction the initial transformation is methylenation of ester **145** to give diene **146** which then undergoes a ring-closing metathesis (RCM) process promoted by excess Tebbe reagent in solution. The Petasis reagent (Cp₂TiMe₂) has also been reported to promote this transformation <1996JA1565>.

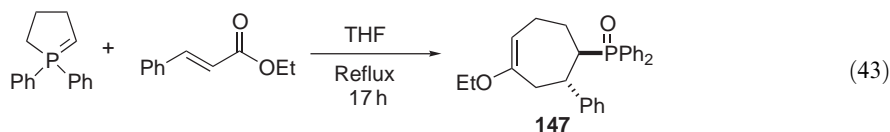


Titanium carbenes prepared by the desulfurizative titanation of thioacetals with $\text{Cp}_2\text{Ti}(\text{P}(\text{OEt})_3)_2$ undergo efficient condensation with esters and lactones in an intermolecular [<1997JA1127>](#) and intramolecular [<2001CC625>](#) fashion (Scheme 46).



Scheme 46

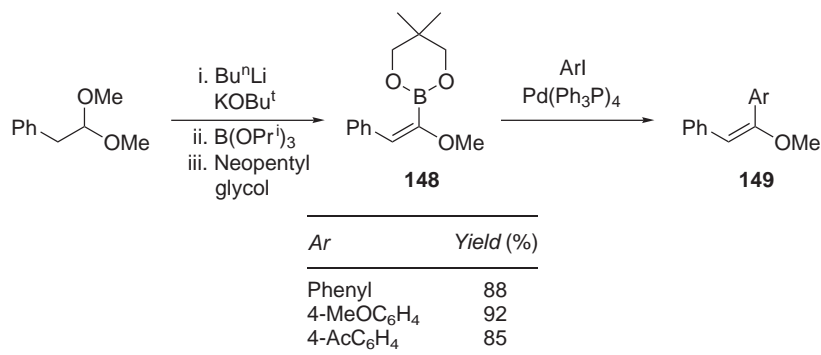
Cyclic phosphonium ylides react with α,β -unsaturated esters in a tandem Michael-intramolecular Wittig process to give cyclic enol ethers **147** in a single step in good yield (Equation (43)) [<1997JOC6627>](#). This reaction appears to be limited to the synthesis of cycloheptene derivatives.



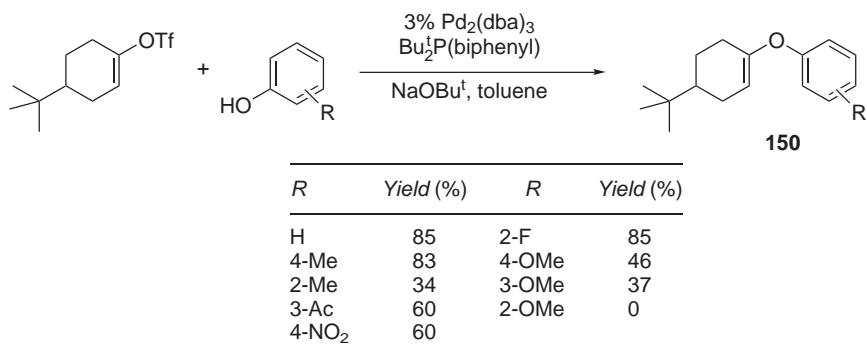
(viii) Homologation of alkenyl ethers and oxygenation of alkenyl electrophiles

Functionalization of alkenyl ethers is readily accomplished by metallation with organolithium reagents followed by reaction with electrophiles. Deprotonation occurs at the more acidic α -proton and trapping the intermediate organolithium reagent with other organometallics enables the facile cross-coupling of these species with aryl, alkenyl, and alkynyl electrophiles [<1995COFGT\(2\)635>](#). The synthesis of an α -alkoxyboronic acid has only been reported in the twenty-first century [<2002OL1275>](#) from the trapping of an ethenyllithium with triisopropyl borate (Scheme 47). Arylation of this boronic ester **148** via standard Suzuki coupling provides alkenes **149** in good yields. Likewise, enol triflates can be readily converted into aryl enol ethers **150** by application of conditions developed for aryl ether synthesis (Equation (44)) [<2003CC2222>](#).

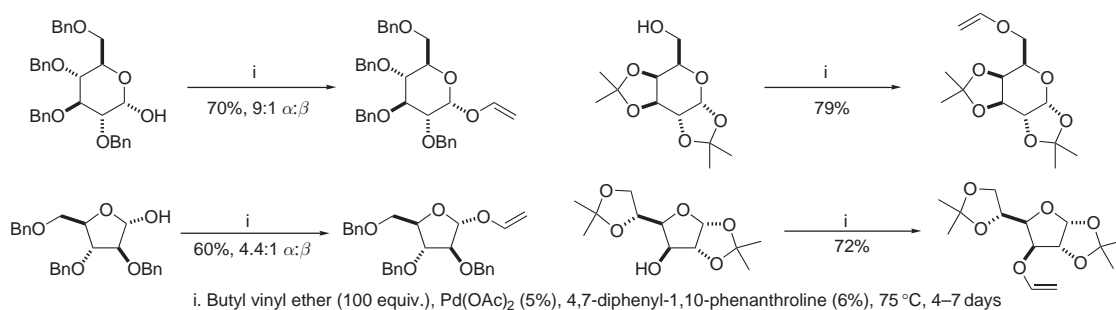
Unactivated enol ethers are also good substrates for the Pd-catalyzed ether exchange reaction with alcohols, which has proven useful for the synthesis of glycosidic vinyl ethers (Scheme 48) <2002OL407>. Negishi coupling of ketene acetal triflates with organozinc halides is a direct method for the synthesis of homologated cyclic enol ethers, and has been used for the formation of a gambierol intermediate **151** (Equation (45)) <2001TL4729>.



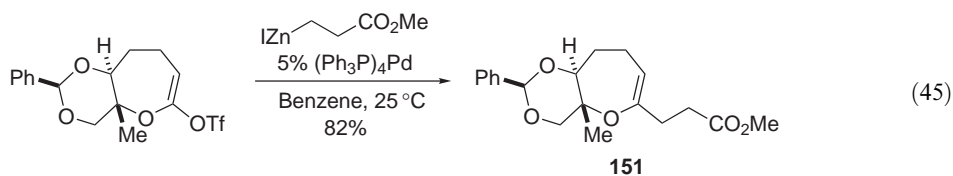
Scheme 47



(44)

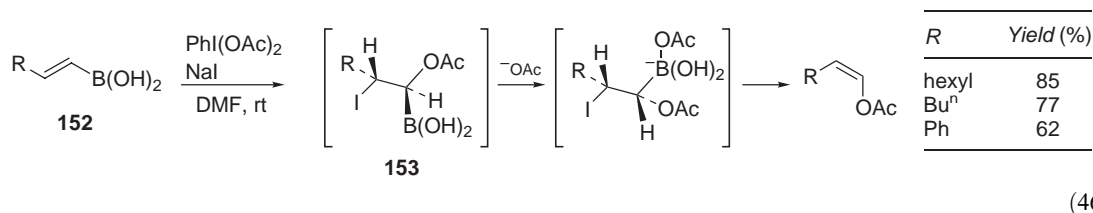


Scheme 48

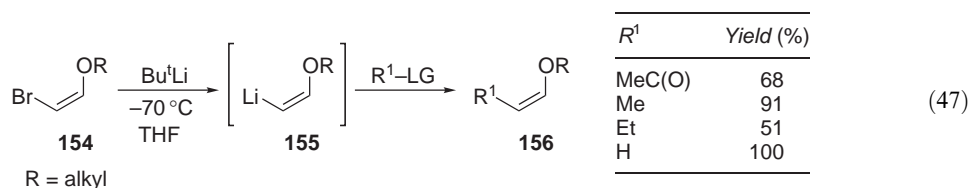


(45)

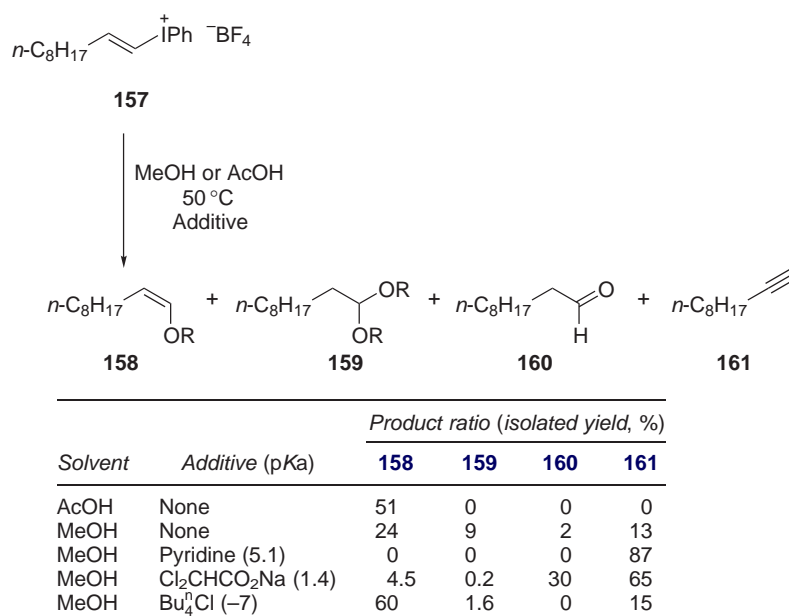
Alkenylboronic acids **152** can be converted into their enol acetate derivatives by treatment with the iodobenzene diacetate [<1998JCS\(P1\)1465>](#). The reaction is postulated to proceed through addition of acetyl hypoiodite (formed *in situ*) to provide saturated intermediate **153** which in the presence of acetate anion *anti*-eliminates boron halide to provide the enol ester with clean inversion of the alkene geometry ([Equation \(46\)](#)). These strategies constitute useful methods for the synthesis of complex aryl alkenyl ethers not readily accessible via other synthetic methods.



Metallation of enol ethers at the β -carbon is not normally observed on direct treatment with base (i.e., BuLi), but can be accomplished by lithium-halide exchange of suitably functionalized alkenyl halide **154**, which is prepared from alkyl ethenyl ethers by a halogenation-elimination sequence [<1996TL7255>](#). Treatment of bromide **154** with Bu^tLi in ethereal solvents at -70°C results in clean formation of the β -lithioenol ether **155** which reacts with electrophiles to provide functionalized enol ethers **156** with retention of the alkene geometry ([Equation \(47\)](#)).



Hydration of vinyl cations is an established method for the synthesis of enols. A new method to access substituted ethenyl cations from vinyl iodonium salts has been reported by Okuyama and co-workers [<2001BCJ543>](#). Solvolysis of (*E*)-1-decenyl(phenyl)iodonium tetrafluoroborate **157** in alcoholic or alcoholic/aqueous solvent mixtures at 50°C results in formation of (*Z*)-enol **158**, acetal **159** and aldehyde **160**, all products of substitution reactions, and acetylene **161** as a result of a 1,2-elimination process ([Scheme 49](#)). The product distribution from this reaction is dependent on the basicity of additives to the reaction, with the elimination pathway strongly favored when the pK_a of conjugate acids of the additives is greater than zero.



Scheme 49

(ix) By olefin metathesis

RCM has emerged as one of the most important new methods for the efficient construction of cyclic enol ethers, in part driven by the ready availability of catalysts for this transformation, and in part due to focus of synthetic activities around polycyclic ether natural products, macrocyclic alkenes, and glycals. The most effective catalysts for the synthesis of cyclic enol ethers as of 2003 are the family of Grubbs' ruthenium carbene catalysts **162** and **163** and the Schrock molybdenum alkylidene catalyst **164** (Figure 4). For alkene–alkene metathesis processes, the use of catalyst **164** was successfully employed in approaches toward the fused ether ring system **165** (Equation (48)) <1998JOC5310> and oxepine glycals **166** <2003TL4057> (Equation (49)). The Grubbs catalysts are more effective in alkene–alkyne RCM reactions, as demonstrated by Clark and co-workers <2002T1973> in their synthesis of alkenyl-substituted enol ethers **167** (Equation (50)). An intermolecular version of this reaction has also been reported with a wide variety of alkenyl ethers and alkynes, providing dienol ethers in good yield (Equation (51)) <2003OL1793>.

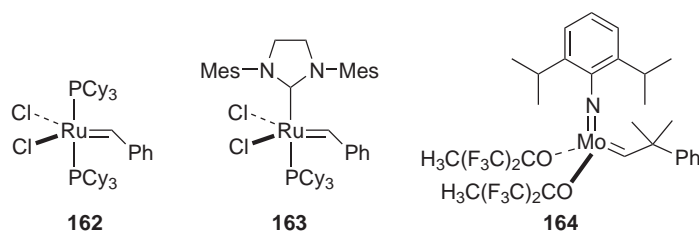
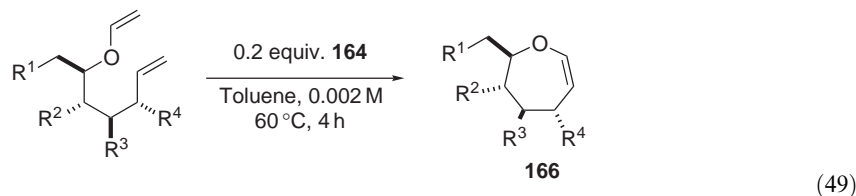
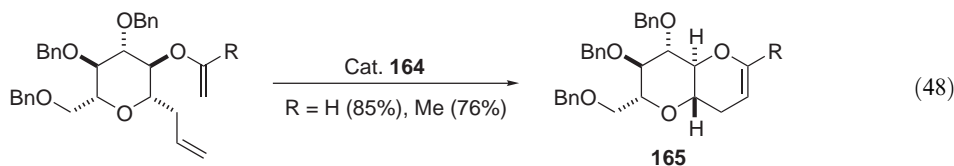
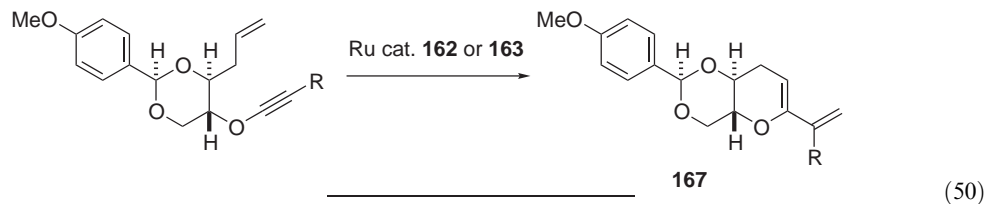


Figure 4

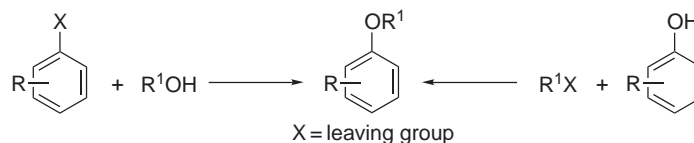


R^1	R^2	R^3	R^4	Yield (%)
OBn	OBn	OBn	OBn	92
OBn	OBn	OBn	H	86
–OCH(Ph)O–		OBn	OBn	71
–OC(Me) ₂ O–		–OC(Me) ₂ O–		89



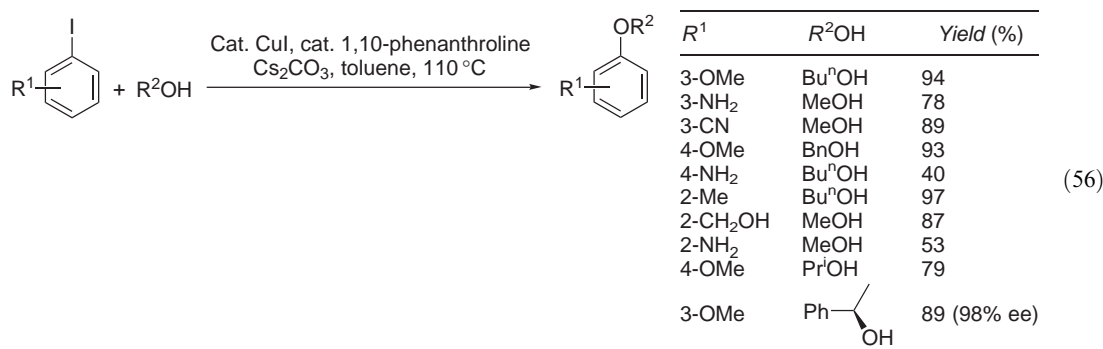
R	Catalyst	Yield (%)
H	162	90
Me	162	98
TMS	162	88
CH ₂ OH	163	84
CH ₂ OAc	162	72

its nucleophilic character <1987TL3627>. A range of fluoroalkyl aryl ethers have been prepared utilizing this method by alkylation of fluoroalkyl iodides <2002TL7353>.

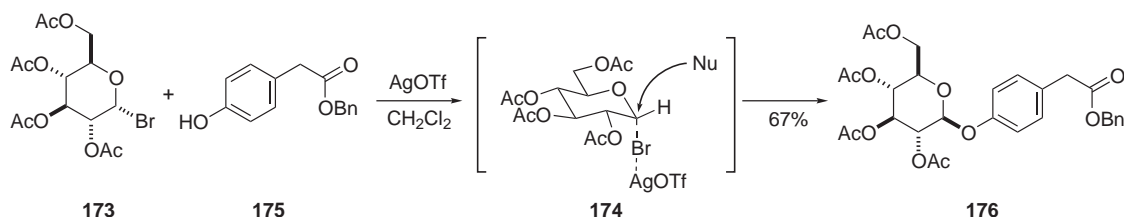


Scheme 50

Aryl ethers are also formed by the aromatic nucleophilic substitution reaction of alkoxides on arenes (Scheme 50). Those leaving groups that are most frequently displaced in this process are nitro groups <2001CL788, 2002MC72> and halogens <2002OPRD823>. Displacement of aryl halides with alkoxides and phenoxides often requires the use of copper additives to promote the reaction <B-1984MI001, 1996SC1887, 2002JMC4931, 2000JOC6487>, with a combination of a Cu(I) salt and a diamine ligand giving the best results <2002OL973>. For example, the reaction of aryl iodides with aliphatic alcohols using catalytic CuI in the presence of 1,10-phenanthroline occurs readily in toluene instead of the polar aprotic solvents typically used in the Ullmann–Goldberg reaction (Equation (56)). The palladium-catalyzed coupling of aryl bromides and chlorides with aliphatic alcohols has also been reported by Buchwald and co-workers <2001JA10770>, although up to 2003, the reaction is limited to primary alcohols.

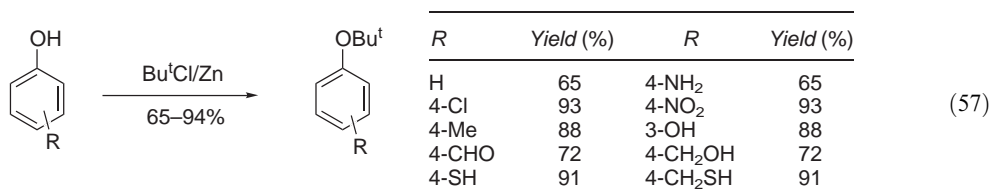


In the presence of strongly electrophilic species, the phenol itself can act as a nucleophile. As an example, ionization of pyranosyl bromide **173** by a Lewis acid (ZnCl₂ <2001CAR459, 2000T3673> or AgOTf <2002OL3607>) generates activated intermediate **174** which reacts with phenol **175** to provide *O*-glycoside **176** as a single anomer (Scheme 51).

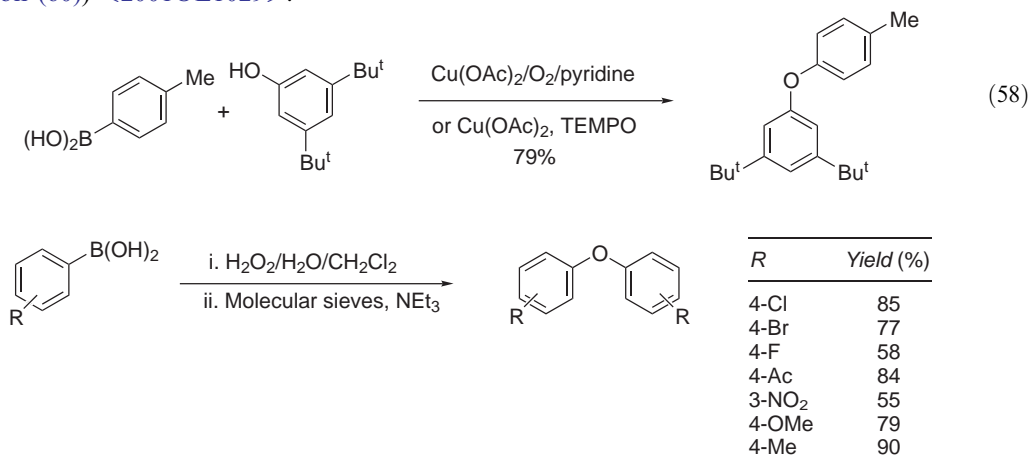


Scheme 51

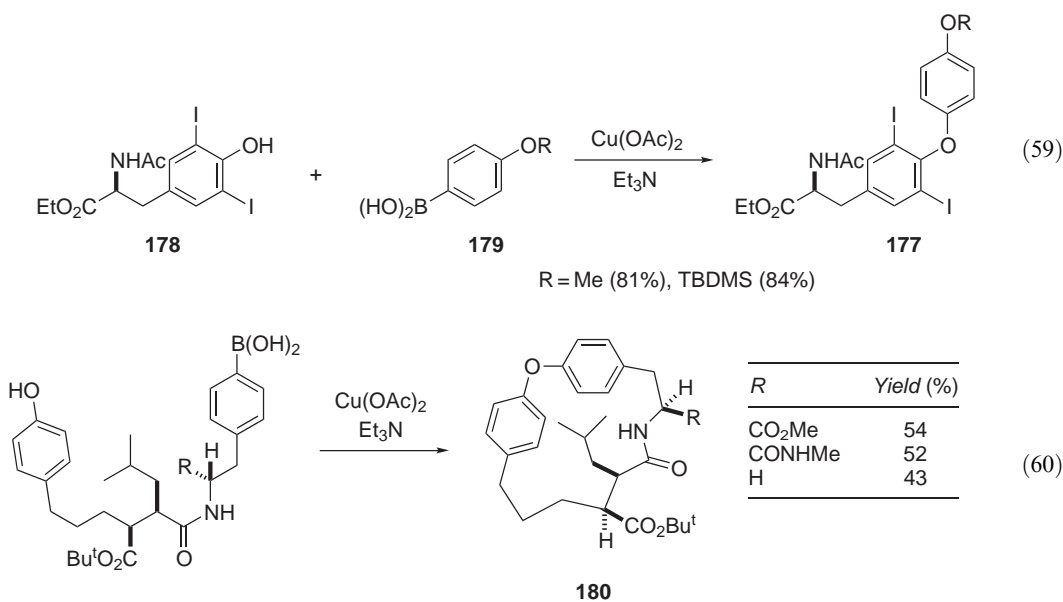
t-Butyl ethers serve as useful protecting groups for phenols due to their reasonable stability toward both acidic and basic conditions <B-1999MI003>. Bandgar and Kasture have reported a convenient method for the preparation of aryl *t*-butyl ethers by the reaction of phenols with *t*-butyl chloride in the presence of zinc dust. Phenols substituted with a variety of other functional groups react chemoselectively only at the phenolic hydroxyl group, and no evidence of *C-t*-butylation is observed (Equation (57)) <2000JCR(S)252>. Bandgar and Kasture proposed that zinc metal and not ZnCl₂ was the active catalyst for the reaction.



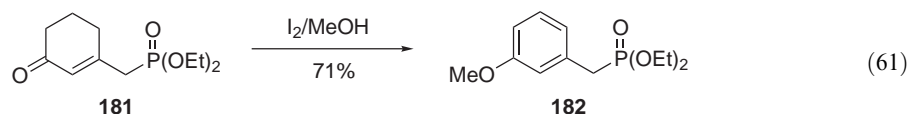
The most notable advance in the synthesis of aryl ethers in the late 1990s and early 2000s has been in the oxidative coupling of alcohols and phenols with aryl boronic acids, which provides a convenient synthesis of aryl ethers under mild reaction conditions. Under oxidative reaction conditions, aryl boronic acids react with phenols (H₂O₂ <1985JHC39>, Cu(OAc)₂/O₂ <2002OL2675>, or Cu(OAc)₂/TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) <1998TL2933, 2001TL3415>) to give the corresponding diaryl ethers (Equation (58)). Symmetric diaryl ethers can be obtained under similar reaction conditions in good-to-excellent yields (Scheme 52) <2001JOC633>. This reaction is tolerant of a wide range of substituents on both boronic acid and phenol, as exemplified in the preparation of diaryl ether **177**, an intermediate in the synthesis of L-thyroxine, by oxidative coupling of phenol **178** with boronic acid **179** in the presence of Cu(OAc)₂ and triethylamine. This reaction proceeds without racemization and without perturbation of the iodo substituents in the starting material or product (Equation (59)) <1998TL2937>. An oxidative diaryl ether synthesis was utilized for an intramolecular macrocyclization to give pseudopeptide **180**, a potent inhibitor of collagenase (Equation (60)) <2001OL1029>.



Scheme 52



Aryl ethers can also be prepared from cyclic nonaromatic precursors. For example, aromatization of enone **181** under oxidative conditions provides phosphonate ester **182** in a formal retro-Birch reduction (Equation (61)) <1996JCS(P2)1455>.

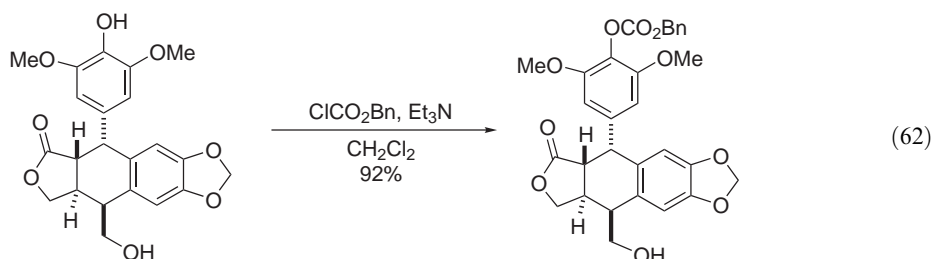


(ii) Aryl esters

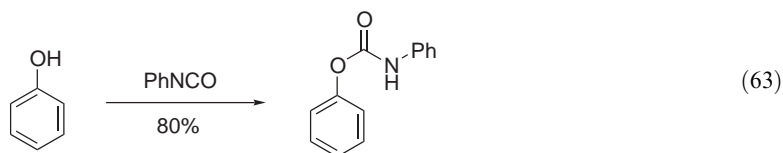
The preparation of aryl esters can be accomplished by a number of methods, the most straightforward of which is the reaction of a phenol with an acid chloride or anhydride <1995COFGT(2)635, B-1999MI003>. Reagents that are utilized for amide synthesis are, in general, effective for the coupling of phenols with carboxylic acids, and include *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide HCl (EDC) <2002MI1806>, dicyclohexylcarbodiimide (DCC) <2002BMCL3435, 2002S1434, 2002JOC8079>, alkyl chloroformates and Et₃N <1985JOC560>, di-2-pyridyl carbonate <1984TL4943>, MeSO₂Cl-Et₃N <1982SC727>, and many other dehydrating agents <B-2001MI004>. Transesterification is also effective although the reaction typically involves harsher conditions, including reacting the preformed phenoxide with an ester <2001TL1631> or by heating an ester with a phenol in the presence of a catalytic amount of Ti(OPrⁱ)₄ <1997JAP(K)09241213>.

(iii) Aryl carbonates and carbamates

Aryl carbonates are not generally very stable species, but they have been found to have some synthetic utility. Protection of the phenol group as a *t*-butyl carbonate is accomplished with (Boc)₂O <2000EJM895>. Selective protection of a phenol in the presence of an aliphatic hydroxyl group has been reported utilizing benzyl chloroformate in dichloromethane (Equation (62)) <2002BMC3463>.



Aryl carbamates are readily prepared from phenol and isocyanates (Equation (63)) <2002BMCL3435> or Me₂NCOCl <2000JHC799>.



2.13.1.3 Hypohalites (RO—Hal)

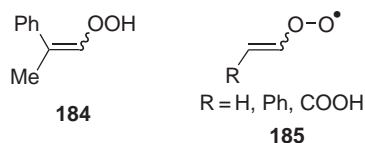
Alkenyl and aryl hypohalites are, in general, transient species with short lifetimes that preclude their isolation. They have been postulated to be intermediates in the oxidation of alcohols with *N*-halosuccinimides and in the halogenation of phenols <1995COFGT(2)635>. There has been little work published in the period 1993–2003 on the study of alkenyl and aryl hypohalites, but scattered accounts discuss theoretical studies of these species such as hypofluorite **183** which are postulated to be involved in atmospheric chemistry of fluorocarbons <2002JPC(A)8917>.



2.13.1.4 Peroxide Functions: RO—OH, RO—OR'

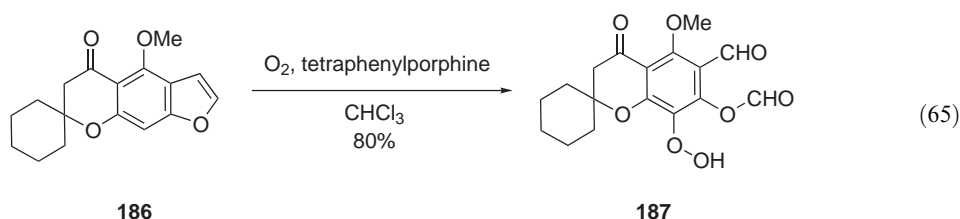
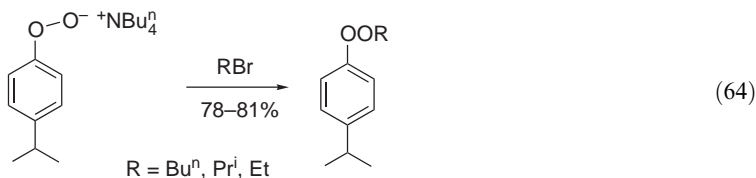
2.13.1.4.1 Alkenyl peroxides

The synthetic use of alkenyl peroxides is almost nonexistent in the literature. One such peroxide, α -methylstyrene peroxide **184**, has been reported as an ecological additive for diesel fuel <1991MI43>. The formation and reactivity of vinyl peroxy radicals **185** in aqueous solution have been studied <1995JPC4549>, but little synthetic value was noted for these species.

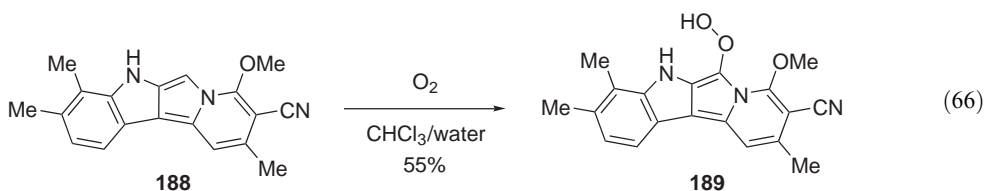


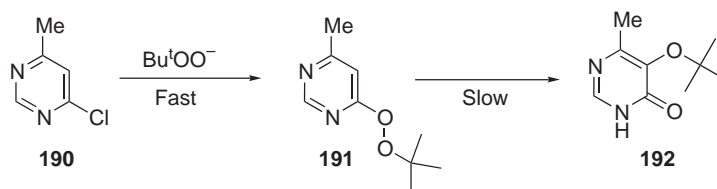
2.13.1.4.2 Aryl peroxides

Aryl peroxides are highly unstable species <1995COFGT(2)635>. There have been relatively few preparations of aryl peroxides reported in the decade 1993–2003. The tetrabutylammonium salt of phenyl peroxide can be formed and alkylated with alkyl bromides to provide the corresponding aryl alkyl peroxides in good yields (Equation (64)) <1994PJC1559>. A photo-oxygenation reaction of spiro-visnagin **186** using tetraphenylporphine as a singlet oxygen sensitizer gives peroxide **187** (Equation (65)) <2000MI227>.



In contrast to the behavior of aryl peroxides, some heteroaryl peroxides are rather stable compounds. Autoxidation of tetracyclic 9*H*,10*H*-indolizino[1,2-*b*]indole-1-one **188** gives heteroaryl peroxide **189** that can be isolated and fully characterized (Equation (66)) <2001JOC426>. **WARNING: extreme caution should be exercised in handling these peroxy compounds because they are potentially explosive.** *t*-Butylhydroperoxide anion is known to react with 4-methyl-6-chloropyrimidine **190** to give a stable pyrimidinyl peroxide **191** that undergoes slow rearrangement to *t*-butoxypyrimidone **192** (Scheme 53) <2002TL3221>.





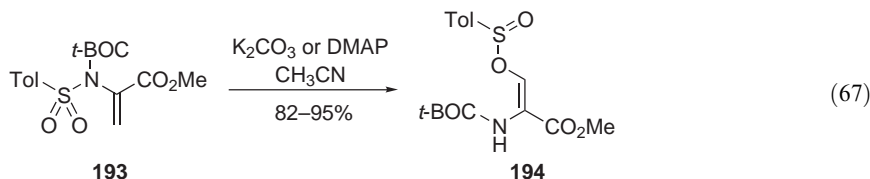
Scheme 53

2.13.1.5 Functions Based on RO—S, RO—Se and RO—Te Units

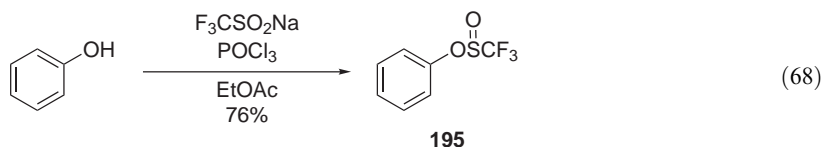
While aryl and alkenyl selenates and tellurates only appear intermittently in the chemical literature, alkenyl and aryl sulfonates, sulfinates, sulfonates, and sulfates are frequently reported and have found utility in a number of synthetic transformations. Classic methods for the preparation of these compounds are the condensation of enolates or phenolates with electrophiles of sulfur or selenium in the desired oxidation state. Tellurium derivatives have been prepared by reaction of enolates with organotellurium electrophiles <1995COFGT(2)635>.

2.13.1.5.1 Alkenyl and aryl sulfinates

A synthesis of β -amino alkenesulfinic ester **194** by the base-promoted rearrangement of *N*-tosyl-dehydroamino ester **193** has been reported by Ferreira and co-workers (Equation (67)) <2000TL7437, 2002TL4495>.

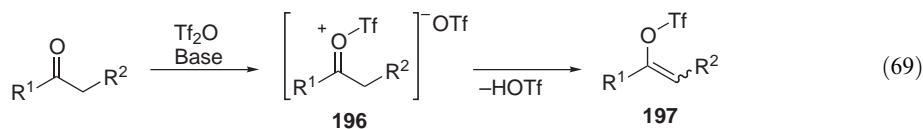


Phenyl trifluoromethyl sulfinate **195** was prepared by condensation of phenol with a sulfinylating agent prepared *in situ* from sodium trifluoromethanesulfinate and POCl_3 in EtOAc (Equation (68)) <1999T7243>. This sulfinylating reagent, which was not fully characterized, also reacts with aliphatic alcohols and aromatic and aliphatic amines in good yield.

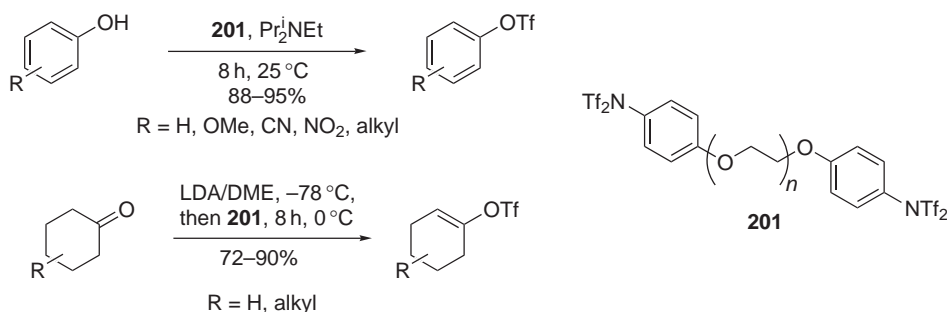
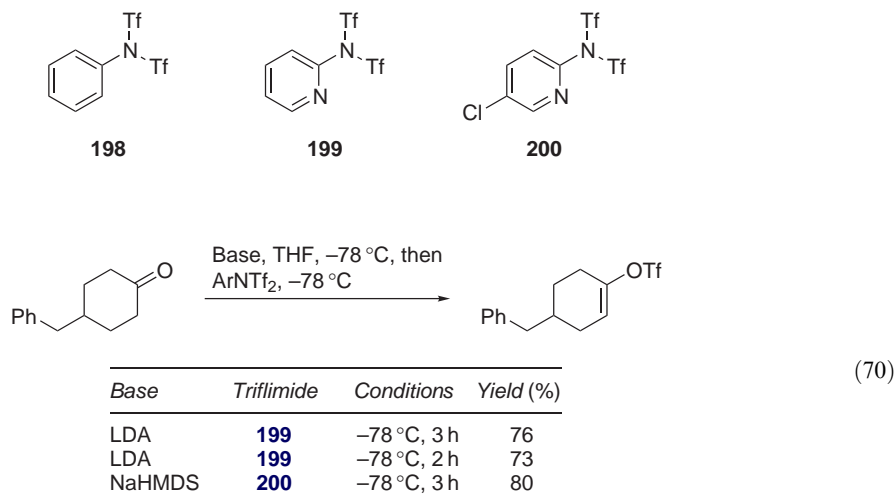


2.13.1.5.2 Alkenyl and aryl sulfonates

Alkenyl and aryl sulfonates are by far the most useful of this class of compounds in organic synthesis at the start of the twenty-first century. Sulfonic esters are traditionally prepared by the reaction of sulfonyl halides or anhydrides with enolates or phenolates, although the oxidation of sulfinic esters has also been reported <1995COFGT(2)635>. In the late 1990s and early 2000s, more attention has been focused on the synthesis of trifluoromethanesulfonate (triflate) esters, as they have demonstrated utility as substrates for transition metal-catalyzed coupling reactions with aryl, alkenyl, and alkyl organometallics, amines, amides, and phenols under mild conditions. An established method for the synthesis of triflates is by treatment of carbonyl compounds or phenols with triflic anhydride and a tertiary amine base (Equation (69)); for the synthesis of enol triflates the reaction is thought to proceed through an oxocarbenium ion intermediate **196** and gives the thermodynamic enol triflate product **197** <19982S85>.

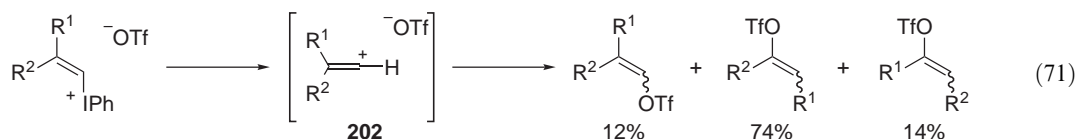


N-Phenyltriflimide **198** was introduced by Hendrickson and Bergeron <1973TL4607> and McMurry and Scott <1983TL979> for the triflation of phenolates and enolates, respectively. Since triflate formation with compound **198** usually requires the temperature to be at 0 °C or higher for complete reaction, some isomerization of kinetic enolates of sensitive substrates may occur. The more reactive 2-pyridyltriflimide **199** and 5-chloro-2-pyridyltriflimide **200** have been introduced to address this issue. These reagents react with lithium and sodium enolates of ketones at –78 °C to provide alkenyl triflates in good yield (Equation (70)) <1992TL6299, 1997OS77>. A polymer-supported variant of the Hendrickson/McMurry reagent **201** has been designed for a workup-free high-yield triflation of phenols and lithium enolates (Scheme 54) <2000OL477>.



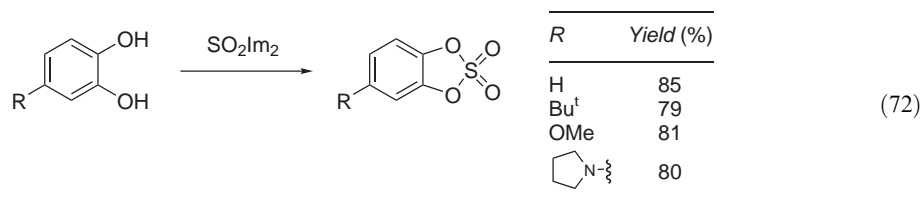
Scheme 54

Finally, enol triflates can be prepared by the trapping of the ethenyl cation resulting from thermal decomposition of alkenyl(aryl)iodonium triflates <1999JA7437>. The product distribution from this reaction reflects the aptitude for primary vinyl cation **202** to rearrange prior to capture of the cation by triflate anion (Equation (71)).



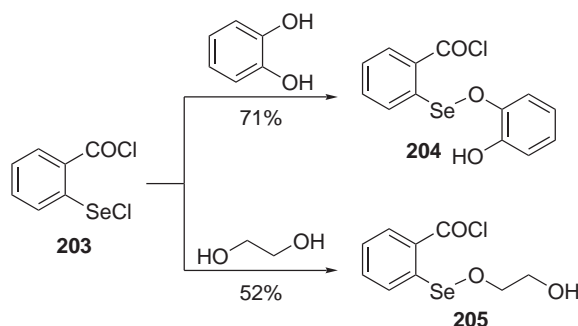
2.13.1.5.3 Alkenyl and aryl sulfates

Alkenyl and aryl sulfates are prepared by reaction of enolates and phenolates with halosulfonates <1995COFGT(2)635>, and this approach is also effective for the synthesis of cyclic sulfates from diols and SO_2Cl_2 <1998SUL75> or SO_2Im_2 (Im = imidazolyl) <1994SC1631> (Equation (72)).



2.13.1.5.4 Compounds containing RO—Se and RO—Te functional groups

Little has been published on the synthesis of compounds containing enolic and phenolic oxygen–selenium and oxygen–tellurium bonds in the decade 1993–2003. A single report describes the reaction of aryl selenyl chloride **203** with catechol and ethylene glycol to give aryl selenoxy ethers **204** and **205** in good yield (Scheme 55) <2002T7531>.

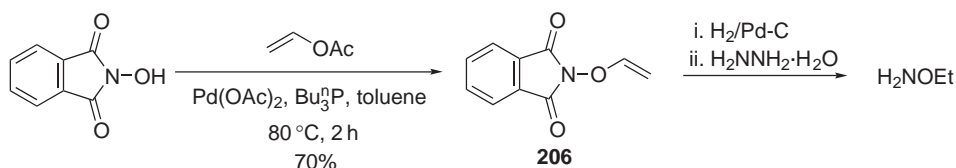


Scheme 55

2.13.1.6 Functions Based on the RO—N Unit

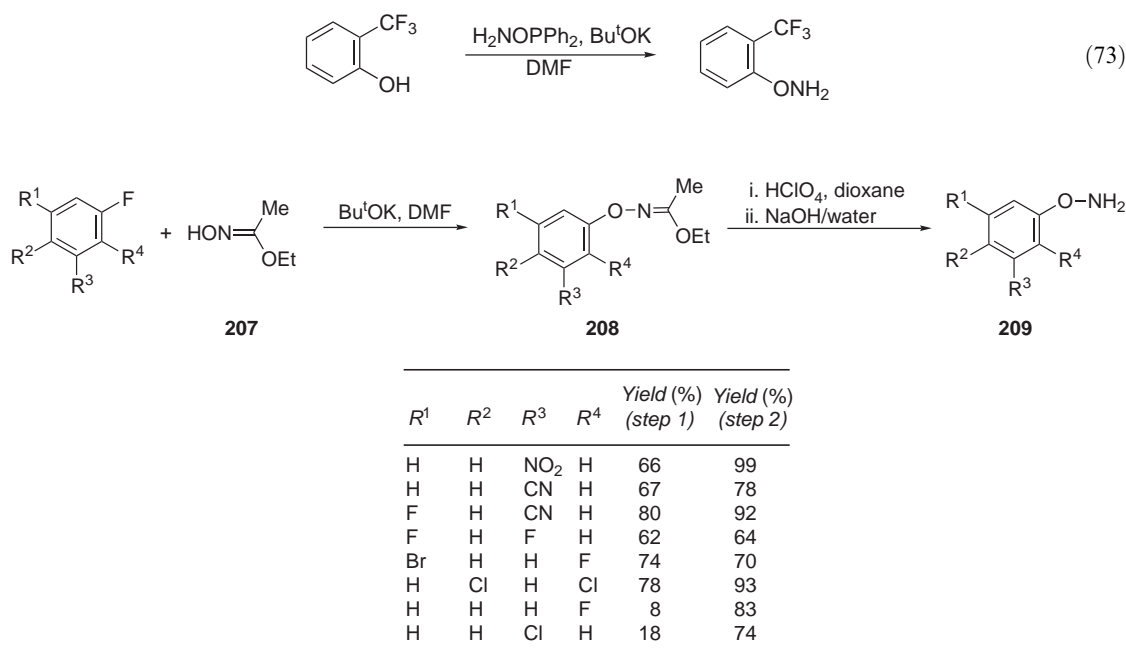
2.13.1.6.1 O-Alkenyl and O-aryl hydroxylamines

There are few examples of *O*-alkenyl hydroxylamines in the literature <1995COFGT(2)635>. One method for preparing this type of compound is the palladium-catalyzed coupling of vinyl acetate with *N*-hydroxyimides to give *N*-vinyloxyimides **206**. The *N*-vinyloxyimides can be hydrogenated to *N*-alkoxyimides and subsequently converted into alkoxyamines (Scheme 56) <1995WOP9525090>.



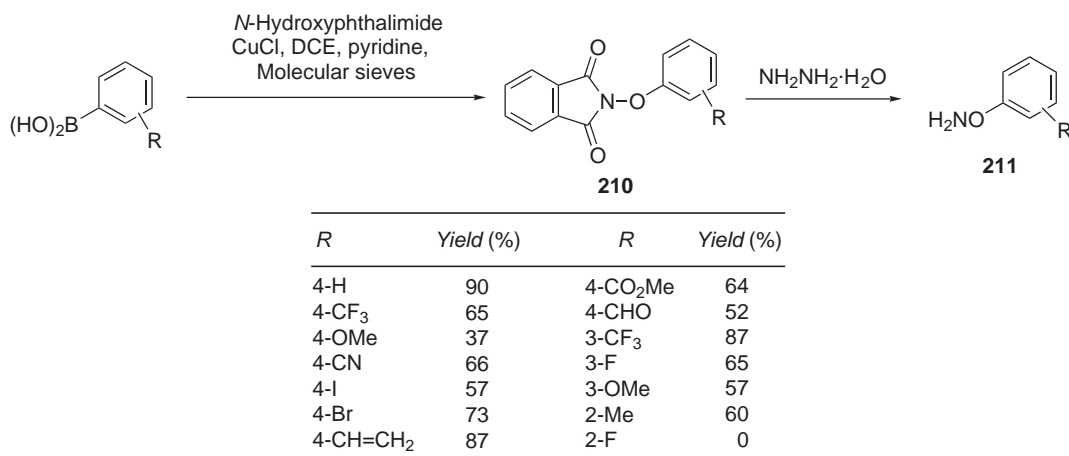
Scheme 56

O-Aryl hydroxylamines are often prepared by the *O*-amination of phenol with an aminating agent (Equation (73)) <1995COFGT(2)635, 2001JAP(K)2001081071> and from the reaction of activated aryl halides with derivatized hydroxylamines such as ethyl *N*-hydroxyacetimidate **207** (Scheme 57) <2001MI477>. Acid hydrolysis of *N*-hydroxyacetimidate intermediate **208** provides *O*-aryl hydroxylamine **209** <1997OPP594>.



Scheme 57

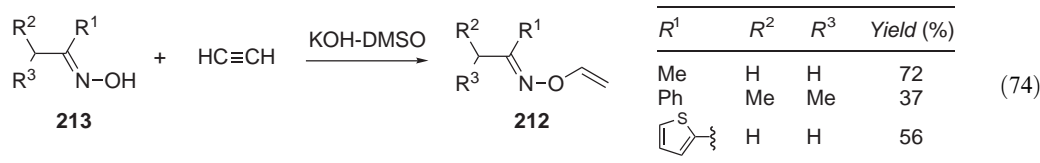
Aryl boronic acids participate in a copper-mediated cross-coupling with *N*-hydroxyphthalimide to provide intermediate **210** (Scheme 58) <2001OL139>. Removal of the phthalimide group with hydrazine hydrate affords aryloxamines **211** in good-to-excellent yields. The reaction is compatible with many functional groups, including halogens, esters, and aldehydes.



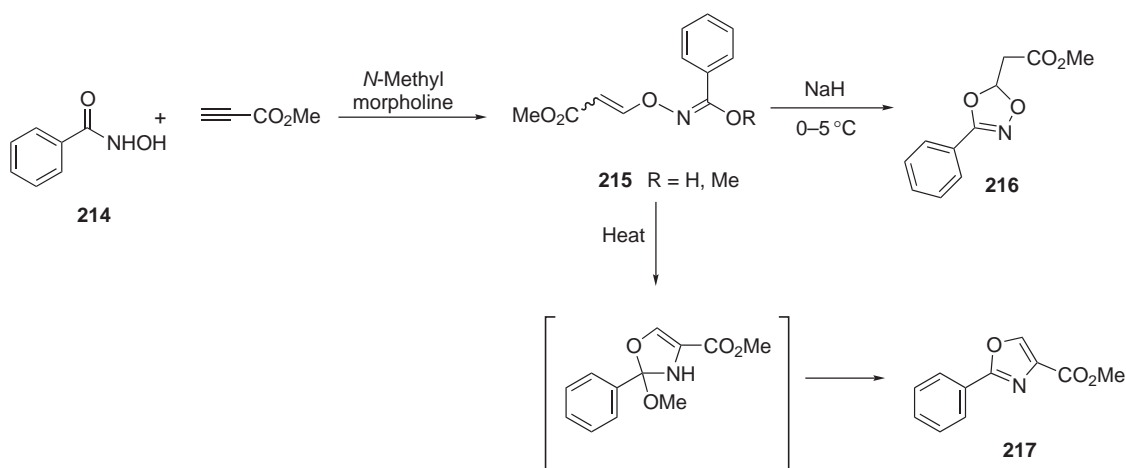
Scheme 58

2.13.1.6.2 *O*-Aryl- and *O*-alkenyloximes

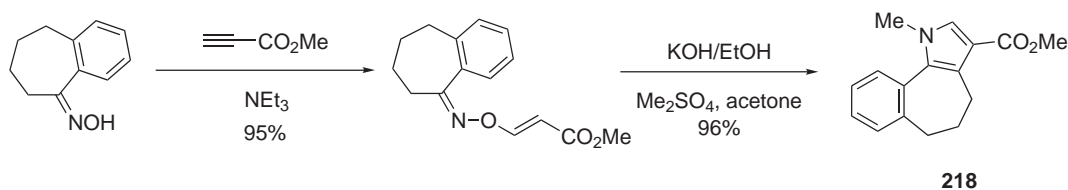
O-Aryl hydroxylamines undergo facile condensation with aldehydes and ketones to give *O*-aryloximes <1995COFGT(2)635, 2001JMC988, 2000JA3358>. Alternatively, *O*-aryloximes can be prepared directly from arylation of oximes with activated aryl halides <1995COFGT(2)635>. *O*-Alkenylketoximes **212** are synthesized from ketoximes **213** and acetylene under strongly basic conditions in moderate-to-good yields (Equation (74)) <2000S1125>.



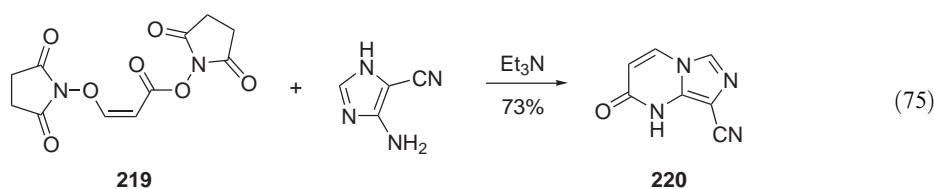
O-Alkenyl- and *O*-aryloximes are versatile intermediates in the syntheses of alkaloids. They are often prepared by Michael addition of hydroxylamine derivatives to α,β -unsaturated esters. For example, addition of benzhydroxamic acid **214** to methyl propiolate gives an *O*-alkenyl imide **215** that cyclizes to give 1,4,2-dioxazoles **216** upon treatment with NaH at 0–5 °C. With heating, **215** cyclizes and eliminates methanol to provide an oxazole **217** (Scheme 59) <2000TL7433>. Murineddu and co-workers <2002CPH754> have utilized an *O*-alkenyloxime as an intermediate in the synthesis of pyrroles **218** as potential cytotoxic agents (Scheme 60). Bis(*O*-succinimide) **219** is a Michael acceptor that has been employed in the preparation of imidazopyrimidines (**220**), Equation (75) <1999JMC1661>. 1,2,4-Oxadiazolidin-3-ones **221** are synthesized from tandem *O,N*-addition of hydroxyureas to methyl propiolate in good-to-excellent yields (Equation (76)) <1998SL1217>.

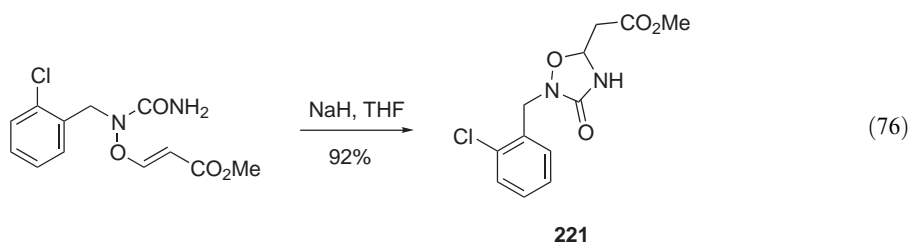


Scheme 59

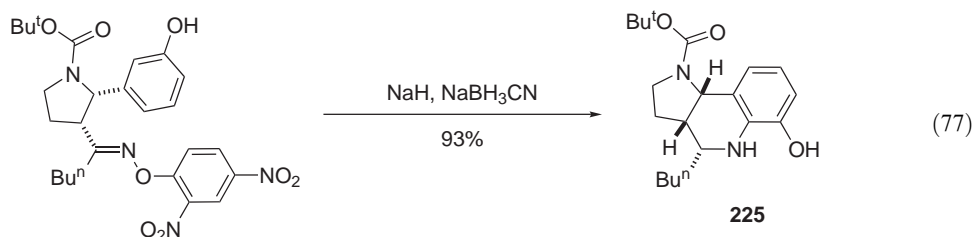
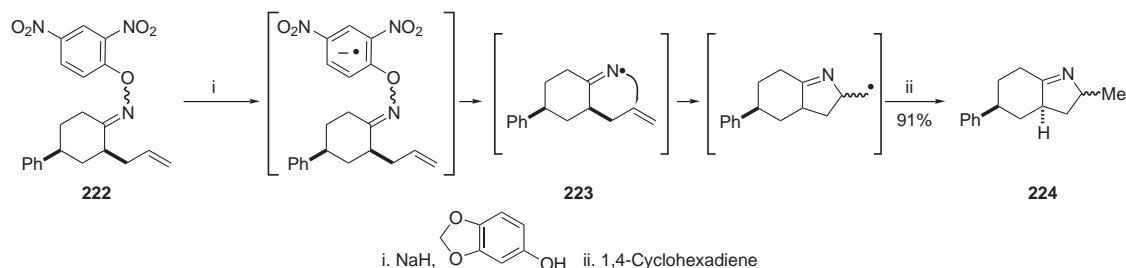


Scheme 60

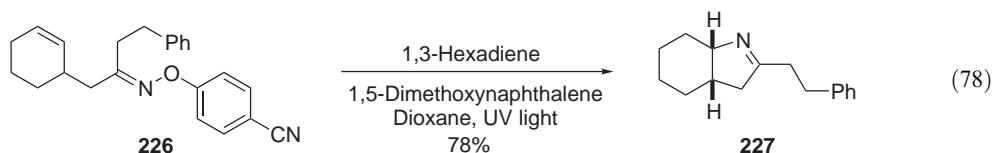




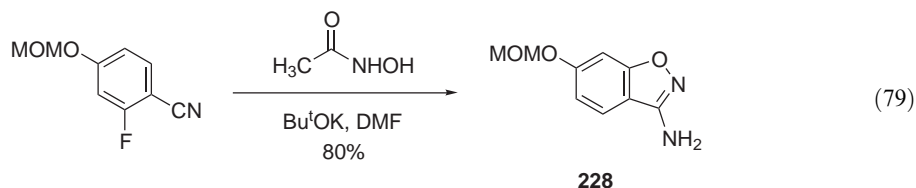
Alkylideneaminyl radicals, which are also known as iminyl radicals, are readily generated from *O*-aryloximes and are useful intermediates in the syntheses of alkaloids. For instance, when *O*-2,4-dinitrophenyloxime **222** is treated with NaH and 3,4-methylenedioxyphenol, heterolytic cleavage of the N—O bond ensues to give iminyl radical **223** which participates in intramolecular cyclization with the allyl group to give dihydropyrrole **224** (Scheme 61) <1999T8915>. This method has been applied to the stereoselective synthesis of xenovenine **225**, a bicyclic 3,5-dialkylpyrrolizidine alkaloid (Equation (77)) <1998BCJ2945>.



O-(*p*-Cyanophenyl)oximes **226** are transformed into 3,4-dihydro-2*H*-pyrroles **227** by a photochemical reaction (Equation (78)). The transformation is believed to proceed via photosensitized electron transfer between 1,5-dimethoxynaphthalene and **226** giving an iminyl radical in an analogous process to that shown in Scheme 61 <2001MI477, 2000CL338>.

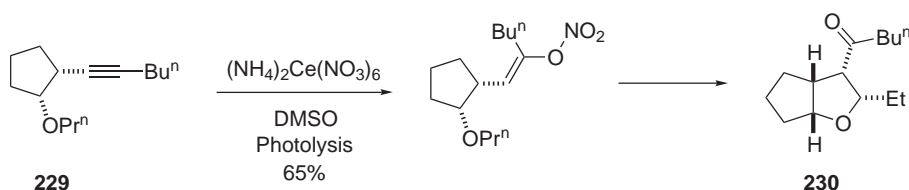


O-Aryloximes have been utilized as ketone linkers in solid-phase synthesis <2003OL7>. The synthesis of aminobenzisoxazole **228** has been demonstrated both in solution phase <1996TL2885> and on solid-polymer support (Equation (79)) <2000JOC2924>.

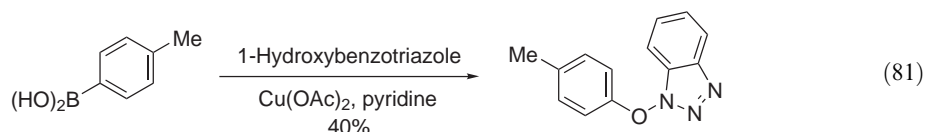
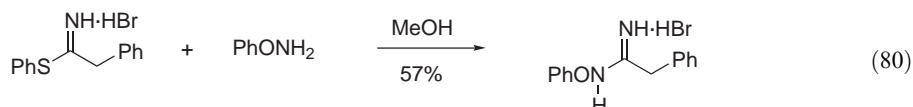


2.13.1.6.3 Miscellaneous RO—N compounds

Alkyne **229** cyclizes under photolytic conditions with cerium ammonium nitrate (CAN) to give the bicyclic tetrahydrofuran **230** in 65% yield (Scheme 62) <2001H377>. The reaction involves an *O*-nitro alkenyl intermediate and proceeds via an oxidative, self-terminating radical cyclization cascade. *O*-Aryl hydroxylamine reacts with thioimide to give *N*-aryloxyamidines (Equation (80)) <1999S927>. 1-Hydroxybenzotriazole also undergoes a copper (II)-mediated process to give the corresponding aryloxytriazole in moderate yields (Equation (81)) <2000SL674>.



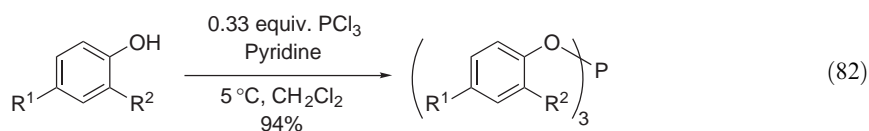
Scheme 62



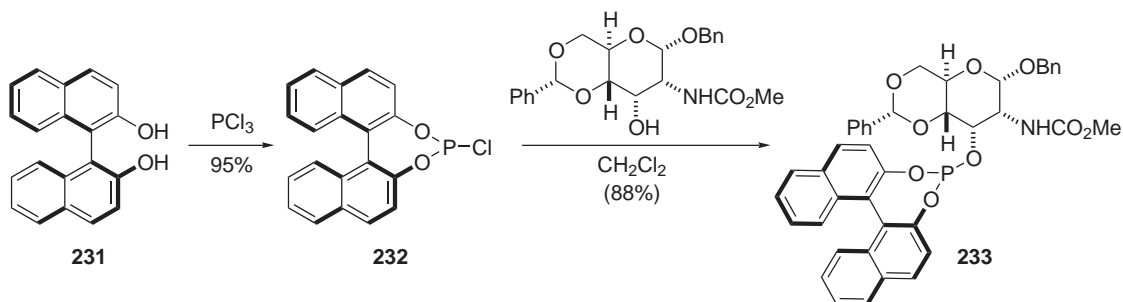
2.13.1.7 Functions Based on RO—P, RO—As, RO—Sb, and RO—Bi Units

2.13.1.7.1 Alkenyl and aryl phosphites

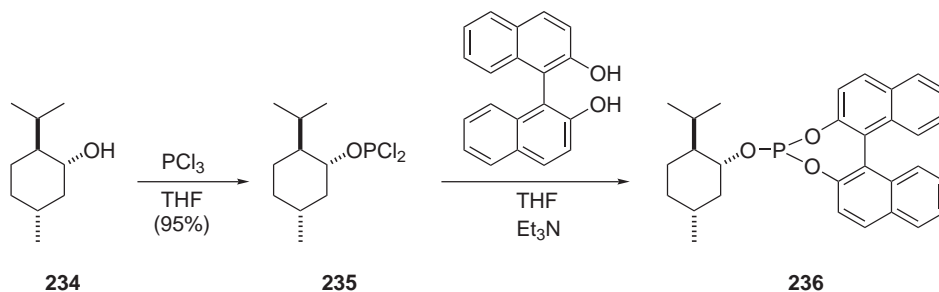
Alkenyl and aryl phosphites have traditionally been prepared by reaction of enolates and phenolates with phosphorus trichloride or phosphorochloridites <1995COFGT(2)635>. The interest in the preparation of aryl phosphites has continued into the twenty-first century due to their use as stabilizers for synthetic rubber and as effective ligands for transition metal-catalyzed reactions. Symmetric aryl phosphites are best synthesized by direct combination of the phenol with PCl₃ with an amine base (Equation (82)); excellent yields can be routinely obtained in this reaction <2003USP2003100787>.



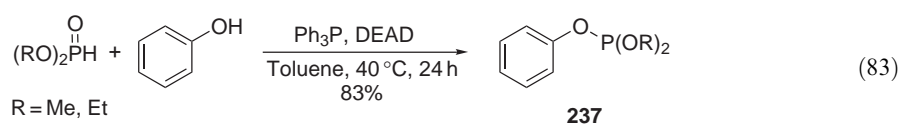
Aryl phosphites with different substituents can be prepared by a number of methods. The condensation of PCl_3 with an aromatic diol (i.e., 1,1'-bi-2-naphthol (BINOL), **231**) gives a phosphochloridite **232** which can be coupled with another alcohol to provide phosphite **233** (Scheme 63) <2002JA734>. Alternatively, reaction of one equivalent of menthyl alcohol **234** with PCl_3 results in formation of a phosphodichloridite **235** which is subsequently treated with BINOL to give phosphite **236** (Scheme 64) <2001TL2897>. The Mitsunobu reaction has also been utilized for the phosphorylation of alcohols. Dimethyl phosphite and diethyl phosphite participate in a condensation reaction with phenol in the presence of Ph_3P and diethyl azodicarboxylate (DEAD) in toluene at 40°C to give the aryl dialkyl phosphites **237** in good yield (Equation (83)) <1996TL1087>.



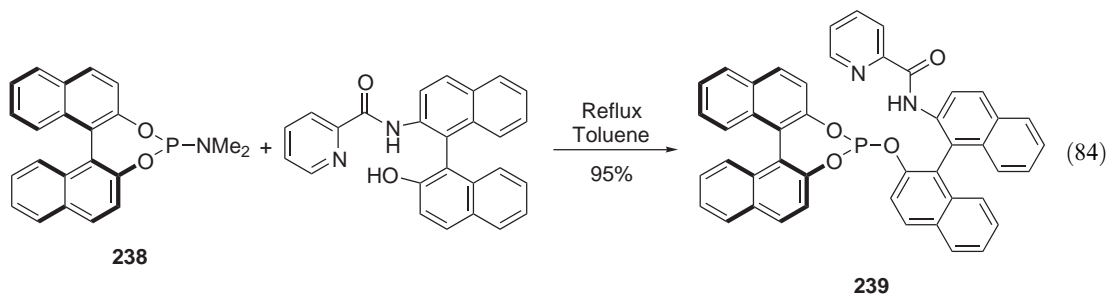
Scheme 63

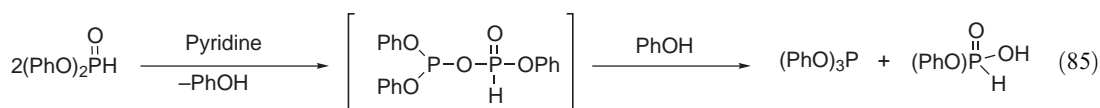


Scheme 64



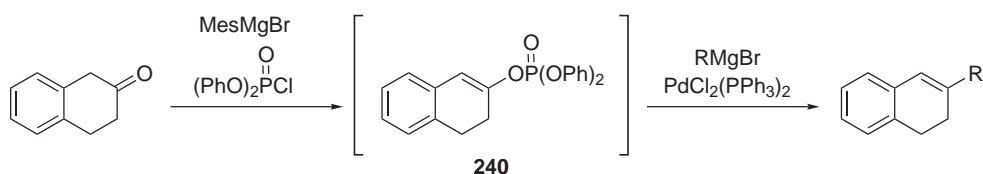
Phosphoramidites derived from diols are also good substrates for formation of phosphites by nucleophilic addition of phenols. This method has been utilized for the synthesis of chiral ligand **239** from enantiopure BINOL phosphoramidite **238** in refluxing toluene (Equation (84)) <2003JOC4542>. It is also possible to access aryl phosphites by the disproportionation reaction of diphenyl phosphite (Equation (85)), but, as of 2003, this process has yet to be proven useful for preparative purposes <1996T9931>.





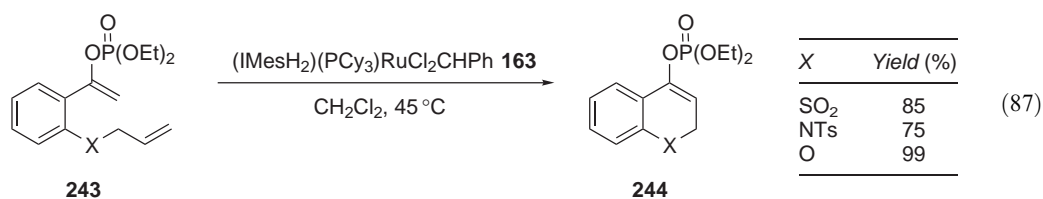
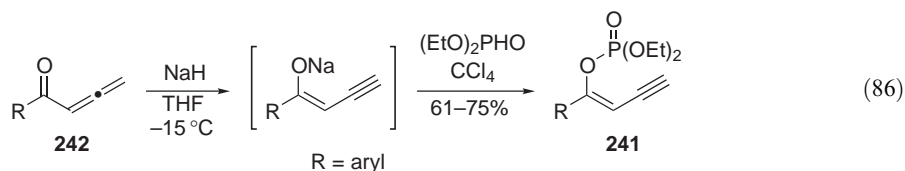
2.13.1.7.2 Alkenyl and aryl phosphates

Alkenyl phosphates, which are also frequently called enol phosphates, have traditionally been prepared by the condensation of enolates with dialkyl chlorophosphates (also known as phosphorochloridates), and this remains, in the early 2000s, the most widely utilized method for their synthesis <1995COFGT(2)635>. Typically enolate preparation involves the use of an alkali metal amide base (LDA, NaHMDS, etc.) and one equivalent of amine is the by-product of this process. When the resulting amine interferes in subsequent reactions, an alternative deprotonation method reported by Miller utilizing hindered Grignard reagents as bases for the preparation of enolates is effective <2002TL7111>. The resulting magnesium enolates react with diphenyl phosphorochloridate to provide the enol phosphates **240**, which are employed directly in a Pd-catalyzed coupling reaction with Grignard reagents (Scheme 65). Alkynyl enol phosphates **241** have been prepared by the reaction of enolates of allenyl ketones **242** with chlorodialkyl phosphate generated *in situ* from a dialkyl phosphite and carbon tetrachloride (the Atherton–Todd reaction). Good yields and excellent (*Z*):(*E*) selectivities are observed with a variety of aryl allenyl ketones (Equation (86)) <2001SC449>. Acyclic enol phosphates **243** can be converted into cyclic enol phosphates **244** by a RCM process employing the second-generation Grubbs' catalyst **163** (Equation (87)) <2003TL4275>.



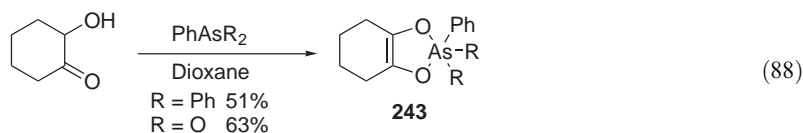
R	Yield (%)
Me	82
Ph	91
<i>p</i> -Tol	82

Scheme 65



2.13.1.7.3 Arsenic, antimony, and bismuth enolates

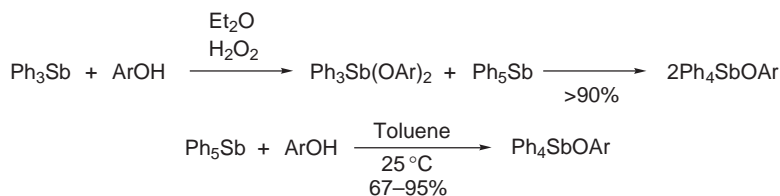
The preparation of enolates of arsenic, antimony, and bismuth is not widely studied, and little additional work has been reported since the publication of COFGT (1995) <1995COFGT(2)635>. A single report describes the condensation of 2-hydroxycyclohexanone with triphenylarsine and phenyl arsine oxide to give the corresponding 1,3,2-dioxarsoles **243** in good yield (Equation (88)) <2002PS(177)497>.



2.13.1.7.4 Arsenic, antimony, and bismuth phenolates

Phenolates of arsenic and antimony are traditionally prepared by reaction of phenolates with aminoarsines and aminostilbenes <1995COFGT(2)635>. It is also possible to utilize haloarsines and halostilbenes as electrophiles in this reaction <1995JCS(P1)2945, 2002SR11319>.

Antimony(V) phenolates have been prepared by the addition of 1 equiv. of phenol to Ph₅Sb in toluene <1995IZV958> and by the redistribution reaction of Ph₅Sb with Ph₃Sb(OAr)₂, which itself is formed from the reaction of Ph₃P with phenols under oxidizing conditions (Scheme 66) <2001RJGC983>.

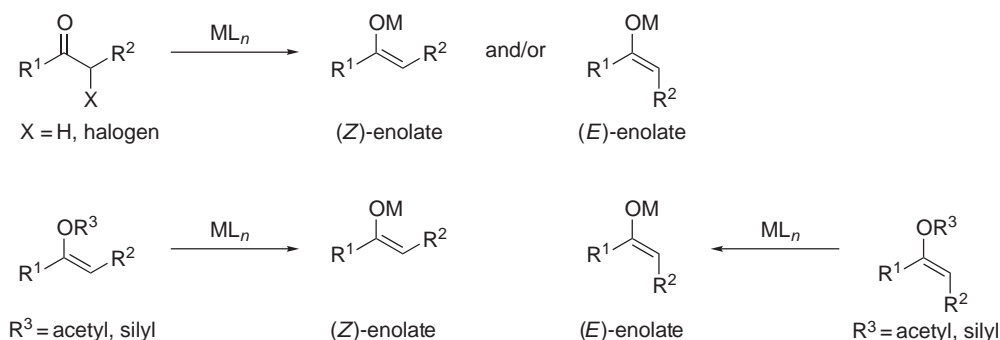


Scheme 66

2.13.1.8 RO–Metal and Metalloid Derivatives

2.13.1.8.1 Metal and metalloid enolates

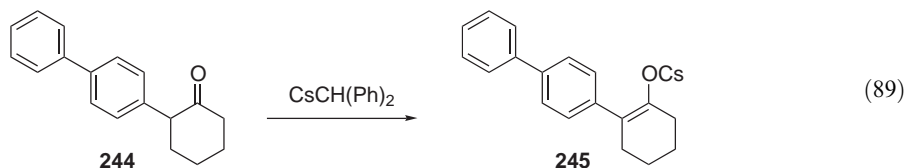
Of all the enol derivatives reviewed in this chapter, enolates are the most frequently utilized in organic synthesis at the start of the twenty-first century as they provide a facile method for the introduction of functionality to an existing substrate, often in a diastereo- and enantioselective fashion. Enolates are most frequently prepared by formation of a carbanion α to a carbonyl group, typically by deprotonation, by metal–halogen exchange, or by cleavage of an enol derivative under basic conditions (Scheme 67). Enolates derived from aldehydes ($R^1 = H$) are difficult to prepare by direct deprotonation due to competing self-condensation, so methods starting from the stable enol esters and enol silanes are often employed <1999JA9465>. When deprotonating ketones ($R^1, R^2 \neq H$) the incipient enolate alkene can adopt either the (*E*) or (*Z*) configuration depending on reaction conditions, with the (*E*)-enolate predominating under kinetic conditions and the (*Z*)-enolate being the thermodynamic product. Enolates prepared from geometrically defined enol derivatives maintain their alkene geometry. Ketones that are not symmetric can also form regioisomeric enolates, with the most substituted enolate generally favored under thermodynamic conditions. Readers are encouraged to consult COFGT (1995) <1995COFGT(2)635> where most of the preferred methods for generating enolates are covered in detail.



Scheme 67

(i) Enolates of group 1 metals

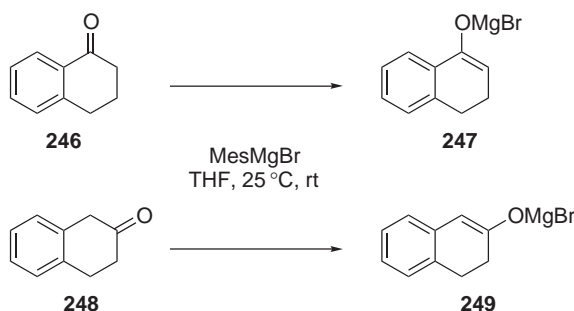
The synthesis of enolates of group 1 metals is most frequently accomplished by the deprotonation of carbonyl compounds with readily accessible, commercially available hindered amine bases, including the lithium, sodium, and potassium amides of diisopropylamine and hexamethyldisilazane (HMDS). Enol silanes and enol esters form enolates on treatment with nucleophilic organometallics, including MeLi <1995COFGT(2)635> and alkali metal alkoxides (Bu^tONa, Bu^tOK <2001EJO1023>) with retention of alkene geometry. It is also possible to convert lithium enolates to other group 1 metal enolates by transmetalation with alkoxides <2000EJI1115>. Streitwieser and co-workers <1999JOC4860> have reported the generation of thermodynamic caesium enolate **245** by the deprotonation of ketone **244** with CsCH(Ph)₂ (Equation (89)). Alkali metal enolates exist in solution as monomers, dimers, and tetramers, with the relative ratio in solution dependent on the solvent. Etheral solvents that can solvate the metal cation (dimethoxyethane (DME) and THF) support a higher concentration of monomer in solution than methyl *t*-butyl ether (MTBE), which cannot adequately solvate the metal <2000OL3739>.

*(ii) Enolates of group 2 metals*

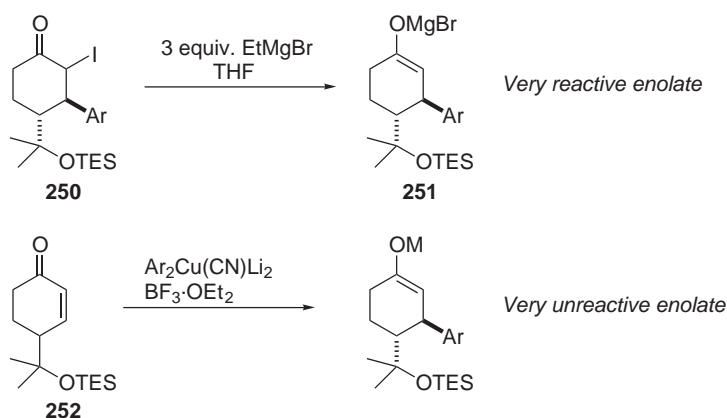
Of the group 2 metals, only magnesium has found widespread use in generation of enolates. Amide bases derived from dialkylamines and Grignard reagents are effective for the deprotonation of enolizable ketones to give magnesium enolates <1995COFGT(2)635>. Hindered Grignard reagents have also been utilized for the deprotonation of ketones, although this process is typically competitive with addition of the Grignard to the carbonyl. For the conversion of tetralone derivatives **246** and **248** to magnesium enolates **247** and **249**, the use of PrⁱMgCl and BuⁱMgCl results in competitive addition of the Grignard reagent to the ketone, but utilizing the very hindered MesMgBr (Mes = mesityl) gives exclusive deprotonation (Scheme 68) <2002TL7111>. Magnesium enolates have also been prepared by the halogen–magnesium exchange reaction between iodoketone **250** and EtMgBr. The resulting enolate **251** is much more reactive than the enolate derived from the Lewis-acid promoted conjugate addition of a higher-order cuprate to the cyclohexenone starting material **252** (Scheme 69) <2001OL2017>.

(iii) Enolates of group 13 metals and metalloids

Boron enolates, also known as enol borinates, are of enormous synthetic value due to their ease of formation, high reactivity, and predictable stereochemical outcome when chiral or prochiral boron enolates are employed in aldol reactions with aldehydes. The preparation of these enolates



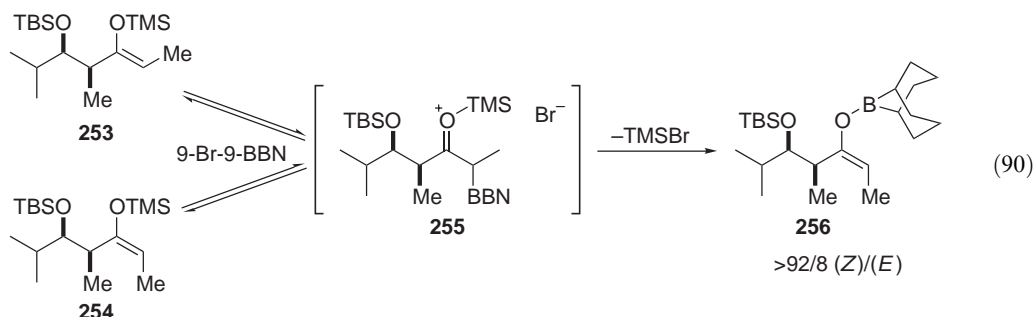
Scheme 68



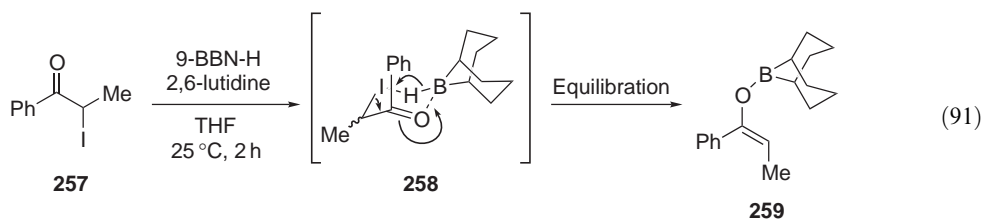
Ar = 2,6-dimethoxy-4-pentylphenyl

Scheme 69

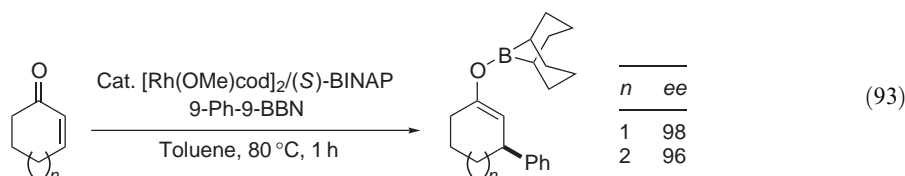
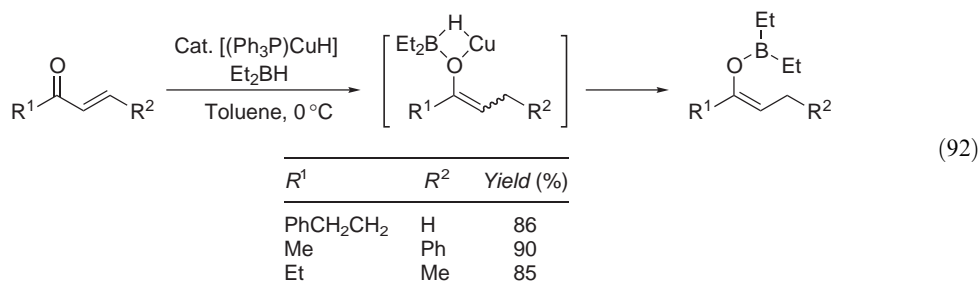
from ketones is straightforward and both (*E*)- and (*Z*)-enolates are reliably obtained by appropriate choice of base and boron reagent [<1995COFGT\(2\)635>](#). It is also possible to prepare enol borinates by transmetalation. Most frequently lithium enolates are employed for this process, but enol silanes **253** and **254** also exchange with dialkylboron bromides to provide the thermodynamic (*Z*)-boron enolate **256** via equilibration through oxocarbenium ion **255**, which occurs under the reaction conditions [<1995TL9245>](#) (Equation (90)).



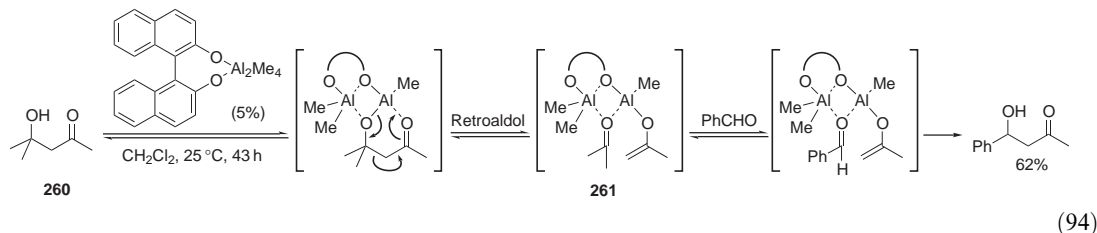
Mukaiyama and co-workers [<2003BCJ813>](#) have demonstrated that it is possible to generate enol borinates from α -iodoketones **257** by treatment with a dialkoxy- or dialkylborane in the presence of pyridine. Boro-deiodination is suggested to occur through a cyclic transition state **258** with concomitant generation of HI, and control of enolate geometry is excellent when 9-borabicyclo[3.3.1]nonane (9-BBN-H) is employed due to equilibration of the resulting mixture of enolates to the (*Z*)-isomer **259** under the reaction conditions (Equation (91)).



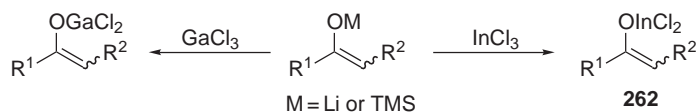
Hydroboration of enones is another direct route for the preparation of enol borinates [<1995COFGT\(2\)635>](#). Two accounts describe transition metal-catalyzed variants of this technique. The conjugate addition of diethylborane to acyclic enones catalyzed by Stryker's reagent $[(\text{Ph}_3\text{P})\text{CuH}]$ results in selective formation of (Z)-boron enolates, even those derived from vinyl ketones which are difficult to hydroborate under standard conditions [<2002AG\(E\)4580>](#). This reaction proceeds by initial hydrocupration of the enone, reduction of the resulting copper(II) enolate with borane, and finally equilibration of the enolate thus formed to the thermodynamic (Z)-isomer (Equation (92)). A rhodium-catalyzed carboboration of cyclic enones has been reported by Hayashi and co-workers [<2003JOC1901>](#) to give intermediate 9-BBN enols (Equation (93)).



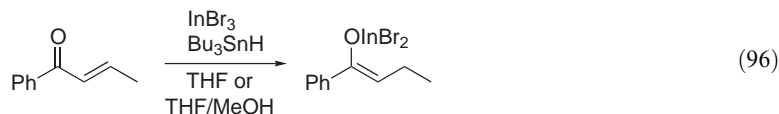
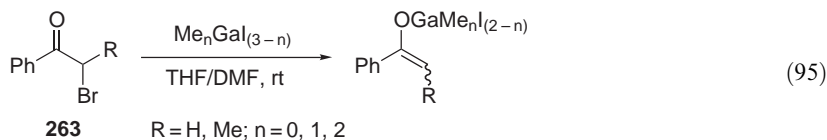
Less development of other group 13 metal enolate chemistry has occurred in the literature up to 2003. A new method for the preparation of aluminum enolates has been reported by Simpura and Nevalainen that relies on the facile aluminum alkoxide-mediated retroaldol reaction of β -hydroxycarbonyl compounds **260** (Equation (94)) [<2000AG\(E\)3422, 2003T7535>](#). Since the retroaldol reaction is reversible, the aluminum enolate **261** is typically consumed as soon as it is produced by running the reaction in the presence of an aldehyde that serves to capture the enolate **261**.



Gallium and indium enolates have only been described in the literature in the early 2000s, and methods for their preparation are thus rather limited. Transmetalation of preformed lithium enolates with GaCl_3 [<2002BCJ2049>](#) and InCl_3 [<2000JCS\(P1\)825>](#), and gallium-silicon exchange in enolsilanes with GaCl_3 [<2003CL298>](#) results in formation of enolates **262** (Scheme 70). Gallium enolates have also been formed by reaction of α -bromoketone **263** with methylgallium iodide in THF/DMF in a reaction similar to the Reformatsky process [<1998TL7751>](#) (Equation (95)). Indium enolates are formed by the conjugate reduction of enones by Br_2InH which is generated *in situ* from InBr_3 and Bu_3SnH [<2002MI283>](#) (Equation (96)).

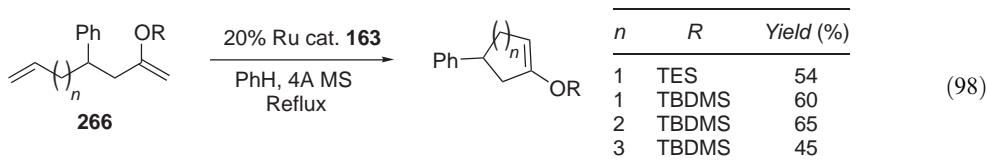
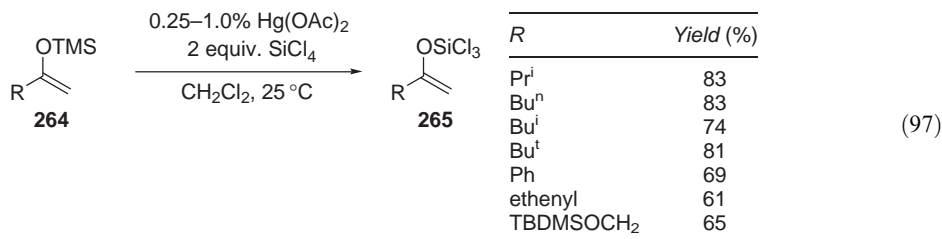


Scheme 70



(iv) Enolates of group 14 metals and metalloids

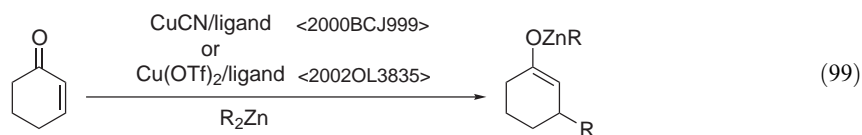
Of the enolates of group 14 metals and metalloids, silyl enol ethers (enol silanes) are by far the most useful from a preparative standpoint. Numerous methods for the synthesis of enol silanes have been reported <1995COFGT(2)635> and many can be easily purified by distillation or column chromatography and stored for extended periods without decomposition. Although there have been few new preparative methods for enol silanes introduced in the decade 1993–2003, two useful procedures for the interconversion of enolsilanes have been reported. Denmark and co-workers <1998JOC9517> have found that $\text{Hg}(\text{OAc})_2$ is an efficient catalyst for the silyl exchange reaction between trimethylsilyl enol ethers **264** and silicon tetrachloride to provide trichlorosilyl enol ethers **265** (Equation (97)). Small-ring cyclic enol silanes have been prepared by RCM of acyclic δ - and ϵ -unsaturated silyl enol ethers **266** using the second-generation Grubbs' catalyst **163** (Equation (98)) <2002CC2490>.



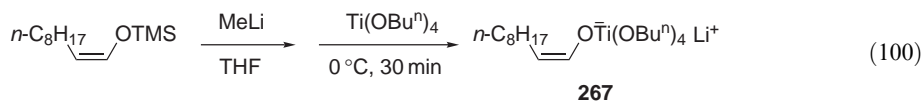
(v) Enolates of transition metals

Enolates of transition metals have been more extensively investigated during the decade from 1993 due to the development of useful new reactions in which these species participate, and extensions of existing technology to new substrates.

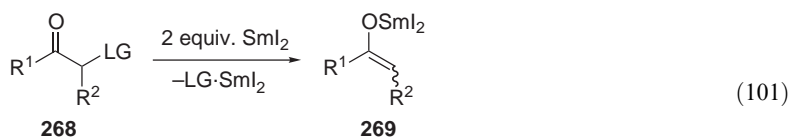
(a) *Zinc*. Zinc enolates are traditionally prepared by reaction with α -halo carbonyl compounds or by transmetalation from other enolates <1995COFGT(2)635>. It is also possible to prepare zinc enolates by the copper (I)- and copper(II)-catalyzed conjugate addition of organo-zinc reagents to enones (Equation (99)) <2000BCJ999, 2002OL3835>.



(b) *Titanium*. Titanium enolates are frequently prepared by transmetallation with lithium enolates, enol silanes, or by direct deprotonation of a carbonyl compound by an amine base in the presence of a titanium(IV) halide <1995COFGT(2)1995>. Oshima and co-workers <1999JA9465> have found that when lithium enolates are treated with titanium tetra-*n*-butoxide, ate complex **267** is formed and is reactive in the aldol condensation with aldehydes and ketones (Equation (100)).

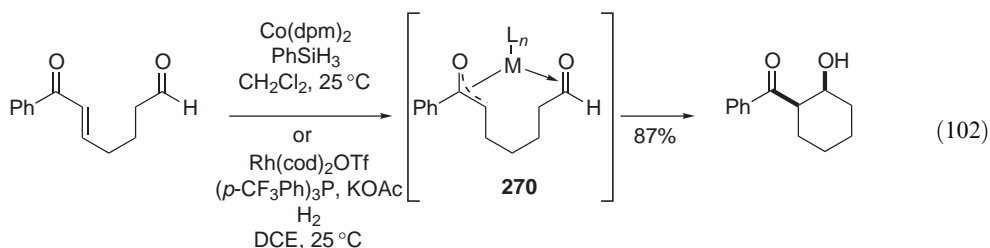


(c) *Samarium*. Samarium(II) iodide is a versatile one-electron reducing agent that has seen growing utility in organic synthesis for the synthesis of carbocycles [<1996CRV307>](#) and the reduction of carbon–heteroatom and heteroatom–heteroatom bonds [<1994RHA165>](#). When carbonyl compounds [268](#) containing α halogens or leaving groups are treated with SmI₂ the α -substituent undergoes reductive cleavage to generate samarium enolate [269](#) (Equation [\(101\)](#)). Ketones with epoxides [<2000CL580>](#), halides [<1999T4595>](#), ethers [<1993JOC4061, 1999T4595>](#), esters [<1999T4595>](#), and β -sulfonylcyclopropyl groups [<1999TL1019>](#) have been reported to participate in this reaction.



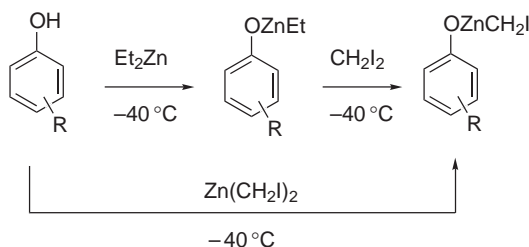
LG = epoxides, halides, ethers, esters, cyclopropanes

(d) *Cobalt, Rhodium, and Palladium.* Krische and co-workers have reported that enolates of rhodium and cobalt are generated by the Co- [2001JA5112](#) and Rh-catalyzed reduction of enones [2002JA15156](#) (Equation (102)). With the cobalt catalyst the stoichiometric reductant is phenylsilane and with rhodium it is hydrogen gas, but for both catalytic systems the intermediate reduction product is enolate [270](#) which subsequently undergoes an intramolecular aldol reaction.

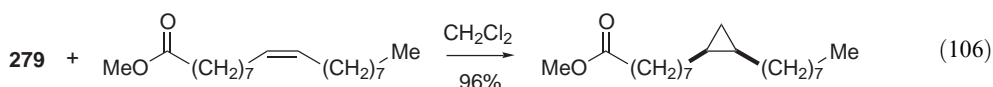
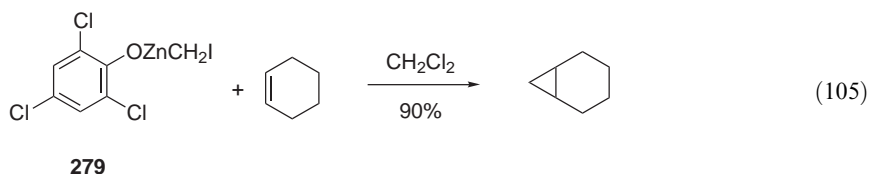


Palladium enolates are typically generated from treatment of a carbonyl compound with an enolizable α -hydrogen with a base in the presence of a palladium(II) halide (Equation (103)). These enolates, which are present in both O- and C-bound variants **271** and **272** depending on ketone substitution and identity of the ligands on Pd, are key intermediates in the Pd-catalyzed α -arylation reaction of carbonyl compounds. Although typically used immediately upon formation, it is possible to isolate palladium enolates **273** by transmetallation of potassium enolates with arylpalladium halides (Equation (104)) <2001JA5816>. The scope of this reaction, including a mechanistic analysis, has been summarized in a review by Culkin and Hartwig <2003ACR234>, and in the work of Buchwald and co-workers <1997JA11108, 2002JA15168>.

Carbenoids with generic composition of $\text{ArOZnCH}_2\text{I}$ have been developed as versatile cyclopropanation agents. They are traditionally prepared by two methods, as shown in [Scheme 72](#). In the first method, the phenol is deprotonated with diethylzinc followed by metal–halogen exchange with methylene iodide. The zinc carbenoid can also be accessed directly by treating a phenol with $\text{Zn}(\text{CH}_2\text{I})_2$. The first method is generally preferred as the latter involves handling of unstable bis(iodomethyl)zinc. Iodomethylzinc phenolates are valuable alternatives to the traditional Simmons–Smith reagents for cyclopropanation due to their ease of preparation, high reactivity toward unactivated olefins and good stability [\[2000AG\(E\)4539\]](#). For example, iodomethylzinc 2,4,6-trichlorophenoxide **279** reacts with cyclohexene to give bicyclo[4.1.0]heptane in 90% yield ([Equation \(105\)](#)). This reagent is compatible with other functional groups, including carboxylic esters ([Equation \(106\)](#)).



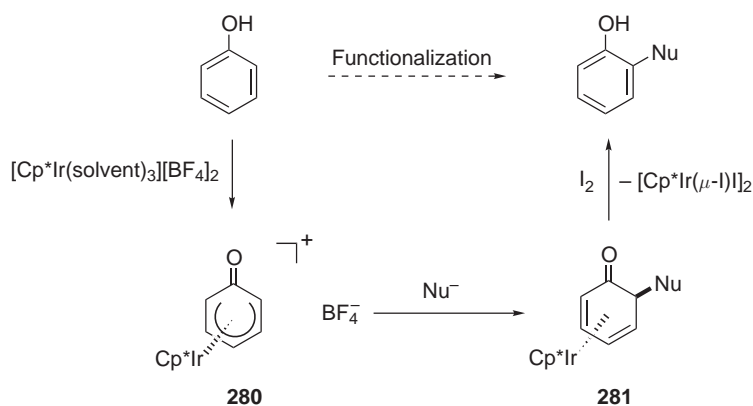
Scheme 72



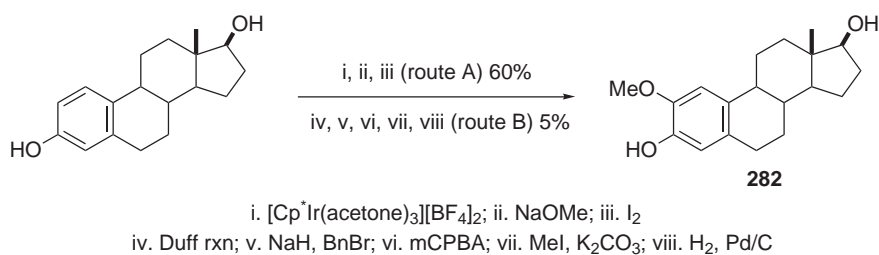
Amouri and co-workers have reported a procedure that allows systematic phenol functionalization by taking advantage of the unique reactivity of arene complexes of $\text{Cp}^*\text{Ir}^{2+}$ [\[1996OM5706\]](#). These (oxo- η^5 -dienyl)iridium complexes **280**, which are generated by treatment of a phenol with the iridium complex $(\text{Cp}^*\text{Ir}(\text{solvent})_3)(\text{HBF}_4)_2$, are susceptible to nucleophilic attack. Addition of a nucleophile gives stable η^4 -dienone **281**, which is then decomplexed from iridium under oxidative conditions to provide the *ortho*-substituted phenol and recyclable iridium complex $(\text{Cp}^*\text{Ir}(\mu\text{-I})_2)$ ([Scheme 73](#)). This method has been applied to the preparation of 2-methoxyestradiol **282**, an anticancer agent that possesses important physiological properties [\[1995JMC2041\]](#). 2-Methoxyestradiol is obtained from β -estradiol in 60% yield in three steps (route A) [\[1997OM1765\]](#), which compares favorably to a previously published route (route B) which requires five steps to afford the same compound in only 5% overall yield ([Scheme 74](#)).

Osmium complexes of phenols have been exploited for their synthetic use. The η^2 -phenol complex **283** is nucleophilic and participates in conjugate addition reactions with a variety of Michael acceptors preferentially at the C-4 position of the phenol ([Scheme 75](#)). The cyclohexadienone intermediate **284** is then rearomatized to complex **285** upon treatment with base, and subsequent decomplexation by heating gives the *para*-substituted phenol **286** [\[1997CRV1953\]](#).

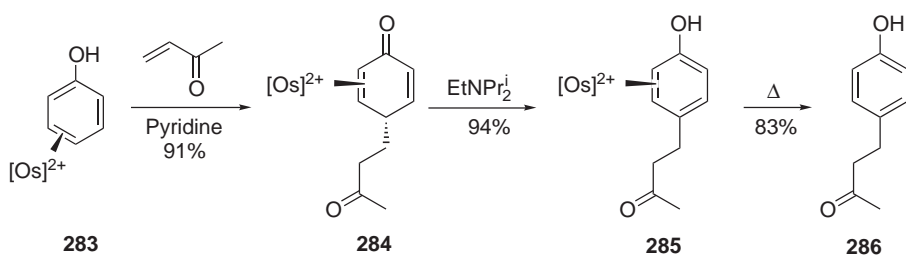
Silicon phenolates, commonly known as silyl ethers (ArOSiR_3), are in general stable to basic reagents, including organolithium reagents, Grignard reagents, lithium aluminum hydride, and phosphonium salts employed in the Wittig reaction. The ease of the introduction and the removal of silyl ethers make them popular choices of protecting groups for phenols [\[B-1999MI003\]](#). Silyl binaphtholates are converted into binaphthols under oxidative conditions; the silyl ethers in these compounds **287a** and **287b** serve to preorganize the system for regioselective oxidative coupling and provide binaphthol derivatives **288a** and **288b** in good yield ([Scheme 76](#)) [\[2002JOM\(661\)169\]](#).



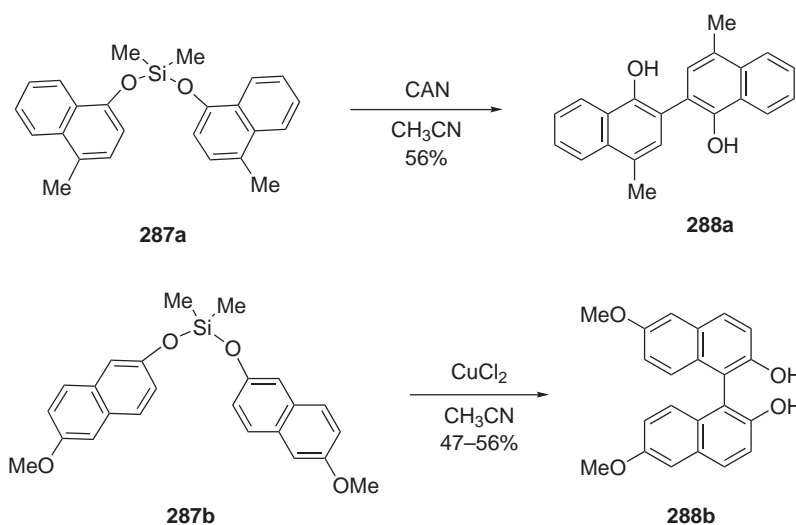
Scheme 73



Scheme 74



Scheme 75



Scheme 76

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 1982S85
 1982SC727
 1983TL979
 1984CSR441
 1984JOC1672
 1984TL4943
 1985JHC39
 1985JOC560
 1987JA2824
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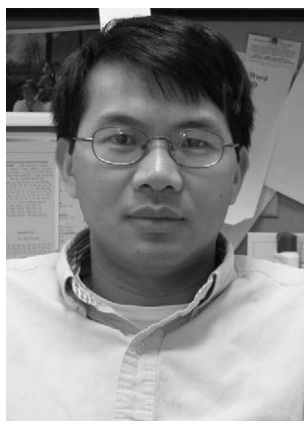
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2.14

Vinyl and Aryl Chalcogenides: Sulfur-, Selenium-, and Tellurium-based Functional Groups

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2.14.1 INTRODUCTION

This chapter describes the preparation of sulfur-, selenium- and tellurium-based functional groups attached to an sp^2 -carbon. The methods described here are often similar to those described for functional groups attached to sp^3 -carbon (see Chapters 2.03 and 2.04).

The material in each section is organized closely to that in COFGT (1995) <1995COFGT(2)705> with emphasis on the functionality of the starting materials rather than the mechanism of reaction. Wherever possible mechanistically similar transformations are placed in one subsection. New subsections including developments in sulfur–phosphorus and selen–phosphorus and sulfur–silicon compounds have been added. The main aim is to offer a comprehensive account of the variety of methods used so that a reader can choose the best one. Sometimes two or more references are given for the same reaction so that the experimental details can be found easily for every transformation.

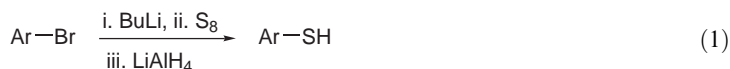
2.14.2 SULFUR-BASED FUNCTIONAL GROUPS ATTACHED TO AN sp^2 -CARBON

2.14.2.1 Arenethiols

Arenethiols are important precursors for other sulfur-containing compounds. A number of methods including aromatic nucleophilic substitution of aryl halides and aryl diazonium salts, reduction of diaryl disulfides, Herz reactions, and some others, are well known, and the literature up to 1995 was covered thoroughly by COFGT (1995) <1995COFGT(2)705>.

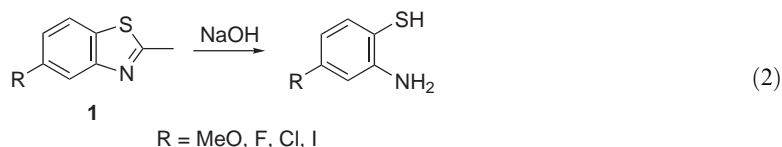
2.14.2.1.1 Arenethiols from aryl halides

The traditional substrates for arenethiol synthesis are aryl halides. Their reactions are well-described in COFGT (1995) <1995COFGT(2)705> and it is necessary to mention only a few modifications of this method. Aryl bromides are converted into arenethiols via the corresponding Grignard reagent <2000JMC1826, 2002CC1918> and by reaction with butyllithium followed by addition of elemental sulfur and finally LAH (Equation (1)) <2000CCC1939>. Yields in this case are comparable with the Grignard reagent modification (68%).



Aryl halides have also been effectively used to prepare arenethiols by nucleophilic substitution with (i) sodium sulfide <2000MI54, 2001JHC1153>, (ii) sodium hydrosulfide in DMF <2002BMCL791>, or (iii) a mixture of disodium disulfide and NaOH in ethanol <2002CPB922>.

Another useful synthetic approach is the transformation of 2-methylbenzothiazoles into *o*-aminobenzenethiols in aqueous NaOH <2002JMC2229>. In this method a free amino group is liberated together with a thiol group from the benzothiazole **1** (Equation (2)).



2.14.2.1.2 Arenethiols from phenols

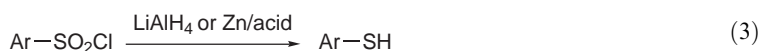
No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)705>.

2.14.2.1.3 Arenethiols from arylamines

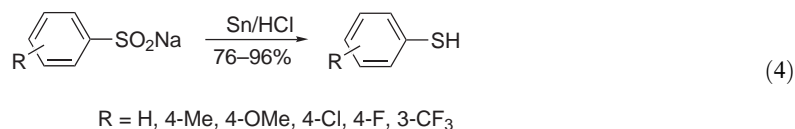
No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)705>.

2.14.2.1.4 Arenethiols by reduction

Arenesulfonic acids and their chlorides are attractive precursors of arenethiols because they are easily accessible from arenes by reaction with chlorosulfonic acid alone or mixed with phosphorus pentachloride (see Section 14.2.3.3) and COFGT (1995) <1995COFGT(2)705>. Arylsulfonyl chlorides are reduced by LAH in THF <2000AJC1> or by zinc in either sulfuric acid <2001IZV537> or chlorosulfonic and hydrochloric acids (Equation (3)) <2002SC2741>. Yields are not usually high.



Conversion of arenesulfonic acids into arenethiols has not been widely applied, although dimethyldichlorosilane is a useful reagent for this transformation <2002TL2145>. The structurally related, but less accessible, arenesulfinic acids in the form of their sodium salts react with tin in concentrated hydrochloric acid to give arenethiols in good yields (Equation (4)) <2001SC1355>.



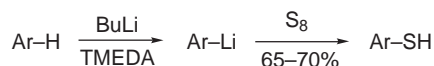
Reduction of disulfides has been widely cited in the earlier literature. New features include use of sodium borohydride <1999JMC3334, 2001JOC4504>, zinc in acetic acid <2000OL1843>, triphenylphosphine <2000JMC3566>, and tris(carboxyethyl)phosphine hydrochloride <2002BMC1263>. Much attention has been directed to catalysis of sodium borohydride reduction by zirconium <2000SC3905> or lithium chloride <2001IJC(B)622> which affords arenethiols in excellent yields (90–96%).

2.14.2.1.5 The Herz reaction

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)705>.

2.14.2.1.6 Arenethiols from arenes

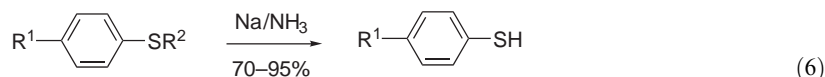
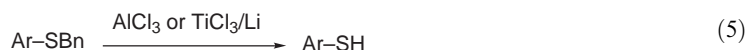
The transformation of arenes through their lithium derivatives into arenethiols is one of the modern synthetic routes. Lithium arenes are usually obtained by reaction of aromatic compounds with butyllithium in the presence of tetramethylethylenediamine [1,2-bis(dimethylamino)ethane] (TMEDA) followed by sulfuration with elemental sulfur (Scheme 1) <1999TL6571, 2000T2895, 2002OL3619>. Yields can reach 65–70%. In some cases two thiol groups can be introduced simultaneously but in different rings <1999EJ11715>.



Scheme 1

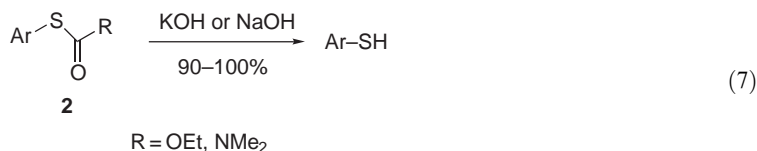
2.14.2.1.7 Arenethiols from arenesulfides

In general, cleavage of substituted aryl sulfides is an attractive synthetic approach involving new derivatives and reagents. A number of groups attached to sulfur atoms by carbon can be replaced by hydrogen. The benzyl group is easily removed by reaction with AlCl_3 at room temperature in benzene <2000CCC280, 2001EJ13119> or with TiCl_3 and lithium in THF <2001IJ(B)1007> with moderate to excellent yields (Equation (5)). Aryl alkyl sulfides can be dealkylated under more vigorous conditions. Sodium in liquid ammonia has frequently been used to remove methyl <1999MI1301, 2002JA11159>, ethyl <2000MI2603>, and isopropyl <2001H145> groups (Equation (6)).

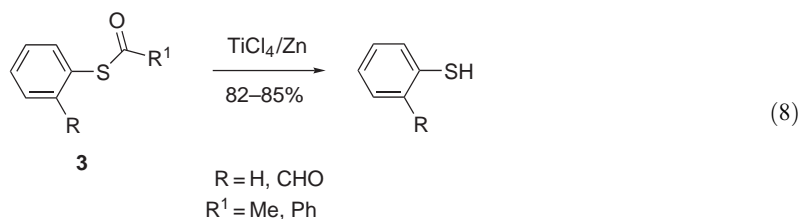


Demethylation of *S*-methylthioarenes can be realized by sodium thioalkoxides <2001JPC(B)9812, 2002JA11159> at temperatures above 100 °C in *N*-methylpyrrolidinone or DMF. The bulky *t*-butyl group is easily removed by heating in aqueous HCl at 80 °C <1999MI325>. The acetylmethoxy group is dealkylated by the action of sodium methoxide <2001MI85>.

t-Butoxycarbonyl aryl sulfides are converted effectively to arenethiols by reaction with TFAA <2000T9833> or with TiCl_4 and zinc <2001SL1956> in dichloromethane at room temperature. The similar and widely used ethoxythiocarbonyl group and its dimethylamide (e.g., **2**) are employed as protecting groups for arenethiols and can be removed by careful heating in alkaline aqueous alcohol solution at 60–65 °C for 2–3 h (Equation (7)) <2000JHC935, 2001OL651, 2002JA4642>.

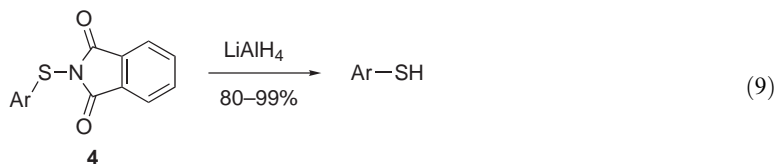


A similar procedure is hydrolysis of acyl or benzoyl sulfides **3** where alkali hydroxides are also used <1999MI1301, 2000OL1843>, but the best results have been obtained when a mixture of TiCl_4 and zinc is employed (Equation (8)) <2001SL1956>. In this case, both acetyl- and benzoyl aryl sulfides gave good yields of arenethiols under mild conditions (10 min at room temperature in CH_2Cl_2).

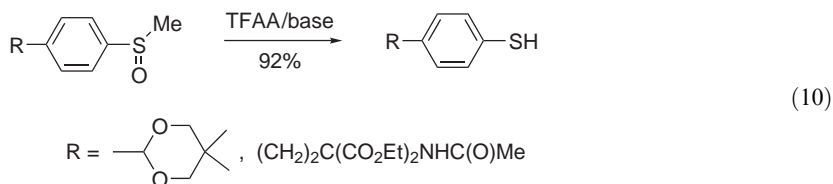


Various reducing agents can be used for the synthesis of arenethiols from arene thiocyanates. The yield depends on the nature of the reagent and can change from quantitative in the case of a mixture dithiothreitol and KH_2PO_4 in aqueous alcohol [\[2000JMC843\]](#) to slightly lower for $\text{NaSH}/\text{NaBH}_4$ [\[2000OL1069\]](#) and to 27% for LAH in THF [\[2000JMC3566\]](#).

The reduction of *S*-phthalimidoarenethiols **4** by LAH in THF is a useful procedure for the preparation of arenethiols [\[2002JOC2019\]](#), and the phthalimido group can be used as a protecting group (Equation (9)).



Trialkylsilyl derivatives can be easily hydrolyzed to arenethiols in acidic conditions [\[2002JA11159, 2000MI683\]](#). Another important development in this area is the recent synthesis of arenethiols by reaction of aryl methyl sulfoxides with TFAA and a base (triethylamine or 2,6-lutidine) (Equation (10)) [\[1999JOC8635, 2000JMC2946\]](#). Yields in this unusual method may be high.



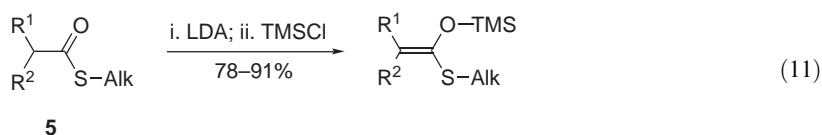
2.14.2.2 Vinyl and Aryl Sulfides and Their Higher-coordinated Derivatives

Various standard procedures are described for the synthesis of vinyl and aryl sulfides. The great number of references in the earlier literature [\[1995COFGT\(2\)705\]](#) and more recent studies demonstrate a permanent interest to these compounds.

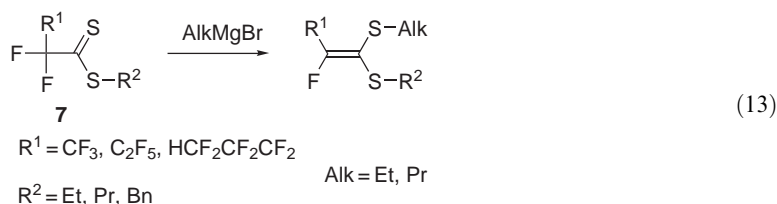
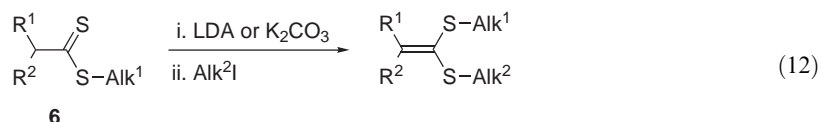
2.14.2.2.1 Vinyl sulfides

(i) Vinyl sulfides by enolization of thioic and dithioic esters

Thioic esters **5** can be converted to *o*-trimethylsilyl vinyl sulfides by reaction with a base and trimethylsilyl chloride (Equation (11)). Lithium diisopropylamide (LDA) is used more often [\[1997JOC6108, 2001CL1080, 2001JOC697\]](#) than lithium tetramethylpiperidine [\[1997CC1919\]](#). Yields may reach 90%.

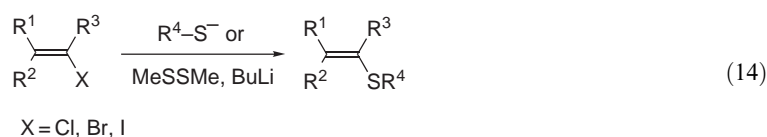


A synthetically equivalent enolization of dithioic esters **6** has been successfully achieved by action of a base (LDA in THF <1997AG(E)371, 1997CC1011> or K₂CO₃ in DMF <2002SC2369>) and an alkyl iodide (Equation (12)). Alkylmagnesium bromides were used for the transformation of α -fluoro-substituted dithioic esters **7** (Equation (13)) <1997TL4063>.



(ii) Vinyl sulfides from vinyl halides

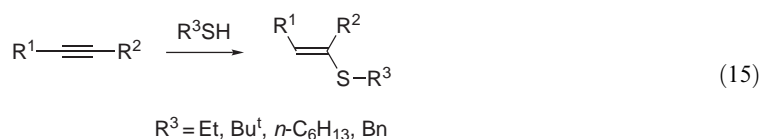
Another traditional synthetic approach is the transformation of vinyl halides (chloro <1995MI29, 1997S573>, bromo <1999JOC23>, or iodo <1997JFC141>) into vinyl sulfides by nucleophilic substitution (Equation (14)). Yields are usually moderate (48–58%) and mixtures of stereoisomers are often formed.



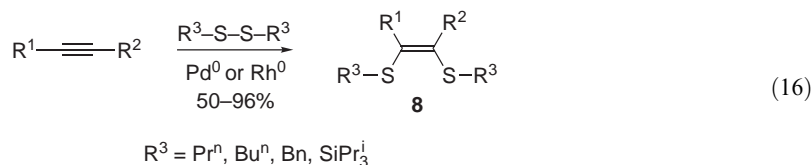
Dimethyldisulfane together with butyl- and *t*-butyllithium was found to be useful to substitute a bromo by a thio group <1997T1735, 1998T9529>.

(iii) Vinyl sulfides from alkynes

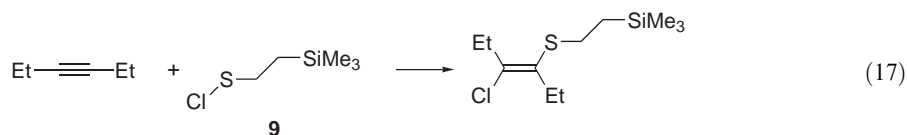
The addition of a thiol to an alkyne in the presence of various bases (KOH <1996T12677>, NaOEt <1997JA479>, and NaH <1998JOC7908>) provides an excellent synthesis of vinyl sulfides (Equation (15)). The reaction is significantly facilitated and the yield increased up to quantitative if electron-withdrawing groups, such as cyano or *p*-toluenesulfonyloxy, are attached to the triple bond <1999JOC6090, 1999ZOR1637>.



The coupling of alkynes with dialkyl- and bis(trialkylsilyl) disulfides can be effectively facilitated by transition metal catalysis (RhH(PPh₃)₄ <2001OL763>, Pd(PPh₃)₄ <2001T5739>), giving vinyl disulfides **8** with moderate-to-excellent yields (50–96%) (Equation (16)). (*Z*)-Isomers are exclusively formed in these reactions.

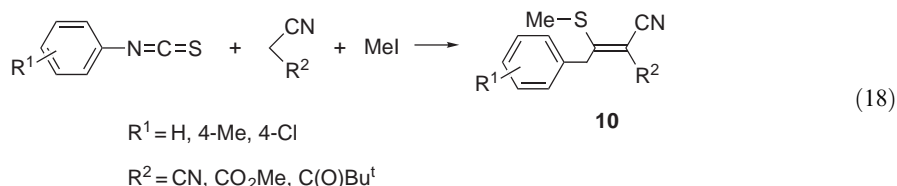


An interesting example of a mild and efficient *trans*-addition of a substituted sulfenyl chloride **9** to hex-3-yne was recently described (Equation (17)) <2001EJO1643>.

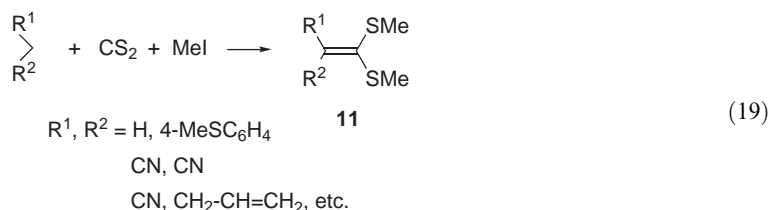


(iv) *Coupling reactions of arylisothiocyanates or CS₂ with compounds bearing an active methylene group*

A remarkable addition of arylisothiocyanates to compounds with an active methylene group followed by methyl iodide alkylation (Equation (18)) provides a useful procedure for vinyl sulfide **10** preparation <1996ZN(B)399, 1997ZN(B)125, 1997M933>.



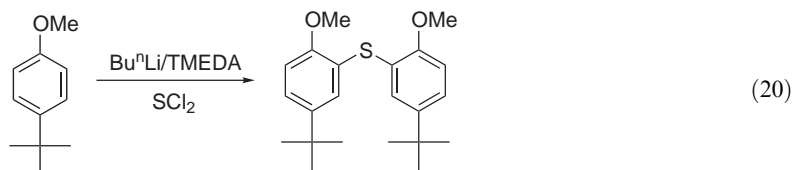
Compounds with active methylene groups can also serve as precursors for bis(methylthio)vinyl derivatives **11**. Reaction with carbon disulfide and sodium hydride followed by methyl iodide addition gave a number of vinyl bissulfides in high yield (Equation (19)) <1997CPB987, 1997JCS(P1)3285, 1999JCR(S)492, 1999JCS(P2)1265, 1999MI235>.



2.14.2.2.2 Aryl sulfides

(i) *Aryl sulfides from arenes*

Arenes can be converted into aryl sulfides using both electrophilic and nucleophilic sulfur reagents. Symmetrical aryl sulfides are prepared by the reaction of arenes with BuⁿLi and TMEDA followed by sulfur dichloride addition (Equation (20)) <1997JCR(M)556>.



A number of sulfur compounds **12** (aromatic and aliphatic) can act as a nucleophilic sulfur source (Equation (21)). Unsymmetrical diaryl sulfides and aryl alkyl sulfides have been synthesized in this way. The scope of this reaction is summarized in Table 1.

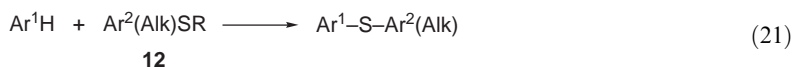
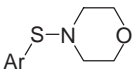
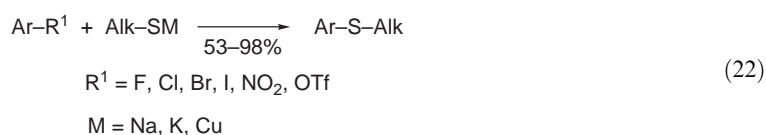


Table 1 Sulfur-containing compounds used for the preparation of aryl and alkyl aryl sulfides from arenes

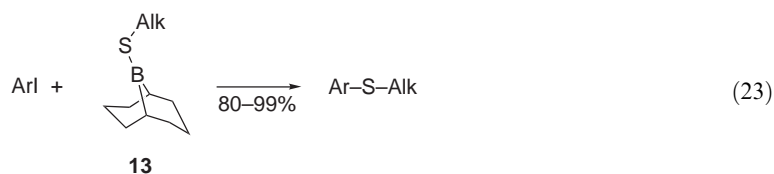
Sulfur substrate 12	Reaction conditions	Yield of sulfide (%)	References
ArSH	PhI(OCOCF ₃) ₂ , rt, 0.5 h	40–88	<1995JOC7144>
Alk—S—SO ₂ Me	0 °C, 0.5 h		<1995JOC8417>
Alk—S—S—Alk	Bu ⁿ Li, TMEDA, –78 °C to rt		<1995JA7261, 1996JHC409, 1996ACS305>
	Bu ^t Li, –78 °C to rt		<2001JOC474>
	Bu ^s Li, TMEDA, –78 °C to rt	90.5	<2000TL3559>
	AlCl ₃ , 100 °C, 4 h	15–22	<1997JOC7464>
	AlCl ₃ , 25 °C, 96 h	76	<2000JCS(P2)1803>
	AlCl ₃	73–77	<1995JCR(S)34>
	Montmorillonite K10, H ₂ SO ₄	23–90	<1997MI413>
	Electrochemical reaction, liq. SO ₂ , –15 °C, 3 h	53–99	<1999TL6357>
	SO ₃ , –78 °C to rt		<1995IZV324>
	POCl ₃ , rt, 6 h	37	<2000IZV178>
			
Ar—S—Cl	Hg(OAc) ₂ , AlBr ₃ , –20 °C, 5 h	70	<1995IZV324>

(ii) Aryl sulfides from aryl halides

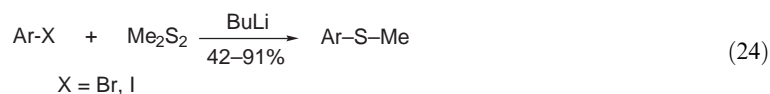
Nucleophilic substitution of aryl halides and related compounds with good leaving groups remains a useful procedure for aryl sulfide preparation. Aryl bromides <1996LA291, 1997JCS(P2)2271, 1997JOC7464, 1997TL5953>, fluorides and chlorides <1997JMC2017>, and iodides <2002OL2803> react with metal sulfides to yield unsymmetrical aryl alkyl sulfides (Equation (22)). Nitro <1995JCR(M)2050> and trifluoromethylcarboxy <1998JOC9606> groups were found to be excellent leaving groups.



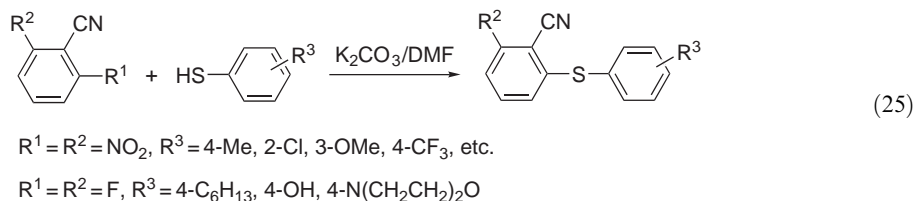
An interesting method for substitution of aryl iodides was found by Japanese authors: 9-alkylsulfanyl-9-borabicyclo[3.3.1]nonanes **13** were successfully used to give aryl alkyl sulfides in good yield (Equation (23)) <1996JOM225>.



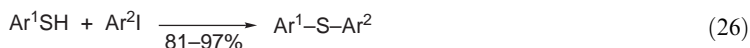
Aryl bromides and iodides have been effectively employed in a reaction with either BuⁿLi <1997JOC7464, 1999JOC3190> or Bu^tLi <2001JOC474> and dimethyl disulfide to prepare aryl methyl sulfides (Equation (24)).

*(iii) Aryl sulfides from arenethiols*

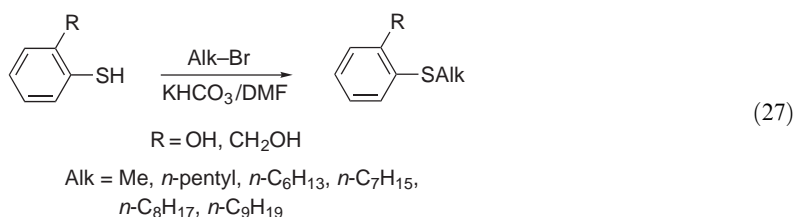
Another useful approach is the reaction of arenethiols with alkyl and aryl halides and related compounds. Nitro and fluoro groups are easily substituted, especially if activated by electron-withdrawing substituents (Equation (25)) <1995JMC3608>.



4-Acetylsulfomethoxybenzene can be converted into an aryl sulfide by reaction with benzenethiol in the presence of a catalyst (zinc and $\text{NiCl}_2\cdot\text{dppf}$ in DMF), but the yield (32%) is not high <1995JOC6895>. Aryl iodides have been shown to be useful compounds in the synthesis of arenesulfides: a mixture of copper(I) iodide, 2,9-dimethyl-1,10-phenanthroline, and sodium *t*-butoxide was used to promote this reaction (Equation (26)) <2002OL2803>.



The only examples of the synthesis of aryl alkyl sulfides from arenethiols and alkyl halides found for the period reviewed were by reaction of alkyl bromides in DMF with KHCO_3 (Equation (27)) <1998JMC4800>.

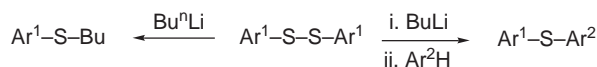


Arenethiols react with arenediazonium salts **14** to produce unsymmetrical diaryl sulfides (Equation (28)) <1995TL8035, 1996JCS(P1)555, 1999TA1051>. Yields may vary from moderate (35%) to high (70%). Alkyl sulfides may also be used in this procedure to give aryl alkyl sulfides <1997CC1537, 2000T165>.



(iv) Aryl sulfides from aryl disulfides

The breaking of the S—S bond in aryl disulfides with further addition of aryl or alkyl groups is an attractive synthetic route for aryl sulfide preparation. Bu^nLi <2001S2259> or Bu^sLi <2001EJO2435> with TMEDA in a mixture of hexane and THF may be used for the synthesis of unsymmetrical aryl sulfides (Scheme 2). Bu^nLi itself may give aryl butyl sulfides <1995T12239>. Grignard reagents also react with aryl disulfides to yield unsymmetrical aryl sulfides <1995JCS(P1)2615>. A number of other reagents and procedures have been used for the conversion of aryl disulfides to aryl sulfides (Table 2).



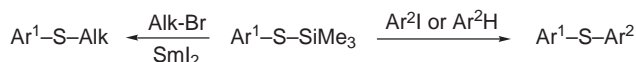
Scheme 2

(v) Aryl sulfides from *S*-substituted arenethiols

Various *S*-substituted arene thiols have been used for aryl sulfide synthesis. Trimethylsilyl aryl sulfides (Scheme 3) give aryl alkyl sulfides in reactions with alkyl bromides in the presence of samarium(II) iodide in THF <1998JCR(S)48>, whereas they give unsymmetrical diaryl sulfides in reactions with either arenes and phenyliodine(III) bis(trifluoroacetate) (yield 61%)

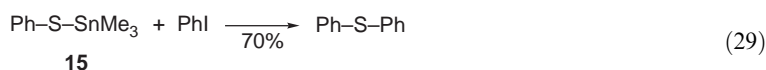
Table 2 Reagents and reaction conditions used for the preparation of diaryl and alkyl aryl sulfides from aryl disulfides

Reagents	Reaction conditions	Yield of sulfide (%)	References
Alkyl bromides	Hydrazine hydrate, 80–90 °C, 2 h		<1997ZOB866>
Alkyl bromides	Zn, AlCl ₃ , 65 °C, 16 h	99	<2000JCR(S)350>
Anilines	Nitric oxide, rt, 18 h		<1996TL4165>
Arenes	SbCl ₅ , 25 °C, 2 h	87–97	<1997JCS(P2)2301>
	H ₂ SO ₄ , TFAA, 25 °C, 2 h	12–85	<1997JCS(P2)2301>
Aryl iodides	Bu ⁿ Li, –78 °C to rt	82	<2001HAC392>

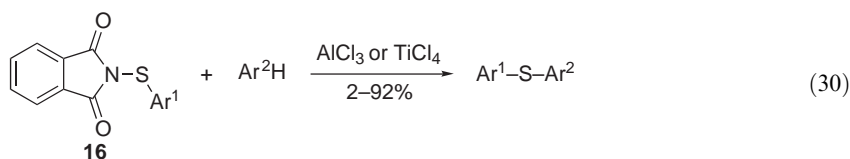
**Scheme 3**

<1995JOC7144> or aryl iodides, K₃PO₄ and palladium(II) dichloro(1,1'-bis(diphenylphosphino)-ferrocene) (yield 78%) <1996JOM225>.

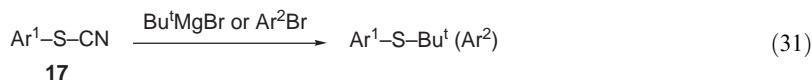
Trimethylstannyl phenyl sulfide **15** may be used in a similar reaction to produce phenyl sulfide but with a lower yield (70%) (Equation (29)) <1996JOM225>.



S-Phthalimidoarenethiols **16** react with arenes to give unsymmetrical aryl sulfides (Equation (30)). The presence and nature of a Lewis acid (AlCl₃ or TiCl₄) is essential for this process and may increase the yield of aryl sulfide significantly <1999CPB980>.



The synthesis of aryl alkyl sulfides <1995TL4361> and unsymmetrical aryl sulfides <1996JOC7677> may be achieved from arene thiocyanates (Equation (31)). The reaction conditions are different in both cases and the yields are moderate (up to 38%)



(vi) *Aryl sulfides by reduction of sulfoxides and sulfones*

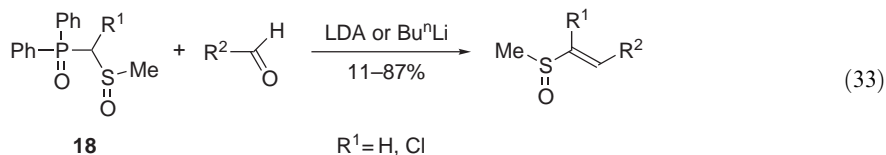
Few new methods have been used for the reduction of sulfoxides and sulfones. The reaction of samarium in aqueous alcohol solution using ultrasound irradiation <2001SL854> and indium with bis(cyclopentadienyl)titanium(IV) dichloride in THF <2002SC63> is effective for aryl alkyl sulfoxide reduction (yields 81–92%) (Equation (32)). Trichlorosilane reacts with aryl sulfones to yield aryl sulfides <1995TL8035>.



2.14.2.2.3 Vinyl sulfoxides

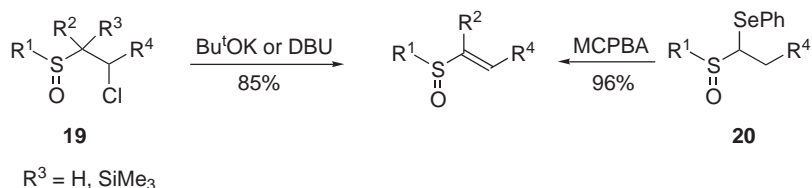
(i) Vinyl sulfoxides from Wittig–Horner-type reagents

Diphenylphosphine oxide reagents **18** are useful for vinyl sulfoxide preparation. (*Z*)-Isomers are usually formed if LDA is used <1995TL781, 1997T10527>, but when BuⁿLi is employed a mixture of (*E*)- and (*Z*)-isomers is obtained (Equation 33) <2000EJO2787>.



(ii) Vinyl sulfoxides by dehydrochlorination of β -chloroethyl sulfoxides

Elimination of hydrochloric acid or trimethylsilylchloride is an attractive synthetic route for vinyl sulfoxides, because the reaction is stereospecific. β -Chloroethyl sulfoxides **19** can be dehydrochlorinated by the action of Bu^tOK in THF (Scheme 4) <1997CPB778>. β -Hydroxyethyl sulfoxides are converted to vinyl sulfoxides via β -chloroethyl sulfoxides by reaction with SOCl₂ and triethylamine and then with DBU <1995JCS(P1)847>. Elimination of trimethylsilyl chloride proceeds smoothly at –78 °C <2001EJO1643> but starting compounds are not readily available. A mild and effective synthesis of vinyl sulfoxides from α -phenylselenosulfoxides **20**, employing oxidation by MCPBA, was developed by Japanese authors <2002JOC640>.



Scheme 4

(iii) Vinyl sulfoxides by oxidation of vinyl sulfides

A standard synthetic procedure for vinyl sulfoxides is the oxidation of vinyl sulfides (Equation (34)). A number of the methods developed in recent years are shown in Table 3.

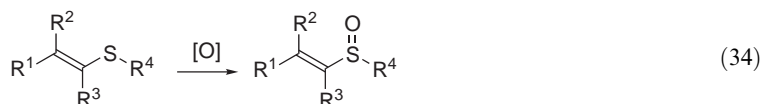


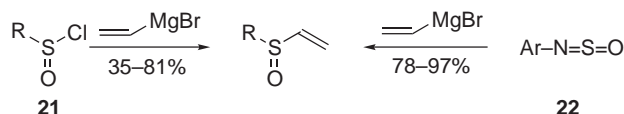
Table 3 Oxidation of vinyl sulfides into vinyl sulfoxides

Reagent	Yield (%)	References
MCPBA		<1995H249>
Perfluoro- <i>cis</i> -2-butyl-3-propyloxaziridine	82–98	<1996S399>
MeCO ₃ H	35	<1996JA7492>
HNO ₃ /H ₂ SO ₄	65–87	<1999S231>
Bu ^t OOH	69	<1999ZOR1785>
H ₂ O ₂	62	<1999ZOR1785>

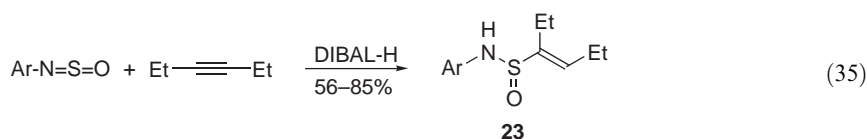
(iv) Miscellaneous methods

Vinylmagnesium bromide was found to be a useful reagent in the synthesis of vinyl sulfoxides. It reacts with sulfinyl chlorides **21** in THF at low temperature <1996JA7492, 1998JA8011> and

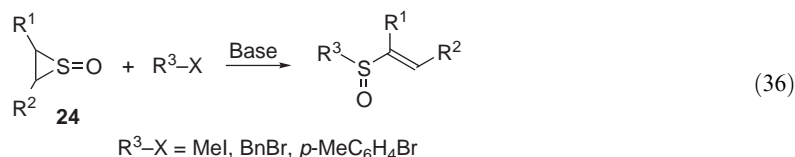
with arylsulfinylamines **22** <1996BSF329> to give the desired compounds, usually in high yields (Scheme 5). Arylsulfinylamines may also be used in a reaction with alkynes to produce *S*-imino-vinyl sulfoxides **23** in moderate-to-excellent yields (Equation (35)) <1996BSF329>.



Scheme 5



The reaction of thiirane-1-oxides **24** with benzyl and alkyl halides is an attractive route to vinyl sulfoxides. Various bases have been used for this transformation, including LDA, LiN(SiMe₃)₂, NaN(SiMe₃)₂, and KN(SiMe₃)₂ (Equation (36)) <1995JA184>. The reaction is not stereospecific and often leads to mixtures of isomers.



2.14.2.2.4 Aryl sulfoxides

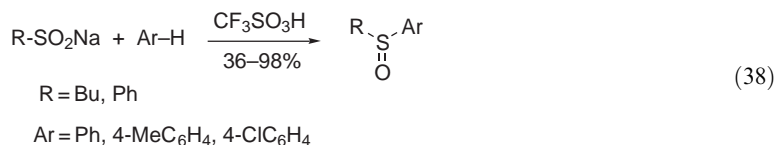
Aryl sulfoxides are important reagents for asymmetric synthesis. There are many methods for their preparation, but not all allow synthesis of enantiomerically pure sulfoxides. The most widely used procedure is oxidation of the corresponding aryl sulfides (Equations (37)). New oxidation methods are presented in Table 4.



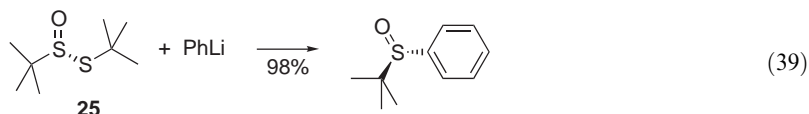
Table 4 Synthesis of aryl sulfoxides via oxidation of aryl sulfides

Asymmetric oxidation			Nonasymmetric oxidation		
Reagents	Yield (%)	References	Reagents	Yield (%)	References
Ti(OPr ⁱ) ₄ , (R,R)-DET, cumene hydroperoxide Bu ^t OOH,	51 67–94	<1995JOC8086> <2000JOC2843>	MCPBA NaIO ₄ H ₂ O ₂ /V ₂ O ₅ MeCO ₃ H NaClO ₂ /Al ₂ O ₃ , Mn(acac) ₃	83 70 29 79	<1995JMC4670> <1995MI2974> <1995IZV2241> <1996SC331>
VO(acac) ₂ H ₂ O ₂ 1,1,1-trifluoro- acetone	85 90	<1996JCS(P1)333> <1997SC441> <2001BMCL501>		80 67	<1996JCS(P1)2693> <1996JMC4181>
			Oxone, wet alumina K ₂ S ₂ O ₈ , AcOH PhI(OH)(OTs) H ₂ O ₂ /TiCl ₃ H ₂ O ₂ /TFA	 92 93 83 68	 <1996JMC3929> <1997SC1315> <1998JOC4256> <2002S1917> <2000JMC4160>

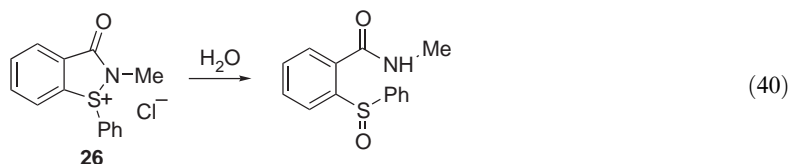
Other methods described since 1995 give mostly mixtures of stereoisomers. Alkylation and arylation of sulfinic acids and their derivatives is an attractive route for aryl sulfoxides. Sodium salts of butyl and phenyl sulfinic acids react with arenes in the presence of trifluoromethanesulfonic acid to yield unsymmetrical aryl sulfoxides (Equation (38)) <1996CC2099>.



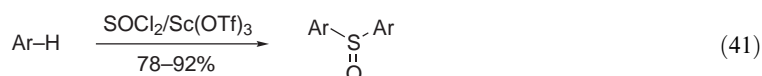
Sulfinic esters can also be converted into aryl sulfoxides by the action of Grignard reagents <1996TL8387>, Bu^tLi <1997JOC857>, or aryl bromide/Bu^tLi <1998TA3797>. An effective procedure is reaction of the *t*-butanethiosulfinate **25** and phenyllithium in THF at low temperature <1998JA8011>. This reaction was found to be completely stereospecific (Equation (39)). Arylsulfinyl chlorides react with arenes in the presence of AlCl₃ to afford aryl sulfoxides <1997JOC5526>.



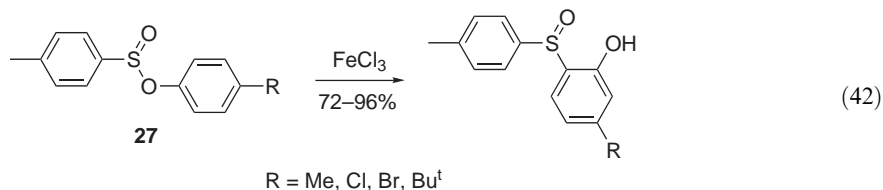
Hydrolysis of isothiazolone salts **26** is an easy and efficient method to prepare diaryl sulfoxides with various substituents in both rings (Equation (40)) <2001JCS(P2)339, 2001TA745>. Yields vary from moderate to excellent.



Lithium sulfenylarenes are known to be alkylated with methyl and ethyl halides into aryl alkyl sulfoxides <1999MI381>. An important development in the synthesis of symmetrical aryl sulfoxides is the recently discovered transformation of arenes with SOCl₂ in the presence of scandium triflate (Equation (41)) <2002SL784>. Yields are high.



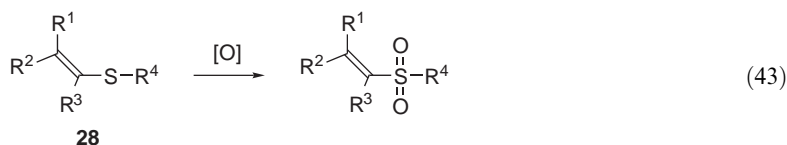
Finally, a remarkable rearrangement of *p*-tolylsulfinic aryl esters **27** with the help of FeCl₃ in dichloromethane yields diaryl sulfoxides in good yield (Equation (42)) (72–96%) <2001TL8119>.



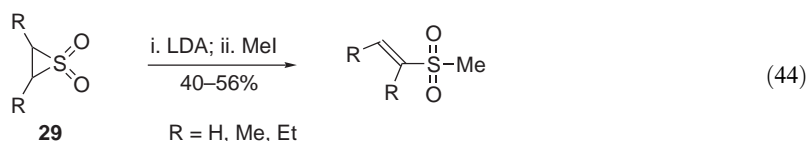
2.14.2.2.5 Vinyl and aryl sulfones

(i) Vinyl sulfones

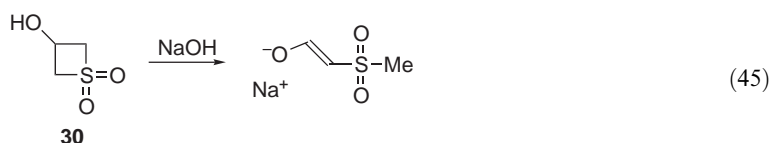
Vinyl sulfones can be prepared by a number of methods. The most widely used route is oxidation of corresponding vinyl sulfides **28** (Equation (43)). Standard reagents have been used in recent years, including 3-chloroperoxybenzoic acid (MCPBA) (yield 83%) <1998S39>, peracetic acid (yield 65%) <1998T487>, and oxone (yield 90%) <1996JCS(P1)2803>.



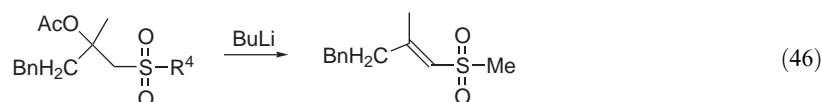
Ring opening of thiirane 1,1-oxides and 1,1-dioxothietane is new and has become a prominent procedure since these compounds became available. Treatment of thiirane 1,1-dioxides **29** with LDA followed by addition of methyl iodide leads to methyl vinyl sulfones (Equation (44)) <1997JCS(P1)323>. The reaction is stereoselective and only (*E*)-isomers are formed.



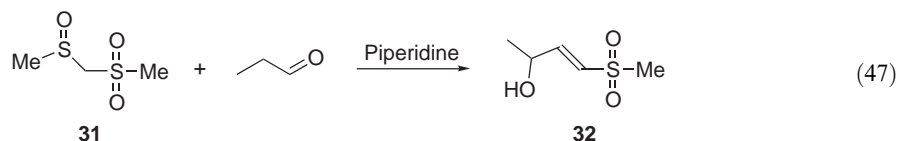
1,1-Dioxo-thietan-3-ol **30** was easily hydrolyzed into 3-hydroxyvinyl methyl sulfone (Equation (45)) <1997JCS(P2)425>.



The high acidity of protons α to a sulfone group permits the preparation of vinyl sulfones via elimination of acetic acid, for example (Equation (46)) <1996HCA961>.

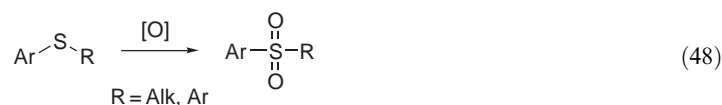


Methanesulfinylmethanesulfonylmethane **31** reacts with propionaldehyde to yield the α -hydroxy-vinyl sulfone **32** (Equation (47)) <1997BCJ3091>.



(ii) Aryl sulfones

Oxidation of aryl sulfides is the most obvious route for aryl sulfone preparation (Equation (48)). Table 5 lists a number of recently used oxidants.



Aryl sulfoxides can be transformed to the corresponding sulfones by the action of sodium hypochlorite in MeCN (yield 95%) <1996OPP234>.

The Friedel–Crafts sulfonylation of arenes has become a useful procedure for the synthesis of both diaryl and aryl alkyl sulfones (Equation (49)). New developments in this area are connected with the use of new catalysts which improve the yields. The synthesis of new aryl sulfones is summarized in Table 6.

Table 5 Oxidation of aryl sulfides into aryl sulfones

<i>Reagent</i>	<i>Reaction conditions</i>	<i>Yield (%)</i>	<i>References</i>
Oxone	MeOH, THF, H ₂ O, 4 h	54–99	<1995JMC4570>
Magnesium monoperoxyphthalate			<1996BMCL87>
Peracetic acid	AcOH, 60 °C, 2 h		<1997CPB987>
Sodium perborate	AcOH, rt, 3 h	82	<1996H2747>
CrO ₃ , H ₂ SO ₄	rt, 2 h	72	<1998TL1889>
OsO ₄	H ₂ O, acetone	95	<1998BMCL2777>
H ₂ O ₂	Na ₂ WO ₄ , H ₂ SO ₄ , 50 °C, 3 h	86	<1999JMC1274>

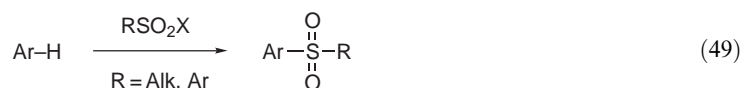
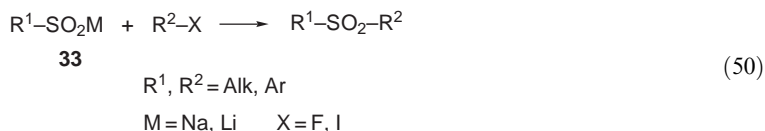


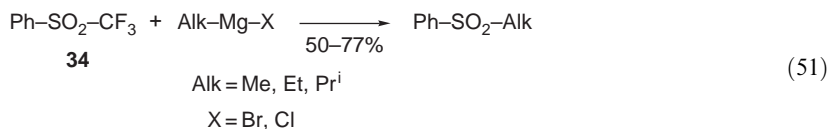
Table 6 Friedel–Crafts sulfonylation of arenes

RSO_2X	Reaction conditions	Yield (%)	References
(MeSO ₂) ₂ O	In(OTf) ₃		<2001SL830>
MeSO ₂ F	SbF ₅ , 35 °C, 3 h	14–74	<1998ZOR1644>
MeSO ₃ H	SOCl ₂ , CF ₃ SO ₃ H, 125 °C, 3 h	65	<2000EJO2253>
(MeSO ₂) ₂ O	CF ₃ SO ₃ H, B(CF ₃ SO ₃) ₃ , 20 °C, 4 h	61–91	<1998ZOR1644>
ArSO ₃ H	Fe(3+)-montmorillonite, 138 °C, 24 h	52–68	<2000JCS(P1)2689>
	Nafion-H, Δ, 8 h	78–80	<2001CC1696>
ArSO ₂ Cl	Zn, toluene, 15 s, microwave irradiation	70–77	<2001SC1065>
	In(OTf) ₃ , 120 °C, 2 h	71	<2001SL830>
	Sn(OTf) ₂ , 120 °C, 8 h	40	<2001T241>
	FeCl ₃ , 120 °C, 1 min, microwave irradiation		<2001JOC421>
	LiClO ₄ , Δ, 5 h	84	<2002SL735>
	AlCl ₃ , Δ, 15 min	71–73	<2001IJC(B)237>

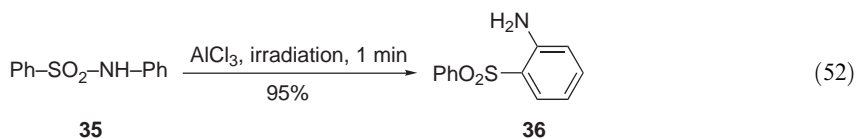
Another desirable approach is alkylation or arylation of sulfinic acids. Both alkylsulfinic [<1997JMC1619>](#) and arylsulfinic acids in the form of their sodium or lithium salts [33](#) [<1997JMC2017, 1999MI381>](#) have been successfully transformed into aryl sulfones ([Equation \(50\)](#)).

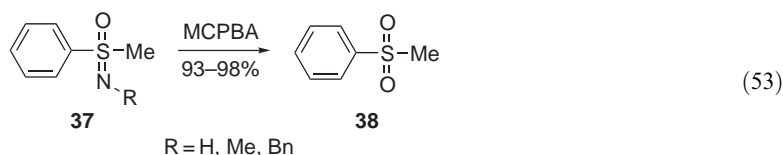


Phenyl trifluoromethyl sulfone **34** reacts with Grignard reagents to yield phenyl alkyl sulfones (Equation (51)) <2001TL2281>.



N-Phenylbenzenesulfonamide **35** can be efficiently converted to 2-benzenesulfonyl-aniline **36** by irradiation in the presence of AlCl₃ (Equation (52)) <2000JCR(S)200>. *S*-Methyl-*S*-phenylsulfoximides **37** are oxidized by MCPBA to methyl phenyl sulfone **38** (Equation (53)) <2000EJO1457>.





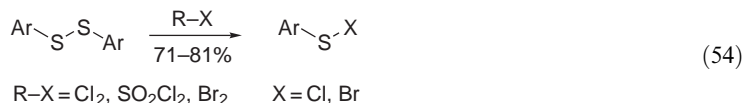
2.14.2.3 Vinyl and Arenesulfonyl Halides and Their Higher-coordinated Derivatives

Arenesulfonyl halides and their higher coordinated derivatives were discussed in detail in COFGT (1995), because they are widely used as reagents in organic synthesis. Vinylsulfonyl halides were also described in COFGT (1995).

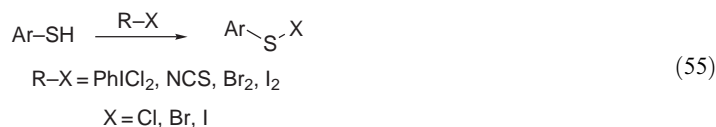
2.14.2.3.1 Arenesulfonyl halides

The most attention has been paid to chlorides. Arenesulfonyl bromides have been prepared using similar procedures. The fluorides and iodides have received little attention in recent years.

The traditional substrates for the synthesis of arenesulfonyl halides are diaryl disulfides (Equation (54)). The chlorides can be prepared by reaction with chlorine <1996JOC1533, 1998SC893> or sulfonyl chloride <1996JA4276, 1996JCS(P1)359>, and bromides by reaction with bromine <1996JOC1533>. Iodine catalysis is essential in this reaction.



Arenethiols are also convenient starting materials for arenesulfonyl halide preparation. The chlorides were synthesized by reaction with *N*-chlorosuccinimide <1997TL8573> or iodobenzene dichloride (Equation (55)) <1998JA352>. The bromides <1996H2567> and iodides <1998CC1915> are prepared by reaction with the corresponding halogen.



Other methods are not widely used. Aryl benzyl sulfides have been found to be useful for arenesulfonyl chloride <1999JOC6182> and arenesulfonyl bromide <1997DOK777> preparation. Arenesulfonyl chlorides can be synthesized from *S*-acetylenethiols <1996JOC1702>, sulfenate derivatives <1996TL679>, and hydroxysulfanylarenes <2000EJI921>.

2.14.2.3.2 Arenesulfonyl halides

Chlorides are better known than other arenesulfonyl halides. Mainly thionyl chloride and sulfonyl chloride have been used for their synthesis from a number of substrates including arenes, arenethiols, diaryl disulfides, arenesulfinic acids, and aryl sulfoxides. Recent arenesulfonyl chloride preparations are presented in Table 7.

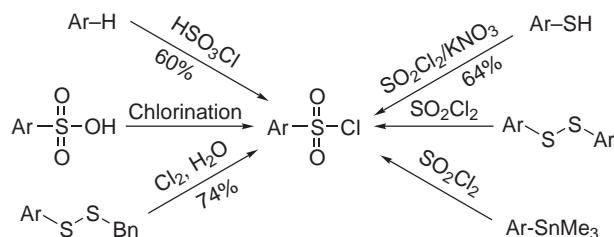
2.14.2.3.3 Vinyl and arenesulfonyl halides

No new data for vinylsulfonyl halides has been reported since the publication of COFGT (1995) <1995COFGT(2)705>.

Table 7 Synthesis of arenesulfinyl chlorides

$\text{Ar}-\text{S}(=\text{O})\text{Cl}$				
Substrate	Reagent	Reaction conditions	Yield (%)	References
Ar-H	SOCl ₂	Montmorillonite K-10 clay, CHCl ₃ , 50 °C, 2 h	68–87	<2001SL1573>
Ar-SH	SO ₂ Cl ₂	AcOH, toluene, Δ, 18 h		<1997JMC1018>
Ar-S-S-Ar	SO ₂ Cl ₂			<1997JMC1018>
Ar ¹ -S(O)-S-Ar ²	Ph-S-Cl	CDCl ₃ , -10 °C	95	<1996TL9101>
Ar-SO ₂ H	SOCl ₂	30 °C, 1 h		<1995PHA344>
	SOCl ₂	Δ, 1 h		<1995TA1941>
	SOCl ₂	DMF, Δ, 35 h		<1995JCS(P1)2615>
ArS(O)Alk	SO ₂ Cl ₂	CH ₂ Cl ₂ , -78–20 °C, 3.5 h		<2001EJO1643>

Chlorides are the most well known of the arenesulfonyl halides. They can be prepared by a number of methods (Scheme 6). These are given as follows:


Scheme 6

(i) electrophilic aromatic substitution of arenes with chlorosulfonic acid <1995BSF624, 1995EJM403, 1995JA7572, 1998JMC5198>;

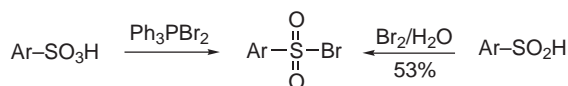
(ii) chlorination of arenesulfonic acids with chlorosulfonic acid <1995JMC1344>, phosphorus oxychloride <1996TL3639>, or *N*-chlorosuccinimide <2001HCA3667>;

(iii) chlorination of arenesulfonyl amides with phosphorus pentachloride <1998JMC5198>;

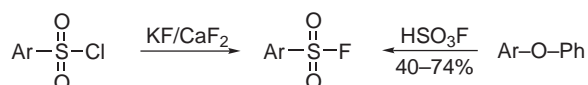
(iv) reaction of arenethiols, diaryl disulfides <1998BMC1447>, and aryl trimethyl stannates <1995CB1195> with sulfonyl chloride; and

(v) reaction of *S*-benzylarenes with chlorine and water <1996CJC1638>.

Arenesulfonyl bromides are available from the reaction of arenesulfonic acids with Ph₃P·Br₂ complex <1998S423> or from arenesulfinic acids and bromine water (Scheme 7) <1999TL7285>.


Scheme 7

The fluoride analogs are synthesized by halogen exchange with the chlorides <2001TL4605> or by a novel method, developed by Russian authors, that involves reaction of phenolic esters with fluorosulfonic acid (Scheme 8) <1995ZOR1197>.

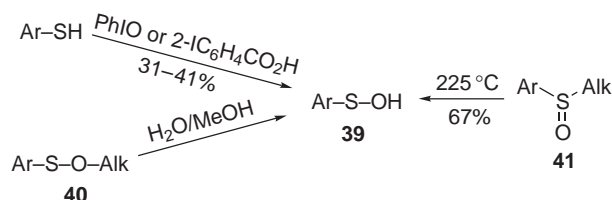

Scheme 8

2.14.2.4 Arenesulfenic, Arenesulfinic, and Vinyl- and Arenesulfonic Acids

The availability and utility of sulfenic, sulfinic, and sulfonic acids are quite different. Arenesulfenic acids are hardly available, whereas arenesulfinic and arenesulfonic acids are common. For vinyl derivatives, only sulfonic acids are known.

2.14.2.4.1 Arenesulfenic acids

Arenesulfenic acids **39** are still rare compounds. Their preparation by oxidation of arenethiols with PhIO <1997JA1460> or 2-iodosobenzoic acid <1997MI325>, by hydrolysis of arenesulfenates **40** <1995BCJ211> or by pyrolysis of *o,o*-disubstituted aryl alkyl sulfoxides **41** <1997JA1460> has been reported (Scheme 9).

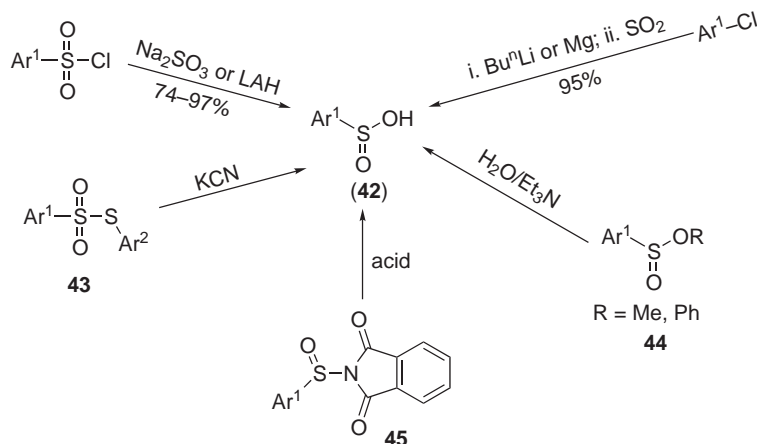


Scheme 9

2.14.2.4.2 Arenesulfinic acids

The reduction of readily available arenesulfonyl chlorides is an attractive route to arenesulfinic acids **42**; reducing agents such as sodium sulfite in aqueous NaOH <1997JMC2017, 1998ZOR455, 1998ZOR1214, 2000JFC85> and LAH in Et_2O have been used (Scheme 10). Yields, as a rule, are excellent.

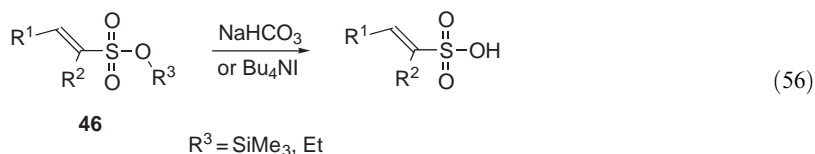
Another desirable approach to arenesulfinic acids is the reaction of *S*-aryl arylthiosulfonic esters **43** with potassium cyanide (Scheme 10) <1999SC3289>. Arenesulfinic acids were isolated as their potassium salts because the acids are not particularly stable. Other routes are (i) from aryl halides via metallation with Bu^nLi <1996T599, 1999JMC3572> or via Grignard reagents <2001T8779> followed by reaction with sulfur dioxide and (ii) from benzenesulfinic esters **44** <1996BCJ3281> or *N*-(arene-4-sulfinyl)phthalimides **45** <2001JPO224> via hydrolysis with water and triethylamine or dilute acid, respectively (Scheme 10).



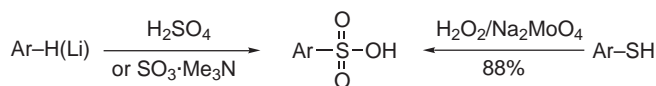
Scheme 10

2.14.2.4.3 Vinyl- and arenesulfonic acids

Vinylsulfonic acids can be synthesized by hydrolysis of their trimethylsilyl <1995CB575> or alkyl esters <2001BMCL313> **46** with NaHCO₃ in water or Bu₄NI in acetone (Equation (56)).



Two standard approaches to arenesulfonic acids have been developed in recent years. These are sulfonylation of arenes by sulfuric acid <1996JOC6814> or phenyllithium by sulfur trioxide–trimethylamine complex <1996JOC1530> and oxidation of arenethiols by hydrogen peroxide with Na₂MoO₄ (Scheme 11) <1997JA5286>.



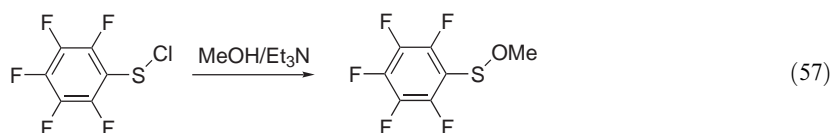
Scheme 11

2.14.2.5 Arenesulfenates, Arenesulfinates, and Vinyl- and Arenesulfonates

Arenesulfenates are rare compounds. In contrast, arenesulfinates and arenesulfonates are important synthetic intermediates and can be prepared by a number of methods. Vinylsulfonates are of interest as dienophiles although their preparation is not well developed.

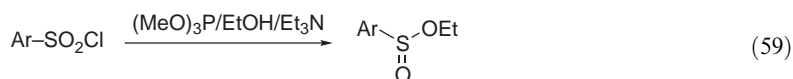
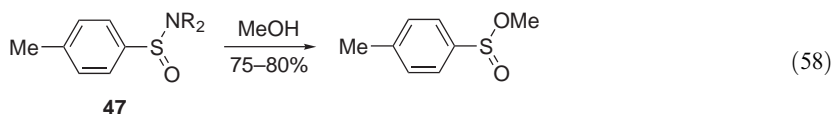
2.14.2.5.1 Arenesulfenates

The only method described in the period of review is the reaction of an arenesulfonyl chloride with methanol and triethylamine (Equation (57) <1998SC893>).

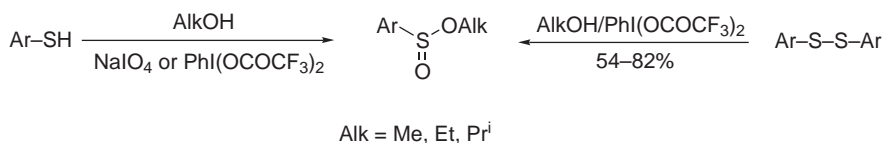


2.14.2.5.2 Arenesulfinates

Electrochemical esterification of sulfinylamides **47** to arenesulfinates by methanol is a new and useful procedure (Equation (58)) <2002OL1763>. Readily available arenesulfonyl chlorides can also be precursors for arenesulfinates. Trimethyl phosphite reduction in the presence of ethanol and triethylamine smoothly yields the target compounds (Equation (59)) <1999JOC5472>.

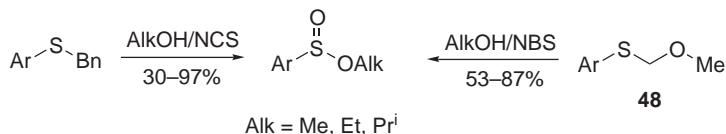


Oxidation of arenethiols by either aqueous sodium periodate <1996JCS(P1)691> or phenyliodoso-bis(trifluoroacetate) <1997SC1321>, and oxidation of diaryl disulfides by the latter reagent in the presence of an alcohol <1997SC1321>, are useful procedures (Scheme 12).



Scheme 12

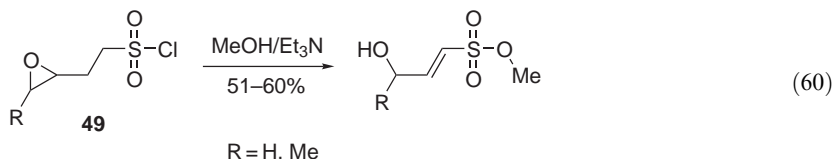
Oxidative alkylation of aryl benzyl sulfides with *N*-chlorosuccinimide <1996JOC9289> and aryl methoxymethyl sulfides **48** with *N*-bromosuccinimide <1995SC2871> has been effectively used to prepare arenesulfonates (Scheme 13).



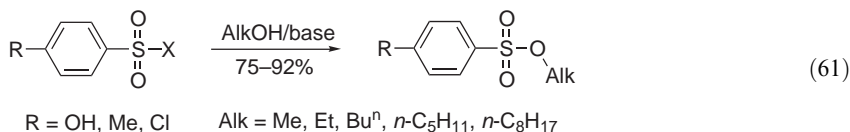
Scheme 13

2.14.2.5.3 Vinyl- and arenesulfonates

The traditional synthesis of vinyl sulfonates by alcoholysis of the corresponding sulfochlorides has been developed by using oxiranylmethanesulfonyl chlorides **49**. In this procedure sulfonate and vinyl groups are formed simultaneously (Equation (60)) <1998SL1411>.



The classical method for arylsulfonic acid ester preparation is alcoholysis of arylsulfonic acids and their chloro- and fluoroanhydrides (Equation (61)). Pyridine can be used as base in this transformation for sulfonyl chlorides <2000MI1842>; *n*-butyllithium and lithium 2,2,6,6-tetramethylpiperidine are used for sulfonyl fluorides <1996JOC1392> and Fe(3+)-exchanged montmorillonite clay for sulfonic acids <2000T7291>.



2.14.2.6 RSOX Functions

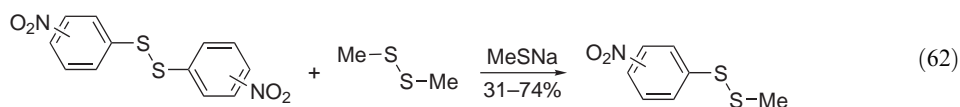
The reader is referred to Chapter 2.03.

2.14.2.7 Aryl Di- and Polysulfides and Their Higher-coordinated Derivatives

Methods for preparation of arylsulfanes Ar-S-(S)_{*n*}-H, aryl polysulfides Ar-S-(S)_{*n*}-R, and higher coordinated derivatives have been well covered in COFGT (1995). Symmetrical diaryl disulfides are well known and can serve as precursors for many sulfur derivatives. Vinyl disulfides are available from vinyl thiolates. No further advances have occurred in the synthesis of vinyl- and arylsulfanes and of vinyl di- and polysulfides since the publication of COFGT (1995) <1995COFGT(2)705>.

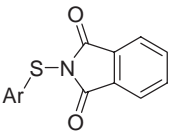
2.14.2.7.1 Aryl disulfides

Aryl methyl disulfides can be prepared by the reaction of diaryl disulfides with methyl disulfide in the presence of MeSNa (Equation (62)) <2000AJC1>.



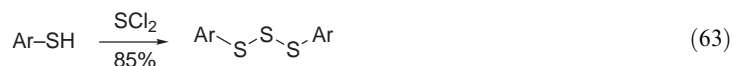
There are a number of methods for the synthesis of symmetrical diaryl disulfides. These include standard procedures such as oxidation of arenethiols and reduction of arenesulfonyl chlorides, as well as novel routes from, for example, *S*-nitrosobenzene or triphenyltin benzenethiolate. These methods are presented in Table 8.

Table 8 Synthesis of symmetrical diaryl disulfides

Substrate	Reagents	Reaction conditions	Yield (%)	References
Ar-SH	H ₂ O ₂	NaOH/H ₂ O, rt, 0.5 h	–	<1998FES752>
	BrCH ₂ NO ₂	Bu ^t OK, THF, rt, 101 min	75	<1999H291>
	MoO ₂ Cl ₂	DMSO, 20 °C, 0.5 h	88	<2002S856>
	H ₂ O ₂	20 °C	–	<2002JMC344>
Ar-S-Alk	Ammonium metavanadate	AcOH, H ₂ O, 40 °C	–	<1997IJC(A)984>
Ar-S-SnPh ₃	Electrolysis	Bu ₄ NF	97	<1996JOC9402>
	LiBEt ₃ H, H ₂ , Pd/C		73–74	<1996G227>
			48	<1996G227>
Ar-S-Cl	Me ₄ Sn	(Ph ₃ P)Pd ⁰ , THF 25 °C, 4 h	84–95	<1996JOC1533>
	Hg(OAc) ₂ , AlBr ₃	CH ₂ Cl ₂ , –20 °C, 5 h	70	<1995IZV324>
Ar-S-Bz	Clay supported ammonium nitrate “Clayan”	Microwave irradiation, 4 min	61	<1999SC2705>
Ar-S-NO	SmI ₂	THF, HMPA, 20 °C, 1 h	81–86	<2000SC4317>
	Air	CHCl ₃ , 20 °C, 10 min	92	<2002T5179>
ArSO ₂ Cl	Sm, TiCl ₄	THF, 60 °C, 2 h	61	<1996SC135>
	NaBH ₂ Se ₃	MeCN, Δ, 3.5 h	60–78	<1996OPP467>
	SmI ₂	THF, HMPA, 60 °C, 0.5 h	77	<1997SC85>
	Sm, NiCl ₂ , KI	HMPA, 60 °C	74	<1997SC2749>
Ar-SO ₂ M	Sm, TiCl ₄	THF, 60 °C, 2 h	76	<1996SC135>
M = Li, Na	Bu ⁿ Li, S ₈	THF/hexane, rt, 15 h	–	<1998OPP107>
	Zn, MoCl ₅	MeCN, Δ, 15 min	94	<2001MI211>
	WCl ₅ , NaI	MeCN, rt, 12 h	95	<1999S500>
Ar-SO ₂ -Alk	Sm, TiCl ₄	THF, Δ, 2 h	51	<1996SC1931>
	Sm, HgCl ₂	THF/H ₂ O, 20 °C	66	<2000SC2559>
Ar-Cl	Na ₂ S, sulfur	EtOH, Δ, 1 h	21	<1997BMC569>
Ar-NH ₂	NaNO ₂ , HCl, Na ₂ S			
Ar ¹ -SO ₂ Ar ²		H ₂ O, 50–60 °C, 10 min	–	<1995MI161>
		CHCl ₃ , Δ	98	<2000IZV1484>

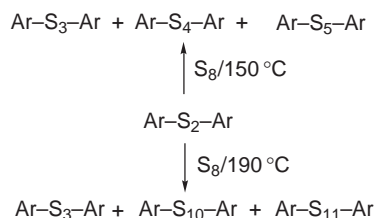
2.14.2.7.2 Aryl polysulfides

Symmetrical diaryl trisulfides are best prepared by Harpp’s method which is the reaction of arenethiols with sulfur dichloride (Equation (63)) <2001ZPK2023>.



A new method of insertion of one or more sulfur atoms into diaryl disulfides has been developed in recent years. Harpp and co-workers <2001TL8607> have shown that triphenylmethylsulfenyl chloride

can be successfully used for selective synthesis of diaryl trisulfides. Diaryl disulfides react with sulfur at high temperature to yield trisulfides together with tetra- and pentasulfides [<2000ZOB1404>](#), and even ArS_{10}Ar and ArS_{11}Ar compounds using more vigorous conditions ([Scheme 14](#)) [<2001ZOB701>](#).



Scheme 14

2.14.2.7.3 Higher-coordinated derivatives of aryl disulfides

Mono-, di-, tri-, and tetraoxides of aryl disulfides (**50–54**) are discussed in the order shown in [Figure 1](#). Three methods have been found to be useful for arenethiosulfinate ester **50** preparation: (i) oxidation of diaryl disulfides [<1996JOC7911>](#); (ii) oxidation of arenethiols ([Scheme 15](#)) [<1999JOC5264>](#); and (iii) reaction of arenesulfinyl chlorides **55** with tributyl(arylthio)stannane **56** ([Equation \(64\)](#)) [<1996BSF1127>](#). In the last case unsymmetrical derivatives are formed.

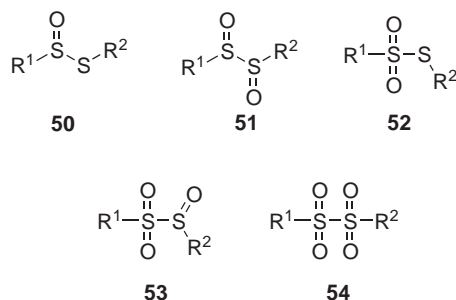
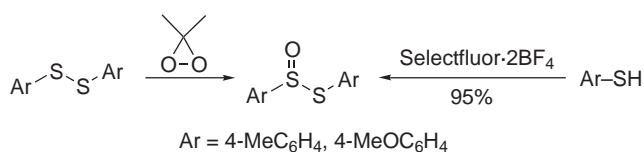
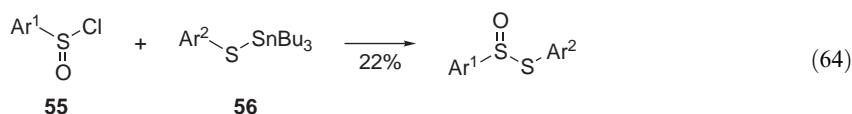


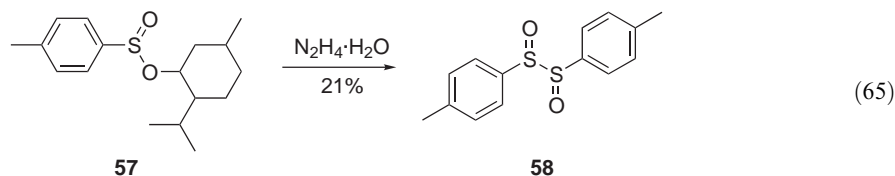
Figure 1



Scheme 15

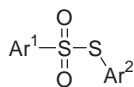


Reductive dimerization of *S*-menthyl-*p*-toluenesulfinate **57** by hydrazine hydrate allows the preparation of di-*p*-tolyl disulfoxide **58** (Equation (65)) <1998AJC907>.



A number of methods have been proposed for the preparation of arenethiosulfonates **59**. Various starting materials and reagents that have been described are collected in Table 9. It is difficult to select a single method as the best and most common for arenethiosulfonate synthesis.

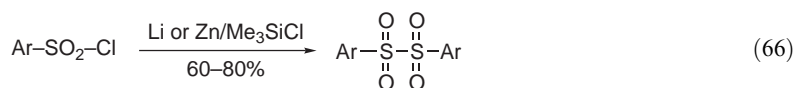
Table 9 Synthesis of arenethiosulfonates



59

Reagents	Reaction conditions	Yield (%)	References
Ar—S—S—Ar + PhI(COCF ₃) ₂	CH ₂ Cl ₂ , rt, 15 min	74	<1997SC1301>
Ar ¹ —SO ₂ Br + Ar ² —SH	Et ₃ N, CCl ₄	42–63	<1997JMC3781>
Ar ¹ —SO ₂ SK + Ph ₂ ICl	MeCN, Δ, 12 h	48–65	<1997SC1309>
Ar ¹ —SO ₂ Na + Ar ² —S—S—Ar ²	Br ₂ , CH ₂ Cl ₂ , rt	70	<1996JOC7545>
	PhI(COCF ₃) ₂ , CH ₂ Cl ₂ , rt, 2 h	60	<1997JFC63>
	I ₂ , CH ₂ Cl ₂ , 20 °C, 1 h	80–90	<2002S343>
Ar—S(O)—NHR	BF ₃ ·Et ₂ O, CH ₂ Cl ₂ , –30 °C, 4 h	29	<1996BSF329>

No further advances have occurred in the synthesis of arenesulfinyl sulfones **53** since the publication of COFGT (1995) <1995COFGT(2)705>. The standard method for the arenesulfinyl sulfonate **54** synthesis, which is reductive dimerization of arenesulfonyl chlorides, has been further developed (Equation (66)). Two reducing agents, lithium <1995TL3849> and zinc <1998SL894>, have been described.



2.14.2.7.4 Arylchlorosulfanes

No further advances have occurred in the synthesis of arylchlorosulfanes since the publication of COFGT (1995) <1995COFGT(2)705>.

2.14.2.8 Vinyl- and Arenesulfenamides, Arenesulfinamides, Arenesulfonamides, and Derivatives

The attention in COFGT (1995) was directed mostly to arenesulfenimides and sulfonylimines, including thiocyanato, isocyanato, *N*-sulfinyl, nitroso, and azido derivatives. Vinylsulfen-, vinylsulfin-, and vinylsulfonamides are practically unknown.

2.14.2.8.1 Vinyl- and arenesulfenamides and derivatives

For aryl derivatives sulfenamides **60**, isocyanato- **61**, diazo- **62**, nitroso- **63**, nitrosulfanylarenes **64**, and thiodiimido **65** derivatives are known (Figure 2).

Arylsulfenamides **66** <2000KGS806> or their bis(trimethylsilyl) derivatives <1998SC3279> are useful precursors to arylsulfenamides: their reaction with ketones in the presence of catalysts (Bu₄NF or *p*-TsOH/Si(OEt)₄) occurs smoothly (Equation (67)). Diphenyl disulfide reacts with aldehydes in the presence of ammonia and silver nitrate to yield arenesulfenamides (Equation (68)) <2002JOC5445>.

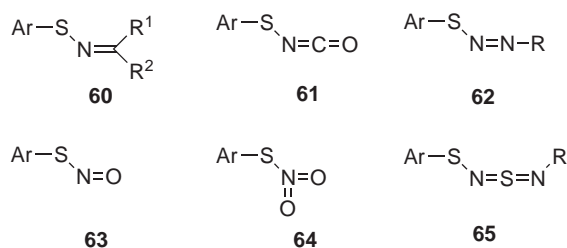
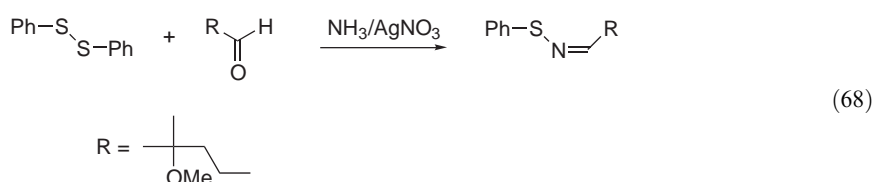
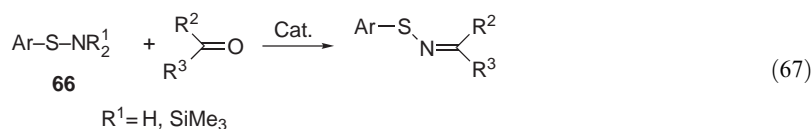
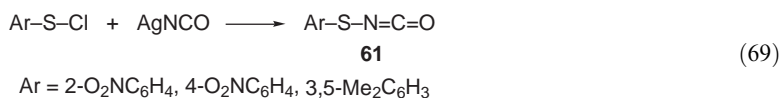


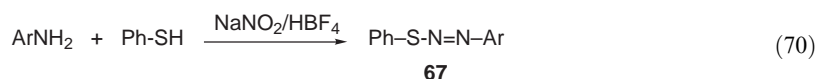
Figure 2



Isocyanatosulfonylarenes **61** are accessible via the reaction of arenesulfonyl chlorides with silver cyanate (Equation (69)) <1995PHA379>.



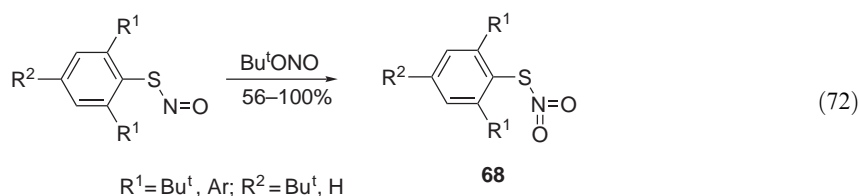
Diazotization of anilines followed by addition of benzenethiol is the only method for the preparation of diazosulfonylarenes **67** (Equation (70)) <1999JOC178>.



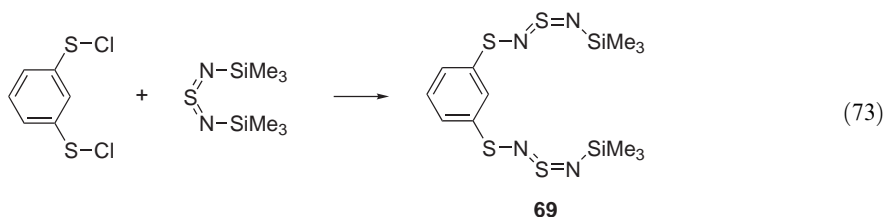
Nitrososulfanylarenes **63** can be synthesized via nitrosation of arenethiols using *t*-butyl nitrite <1997MI59, 2001CL1206>, dinitrogen tetroxide with polyvinylpyrrolidine <2002T5179>, sodium nitrite <1999SC2277, 2000SC1593>, nitrogen oxide <1999JCR(S)668>, or peroxyntirite (Equation (71)) <2002CEJ380>.



Nitrosulfanylarenes **68** are available by oxidation of crowded *S*-nitrosothioarenes with *t*-butyl nitrite (Equation (72)) <2001CL1206>.



Thiodiimido-*S*-arene **69** synthesis is achieved via the reaction of arenesulfonyl chlorides with bis(trimethylsilyl)sulfur diimide (Equation (73)) <1997MI501>.



2.14.2.8.2 Vinyl- and arenesulfinamides and derivatives

Substituted arenesulfinamides **70** are best prepared by the reaction of arenesulfinamides, or their triphenylphosphorane and bistrimethylsilyl derivatives, with ketones (Equation (74)). The variety of the reagents and reaction conditions used is presented in Table 10.

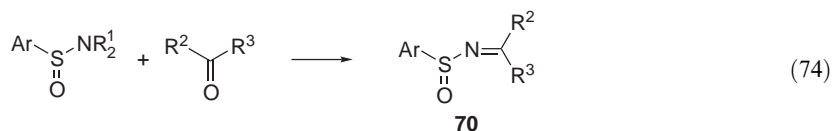
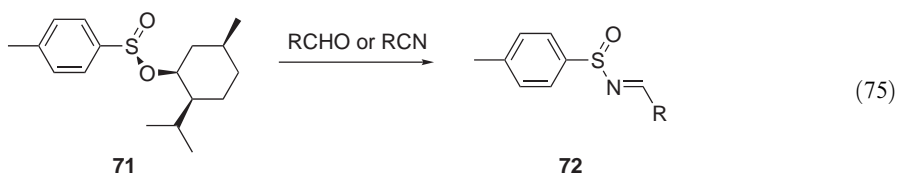


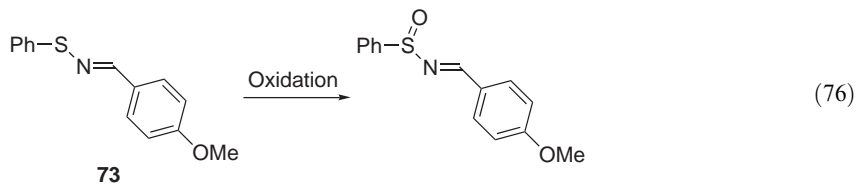
Table 10 Synthesis of substituted arenesulfinamides

Ar-S(O)NR_2^1	Reaction conditions	Yield (%)	References
Ar-S(O)NH_2	4 Å molecular sieves, CH_2Cl_2 , 20 °C, 24 h	93	<1999JOC1403>
	4 Å molecular sieves, CH_2Cl_2 , 20 °C	62–69	<1999JOC6931>
	Ti(OEt)_4	62	<1999JOC1403>
	Ti(OEt)_4	58–80	<2001OL759>
Ar-S(O)-N=PPh_3	Ti(OEt)_4	–	<2001OL1757>
	Benzene, 40 °C, 1.5 h	–	<1998TL7771>
	Benzene, 40 °C, 1.5 h	–	<1999MI345>
	Benzene, 40 °C, 1.5 h	–	<2001EJO1449>
$\text{Ar-S(O)-N(Si(Me}_3)_2)_2$	THF, –78 °C, 3 h	–	<1998TA3919>

Arenesulfonates **71** are also useful precursors for arenesulfinamides **72**: they react with an aldehyde and lithium bis(trimethylsilyl)amide <1997JOC2555, 2001OL759> or with aryl cyanides, methyllithium, and DIBAH <1997JOC2555> to yield the desired compounds **72** (Equation (75)).



Arenesulfonates are also accessible by oxidation of bis(arene)sulfinamides (e.g., **73**) (Equation (76)) <1997JOC2555>.



The standard method for the preparation of arenesulfinyl isocyanates **74**, which is reaction of the corresponding sulfinyl chlorides with silver isocyanate, has been further developed <1997JMC1018>. Triphenylphosphiniminosulfinate **75** is synthesized by the reaction of unsubstituted *p*-toluenesulfinamide with triphenylphosphine and diethyl azodicarboxylate (DEAD) <2001EJO1449> (Figure 3).

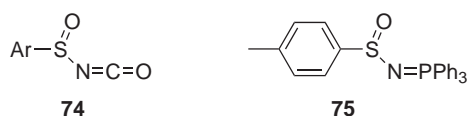


Figure 3

2.14.2.8.3 Vinyl- and arenesulfonamides and derivatives

Vinyl- **76** and arenesulfonamides **77** are well-known compounds, and can be prepared by standard reactions, which include reaction of sulfonyl chlorides with ammonia and amines [<1995COFGT\(2\)705>](#). Arenesulfonamides are also commercially available, and are not discussed further here (Figure 4).

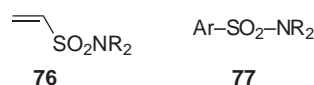


Figure 4

A number of arylsulfonamides with sp^2 nitrogen attached to sulfur atom are known (**78–83**) (Figure 5). Arenesulfonyl isocyanates **78** are available from the reaction of arenesulfonylcarbamic esters **84** with BCl_3 and triethylamine (Equation (77)) [<1998CC2575>](#).

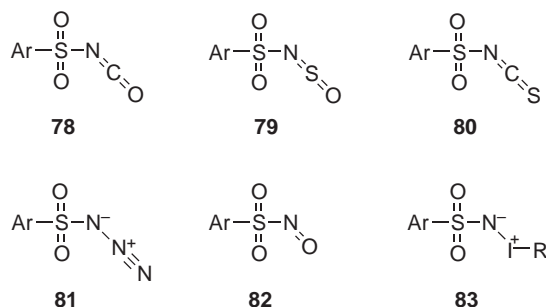
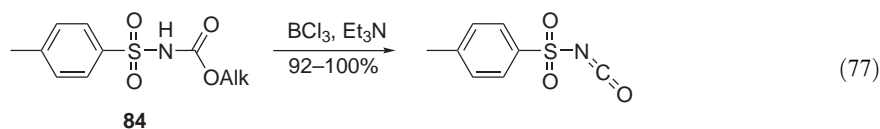
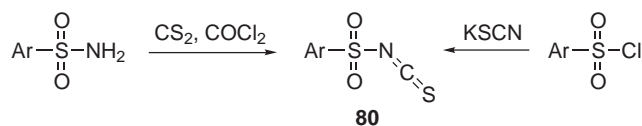


Figure 5

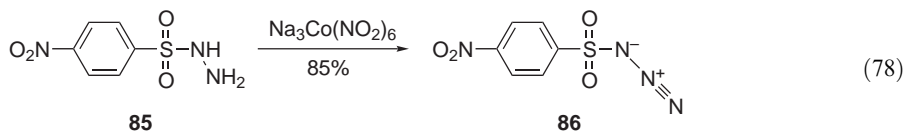


There are two methods for arenesulfonyl isothiocyanate **80** preparation: (i) reaction of arenesulfonamides with carbon disulfide and carbonyl dichloride [<1996T2705, 2001JMC1085>](#) and (ii) nucleophilic substitution of arenesulfonyl chlorides with potassium isothiocyanate (Scheme 16) [<1996EJM1001>](#).

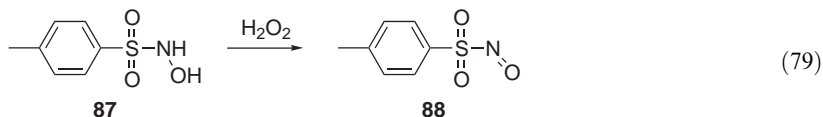


Scheme 16

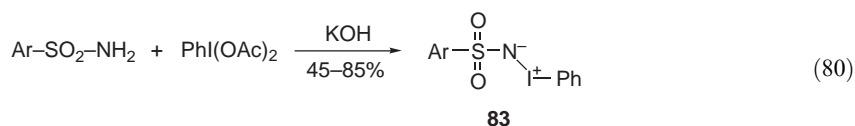
4-Nitrophenylsulfonyl azide **86** has been synthesized by reaction of the corresponding hydrazide **85** with trisodium hexakis(nitrito-*N*)cobaltate ($\text{Na}_3\text{Co}(\text{NO}_2)_6$) (Equation (78)) [<1997JOC7165>](#).



Oxidation of *N*-hydroxy-*p*-toluenesulfonamide **87** with hydrogen peroxide has been reported as a method for *p*-tosylnitrite **88** preparation (Equation (79)) <1996EJM1001>.

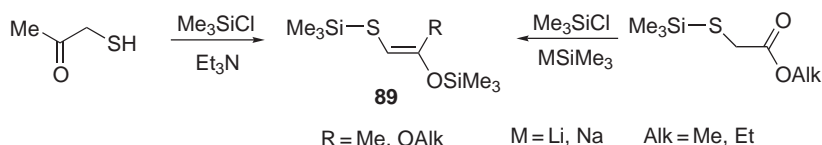


(Arenesulfonylimino)iodoarenes **83** have attracted attention as precursors of nitrenes. The reaction of arenesulfonamides with iodobenzene diacetate is the most widely used method for their synthesis (Equation (80)) <1997JA6040, 1997JOC6512, 1997TL6897, 1998CJC738, 2000JA8013, 2001JCS(P)21714>.



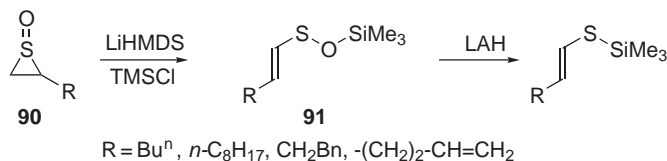
2.14.2.9 Vinyl- and Arylsulfanylsilanes

Vinyl- and arylsulfanylsilanes could be useful intermediates since the trialkylsilyl group is easy to remove, but methods for their preparation have not been well developed. The reaction of β -mercaptoacetone or β -trimethylsilylmercaptoacetic esters with trimethylchlorosilane in the presence of triethylamine <1995IZV353> or lithium (sodium) bis(trimethylsilyl)amide <1994ZOB1491> appears to be the most general route for vinylsulfanylsilanes **89** (Scheme 17). In the first method, sulfanylsilane and vinyl groups are formed simultaneously.



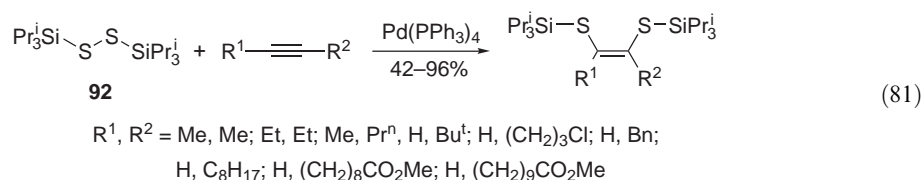
Scheme 17

Thirane-1-oxides **90** are easily opened with the formation of vinyl sulfenates **91** in the reaction with lithium hexamethyldisilazane and trimethylsilyl chloride (Scheme 18) <1996T8387>. Vinyl sulfenates **91** are reduced *in situ* to vinyl trimethylsilyl sulfides by the action of LAH at low temperature <1998SL96>. The reaction is stereoselective and only (*E*)-isomers are formed.

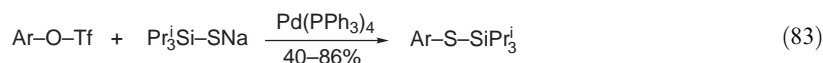
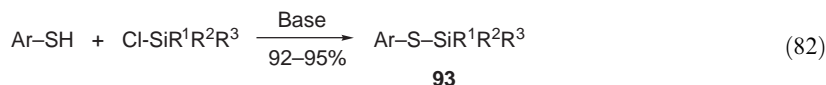


Scheme 18

A recent development in this area is the reaction of alkynes with bis(triisopropylsilyl) disulfide **92** which leads to vinyl sulfanylsilanes in moderate to excellent yields (Equation (81)) <2001T5739>.

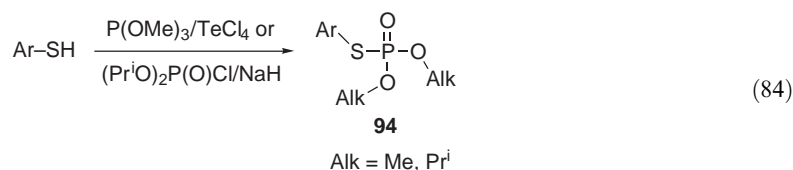


The synthesis of aryl sulfanylsilanes **93** via the reaction of arenethiols with trialkylsilyl chlorides <1994MI29, 1996JOM109> has been further developed by using bases such as sodium hydride <1999JOM82> or Bu^nLi <2002EJI2138> (Equation (82)). Yields are as a rule excellent. The transformation of trifluoromethanesulfonic acid aryl esters with sodium triisopropylsilane thiolate is also an attractive synthetic route to aryl sulfanylsilanes (Equation (83)) <1996TL4523>.



2.14.2.10 Aryl Thiophosphates

Arenethiols are the most common precursors for the synthesis of aryl thiophosphates **94**. Trimethyl phosphite <1995SI243> and phosphorochloridic acid diisopropyl ester <1996BSF951> have been used for their synthesis (Equation (84)). Yields, especially in the first case, are excellent.



2.14.3 SELENIUM- AND TELLURIUM-BASED FUNCTIONAL GROUPS ATTACHED TO AN sp^2 -CARBON

2.14.3.1 Areneselenols and Arenetellurols

Areneselenols and arenetellurols are well-known compounds. A number of methods have been used to prepare these compounds. Diaryl diselenides and diaryl ditellurides are probably the most useful precursors for their synthesis.

2.14.3.1.1 Areneselenols

Various reagents can be used to reduce diaryl diselenides into areneselenols. These include zinc in hydrochloric acid <1996JHC885>, sodium borohydride <1998JA3376, 1999JOC6688, 2000SC2661>, tributylstannane <1999JOC2877>, magnesium <1999IJC(B)225>, barium in ammonia <2000CEJ4062> and samarium iodide <2001TL3125> (Equation (85)). Many areneselenols are isolated as sodium or other metal salts because they are readily oxidized in air. Diaryl tetraselenides can also be reduced to areneselenols by LiAlH_4 <2001OL3569>.

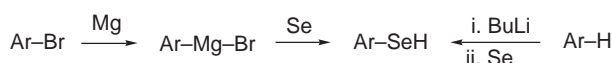


A number of substituted aryl selenides have been converted into areneselenols (Equation (86)) (Table 11).


Table 11 Synthesis of areneselenols from aryl selenides

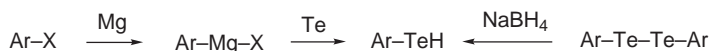
Substrate	Reaction conditions	References
Ar-Se-Alk	Bu ^t OCl, MeOH, 0 °C	<1995JA10153>
	Cp ₂ Zr(H)Cl, THF, 0 °C	<1996JOM9>
Ar-Se-Bn	Na/NH ₃ , -50 °C, 3 h	<1998EJI1071>
Ar-Se-CN	Zn, H ₂ SO ₄	<1996LA1187>
Ar-Se-S-Alk	Et ₃ N, CDCl ₃ , 20 °C	<2001OL3569>
Ar-Se-Br	H ₃ PO ₂ , AcOH	<1996H2567>

Other potential starting materials are arenes, which are transformed to selenols by reaction with butyllithium followed by addition of elemental selenium <1999JOM282, 1999TL6571>, or aryl bromides via the reaction of the corresponding Grignard reagent with selenium <2001ZOB1988> (Scheme 19).


Scheme 19

2.14.3.1.2 Arenetellurols

The synthesis of arenetellurols is similar to the synthesis of selenols. Two standard procedures are used (Scheme 20): reduction of diaryl ditellurides by sodium borohydride <1996JOC5754> and the reaction of Grignard reagents with elemental tellurium <2001ZOB1988>.


Scheme 20

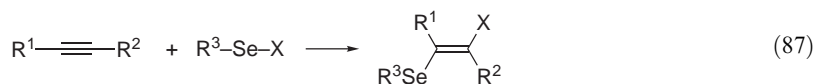
2.14.3.2 Vinyl and Aryl Selenides and Tellurides and Their Higher-coordinated Derivatives

The synthetic approaches to vinyl or aryl selenides and their higher-coordinated derivatives are similar to those for sulfides. No new significant methods for selenides and tellurides have appeared since the publication of COFGT (1995). Tellurium derivatives are in general less available than the corresponding selenium derivatives.

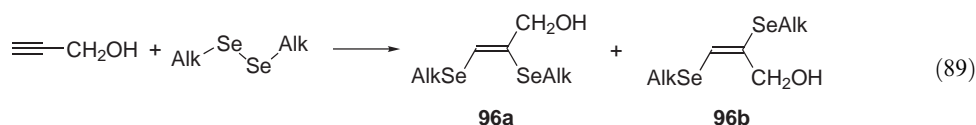
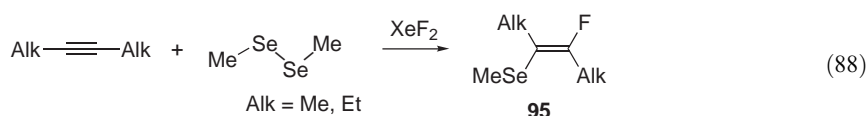
2.14.3.2.1 Vinyl selenides

(i) Vinyl selenides from alkynes

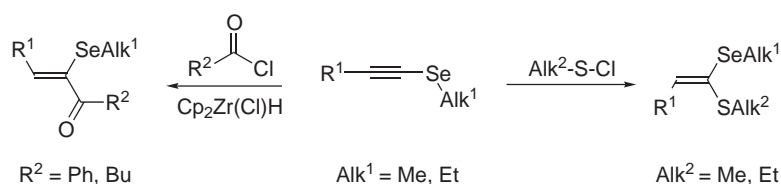
Alkynes are probably the most important precursors for vinyl selenide preparation. Addition of selenyl halides to alkynes is a useful procedure (Equation (87)): chlorides <1995S1521>, bromides (prepared *in situ*) <2000SC307>, and fluorides <2000EJI1307> give vinyl selenides. These reactions are stereoselective and only (*E*)-isomers are formed.



Addition of dimethyl diselenide and xenon difluoride to dialkylacetylenes (Equation (88)) is synthetically equivalent to the previous procedure and (*E*)-fluoromethylselenanylbutenes **95** were isolated <1999MRC333>. Without xenon difluoride, 2,3-bis(alkylselenanyl)propenes (**96a,b**) are produced in a similar reaction but a mixture of stereoisomers is usually formed (Equation (89)) <1998IZV1669>.



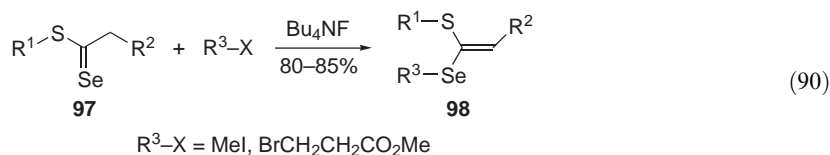
Selanylalkynes can be converted to vinyl selenides by two routes (Scheme 21): addition of acid chlorides followed by reduction with zirconocene hydrochloride (Cp₂Zr(Cl)H) <1998T2371, 1999SC1421> or by addition of various alkylsulfenyl chlorides <2000S775, 2001JCR(S)370>.



Scheme 21

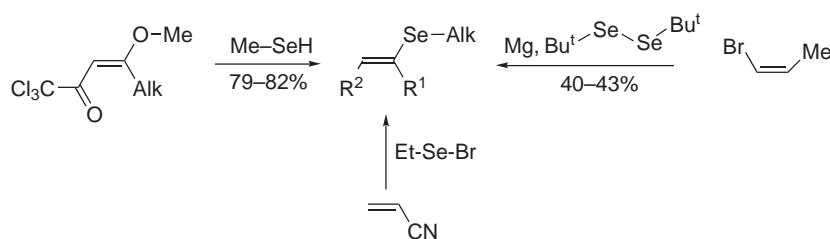
(ii) Vinyl selenides by enolization of selenothioic acid esters

Selenothioic esters **97** are successfully transformed into vinyl selenides **98** by alkylation with alkyl halide (Equation (90)). Methyl iodide is the most widely used reagent <1996CL877, 1997CL545>; yields and selectivity can be enhanced by the use of Bu₄NF <2000CL368, 2001JOC8101, 2001MI1111>.



(iii) Vinyl selenides from alkenes

Various groups can be substituted at a double bond by selenium-containing substrates. These include a methoxy group by methaneselenol <2002S2220>, a cyano group by ethaneselanyl bromide <1997LA541>, and a bromine substituent by magnesium and di(*t*-butyl) diselenide <2001MI458> giving alkyl vinyl selenides (Scheme 22).



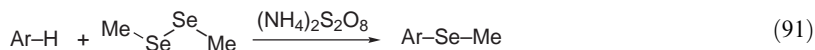
Scheme 22

2.14.3.2.2 Aryl selenides

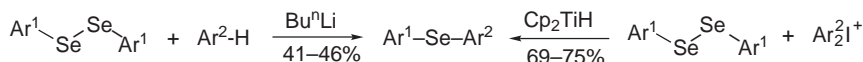
Diaryl and aryl alkyl selenides can be synthesized from various starting materials.

(i) Aryl selenides from arenes

Arenes react with dimethyl diselenide and ammonium peroxydisulfate to give aryl methyl selenides (Equation (91)) <1996H861>.

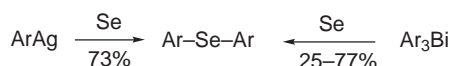


Unsymmetrical diaryl diselenides are accessible by reaction of diaryl diselenides with arenes and Bu^nLi <2001HAC227> and with diaryliodonium salts and titanocene (Cp_2TiH) (Scheme 23) <2001SC1871>.



Scheme 23

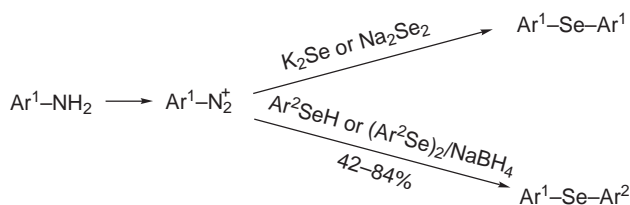
Transformation of pentafluorophenylsilver and elemental selenium into bis(pentafluorophenyl) selenide <2001JFC149> or triarylbiuths and selenium into diaryl diselenides are synthetically related to the above reactions (Scheme 24) <1999JOC3722>.



Scheme 24

(ii) Aryl selenides from arylamines and arenediazonium salts

Arylamines prepared via their diazonium salts are the most useful precursors for aryl selenides. Both symmetrical and unsymmetrical diaryl diselenides can be obtained using this method (Scheme 25). Symmetrical derivatives are prepared by the reaction of diazonium salts with either potassium selenide <1996T13951> or disodium diselenide <2002JCS(P2)262>. Unsymmetrical diaryl diselenides are formed in the reaction of diazonium salts with either areneselenols <1999JPC(A)6074, 2002JOC38> or symmetrical diaryl diselenides, which are reduced *in situ* to selenols by sodium borohydride <2001EJO3933, 2001HAC369, 2002JCS(P2)262>.



Scheme 25

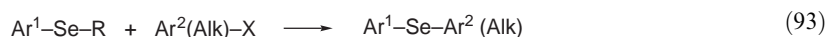
(iii) Aryl selenides from areneselenols

The reaction of areneselenols with alkyl or aryl halides is a well-established method for aryl selenide synthesis (Equation (92)) <1998JA3635, 1999JOC6688, 1999JCS(P1)1915, 2002JOC38>. No new significant procedures have been developed since the publication of COFGT (1995). Yields are usually high.



(iv) Aryl selenides from substituted areneselenols

A number of substituted areneselenols can be used as precursors for aryl selenides (Equation (93)). A variety of the methods are presented in Table 12.

**Table 12** Synthesis of aryl selenides from substituted areneselenols

$\text{Ar}^1\text{--Se--R}$	$\text{Ar}^2(\text{Alk})\text{--X}$	Reaction conditions	Yield (%)	References
Ar--Se--SiMe_3	Alk--X	SmI_2 , THF, Δ , 3 h		<1998JCR(S)350>
Ar--Se--Cl	Ar--Li	Et_2O , -20 to 70°C	61	<1999EJI1359>
	Ar--H	Et_3N , MeCN, 20°C , 2 h	72	<2002T7531>
Ar--Se--CN	MeI	NaBH_4 , MeOH	83	<2002JA1902>
Ph--Se--SnBu_4	ArN_2^+	$\text{PdCl}_2(\text{PPh}_3)_4$, DMF, 100°C , 4 h	94–97	<2000JOM96>
Ph--Se--Alk	MeMgI	THF	60	<1997T7445>

(v) Aryl selenides from diaryl diselenides

The disconnection of the Se–Se bond in diaryl diselenides by a number of reducing agents following by addition of alkyl or aryl halides is a useful procedure for aryl selenides (Equation (94)). Various methods are summarized in Table 13. Diaryl diselenides can also react with trimethylindium to yield aryl methyl selenides <1999JOM42>.

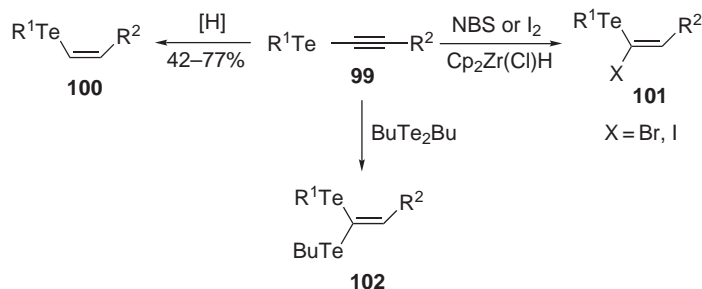
**Table 13** Synthesis of aryl selenides from diaryl diselenides

R--X	M	Reaction conditions	Yield (%)	References
AlkBr	Mg	Et_2O , -78°C , 1 h	66	<1996HCA1957>
	In	THF, 25°C , 24 h	74	<2001MI129>
	Zn	K_2HPO_4 , MeCN, H_2O , 1 h	78	<2001TL4597>
	Sm	Me_3SiCl , THF	–	<1998JCR(S)598>
	LAH	THF, HMPA, 5 h	98	<1997BSF823>
MeI	NaBH_4	Et_2O , 0°C , 0.5 h	79–82	<1999CPB956>
		THF, H_2O	87–97	<1999JPC(A)9906>
AlkI	Zn	K_2HPO_4 , MeCN, 1 h	61–95	<2001TL4597>
Arl	NaBH_4	SmI_2 , DMF, THF, 70°C , 2 h	45–72	<2001HAC539>
ArBr(I)	Mg	Et_2O	60–69	<2002JOC38>

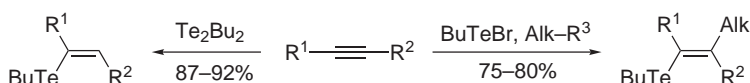
2.14.3.2.3 Vinyl tellurides

Vinyl tellurides can be synthesized by a number of methods. Alkynes are probably the most useful precursors. Reduction of tellanylalkynes **99** by diisobutylaluminum hydride (DIBAL-H) <1995T12971> or, even better, by zirconocene hydrochloride <1996TL7537, 1998T2371> or by diborane <2000SC1903> allows the preparation of vinyl tellurides **100** in moderate to high yield (Scheme 26). Tellanylalkynes **99** can also add bromine or iodine with further reduction by zirconocene hydrochloride to yield 1-halogenvinyl tellurides **101** <1998T2371> or by dibutyliditellane to give bis(tellanyl)alkynes **102** <1998JCS(P1)591> (Scheme 26).

Vinyl tellurides are also available by addition of tellurium-containing substrates to alkynes (Scheme 27). These include butyltellurium bromide, followed by substitution of bromine by an alkyl group, <1998TL8735, 2000JOC54, 2000JOC61, 2001TL7167> or dibutyliditellane <2000TL5103>.

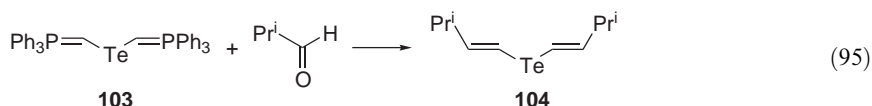


Scheme 26



Scheme 27

Vinyl butyl tellurides can be prepared by the reaction of alkynes with butyllithium and elemental tellurium <2001JOM43>. The Wittig-type reagent **103** is useful for synthesizing bis-vinyl tellurides (e.g., (104)) (Equation (95)) <1999JOM44>.



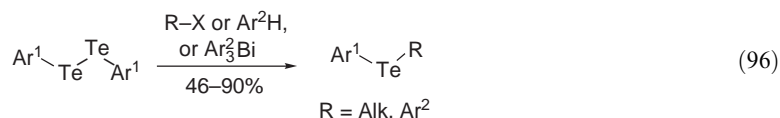
2.14.3.2.4 Aryl tellurides

Symmetrical diaryl tellurides have been synthesized by two methods (Scheme 28): (i) reaction of elemental tellurium with aryl bromides and *t*-butyllithium <1995MI233> or (ii) reaction of elemental tellurium with pentafluorophenylsilver <2001JFC149>.

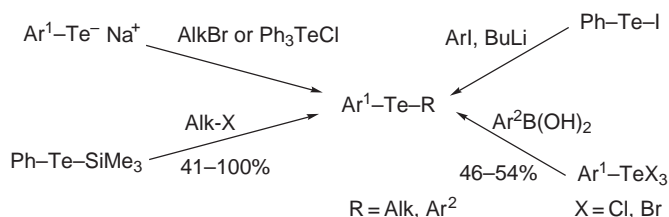


Scheme 28

A number of starting materials have been used for the preparation of unsymmetrical diaryl and aryl alkyl tellurides. Symmetrical diaryl ditellurides are the most practical precursors. Their reaction with alkyl or aryl halides (mostly iodides) <1998JOM145, 2000JOC2127, 2000SC1365, 2001JCS(P2)1899>, with arenes <2001HAC227>, and with triarylbi-muth <1999JOC3722> is an attractive route to aryl tellurides (Equation (96)). Addition of a reducing agent (titanocene, NaBH₄) or a base (BuⁿLi) is essential for the success of the reaction.



Aryltellurium derivatives can be employed in various forms: aryl telluride anions react with alkyl bromides <1996JOC5754> and with triphenyltellurium chloride <1996AG2822>, phenyl-tellurotrimethylsilane with alkyl halides <2001TL5061>, phenyltellurium iodide with aryl iodides and BuLi <1995CL571>, and aryltellurium trichloride (or bromide) with arylboronic acids <1999JOC8161, 2002TL1387> to yield unsymmetrical aryl tellurides (Scheme 29).



Scheme 29

2.14.3.2.5 Selenoxides and telluroxides and related compounds

Selenoxides **105** are generally prepared via oxidation of selenides. Various reagents are used for this transformation. The best is *t*-butyl hypochlorite <1995JCS(P1)2375, 1999JOC8242, 2001HAC227> (yields 79–98%) and others are *m*-chloroperbenzoic acid (MCPBA) <1996H2567, 2001MI119, 2002ZN(B)145>, nitrogen dioxide <1996JCS(P1)2731>, peroxyxynitrite <1996MI1057>, and hydrogen peroxide <1997ACS1186, 2001BMC1459>.

Two methods can be recommended for aryl telluroxide **106** synthesis: (i) oxidation of aryl tellurides by Bu^tOCl (yields 72–98%) <1998JA1230, 2000JOC2127, 2001HAC227> or by MCPBA (yield 30%) <2002ZN(B)145> and (ii) hydrolysis of aryltellurium dibromides (yield 25%) <1996ZN(B)832> (Figure 6).

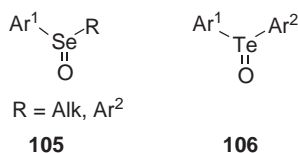


Figure 6

2.14.3.2.6 Selenones and tellurones

Unsymmetrical diaryl diselenones **107** can be easily synthesized by exhaustive oxidation of diaryl selenides with peracetic acid <2000MI121>. Yields are moderate (48–60%). No further advances have occurred for tellurones **108** since the publication of COFGT (1995) <1995COFGT(2)705> (Figure 7).

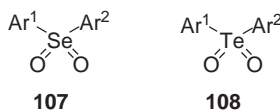


Figure 7

2.14.3.3 Vinyl- and Areneselenyl and -telluryl Halides and Their Higher-coordinated Analogs

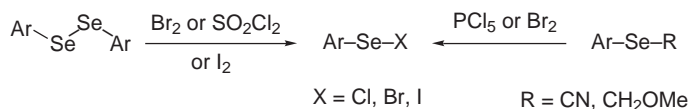
Areneselenyl halides are readily available by halogenolysis of various areneselenyl derivatives. For arenetellurenyl halides only iodides can be isolated. Seleninyl and tellurinyl halides are much less accessible.

2.14.3.3.1 Areneselenyl and arenetellyrenyl halides

(i) Areneselenyl halides

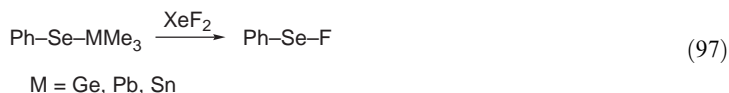
The most obvious route to areneselenyl halides is halogenolysis of diaryl diselenides: bromides are obtained by the action of bromine <1995AG1872, 1996JCS(D)2719, 1999CEJ1411, 2000IJ307, 2002TL4071>, chlorides from sulfonyl chloride <1999CEJ1411>, and iodides from iodine

<1999CEJ1411>. Substituted areneselenols can also be useful precursors for areneselenyl halides (Scheme 30): selenocyanate for chlorides <1997SC4049> or bromides <2000OL989>, and aryl-methoxymethyl selenides for bromides <2001MI189>.



Scheme 30

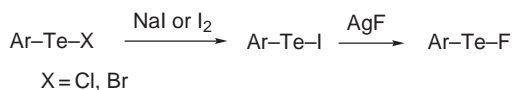
Benzeneselenyl fluoride is accessible from the reaction of phenylselenotrimethylgermane, plum-bane, and tinnane with xenon difluoride (Equation (97)) <2000EJI1307>.



There are other uncommon methods for forming areneselenyl halides. These include: (i) heating of arylselenium methyl bromide <1996H2567> or arylselenium trichloride <1999ZN(B)1170>, (ii) reaction of diarylmercury with diselenium dichloride <1995CB741>, and (iii) exchange of chlorine in arylbenzeneselenyl chlorides with bromine by trimethylsilyl bromide <1999EJI1359>.

(ii) Arenetellurenyl halides

Diaryl ditellurides are precursors for arenetellurenyl halides: chlorides were isolated in the reaction with CuCl₂ <1997MI291> and iodides in the reaction with iodine <2001JOC74>. The reduction of aryltellurium trihalide by hydrazine hydrate is a useful procedure for arenetellurenyl chlorides, bromides, and iodides <1996JOM53, 1997JOM257>. Arenetellurenyl iodides can be prepared by an exchange reaction with the corresponding chlorides <1996JOM53> and bromides <1997JOM257>, and in turn iodine exchange with fluorine by the action of silver fluoride (Scheme 31) <1997JOM257>.



Scheme 31

2.14.3.3.2 Vinyl- and areneseleninyl and -tellurinyl halides

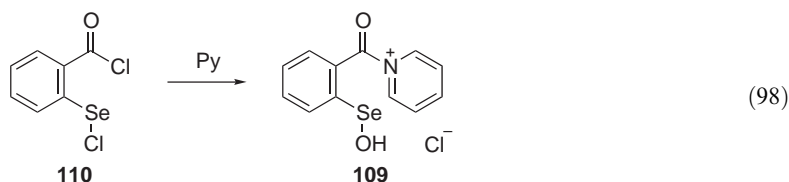
No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)705>.

2.14.3.4 Functions Based on RSeOH Units and Their Higher-coordinated Derivatives

Areneselenenic, areneseleninic, and areneselenonic acids are well known and methods for their preparation are similar to those for the corresponding sulfur derivatives. No tellurium compounds are available.

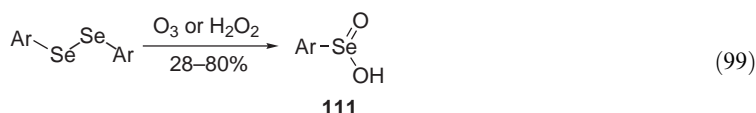
2.14.3.4.1 Areneselenenic acids

Areneselenenic acids are, in general, unstable compounds. A useful method to increase the stability of these acids by forming salts **109** was described by Polish authors <2002PJC953>. The reaction of 2-chloroselenylbenzoyl chloride **110** with pyridine, or other six-membered nitrogen heterocycles, gives the corresponding selenenic acids, but yields are low (27–33%) (Equation (98)).



2.14.3.4.2 Areneselenenic acids

Oxidation of readily available diaryl diselenides by ozone <2001AG(E)2460, 2002JCS(P1)2151> or by hydrogen peroxide <1999EJI1359> is an attractive synthetic route to areneselenenic acids **111** (Equation (99)). Other methods include oxidation of selenocyanates with hydrogen peroxide <2001BMC1459> or oxidation of sterically hindered stable selenenic acids with MCPBA <2001OL3569>.

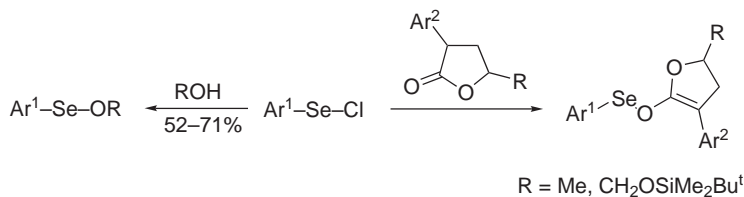


2.14.3.4.3 Areneselenonic acids

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)705>.

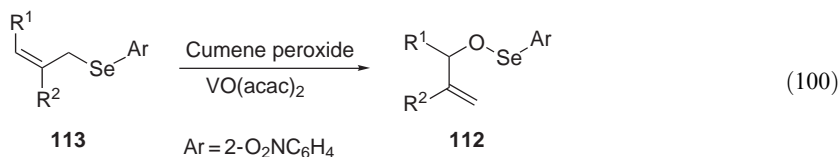
2.14.3.5 Functions Based on R¹SeOR² Units and Their Higher-coordinated Derivatives

Areneselenenyl chlorides are the most suitable precursors for areneselenenic esters. They react with alcohols <2002T7531> and with butyrolactone derivatives in the presence of LDA <2000BMCL1893, 2001JMC2701> to give useful materials (Scheme 32).



Scheme 32

An unusual method for making areneselenenic esters **112** was described recently and involves oxidative rearrangement of *o*-nitrophenyl β-alkenyl selenides (**113**, Equation (100)) <2000CC2031>.



No further advances have occurred in chemistry of selenenic esters since the publication of COFGT (1995) <1995COFGT(2)705>.

2.14.3.6 Aryl Di- and Polyselenides and Aryl Ditetellurides

Aryl diselenides and aryl ditellurides are probably the most used precursors for other arylselenium and tellurium compounds, and methods for their preparation are well developed. Among polyselenides and polytellurides, only triselenides are known.

2.14.3.6.1 Aryl di- and polyselenides

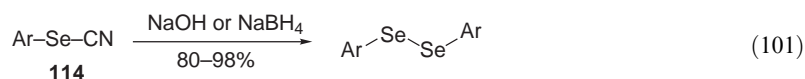
(i) Aryl diselenides

The transformation of arenes or aryl halides into aryl diselenides using a base and elemental selenium is an attractive synthetic route (Scheme 33). Arenes react with Bu^nLi and selenium <1997CEJ1894, 1998CC1867, 2001JA839, 2002CEJ1125>, but the yields of diaryl diselenides are usually moderate (40–66%). Selenium and Bu^tLi <1995AG1872, 2000TL3241> or Bu^nLi <2001JA839> are the reagents of choice for transformations of aryl halides. Another desirable synthetic approach is the reaction of Grignard reagents with selenium <2001JCS(P)224, 2002JOC38>.



Scheme 33

Arylselenocyanates **114** can be recommended as useful precursors for diaryl diselenides, because yields are higher than for other methods (Equation (101)). The use of a base (NaOH <1996JHC1275, 2002JA1902>, NaOMe <2000JCS(P)1429>) or a reducing agent (NaBH_4 <1999SC1201, 1999T14261>) is essential in this reaction.



The conversion of (triphenylstannyl) aryl selenides **115** <1997JOC3103> and selenocarbonic acid derivatives **116** <1998JOC2397> into diaryl diselenides has also been reported (Figure 8).

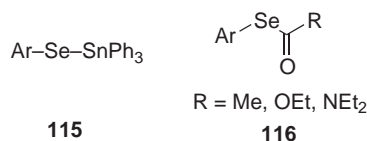


Figure 8

(ii) Aryl polyselenides

Symmetrical diaryl triselenides **117** can be formed, together with corresponding diselenides, by the reaction of arenes with Bu^tLi and elemental selenium <1998TA3625>. Diaryl tetraselenides **118** with bulky substituents in *ortho*- and *para*-positions are accessible from aryl bromides, Bu^tLi , and selenium <2001OL3569>. The presence of air appears to be important for this transformation (Figure 9).

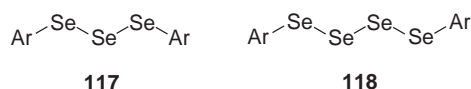
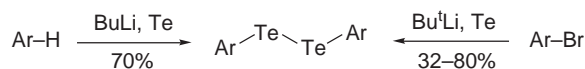


Figure 9

2.14.3.6.2 Aryl ditellurides

Diaryl ditellurides are prepared by various methods. The most attractive route is the reaction of arenes <1999JOM282, 2001JFC207> and aryl bromides <1999JOC8161> with BuLi and elemental tellurium (Scheme 34).



Scheme 34

The traditional method involving reduction of aryltellurium trichlorides **119** with sodium metabisulfite <1997MI291> is rarely used because of the limited availability of the starting material. Diaryl ditellurides can also be synthesized from aryltriphenylbismuths **120** and tellurium <1999JOC3722> but diaryl telluride is the main product in this transformation.

A newer method of diaryl ditellurides synthesis from arylboronic acids **121** and TeCl₄ has attracted a great deal of attention <2002TL1387>. Yields may reach 95% (Figure 10).

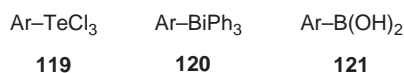
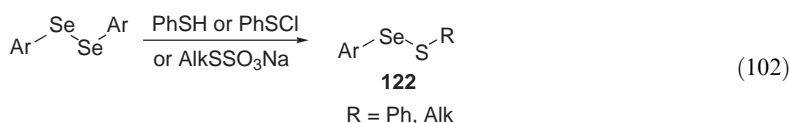


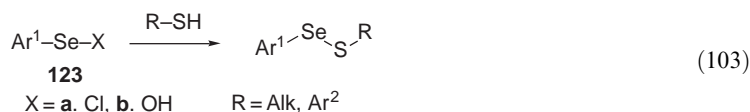
Figure 10

2.14.3.7 RSeS and RTeS Functions

Arylselenyl sulfides **122** can be prepared from a number of selenium precursors. Diaryl diselenides are the most widely used selenium starting materials. They can give arylselenyl sulfides in reactions with benzenethiol <2001JA839>, benzenesulfonyl chloride <2000JCR(S)374>, and alkylthiosulfurous acid sodium salts <2000JCR(S)374> (Equation (102)). Synthetically equivalent is the use of benzeneselenol and dibutyl diselenide <2001OL3569>.



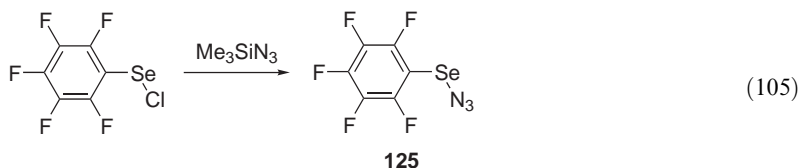
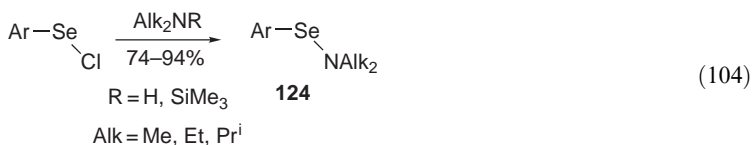
Areneselenyl chlorides **123a** <2002T7531> and areneseleninic acids **123b** <2001OL3569, 2002JA1902> can react with thiols to yield arylselenyl sulfides. Yields may vary from quantitative to moderate (30%) (Equation (103)).



No further advances have occurred in synthesis of RTeS functions since the publication of COFGT (1995) <1995COFGT(2)705>.

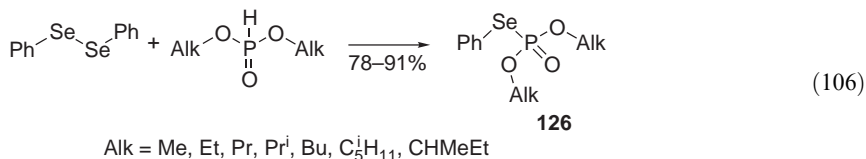
2.14.3.8 RSeN Functions

Areneselenamides **124** can be prepared from areneselenyl chlorides and dialkylamines <2001PJC823> or their trimethylsilyl derivatives <1999EJI1359> (Equation (104)). A synthetically similar approach has been used to prepare pentafluorobenzeneselenyl azide **125** (Equation (105)) <2001MI119>.



2.14.3.9 Aryl Selenophosphates

Aryl selenophosphates **126** are available from the reaction of diphenyl diselenide with dialkyl esters of phosphonic acid in the presence of phenyliodosodiacetate (Equation (106)) <2000JCR(S)370, 2001SC421>. Lithium arylselenates can also be used as precursors for aryl selenophosphates in the reaction with diethyl chlorophosphate <1996JA7000>.



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Biographical sketch



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2.15

Vinyl- and Arylnitrogen Compounds

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2.15.1 VINYL- AND ARYLNITROGEN COMPOUNDS

This chapter describes new developments in the preparation of vinyl- and arylnitrogen compounds, during the period 1995 and mid-2003. Methods prior to 1995 are fully covered in COFGT (1995) <1995COFGT(2)737>.

2.15.2 ENAMINES AND ARYLAMINES

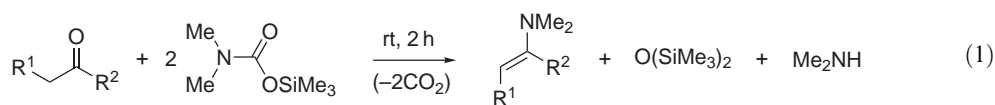
Since the publication of COFGT (1995) <1995COFGT(2)737>, a number of reviews <1997MI183, 1997MI517, 2000JCS(P1)125>, chapters <1997AHC(67)207, 1999AHC(72)283>, and monographs <B-1994MI001> have been published on the chemistry of vinylamines (enamines). This section is an update on all the new methods for the synthesis of enamines and arylamines that have been reported after the publication of COFGT (1995) <1995COFGT(2)737>. For a review of the literature prior to 1995 see COFGT (1995) <1995COFGT(2)737>.

2.15.2.1 Enamines

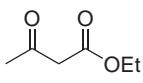
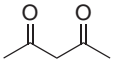
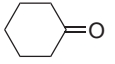
2.15.2.1.1 From carbonyl compounds, acetals, ynamines, nitriles, and others

The classical approach for the preparation of enamines is the condensation of an amine and a carbonyl compound under azeotropic removal of water or in the presence of a dehydrating agent. The reaction is usually performed under mineral or Lewis acid catalysis for less reactive systems. However, this method presents several limitations, such as harsh reaction conditions, lack of regio- and chemoselectivity, and low functional group tolerance. A recent improvement is the application of microwaves in the presence of montmorillonite K-10 <1997TL2039> or envirocat EPZG[®] <1996MI(6)147, 1997SL1245> as environmentally benign acid catalysts under solvent free conditions. Secondary amines can be condensed with ketones in minutes with good yield following this method.

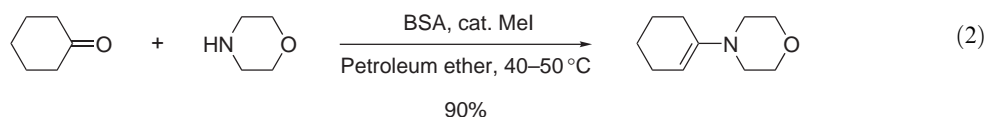
The reaction of *N,N*-dialkylamino-*O*-trimethylsilyl carbamates with ketones gives the corresponding enamines under mild conditions in 50–95% yield (Equation (1)) <2000TL8937>. This procedure is especially attractive for the preparation of enamines from volatile amines. However, the reaction lacks generality, acetone and aldehydes giving self-condensation products, and requires 2 equiv. of carbamate to drive the reaction to completion.



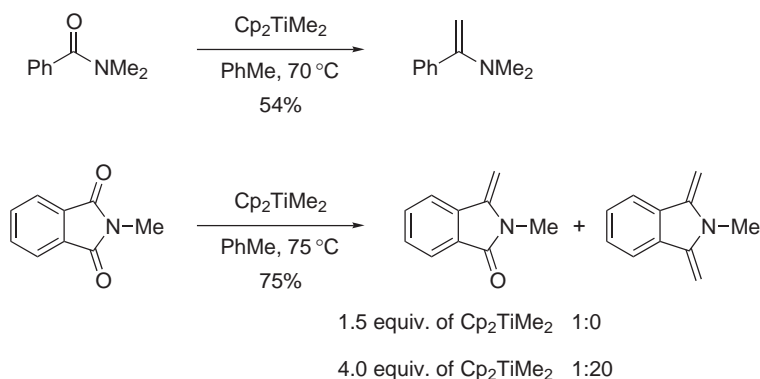
$R^1 = \text{alkyl}; R^2 = \text{alkyl, OEt}$

Ketone	Yield (%)
	86
	95
	55

Good-to-excellent yields of enamines are obtained from ketones by reaction with secondary amines in the presence of an equimolar amount of *N,O*-bis(trimethylsilyl)acetamide (BSA) and catalytic MeI or TsOH (Equation (2)) <1998JOC377>.

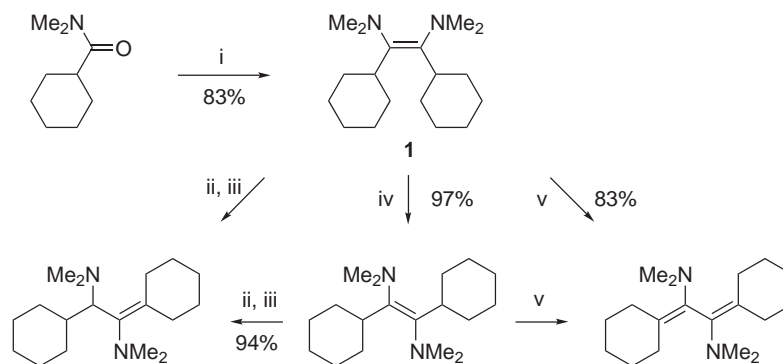


Amides and lactams can be methylenated with dimethyltitanocene to give the corresponding enamines in moderate-to-good yield (Scheme 1) <1995TL2393>.

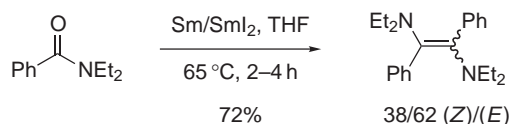


Scheme 1

Tertiary amides suffer deoxygenative coupling to give symmetrical β -aminoenamines in excellent yield by treatment with a number of reagents, including PhMe_2SiLi <1998CC711, 1998CC713>, samarium, or magnesium metal in the presence of a catalytic amount of samarium diiodide <1992JA8729> and ytterbium metal in the presence of a catalytic amount of ytterbium diiodide <1995MI461> (Scheme 2). These reactions are thought to proceed via carbenoid intermediates. With PhMe_2SiLi , (*Z*)-enamines **1** are exclusively obtained and the products showed a number of unexpected reactions (Scheme 2).

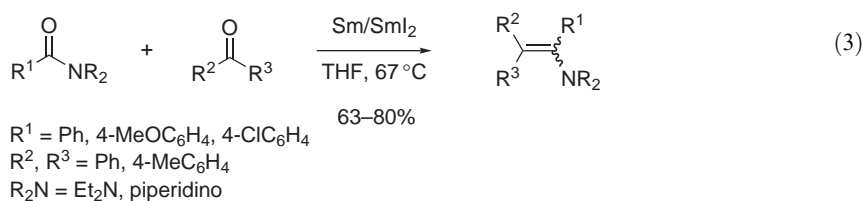


i. PhMe_2SiLi , THF, -78 to -20 $^\circ\text{C}$; ii. $(\text{CO}_2\text{H})_2$, recrystallize from EtOAc; iii. NaOH, H_2O ; iv. PtO_2 , MeOH, 50 $^\circ\text{C}$, 15 min; v. Pd/C, MeOH, rt, 4 h



Scheme 2

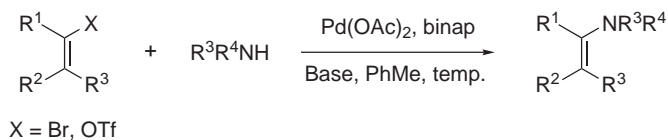
The mixed Sm/SmI_2 reagent also promotes an efficient deoxygenative cross-coupling of diaryl ketones and aryl amides to yield enamines (Equation (3)) <2002T503>. When alkyl amides or alkyl aryl ketones are used, the reaction affords a complex mixture of products. This cross-coupling can also be effected in moderate yield using magnesium metal in the presence of catalytic SmI_2 <2002MI1463>.



R^1	NR_2	R^2	R^3	Yield (%)
Ph	NEt_2	Ph	Ph	80
Ph	Piperidino	Ph	$4\text{-MeC}_6\text{H}_4$	83
Ph	NEt_2	Ph	Me	0

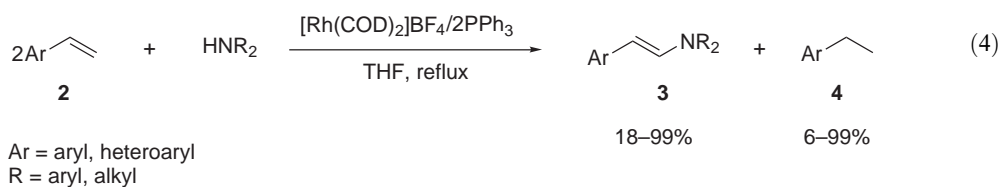
In recent years considerable progress has been made on the development of metal-catalyzed cross-coupling reactions for the formation of C-heteroatom bonds as a powerful synthetic tool. A promising new procedure for the preparation of enamines is the palladium catalyzed cross-coupling between secondary amines and vinyl bromides <2002CC2362> or vinyl triflates <2002TL9085> (Table 1). The reaction is very efficient and proceeds under mild, non-acidic conditions. The resultant enamines can be isolated easily in high purity after dilution with hexanes and filtration through celite. The possible extension of this reaction to the more stable and readily available vinyl chlorides is an interesting perspective for this new procedure.

A highly atom-economic synthesis of enamines is the oxidative amination of alkenes catalyzed by transition metal complexes. A cationic rhodium complex catalyzes the amination of alkenes 2 with secondary amines yielding regioselectively the corresponding *anti*-Markovnikov enamines 3 together with the product of hydrogenation of the alkene 4 (Equation (4)) <1997AG(E)2225, 1998JOM(566)277, 1999EJI1121, 2000M1327>.

Table 1 Palladium-catalyzed amination of vinyl bromides and vinyl triflates


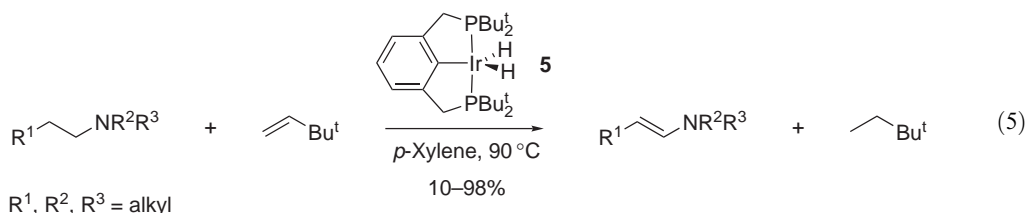
Alkene	Amine	Base	Temp. (°C)	Product	Yield (%) ^a	References
		NaOBu ^t	90		96 ^b	<2002CC2362>
	PhNHMe	NaOBu ^t	90		96	<2002CC2362>
		NaOBu ^t	90		91	<2002CC2362>
	PhNHMe	NaOBu ^t	90		90	<2002CC2362>
		Cs ₂ CO ₃	80		100	<2002TL9085>
		Cs ₂ CO ₃	80		90	<2002TL9085>
	(PhCH ₂) ₂ NH	Cs ₂ CO ₃	80		<5	<2002TL9085>

^a Isolated yield (conversion measured by ¹HNMR). ^b Pd₂(dba)₃ was used instead of Pd(OAc)₂.



The isomerization of allylic amines to the corresponding thermodynamically more stable enamines under basic or metal-catalyzed conditions is a well-established synthetic method <B-1994MI467>. A recent improvement is the use of $\text{RhH}(\text{CO})(\text{PPh}_3)_3$ as a catalyst able to promote the isomerization in very high yield and under very mild conditions <1996PJC133>. Using this procedure, formation of appreciable amounts of unstable primary and secondary simple enamines is possible <2001JA11083>.

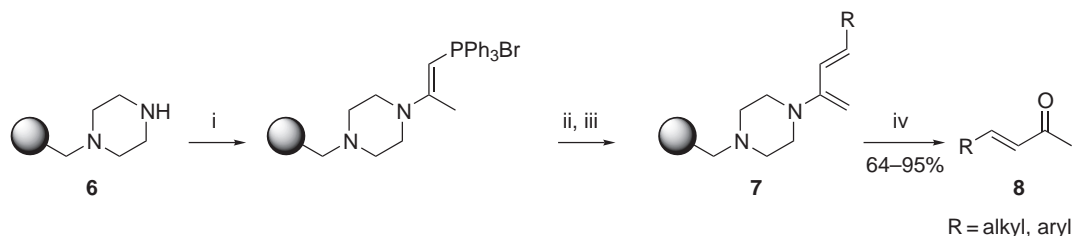
A catalytic synthesis of enamines from tertiary amines has been described by Goldman <2003CC2060>. The iridium complex **5** catalyzes the dehydrogenation of tertiary amines in the presence of *t*-butylethylene or norbornene as sacrificial hydrogen acceptor affording moderate to good yields of enamines (Equation (5)). This procedure allows a facile synthesis of simple enamines that are often difficult to prepare due to their tendency to hydrolyze, oxidize or polymerize. Surprisingly, the presence of the catalyst inhibits decomposition of the enamine products.



Amine	Product	Yield (%)
Pr^iNEt	$\text{CH}_2=\text{CHNPr}_2$	98
Et_3N	$\text{CH}_2=\text{CHNEt}_2$	64
		67 92 ^a

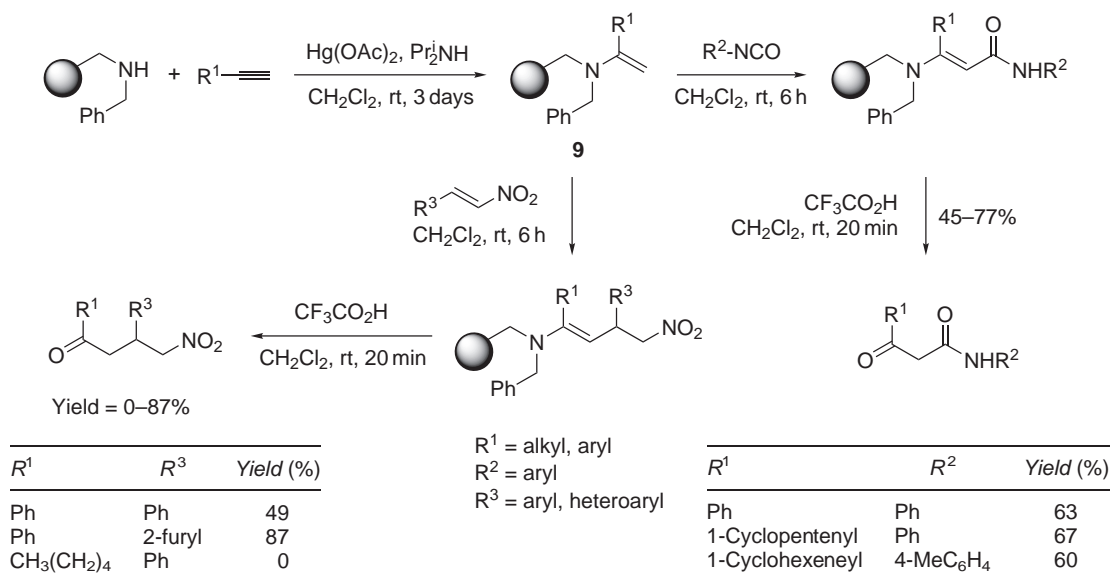
^a Norbornene was used instead of *t*-butylethylene.

Enamines have been prepared in solid phase and used as starting materials for subsequent reactions. A series of 2-amino-1,3-dienes **7** have been synthesized on Merrifield resin from polymer-bound piperazine **6** by treatment with propargyl triphenylphosphonium bromide followed by Wittig reaction with different aldehydes (Scheme 3) <1997TL7111>. Mild acidic cleavage of the dienes **7** gave the α,β -unsaturated ketones **8**. The addition of secondary amines to terminal alkynes catalyzed by mercury(II) salts <1980JCS(P1)2732> has been extended to solid phase using Wang polystyrene resin (Scheme 4) <2000TL5683>. The resultant enamines **9** react with selected electrophiles to give the expected addition products that can be released from the resin by mild acid hydrolysis of the enamine in moderate to good yield. Aromatic acetylenes with electron-withdrawing substituents fail to give the expected reaction products. Polystyrene-supported piperazine has been condensed with arylacetaldehydes under Dean-Stark conditions to give (*E*)-2-arylenamines that have been used for the synthesis of 1,4-diarylpyrazoles <2001JCS(P1)2817>.



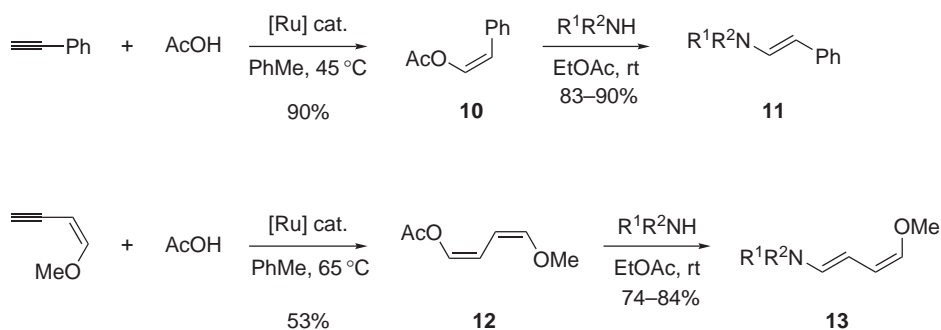
i. Propargyltriphenylphosphonium bromide, CH_2Cl_2 , rt, 3 h; ii. KOBu^t , THF, 0°C , 5 min;
iii. RCHO , reflux, 16 h; iv. 3% $\text{CF}_3\text{CO}_2\text{H}$ in CH_2Cl_2 , 10 min.

Scheme 3



Scheme 4

(*E*)-Enamines **11** and 1-amino-1,3-dienes **13** have been prepared in 74–90% yield by reaction of secondary amines with (*Z*)-alk-1-en-1-yl acetates (e.g., **10**) or (*Z*)-4-methoxybuta-1,3-dien-1-yl acetate **12**. Compounds **10** and **12** can be obtained by *anti*-Markovnikov addition of acetic acid to terminal alkynes and enynes, respectively, catalyzed by $(\text{Ph}_2\text{P}-(\text{CH}_2)_4\text{PPh}_2)\text{Ru}(\eta^3\text{-CH}_2\text{C}(\text{Me})=\text{CH}_2)$ (Scheme 5) <1997SL807>. Both steps can be performed in the same pot avoiding the isolation of the intermediate alkenyl acetate.

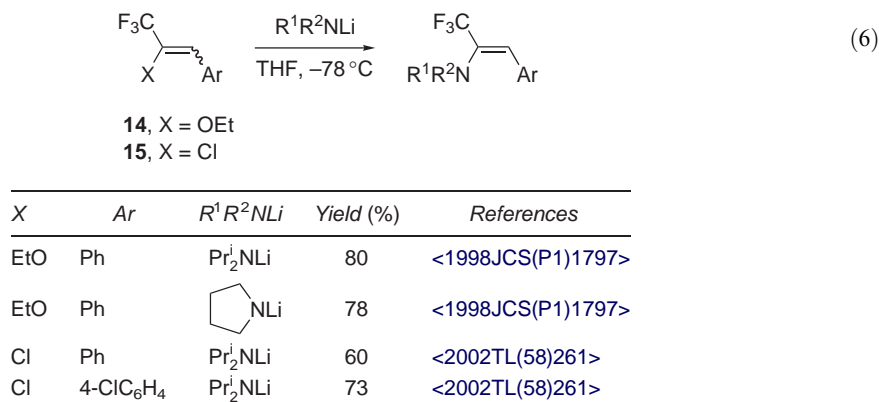


$R^1R^2\text{NH} = \text{pyrrolidine, morpholine, piperidine, MeNHCH}_2\text{CH}=\text{CH}_2$

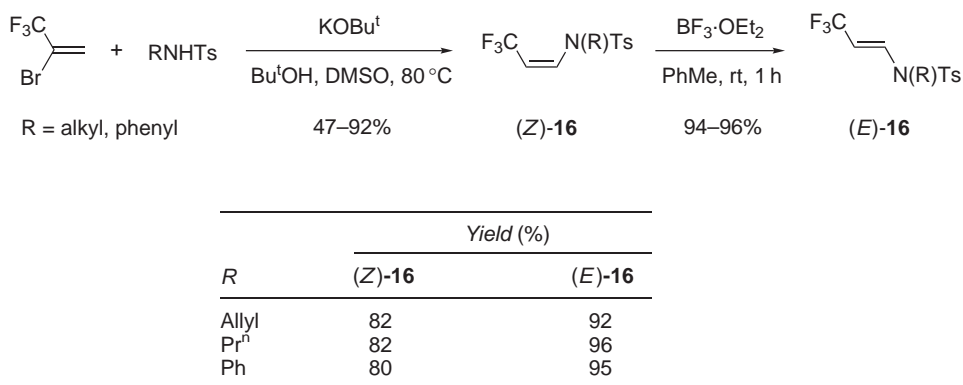
$R^1R^2\text{NH}$	Yield (%)	
	11	13
	83	84
	87	74

Scheme 5

Substituted anilines and heterocyclic amines can be directly added to phenyl acetylene in the presence of catalytic amounts of CsOH·H₂O in NMP at 90–120 °C to give enamines in 42–83% yield as mixtures of (*E*)- and (*Z*)-isomers <1999TL6193>. (*Z*)-2-Aryl-1-perfluoroalkyl enamines can be obtained regio- and stereoselectively by addition of *N*-lithiated secondary amines to the corresponding enol ether **14** <1998JCS(P1)1797> or 2-aryl-1-chloro-1-perfluoroalkylethylene **15** <2002TL261> (Equation (6)). The resultant enamines can be further functionalized by treatment with *t*-butyllithium to form vinylic anions followed by reaction with aldehydes or methyl chloroformate <1998JCS(P1)1797>.



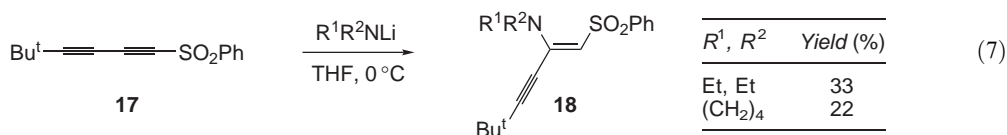
(*Z*)-2-Trifluoromethyl enamines **16** are prepared stereoselectively in high yield by reaction of 2-bromo-3,3,3-trifluoropropene with *N*-alkyltoluenesulfonamides and potassium *t*-butoxide <2002TL265>. The resultant (*Z*)-isomers are converted to the thermodynamically more stable (*E*)-isomers by heating at 190 °C in decahydronaphthalene or by Lewis acid catalysis at room temperature (Scheme 6).



Scheme 6

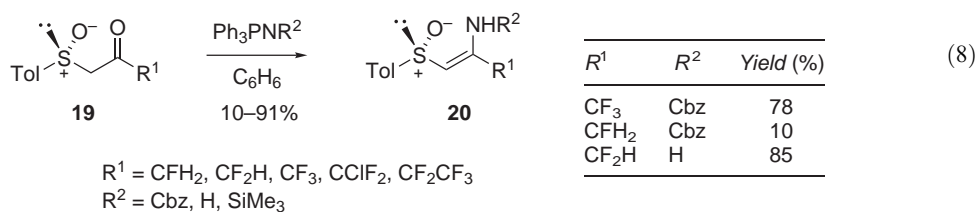
2.15.2.1.2 Sulfonyl and sulfinyl enamines, enaminothiones, and β-thioenamines

The nucleophilic β-addition of secondary amines to alkyne sulfones is a well-established method for the preparation of β-sulfonyl enamines <1995COFGT(2)737>. The reaction does not work for alkyl- or aryl-substituted alkynes when sterically hindered secondary amines are used. However, highly hindered amines such as diisopropylamine, isopropyl-*t*-butylamine, 2,2,6,6-tetramethylpiperidine, and hexamethyldisilazide readily add to (tolylsulfonyl)ethyne at room temperature to give the corresponding (*E*)-β-sulfonyl enamines in almost quantitative yield <1996SC4597>. The rather unstable sulfonyl-buta-1,3-diyne **17** adds *N*-lithiated secondary amines regioselectively at the β-position relative to the sulfonyl group to give enamines **18** (Equation (7)) <2002JCS(P1)1413>.

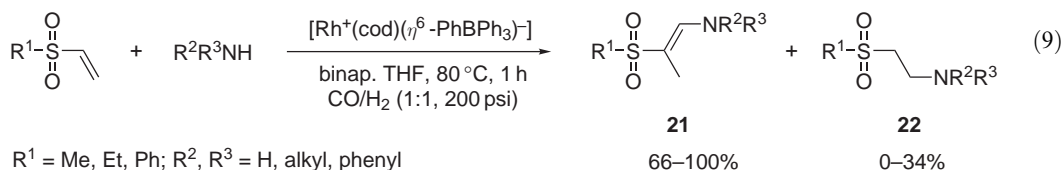


2-Propargyl phenyl sulfones and 2-propargyl phenyl sulfoxides react with diethylamine in MeOH at reflux to form the corresponding β -sulfonyl and β -sulfinyl enamines, respectively, in 90–98% yield <1997SC2993>.

Enantiomerically pure α -(fluoroalkyl)- β -sulfinyl enamines **20** have been synthesized by azawittig reaction of triphenyliminophosphoranes with sulfinyl ketones **19** (Equation (8)) <1996JOC3375>. These enamines exist predominantly as (*Z*)-isomers.

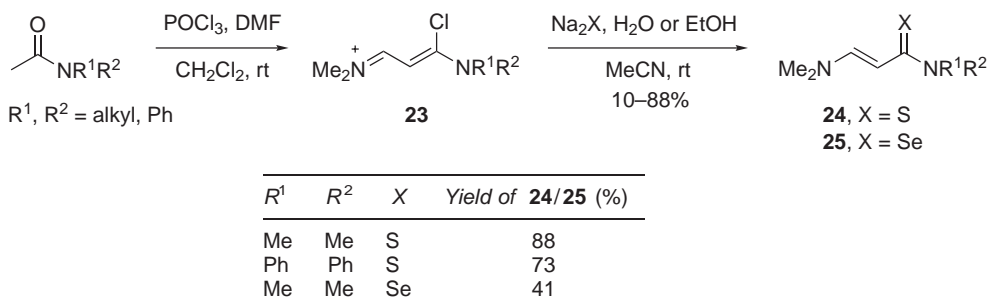


Alper has described a novel type of reaction (hydroaminovinylation) that yields β -sulfonyl enamines **21** with excellent regio- and stereoselectivity from vinyl sulfones and primary or secondary amines (Equation (9)) <2001JA7719>. This one-pot transformation is catalyzed by the zwitterionic rhodium complex $[\text{Rh}^+(\text{cod})(\eta^6\text{-PhBPh}_3)^-]$ together with a chelating phosphine ligand. It is a tandem process that consists of a hydroformylation of the alkene and subsequent condensation with the secondary amine. The Michael addition-type product **22** is a minor by-product. Vinyl sulfoxides and vinyl phosphonates are also good substrates for this reaction yielding the corresponding enamines with a sulfinyl or a phosphonate group at the β -position, respectively.



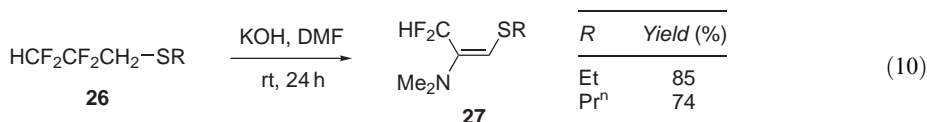
R^1	$\text{R}^2\text{R}^3\text{NH}$	Yield (%)	
		21	22
Me	Bu^nNH_2	60	34
Me	Et_2NH	84	16
Ph	Pr^iNH_2	89	11

A new synthesis of 3-aminothioacrylamides **24** and 3-aminoselenoacrylamides **25** has been described by Hartmann <2000S805>. Treatment of *N,N*-disubstituted acetamides with the Vilsmeier reagent affords 3-amino-3-chloropropenyldenedimethyliminium salts **23** that are reacted subsequently with sodium sulfide or sodium selenide to give products **24** and **25**, respectively (Scheme 7).

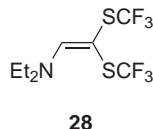


Scheme 7

1,1-Dihydrotetrafluoropropyl sulfides **26** react with KOH in DMF to give thioenamines **27** (Equation (10)) <2000HAC383>.



Treating triethylamine with CF₃SCl affords 1-(*N,N*-diethylamino)-2,2-bis-[(trifluoromethyl)thio]ethene **28** <1995JFC(70)45>.



2.15.2.1.3 Enaminones

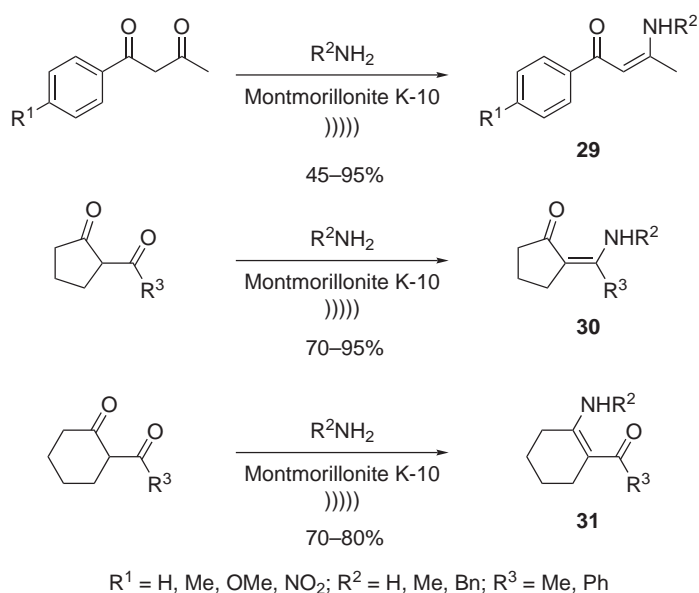
The synthesis of enaminones <2000RCR1021> as well as their use as synthons <B-1994MI523> for the preparation of heterocycles <1997AHC(67)207, 1997MI(1)179> and natural products <1997PAC583, 1999PAC979> have been reviewed since the publication of COFGT (1995) <1995COFGT(2)737>.

The classical preparation of enaminones by condensation of ammonia or a primary or secondary amine with a 1,3-dicarbonyl compound has been improved in several aspects. Stefani has shown that alkyl and aryl primary amines can be condensed with β -ketoesters or 1,3-diketones at room temperature using water as solvent without acid catalysis <2000S1526>. Yields are moderate to good and no amide by-products are formed, but the reaction is limited to water-soluble primary amines. Improved homogeneous reaction conditions for the preparation of β -enamino esters from the corresponding β -ketoesters has been described by Cohen <2002TL1977>. Symmetrical disubstituted ureas can be used as equivalents of ammonia or volatile primary amines for condensation with 1,3-diketones or 3-ketoesters without solvent by adsorption on montmorillonite K-10 and microwave irradiation <1994SL935>. Enaminones are obtained in 54–99% yield in very short reaction times (<10 min). Trimethylsilyl trifluoromethanesulfonate is a very efficient catalyst for the condensation of secondary cyclic amines and 1,3-diketones and 3-ketoesters in benzene at reflux to give enaminones in 35–92% yield <1997SC4275>. The condensation of bulky primary and secondary amines with ethyl acetoacetate or pentane-2,4-dione can be promoted at room temperature by high pressure or by catalysis with ytterbium triflate <1996TL3691>.

The regioselective preparation of unsymmetrical β -enamino ketones is a challenging task. The regioselectivity of enamine formation from α -acetyl cycloalkanones is reported to depend on ring size <1995CJC16>. The enamines **29–31** derived from the more reactive carbonyl group can be obtained in good yields and with high regioselectivities by dispersing 1,3-diketones and primary alkylamines on montmorillonite K-10 under sonication (Scheme 8) <1998S1019>. This heterogeneous reaction proceeds with higher selectivity and milder conditions than the corresponding homogeneous reaction. The exocyclic enamine can be obtained with high regioselectivity using the diketonatoborondifluoride derivative **32** of the corresponding 1,3-diketone as starting material (Scheme 9) <2002MI28, 2003EJO2845, 2003SL493>. The diketonatoborondifluoride derivatives are stable compounds that can be prepared very easily and in high yield by treatment of the corresponding 1,3-diketone with BF₃·OEt₂ at room temperature <1924JCS1963, 1969JCS(A)526, 1970JOC3220>. At least three equiv. of amine are necessary to avoid any side-products.

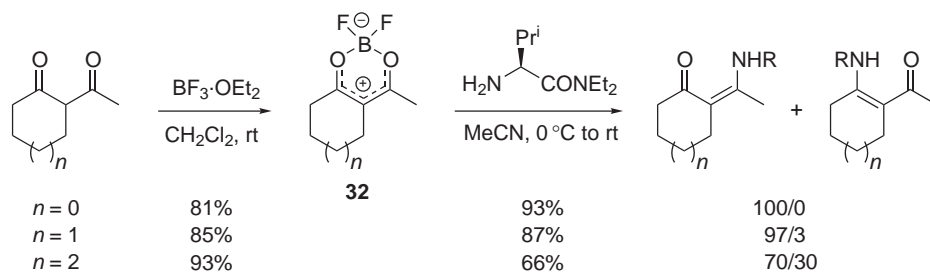
Whiting has described an unusual synthesis of 3-aminoacrylates by a Michael addition-elimination sequence of secondary and tertiary alkylamines to (*Z*)-iodoacrylate **33** (Scheme 10) <2001TL8387>. Tertiary amines undergo a concomitant *N*-dealkylation to give (*E*)-dialkylaminoacrylates **34** and an equimolar amount of the quaternary ammonium salt **35** in almost quantitative yield. Two equiv. of the amine are consumed in the reaction. The less nucleophilic *N,N*-diethylaniline did not react under the reaction conditions.

The reaction of 3-chloroacroleins **36** with 2 equiv. of a secondary dialkylamine affords enamino ketones **38** via iminium salts **37** (Scheme 11) <1996TL8751, 1998MI1133>.

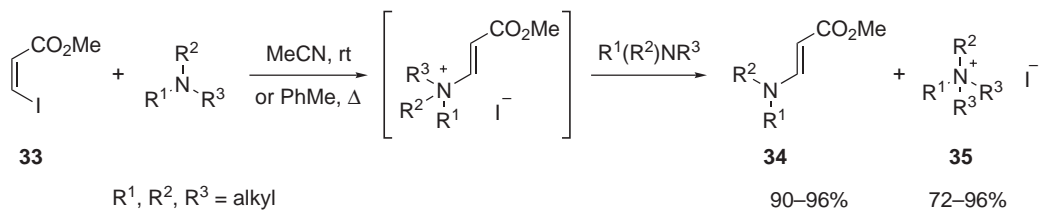


Product	R^1/R^3	R^2	Yield (%)
29	H	H	67
29	NO ₂	Pr ⁱ	40
30	Me	H	95
30	Ph	Me	70
31	Me	Bn	70

Scheme 8

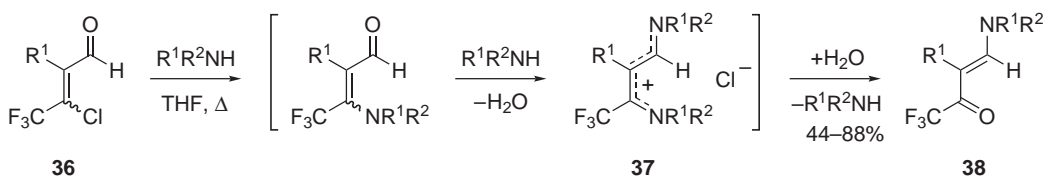


Scheme 9



R^1, R^2	R^3	Yield (%)	
		34	35
Et, Et	Et	95	77
Pr ⁱ , Pr ⁱ	Et	91	70
(CH ₂) ₄	Me	92	74
(CH ₂) ₄	H	91	72

Scheme 10

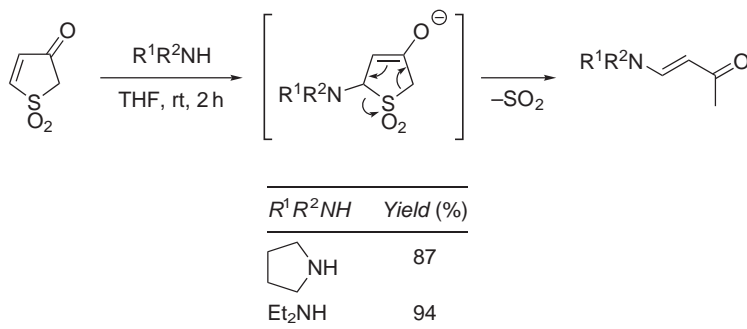


R^1	R^1R^2NH	Yield (%)
Ph	Et_2NH	70
4-ClC ₆ H ₄	Et_2NH	51
CO ₂ Et	Pr^iNH	57

Scheme 11

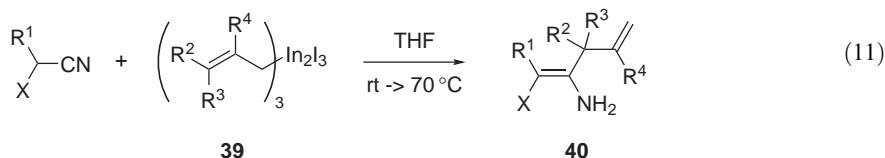
A systematic study of the reaction between benzylamines and polyfluoro 1,3-dicarbonyl compounds has been performed leading to optimized conditions for the large-scale preparation of the corresponding β -enaminones that are useful starting materials for the preparation of fluorinated amines and amino acids <2003TL1647>.

3-Oxo-2,3-dihydrothiophene 1,1-dioxide, prepared by oxidation of commercially available 3-methoxythiophene with dimethyldioxirane, reacts with amines with extrusion of sulfur dioxide to afford high yields of enaminones (Scheme 12) <1999JCS(P1)3085>.



Scheme 12

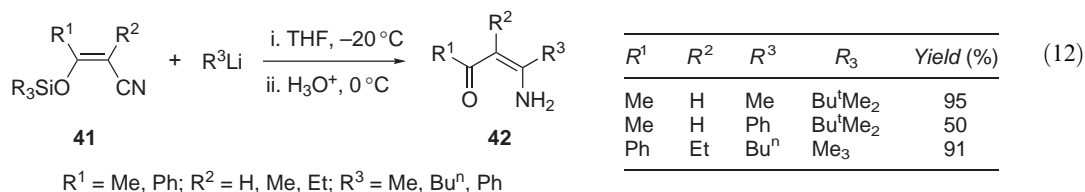
Several new methods for the preparation of enaminones by addition of C-nucleophiles to nitriles have been described. The reaction of allylindium reagents **39** with activated nitriles provide (*Z*)-allylenamines **40** in 55–100% yield (Equation (11)) <1998TL4729, 1999JOC4095>. No reaction takes place using the corresponding allylmagnesium reagent, presumably due to deprotonation of the activated methylene.



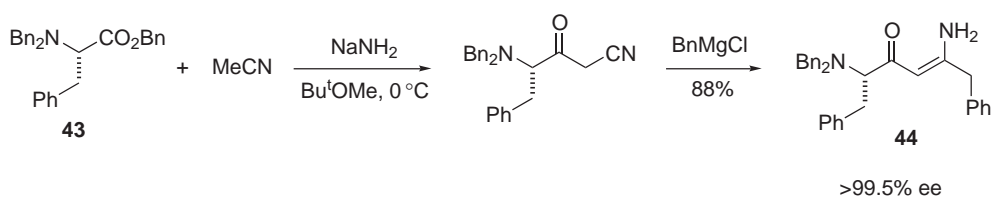
$X = \text{CO}_2\text{Me}, \text{CON}(c\text{-C}_6\text{H}_{11}), \text{CN}$
 $R^1 = \text{H}, \text{Ph}; R^2, R^3 = \text{H}, \text{Me}, \text{Ph}; R^4 = \text{H}, \text{Me}$

X	R^1	R^2	R^3	R^4	Yield (%)
CO ₂ Me	H	H	H	H	100
CON(<i>c</i> -C ₆ H ₁₁)	H	H	H	H	55
CO ₂ Me	Ph	H	H	H	65
CO ₂ Me	H	H	H	Me	90
CO ₂ Me	H	Me	Me	H	64

(*Z*)-3-Silyloxyacrylonitriles **41**, obtained via base-induced ring cleavage of isoxazole precursors, react with organolithium compounds to give high yields of enaminones **42** (Equation (12)) <1995SC1005>.

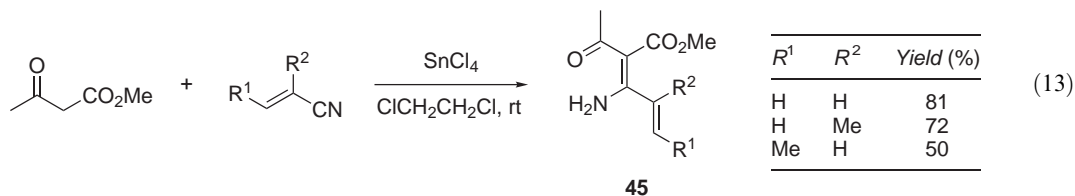


A high-yielding one-pot synthesis of α -amino enaminones **44** from *N,N*-dibenzylamino esters **43** has been realized by addition of the anion of acetonitrile followed by reaction with a Grignard reagent (Scheme 13) <1997TL4191, 1998WOP9854122>. The process takes place without detectable racemization in methyl *t*-butyl ether as solvent.

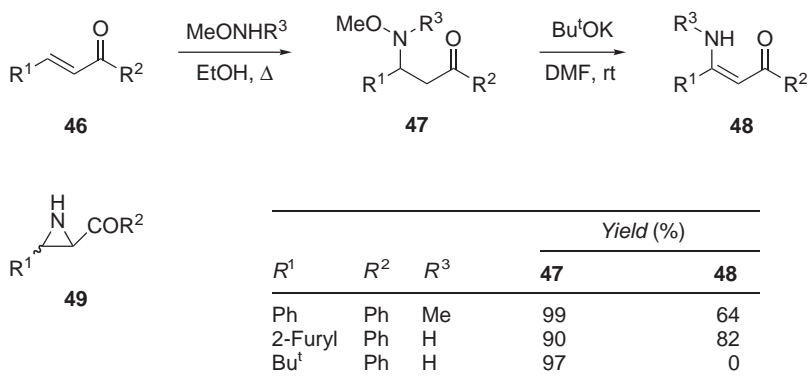


Scheme 13

Tin(IV) tetrachloride promotes the selective nucleophilic addition of methyl acetoacetate to the cyano group of α,β -unsaturated nitriles to give enaminoketoesters **45** (Equation (13)) <2002T9709>.

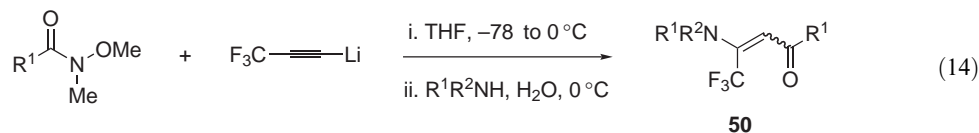



3-(*O*-Methylhydroxylamino)ketones **47**, prepared by addition of *O*-methylhydroxylamine to 1,3-diaryl-2-propen-1-ones **46**, undergo base-induced β -elimination to afford enaminoketones **48** in moderate to good yield (Scheme 14) <1998TL8117>. The reaction is limited to 1,3-diaryl substituted propenones. More than two equiv. of base are required to avoid formation of aziridinoketones **49**, the exclusive product when only one equiv. of base is used.



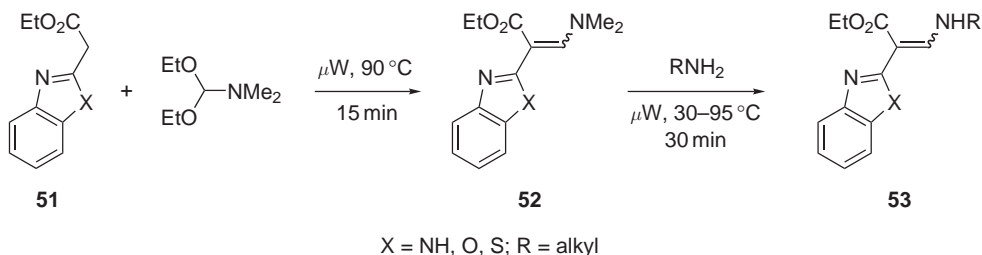
Scheme 14

Jeong has prepared a series of 3-trifluoromethyl enamminones **50** in good yield by addition of trifluoropropynyl lithium to *N*-methoxy-*N*-methylbenzamide followed by treatment with primary and secondary amines in the presence of water (Equation (14)) <2002TL7171>.



R^1	$\text{R}^1\text{R}^2\text{NH}$	Yield (%)
Ph	Me_2NH	73
Ph	BnNH_2	65
Ph	Ph	31
4-MeC ₆ H ₄		98

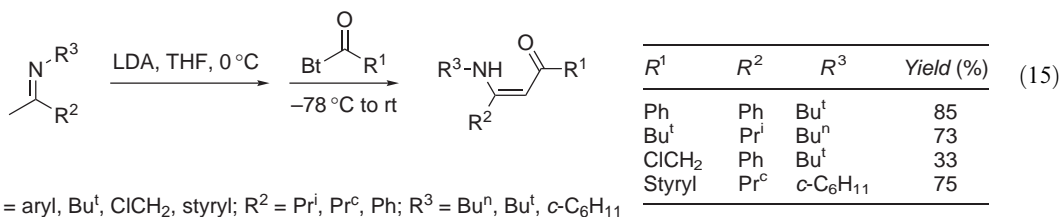
3-Dimethylenamino acrylates **52** can be obtained in high yield in only 15 min by reacting equimolar amounts of *N,N*-dimethyl formamide diethyl acetal and esters **51** without solvent under focused microwave irradiation (Scheme 15) <1998TL8453>. Compounds **52** suffer an efficient transamination reaction upon treatment with a series of primary alkylamines with microwave heating to give enamino esters **53**. A similar solvent-free process assisted by microwaves has been used by Thiel to prepare 1-aryl-3-dimethylaminoprop-2-enones in almost quantitative yield <2001S55>.



X	R	Yield (%)	
		52	53
NH	Bu ^t	82	97
O	Pr ⁱ	83	95
S	Pr ⁿ	70	93

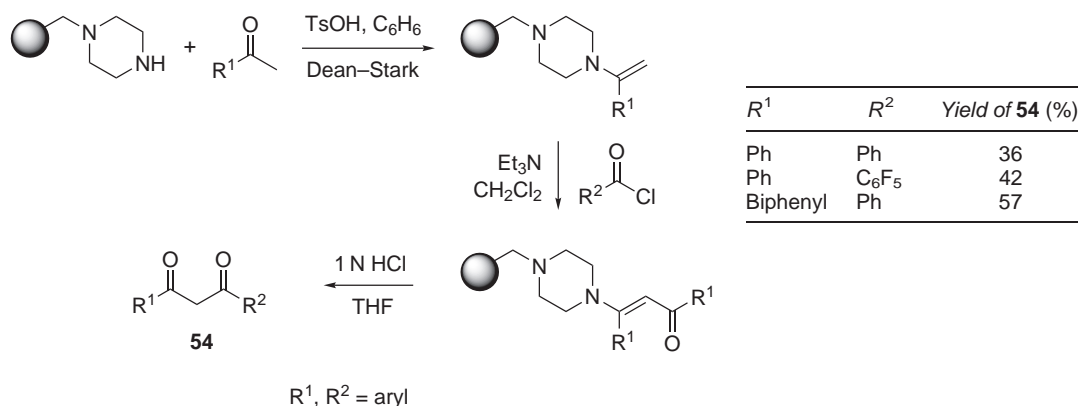
Scheme 15

Katritzky has described the use of *N*-acylbenzotriazoles for the *C*-acylation of metalated ketimines to give enamminones in good-to-excellent yield (Equation (15)) <2000S2029>. Side reactions are observed when the *N*-acylbenzotriazole has a chloromethyl group attached to carbonyl.



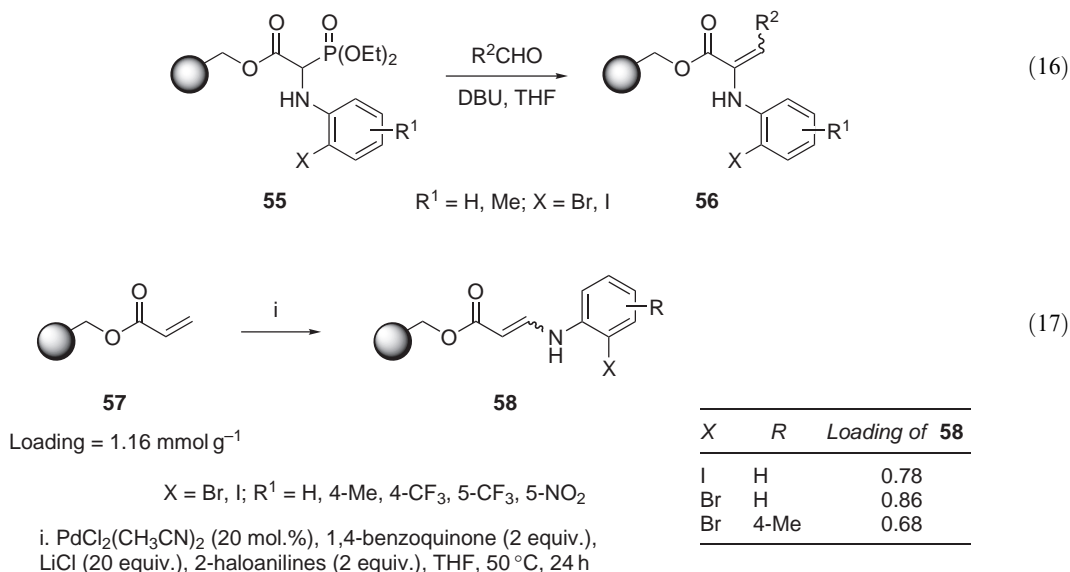
Enaminones have been prepared in solid phase and used as starting materials for the synthesis of heterocycles. The most important methodologies used for the solution-phase synthesis of enaminones have been adapted to solid phase. There are several reports on the preparation of enaminones on

polystyrene-based resins by condensation of 1,3-dicarbonyl compounds and primary amines with either the primary amine <1996JOC924, 1996WOP9633972, 2000JOC6160> or the dicarbonyl compound <1998BMCL2381, 1998TL8263, 2000TL6253, 2001WOP0158870, 2002JCO191, 2003JOC6011> attached to the solid support. Immobilized enaminones have been prepared also by addition of primary alkylamines to solid-supported propynoic amides <2000JOC6160> or by C-acylation of polystyrene-supported enamines with aromatic isocyanates (Scheme 4) <2000TL5683> or carboxylic acid chlorides (Scheme 16) <2003TL1067>. Mild acid hydrolysis of the supported enaminones provides a traceless synthesis of 1,3-dicarbonyl compounds **54**.



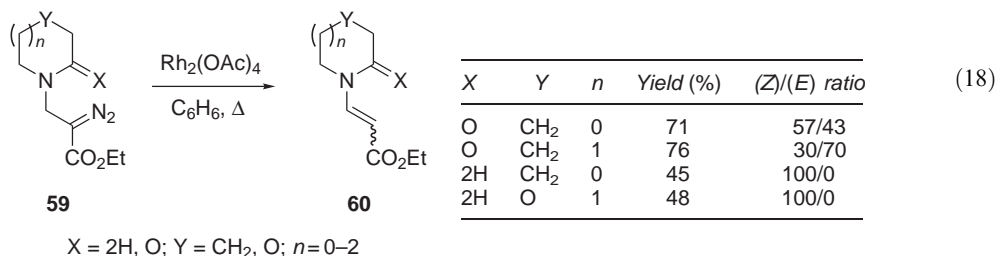
Scheme 16

Kondo has developed several procedures for the preparation of immobilized enaminones for application in the synthesis of heterocycles. Horner-Emmons reaction of solid-supported α -phosphonyl glycine **55** and aromatic aldehydes affords enaminones **56** that have been used for the synthesis of indoles (Equation (16)) <2002CC210, 2002JCS(P1)2137>. In a different approach, enaminones **58** were prepared by palladium-catalyzed oxidative amination of REM resin **57** <1996TL3209, 1997JA3288> with 2-haloanilines in the presence of 1,4-benzoquinone (Equation (17)) <2002JCO191, 2003JOC6011>.



Spivey has prepared a series of enaminones by reacting $\text{Bu}^t\text{O-CH(NMe}_2)_2$ (Bredereck's reagent) with aryl methyl ketones supported on Argogel resin through a germane linker for the traceless synthesis of a library of pyrazoles <2000JOC5253>.

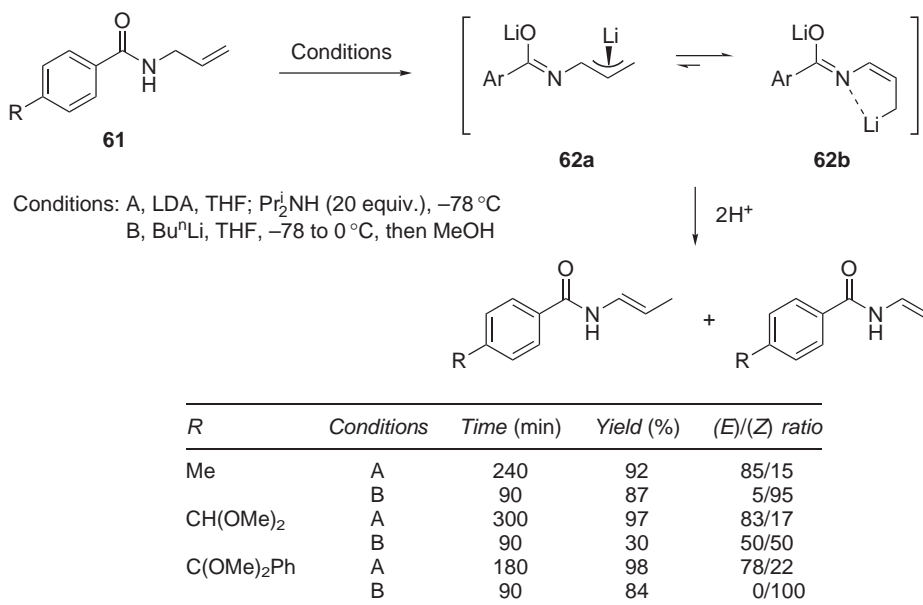
Treatment of cyclic diazoamines **59** (X = 2H) and diazoamides **59** (X = O) with a catalytic amount of rhodium(II) acetate gave the corresponding cyclic enamines **60** (X = 2H) or cyclic enamides **60** (X = O) by β -hydride elimination of the metal carbene intermediate (Equation (18)) <2002S471>. Interestingly, in the case of X = 2H the (Z)-enamine is produced stereoselectively.



2.15.2.1.4 N-Acylenamines

A review on the synthesis and reactivity of the simplest member of this family, *N*-vinyl formamide, has been published <2000JPR(342)115>.

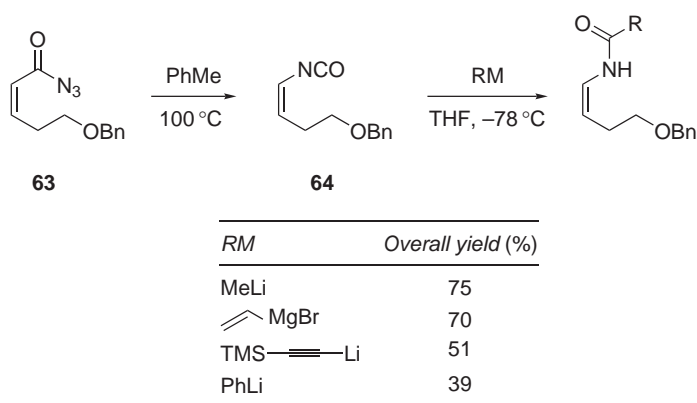
Isomerization of readily available *N*-allyl amides is one of the most convenient methods for the preparation of *N*-acylenamines and is a key step for the deprotection of those amino groups. Considerable progress has been made in this area in the 1980s. The isomerization can be catalyzed by base or by transition metal complexes. Starting from *N*-allylbenzamides **61** and depending on the base and the conditions used, the stereoisomer derived from protonation of the kinetic **62a** or thermodynamic **62b** dilithiated species can be selectively obtained in good yield (Scheme 17) <2001TL3571>. Among other metal catalysts, ruthenium <1996PJC133, 1996PJC813, 1996PJC1223, 1997PJC747, 2000JOC2204, 2001TL7095, 2002MI(189)169> and iron <2002SL1313> complexes are able to promote the isomerization in high yield and with moderate-to-high (*E*)/(*Z*) selectivity depending on the catalyst and the substituents on the starting *N*-allyl amide (a good account of previous work with other metal catalysts is given in the references cited above).



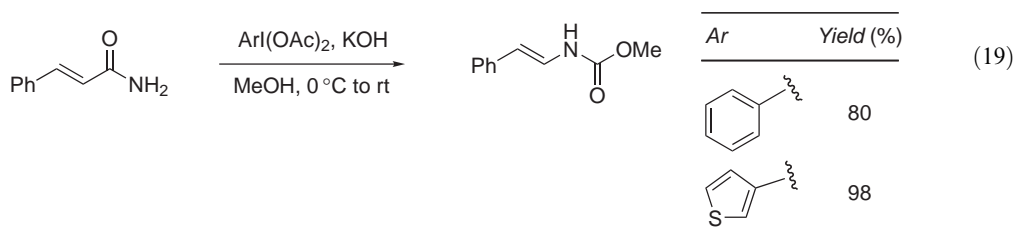
Scheme 17

A stereoselective synthesis of *N*-acylenamines was accomplished by Curtius rearrangement of α,β -unsaturated acyl azides **63** and subsequent nucleophilic addition to the resultant isocyanate **64** (Scheme 18) <2000SL397, 2002CL128>. Vinyl isocyanate isomerization has been observed when applying this methodology to (*Z*)-cinnamic acid, which gives exclusively the (*E*)-enamide

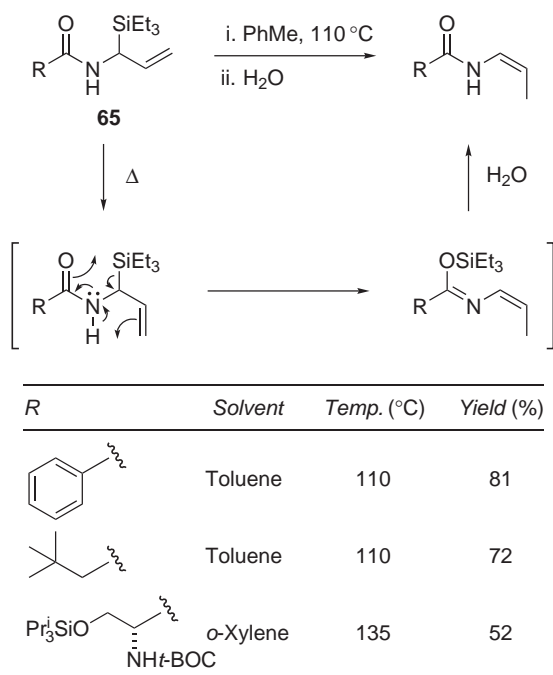
<2000TL3735>. Related to this, the Hofmann rearrangement of α,β -unsaturated amides is an old method for the stereoselective preparation of enamides. (Diacetoxyiodo)arenes promote this transformation under basic conditions in very high yield and high stereoselectivity (Equation (19)) <1993JOC2478, 2000JOC8391>.



Scheme 18



Danishefsky and Lin have reported a novel and very mild synthesis of (*Z*)-enamides from silyl amides **65** by a concurrent ene- and silatropic-type bond reorganization (Scheme 19) <2002AG(E)512, 2003JA5111>. The procedure has been applied successfully to highly functionalized substrates.

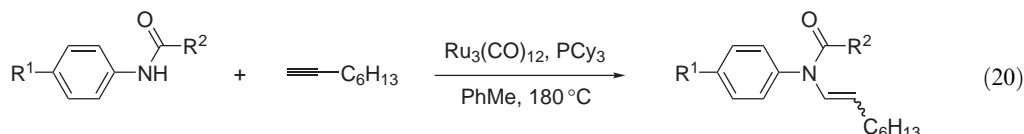


Scheme 19

Another efficient procedure for the stereoselective preparation of enamides is the cross-coupling reaction of amides or carbamates with vinyl halides in the presence of nickel [<1998WOP9800399>](#) or copper [<2000OL1333, 2001CEJ5286, 2002OL3103, 2003OL3667>](#) complexes.

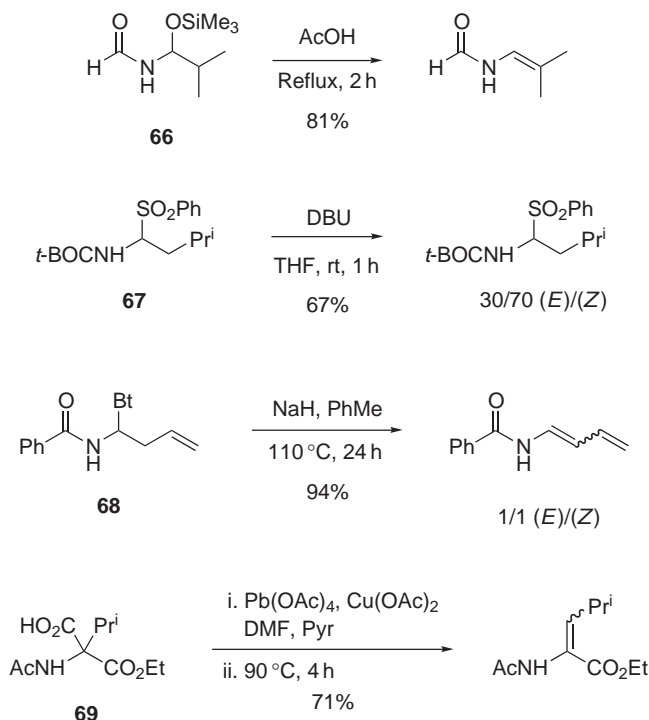
Vinyl silanes can be converted into enamides by a sequence of reactions comprising epoxidation, nucleophilic ring opening of the resulting epoxysilanes with NaN_3 , reduction of the azide, and a one-pot *N*-acylation/Peterson elimination process [<2001OL3955>](#). This method has a wide scope and, most importantly, is stereospecific, the stereochemistry of the starting silane being fully transferred into the final product in a predictable way.

N-Aryl substituted amides can be added to nonactivated terminal alkynes using a ruthenium catalyst to afford the corresponding (*E*)-enamides with high regio- and stereoselectivity (Equation (20)) [<1995CC413>](#).



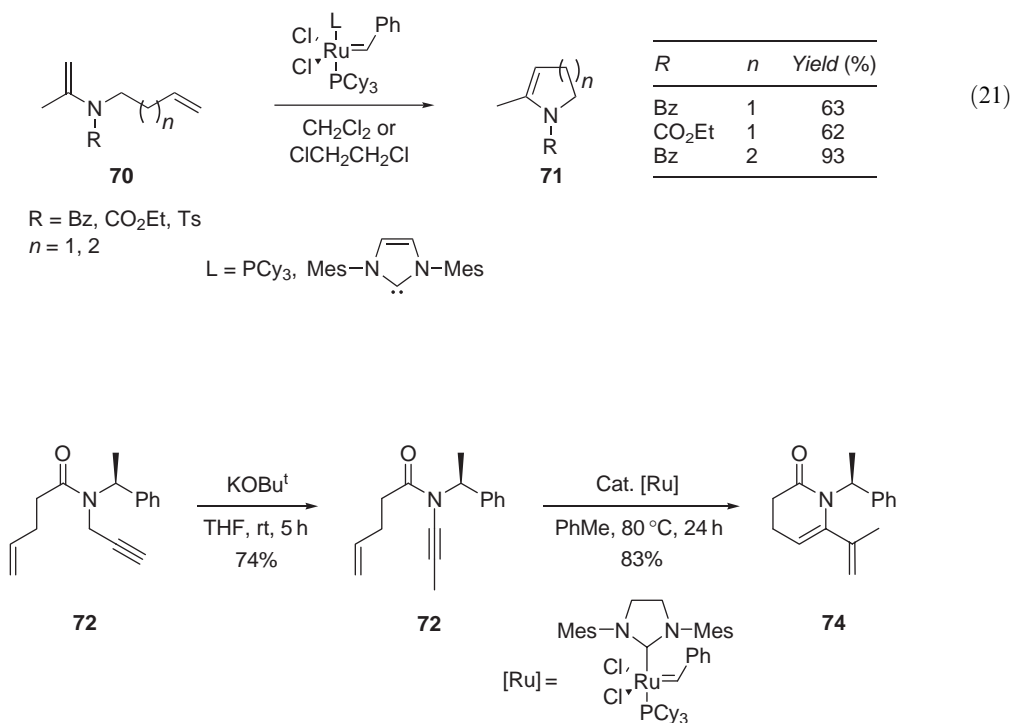
R^1	R^2	Yield (%)	(<i>E</i>)/(<i>Z</i>) ratio
H	H	67	93/7
MeO	H	58	89/11
H	Me	65	100/0

N-Acylenamines have been prepared by different elimination reactions starting from 1-acylamino-1-(trimethylsiloxy)alkanes **66** [<1996JCS\(P1\)895>](#), α -amidoalkyl phenyl sulfones **67** [<1997SL491, 1997T4835, 2000SL73>](#), *N*-(α -benzotriazol-1-ylalkyl) amides **68** [<1995JOC4002, 2000HCA2712>](#) and ethyl hydrogen acetoamidomalonate derivatives **69** [<1998CL675>](#) (Scheme 20).



Scheme 20

Acyclic alkene-containing enamides **70** have been converted into five- and six-membered cyclic enamides **71** in 24–68% yield by ring-closing metathesis using ruthenium-based catalysts (Equation (21)) <2001OL2045>. Ring-closing metathesis has also been applied to the preparation of cyclic enamides **74** from inamides **73** obtained by base-induced isomerization of propargyl amides **72** (Scheme 21) <2002OL2417>.



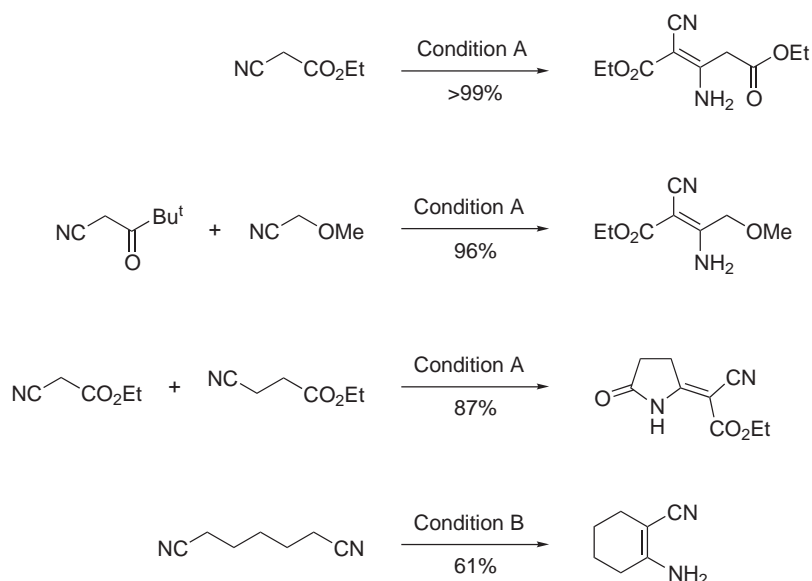
Scheme 21

2.15.2.1.5 α - and β -Cyanoenamines

An improved protocol for the synthesis of α -cyanoenamines by Peterson olefination using Bu^tLi as the base has been described <2003S414>. A common procedure for the preparation of β -cyanoenamines is the nucleophilic addition of α -deprotonated alkanonitriles to other nitriles, most commonly an aromatic nitrile. This reaction is classically performed under basic conditions. Recent examples include the use of ultrasonically dispersed potassium <2001OPP351>, KOBu^t <1998JHC805>, LDA <1999M441>, and NaH <2000BMCL1211> as bases.

Murahashi and co-workers have found that the addition of nitriles to the CN triple bond of nitriles to give β -cyanoenamines can also be performed under very mild neutral conditions using an iridium hydride complex catalyst <1998JA4244>. The catalyst is able to simultaneously activate both the C _{α} –H bond of nitriles as pronucleophiles and the CN triple bond of nitriles as electrophiles with high chemoselectivity. This reaction is highly stereoselective and high yielding and allows very efficient intermolecular cross-couplings of activated nitriles with nonactivated nitriles as well as the intramolecular coupling of nonactivated alkanedinitriles (Thorpe–Ziegler-type reaction) to give cyclic cyanoenamines when a more basic iridium catalyst is used (Scheme 22).

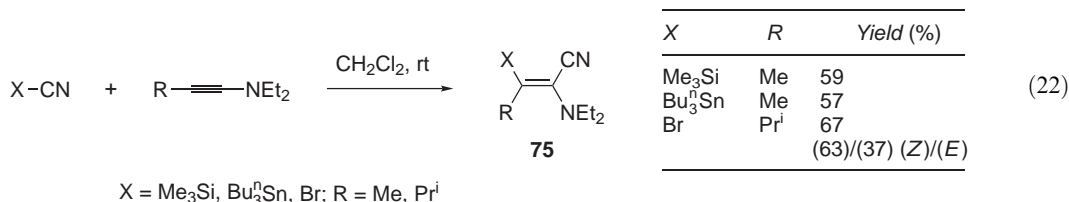
Addition of allylindium to malononitrile provides (*Z*)- β -cyanoenamine **40** (X = CN, R¹ = R² = R³ = R⁴ = H) in 77% yield (Equation (11)) <1998TL4729, 1999JOC4095>.



Scheme 22

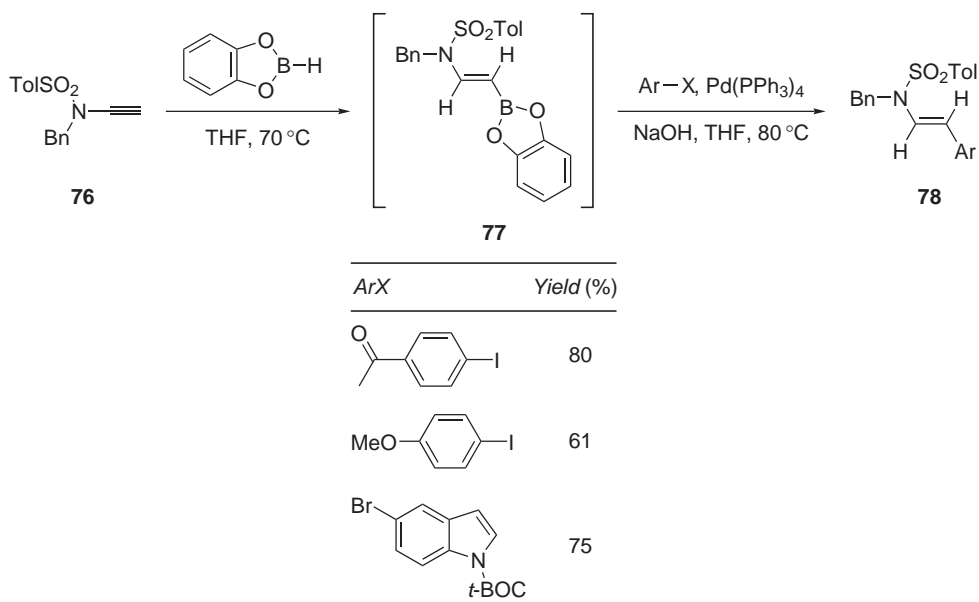
2.15.2.1.6 Miscellaneously substituted enamines

1-Alkynylamines (ynamines) <1995COFGT(2)1039> are highly versatile precursors for a number of element-substituted enamines. Thus, trimethylsilyl cyanides, tributyltin cyanides, and cyanogen bromide react with ynamines regio- and stereoselectively to give β -substituted α -cyanoenamines **75** by a *syn*-addition process (Equation (22)) <2001T10309>. In the case of cyanogen bromide, the initial (*Z*)-isomers undergo a facile isomerization into (*E*)-isomers.

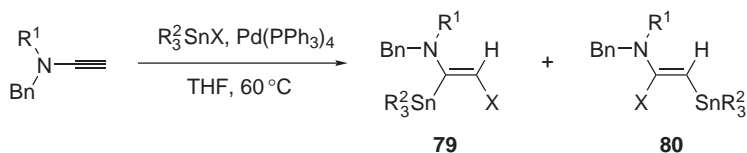


Hydroboration of ynamide **76** with catecholborane proceeded chemo-, regio-, and stereoselectively to give the unstable monohydroboration product **77**, which was subjected to Suzuki–Miyaura cross-coupling with a series of structurally diverse aryl bromides and aryl iodides to give (*E*)- β -arylenamides **78** (Scheme 23) <2000T8473>. In a complementary approach, Cintrat and co-workers have described the palladium-catalyzed stannylation of ynamides to give enamides **79** and **80** with complete stereoselectivity and moderate-to-high regioselectivity depending on the substitution pattern on nitrogen. α -Stannyl enamides **79** were cross-coupled with a wide range of electrophiles under modified Stille conditions to give differently α -substituted enamides **81** with complete stereocontrol (Scheme 24) <2001JOC7385, 2001S705, 2002CEJ1637, 2003S1391>.

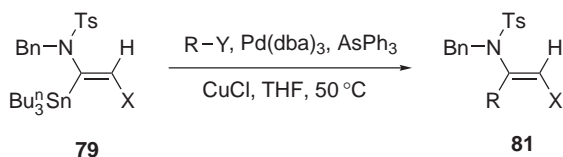
β -Phosphino-substituted α -cyanoenamines **83** were obtained by hydrocyanation of phosphorus-substituted ynamines **82** with acetone cyanohydrin as a source of hydrogen cyanide (Equation (23)) <2001T10309>. The kinetic *syn*-addition product (the (*Z*)-isomer) slowly isomerizes to the more stable (*E*)-isomer.



Scheme 23



R^1	R^2	X	Yield of 79 (%) (79/80 ratio)
Bz	Bu ⁿ	H	80 (85/15)
Bz	Bu ⁿ	Me ₃ Si	49 (55/45)
Ts	Bu ⁿ	Me ₃ Si	91 (100/0)
Bz	Me	Me ₃ Sn	86 (100/0)



R-Y = ArBr, ArI, RCOCl, BnBr, allyl bromide, propargyl bromide

X	R-Y	Yield (%)
H	<chem>Brc1ccccn1</chem>	51
H	<chem>BrC(=O)c1ccccc1</chem>	77
Me ₃ Si	<chem>BrCc1ccccc1</chem>	80

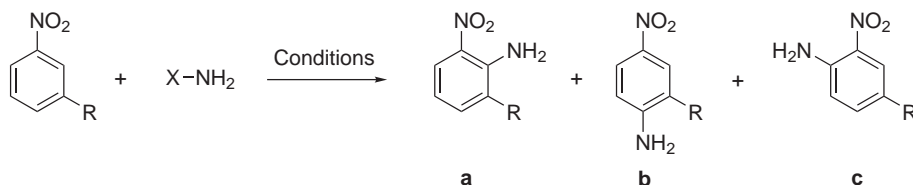
Scheme 24

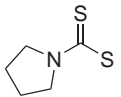
2.15.2.2 Arylamines

Amazing progress has been made during the 1990s on the application of transition metal catalysts for the synthesis of arylamines. The most important developments have taken place in the field of nucleophilic amination of aromatic substrates, covered in several review articles and book chapters <1997SL329, 1998ACR805, 1998ACR852, 1998AG(E)2046, 1998JCS(P1)2615, 1999JOM(576)125, 1999T11399, B-2002MI(1)1051, 2002T2041, 2002TCC(219)131, 2003AG(E)5400>. The following sections will summarize metal-catalyzed methods as well as other new tools developed for the synthesis of aromatic amines since the publication of COFGT (1995) <1995COFGT(2)737>.

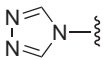
2.15.2.2.1 From hydrides (RH)

The classical approach to the synthesis of aromatic amines involving electrophilic aromatic nitration followed by reduction of the nitro group suffers from some limitations, the most serious being the harsh reaction conditions usually required, which may be incompatible with some functional groups, and the problem of regioselectivity. Vicarious nucleophilic substitution (VNS) of hydrogen <1998JPO341> has the advantage of being a single step and not requiring strongly acidic or oxidizing reaction conditions, although it is restricted to electrophilic arenes. Reagents for VNS with amine nucleophiles have the general formula X-NH₂, where X is an auxiliary group capable of stabilizing a negative charge and being eliminated as HX from the σ -adduct intermediate. 4-Amino-1,2,4-triazole <1986JOC5039>, 1,1,1-trimethylhydrazinium iodide <1996JOC2934, 2001T4753, 2003JOC2498>, *O*-alkylhydroxylamines in the presence of copper <1996JOC442, 1999JCS(P1)1437> or zinc <1998JCS(P1)1519> catalysts, hydroxylamine <2001JCS(P1)376> and sulfenamides <1992JOC4784, 1998JOC4878> have been used for this purpose (Scheme 26). Direct amination of nitroarenes by VNS of hydrogen has also been performed with primary amines and amides under electrochemical oxidation conditions with or without base in useful yields (15–85%) <2001MI1176, 2002EJO251>.



X	R	Conditions	Yield (%) (a/b/c ratio)
Me ₃ N ⁺	H	KOBu ^t , DMSO, rt	85 (61/39/NA)
Me ₃ N ⁺	Cl	KOBu ^t , DMSO, rt	83 (32/49/19)
Me ₃ N ⁺	I	KOBu ^t , DMSO, rt	76 (45/38/17)
MeO	H	KOBu ^t , Cat. CuCl, DMF, rt	93 (71/29/NA)
MeO	Me ₂ N	KOBu ^t , Cat. CuCl, DMF, rt	99 (10/75/15)
	H	KOBu ^t , DMF, rt	85 (16/84/NA)



X	Conditions	Yield (%)
HO	KOH, ZnCl ₂ , EtOH, rt	54
	KOBu ^t , DMSO, rt	76

Scheme 26

Dinitrobenzenes have been directly aminated with a solution of potassium permanganate in liquid methylamine to give the corresponding mono- and bis-(methylamino)-substituted derivatives in moderate yield <1995RTC(114)13>. Hydrazoic acid reacts with aromatic compounds in the presence of both trifluoromethanesulfonic acid and TFA to give primary arylamines without diamine contaminants in good yield <1993JCS(P1)867>.

Electrophilic amination is receiving increasing attention as an important synthetic process to create C—N bonds <1997SL741>. Narasaka has described the use of *N,N*-dimethyl-2-imidazolidinone *O*-methoxyacetyloxime for the electrophilic amination of electron-rich arenes under SnCl_4 catalysis to give the corresponding *N*-arylimines, which can be converted to anilines by hydrolysis with CsOH and to *N*-methylanilines by LiAlH_4 reduction <2003CL548>.

2.15.2.2.2 From nitro derivatives

Reduction of nitroarenes to the corresponding arylamines is a fundamental organic transformation that can be performed with a vast variety of reagents as covered in COFGT (1995) <1995COFGT(2)737> and in several recent review articles <1996CRV2035, 1997MI415, 2003MI(345)103> and monographs <B-1999MI003, B-2001MI389, B-2001MI004>. Selectivity is a key issue when the reduction is performed on polyfunctionalized arenes and a number of new reagents and catalysts have been developed that permit a high level of chemo- and even regioselectivity (Table 2).

Table 2 Chemoselective reduction of nitroarenes to arylamines

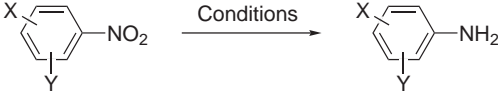


		
Conditions	<i>X, Y</i> (yield)	References
Cat. NiMCM-41, KOH, Pr^iOH , 83 °C, 3.5–5 h	2-Cl (85%), 4-Br (91%), 4-OMe (90%), 2-NH ₂ (85%), 4-COMe (83%), 4-CN (76%)	<2002OL4297>
Cat. $\text{Zr}_{0.8}\text{Ni}_{0.2}\text{O}_2$, KOH, Pr^iOH , 83 °C, 3–6 h	4-Cl (85%), 4-COMe (88%), 2-OMe (86%)	<1997CC1119>
Cat. Raney Ni, HCO_2H or HCO_2NH_4 , MeOH, rt, 10–30 min	2/3/4-OH (85–90%), 2/4-CHO (89–90%), 4-COPh (90%), 2/3/4-Br (91–92%), 3-I (89%), 4-CH=CH-CO ₂ H (90%), 4-CN (92)	<2000SC2889>
Cat. Raney Ni, NH_4Cl , H_2O , 80–90 °C, 1.5–3 h	2-NHCOMe (91%), 2-OH (91%), 2-Cl (80%), ^a 3-CHO (66%), 3-CONH ₂ (57%)	<2003CJC197>
Cat. Raney Ni, $\text{NH}_2\text{NH}_2 \cdot \text{HCO}_2\text{H}$, MeOH, rt, 2–6 min ^b	3-OH (94%), 4-OMe (95%), 4-OAc (93%), 3-CO ₂ H (94%), 4-CH=CH-CO ₂ H (90%), 3-Cl (92%), 3-Br (94%)	<2002T2211>
Cat. PdCl_2 , BINAS or TPPTS, ^c NaOH, CO (120 bar), H_2O /xylene, 100 °C	2-Cl,4-COMe (56–70%), 2-Cl,4-CF ₃ (45–85%), 4-Cl,2-CN (60%), 3-Cl,2-OH (5–10%), 3-CH=CH ₂ (50%)	<1995TL9305>
Cat. Pd/C or Pt/C, ZnX_2 (X = Cl, Br, I), H_2 (1 atm), 22 °C, 4 h	4-Cl, 3-Me (91–98%), 4-Br, 3-Me (94–99%), 4-I,3-Me (87–97%)	<2003SI657>
Cat. Pd/C, NH_4OAc , H_2 , MeOH, rt, 3 h	4-CO ₂ (CH ₂) ₂ OBn (90%)	<1998T13981>
Cat. Pd/C, ethylenediamine, H_2 , THF, rt, 8 h	4-(CH ₂) ₂ NHCbz (60%)	<2000T8433>
Cat. Pd/C, ethylenediamine, H_2 , THF, rt, 8 h	4-CO ₂ -  (96%)	<2000CEJ2200>
	4-O-  (94%)	

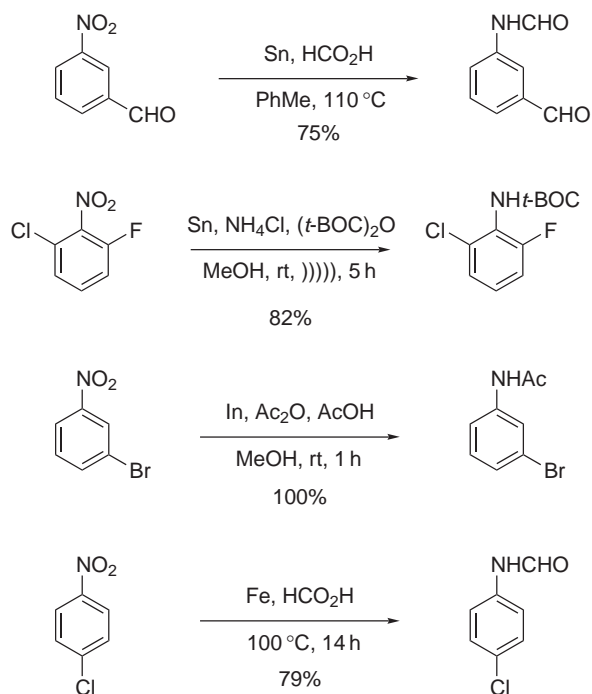
Table 2 (continued)

Conditions	X, Y (yield)	References
Cat. $\text{Ru}_3(\text{CO})_{11}$, Et_3N or Pr^i_2NH , CO (20 atm), Diglyme, H_2O , 150°C , 2 h	2-Cl (>99%), 4-Cl (>99%), 2-Br (>99%), 4-CN (99%), 4-COPh (>99%)	<1995JMOC203>
Cat. $\text{RhCl}(\text{PPh}_3)_3$, Et_3SiH , PhMe, 110°C , 2–6 h	4-OMe (86%), 4-Cl (71%), 4-Br (0%), 3-COMe (71%), 4-CO ₂ Me (49%)	<1996SC973>
Cat. $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, μW , 7–10 min	4-MeO (96%), 4-Cl (96%), 4-I (91%), 2-OH (81%)	<2001TL5347>
Cat. $[\text{Fe}_x\text{O}_y]$, $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, EtOH, 70°C	3/4-N=N-Ar (44–99%)	<1999MI9>
Zn, $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, MeOH, rt, 3.5–10 min	4-Cl (93%), 4-Br (95%), 3-I (91%), 2-OH (93%), 4-OMe (95%), 2-NH ₂ (93%), 4-COMe (93%), 2-CO ₂ H (92%), 4-CN (91%), 4-CH=CH-CO ₂ Me (91%)	<2003IJC(B)180>
Cat. $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, $\text{Me}_2\text{N}-\text{NH}_2$, MeOH, 85°C , 18–25 h	4-Cl (89%), 4-OH (100%), 4-CO ₂ Me (88%), 4-CN (42%)	<1995TL2411>
Cat. $\text{Fe}(\text{II})$ -phthalocyanine, NaBH_4 , $\text{BrCH}_2\text{CH}_2\text{OH}$, Diglyme, rt, 0.25–20 h	4-CO ₂ Me (75%), 4-I (81%), 4-CH ₂ CN (98%), 4-NHCbz (87%)	<2001TL167>
In, HCl, THF/ H_2O , rt, 0.5–1 h	4-Br (98%), 4-Br,3-Me (84%), 4-OMe (89%), 3-F, 4-F (75%), 2-CH ₂ CH=CH-CO ₂ Et (77%)	<2001S81>
Cat. Cp_2TiCl_2 , Sm, THF/MeOH, rt, 10 min	4-I (91%), 2-Cl (73%), 4-Cl (84%), 3-Br (78%), 2-OH (73%)	<1997SC1059>
Cat I_2 , Sm, NH_4Cl , THF/ H_2O , rt, 4–6 h	4-Br (70%), ^d 3-Br (63%), 4-Cl (65%), 3-I (68%)	<1999SL1065>
Cat I_2 , Sm, MeOH, 65°C , 3–8 h	4-OMe (88%), 4-Br (86%), 2-CO ₂ Et (86%)	<1998TL7243>
Cat. 1,1'-dioctyl-4,4'-bipyridinium dibromide, Sm, MeOH, rt, 1–19 h	2-CN (88%), 4-Cl (78%), 4-Br (85%), 4-NHTs (96%), 3-CH=CH ₂ (82%), 4-CH ₂ CH ₂ N ₃ (92%), 4-CH ₂ CH ₂ NO ₂ (83%)	<2001JOC919>
Mg, $(\text{NH}_4)_2\text{SO}_4$, MeOH, 50°C , 10–35 min	4-Cl (90%), 4-I (83%), 4-CO ₂ H (75%), 4-COMe (75%), 4-CN (78%)	<1995SC4025>
Al, NH_4Cl , MeOH,)))), rt, 1–3 h	4-Cl (805), 2-Cl (70%), 3,4-Cl ₂ (75%), 2-OH (90%), 3-CO ₂ H (70%)	<1999TL7855>
NaBH_4 , $(\text{NH}_4)_2\text{SO}_4$, EtOH, rt, 0.3–2 h	4-Cl (90%), 4-I (80%), 2-CO ₂ H (70%), 4-COMe (76%), 4-CN (80%), 3-CH=CH ₂ (75%)	<1995CL725>
NaBH_4 , BCl_3 or SbCl_3 , EtOH, rt, 10–90 min	2-OH (95%), 4-OH (90%), 2-OEt (85%), 4-NH ₂ (91%), 4-Cl (92%), 4-CO ₂ H (95%)	<1995SC3799>
$\text{Ca}(\text{BH}_2\text{S}_3)_2$, THF, 65°C , 0.7–7 h	4-OH (89%), 3-Cl (84%), 4-Cl (90%), 4-NH ₂ (88%), 4-CO ₂ H (88%)	<2000SC587>
$\text{CIP}(\text{OEt})_2$, Pr^i_2NEt , CHCl_3 , rt, 0.5–24 h	4-CHO (>95%), 3-Cl,4-Me (>95%), 4-COMe (>95%), 4-CN (20%), ^c 4-OMe (20%) ^d	<1998JOC393>
57% HI, 90°C , 2–4 h	2-Br (60%), 4-Br, 2-SO ₂ NH ₂ (90%), 4-COMe (80%), 4-CN (85%), 4-SMe (55%)	<2001TL5601>
Bakers' yeast, H_2O , DMSO or EtOH, 32°C , 2–4 d	4-CN (79%), 4-COMe (85%), ^c 2-NO ₂ (78%), 4-NO ₂ (60%), 4-SOMe (25%)	<1994TL7867>

^a Dehalogenation is also observed (20%). ^b The rest is starting material. ^c Water-soluble sulfonated phosphines. ^d *N,N'*-Diaryl hydrazine is also produced (18%). ^e Nitrile groups are also reduced under these conditions.

Metal reduction in the presence of carboxylic acids and other acylating reagents have been used for the direct one-pot conversion of nitroarenes to the corresponding *N*-arylamides or carbamates in good yield and with high chemoselectivity. Iron <2002MI1359>, indium <2003TL77>, and tin <1997SL1069, 2002SL771> have been used successfully for this purpose (Scheme 27).

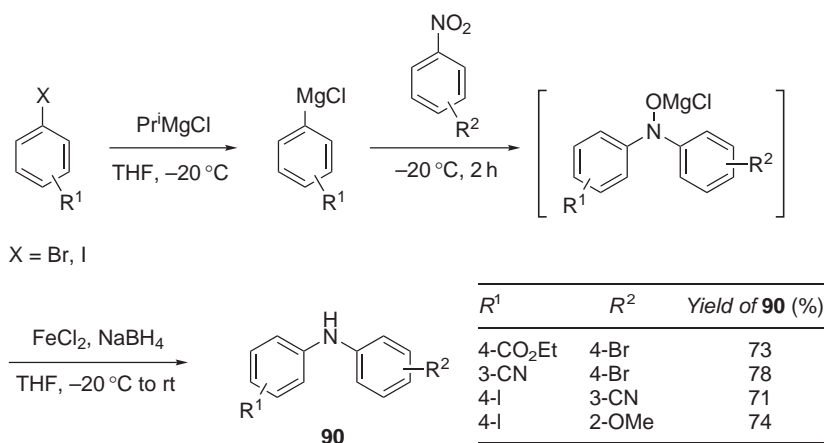
In spite of the large number of reagents that reduce nitroarenes to arylamines, only a few can be used to perform this reduction on solid-supported nitroarenes due to the fact that the reducing



Scheme 27

species needs to be soluble under the reaction conditions to be able to reach the attached substrate. Stannous chloride [<1996TL8081, 1997JOC3874, 1998JOC1172, 1998TL179, 1998TL201, 2001AG\(E\)381, 2003CEJ3282>](#), sodium dithionite in refluxing ethanol [<1996TL7595, 2000TL6531>](#), $\text{NaBH}_4/(\text{Cu}(\text{acac})_2)$ [<1996TL4887>](#), CrCl_2 [<1999TL245>](#), $\text{CrCl}_2/\text{Mn}/\text{TMSCl}$ [<1999AG\(E\)2777>](#), and $\text{Pd}(\text{OAc})_2/\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ [<2002SC1181>](#) have been used with success for the chemoselective reduction of solid-supported nitroarenes to arylamines.

Polyfunctional diarylamines **90** can be readily obtained in good yield by treating a nitroarene with an excess (>2 equiv.) of a functionalized arylmagnesium compound, prepared by a bromide- or iodide-magnesium exchange reaction [<2003AG\(E\)4302>](#), followed by *in situ* reduction of the unstable intermediate diarylhydroxylamine with $\text{NaBH}_4/\text{FeCl}_2$ (Scheme 28) [<2002JA9390, 2003AG\(E\)1444>](#). Nitrosoarenes are thought to be intermediates in the reaction and can be used instead of nitroarenes following the same procedure to give diarylamines in moderate yield [<2003SL885>](#). This method is complementary to the transition metal-catalyzed *N*-arylation of arylamines and has a broad synthetic scope.



Scheme 28

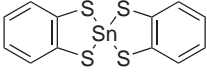
2.15.2.2.3 From azides

Arylamines can be obtained by reduction of the corresponding azides with a large variety of reagents as described in a recent review <2002OPP109> and in Larock's monograph <B-1999MI003>. Table 3 includes recent examples of chemoselective reduction of aromatic azides in the presence of other functional groups. Reduction of solid-supported aryl azides to the corresponding arylamines has been performed with $\text{SnCl}_2/\text{PhSH}/\text{Et}_3\text{N}$ (1:4:5) in CH_2Cl_2 <1997JOC6102>. Chemoselective reduction of aryl azides with concomitant *N*-acetylation has been achieved by treatment with TMSCl in Ac_2O at reflux <1999SL553>. Ether, ester, and halide groups remain unaffected. Reduction of aryl azides with Et_3SiH catalyzed with $\text{Pd}(\text{OH})_2/\text{C}$ in EtOH in the presence of *t*- BOC_2O generated the corresponding *t*-butylcarbamates in almost quantitative yield <1997TL2129>. Similarly, azides can be directly transformed into the corresponding *t*-butylcarbamates in very good yields by hydrogenation in the presence of *t*- BOC_2O using Lindlar's catalyst in MeOH at room temperature <2002EJO3740>. This method is extremely chemoselective, the rather labile *N*-Cbz and benzyl ester groups being inert under the reaction conditions.

Table 3 Chemoselective reduction of aryl azides to arylamines

Conditions	X, Y (yield)	References
Cat. $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, H_2O , rt, 20 min TMSCl , NaI , MeCN , rt, 5–10 min	4- NO_2 , 3- CO_2Me (92%) 4-Br (97%), 2,4- Cl_2 (97%), 4- NO_2 (96%), 2- CO_2H (98%), 2-CHO, 3-OH, 4-OMe (98%)	<2000S646> <1997TL6945>
In, NH_4Cl , EtOH , 78 °C, 1 h ($\text{PhCH}_2\text{NEt}_3$) $_2\text{MoS}_4$, MeCN , H_2O , 4–6 h $\text{S}(\text{SiMe}_3)_2$, MeOH , rt, 1.5–6 h	2- CO_2H (96%), 2- CO_2Me (92%) 4-COMe (90%), 4- CO_2Me (92%) 2-CHO (78%), 2- NO_2 (86%), 4- NO_2 (92%), 2-CN (90%)	<1999TL3937> <1995JOC7682> <1995JOC2254>
Cat. (Bu_3Sn) $_2\text{O}$, PhSiH_3 , Pr^nOH , AIBN, PhH , 90 °C, 1.5–2 h $\text{BHCl}_2 \cdot \text{SMe}_2$, CH_2Cl_2 , rt, 1.5–2 h $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, NH_3 , MeOH , rt, 2.5 h	4-OMe (94%) H (94%) ^a 4-Cl (98%), 2-COMe (96%), 2- CO_2H (96%), 2-COPh (94%)	<1998JOC2796> <2002T10059> <2000TL7743>
HI, H_2O , rt, 1.5–2 h	4-Cl (90%), 2- CO_2H (95%), 2- CO_2Me , 3,4-(OMe) $_2$ (90%)	<2002TL6629>
FeCl_3 , NaI , MeCN , rt, 10–20 min	4-Cl (95%), 4-OMe (75%), ^b 4- NO_2 (98%), 2- CO_2H ^c	<2002TL6861>
Zn, FeCl_3 , EtOH , rt, 4–6 h	4-Cl (90%), 4-Br (90%), 2- NO_2 (80%), 4-OMe (86%), 2-COMe (85%), 2- CO_2H (80%)	<2000CL816>
SmI_2 , THF, rt, 30 min	4-OMe (95%), 2-Cl (90%), 4-Cl (88%), 2-COMe (98%), 4-COMe (90%), 2-CHO (79%)	<1995TL7313, 1995TL7427>
Cat. I_2 , Sm, MeOH , rt, 6 h	4-Cl (86%), 4-Br (93%), 4-I (91%), 2- CO_2H (70%) ^d	<1997TL1065>
CpTiCl_2 , Sm, THF, 70 °C, 10 min Sm, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, THF, 40 °C, 2.5 h	4-Cl (78%), 4-Br (81%), 2,4- Cl_2 (80%) 4-Cl (85%), 4-Br (83%), 4-I (87%), 2- NO_2 (82%), 2,4- Cl_2 (83%)	<1996SC2911> <2002SC189>
Zn, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, THF, rt, 2–2.5 h	4-Cl (85%), 4-Br (92%), 4- NO_2 (80%), 4-OMe (85%), 4-COMe (80%)	<1997SL1253>
Fe, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, THF, rt, 25–60 min	4-Cl (85%), 4- NO_2 (85%), 4-OMe (90%), 4-COMe (80%), 4-OH (15%)	<1996TL4559>
Zn, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, THF, rt, 0.5–1 h	3-Cl (85%), 4-Br (83%), 2- NO_2 (80%), 4-OMe (90%), 4-COMe (80%)	<1997CL789>
Zn, NH_4Cl , EtOH , H_2O , 80 °C, 2 h	4- CO_2Me (98%)	<2002SC3279>
AlI_3 , PhH , 80 °C, 10–15 min	3-Cl (89%), 3-OH (92%), 3- NO_2 (95%), 3-OMe (93%), 4-COMe (92%)	<1999IJC(B)128>

Table 3 (continued)

Conditions	X, Y (yield)	References
Me ₂ N-NH ₂ , FeCl ₃ ·6H ₂ O, MeOH, rt, 1–3h	4-Cl (78%), 4-NO ₂ (81%), 2-COMe (80%), 2-CO ₂ H (90%), 2-CO ₂ Me (80%), 2-CO ₂ H, 4-OMe, 5-OH (90%)	<1998CL593>
NaBH ₄ , LiCl, THF, 0 °C to rt, 30 min	4-OMe (94%), 4-OH (90%), 2-CO ₂ H (85%)	<2000SC4495>
[Zn(BH ₄) ₂ (DABCO)], THF, 70 °C, 50 min	4-Cl (92%), 4-NO ₂ (97%), 4-CO ₂ Et (92%), 3-CN (94%)	<1998SC1257>
 , NaBH ₄ , THF-buffer, 15 °C, 15min	4-CO ₂ Me (100%)	<2000OL397>
Bakers' yeast, H ₂ O, MeOH, rt, 2–5 h	4-Cl (90%), 4-Br (82%), 3-I (80%), 4-NO ₂ (85%), 4-OH (15%)	<1996SL1193, 1997CC1015>

^a Nitrobenzene, benzonitrile, and ethyl benzoate do not react under these conditions. ^b Reaction product is 4-aminophenol. ^c Intermolecular cyclization to the corresponding dilactam occurred. ^d Product was methyl 2-aminobenzoate.

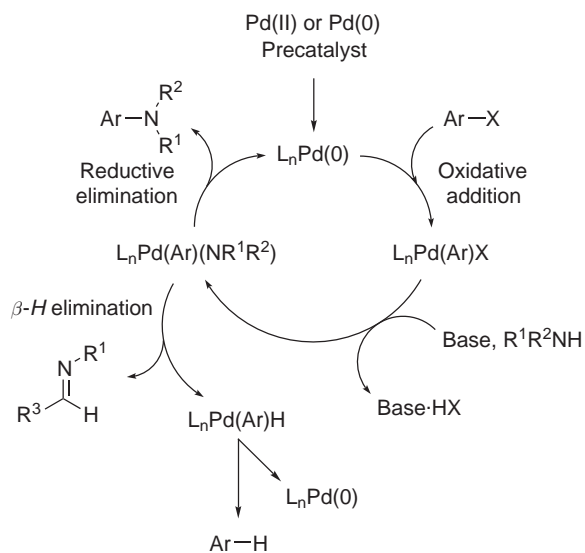
2.15.2.2.4 From halides and sulfonates

Nucleophilic aromatic substitution (S_NAr) of aryl halides and sulfonates is a very convenient method for the direct and regioselective synthesis of arylamines. Direct substitution usually requires a large excess of reagent, highly polar solvents, and high temperatures and/or pressures unless highly electrophilic arenes are used. Transition metal-catalyzed cross-coupling of aryl halides and sulfonates with nitrogen nucleophiles is a more practical, atom-economical, mild, and powerful new method that has seen a major development since the publication of COFGT (1995) <1995COFGT(2)737>, thanks to the pioneering studies of Hartwig and Buchwald, which considerably expanded the original methodology of Migita <1983CL927> for the coupling of tin amides. Palladium, nickel, and copper complexes are the most common catalysts used for this transformation. This very active area of research has been thoroughly reviewed up to the end of 2002 <1997CUOC287, 1997SL329, 1998ACR805, 1998ACR852, 1998AG(E)2046, 1998JCS(P1)2615, 1999JCS(P1)2645, 1999JOM(576)125, 1999T11399, 2002AG(E)4176, 2002JOM(653)69, B-2002MI(1)1051, 2002T2041, 2002TCC(219)131, 2003AG(E)5400>, but synthetic improvements and new mechanistic information are constantly appearing. The following sections briefly present the current state of the art and the most recent efforts towards the development of a “universal toolkit” (metal source, ligand, base, and solvent) that could allow the broadest substrate scope, with mildest reaction conditions, high turnover numbers, and fast reaction rates.

(i) Palladium-mediated methods

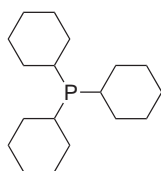
Palladium-catalyzed methods are the most highly developed and versatile. The generally accepted mechanism proposed for Pd-catalyzed amination (Scheme 29) <2000JA4618, 2001CEJ475, 2002JA14104, 2002OM491, 2003JA10066> involves the oxidative addition of the aryl halide or sulfonate to the Pd(0) catalyst to generate a Pd(II) species that reacts with the amine in the presence of stoichiometric base to form a novel L_nPd(Ar)NR¹R² complex. Reductive elimination produces the arylamine and regenerates the Pd(0) catalyst. Competing β-hydrogen elimination to give the reduced arene and an imine as by-products is a side reaction that needs to be minimized. Precoordination of the alkoxide base <2001JA12905> or of the amine <2002JA14104> to the Pd(0) catalyst prior to the oxidative addition step are possible mechanistic alternatives for this complex process. The general reactivity order observed for the amines in this reaction is: secondary cyclic amines > primary amines > secondary acyclic amines, and for the arene partner: aryl iodides > aryl bromides >> aryl chlorides. Electron-withdrawing substituents on the arene accelerate the reaction while electron-donating or *ortho* substituents have the opposite effect.

Buchwald and Hartwig have shown that the supporting ligands on the metal center play a crucial role on the efficiency of the catalytic process. First generation catalysts used P(*o*-Tol)₃ as ligand and NaOBu^t <1995AG(E)1348> or LiN(SiMe₃)₂ <1995JA4708> as the base in toluene or

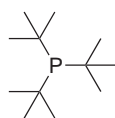
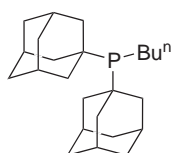


Scheme 29

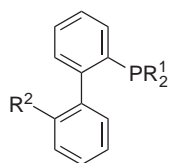
THF at 80–110 °C. However, the original conditions lacked generality since they were only truly efficient for coupling nonhindered electron-poor or neutral aryl bromides or aryl iodides with cyclic secondary alkylamines and were not compatible with base-sensitive substrates containing ester, aldehyde, enolizable ketones, or nitro groups. These problems were partially solved with the introduction of second generation catalysts based on chelating phosphanes such as binap <1996JA7215, 2002OS23> or DPPF <1996JA7217>, which produce less reduced arene side-product. The new conditions have a wider synthetic scope allowing the use of primary alkyl and arylamines, electron-deficient aryl triflates and heteroaromatic halides. As in the Pd/P(*o*-Tol)₃ system, NaOBu^t is most often used as base, although alkoxide bases containing β-hydrogens such as NaOMe and NaOPrⁱ can also be used <2000JOC2612> as well as weaker bases such as Cs₂CO₃ <1997TL6359>, K₃PO₄ <1998JA9722>, K₂CO₃, and Rb₂CO₃ <2000TL481>, which are compatible with base-sensitive substrates and with electron-deficient aryl triflates. Secondary acyclic amines are still reluctant to undergo efficient arylation under these improved conditions. Third generation catalysts based on electron-rich and sterically demanding bi- and mono-dentate phosphanes **91–110**, phosphinous acid **111**, bicyclic triaminophosphine **112**, and *N*-heterocyclic carbenes (carbene precursors: **113–115**) <2002AG(E)1290, 2002JOM(653)69> considerably expanded the scope of the methodology, allowing: (i) the coupling of readily available and inexpensive aryl chlorides <2002AG(E)4176>, aryl tosylates <1998JA7369, 2003JA6653, 2003JA8704>, and electron-deficient aryl fluorides <2003JA1696>; (ii) the possibility of using smaller amounts of catalyst (<0.05 mol.% Pd), other bases such as solid KOH <2001JOC7729> or aqueous KOH in combination with a phase-transfer catalyst <2002JOC6479>, and (iii) the performing of many of these reactions at room temperature or using water as the solvent <2003JA6653>. Many of these new ligands are now commercially available and some of them are air-stable or give air- and moisture-stable Pd-complexes <2002OL2229>. A large and structurally diverse collection of ligands is listed in a recent article by Hartwig that describes a high-throughput screening procedure for the palladium-catalyzed amination of aryl halides <2003JA6977>. As sources of palladium, Pd(DBA)₂, Pd₂(DBA)₃·CHCl₃, and Pd(OAc)₂ are the most common and (Pd(O₂CCF₃)₂) has been recently shown to give superior results in some amination reactions <2003JOC2861>, although binuclear Pd(I)–Pd(I) complexes **116** and **117** <2002AG(E)4746> and palladacycles **118–123** <1999JOM(576)23, 2001EJO1917> have been recently introduced as single component, highly efficient and air-stable precatalysts for this and related cross-coupling reactions. It has been shown that the rate of the coupling reaction is not only dependent on the intrinsic properties of the ligand and the coupling partners, but also on the Pd/ligand ratio (1:1 or 1:2). Table 4 and Schemes 30–33 show a collection of selected recent examples of Pd-catalyzed cross-coupling of different aryl halides and sulfonates with a range of different *N*-nucleophiles for the preparation of arylamines. The examples are intended to give a general idea of the scope, efficacy, and chemoselectivities that can be obtained with the different catalysts and reaction conditions.

**91**

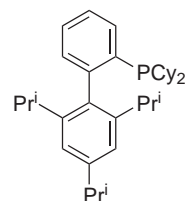
<1997TL4807>

**92**<1998TL617,
1998TL2367,
1999JOC5575>**93**

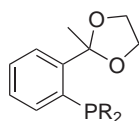
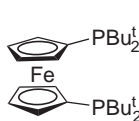
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**94** R¹ = Cy, R² = NMe₂

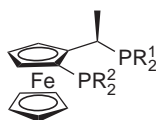
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95 R¹ = Cy, R² = H**96** R¹ = Bu^t; R² = H<1999AG(E)2413,
2000JOC1158>**97**

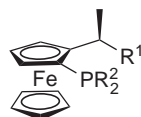
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**98** R = Ph**99** R = Cy<1999TL1237,
1999OM1840>**100**

<1998JA7369>

**101** R¹ = Bu^t, R² = Ph**102** R¹ = R² = Cy

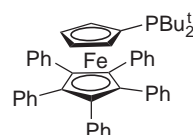
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**103** R¹ = OMe, R² = Ph

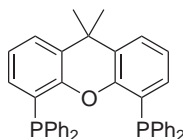
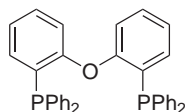
<1997TL6359>

104 R¹ = NMe₂, R² = Ph

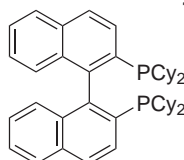
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**105**

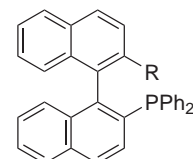
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**106**<1999JOC6019,
2001JOC2560>**107**

<1998TL5327>

**108**

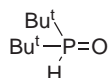
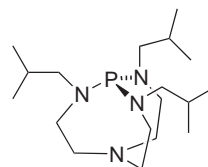
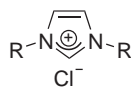
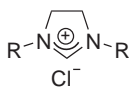
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**109** R = OMe

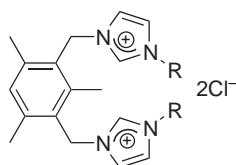
1999OL35

110 R = NMe₂

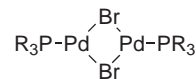
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**111**<2001AG(E)1513,
2001JOC8677>**112**<2003OL815,
2003JOC452>**113**R = 2,6-PrⁱC₆H₃
<1999OL1307,
2001JOC7729>**114**

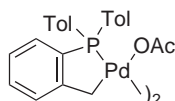
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**115** R = 2,4,6-PrⁱC₆H₂

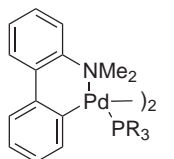
<2001OL1371>

**116** R₃P = P(1-adamatyl)Bu^t**117** R₃P = PBu^t₃

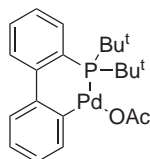
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**118**

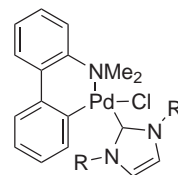
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**119** PR₃ = HPBu^t₂**120** PR₃ = HPCy₂**121** PR₃ = HP(2-norbornyl)₂

<2002AG(E)3668>

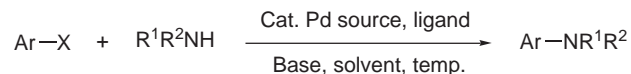
**122**

<2003OL2413>

**123** R = 2,6-PrⁱC₆H₃

<2003OL1479>

Table 4 Palladium-catalyzed amination of aryl halides and sulfonates



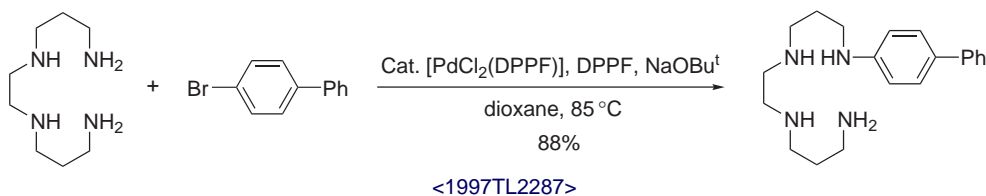
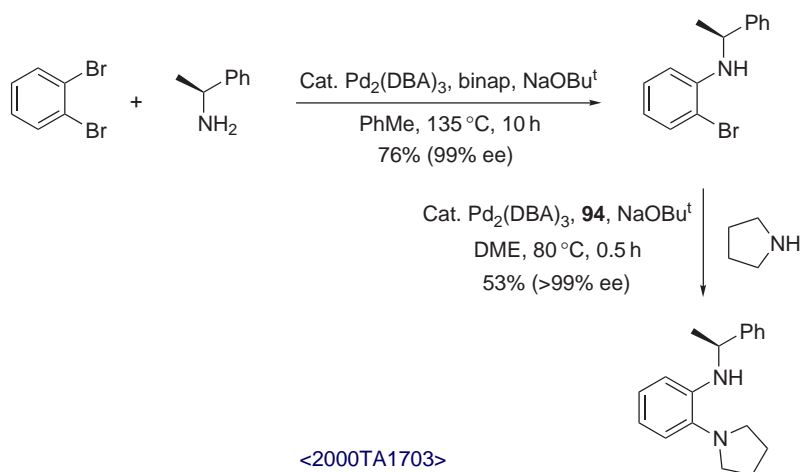
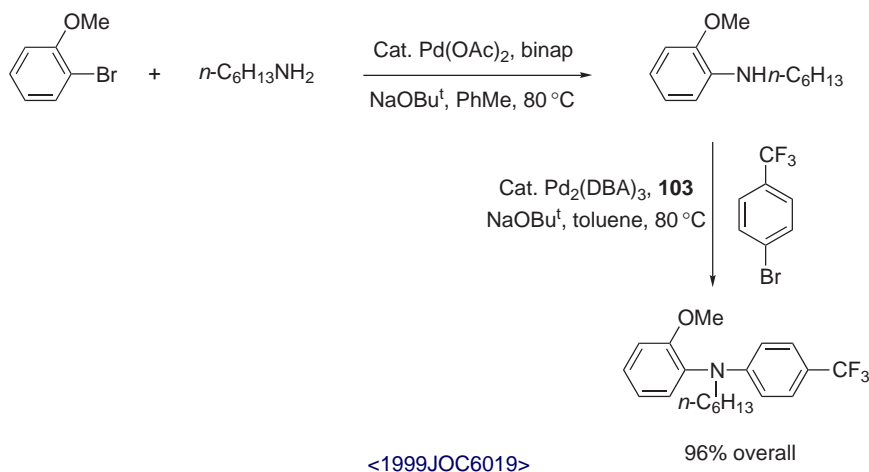
<i>X</i>	<i>Ar</i>	<i>R</i> ¹ <i>R</i> ² <i>NH</i>	<i>Pd (Pre-)catalyst, base, solvent, temp.</i>	<i>Catalyst loading</i> (mol.% Pd)	<i>Time (h)</i>	<i>Yield (%)</i>	<i>References</i>
Br	4-Bu ^t	PhNH	Pd(OAc) ₂ , binap, NaOBu ^t , PhMe, 80 °C	0.5	19	94	<2000JOC1144>
Br	2,6-Me ₂	PhNH	Pd ₂ (DBA) ₃ , binap, NaOBu ^t , PhMe, 100 °C	0.5	18	87	<2000JOC1144>
Br	4-Bu ^t	Bu ⁿ ₂ NH	Pd ₂ (DBA) ₃ , 103 , NaOBu ^t , PhMe, 80 °C	5	5	93	<1997JOC1568>
Br	4-Bu ^t	Bu ⁿ ₂ NH	Pd ₂ (DBA) ₃ , 103 , Cs ₂ CO ₃ , PhMe, 100 °C	3	27	73	<1997TL6359>
Br	4-CO ₂ Me	BnNHMe	Pd(OAc) ₂ , binap, Cs ₂ CO ₃ , PhMe, 100 °C	3	16	75	<1997TL6359>
Br	4-CN	4-MeC ₆ H ₄ NH ₂	Pd ₂ (DBA) ₃ , binap, Cs ₂ CO ₃ , PhMe, 100 °C	1	26	8	<1997TL6359>
Br	2,6-Me ₂	<i>n</i> -HexylNH ₂	Pd ₂ (DBA) ₃ , 94 , NaOBu ^t , DME, rt	2.5	11–27	88	<1998JA9722>
Br	2,6-Me ₂	2,6-Pr ⁱ ₂ C ₆ H ₃ NH ₂	Pd(OAc) ₂ , binap, NaOBu ^t , PhMe, 100 °C	5	18	87	<1998TL5327>
Br	2,6-Me ₂	2,6-Pr ⁱ ₂ C ₆ H ₃ NH ₂	Pd(OAc) ₂ , DPPF, NaOBu ^t , PhMe, 100 °C	5	18	88	<1998TL5327>
Br	2,6-Me ₂	2,6-Pr ⁱ ₂ C ₆ H ₃ NH ₂	Pd(OAc) ₂ , 107 , NaOBu ^t , PhMe, 100 °C	5	18	90	<1998TL5327>
Br	2-Me	Bu ⁿ ₂ NH	Pd(OAc) ₂ , Bu ^t ₃ P, NaOBu ^t , toluene, rt	2	6	81	<1999JOC5575>
Br	4-Me	PhNHMe	Pd ₂ (DBA) ₃ , 113 , KOBu ^t , dioxane, rt	1	3–30	89	<1999OL1307, 2001JOC7729>
Br	4-Cl	Piperidine	Pd ₂ (DBA) ₃ , 113 , KOBu ^t , dioxane, rt	1	3–30	94	<1999OL1307, 2001JOC7729>
Br	3,5-Me ₂	Ph ₂ NH	Pd ₂ (DBA) ₃ , 96 , NaOBu ^t , PhMe, rt	1	23	89	<2000JOC1158>
Br	2,6-Me ₂	PhNHMe	Pd ₂ (DBA) ₃ , 95 , NaOBu ^t , PhMe, 80 °C	0.5	16	74	<2000JOC1158>
Br	Bu ^t	Ph ₂ NH	116 , NaOBu ^t , THF, rt	0.5	0.25	96	<2002AG(E)4746>
Br	4-OMe	PhNHPr ⁱ	Pd(OAc) ₂ , Bu ^t ₃ P, NaOBu ^t , PhMe, 110 °C	0.5	2	76	<2003JOC1163>
Br	4-OMe	PhNHPr ⁱ	117 , NaOBu ^t , PhMe, 110 °C	0.5	2	93	<2003JOC1163>
Br	4-OMe	2,6-Me ₂ C ₆ H ₃ NH ₂	Pd(OAc) ₂ , 112 , NaOBu ^t , PhMe, 80 °C	2	9–15	97	<2003JOC452>
I	3,5-Me ₂	(<i>n</i> -Hexyl)NHMe	Pd ₂ (DBA) ₃ , 99 , NaOBu ^t , PhMe, 105 °C	2	0.25	91	<1999OM1840, 1999TL1237>
I	4-Cl	Piperidine	Pd ₂ (DBA) ₃ , 113 , KOBu ^t , dioxane, rt	1	3–30	97	<1999OL1307, 2001JOC7729>
I	3,5-Me ₂	PhNHET	Pd ₂ (DBA) ₃ , 94 , NaOBu ^t , THF, rt	0.5	2–12	>99	<2001JOC2560>
I	3-CO ₂ Me	PhNHMe	Pd ₂ (DBA) ₃ , 94 , NaOBu ^t , dioxane/Et ₃ N (2:1), 120 °C	1	12	84	<2001JOC2560>
I	4-OMe	Morpholine	Pd(OAc) ₂ , 112 , NaOBu ^t , PhMe, 80 °C	2	9–12	79	<2003JOC452>
Cl	4-CF ₃	Piperidine	118 , KOBu ^t , LiCl, PhMe, 135 °C	1	24	74 ^a	<1997TL2073>
Cl	4-CF ₃	PhNHMe	118 , KOBu ^t , LiCl, PhMe, 135 °C	1	24	60 ^b	<1997TL2073>
Cl	4-Me	<i>N</i> -Methylpiperazine	PdCl ₂ · 91 ₂ , NaOBu ^t , PhMe, 120 °C	1	12	62–81	<1997TL4807>
Cl	2-Me	<i>N</i> -Methylpiperazine	PdCl ₂ · 91 ₂ , NaOBu ^t , PhMe, 120 °C	1	12	25–36	<1997TL4807>
Cl	H	PhNHMe	PdCl ₂ · 91 ₂ , NaOBu ^t , PhMe, 120 °C	1	12	60	<1997TL4807>
Cl	2-Me	Bu ⁿ NH ₂	Pd ₂ (DBA) ₃ , 100 , NaOBu ^t , PhMe, 110 °C	1	24	57	<1998JA7369>

Table 4 (continued)

<i>X</i>	<i>Ar</i>	<i>R</i> ¹ <i>R</i> ² <i>NH</i>	<i>Pd</i> (Pre-)catalyst, base, solvent, temp.	Catalyst loading (mol.% Pd)	Time (h)	Yield (%)	References
Cl	2-Me	Bu ⁿ NH ₂	Pd(OAc) ₂ , 101 , NaOBu ^t , PhMe, 85 °C	1	2	89	<1998JA7369>
Cl	2-Me	Bu ⁿ NH ₂	Pd(OAc) ₂ , 102 , NaOBu ^t , PhMe, 85 °C	1	2	94	<1998JA7369>
Cl	H	3-MeC ₆ H ₄ NHPh	Pd(OAc) ₂ , 92 , NaOBu ^t , <i>o</i> -xylene, 130 °C	0.025	3	>99	<1998TL2367>
Cl	4-OMe	Bu ⁿ NH ₂	Pd ₂ (DBA) ₃ , 94 , NaOBu ^t , PhMe, 80 °C	0.5	11–27	90	<1998JA9722>
Cl	4-CO ₂ Me	<i>n</i> -HexylNH ₂	Pd ₂ (DBA) ₃ , 94 , K ₃ PO ₄ , dioxane, 80 °C	0.5	11–27	83	<1998JA9722>
Cl	2-OMe	<i>n</i> -OctylNH ₂	Pd ₂ (DBA) ₃ , 99 , NaOBu ^t , PhMe, 105 °C	2	3	83	<1999OM1840, 1999TL1237>
Cl	3,5-Me ₂	(<i>n</i> -Hexyl)NHMe	Pd ₂ (DBA) ₃ , 99 , NaOBu ^t , PhMe, 105 °C	2	1	95	<1999OM1840, 1999TL1237>
Cl	4-OMe	Ph ₂ NH	Pd(DBA) ₂ , Bu ^t ₃ P, NaOBu ^t , toluene, 70 °C	5	16	97	<1999JOC5575>
Cl	4-Me	Piperidine	Pd ₂ (DBA) ₃ , 113 , KOBu ^t , dioxane, 100 °C	1	3–24	96	<1999OL1307, 2001JOC7729>
Cl	4-Me	PhNHMe	Pd ₂ (DBA) ₃ , 113 , KOBu ^t , dioxane, 100 °C	1	3	99	<1999OL1307, 2001JOC7729>
Cl	4-OMe	PhNH ₂	Pd ₂ (DBA) ₃ , 113 , KOBu ^t , dioxane, 100 °C	1	3–24	91	<1999OL1307, 2001JOC7729>
Cl	4-OMe	2,4,6-Me ₃ C ₆ H ₂	Pd ₂ (DBA) ₃ , 113 , KOBu ^t , dioxane, 100 °C	1	3–24	59	<1999OL1307, 2001JOC7729>
Cl	4-OMe	Morpholine	Pd(OAc) ₂ , 96 , NaOBu ^t , PhMe, rt	2	20	90	<1999AG(E)2413, 2000JOC1158>
Cl	4-OMe	4-MeO-C ₆ H ₄ NH ₂	Pd ₂ (DBA) ₃ , 96 , NaOBu ^t , PhMe, 80 °C	0.5	8	94	<1999AG(E)2413, 2000JOC1158>
Cl	2,6-Me ₂	2,6-Pr ⁱ ₂ C ₆ H ₃	Pd(OAc) ₂ , 96 , NaOBu ^t , PhMe, 110 °C	1	24	86	<1999AG(E)2413, 2000JOC1158>
Cl	4-Me	PhNHMe	Pd ₂ (DBA) ₃ , 96 , NaOBu ^t , PhMe, 80 °C	0.05	22	95	<1999AG(E)2413, 2000JOC1158>
Cl	4-CO ₂ Me	4-NO ₂ -C ₆ H ₄ NH ₂	Pd ₂ (DBA) ₃ , 96 , K ₃ PO ₄ , DME, 100 °C	1	18	81	<1999AG(E)2413, 2000JOC1158>
Cl	4-Me	PhNHMe	Pd ₂ (DBA) ₃ , 96 , NaOBu ^t , PhMe, 80 °C	0.05	22	95	<1999AG(E)2413, 2000JOC1158>
Cl	4-Me	Bu ⁿ ₂ NH	Pd ₂ (DBA) ₃ , 114 , NaOBu ^t , DME, rt	1	20	86	<2000OL1423>
Cl	4-OMe	Morpholine	Pd ₂ (DBA) ₃ , 114 , NaOBu ^t , DME, rt	1	5	96	<2000OL1423>
Cl	4-OMe	Piperidine	Pd ₂ (DBA) ₃ , 111 , NaOBu ^t , PhMe, 100 °C	2.5	12	67	<2001AG(E)1513>
Cl	2,6-Me ₂	2,6-Pr ⁱ ₂ C ₆ H ₃ NH ₂	Pd(OAc) ₂ , 93 , NaOBu ^t , PhMe, 120 °C	0.5	20	70	<2002JMOC(182-183)515>
Cl	2,6-Me ₂	2,6-Me ₂ C ₆ H ₃ NH ₂	Pd(OAc) ₂ , 93 , NaOBu ^t , PhMe, 120 °C	0.5	20	85	<2002JMOC(182-183)515>
Cl	2-Me	Morpholine	116 , NaOBu ^t , THF, rt	0.5	0.25	84	<2002AG(E)4746>
Cl	4-OMe	Bu ⁿ ₂ NH	116 , NaOBu ^t , THF, rt	0.5	0.25	87	<2002AG(E)4746>

Cl	4-OMe	PhNHMe	121 , NaOBu ^t , PhMe, 110 °C	0.5	15	100	<2002AG(E)3668>
Cl	4-Me	Morpholine	Pd(DBA) ₂ , 105 , NaOBu ^t , PhMe, 100 °C	0.1	19	92	<2002JOC5553>
Cl	4-OMe	Ph ₂ NH	112 , Pd(DBA) ₂ , NaOBu ^t , PhMe, 80 °C	4		91	<2003OL815>
Cl	4-CN	Et ₂ NH	112 , Pd(OAc) ₂ , NaOBu ^t , PhMe, 80 °C	5		56	<2003OL815>
Cl	4-OMe	Pyrrolidine	122 , KOH, PhMe, 90 °C	1	20	94	<2003OL2413>
Cl	4-Me	3-MeO ₂ C-C ₆ H ₄ NH ₂	122 , Et ₃ N, NaOMe, PhMe, 60 °C	1	2	90	<2003OL2413>
Cl	4-Me	Morpholine	123 , NaOBu ^t , THF, 70 °C	1	0.5	98	<2003OL1479>
Cl	4-OMe	PhNHMe	123 , NaOBu ^t , THF, 70 °C	2	0.5	96	<2003OL1479>
Cl	4-OMe	Bu ⁿ ₂ NH	123 , NaOBu ^t , THF, 70 °C	1	1	87	<2003OL1479>
OTf	4-OMe	Morpholine	Pd (OAc) ₂ , 96 , NaOBu ^t , PhMe, rt	1	24	79	<2000JOC1158>
OTf	4-OMe	4-NO ₂ -C ₆ H ₄ NH ₂	Pd ₂ (DBA) ₃ , 96 , K ₃ PO ₄ , DME, 80 °C	1	16	76	<2000JOC1158>
OTf	4-OMe	Morpholine	123 , NaOBu ^t , THF, 70 °C	1	2	95	<2003OL1479>
OTs	4-CN	PhNH ₂	Pd ₂ (DBA) ₃ , 100 , NaOBu ^t , PhMe, 110 °C	1	16	79	<1998JA7369>
OTs	4-Me	<i>n</i> -HexylNH ₂	Pd(OAc) ₂ , 101 , NaOC ₆ H ₂ -2,4,6-Bu ^t ₃ , PhMe, 110 °C	1	2	83	<1998JA7369>
OTs	H	<i>n</i> -OctylNH ₂	(PhCN) ₂ -PdCl ₂ , 101 , NaOBu ^t , toluene, rt	1	6	72	<2003JA8704>
OTs	4-NHAc	Morpholine	Pd(OAc) ₂ , 97 , K ₂ CO ₃ , Bu ^t OH, 110 °C	2	11–24	99	<2003JA6653>
OTs	3-CO ₂ Me	Morpholine	Pd(OAc) ₂ , 97 , Cs ₂ CO ₃ , Bu ^t OH/PhMe (1:5), 110 °C	2	11–24	>99	<2003JA6653>

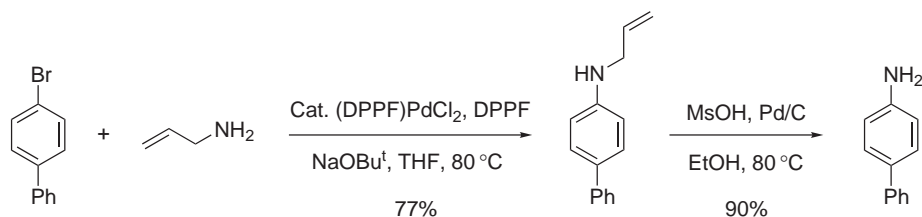
^a *Para/meta* ratio = 7:1. Without Pd-catalyst a 1:1 *para/meta* ratio is obtained (via aryne intermediate). ^b *Para/meta* ratio = 20:1.



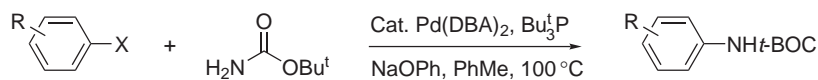
Scheme 30

An enantioselective variant of the Pd-catalyzed amination reaction of aryl halides has been developed for the kinetic resolution of 4,12-dibromo[2,2]paracyclophane **124** using chiral bisphosphane **125** in the presence of the halide scavenger TIPF_6 (Scheme 34) <1997JOC6462>.

Palladium-catalyzed amination has also been performed using polymer-supported aryl halides <1996TL6993, 1996TL7181> or polymer-supported amines <2002JCO179, 2002JCS(P1)2137, 2002OL4689>. Methods to recycle the catalyst include the use of water-soluble sulfonated phosphanes in an aqueous biphasic system using NaOH as base <1998CC1509>, Pd particles immobilized on inorganic solid supports <1999JOM(592)225>, and polymer supported phosphanes <2001JOC3820>. As for other metal-catalyzed organic reactions <2002ACR717, B-2002MI379>, microwave irradiation has a significant accelerating effect on the Pd-catalyzed amination of aryl halides and sulfonates, reducing the reaction times to 4–15 min and giving cleaner reaction mixtures and higher yields of arylamines <2002S1597, 2003OL897>.

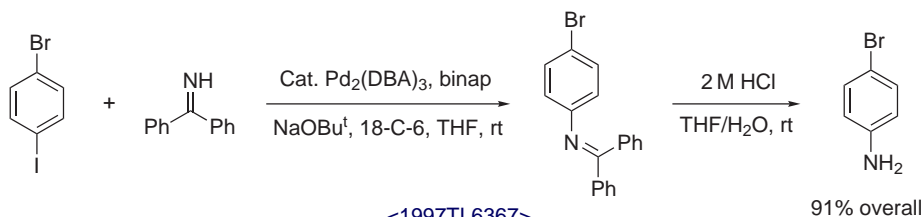


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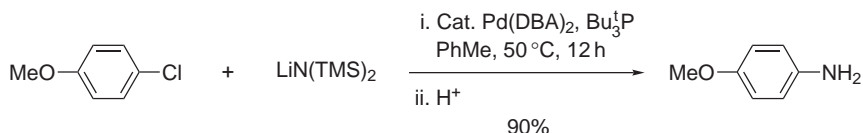


X	R	Yield (%)
Br	4-Me	80
Cl	4-Me	59
Br	4-OMe	62

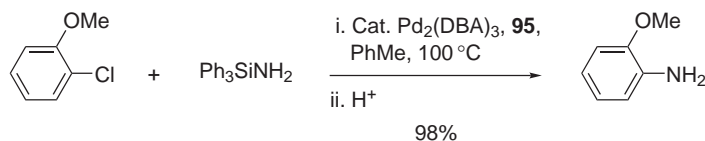
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<1997TL6367>



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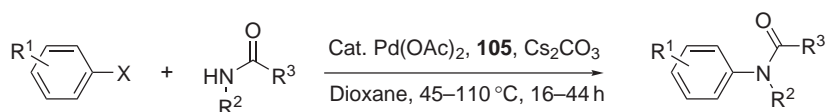


<2001OL3417>

Scheme 31

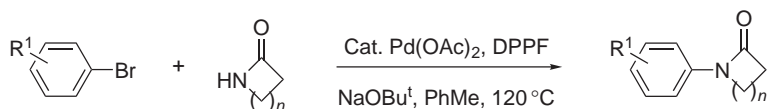
(ii) Nickel-mediated methods

Amination of aryl chlorides can also be catalyzed by nickel complexes, a process known since 1950 <1975JOC2267, 1996TL7595>. Wolfe and Buchwald have described a mild procedure catalyzed by $\text{Ni}(\text{COD})_2$ using DPPF or 1,10-phenanthroline as ligands in the presence of NaOBu^t as the base that tolerates a variety of functional groups including ethers, nitriles, acetals, and nonenolisable ketones (Scheme 35) <1997JA6054>. 2,2'-Bipyridine <1998TL5359, 1999T12829, 2000TL2875, 2000TL2881, 2001T7657, 2001TL247, 2002T6913> or the dihydroimidazolidene carbene prepared from precursor **114** <2001TL5689, 2002TL3029, 2003OL2311> have been used as ligands in efficient $\text{Ni}(0)$ -catalyzed amination of aryl chlorides and aryl bromides. Interesting selectivities can be obtained using this methodology (Scheme 35) <2000TL2881, 2002T6913>. A heterogeneous Ni/C precatalyst has been developed by Lipshutz <2000AG(E)4492, 2003JOC1190> for the amination of aryl chlorides in the presence of DPPF



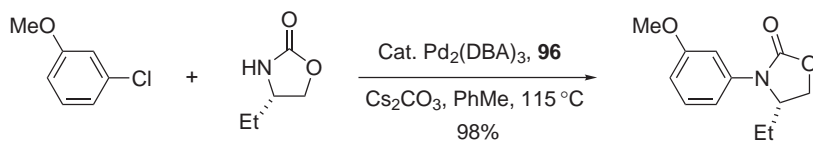
R^1	X	R^2	R^3	Yield (%)	References
4-CN	Br	H	Ph	93 ^a	<2000OL1101>
4-CN	Cl	Ph	Ph	74	<2000OL1101>
4-Bu ^t	OTf	H	Ph	94	<2000OL1101>
3-CO ₂ Me	Br	Et	OEt	66 ^b	<2000OL1101>
3-OMe	Br	Me	H	99	<2000OL1101>
4-Bu ^t	OSO ₂ Ph	Me	H	88 ^c	<2003JA6653>

^a THF as solvent. ^b Pd₂(DBA)₃ was used in place of Pd(OAc)₂. ^c **97** was used in place of **105**.



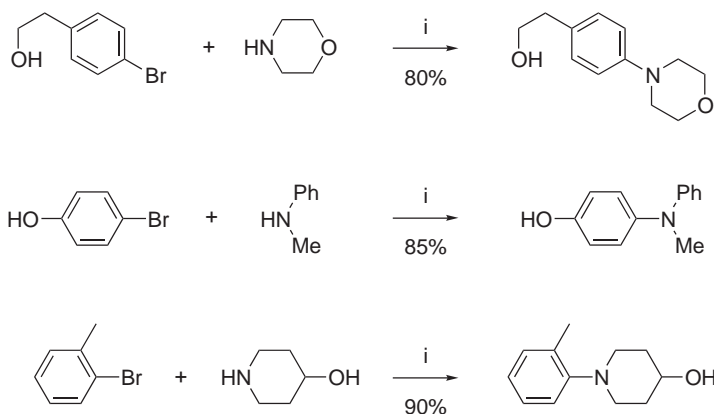
R^1	n	Yield (%)
4-CF ₃	1	52
H	2	82
4-COPh	3	89
H	4	43

<1999TL2035>



<2003OL2207>

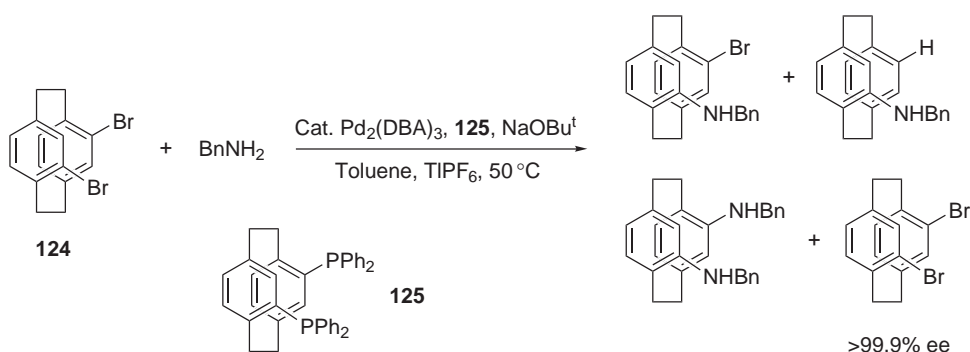
Scheme 32



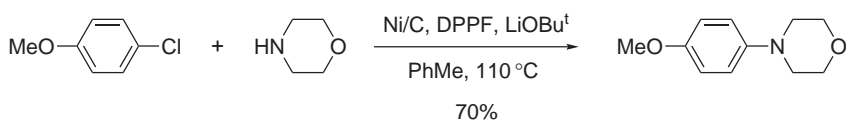
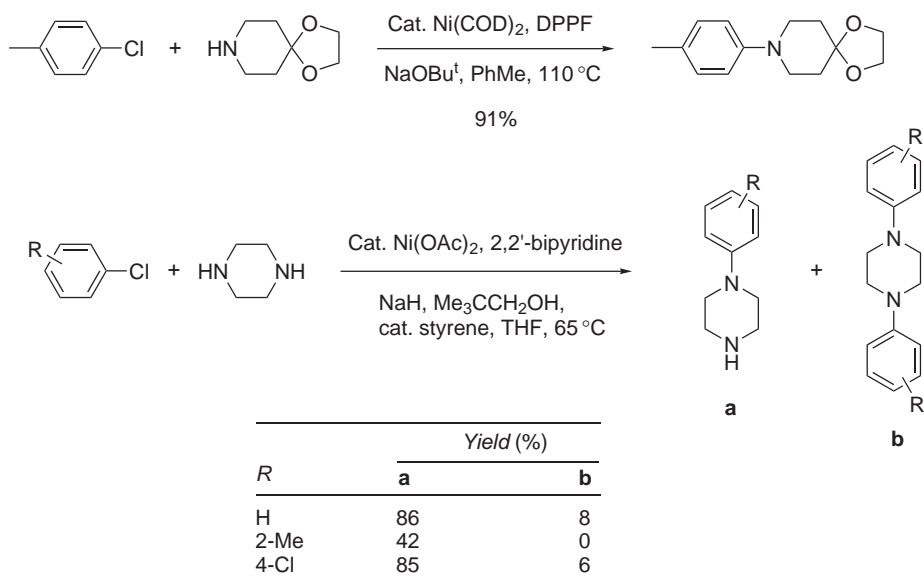
i. cat. Pd₂(DBA)₃, **95**, LiN(TMS)₂, THF, 65 °C, 14–25 h

<2002OL2885>

Scheme 33



Scheme 34



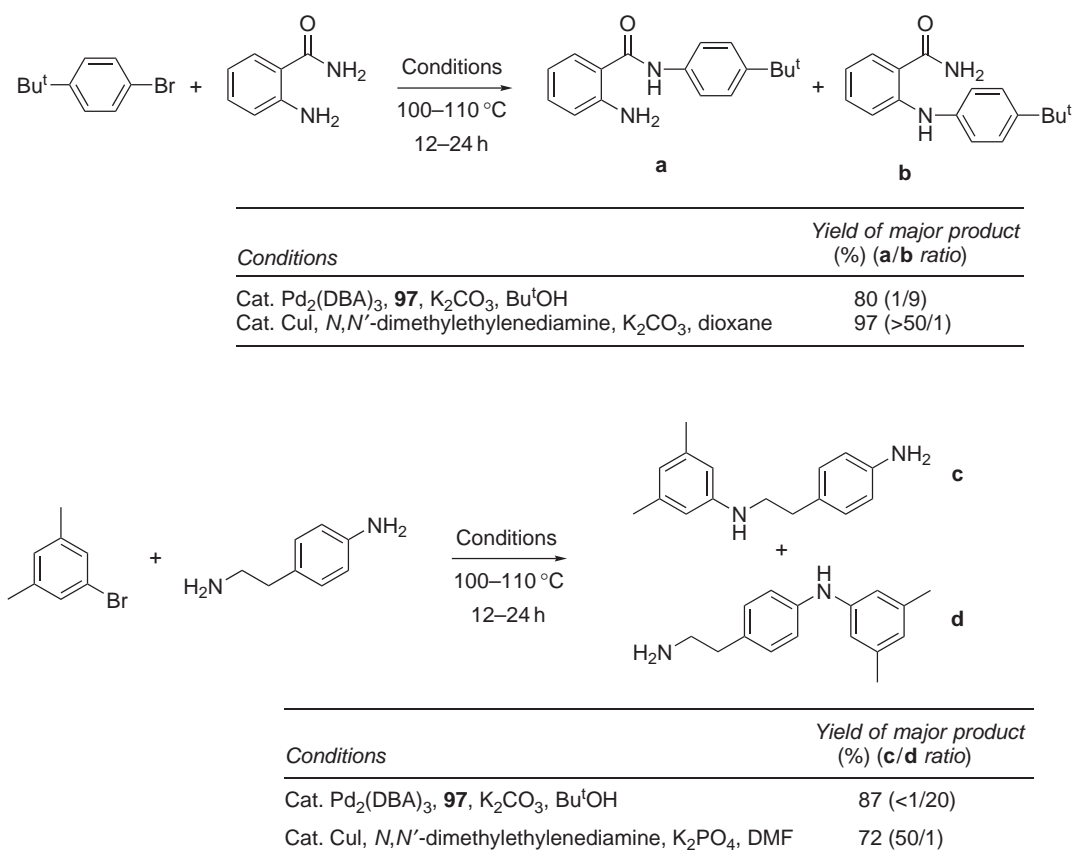
Scheme 35

and LiOBu^t. These Ni-catalyzed procedures have a wide synthetic scope, allowing the efficient coupling of electron-poor and electron-rich aryl chlorides with primary and secondary amines in moderate-to-excellent yields. The main side-products are homocoupled arene and reduced arene.

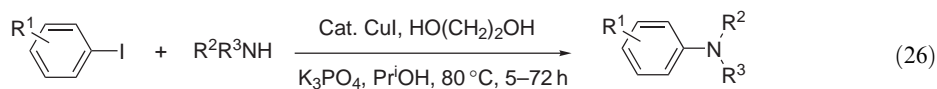
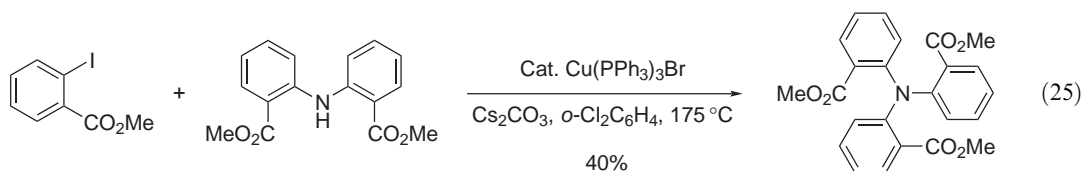
(iii) Copper-mediated methods

The Ullmann amination and Goldberg amidation of aryl halides promoted by copper salts (which usually have been plagued by poor substrate scope and require harsh reaction conditions, stoichiometric amounts of copper reagents and highly polar solvents) have witnessed important developments recently, thanks to the discovery of the accelerating effect induced by ligands on the metal. Ma found that α - and β -amino acids had a significant accelerating effect in CuI-catalyzed coupling with aryl bromides and aryl iodides using K₂CO₃ as base in DMA at 90 °C [<1998JA12459, 2001OL2583, 2001SI1423, 2003JOC442, 2003OL2453>](#). Later, Buchwald reported another mild copper-catalyzed coupling reaction [<1999TL2657>](#). *N*-Arylation of imidazole could

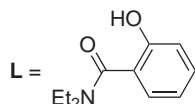
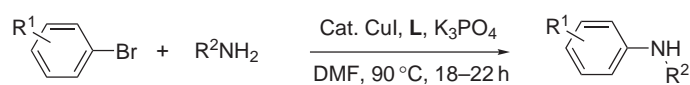
be performed using $\text{Cu}(\text{OTf})_2$ -benzene as catalyst precursor and Cs_2CO_3 as a base in xylene at 110–120 °C. The addition of 1,10-phenanthroline and DBA was crucial to the success of the process. The combination of air stable CuI and 1,2-diamine ligands in the presence of K_3PO_4 , K_2CO_3 or Cs_2CO_3 constitute an efficient and general catalytic system for *N*-amidation of aryl and heteroaryl iodides and bromides and in some cases even unactivated aryl chlorides <2001JA7727, 2002JA7421>. The degree of substitution, and consequently the steric bulk, of the diamine ligands played the most important role. *N,N'*-Dimethylethylenediamine and *trans-N,N'*-dimethyl-1,2-cyclohexanediamine gave the best results. The reaction was tolerant to a variety of functional groups and, interestingly, shows a chemoselectivity that is complementary to analogous couplings catalyzed by Pd(0) (Scheme 36) <2003JA6653>. Well-defined soluble copper complexes such as $\text{Cu}(\text{PPh}_3)_3\text{Br}$ <2001TL4791> and $\text{Cu}(\text{PPh}_3)(1,10\text{-phenanthroline})$ <2001OL4315> in the presence of Cs_2CO_3 or KO^tBu as the base, respectively, are efficient catalysts for the amination of aryl iodides (Equation (25)). Ethylene glycol and hindered phenols are excellent ligands for the copper-catalyzed amination of aryl iodides and aryl bromides, respectively, in air (Equation (26)) <2002OL581>. More recent developments include the use of 2-*N,N*-dimethylaminoethanol <2003TL6289>, *N,N*-diethylsalicylamide <2003OL793>, L-proline, or *N*-methylglycine <2003OL2453> as copper ligands for the efficient Ullmann amination of both aryl iodides and aryl bromides with primary and secondary amines at relatively mild temperatures (40–90 °C) (Scheme 37). Triarylamines can be prepared in a single step by CuI-catalyzed amination of aryl iodides using KO^tBu as the base without any ligand or in the presence of chelating dinitrogen or diphosphane ligands (Equation (27)) <2002TL7143>. Microwave heating has been used to accelerate the *N*-arylation of sulfonamides with aryl bromides and aryl iodides catalyzed using CuI in NMP <2003TL3385>. These Ullmann-type couplings remain the method of choice for the preparation of arylamines from aryl halides on a large scale and avoid the toxicity problems associated with the use of the palladium catalysts, also considerably more expensive.



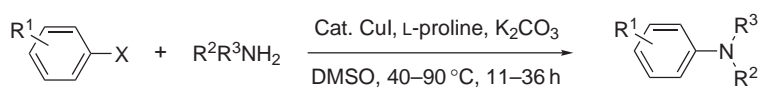
Scheme 36



R^1	R^2R^3NH	Yield (%)
3-Br	BnNH ₂	83
2-CO ₂ H	BnNH ₂	71
H	Morpholine	76
H	MeO(CH ₂) ₂ NH ₂	91

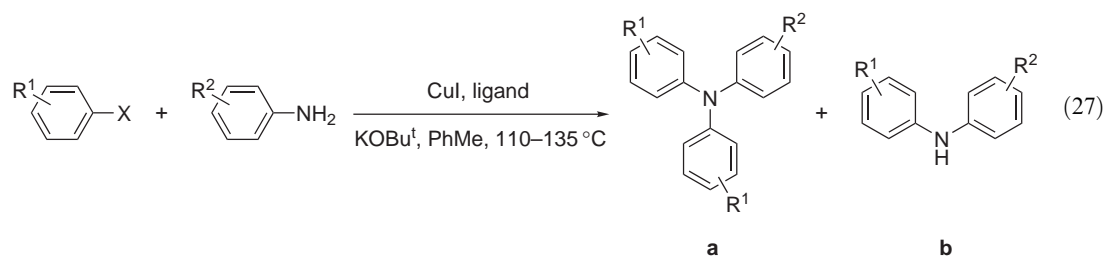


R^1	R^2NH_2	Yield (%)
3-NH ₂	<i>n</i> -C ₆ H ₁₃ NH ₂	80
4-SMe	BnNH ₂	89
2-CH ₂ OH	<i>n</i> -C ₆ H ₁₃ NH ₂	81



X	R^1	$R^2R^3NH_2$	Yield (%)
I	4-OMe	BnNH ₂	84
I	4-Br	BnNH ₂	81
Br	4-Ph	BnNH ₂	53
I	H	4-MeOC ₆ H ₄ NH ₂	82

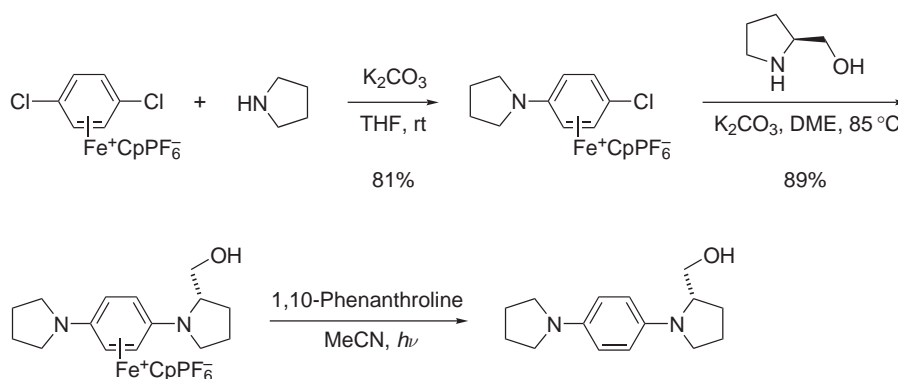
Scheme 37



X	R^1	R^2	Ligand	Yield (%)	
				a	b
I	H	H	None	70	7
Br	H	H	None	45	12
Cl	H	H	None	28	12
I	4-OMe	2-OMe	None	71	14
I	H	H	2,2'-Bipyridine	95	2
I	H	H	1,10-Phenanthroline	91	4
I	H	H	DPPP	80	6

(iv) *Methods mediated by other transition metals*

Transition metal η^6 -arene complexes have been used to increase the electrophilicity of arenes and accelerate substitution of otherwise unreactive aryl halides, but stoichiometric amounts of the transition metal complex are required. Complexation with tricarbonylchromium [<1996TL8487>](#), tricarbonylmanganese [<1997TL623>](#), cyclopentadienylruthenium [<2000JOC3466>](#), pentamethylcyclopentadienylruthenium, or cyclopentadienyliron [<1997JOM\(544\)197, 2000CCR219>](#) activates the aromatic ring towards amines and other nucleophiles due to the electron-withdrawing nature of the metallic moieties. The activation of aryl halides towards nucleophilic attack increases in the order: $(\text{CO})_3\text{Cr} \ll \text{CpRu}^+ \text{ca. CpFe}^+ < (\text{CO})_3\text{Mn}^+ < 1981\text{JCS(P2)193, 1999CCR183}>$. Decomplexation is usually performed *in situ* to afford the arylamine ([Scheme 38](#)). Sequential substitution of dihaloarenes [<1996JOC1297, 1997TL5123, 2000JOC3466, 2003JOC2161>](#) and substitution reactions using solid-phase attached substrates [<2002JOC5257>](#) have been described ([Scheme 38](#)).



Scheme 38

(v) *Other methods*

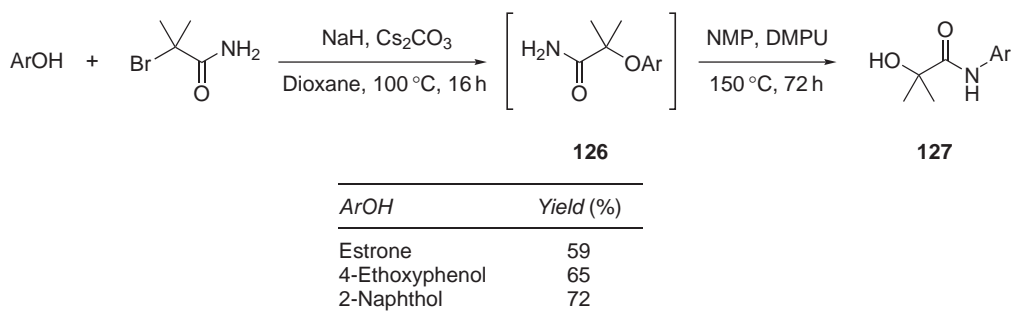
Conventional nonmetal-catalyzed nucleophilic aromatic substitution is the method of choice when EWGs are present on the arene. Fluoride is the best leaving group in these conventional substitutions. Recent developments include: (i) the use of KF on alumina and 18-crown-6 as a catalyst system for the synthesis of diarylamines from electrophilic aryl fluorides in acetonitrile or DMSO as solvent [<1998JOC6338>](#), (ii) the use of microwaves to reduce reaction times for the direct nucleophilic substitution of aryl halides with amines in solution [<1998TL2471>](#) or without solvent in the presence of Al_2O_3 , [<2000GC115>](#), and (iii) the use of ionic liquids as both solvent and promoter for the room temperature reaction of secondary alkylamines with activated aryl halides [<2003TL2217>](#). Direct substitution has been described also for the solid-phase synthesis of arylamines [<1996TL4671, 1997JOC3874>](#).

Metal-halogen exchange followed by electrophilic amination of the resultant aryl carbanion is an unconventional way of generating arylamines [<2003BCJ1063>](#). Different approaches depending on the aminating reagent and the organometallic species used have been developed and are described in a recent review [<2000CEJ1281>](#).

2.15.2.2.5 *From phenols and derivatives*

Transformation of phenols into the corresponding sulfonate esters followed by metal-catalyzed or direct nucleophilic aromatic substitution with primary or secondary amines is the most convenient and general protocol for the preparation of arylamines from phenols, as already described in [Section 2.15.2.2.4](#).

Acylation of phenols with 2-bromo-2-methylpropionamide followed by Smiles rearrangement of the resulting 2-aryloxypropionamide **126** in a one-pot procedure gives 2-hydroxy-2-methyl-*N*-arylpropionamides **127** that can be hydrolyzed to the corresponding arylamine ([Scheme 39](#)) [<1997TL6303>](#). A related two-step approach for the preparation of *N*-alkylanilines from phenols by alkylation with *N*-alkylchloroacetamides followed by base-promoted Smiles rearrangement has been described by Goswami [<1996JCR\(S\)424>](#).

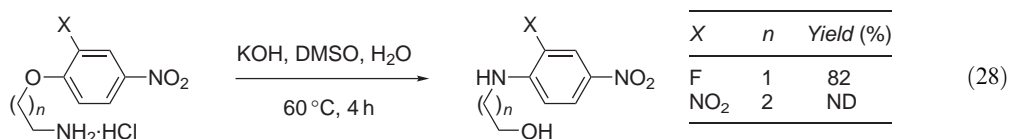


Scheme 39

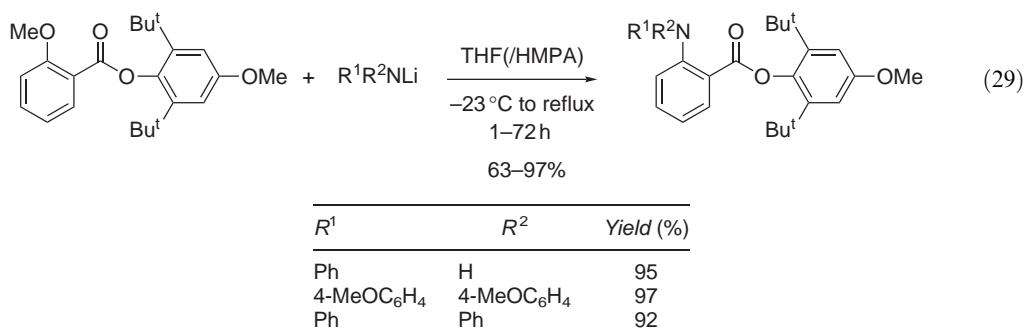
A simple, fast, and efficient procedure for the preparation of aminonaphthalenes from the corresponding naphthols using the Bucherer reaction under microwave irradiation in aqueous solvent has been described by Zanocco <2001SC2143>.

2.15.2.2.6 From ethers

The effect of the nature of the base and solvent on the Smiles rearrangement of α -aryloxyacetamides to the corresponding *N*-aryl-2-hydroxyacetamides has been studied. Stoichiometric NaOMe in DMF at 25 °C gives the best results (65–99% yield) <1997TL11919>. Alkylnitroarylethers with a pendant primary or secondary amino group suffer a facile Smiles rearrangement upon treatment with KOH in DMSO/H₂O to give the corresponding *N*-alkylnitroaniline (Equation (28)) <2002S2421>.



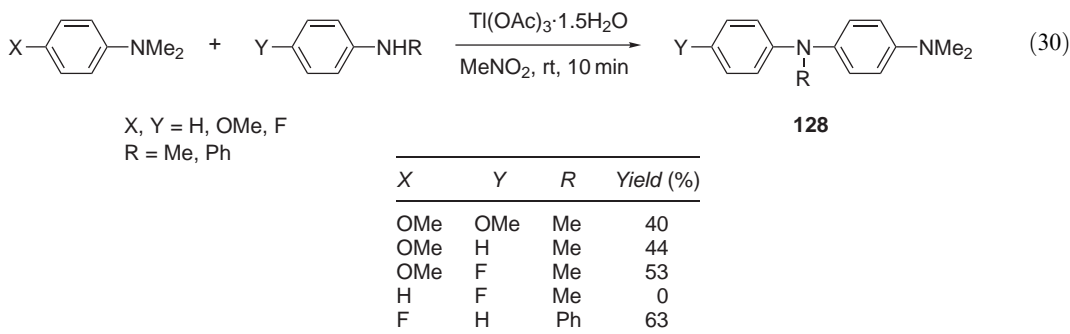
Direct substitution of aromatic ethers by lithium amides was described by Wynberg in 1993 <1993JOC5101>. This procedure has been successfully applied to the synthesis of triarylamines by substitution of a methoxy group in arenes activated with a hindered ester group (Equation (29)) <1996S514>.



2.15.2.2.7 From amines

The synthesis of arylamines from other amines by metal-catalyzed or direct aromatic substitution of aryl halides and sulfonates has already been described in Section 2.15.2.2.4. A recent review describes the preparation of secondary arylamines by direct or reductive *N*-alkylation of primary arylamines <2001T7785>.

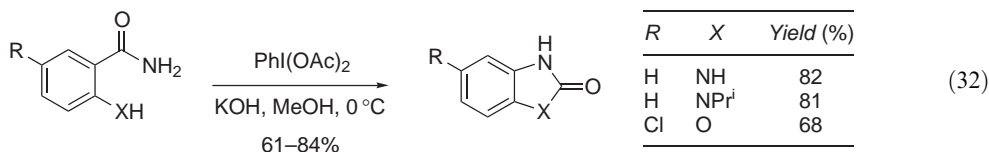
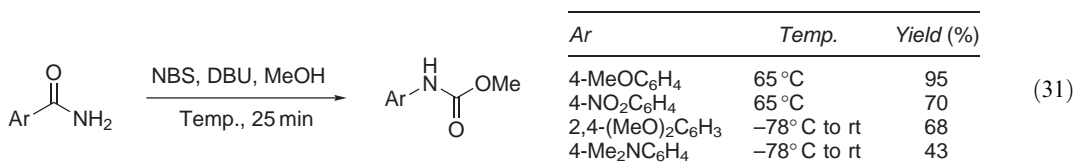
N,N-Dimethylanilines react with secondary anilines in the presence of thallium triacetate in a novel oxidatively activated aromatic substitution reaction to afford 1,4-benzenediamines **128** in moderate yield (Equation (30)) <1999JOC2459>.



2.15.2.2.8 From carboxylic acids and derivatives

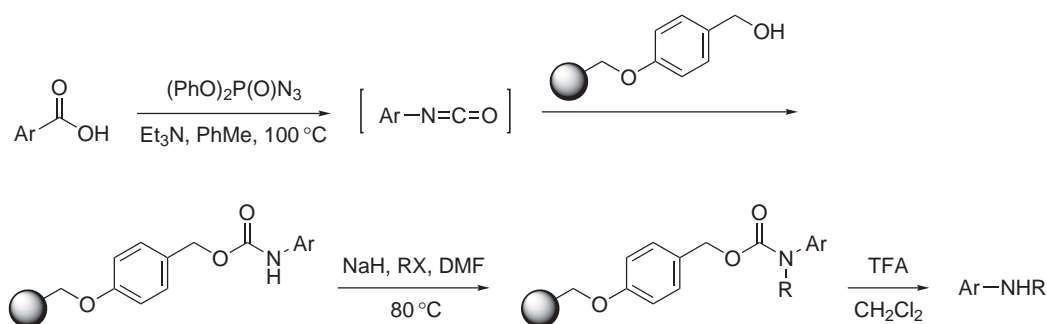
The Hofmann rearrangement of aromatic amides and the Curtius rearrangement of aromatic acyl azides are two classical procedures to convert aryl carboxylic acids and derivatives into the corresponding arylamines and derivatives. New developments in this field will be briefly described.

Keillor has reported a very mild and practical procedure for the preparation of methyl carbamates from a variety of alkyl and aryl primary amides by treatment with NBS and DBU in MeOH at reflux (Equation (31)) <1997JOC7495, 1997TL313>. The carbamates are obtained in very good yields and can be easily hydrolyzed to the free amines. The procedure is mild enough, compared to other methods, to be applied successfully to *p*-methoxybenzamide without further oxidation of the product <2002OS234>. A number of hypervalent iodine derivatives promote the Hofmann rearrangement of primary amides under mild conditions <2003TCC(224)185, 2003TCC(224)209>. When treated with iodobenzene diacetate in methanolic KOH, aryl carboxamides with a hydroxyl or a primary or secondary amino group at the *ortho* position give 2-benzoxazolones or 2-benzoimidazolones, respectively, by intramolecular cyclization of the intermediate isocyanate generated by Hofmann rearrangement (Equation (32)) <2001S541>.



Treatment of 4-substituted aroyl azides with NaBH₄ in TFA gives the corresponding 4-substituted *N,N*-di(2,2,2-trifluoroethyl)anilines in high yield. When electron-withdrawing groups (NO₂, CN) are present, mixtures of the aniline and the *N*-(2,2,2-trifluoroethyl)aniline are obtained <1996TL7213>.

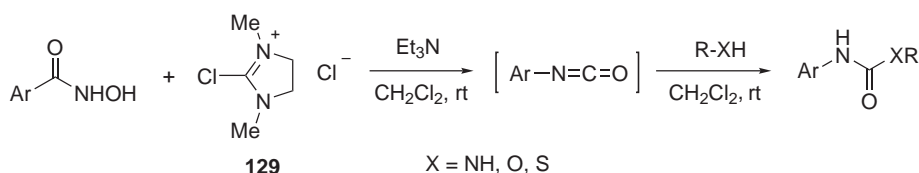
Morishima has described a method for the efficient synthesis of secondary arylamines and heteroarylamines (Scheme 40) <1999TL1721>. Aryl and heteroaryl carboxylic acids were transformed into the corresponding carbamates by Curtius rearrangement with diphenylphosphoryl azide followed by trapping of the resultant isocyanates with Wang-OH resin. *N*-Alkylation of the resin-bound carbamate under Mitsunobu conditions or using NaH followed by acid-promoted cleavage from the resin afforded the secondary arylamines or heteroarylamines. A parallel approach using resin-bound secondary amines to trap the intermediate isocyanate has been described by Migawa for the preparation of *N,N'*-disubstituted ureas <2000OL3309>.



Ar	R	Yield (%)	Purity (%)
4-NO ₂ C ₆ H ₄	H	>95	94
4-MeC ₆ H ₄	allyl	77	91
4-MeC ₆ H ₄	Et	93	94

Scheme 40

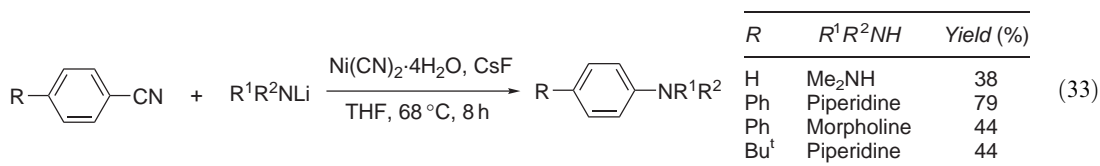
2-Chloro-1,3-dimethylimidazolinium chloride **129** is a powerful dehydrating agent that promote the rearrangement of alkyl and aryl hydroxamic acids into isocyanates that can be trapped with amines, alcohols, or thiols to give the corresponding ureas, carbamates, or thiocarbamates, respectively, in moderate-to-good yields (Scheme 41) <1999JOC5832>. Similarly, diaryl or aryl alkyl oximes suffer a Beckmann-like rearrangement to give aryl carboxamides in good yields with this reagent.



Ar	R-XH	Yield (%)
Ph	Bu ⁿ NH ₂	57
Ph	MeOH	82
Ph	2-MeC ₆ H ₄ SH	83

Scheme 41

Aryl nitriles have been found to undergo a novel nickel-catalyzed cross-coupling with lithium amides of secondary alkylamines to give the corresponding arylamines in moderate-to-good yields (Equation (33)) <2003S1643>.

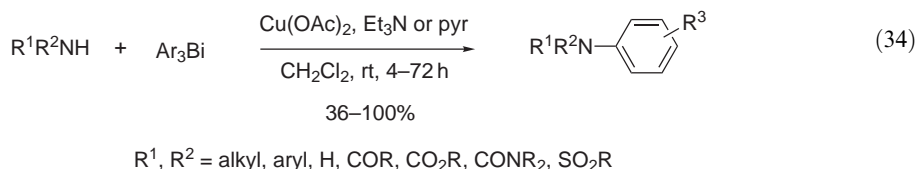


2.15.2.2.9 From arylbismuth, aryllead, arylboron, aryltin, arylsilicon, and diaryliodonium reagents

Copper-promoted carbon–nitrogen bond cross-coupling reactions of NH-containing substrates are typically performed under Ullmann-type conditions using aryl halides, as described in

Section 2.15.2.2.4. Methods that use alternate transmetallating agents have emerged as a powerful new synthetic methodology and three recent reviews have been published <2001T5683, 2002CUOC597, 2003AG(E)5400>. These new methods are an important addition to the growing arsenal of transition metal-mediated C—N bond cross-coupling reactions.

Copper-catalyzed *N*-arylation reactions using arylbismuth <1985ZOB466, 1985ZOB2514, 1986TL3615, 1987TL887, 1988TL1115, 1989TL937> and aryllead reagents <1987TL3111, 1989TL1377, 1991JCS(P1)2095> were discovered in the 1980s independently by both Barton and Dodonov. Later, Barton found that Cu(OPiv)₂ was a very efficient soluble catalyst for the arylation of alkyl- and arylamines with Ar₃Bi(OAc)₂ in very high yields <1997T4137>. The influence of the steric hindrance of the aryl group on the reactivity of these Bi(V) reagents has been studied by Finet <1999T1341>. Chan has found that triarylbiuthane is able to efficiently arylate a variety of NH-containing compounds at room temperature using stoichiometric Cu(OAc)₂ in the presence of triethylamine or pyridine <1996TL9013>. The copper(II) salt acts as both, oxidant (of Bi(III) to Bi(V)) and catalyst. No reaction takes place in the absence of the tertiary amine. Amides, ureas, carbamates, imides, and sulfonamides are arylated in excellent yields (Equation (34)). Diarylamines can be prepared in good yield using this procedure starting from aminobenzanilides, *N*-arylation taking place selectively at the amino rather than at the amido nitrogen <2000JOC7747>.

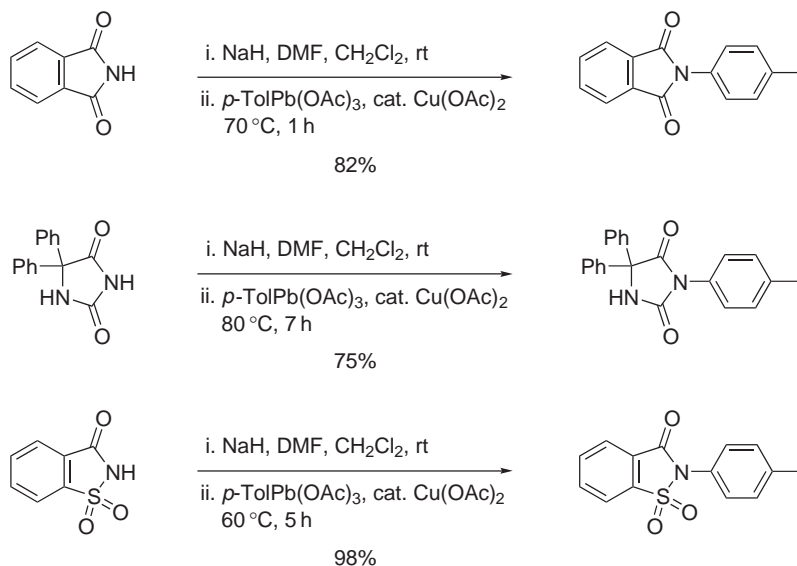


$\text{R}^1\text{R}^2\text{NH}$	R^3	Base	Yield (%)
	H	Et ₃ N	94
	4-OCF ₃	Et ₃ N	94
	H	pyridine	83

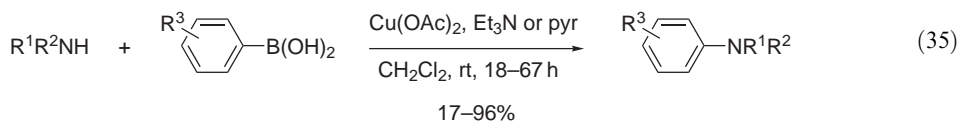
The *N*-arylation of amines with aryllead triacetate catalyzed by copper(II) acylates has a narrower scope than the corresponding reaction with arylbismuth reagents. The main advantage of aryllead triacetates is that *N*-arylation with highly electron-rich arenes can take place in preparatively useful yields at room temperature <1998JCR(S)4, 2000H(53)2535, 2000MI563, 2002SC2893>, although the efficiency of the reaction is highly dependent on the basicity of the amine and competitive oxido-reduction of the aryllead reagent is sometimes observed with easily oxidized substrates when steric hindrance is important. Avendaño has shown that amides, sulfonamides, imides, and hydantoins can be *N*-arylated with *p*-tolyllead triacetate at 60–80 °C under Cu(II)-catalysis in good-to-excellent yields (Scheme 42) <1996JOC5865>. In general, better yields are obtained if the sodium salt of the amide is used.

The copper-promoted *N*-arylation reaction with arylboronic acids has experienced rapid development since its discovery in 1998 by Chan (Equation (35)) <1998TL2933>. The reaction takes place under very mild conditions (room temperature, mild base, atmospheric pressure), has a wide substrate scope (primary and secondary alkyl or arylamines, amides, imides, ureas, carbamates and sulfonamides), and is tolerant to many functional groups on the arylboronic acid <1998TL2941, 1999T12757, 2000SL674, 2003TL3863>. Additionally, thanks to the great usefulness of Suzuki-Miyaura cross-coupling reactions, a wide variety of diverse arylboronic acids are now commercially available. Stoichiometric amounts of Cu(II) diacylates and a tertiary amine base are required as promoters and addition of molecular sieves improves the yields. Cundy has studied the cross-coupling of a range of NH nucleophiles with electronically diverse arylboronic acids but could not find any obvious general reactivity trends <1998TL7979>. α -Aminoesters can

be *N*-arylated in high yields by this procedure with little or no racemization <2003TL1691>. Sequential Cu(OAc)₂-promoted *N*-arylation and Pd-catalyzed Suzuki–Miyaura C–C coupling using halo-substituted N–H heteroarenes have been described <1999T12757, 2000TL9053>.



Scheme 42

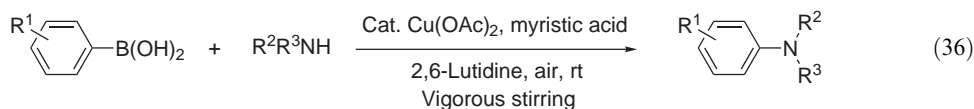


$\text{R}^1, \text{R}^2 = \text{alkyl, aryl, H, COR, CO}_2\text{R, CONR}_2, \text{SO}_2\text{R}$

$\text{R}^1\text{R}^2\text{NH}$	R^3	Base	Yield (%)
	4-Me	pyridine	63
	4-F	Et ₃ N	93
	4-OMe	Et ₃ N	41
	4-Me	Et ₃ N	45
	4-Me	pyridine	92

Several catalytic versions of the *N*-arylation reaction with arylboronic acids have been developed. Collman has found that the reaction of imidazoles with arylboronic acids can be efficiently catalyzed with $[\text{Cu(OH)}\cdot\text{TMEDA}]_2\text{Cl}_2$ in either aqueous or anhydrous solvent (CH_2Cl_2) under an

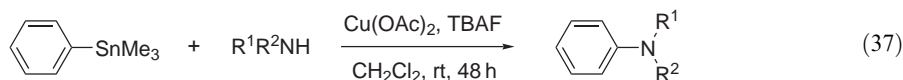
air or an oxygen atmosphere <2000OL1233, 2001JOC1528, 2001JOC7892>. Lam has shown that the cross-coupling with amines and N—H heteroarenes can be catalyzed with $\text{Cu}(\text{OAc})_2$ when a variety of oxidants are employed. Catalytic $\text{Cu}(\text{OAc})_2/\text{TEMPO}$ in air or catalytic $\text{Cu}(\text{OAc})_2/\text{O}_2$ systems using triethylamine as base work efficiently for the majority of the substrates assayed <1999T12757>. Buchwald has described the use $\text{Cu}(\text{OAc})_2$ as a catalyst, 2,6-lutidine as base, and myristic acid as an additive for the coupling of alkylamines and functionalized anilines with arylboronic acids in the presence of air in moderate-to-good yields (Equation (36)) <1999T12757>. This catalyst system has been applied to the *N*-arylation of aziridines in moderate-to-good yields <2003JOC2045>.



R^1	$\text{R}^2\text{R}^3\text{NH}$	Yield (%)
4-Me	PhNH_2	91
2-Me	PhNH_2	58
4-Me	4-AcNH-C ₆ H ₄ NH ₂	50
4-Me	piperidine	56

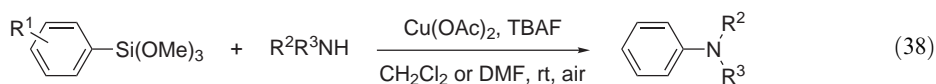
Solid-supported primary and secondary amines <2002JCO179>, N—H heteroarenes <1999TL1623>, and sulfonamides <2000JCO29> have been *N*-arylated with arylboronic acids using $\text{Cu}(\text{OAc})_2$ in the presence of triethylamine as promoter in good-to-excellent yields. Microwave irradiation dramatically decreased reaction times and improved yields and purities of the final products <1999TL1623>.

Aryltrialkylstannanes can replace arylboronic acids in the copper-promoted *N*-arylation reaction, although much lower yields are obtained in general under the same experimental conditions <1998TL2941, 2000SL674>. However, addition of TBAF improves the yields considerably by facilitating the transmetalation step through formation of a hypervalent stannane anion <2002TL3091>. In this case, addition of triethylamine did not increase the yields further. A number of NH nucleophiles can be efficiently arylated under these conditions, including arylamines, primary amides, and primary sulfonamides (Equation (37)).



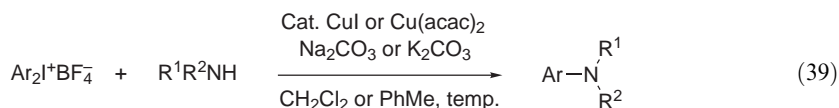
$\text{R}^1\text{R}^2\text{NH}$	Yield (%)
	80
	72
	48 (5:1 mixture of mono- and diarylated compound)

Hypervalent arylsiloxanes, generated by addition of TBAF to aryltrimethoxysilanes, have been shown to be efficient arylating agents for a variety of NH nucleophiles in the presence of stoichiometric amounts of $\text{Cu}(\text{OAc})_2$ at room temperature, in the absence of any other added base and under an air atmosphere (Equation (38)) <2000JA7600>. The reaction is much faster than with arylboronic acids. *N*-Arylation of amides is only efficient for substrates that contain an α -heteroatom that is able to chelate the copper promoter <2001TL2427>.



R^1	$\text{R}^2\text{R}^3\text{NH}$	Yield (%)
4-OMe		58
H		61
4-Cl		27

Diaryliodonium salts participate in copper-catalyzed *N*-arylation of secondary alkylamines, arylamines, N—H heteroarenes, and amides (Equation (39)) <2002HAC617, 2002SC903, 2002SL427>. The reaction is performed with catalytic CuI or Cu(acac)₂ in the presence of Na₂CO₃ or K₂CO₃ as a base in CH₂Cl₂, toluene, or DMF under mild conditions. Regioselective *N*-arylation of tributylstannylated heteroarenes takes place at room temperature in the absence of base using a stoichiometric amount of Cu(OAc)₂ <2002TL6217>.



Ar = Ph, 4-C₆H₄, 4-MeOC₆H₄

Ar	$\text{R}^1\text{R}^2\text{NH}$	Catalyst	Base	Solvent	Temp.	Yield (%)
Ph	piperidine	CuI	Na ₂ CO ₃	CH ₂ Cl ₂	rt	65
Ph		CuI	Na ₂ CO ₃	CH ₂ Cl ₂	rt	70
Ph		Cu(acac) ₂	K ₂ CO ₃	PhMe	50 °C	70
Ph		CuI	K ₂ CO ₃	PhMe	50 °C	42

2.15.3 SALTS OF ENAMINES AND ARYLAMINES

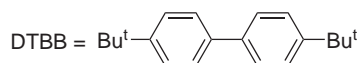
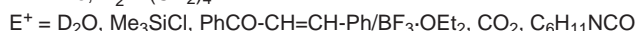
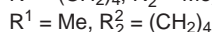
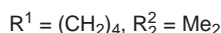
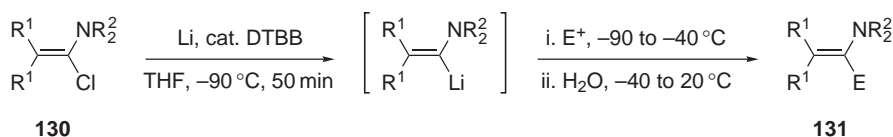
This section is an update on all new methods for the synthesis of salts of enamines and arylamines that have been developed since the publication of COFGT (1995) <1995COFGT(2)737>.

2.15.3.1 Salts of Enamines

A review of the acid and base properties of enamines has been published <B-1994MI695>. NMR spectroscopy and quantum-mechanical calculations have shown that the favored site of protonation of β -cyanoenamides is the nitrogen of the cyano group <1998JA12942>. The protonation of α -ketoenamides has been shown by NMR spectroscopy to depend on the nature of the protonating agent <2001MC70>. Carboxylic acids produce C-protonation at the C _{β} of the enamine to

give regioselectively the corresponding iminium salt, whereas hard mineral acids such as HCl produce mainly or exclusively *N*-protonation to give the corresponding enammonium salt or a mixture of *C*- and *N*-protonation products, depending on the structure of the enamine.

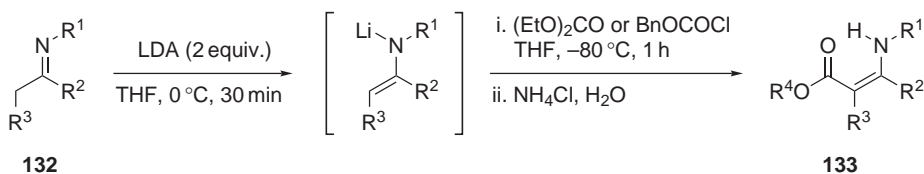
β -Lithiated enamines and their use in the synthesis of β -functionalized enamines and the corresponding α -substituted ketones obtained after acidic hydrolysis has been reviewed in COFGT (1995) <1995COFGT(2)737> and no new developments on this chemistry have been published since. α -Chloroenamines **130** react with excess lithium and a catalytic amount of 4,4'-di-*t*-butylbiphenyl (DTBB) in THF at -90°C to generate α -lithioenamines that can react with added electrophiles to give the expected functionalized enamines **131** (Scheme 43) <2002MI38>. In the case of aldehydes, it was necessary to perform the lithiation in the presence of the electrophile (Barbier conditions) at -40°C . Hydrolysis of the obtained enamines was performed either with silica gel or with hydrochloric acid to yield the corresponding functionalized ketones.



R^1	NR_2^2	E	Yield (%)
$(\text{CH}_2)_4$	NMe_2	D	81
$(\text{CH}_2)_4$	NMe_2	SiMe_3	71
$(\text{CH}_2)_4$	NMe_2	Bu^tCHOH	62

Scheme 43

N-Lithiated enamines, readily prepared from imines **132**, react with diethyl carbonate or benzyl chloroformate at -80°C to give the corresponding β -enamino esters **133** (Scheme 44) <1995T8613>.

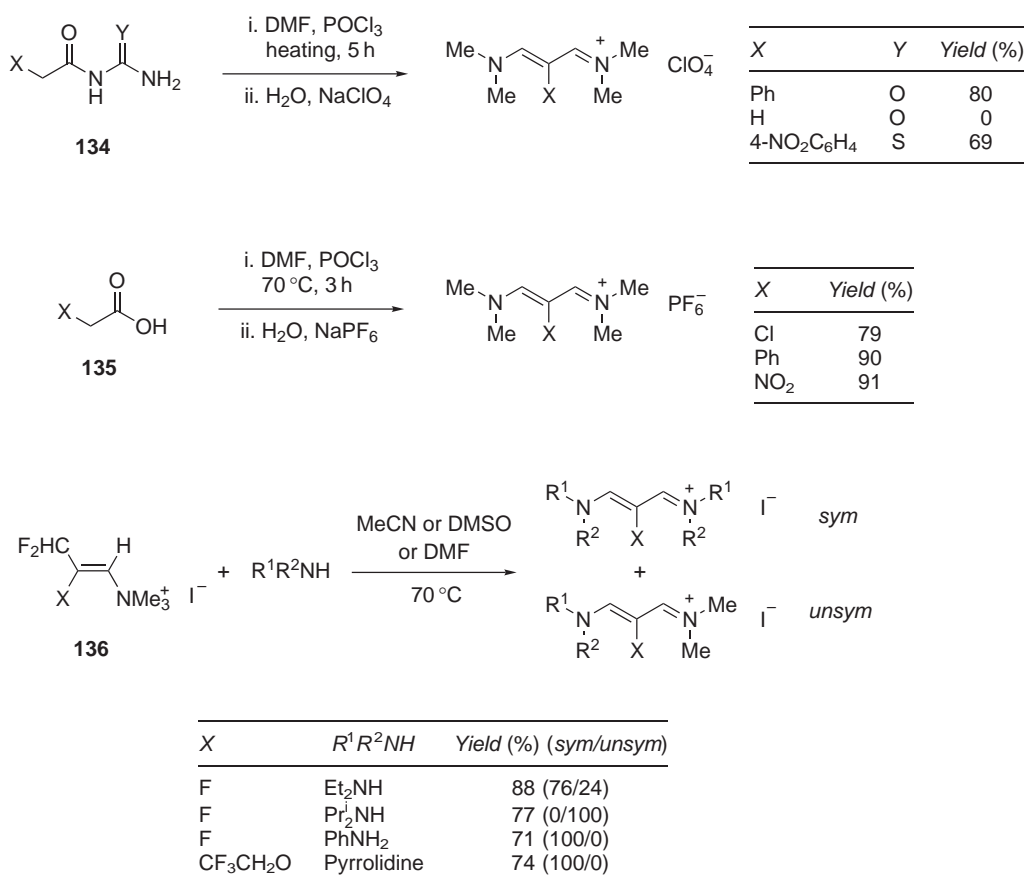


R^1, R^2	R^3	R^4	Yield (%)
$(\text{CH}_2)_3$	H	Et	70
$(\text{CH}_2)_3$	H	Bn	76
Pr^i, H	Me	Et	59

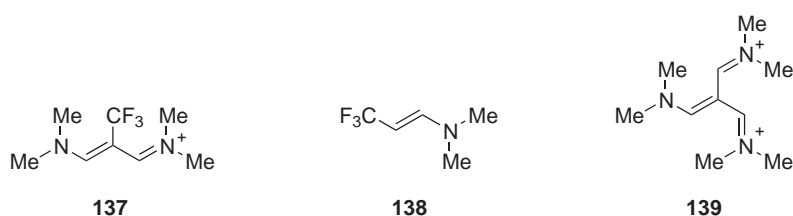
Scheme 44

Lithium dianions of enamminones react regioselectively with *N,N*-dimethylcarbamoyl chloride to give *N,N*-dimethylcarbamoylenaminones <1997T6893>. Enaminones of chiral amines are acylated with high stereoselectivity using this procedure. The preparation and crystal structures of a series of lithiated enamines have been described <1997JCS(D)3421, 1998JCS(D)3431, 1999CC1401, 1999JCS(D)1263>.

Vinamidinium (1,5-diazapentadienium) salts, vinylogs of amidinium compounds, are versatile three-C building blocks in organic synthesis, reacting with nucleophiles at C $_{\alpha}$ and with electrophiles at the C $_{\beta}$ <1994JPR(336)390, 2000JFC(105)295, 2003MI238>. Some new methods for the synthesis of these compounds have been reported during the 1990s (Scheme 45). The reaction of Vilsmeier–Haack–Arnold reagent (prepared *in situ* from DMF and POCl $_3$) with acyl(thio)ureas **134** <1997TL6263, 1999SC73> or with substituted acetic acids **135** <2000JOC4571, 2001JOC251> resulted in the formation of β -substituted vinamidinium salts in moderate-to-good yields. β -Fluoro- and β -polyfluoroalkoxy-substituted vinamidinium salts were prepared by reaction of enammonium salts **136** with primary or secondary amines in an aprotic polar solvent (MeCN, DMSO, DMF) at 70 °C <2000JFC(105)295>. Davies has described that the reaction of 3,3,3-trifluoropropanoic acid with POCl $_3$ in DMF generates either the expected 2-trifluoromethylvinamidinium salt **137** (68%) or the novel dimethylaminomethylene vinamidinium salt **139** (67%) depending on the reaction conditions <2002OL2969>. The trifluoromethyl enamine **138** has been identified as a common reaction intermediate for both processes.



Scheme 45



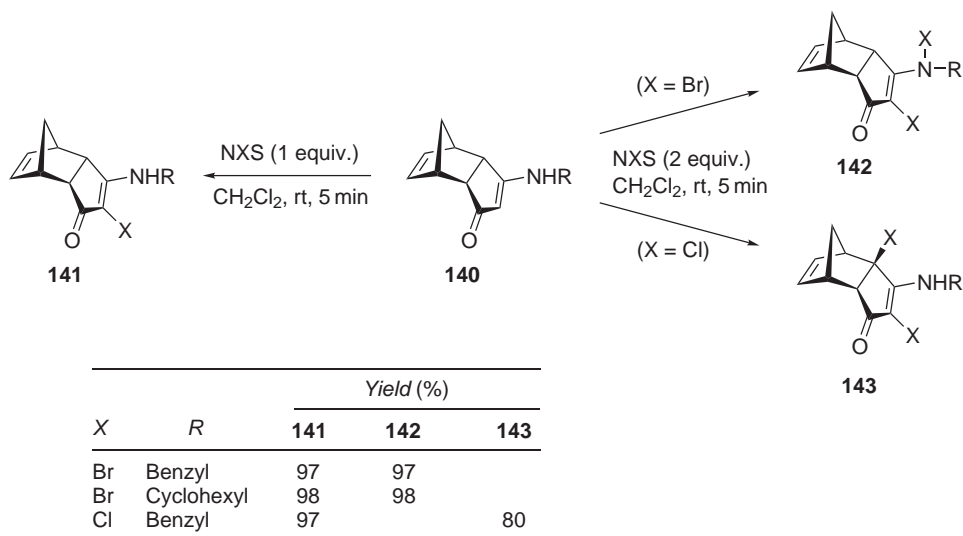
2.15.3.2 Salts of Arylamines

Aromatic amines can be protonated by mineral acids or by sufficiently strong organic acids. Tertiary arylamines can be transformed into the corresponding ammonium salts by reaction with a number of alkylating agents. No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)737>.

2.15.4 N-HALOENAMINES AND ARYLAMINES

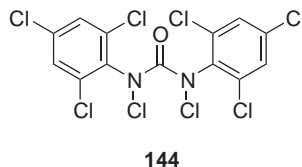
This section is an update of all new methods for the synthesis of *N*-haloenamines and arylamines that have been developed since the publication of COFGT (1995) <1995COFGT(2)737>.

N-Haloamines are generally prepared by halogenation of primary or secondary amines. The halogenation of tricyclic enaminones **140** with *N*-halosuccinimides gives exclusively and in high yield the α ,*N*-dihalo derivative **142** or the α , γ -dihalo derivative **143** depending on the reaction conditions (Scheme 46) <2002T1361>. Reaction with a limited amount (1 equiv.) of *N*-halosuccinimide produces the α -halogenated product **141** in almost quantitative yield. Reaction with an excess (2 equiv.) of NBS gave product **142** in very high yield while NCS produced exclusively isomer **143** under the same reaction conditions.



Scheme 46

An improved procedure for large-scale preparation of the chlorinating agent *N,N'*-dichlorobis-(2,4,6-trichlorophenyl)urea **144** by a two-step chlorination of diphenylurea with Cl_2 has been described <1999JOC8031>. Although its reactivity with organic substrates has not been fully explored, it is claimed to be more stable than NCS, and has a higher chlorine content.

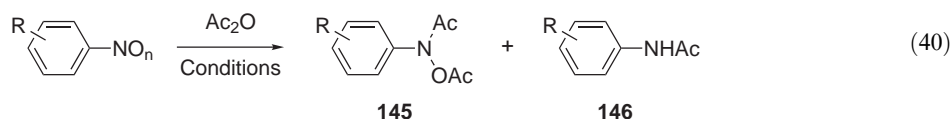


2.15.5 HYDROXYLAMINES AND RELATED FUNCTIONS

This section is an update on all new methods for the synthesis of vinyl and aryl hydroxylamines and *N*-oxides that have been developed after the publication of COFGT (1995) <1995COFGT(2)737>.

2.15.5.1 Hydroxylamines

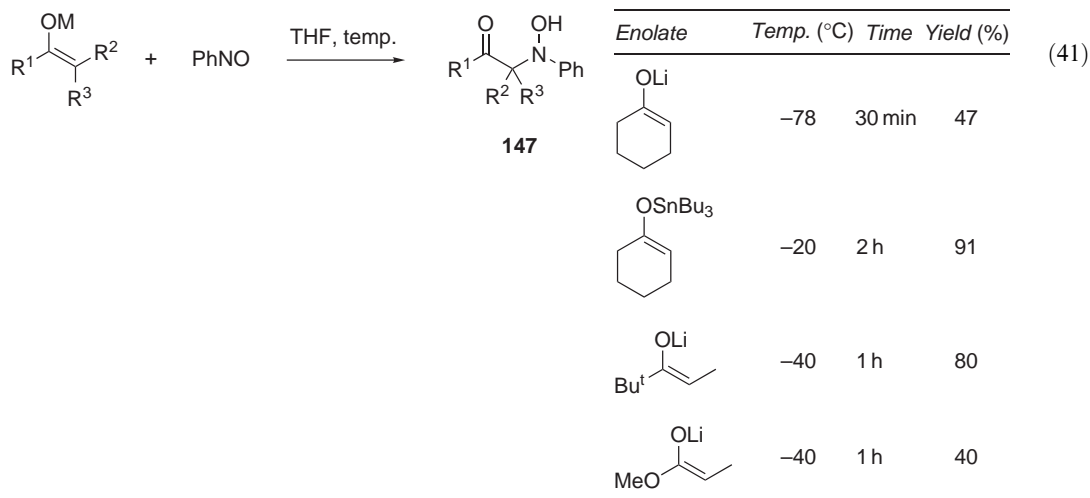
Partial reduction of nitro compounds is one of the most common and satisfactory methods for the preparation of hydroxylamines. General procedures used for this purpose are reviewed in COFGT (1995) <1995COFGT(2)737>. *N,O*-Diacetylated *N*-arylhydroxylamines **145** have been obtained in good yield by reduction of nitro- or nitrosoarenes with Zn <1998JCR(S)46> or In/InCl₃ <2001SC3577> in the presence of acetic anhydride (Equation (40)). The corresponding acetanilide **146** is formed as a by-product due to overreduction. When the reduction with zinc metal is performed in the presence of excess allyl bromide, the corresponding *N,O*-diallylated product is obtained in moderate yield together with minor amounts of *N,N*-diallylated aniline <1999H1921>.

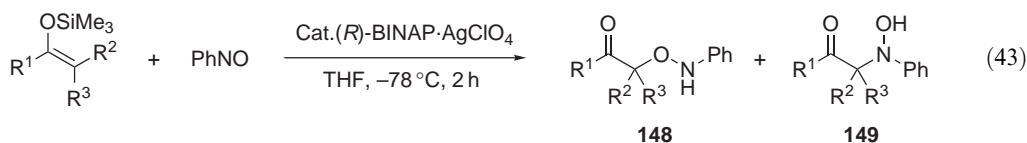
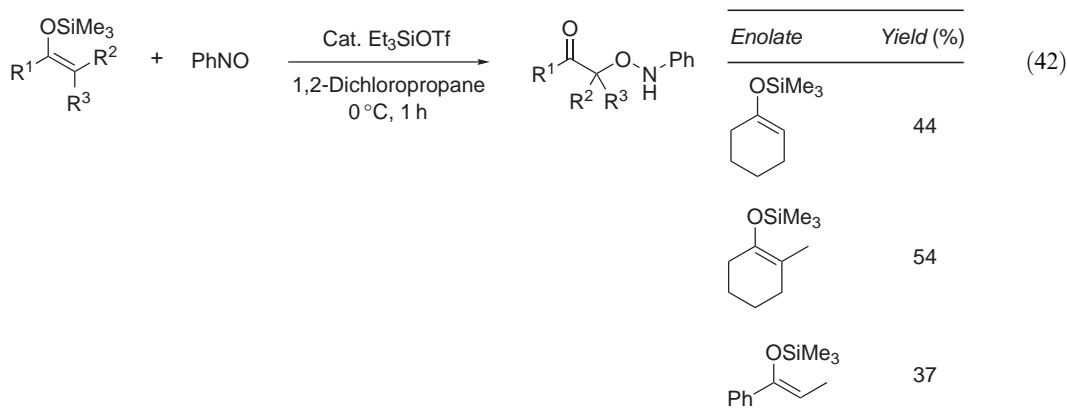


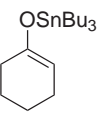
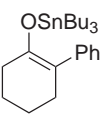
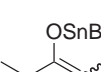
Conditions: A, Zn, CH₂Cl₂, rt, 50–120 min
 B, In, InCl₃ (0.2 equiv.), MeOH (2 equiv.), CHCl₃, rt, 1–48 h

<i>n</i>	<i>R</i>	Conditions	Time	Yield (%)	
				145	146
2	H	A	50 min	87	5
1	H	A	50 min	95	traces
2	H	B	20 h	81	13
2	3-Br	A	50 min	91	7

C-Nucleophiles add very efficiently to nitrones <2000S759, 2000SL442, 2002CUOC695> and nitroso compounds <1994CRV1621> to give *N,N,O*-trisubstituted and *N,N*-disubstituted hydroxylamines, respectively. Yamamoto has reported a general method for the reaction of nitroso compounds with a variety of alkali metal or tin enolates to generate α -hydroxylamino carbonyl derivatives **147** (Equation (41)) <2002OL3579>. Moderate to very good yields were obtained without any Lewis acid catalyst and the reaction was completely *N*-selective. When the reaction was performed under Lewis acid catalysis, exclusive *O*-selective addition was observed for silyl enolates (Equation (42)) <2002AG(E)2986>. Of a number of Lewis acids tested, trialkylsilyl triflates were especially efficient. The same authors have developed an enantioselective version of this process using tin enolates and a BINAP-silver complex as catalyst (Equation (43)) <2003JA6038>.

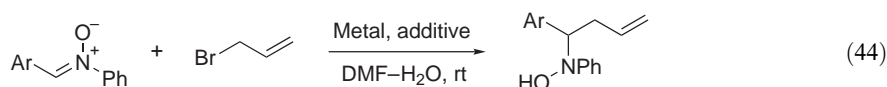




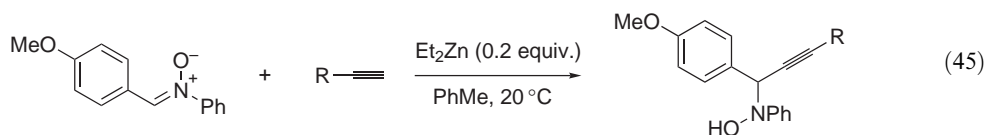
Enolate	Yield (%)	148/149 ratio	ee% of 148
	95	>99/1	95
	97	85/15	91
	92 ^a	81/19 ^a	94 ^a

^a Catalyst: (R)-TolBINAP·AgClO₄.

Reaction of *N*-arylnitrones of aromatic aldehydes with allyl bromide in the presence of indium metal <2000TL9311> or samarium metal and Bu₄NBr <2001TL7883> in DMF-H₂O gives homoallylic hydroxylamines in good yield (Equation (44)). Terminal alkynes react with *N*-arylnitrones in the presence of a substoichiometric amount of diethylzinc in toluene to afford *N*-propargyl-hydroxylamines in good yield (Equation (45) <2002OL1463>).



Ar	Metal	Additive	Time (h)	Yield (%)
Ph	In	None	3	90
Ph	Sm	Bu ₄ NBr	1.5	85
3-HOC ₆ H ₄	In	None	4	75
3-NO ₂ C ₆ H ₄	Sm	Bu ₄ NBr	1.5	80

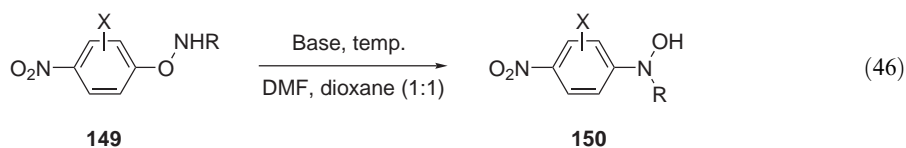


Alkyne	Time (h)	Yield (%)
	1.5	72
	1.5	56
	2	61

N-Allyl-*N*-arylhydroxylamines can be directly prepared by the ene reaction of nitrosoarenes with readily available alkenes (nitroso ene reaction). A very recent comprehensive review by Adam and Krebs on this synthetically promising ene reaction has been published covering mechanistic aspects, selectivity, synthetic applications, and new catalytic variations [<2003CRV4131>](#).

C-Nitroso compounds can also act as nucleophiles [<2001MI\(538\)41>](#). Thus, nitrosobenzene reacts with aldehydes [<1995TL9547>](#) in the presence of Fe^{3+} salts and with acyl chlorides in the presence of a catalytic amount of HCl [<2001TL8519>](#) to give the corresponding *N*-phenyl- and *N*-*p*-chlorophenylhydroxamic acids, respectively, although no yields were reported.

O-(Halo-4-nitrophenyl)hydroxycarbamates **149** react with bases under mild conditions to give arylhydroxylamines **150** in moderate yield (Equation (46)) [<2002TL6735>](#). Crossover experiments have shown that the reaction occurs both inter- and intramolecularly.



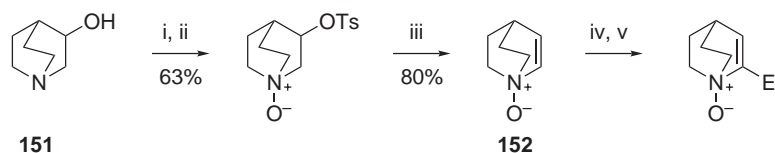
X	R	Base	Temp. (°C)	Yield
2,6-Cl ₂	<i>t</i> -BOC	NaHCO ₃	22	53
2-Cl	Cbz	K ₂ CO ₃	55	69
2-Br	<i>t</i> -BOC	K ₂ CO ₃	55	79

2.15.5.2 Nitrones

No further advances have occurred in this area since the publication of COFGT (1995) [<1995COFGT\(2\)737>](#).

2.15.5.3 *N*-Oxides

Quinuclidine enamine *N*-oxide **152** can be prepared from commercially available 3-hydroxy-quinuclidine **151** by the route shown in Scheme 47. The corresponding borane complex of the enamine was prepared by an analogous route. Both derivatives can be functionalized at the α -position by regioselective deprotonation of the double bond with Bu^tLi and subsequent reaction with a variety of electrophiles [<1999TL271>](#).



i. TsCl, Et₃N, CH₂Cl₂; ii. MCPBA, CH₂Cl₂; iii. KOBu^t, THF, -78 °C to rt;
iv. Bu^tLi, THF, -78 °C; v. E⁺

E ⁺	Product	Yield (%)
Br ₂		74
PhCHO		78
Bu ⁿ SnCl		75
		60

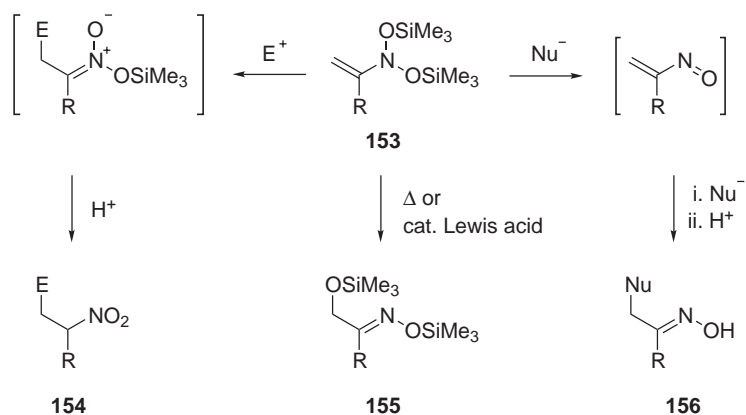
Scheme 47

2.15.5.4 *N,N*-Bis-(silyloxy)enamines and *N,N*-Bis-(silyloxy)arylamines

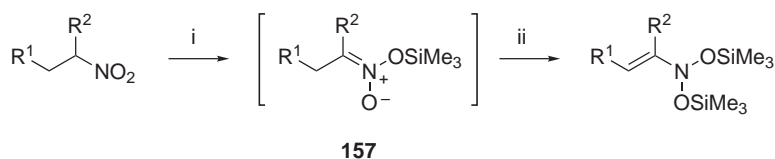
N,N-Bis-(silyloxy)enamines **153** were first prepared by Feger and Simchen in 1986 by double silylation of nitro compounds using powerful silylating agents such as trialkylsilyl triflates <1986LA1456>. More recently, Ioffe and co-workers have developed improved preparation procedures <1998S181, 2000JCS(P1)2926> and have extensively studied the reactivity <2001JOC3196, 2001MI1936> and structure <2002JA11358> of this interesting group of compounds. Remarkable is their intriguing ability to react with both nucleophiles <1986LA1456, 1998S181, 1999S1767, 2000MI1261, 2002HCA3489, 2002MC99, 2002MI1455, 2003S1339> and electrophiles <2000JOC8826, 2001JOC3196, 2003MC74> at the C_β to give oximes **156** and nitro compounds **154**, respectively (Scheme 48). Besides, *N,N*-bis-(silyloxy)enamines are prone to rearrangement into α-silyloxy oximes **155** by heating or by Lewis acid catalysis <1986LA1456>.

Ioffe and co-workers have found that *N,N*-bis-(silyloxy)enamines can be readily prepared in good yield and as stable compounds by reaction of primary or secondary aliphatic nitro compounds with 2 equiv. of TMSBr in the presence of Et₃N followed by aqueous work-up (Scheme 49) <1998S181>. In the case of nitrocyclohexane or of sterically hindered nitroalkanes, a two-step procedure was required via the intermediate silyl nitronate **157**. However, this procedure failed when applied to the preparation of *N,N*-bis-(silyloxy)enamines with a functionalized double bond. In this case, decomposition of the product into quaternary ammonium salts **158** occurred (Scheme 50) <1986LA1456, 1998S181, 2000JCS(P1)2926>. This problem was easily circumvented by lowering the reaction temperature and using a stronger silylating agent such as the trialkylsilyl triflates used previously by Feger and Simchen (Scheme 50) <2000JCS(P1)2926, 2001T2221>.

N,N-Bis-(*t*-butylsilyloxy)aminobenzene **159** was prepared by double silylation of 1-nitro-1-3-cyclohexadiene with TBDMSOTf in the presence of Et₃N. This compound is a synthetic equivalent of nitrosobenzene (Scheme 51) <2000MI1649>. Double silylation of 1-(4-nitrophenyl)-2-nitroethane with TMSOTf/Et₃N gave a mixture of *N,N*-bis-(silyloxy)aniline **160** and *N,N*-bis-(silyloxy)enamine **161** (Scheme 51) <2002JA11358>. When TMSBr/Et₃N was used as the silylating agent, compound **161** was the exclusive product.



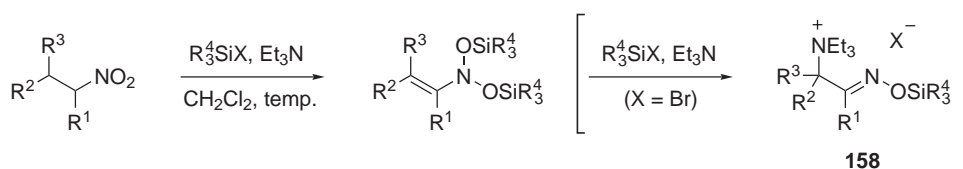
Scheme 48



i. Method A: TMSBr, Et₃N, ClCH₂CH₂Cl. Method B: (1) DBU, CH₂Cl₂; (2) TMSBr;
 ii. TMSBr, Et₃N, ClCH₂CH₂Cl

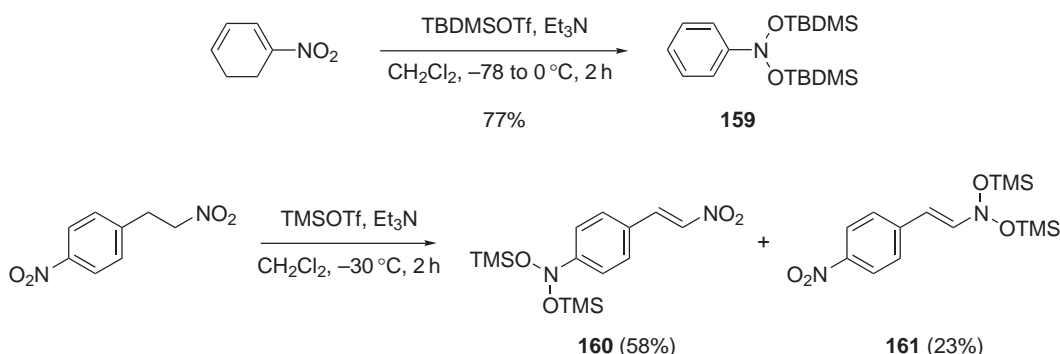
<i>R</i> ¹	<i>R</i> ²	Reaction conditions	Yield (%)
H	H	Method A, 3 h at 0 °C, 7 h at −20 °C	97
Me	H	Method A, 3.5 h at 0 °C, 40 h at −20 °C	92
H	Me	Method A, 48 h at −30 °C	89
CH(OSiMe ₃)Pr ⁱ	H	Method B, 17 d at 20 °C	62

Scheme 49



<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>R</i> ⁴	Temp. (°C)	Time (h)	Yield (%)
CO ₂ Et	H	H	Me ₃ SiOTf	−75	5	94
H	CO ₂ Et	H	Me ₃ SiOTf	−75	2.5	87
Me	CO ₂ Et	H	Me ₃ SiOTf	−30	3	85
H	COMe	H	Bu ^t Me ₂ SiOTf	−75	2	84

Scheme 50



Scheme 51

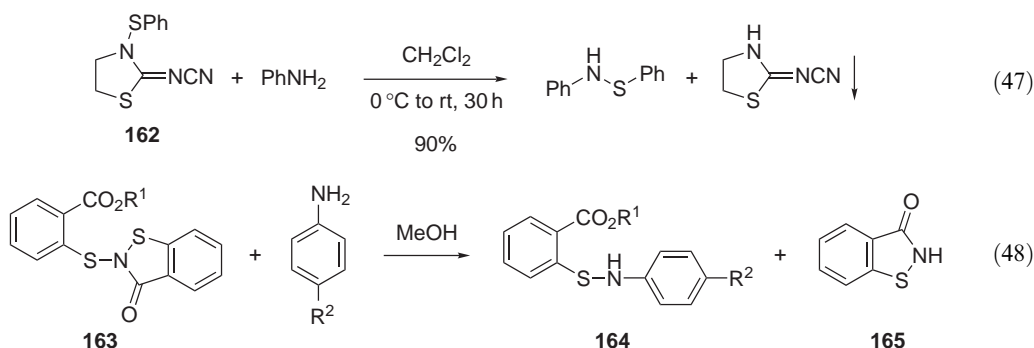
2.15.6 THIOHYDROXYLAMINES AND RELATED FUNCTIONS

This section is an update on all new methods for the synthesis of vinyl and aryl thiohydroxylamines and related functions that have been reported since the publication of COFGT (1995) <1995COFGT(2)737>.

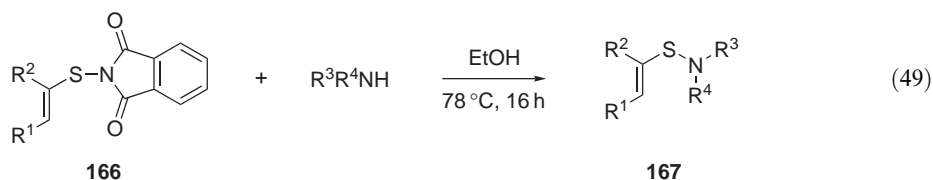
2.15.6.1 Sulfenamides

Sulfenamides (sulfenic acid amides), compounds containing trivalent nitrogen bonded to divalent sulfur, have many industrial applications and are also useful synthetic reagents <1996UK452, 1996ZOR1287> with interesting chiroptical properties <1997AG(E)2216, 2000JOC8613>.

The most common method employed for the synthesis of sulfenamides is the reaction of primary or secondary amines with sulfenyl halides <1995COFGT(2)737>. Recently, more stable sulfenylating reagents have been developed. Thus, Tanaka has described the use of 3-phenylsulfonyl-2-(*N*-cyanoimino)thiazolidine **162** for the synthesis of sulfenamides and unsymmetrical disulfides in excellent yields and under very mild conditions (Equation (47)) <2000SL33>. Shimizu has described that *S*-[2-(3-oxo-1,2-benzisothiazolyl)]-2-mercaptobenzoates **163** react with primary amines on the *S* of the 2-sulfenamoyl group to give *N*-substituted 2-sulfenamoylbenzoates **164** in moderate to very high yield (Equation (48)) <2002T3779>. Schwan has described a facile transamination of *N*-(1-alkenylthio)phthalimides **166** with primary and secondary amines to give 1-alkenesulfenamides **167** in moderate yield Equation (49) <1996JOC4232>. The starting 1-alkenesulfenamides **166** were readily prepared from thirane *S*-oxides by deprotonation with lithium bis-(trimethylsilyl)amide and reaction with phthaloyl chloride.



R ¹	R ²	Time (h)	Temp. (°C)	Yield (%)	
				164	165
Me	OMe	1.5	65	97	71
Me	Me	7.5	rt	83	66
Me	Cl	10	65	63	61
Et	Me	3	65	99	60



$\begin{array}{c} \text{R}^2 \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{R}^1 \end{array}$	$\text{R}^3\text{R}^4\text{NH}$	Yield (%)
$\begin{array}{c} \text{Bu}^n \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{C}_6\text{H}_4 \end{array}$	$\text{HN}-\text{CH}_2\text{CH}=\text{CH}_2$ 	68
$\begin{array}{c} \text{C}_6\text{H}_5 \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{C}_6\text{H}_4 \end{array}$	PhNH_2	50

Sulfenamides can be also prepared by reaction of aromatic thiols and amines in the presence of oxidizing reagents <1995COFGT(2)737>.

2.15.7 SELENIUM AND TELLURIUM ANALOGS OF THIOHYDROXYLAMINES AND THEIR DERIVATIVES

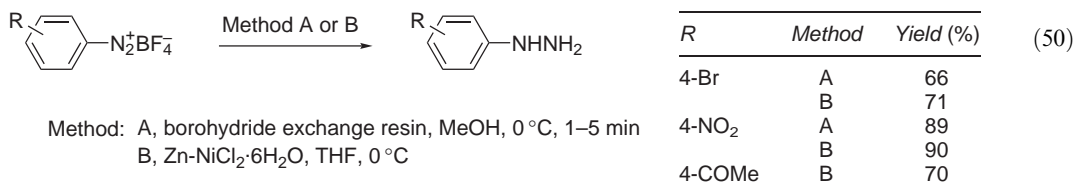
No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)737>.

2.15.8 HYDRAZINES AND RELATED FUNCTIONS

This section is an update on all new methods for the synthesis of vinyl- and arylhydrazines and related functions that have been developed since the publication of COFGT (1995) <1995COFGT(2)737>.

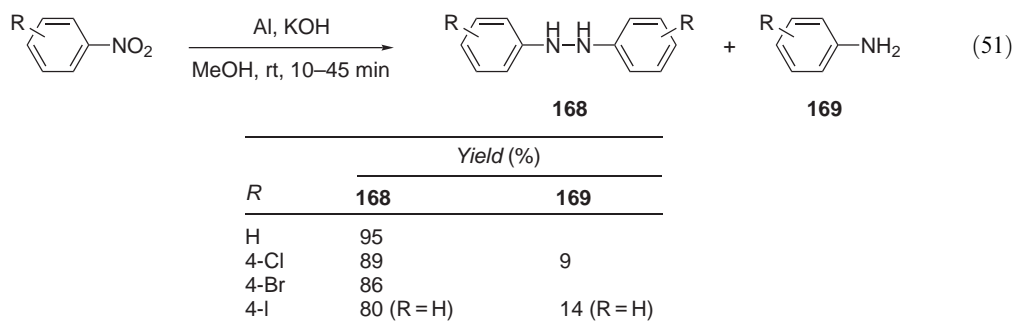
2.15.8.1 Hydrazines

A classical method for the preparation of arylhydrazines is the reduction of diazonium salts, readily available from the corresponding anilines. Sulfite, stannous chloride in acidic solution, sulfur dioxide, triphenylphosphine, or phosphites can be used as reducing agents <1995COFGT(2)737>. However, many of these reagents are unsuitable if other easily reducible groups are present. Borohydride supported on anion exchange resin has been described as a simple and convenient reagent for the selective reduction of aryl diazonium tetrafluoroborates to the corresponding arylhydrazines in MeOH (Equation (50)) <1997SC635>. The method tolerates some functional groups like bromo, chloro, fluoro and nitro in the molecule and the reagent can be easily separated and recycled. A more chemoselective reagent for this transformation is the system Zn-NiCl₂·6H₂O in THF (Equation (50)) <1999JCR(S)714>. If use of acidic conditions is to be avoided, direct amination of anilines to the corresponding substituted hydrazines can be performed with electrophilic aminating reagents, such as Genêt's allyl *N*-[(arylsulfonyl)oxy]carbamates <2003BCJ1063>.

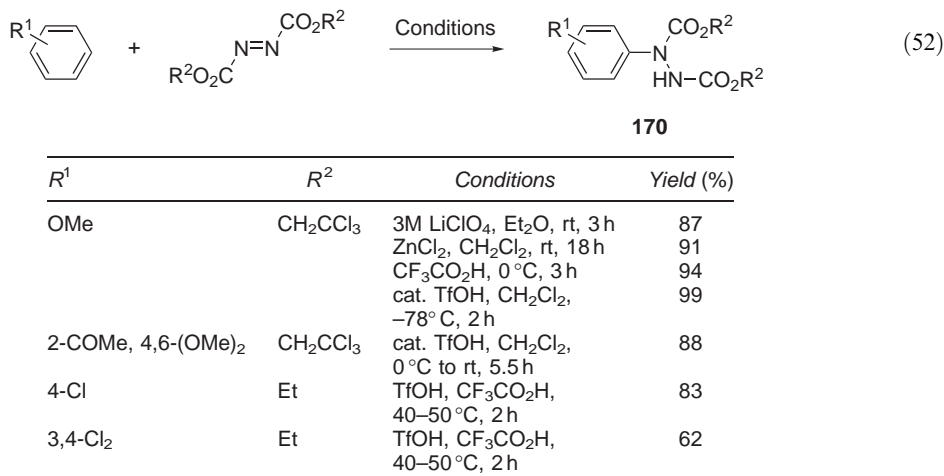


Arylhazines can also be prepared by reduction of azo- and azoxyarenes with a number of reducing reagents <1991COS(8)381>. Recent procedures include the use of sodium dithionite in the presence of dioctyl viologen as an electron-transfer catalyst in acetonitrile–water <1996TL6721> and hydrazine hydrate in the presence of hydrated zirconia <1997TL2137> or ultrasonically activated nickel <1999SC3031> as catalysts.

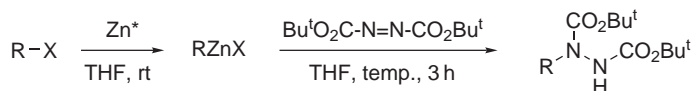
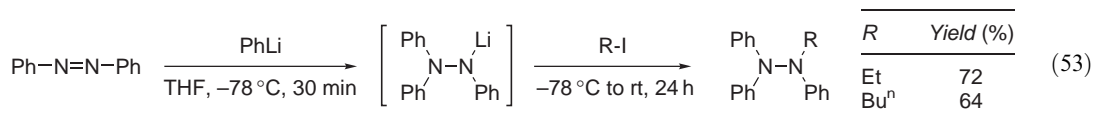
The controlled reduction of nitroarenes to give coupled products such as azoxyarenes, azoarenes, and hydrazines is an interesting area of research from both a synthetic and mechanistic point of view since these compounds are reaction intermediates between nitro groups and amines <2002JA7007>. Kurana has described the preparation of symmetrical *N,N'*-diarylhazines **168** by reduction of nitroarenes with aluminum and KOH in MeOH at room temperature in very high yields (Equation (51)) <1999JCS(P1)>. Small amounts of the corresponding arylamine **169** are formed in some cases. Other reported methods to perform this transformation are reviewed in this reference.

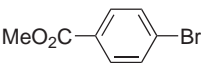
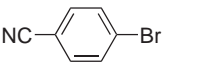
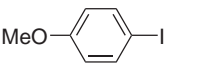


Aromatic hydrazines can also be prepared by electrophilic aromatic substitution of electron-rich arenes with azodicarboxylates. This method was first reported by Leblanc using bis-(2,2,2-trichloroethyl) azodicarboxylate in the presence of Lewis acids such as LiClO₄ in diethyl ether or acetone <1993TL2441>, ZnI₂, ZnCl₂ or BF₃·OEt₂ in CH₂Cl₂ <1994JOC682> or protic acids such as TFA and trifluoromethanesulfonic acid <1995JOC4268> in CH₂Cl₂ (Equation (52)). A mild protocol for the deprotection of the resultant hydrazides **170** to the corresponding hydrazines with Zn in MeOH/H₂O/NH₄Ac has been reported <1997SC3613>. Kim has developed improved conditions for this electrophilic amination of arenes using diethyl azodicarboxylate in TFA (Equation (52)) <2001MI131>. The reaction also takes place with non-activated arenes provided that trifluoromethanesulfonic acid is added as catalyst. Exclusive formation of the *para*-substituted hydrazide is observed in all cases for this electrophilic amination regardless of the reaction conditions and, not surprisingly, the reaction fails with some 1,4-disubstituted arenes.



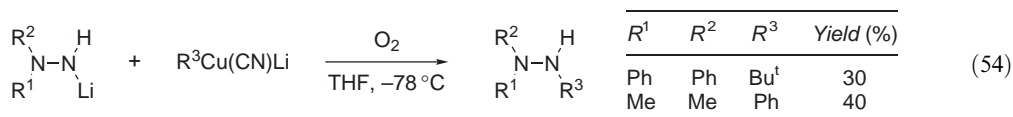
Arylhydrazines can be prepared in moderate-to-good yields by electrophilic amination of aryllithium reagents with azobenzenes (Equation (53)) <1995S651> or aryl Grignard reagents <1987TL4933> and aryl zinc halides <1998TL9157> with di-*t*-butyl azodicarboxylate (Scheme 52). The organozinc reagents <1998T8275, 2000AG(E)4415, 2001OR417> are readily accessible with a range of functionality from the corresponding bromo- or iodoarenes by reaction with highly reactive zinc (Zn*) <2000ACA52>.



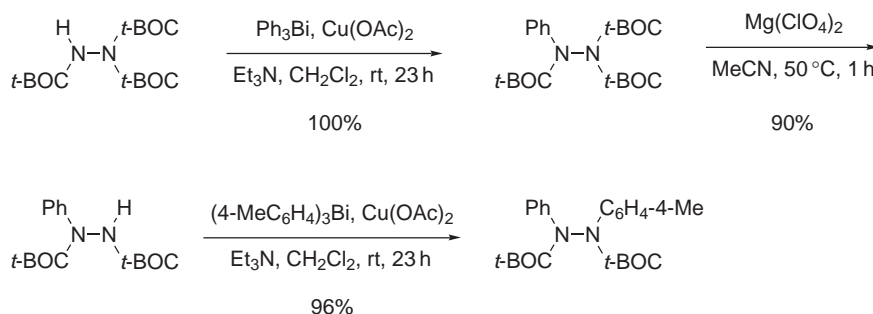
<i>RX</i>	Temp. (°C)	Yield (%)
	70	40
	70	66
	25	55

Scheme 52

Amidocuprates, prepared by reacting lithium amides or lithium hydrazides with an equimolar amount of monoanionic cuprate, suffer an unusual intramolecular oxidative coupling reaction upon exposure to oxygen at low temperatures to afford amines and hydrazines, respectively, in low-to-moderate yields (Equation (54)) <1996JOC1677>.

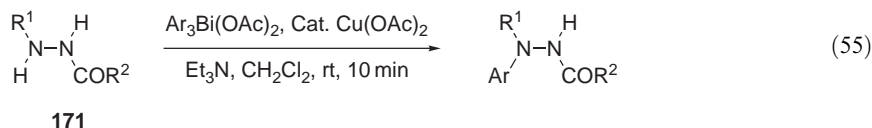


N-Arylation of partially protected hydrazines is a versatile new method for the preparation of a series of substituted arylhydrazines under mild conditions. Triprotected hydrazine can be *N*-arylated in excellent yields with triarylbismuth reagents in the presence of stoichiometric amounts of Cu(OAc)₂ and Et₃N. A range of *N*-protecting groups can be used in this reaction including phthalimido <2000SC131>, benzyloxycarbonyl, and *t*-butoxycarbonyl, allowing selective deprotections and further *N*-arylations to be carried out easily (Scheme 53) <2000S1591>.



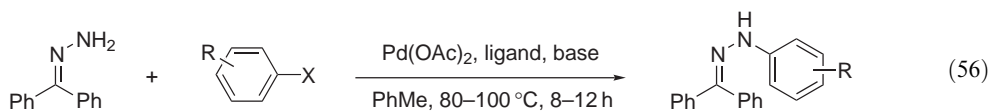
Scheme 53

However, when this method was applied to the arylation of *N,N'*-disubstituted hydrazines **171**, partial oxidation to hydrazones was observed <2002TL6213>. The use of triarylbismuth diacetates, instead of triarylbismuthanes, in the presence of a catalytic amount of Cu(OAc)₂ and Et₃N, allowed the successful regioselective monoarylation of these hydrazine derivatives in good to very high yields (Equation (55)) <2002TL6213>. This arylation reaction can be performed even without a copper catalyst, although a longer reaction time is required.



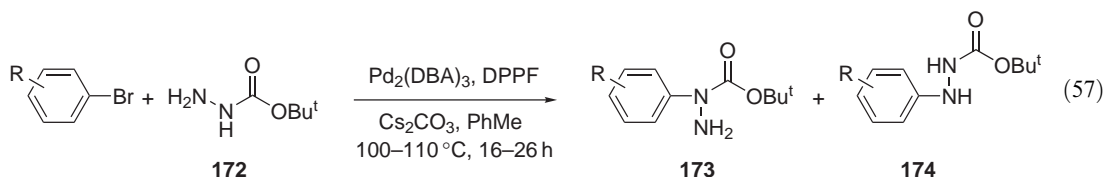
<i>R</i> ¹	<i>R</i> ² CO	Ar	Yield (%)
Bn	<i>t</i> -BOC	Ph	95
Me	Cbz	4-Me-C ₆ H ₄	82
Me	Ac	1-Naphthyl	80

Buchwald and Hartwig independently reported the preparation of *N*-aryl hydrazones by palladium-catalyzed arylation of benzophenone hydrazone with aryl bromides and iodides using binap or DPPF as ligands and NaOBu^t or Cs₂CO₃ as base <1998AG(E)2090, 1998JA6621> and with aryl chlorides using phosphane **96** (Section 2.15.2.2.4.(i)) as ligand (Equation (56)) <2000JOC1158>.

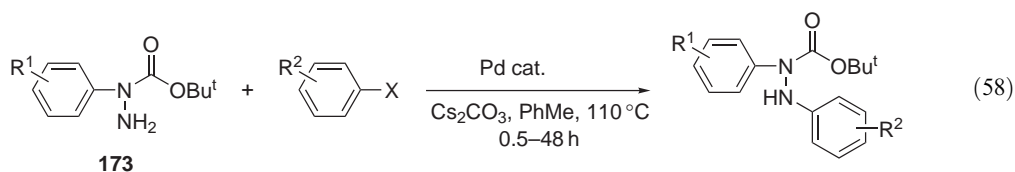


X	R	Ligand	Base	Yield (%)
Br	4-Me	DPPF	Cs ₂ CO ₃	86
		binap	NaOBu ^t	97
Br	4-COMe	DPPF	Cs ₂ CO ₃	96
Br	3,4-(OMe) ₂	binap	NaOBu ^t	85
I	2-Me	DPPF	NaOBu ^t	91
Cl	2-OMe	96	NaOBu ^t	91

Skerlj has described the regioselective palladium-catalyzed arylation of *N-t*-BOC hydrazine **172** with aryl bromides (Equation (57)) <1999TL3543>. High yields were only obtained with arenes having electron-withdrawing groups in the *para* position. The regioselectivity of the reaction depended upon the position of the substituents on the arene. The amidation products **173** are obtained regioselectively with *para*- and *meta*-substituted aryl bromides, whereas the amination products **174** are the major or exclusive product formed with *ortho*-substituted aryl bromides. While the direct arylation of arylhydrazines with aryl halides under catalytic conditions has not been reported yet, arylhydrazides **173** can be further arylated with aryl halides or aryl triflates using palladium catalysis (Equation (58)) <2003JOC979>. Arterburn has described the palladium-catalyzed monoarylation of *N,N'*-di-*t*-butoxycarbonylhydrazine under similar conditions using 2-pyridyl chlorides, bromides, and triflates <2001OL1351, 2003JOC7063>.

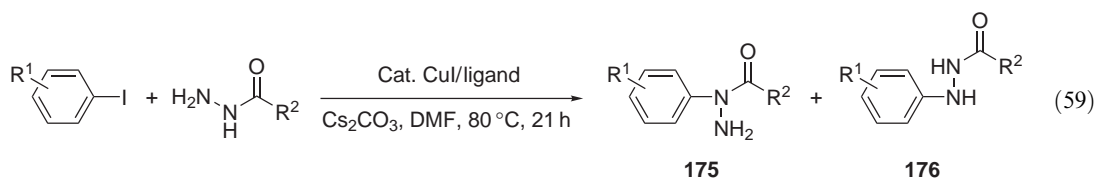


R	Yield (%)	
	173	174
4-CO ₂ Me	83	
4-CF ₃	76	
2-Me, 4-CO ₂ Me		69
2-Cl, 4-NO ₂		74



R^1	R^2	X	Pd cat.	Yield
4-NO ₂	4-NO ₂	Br	Pd ₂ (DBA) ₃ /DPPF	87
		OTf	Pd ₂ (DBA) ₃ /DPPF	97
	2-OMe	I	Pd(OAc) ₂ /PBU ₃	78
4-OMe	4-OMe	I	Pd(OAc) ₂ /PBU ₃	84

Buchwald has reported a convenient method for the *N*-arylation of hydrazides with substituted aryl iodides in the presence of a copper catalyst and Cs₂CO₃ <2001OL3803>. This coupling reaction showed the same regioselectivity trends observed for the corresponding palladium-catalyzed reaction <1999TL3543>. Thus, the coupling of *N*-*t*-BOC hydrazine with *para*- and *meta*-substituted aryl iodides afforded the *N*-arylated products **175** regioselectively, whereas the arylation of benzoic hydrazide with *ortho*-substituted aryl iodides yields the *N'*-arylated products **176** exclusively (Equation (59)).



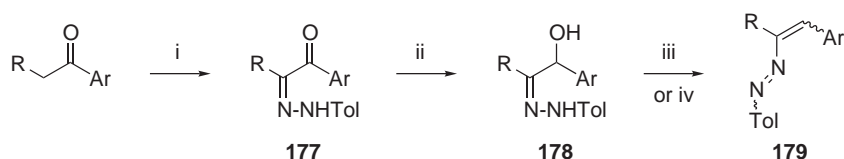
R^1	R^2	Ligand	Yield (%)	
			175	176
4-OMe	<i>t</i> -BOC	1,10-phenanthroline	85	
4-Br	<i>t</i> -BOC	1,10-phenanthroline	71	
4-CO ₂ Et	<i>t</i> -BOC	none	64	
2-Me	PhCO	none		69
2-CO ₂ Et	PhCO	none		63

2.15.8.2 Azo Compounds

2.15.8.2.1 Azoalkenes

Conjugated azoalkenes are highly versatile synthetic intermediates <1986OPP299, 1995PHC1, 1996MI212, 1997SL1128> and may undergo two types of reactions. First, they can react with a series of dienophiles and heterodienophiles in [3 + 2]- and [4 + 2]-cycloadditions affording a wide variety of heterocyclic compounds. Second, they are good substrates for 1,4-conjugate addition reactions with different nucleophiles yielding functionalized hydrazones that can be further employed in the synthesis of heterocycles or can be hydrolyzed to give the corresponding carbonyl derivatives. Numerous synthetic methods are known for the preparation of conjugated azoalkenes <1986OPP299, 1993HOU(E15)909, 1995COFGT(2)737>, the most important being the 1,4-elimination of suitably substituted hydrazones and the oxidation of hydrazones. South has described the synthesis of 4-chloro- <1995TL5703> and 4,4-dichloroazodienes <1996TL1351> by treatment of the corresponding dichloro- or trichlorohydrazones with Hünig's base. These azodienes were trapped *in situ* by reaction with electron-rich alkenes to yield chlorosubstituted heterocycles. Tavani has developed a synthesis of 1-aryl-2-(*p*-tolylazo)alkenes **179** from alkyl aryl ketones by a three-step procedure involving the dehydration reaction of hydrazono alcohols **178** under acidic conditions or by treatment with acetic anhydride in pyridine (Scheme 54) <1998T5315>.

Banert has described the first preparation of allenyl azo compounds using the known [2,3]-sigmatropic rearrangement of 1,1-diazenes <2003CL360>. Thus, manganese dioxide oxidation of propargylhydrazines **180** generated the short-lived 1,1-diazenes **181** that rearranged to the new



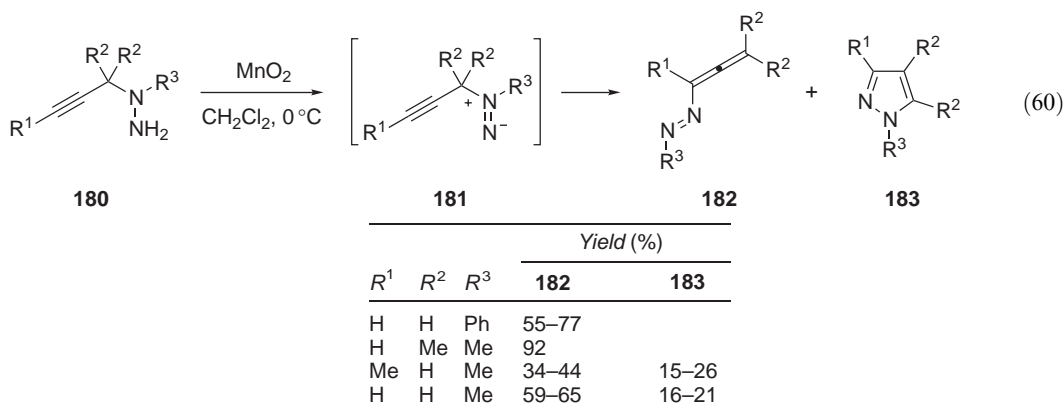
i. KOBu^t , DMSO, ToI-N=N-SBu^t , 25°C ; ii. NaBH_4 , MeOH, 0°C ; iii. cat. H_2SO_4 , Et_2O , 25°C ; iv. Ac_2O , pyr, 50°C

R	Ar	Yield (%)		
		177	178	179
H	Ph	96	80	85 ^a
H	2-MeO-C ₆ H ₄	68	85	84 ^a
Me	Ph	60	96	30 ^b
Bu ^t	4-MeO-C ₆ H ₄	52	97	79 ^b

^a Obtained using conditions iii. ^b Obtained using conditions iv.

Scheme 54

allenyl azo compounds **182** and pyrazoles **183** (Equation (60)). Isomerization of allenes **182** under basic conditions or nucleophilic addition leads to hydrazones or pyrazoles.



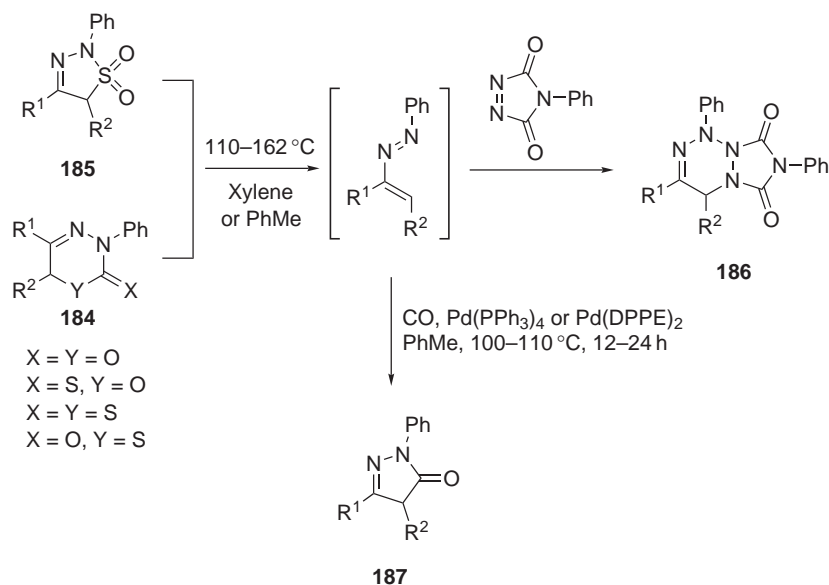
Boeckman has developed a novel procedure for the generation of conjugated azoalkenes in the absence of nucleophiles and other undesirable products by thermolysis of the following new and stable heterocyclic precursors: oxadiazinones **184** (thermal extrusion of CO_2) and thiadiazole dioxides **185** (thermal extrusion of SO_2) (Scheme 55) <2001OL3647>. The resulting diazadienes have been trapped *in situ* with *N*-phenyldiazamaleimide to give the Diels–Alder adducts **186**. Alternatively, the azoalkenes were reacted with CO in a novel Pd(0)-catalyzed carbonylation reaction to give 2,3-pyrazol-1(5*H*)-ones **187** in good to excellent yields.

2.15.8.2.2 Aromatic azo compounds

Azoarenes have attracted increasing interest recently due to their characteristic photoresponsive properties <1994CRV31, 1994CRV195, 2000CRV1817>.

(i) From oxidation of primary aromatic amines

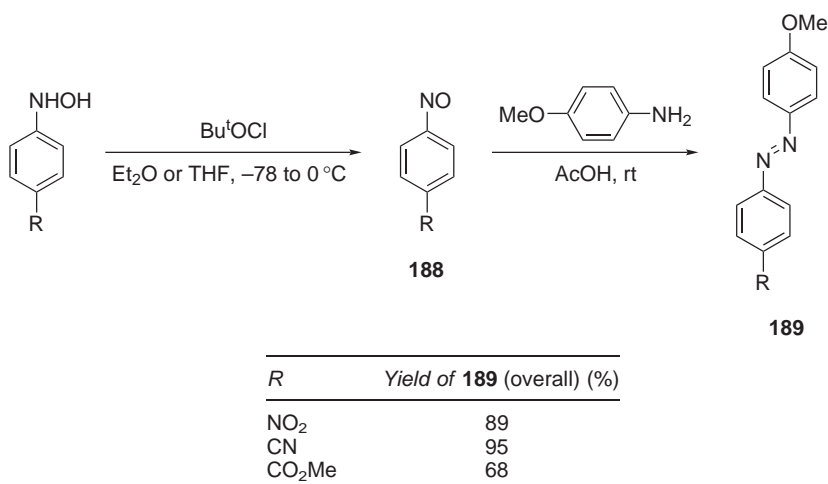
Unsymmetrical azoarenes are commonly prepared from primary aromatic amines by diazotization followed by diazo coupling with electron-rich arenes <B-1978MI511, B-1994MI005>. Das has described the immobilization of diazonium ions on a cation-exchange resin and their reaction with electron-rich heteroarenes and naphthols to give the corresponding azo compounds in moderate yield <1995IJC(B)161, 1997T9749, 1998IJC(B)155>. This procedure allowed the use of organic solvents and neutral conditions for the coupling reaction.



Precursor	R^1	R^2	Yield (%)	
			186	187
184 ($\text{X}=\text{Y}=\text{O}$)	Ph	Ph	84	58
184 ($\text{X}=\text{S}, \text{Y}=\text{O}; \text{X}=\text{Y}=\text{S}; \text{X}=\text{O}, \text{Y}=\text{S}$)	Ph	4- $\text{NO}_2\text{C}_6\text{H}_4$	80–85	
185	Ph	H	92	54
185	Ph	Ph	85	78

Scheme 55

The Mills coupling reaction between aromatic nitroso compounds and amines in acetic acid [<B-1969MI215>](#) is a valuable complementary method for the preparation of unsymmetrical azoarenes provided that the nitroso compound is readily accessible. Miller and Marks have developed a new and mild procedure for the preparation of a range of aryl nitroso compounds by oxidation of arylhydroxylamines with *t*-butyl hypochlorite under homogeneous conditions. Subsequent Mills coupling with *p*-anisidine of the crude nitroso derivatives **188** gave the corresponding azo products **189** in high yields (see [Section 2.15.9.1.2](#)) (Scheme 56) [<1999JOC4976>](#).



Scheme 56

Symmetrical azoarenes can be obtained by oxidative coupling of primary arylamines with a number of oxidizing agents <1995COFGT(2)737>. Nouredding has described the use of potassium permanganate supported on copper(II) sulfate pentahydrate as a mild reagent to perform this transformation under heterogeneous conditions in CH_2Cl_2 with high to quantitative yields <1999S939>. Contrary to what is observed for the corresponding oxidation under homogeneous conditions, no oxidation of the benzylic C occurs in the coupling of *ortho*-alkylsubstituted anilines with this supported reagent. Using 2,4,6-tri-*t*-butylphenol <2000IJC(B)545> or galvinoxyl <1999SC2271> as catalysts, anilines can be efficiently oxidized to azobenzenes at room temperature under phase-transfer conditions with potassium ferricyanide in 2N aqueous KOH. 1,4-Dibenzyl-1,4-diazoniobicyclo[2,2,2]octane chloroformate is another mild and selective reagent to perform this transformation in very high yield in acetonitrile at reflux <2000IJC(B)863>.

(ii) *From oxidation of hydrazines*

A wide range of mild oxidizing agents are able to convert hydrazines and hydrazides into the corresponding azo derivatives in high yield <1995COFGT(2)737>. New developments include the use of the following: cat. galvinoxyl/ $\text{K}_3\text{Fe}(\text{CN})_6/\text{NaOH}$ under phase-transfer conditions <1996SC3579>; cat. $\text{FeSO}_4/\text{KClO}_3/\text{H}_2\text{SO}_4$ in aqueous acetone <1997SC3723, 2001SC1691>; NBS/pyridine <1997SC1737, 1999SC423, 2003JOC979>; NO_2 in DMF <1998OPP97>; cat. 4-hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy/ $\text{K}_3\text{Fe}(\text{CN})_6/\text{NaOH}$ under phase-transfer conditions <1999SC157>; CAN in aqueous acetone <2000SC1807>; NO_2 absorbed in polyethylene glycol <2001GC186>; active MnO_2 supported on $\text{H}_2\text{SO}_4/\text{SiO}_2$ <2002IJC(B)220>; $\text{NaNO}_2/\text{Ac}_2\text{O}$ <2002JCR(S)284>; $\text{NaNO}_2/\text{NaHSO}_4\cdot\text{H}_2\text{O}/\text{SiO}_2$ <2002JCR(S)540, 2002SC2791>; $\text{NaBrO}_3/\text{H}_2\text{SO}_4$ in aqueous acetone <2002SC1781>.

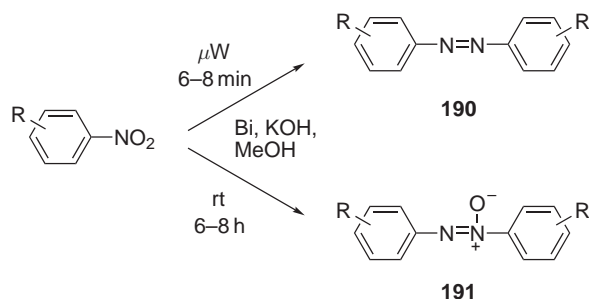
(iii) *From reduction of aromatic nitro compounds*

There are a variety of reducing agents that have been used to reduce nitroarenes to symmetrically substituted azo compounds **190** <1995COFGT(2)737>, but many of them are not tolerant to the presence of other reducible groups. Khurana has described the use of magnesium turnings in methanol for the reductive coupling of nitroarenes to the corresponding azoarenes in moderate-to-good yield <1996BCJ407>. Cyano, formyl, ester, ether, amino, and chloro substituents are unaffected but iodo and bromo groups undergo dehalogenation. However, overreduction to hydrazoarenes in low-to-moderate yield is always observed with this procedure. Gowda has described the use of lead powder and ammonium <2002S460> or triethylammonium <2003TL5835> formates in methanol at reflux to selectively reduce aromatic nitro compounds containing additional reducible groups ($-\text{CO}_2\text{H}$, $-\text{Cl}$, $-\text{OEt}$) to the corresponding azo compounds in very high yields (88–94%). Bismuth powder and KOH in methanol under microwave irradiation is also a highly selective and mild reducing system to carry out this transformation to give compounds **190** with substrates containing easily reducible groups such as halogens, esters, ketones, and conjugated double bonds (Scheme 57) <2000JCS(P1)67>. If the reduction is performed at room temperature, the corresponding azoxy compound **191** can be selectively obtained in good yield.

(iv) *Other methods*

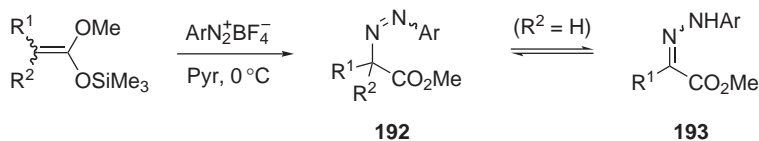
The reaction of arene diazonium salts with various C-nucleophiles leads to the formation of azo compounds (or their corresponding tautomeric hydrazono derivatives) without releasing nitrogen, although complex mixtures of products with low yields of the azo compound are often obtained <B-1978MI247>. Tanaka found that, while ketone silyl enol ethers react with arenediazonium tetrafluoroborates in pyridine with loss of nitrogen to give the α -arylation product <1994JCS(P1)283>, the corresponding silyl enol ethers derived from esters yield the α -azo **192** or α -hydrazono **193** esters in good-to-excellent yields (Scheme 58) <1994JCS(P1)289>. The latter are generated by isomerization of the initially formed α -azo esters **192**.

Arenediazonium *o*-benzenedisulfonimides **194** are highly stable in the dry state (see Sections 2.15.8.4 and 2.15.9.13.2) and react with aryl or *t*-butyl Grignard reagents at low temperature to give the corresponding C-coupling azo products **195** in good-to-high yields (Equation (61)) <1998S1235>.



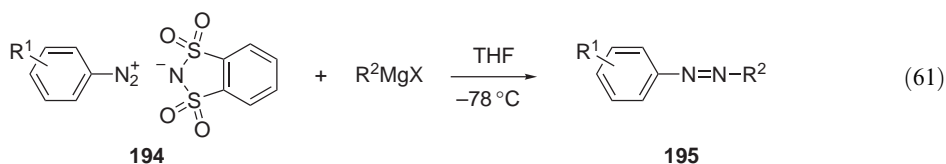
R	Yield (%)	
	190	191
4-Br	85	85
4-I	82	78
4-COMe	83	80
4-(CH=CH-CO ₂ Me)	75	82

Scheme 57



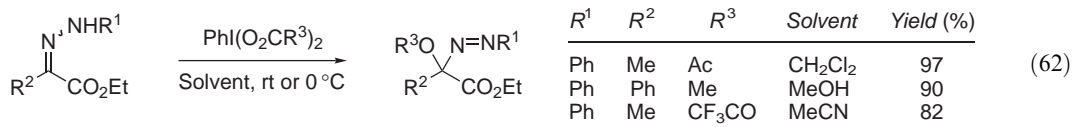
R ¹	R ²	Ar	Yield (%)	
			192	193
Ph	H	Ph		83
Ph	Et	Ph	90	
Me	Me	4-ClC ₆ H ₄	72	

Scheme 58



R ¹	R ²	Yield (%)
Ph	4-ClC ₆ H ₄	69
4-MeOC ₆ H ₄	Ph	91
4-ClC ₆ H ₄	Bu ^t	83

α -Acetoxy or methoxy azo compounds can be readily synthesized in very high yields from phenylhydrazones and alkylhydrazones by oxidation with bis-(acetoxy)- or bis-(trifluoroacetoxy)-iodobenzene in different solvents (Equation (62)) <1996T14673>.



R ¹	R ²	R ³	Solvent	Yield (%)
Ph	Me	Ac	CH ₂ Cl ₂	97
Ph	Ph	Me	MeOH	90
Ph	Me	CF ₃ CO	MeCN	82

2.15.8.3 Azoxy Compounds

The chemistry of azoxy compounds has been reviewed <1992HOU(E16)119, 1995COFGT(2)737>.

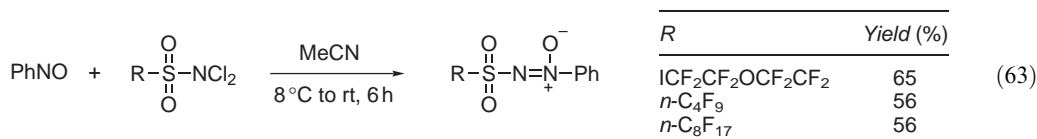
2.15.8.3.1 α,β -Unsaturated azoxy compounds

No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)737>.

2.15.8.3.2 Aromatic azoxy compounds

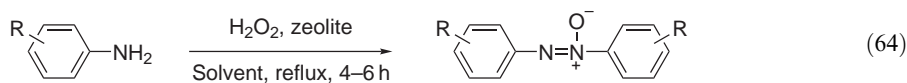
(i) From aromatic nitroso compounds

Nitrosobenzene has been condensed with *N,N*-dichloroperfluoroalkanesulfonyl amides without any promoter to give the corresponding azoxy compounds in good yield (Equation (63)) <1998JFC59>.



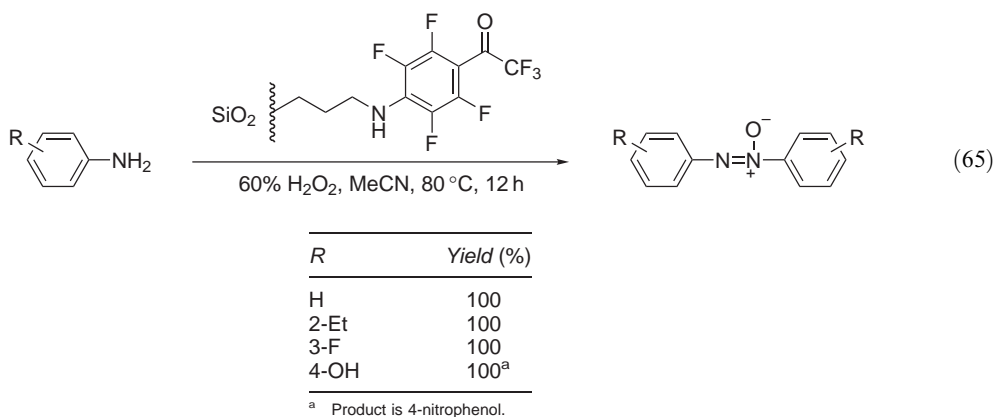
(ii) From aromatic amines

The oxidation of arylamines can produce a range of products in various oxidation states depending on the oxidant and the reaction conditions <1991COS(7)735>. Azoxy compounds are formed by reaction of nitroso products with hydroxylamine intermediates in these oxidation reactions and several methods are known to produce this overall transformation selectively in moderate-to-good yields. Titanosilicates TS-1 <1994CC1215, 1995T11305> and TS-10 <2001GC285> are efficient catalysts for the oxidation of arylamines to azoxy compounds using 30% H₂O₂ or *t*-butyl hydroperoxide as the oxidants (Equation (64)). Azo compounds have been shown not to be intermediates in this oxidation process since they are completely inert under the reaction conditions <1995T11305>. However, aryl azo compounds can be oxidized to the corresponding azoxy derivatives with H₂O₂ if methyltrioxorhenium is used as the catalyst <1996TL805>.



R	Zeolite	Solvent	Yield (%)
H	ET-1	acetone	75
	ET-10	MeOH	77
3-Me	ET-1	acetone	41
	ET-10	MeOH	70
4-OMe	ET-1	acetone	10
	ET-10	MeOH	26
4-NO ₂	ET-1	MeOH	65
	ET-10	MeOH	2.6

p-Toluenesulfonic peracid, generated *in situ* from *p*-toluenesulfonylimidazole and H₂O₂ in aqueous NaOH, is a strong but chemoselective oxidant that converts aniline into azoxybenzene in 65% yield <1996T5773>. A perfluorinated ketone attached to silica is a recyclable and highly efficient catalyst to perform the oxidation of anilines into the corresponding azoxy derivatives with 60% H₂O₂ (Equation (65)) <2001CC487>. Alkyl- and halogen-substituted anilines gave the azoxy products in quantitative yields while anilines with hydroxy or nitro groups yielded the corresponding nitro derivatives except when nitro was *ortho* to the amino group. In this latter case the compounds were inert to the oxidation conditions.



(iii) From aromatic nitro compounds

The bimolecular reduction of aromatic nitro compounds to azoxy compounds can be accomplished with a number of reducing agents <1995COFGT(2)737>. More recent developments to perform this transformation in high yields and with high chemoselectivity include the use of the following reducing systems: Zn/AlCl₃ <2003IJC(B)672> or Zn/BiCl₃ <1994TL3167> in acetonitrile at room temperature; Zn/CdCl₃ in acetonitrile at reflux <1996TL351>; Bi/NaBH₄ in EtOH at room temperature <1996SC3903>; milling with Bi shots under solvent-free conditions <2002JOC8254>; Bi/KOH in MeOH at room temperature (Scheme 57) <2000JCS(P1)67>. Ester, ether, nitrile, and halogen groups on the arene remain unaffected with all these methods.

2.15.8.4 Systems Containing *N,N,N,N,N* Functionalities

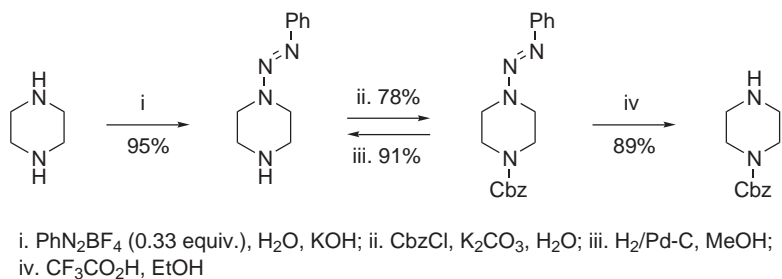
Triazenes are a very useful group of compounds due to their interesting anticancer activity and their applications in organic synthesis as protecting groups or as intermediates for the preparation of novel heterocyclic systems, and in organometallic chemistry as metal-complexing agents <2002AG(E)3338>. The methods of synthesis of triazenes were fully optimized more than 70 years ago and have changed little since. The coupling of aryl diazonium salts with *N*-nucleophiles or the addition of *C*-nucleophiles to alkyl or aryl azides still remain the methods of choice <1995COFGT(2)737, 2002AG(E)3338>.

Triazenes have been prepared in the solid state in quantitative yields by gas–solid diazotization of crystalline anilines with NO₂ (or NOCl) followed by direct coupling of the resultant benzene-diazonium nitrate hydrates (or chlorides) with gaseous amines (Me₂NH) <1997JPR(339)256> or with solid amines (Ph₂NH, anilines) by co-grinding <2002CEJ1395>. Crystal disintegration due to phase transformation, as product is being formed, allowed the reactions to run to completion in the solid state. The triazene products are obtained as their nitrate salts from which the free triazenes can be obtained after neutralization with aqueous NaOH.

Treatment of arylamines with Na₃Co(NO₂)₆ in aqueous solution at room temperature gave symmetrical 1,3-diaryltriazenes in excellent yields (86–99%) <1997JOC7165>. Halide, ester, ketone, nitrile, nitro, and primary amido groups on the arene are tolerated, and the triazenes are simply isolated by filtration. This transformation is probably produced by a sequence of reactions that involves nitrosation of the aromatic amino group, transformation of the initially formed *N*-nitroso compound into a diazonium salt, and subsequent reaction with another molecule of arylamine.

The highly stable arenediazonium *o*-benzenedisulfonimides **194** (see Sections 2.15.8.2.2.(iv) and 2.15.9.13.2) react with dimethyl- or diethylamine in aqueous solution to give the corresponding triazenes in very high yields (>90%) <2001S2180>. This reaction can be reversed quantitatively by heating a solution of the triazenes with *o*-benzenedisulfonimide in acetic acid. The triazene products have been transformed into the corresponding aryl halides by heating with the corresponding hydrogen halides or with anhydrous methanesulfonic acid and tetraalkylammonium halides in acetonitrile.

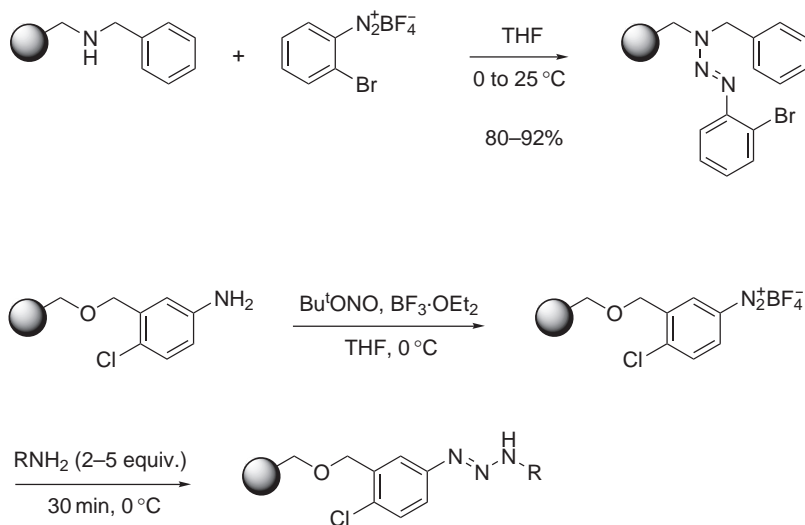
Aryldialkyltriazenes have been used as a protected form of the amino group of anilines <1993JOC2104> and secondary amines <1999SL1304, 2001T5825>. These triazenes can be prepared in good yield by coupling an aryl diazonium salt with a secondary amine in aqueous KOH <1993JOC2104> (for water-soluble amines) or in pyridine and methanol in CH_2Cl_2 <2001T5825> (for water-insoluble amines). Although alcohols are known to reduce diazonium ions <1958JA6072>, this reduction is slower than the coupling with amines and the use of methanol speeds up the formation of the triazene by facilitating the dissolution of the diazonium salt. The triazene moiety is stable to several reducing (NaBH_4 , LiAlH_4 , $\text{H}_2/\text{Pd}-\text{C}$) and oxidative (chromium-based oxidants, peracids, $\text{TEMPO}/\text{NaOCl}$) conditions, strong bases (Bu^tLi), and alkylating agents. The free secondary amines can be regenerated by treatment with TFA in CH_2Cl_2 or EtOH <1999SL1304, 2001T5825> or by treatment with HSiCl_3 <2000TL3813>. The free anilines can be regenerated by hydrogenolysis with nickel–aluminum alloy in methanolic KOH <1993JOC2104>. As an amino protecting group, triazenes have been shown to be orthogonal to benzyl and benzyloxycarbonyl groups (Scheme 59) <2001T5825>.



Scheme 59

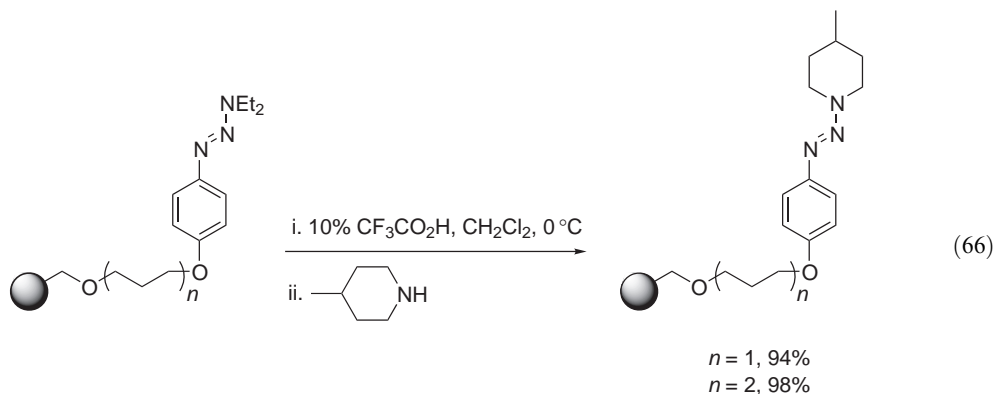
Das has described the immobilization of diazonium ions on a cation-exchange resin and their subsequent coupling with secondary amines under neutral conditions to give the corresponding triazenes in solution in 54–72% yield <1994TL9107>.

Triazenes were introduced as traceless linkers in solid-phase organic synthesis by Moore <1994JA10841, 1996JOC8160> and later popularized by Brase and co-workers <1998AG(E)3413, 1999TL2105, 2000CEJ1899>. Two strategies have been employed for the synthesis of polymer-supported triazenes: (i) coupling of arenediazonium salts with supported secondary amines <1994JA10841, 1996JOC8160, 1998AG(E)3413> and (ii) coupling of primary or secondary amines with supported diazonium salts <1999TL2105, 2000AG(E)3681> (Scheme 60). The diazonium ions are conveniently prepared as tetrafluoroborate salts by reacting a primary



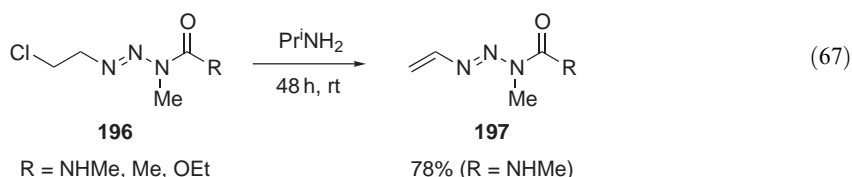
Scheme 60

aromatic amine with $\text{Bu}^t\text{ONO}/\text{BF}_3\cdot\text{OEt}_2$ under nonaqueous conditions, either in solution or in the solid phase (see Section 2.15.9.13.2). Simple alkylaryltriazenes have been prepared on Merrifield resin following these methodologies and used as supported reagents for the alkylation of carboxylic acids <2001AG(E)381, 2003CEJ2582> and sulfonic acids <2001TL7833>. Polystyrene-supported triazenes have also been synthesized from supported diethylamino triazenes that were used as stable masked precursors for the generation of supported diazonium ions upon mild treatment with a cold solution of TFA in dichloromethane (Equation (66)) <2003TL2441>.



A new synthesis of arylamines has been described by Kabalka using allylaryltriazenes as intermediates <1997TL5777>. The triazenes are generated by addition of aryl Grignard and lithium reagents to crude allyl azide. *In situ* acidic hydrolysis of the triazenes generated the arylamines in moderate-to-good yields (53–83%).

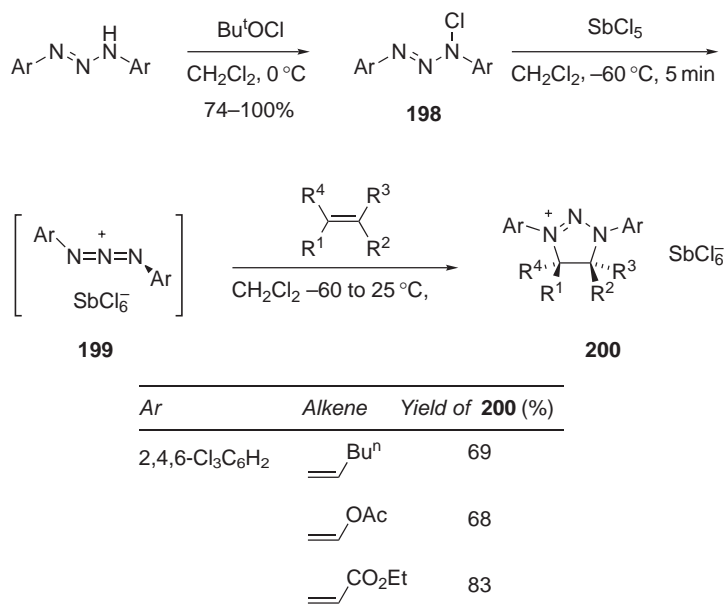
1-Vinyl-3-methyl-3-acyltriazenes **197** are readily prepared by reaction of alkylamines with 1-(2-chloroethyl)-3-alkyl-3-acyltriazenes **196** (Equation (67)) <1995JOC4641>. This facile dehydrohalogenation is attributed to the activating effect of the adjacent triazeno moiety. Isopropylamine was the most efficient base for the elimination reaction, while no conversion was observed with pyridine or triethylamine.



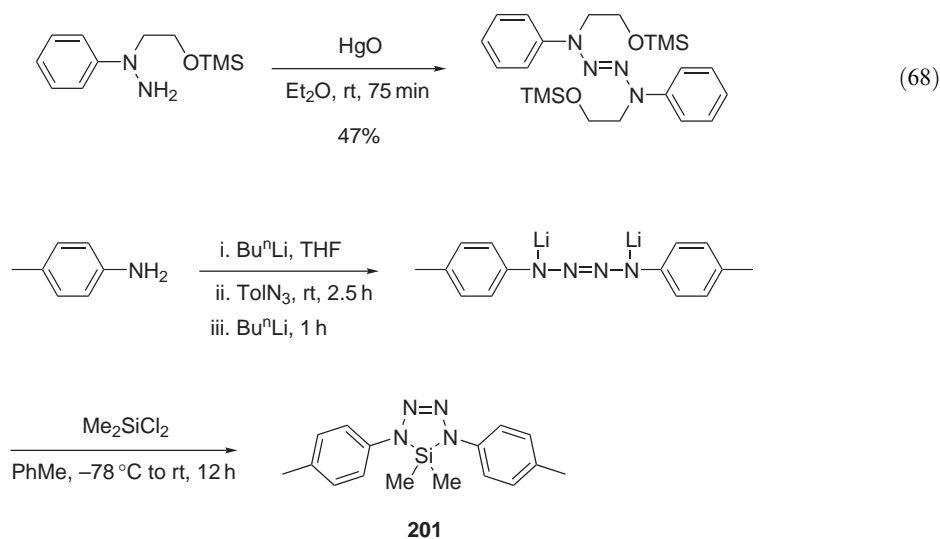
Aryltriazenes connected by an alkyl linker are known as bis-triazenes and have been reported as potentially lethal DNA cross-linkers. Their methods of synthesis, typically by diazonium coupling with alkyldiamines, have been reviewed <2001OPP59>.

A new N_3 -functional group, 1,3-diaza-2-azoniaallene ion **199**, has been described by Jochims (Scheme 61) <1997S233, 1997T5755, 1998JCS(P1)1755>. These unstable ions suffer facile [3 + 2]-cycloaddition reactions with dipolarophiles (alkenes, 1,3-butadienes, alkynes, carbodiimides and cyanamide) to furnish 1,2,3-triazolium **200** and tetrazolium salts. 1,3-Diaza-2-azoniaallene ions are prepared at low temperatures ($\leq 50^\circ\text{C}$) by reaction of *N*-chlorotriazenes **198** with Lewis acids, typically SbCl_5 , and trapped *in situ* with dipolarophiles. The *N*-chlorotriazenes are easily obtained by chlorination of triazenes with Bu^tOCl .

1-Tetrazenes are prepared by coupling of arene diazonium salts with hydrazines <1995COFGT(2)737>. The isomeric 2-tetrazenes can be obtained by oxidative coupling of 1,1-disubstituted hydrazines or by reaction between aryl azides and lithium anilides <1990HOU(E16)1228>. Recent examples are the synthesis of hydroxyalkyl-substituted 2-tetrazenes reported by Porath and co-workers (Equation (68)) <1998EJO1431, 2002ZN(B)365> and the preparation of 1-sila-2,5-diaryltetrazenes **201** reported by Frenzel and co-workers (Scheme 62) <1997CB1579>.

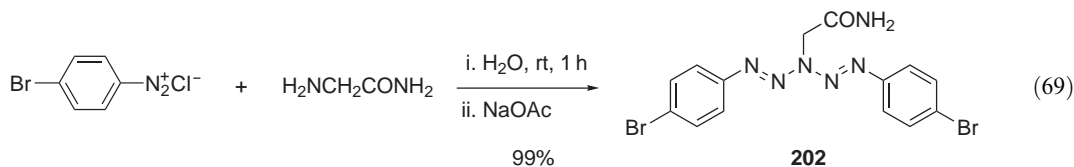


Scheme 61



Scheme 62

Vaughan has reported that the coupling of arene diazonium salts with glycineamide gives the expected 1-aryl-3-(carbamoylmethyl)triazenes for arenes possessing electron-withdrawing groups (ester, cyano or nitro) at the *ortho*- or *para*-position, but the *p*-bromo-substituted diazonium salt yields exclusively pentazadiene **202** (Equation (69)) <1996JOC210>.



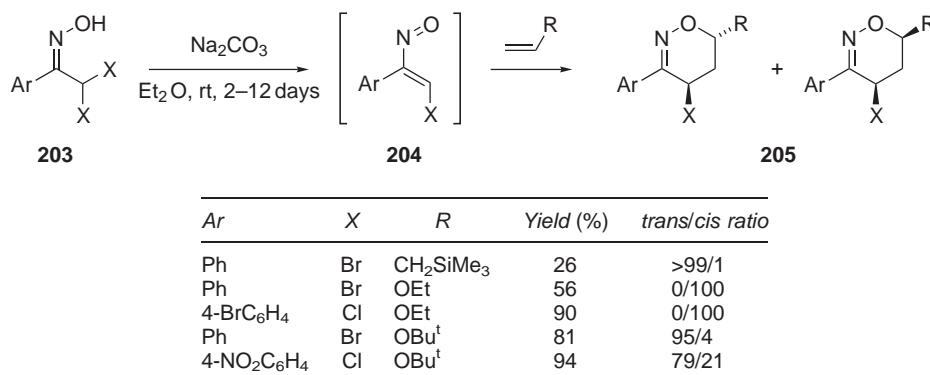
2.15.9 N-VINYL AND N-ARYL COMPOUNDS OF THE TYPE RNY AND RN⁺Z (e.g., ARN₂⁺)

2.15.9.1 Nitroso Compounds

This section is an update on all new methods for the synthesis of vinyl and aryl nitroso compounds that have been developed since the publication of COFGT (1995) <1995COFGT(2)737>. The synthesis and reactions of nitroso compounds have been reviewed <1995MI357, 1997MI415, 1999JCS(P1)749, 2000JCS(P1)3695>.

2.15.9.1.1 α,β -Unsaturated nitroso compounds

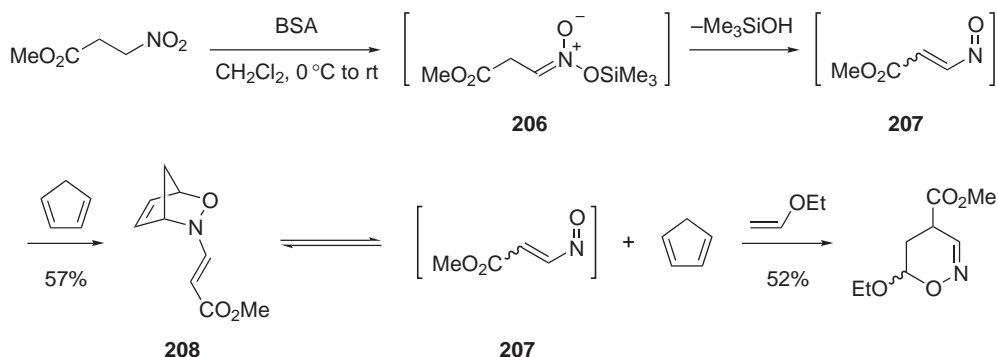
The preparation, properties, and reactions of conjugated nitrosoalkenes have been reviewed by Lyapkalo <1998UK523>. Conjugated nitrosoalkenes are a highly useful group of synthetic intermediates that participate in a number of processes including [4 + 2]-cycloaddition reactions (as heterodienes or as heterodienophiles), ene-reactions, [2 + 2]-cycloadditions, and 1,2- or 1,4-additions of nucleophiles. Due to their high reactivity, conjugated nitrosoalkenes are generally unstable and are usually generated *in situ*. The most common method of preparation is the 1,4-dehydrohalogenation of α -halooximes with bases <1981HCA1208, 1992JOC339, 1995COFGT(2)737>. Kim has described the preparation of α -aryl- β -monohalo- α -nitrosoethyl- enes **204** by treatment of 1-aryl-2,2-dihalo oximes **203** with anhydrous sodium carbonate in dry ether at room temperature (Scheme 63) <2001JOC7334>. Nitrosoalkenes **204** have been trapped *in situ* with various dienophiles to give 6-substituted 3-aryl-4-halo-5,6-dihydro-4*H*-1,2-oxazines **205** with very high regioselectivity and in moderate-to-good yield.



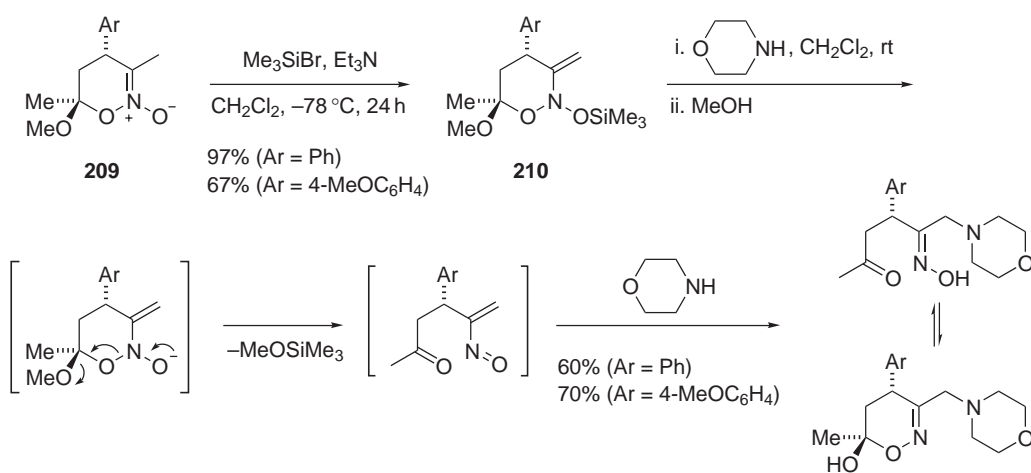
Scheme 63

An alternative approach to nitrosoalkenes that bear an electron-withdrawing substituent in the β -position has been developed by Ioffe <1997T13085, 2000OL1323>. Thus, silylation of methyl 3-nitropropionate with *N,O*-bis(trimethylsilyl)acetamide (BSA) proceeds with initial formation of the trimethylsilyl nitronate **206** followed by Me₃SiOH elimination to generate the β -functionalized nitrosoalkene **207**, which functions as a good heterodienophile in Diels-Alder reactions with cyclic dienes (Scheme 64). Cycloadduct **208** can undergo facile *retro*-[4 + 2]-cycloaddition in solution to regenerate intermediate **207** that can be trapped by an external dienophile.

Conjugated nitrosoalkenes have been proposed as intermediates in the reaction of *N,N*-bis(silyloxy) enamines with nucleophiles (see Section 2.15.5.4 and Scheme 48). More recently, Ioffe has observed the generation of intermediate nitrosoalkenes in the reaction of 2-silyloxy-1,2-oxazines **210** with morpholine (Scheme 65) <2003JOC9477>. Compounds **210**, which can be regarded as acetals of conjugated nitroso alkenes, are obtained by silylation of 3-alkyl-substituted 1,2-oxazine *N*-oxides **209**, which are themselves easily prepared by the hetero-Diels-Alder reaction between nitroalkenes and alkenes <1996CRV137>.



Scheme 64



Scheme 65

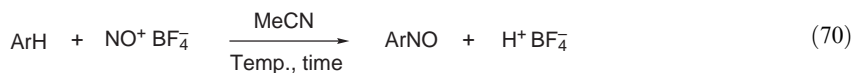
Reports on the generation of stable, monomeric nitrosoalkenes are rare and most of them are nitrosodithiafulvene or -diselenafulvene systems in which the nitroso group is stabilized by electron donation from the chalcogen atoms <1996JOC2877, 1997JOC2616, 1998T3919>.

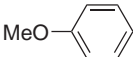
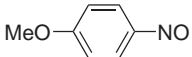
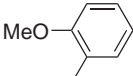
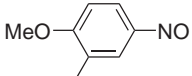
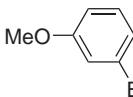
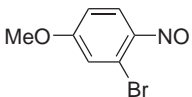
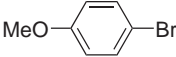
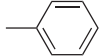
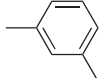
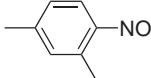
2.15.9.1.2 Aromatic nitroso compounds

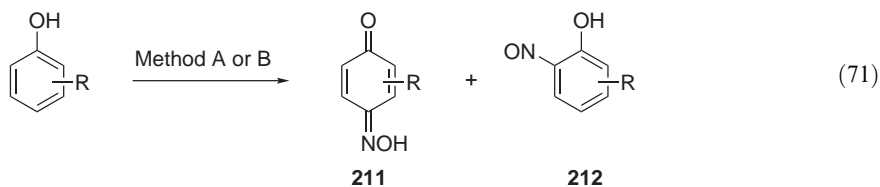
The methods of preparation of aromatic nitroso compounds have been reviewed <B-1969MI215, 1990HOU(E16)979, 1995COFGT(2)737>.

Electrophilic aromatic nitrosation is the most direct method for the synthesis of aromatic nitroso compounds. This reaction is restricted to electron-rich arenes and is usually slower and much more regioselective than the related and more common aromatic nitration. The disparity between both electrophilic aromatic substitution reactions has been rationalized on mechanistic grounds <2003JA3273>. In the usual preparative procedure, nitrous acid is generated by reaction of nitrite salts with strong (aqueous) mineral acids that also promote the formation of nitrosonium ions (NO^+), the active nitrosating species. A major problem in preparative work is the instability of the aromatic nitroso products. This difficulty has been circumvented in part by the development of non-acidic, non-nucleophilic, anhydrous conditions employing nitrosonium tetrafluoroborate in acetonitrile under an inert atmosphere <1994JOC5573>. With this system, substituted anisoles and polymethyl benzenes have been nitrosated in high yields (Equation (70)). However, the reaction is slow and the method is unsuccessful with *o*-xylene and toluene. A more effective nitrosating system under acidic, non-aqueous conditions is obtained by saturating

with nitric oxide a TFA solution or a mixture of acetic and sulfuric acid <1997JCS(P2)663, 1999JCS(P2)699, 2000JCS(P2)229>. In the first case, the N(III) species is introduced as N_2O_3 , which is generated *in situ* from NO by reaction with a measured amount of oxygen injected into the system. Alternatively, commercially available nitrosyl sulfuric acid is added in the case of acetic–sulfuric acid mixtures. Purging with nitric oxide eliminates the accompanying nonselective nitrous acid-catalyzed nitration and stabilizes the nitroso products by complexation with the nitrosonium ion. Using this method, anisole is nitrosated in good yield (90%) and toluene can also be nitrosated albeit slowly and in modest yield (16%). Nitrosation can be performed under mildly basic, nonaqueous conditions using isoamyl nitrite in DMF in the presence of K_2CO_3 (Equation (71)) <1996JOC2774>. *para*-Directed nitrosations are observed under these basic conditions to yield *p*-quinone monooximes **211**, whereas acidic nitrosations affords mainly *ortho*-directed products **212**.



ArH	Temp. (°C)	Time (h)	ArNO	Yield (%)
	25	0.5		87
	0	0.5		83
	25	30		40
	25	30		
	25	24		
	25	24		70

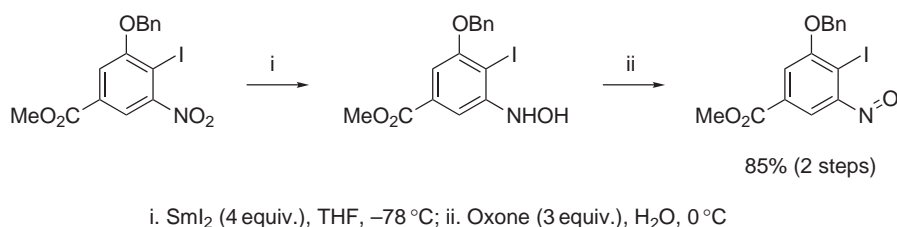


Method A: NaNO_2 , $\text{EtCO}_2\text{H}/\text{H}_2\text{O}$, -5°C
 Method B: isoamyl nitrite, K_2CO_3 , DMF, rt

R	Method	Yield (%)	
		211	212
3-OMe	A	13	63
3-OMe	B	39	15
H	B	88	
2-CHO	B	78	
2-CO ₂ H	B	NR	NR
2-Cl	B	60	

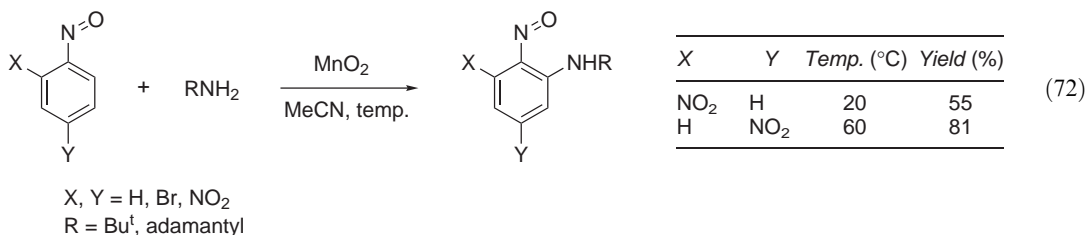
A number of reagents are able to oxidize primary anilines to the corresponding nitroso derivatives <1995COFGT(2)737>. Particularly efficient and selective are catalytic systems that use H_2O_2 as the oxidant. Catalysts based on molybdenum(VI) <1993CC1510, 1993JA11814, 1996JOC5770, 2000JOC123>, tungsten(VI) <1995ZOR1849>, methylrhenium trioxide <1995JOC1326>, and the titanium silicate TS-1 <1996CC1215> have been described.

Aromatic nitroso compounds can be conveniently prepared from nitroarenes by a two-step sequence of zinc reduction to the hydroxylamine (see Section 2.15.5.1) followed by oxidation with FeCl_3 , a process that can be performed in a one-pot procedure <1999TL6557>. An alternative improved procedure for the oxidation step uses Bu^tOCl as the oxidizing reagent (Scheme 56) <1999JOC4976>, thus avoiding the heterogeneous conditions required by previous methods. A similar two-step/one-pot reduction–oxidation sequence has been described using samarium(II) diiodide as the reducing agent and Oxone[®] as the oxidant. This method has been successfully applied to an aryl iodide system (Scheme 66) <1995JA4722>.



Scheme 66

A new synthesis of *N*-substituted *ortho*-nitrosoanilines has been achieved by reaction of primary amines bearing a tertiary alkyl group with nitrosobenzenes (Equation (72)) <1999EJO29>. The reaction proceeds by oxidative nucleophilic substitution of hydrogen, this substitution being faster than that of bromo and nitro groups at *ortho* or *para* positions. Improved yields of product are obtained when the reaction is performed in the presence of oxidizing agents (e.g., MnO_2).



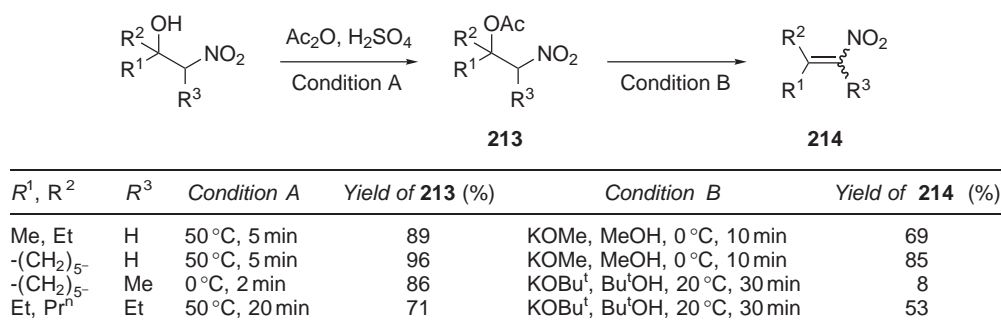
2.15.9.2 Nitro Compounds

This section is an update on all new methods for the synthesis of vinyl and aryl nitro compounds developed since the publication of COFGT (1995) <1995COFGT(2)737>. The synthesis and reactions of nitro compounds have been reviewed <B-1990MI006, 1995MI357, 1997MI415, 1999JCS(P1)749, 2000JCS(P1)3695, B-2001MI007, 2002JCS(P1)2586>.

2.15.9.3 Nitroalkenes

The chemistry of conjugated nitroalkenes is the subject of a monograph <B-1994MI008>. Conjugated nitroalkenes are highly useful and versatile intermediates that participate in a diversity of C—C bond-forming reactions such as Michael additions (as acceptors) <2002EJO1877> and Diels–Alder cycloadditions (as dienophiles or as heterodienes) <1996CRV137, 1997TCC1>. Moreover, the nitro group can serve as a masked functionality for a variety of further synthetic transformations.

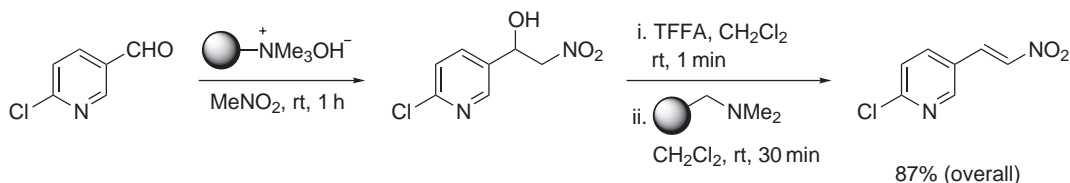
Conjugated nitroalkenes are classically prepared by the Henry reaction of a nitroalkane with a carbonyl compound and subsequent dehydration of the resultant 2-nitroalkanol <1995COFGT(2)737>. The nitroaldol reaction is routinely performed in the presence of a wide range of basic catalysts <1991COS(2)321, 2001T915>, some of which also promote the dehydration step, particularly in the case of aromatic aldehydes. New advances have taken place in the application of heterogeneous catalysts, solvent-free conditions and microwave and ultrasound irradiation. Bandgar has described the use of Envirocat EPZG[®] as a recyclable heterogeneous catalyst for the synthesis of conjugated nitroalkenes by condensation of nitromethane or nitroethane with aromatic or aliphatic aldehydes (under solvent-free conditions at 100 °C) in very high yield (90–97%) <1996SL149>. Other heterogeneous catalysts recently described for the direct synthesis of conjugated nitroalkenes by condensation of nitroalkanes and aromatic aldehydes or carbocyclic ketones include the following: alkali metal cation-exchanged zeolites (under solvent-free conditions at 140 °C) <2000JCA(191)348>, morpholine adsorbed on silica gel (in MeCN at room temperature) <2000M(131)949>, agar-agar aqua gel containing 10% KOH (in MeCN/EtOH at room temperature) <2000SC2071>, sulfated zirconia (under solvent-free conditions with microwave irradiation) <2001IJC(B)1239>, aminopropyl MCM-41 silica (without solvent at 90 °C) <2001TL2401>, and K₂CO₃/Al₂O₃ (under solvent-free conditions with microwave irradiation) <2002SC3481>. Ballini has shown that Amberlyst A-21 is a cheap and superior heterogeneous catalyst for the Henry reaction of primary and secondary nitroalkanes with aromatic and aliphatic aldehydes without promoting dehydration to the corresponding nitroalkene <1996T1677> (for other similarly efficient homogeneous catalysts see <2001T915>). This very mild procedure avoids epoxide formation when bromonitromethane is employed. Several reagents and conditions can be used for the dehydration of the ensuing nitroaldol products <1995COFGT(2)737> and new procedures have been developed. Barua has described the use of CCl₄/Ph₃P/Et₃N under reflux to give the corresponding (*E*)-nitroalkenes stereoselectively and in good yields (80–95%) <1994S685>. However, nitroaldol products derived from ketones, which contain a tertiary hydroxyl group, remain unreactive. Loubinoux has developed a two-step procedure for dehydrating these tertiary β-nitro alkanols to the corresponding conjugated nitroalkenes with high regioselectivity by acetylation and subsequent treatment with 1 equiv. of potassium methoxide or *t*-butoxide (Scheme 67) <1996SC4329>. When Et₃N is used as the base, the corresponding regioisomeric allylic nitroalkenes are obtained. Related to this procedure, 2-nitro-1,3-dienes have been generated *in situ* from 4-acyloxy-2-substituted-3-nitro-1-butenes by heating or by treatment with sodium acetate and their cycloaddition reactions with different substrates have been studied <1996T9275>. Various zeolites catalyze the formation of aliphatic, aromatic, and heteroaromatic (*E*)-nitroalkenes from the corresponding nitroaldol products (including those containing a tertiary hydroxyl group) in good yield (73–93%) and with complete stereoselectivity by heating in benzene at reflux <1997JCR(S)336>.



Scheme 67

New homogenous conditions for the condensation of aromatic aldehydes and nitroalkanes to give (*E*)-nitroalkenes have been described. These are (i) piperidine <1994S258> or ammonium acetate <1997TL5131> under solvent-free conditions using microwave irradiation, (ii) ultrasound in the presence of ammonium acetate and acetic acid at room temperature <1998TL8013>, and (iii) tetraethylammonium superoxide (generated from tetraethylammonium bromide and potassium superoxide) in DMF at room temperature <2001IJC(B)391>.

Ley has described the preparation of a conjugated nitroalkene by a nitroaldol reaction and subsequent dehydration as part of a new synthetic route to the analgesic agent (\pm)-epibatidine using polymer-bound reagents without chromatographic purification steps (Scheme 68) <1999JCS(P1)1253>. Amberlite-IRA 420(OH⁻) resin was found to be a suitable base for the Henry reaction and dimethylaminomethyl polystyrene resin promoted the room-temperature elimination of the hydroxyl group after derivatization as the corresponding trifluoroacetyl ester.

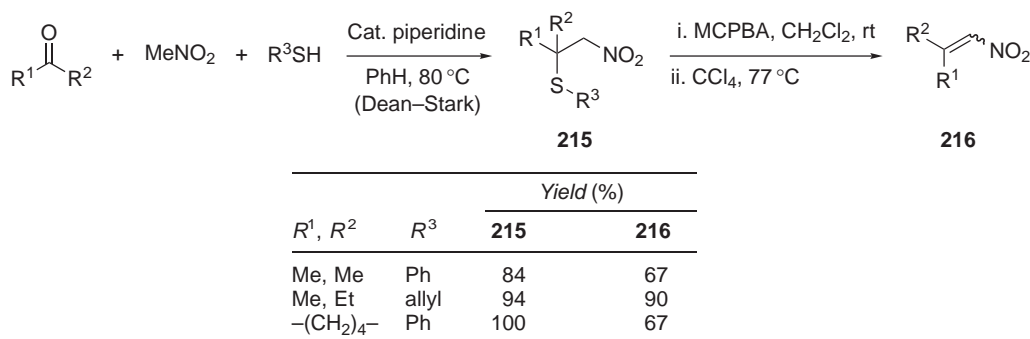


Scheme 68

The dehydration of nitroaldol products usually furnishes mixtures of (*E*)- and (*Z*)-isomers for nitroalkenes bearing an alkyl substituent in the α -position with respect to the nitro group. Stanetty has found that (*Z*)-nitroalkenes or mixtures of (*E*)- and (*Z*)-isomers can be converted to pure (*E*)-isomers by treatment with a catalytic amount of triethylamine or (polymer-bound) triphenylphosphine <1998TL811>.

Wade has described a simple protocol for the generation of nitroethylenes possessing a second electron-withdrawing group (CO₂Et, CPh, SO₂Ph) at the α -position <2002TL2585>. These highly reactive nitroethylenes can be generated *in situ* by condensing formalin and the corresponding nitroalkanes in the presence of acetic acid. Performing the reaction in the presence of added dienes affords the corresponding Diels–Alder cycloadducts in good overall yields. Alternatively, performing the condensation in the presence of thiophenol affords the corresponding β -nitrosulfides, from which the nitroethylenes can be regenerated by ozone oxidation at low temperature and elimination of the resulting sulfoxide.

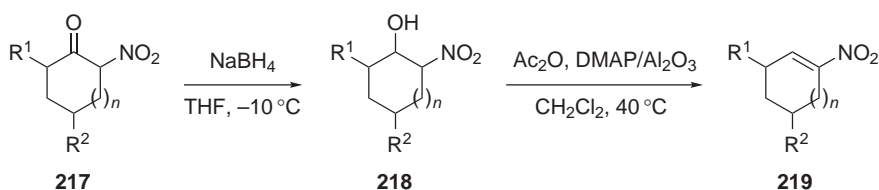
The Henry reaction is impractical for the preparation of 2,2-disubstituted-1-nitroalkenes due to its reversibility when ketones are used <1991COS(2)321>. Different alternative synthetic procedures have been developed to circumvent this limitation <1995COFGT(2)737>. Combining previous methodologies, Yao has described a new procedure that starts with the reaction of ketones, nitromethane, and a catalytic amount of piperidine or ethylenediamine in the presence of a mercaptan to afford β -nitrosulfides **215** in high yield (Scheme 69) <2001JOC1984>. Oxidation to the corresponding sulfoxides with MCPBA and subsequent thermal elimination affords 2,2-disubstituted-1-nitroalkenes **216** in moderate-to-good yield. An improved one-pot version of this method that uses a stoichiometric amount of piperidine and different solvents and oxidation conditions has been developed <2003T4979>.



Scheme 69

Nitroalkenes can be prepared by Horner–Wadsworth–Emmons reaction using diethyl 1-nitrophosphonates <2000SL1154>. Aromatic and α,β -unsaturated aldehydes gave the corresponding conjugated nitroalkenes in moderate to good yields, whilst α branched aliphatic aldehydes gave poor yields and ketones were unreactive.

Ballini has described a new synthesis of 1-nitrocycloalkenes **219** from the corresponding 2-nitrocycloalkanones **217** (Scheme 70) <1994TL5731>. Thus, sodium borohydride reduction under carefully optimized conditions gave 2-nitrocycloalkanols **218** containing minor amounts of the final nitrocycloalkene product **219**. The subsequent dehydration of the cycloalkanols was achieved by acetylation and *in situ* dehydroacetylation with basic alumina in the presence of DMAP in refluxing dichloromethane.



R^1	R^2	n	Yield (%)	
			218 ^a	219
H	H	1	75 (2)	78
Me	H	1	65 (8)	60
H	Bu ^t	1	75 (7)	55
Me	H	10	72 (20)	78

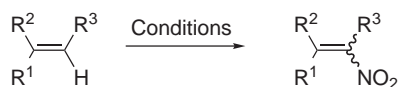
^a In parentheses, yields (%) of **219** obtained during reduction of **217** to **218**.

Scheme 70

Several methods have been developed for the direct preparation of conjugated nitroalkenes by nitration of the corresponding alkenes (Table 5). High regioselectivities are usually obtained for terminal or conjugated alkenes. 2-Nitroalkanol are sometimes formed as by-products, which need to be dehydrated by subsequent treatment of the reaction mixtures with dehydrating agents.

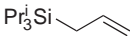
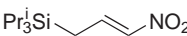
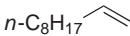
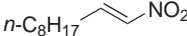

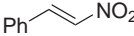
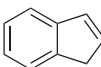
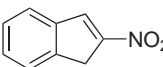
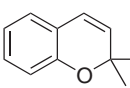
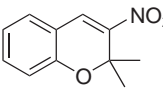
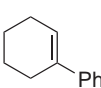
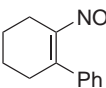

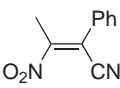
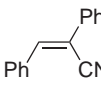
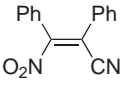
Vinyl silanes **220** suffer regioselective electrophilic substitution by treatment with acetyl nitrate in dichloromethane at low temperature to afford the corresponding 1-nitrocycloalkenes **221** in moderate to good yields (Equation (73)) <1999CC1079>. In the case of medium and large ring vinyl silanes, 1,1-dinitro-2-nitrates **222** are formed as major products.

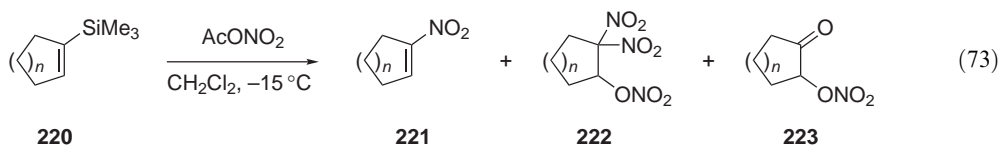
Table 5 Synthesis of conjugated nitroalkenes by nitration of alkenes



Alkene	Product	Conditions	Yield (%)	References
		NaNO ₂ , CAN, AcOH, CHCl ₃ ,)))) , 4 h	86	<1994CC1425>
		NO (1 atm), CCl ₄ , HY-zeolite, 75 °C, 2 h	78	<1998TL2695>
		NaNO ₂ , CAN, AcOH, CHCl ₃ ,)))) , 4 h	99	<1994CC1425>
		NO (1 atm), CCl ₄ , HY-zeolite, 75 °C, 2 h	80	<1998TL2695>

Table 5 (continued)

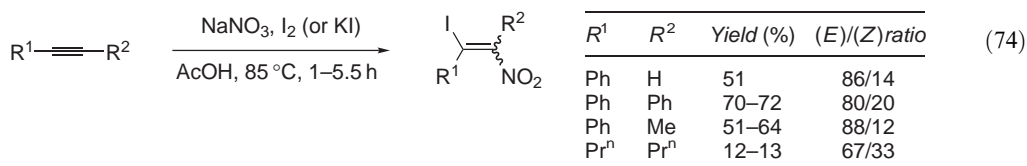
Alkene	Product	Conditions	Yield (%)	References
		NaNO ₂ , CAN, AcOH, CHCl ₃ ,)), 4 h	81	<1994CC1425>
		i. NO (1 atm), ClCH ₂ CH ₂ Cl, rt; ii. Al ₂ O ₃ , reflux	92	<1995BCJ3629, 1995CL505>
		NO (1 atm), CCl ₄ , HY-zeolite, 75 °C, 2 h	71	<1998TL2695>
		NaNO ₂ , CAN, AcOH, CHCl ₃ ,)), 4 h	82	<1994CC1425>
		i. NO (1 atm), ClCH ₂ CH ₂ Cl, rt; ii. Al ₂ O ₃ , reflux	95	<1995BCJ3629, 1995CL505>
		i. KNO ₂ , 18-crown-6, I ₂ , THF, rt,)), 0.5 h; ii. Et ₃ N, rt, 0.5 h	84	<1996S195>
		NO (1 atm), CCl ₄ , HY-zeolite, 75 °C, 2 h	79	<1998TL2695>
		Clayfen (Fe(NO ₃) ₂ on clay), no solvent, microwaves, 3 min	68	<1998TL3977>
		NaNO ₂ , Cu(BF ₄) ₂ , I ₂ , MeCN, rt, 7 h	47	<2000TL979>
		NaNO ₂ , CAN, AcOH, CHCl ₃ ,)), 4 h	54	<1994CC1425>
		i. NO (1 atm), ClCH ₂ CH ₂ Cl, rt; ii. Al ₂ O ₃ , reflux	91	<1995BCJ3629, 1995CL505>
		NO (1 atm), CCl ₄ , HY-zeolite, 75 °C, 2 h	68	<1998TL2695>
		i. NO (1 atm), ClCH ₂ CH ₂ Cl, rt; ii. Al ₂ O ₃ , reflux	68	<1995BCJ3629, 1995CL505>
		i. KNO ₂ , 18-crown-6, I ₂ , THF, rt,)), 1 h; ii. Et ₃ N, rt, 0.5 h	79	<1996S195>
		NO/NO ₂ , I ₂ , CCl ₄ , -5 °C, 1 h	80	<1999OPP117>
		NO/NO ₂ , I ₂ , CCl ₄ , -5 °C, 1 h	90	<1999OPP117>



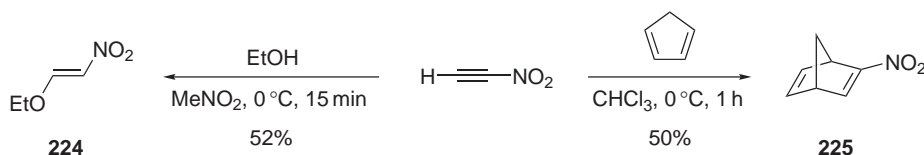
<i>n</i>	Yield (%)		
	221	222	223
1	50		
2	73		
3	70		
4		75	
8		56	32

Robins has described an efficient *C*-nitration of uracil derivatives [<1999JOC2149>](#). Thus, treatment of 1,3-dimethyluracil with copper(II) nitrate in acetic anhydride at room temperature [<1980JCS\(P1\)2567>](#) gave 1,3-dimethyl-5-nitrouracil in 90% yield. Similar treatment of 1-methyluracil gave 1-methyl-3-nitrouracil as the major product in 77% yield. Rearrangement of this *N*-nitro product into the corresponding 5-nitro isomer (73%) occurred in concentrated sulfuric acid. The 5-nitro isomer was obtained directly from 1-methyluracil in 80% yield by treatment with fuming nitric acid.

Alkynes can also be nitrated to yield conjugated nitroalkenes. Thus, treatment of alkynes with sodium nitrate in the presence of iodine or potassium iodide in acetic acid at 85 °C yields α -iodo- β -nitroalkenes in low-to-moderate yields as mixtures of geometrical isomers with high regioselectivity (Equation (74)) [<1998SC833, 1999ZOR1296>](#).

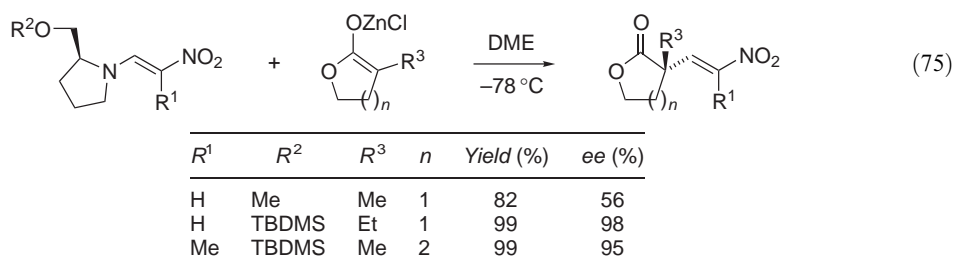


Nitroacetylene, prepared by reaction of NO₂PF₆ with trimethylsilylacetylene, reacts readily with nucleophiles and with cyclopentadiene to afford nitroalkenes **224** and **225**, respectively (Scheme 71) [<2002S2013>](#).



Scheme 71

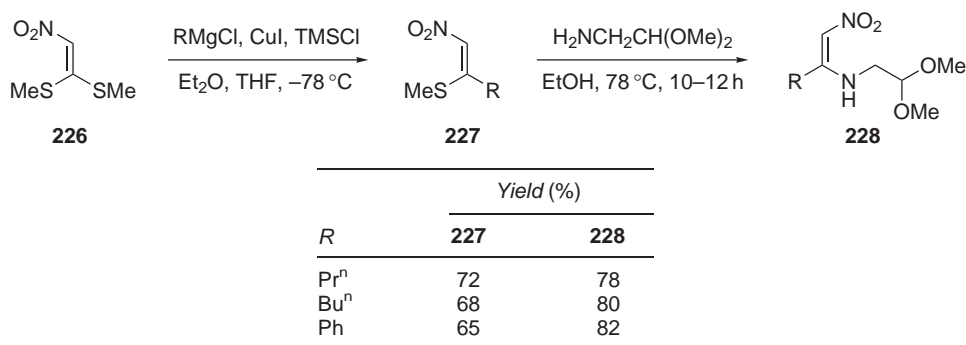
Several new procedures for the preparation of variously substituted nitroalkenes from other nitroalkenes have been described. Thus, treatment of 1-nitroalkenes with HCl and Oxone[®] in DMF at room temperature affords 1-chloro-1-nitroalkenes in 42–85% yields [<1997SC1885>](#). Stanetti has described the synthesis of (*E*)-nitroalkenes by the copper(I)-mediated addition-elimination reaction of organolithium and Grignard reagents to 2-nitro-1-phenylthiopropene following a similar procedure to that previously described by Knochel [<1991TL441, 1992JOC5431>](#). Node has described an improved method for the asymmetric nitroolefination of α -alkyl- γ - and δ -lactones by the addition-elimination reaction of the zinc enolates to chiral nitroenamines (Equation (75)) [<1995T10857, 1995TL99, 1998H\(47\)839>](#).



2.15.9.3.1 β -Nitroenamines

Rajappa has published an update <1999T7065> of his earlier review <1981T1453> on the synthesis, structure, spectral properties, and reactivity of β -nitroenamines.

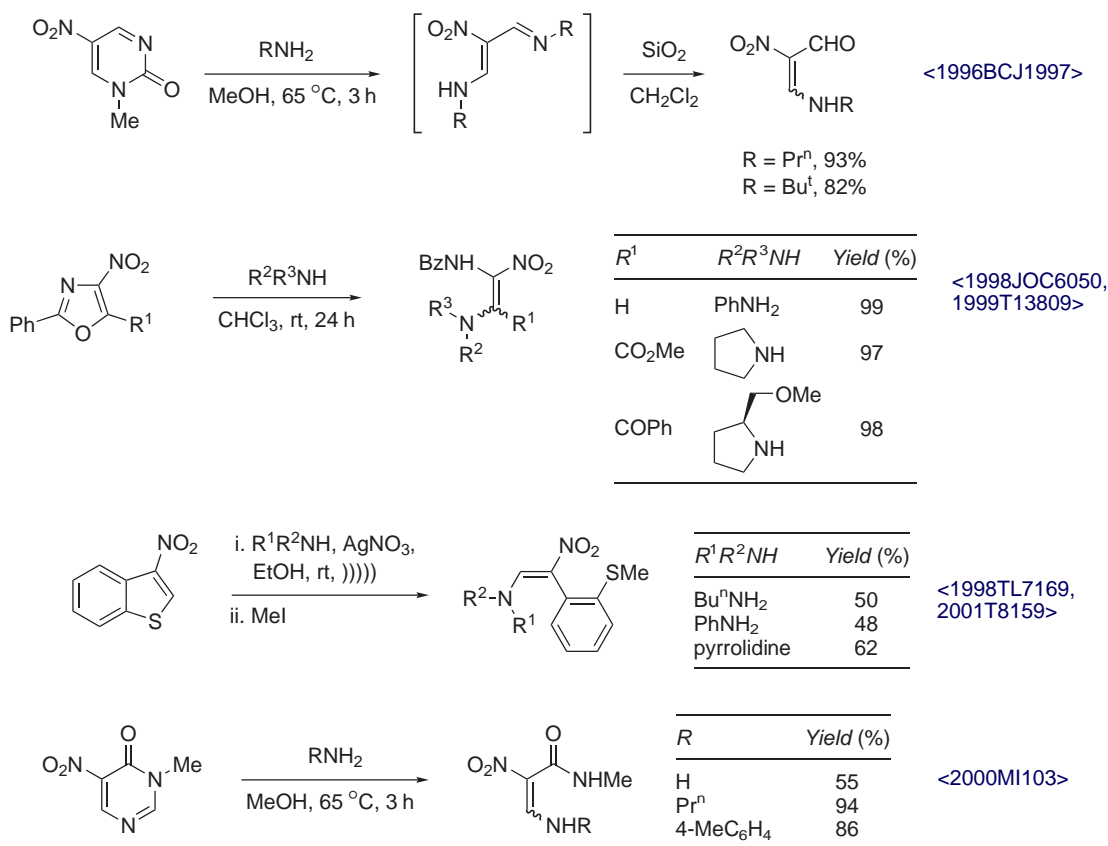
Of the different methods known for the preparation of 2-nitroenamines <1995COFGT(2)737>, those that involve a conjugate addition–elimination reaction of a primary or secondary amine on a preformed nitroalkene derivative containing a leaving group at the β -position are most popular. Acyclic and heterocyclic nitroalkenes with a β -halo-, β -alkoxy, β -alkylthio- or β -alkylamino-group have been used for this purpose. Node has described the preparation of chiral nitroenamines by transamination of simple *N,N*-dialkylamino-2-nitroenamines with chiral pyrrolidines and their application in asymmetric nitro-olefination reactions (Equation (75)) <1995T10857, 1995TL99, 1998H(47)951>. Gómez-Sánchez has also described the preparation of different 2-nitroenamines by transamination reaction of 1-arylamino-2-nitroalkenes substituted with other electron-withdrawing groups at C_2 <1998JCS(P2)1797>. Ila, Junjappa and coworkers have developed a method for the preparation of 2-methylthio-2-alkyl/aryl-1-nitroethylenes **227** via conjugate addition–elimination of organocopper reagents to nitroketene dithioacetal **226** in the presence of trimethylsilyl chloride (Scheme 72) <1998T12973>. Subsequent reaction with aminoacetaldehyde dimethyl acetal afforded 2-nitroenamines **228** that are transformed into substituted 3-nitropyrroles under acidic conditions. Several reports have described the preparation of 2-nitroenamines by ring-opening reactions of different *C*-nitro heterocycles with primary or secondary amines (Scheme 73).



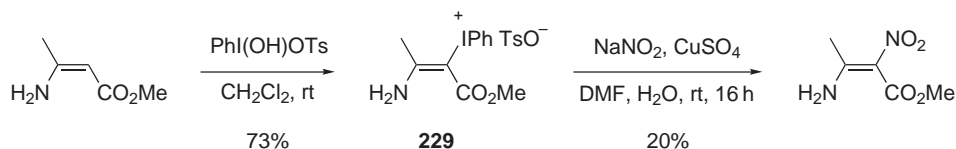
Scheme 72

Not only the amine but also the nitro group can be introduced into an alkene system by a substitution reaction to yield a 2-nitroenamine. Thus, the alkenyl phenyliodonium tosylate **229**, derived from methyl 3-aminocrotonate, reacts with sodium nitrite in the presence of copper(II) sulfate to afford methyl 2-nitro-3-aminocrotonate, although in low yield (Scheme 74) <1998T1005>.

N-Aculenamines can be nitrated with acetyl nitrate to afford 2-nitroenamines. However, products of further nitration and allylic oxidation are also formed under the reaction conditions <1996TL2079, 1997T16161>.

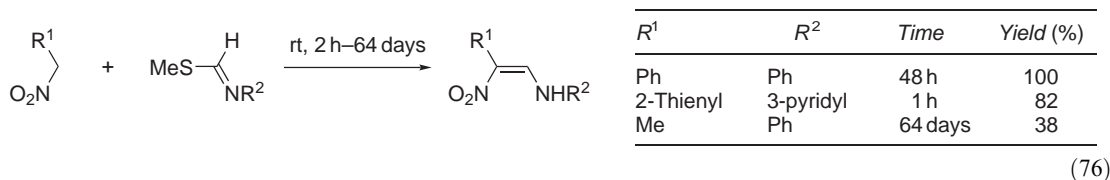


Scheme 73

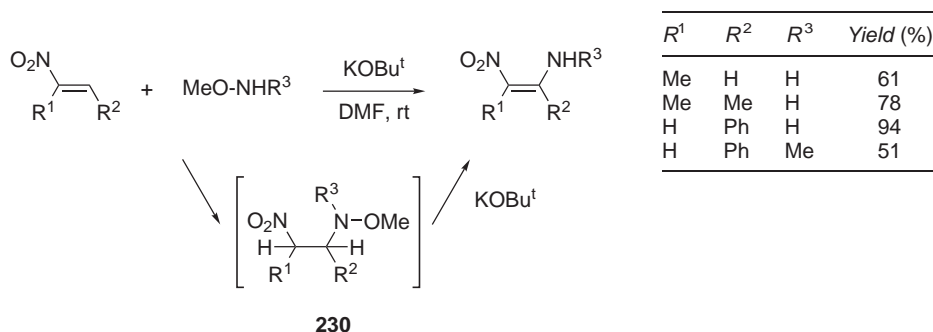


Scheme 74

Nitroenamines with an aryl or heteroaryl group at C-2 can be prepared in excellent yields by the reaction of substituted nitromethanes with *S*-methyl methaneimidothioates at room temperature in the absence of solvent (Equation (76)) <1998S139>. However, the reaction with nitroethane is very sluggish and proceeds slowly and with low yield.



Nitroalkenes without a leaving group at the β -position can be directly aminated with methoxyamines in the presence of an excess of base, via vicarious nucleophilic substitution of hydrogen, to yield 2-nitroenamines in good to excellent yields (Scheme 75) <1998JCS(P1)2975>. In the

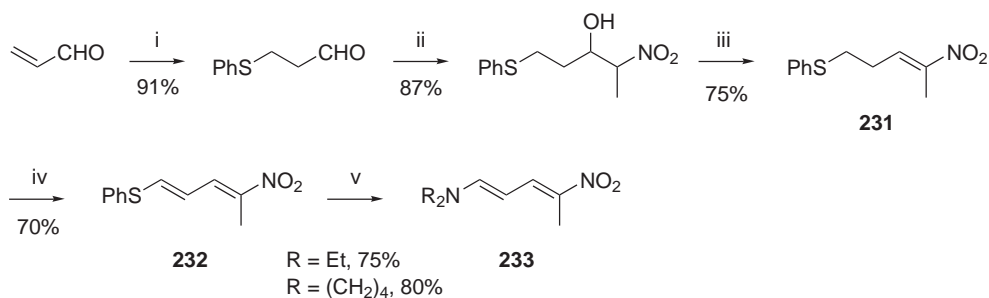


Scheme 75

absence of base, *O*-methyl-*N*-(β -nitroethyl)hydroxylamine derivatives **230** are formed quantitatively and can be transformed to the final 2-nitroenamines in high yield upon treatment with base (2 equiv.).

2.15.9.3.2 Nitro-, di-, and polyenamines

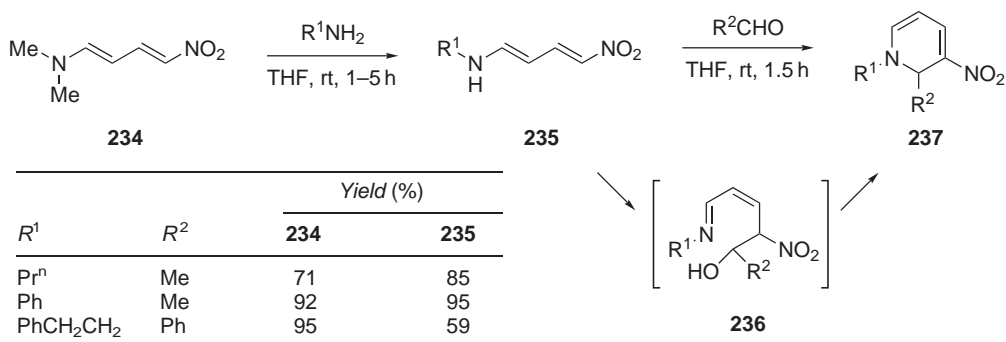
Nitrodienamines and nitropolyenamines are interesting intermediates in organic synthesis due to their diverse reactivity as enamines, dienes, and push-pull unsaturated systems <1995COFGT(2)737, 1999T7065>. Ono has described a practical synthesis of 1-dialkylamino-4-nitro-1,3-butadienes **233** of ((*E*),(*E*))-configuration (Scheme 76) <1996JCS(P1)1905>. Thus, Michael addition of thiophenol to acrolein, followed by Henry reaction with nitroethane and dehydration, gives nitroalkene **231**. Subsequent chlorination and HCl elimination upon base treatment yields diene **232**. The phenylthio group can be readily replaced by dialkylamino groups upon treatment with secondary alkylamines to give compounds **233** in good yields.



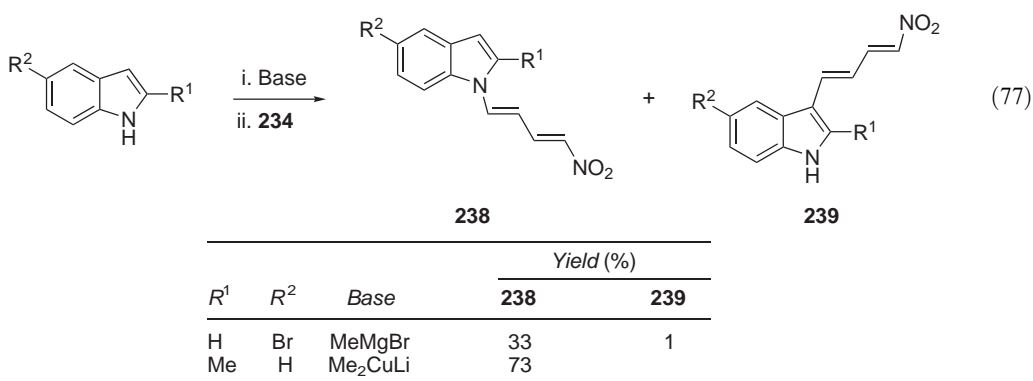
i. PhSH, THF, 0 °C to rt, 3 h; ii. EtNO₂, DBU, MeCN, rt, 24 h; iii. Al₂O₃, CH₂Cl₂, 50 °C 24 h;
 iv. (a) SO₂Cl₂, CH₂Cl₂, 0 °C, 30 min; (b) Et₃N, 0 °C, 30 min; v. R₂NH, MeOH, rt, 8 h

Scheme 76

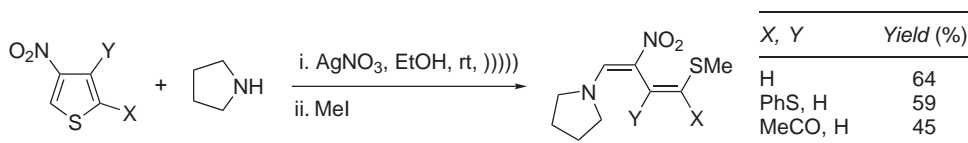
Like its parent 2-nitroenamines, nitrodienamine **234** readily undergoes conjugate addition-elimination reactions with primary amines to yield nitrodienamines **235**, which subsequently react with aldehydes, via **236**, to afford 3-nitro-1,2-dihydropyridines **237** in moderate to very good yields (Scheme 77) <1999CPB1246, 2000CPB436, 2000CPB1898>. Nitrodienamine **234** reacts with Grignard, organocopper and organolithium reagents derived from indole <1997H(45)1271, 1999H(51)2687, 2000H(53)2701> and pyrrole <2000H(53)1351> systems to yield 4-nitro-1,3-butadiene derivatives (Equation (77)).



Scheme 77

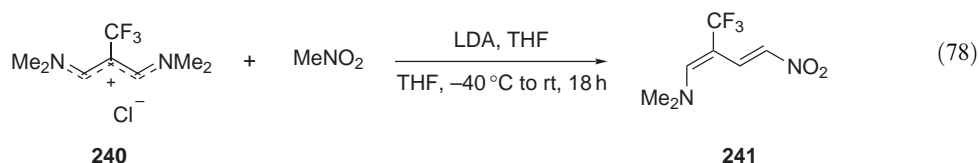


Optimized conditions have been reported for the ring-opening reactions of 2-substituted 4-nitrothiophenes with pyrrolidine in the presence of silver nitrate and subsequent *S*-methylation to yield 4-substituted 4-methylthio-2-nitro-1-pyrrolidino-1,3-butadiene (Scheme 78) <2001T8159>.



Scheme 78

β -Trifluoromethyl vinimidinium salt 240 reacts smoothly with the carbanion from nitromethane to give the corresponding nitrodienamine 241, the product of mono-addition–deamination in moderate yield (Equation (78)) <2001JFC(111)91>.



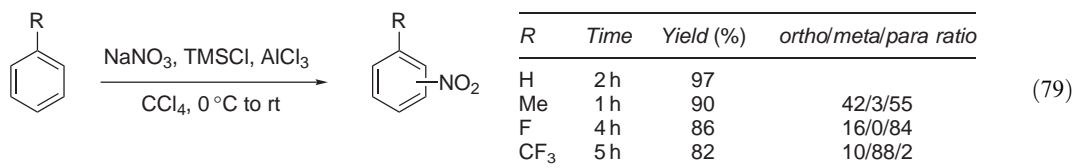
2.15.9.3.3 Aromatic nitro compounds

(i) Aromatic electrophilic substitution

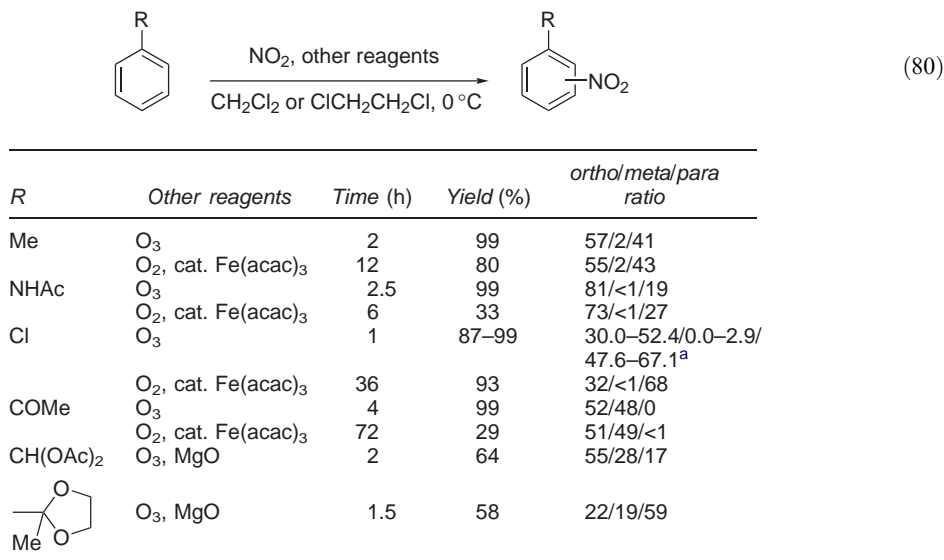
The preparation of aromatic nitro compounds is classically carried out via electrophilic aromatic substitution using reagents capable of forming the nitronium ion (NO₂⁺). Nitric acid, its metal salts, mixed anhydrides, nitrate esters, nitronium salts, and nitrogen oxides in the presence of Brønsted or

Lewis acids have been used for this purpose <B-1989MI008, 1991COS(6)103>. Two recent reviews, dealing mainly with mechanistic aspects, have been published <1998ACS11, 2003MI287>.

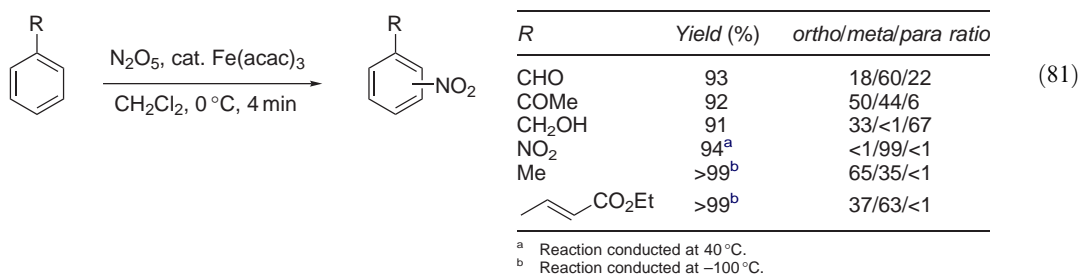
Aromatic nitration is a notoriously unfriendly process for the environment. Additional problems associated with its application in organic synthesis include the control of regioselectivity, over-nitration and competitive oxidation of substrates. A number of novel reagents and strategies have been developed to address these problems. Olah has described a simple nitration procedure using a mixture of sodium nitrate and chlorotrimethylsilane in the presence of anhydrous AlCl_3 in carbon tetrachloride (Equation (79)) <1994S468>. Nitril chloride is generated *in situ* and activated and mildly deactivated arenes are mononitrated at 0°C to room temperature in good-to-excellent yields. The mixed $\text{HNO}_3/2\text{CF}_3\text{SO}_3\text{H}\cdot\text{B}(\text{O}_3\text{SCF}_3)_3$ superacid system has been described by Olah for efficient nitration of strongly deactivated aromatic compounds under relatively mild conditions <1995JOC7348>. Yields and regioselectivities are usually high and the reaction is compatible with many functional groups.



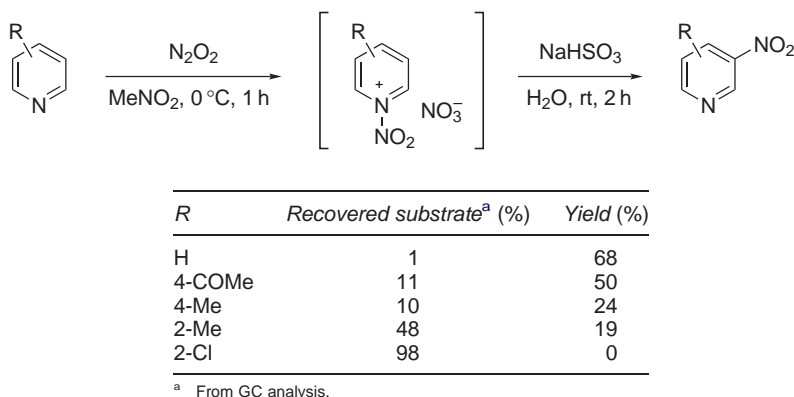
Suzuki has developed a novel, environmentally friendly and very mild aromatic nitration (referred to as “kyodai-nitration”) under nonacidic conditions using nitrogen dioxide in the presence of ozone in dichloromethane at low temperatures (-10 to 0°C) that gives excellent conversion of a wide variety of aromatic compounds (Equation (80)) <1995SL383, 1998ZOR1591, 1999S1291, 2000S1539, 2001JOC4356>. The active nitrating agent is thought to be N_2O_5 , generated *in situ* from NO_2 and O_3 . Arenes containing acid-sensitive groups such as acetals can be smoothly nitrated <1995BCJ1535> but aryl sulfides are converted to nitroaryl sulfones <2002S1065>. The same group has developed an even more environmentally friendly nitration process with nitrogen dioxide and molecular oxygen in the presence of $\text{Fe}(\text{acac})_3$ as catalyst at 0°C (Equation (80)) <1996JCS(P1)2385>. The regioselectivity of both nitration methods differs from that of conventional nitration procedures in that aromatic compounds with electron-withdrawing groups are nitrated preferentially at the *ortho* position, reflecting the different reaction mechanisms involved in each case with participation of radical cation intermediates in kyodai-type nitrations <1996JCS(P2)677>. Zeolites are very efficient solid acid catalysts for NO_2/O_3 and NO_2/O_2 nitrations often affording higher regioselectivities than homogeneous catalysts (see below). Related to these methods, Smallridge has described a very fast and mild nitration procedure that uses preformed N_2O_5 in the presence of $\text{Fe}(\text{acac})_3$ as catalyst in dichloromethane at 0°C (Equation (81)) <2001TL6767>. These nonoxidizing conditions are compatible with a wide range of functional groups and result in near quantitative yields in four minutes at temperatures as low as -100°C for activated systems.



^a Isomer ratio depends on initial substrate concentration.

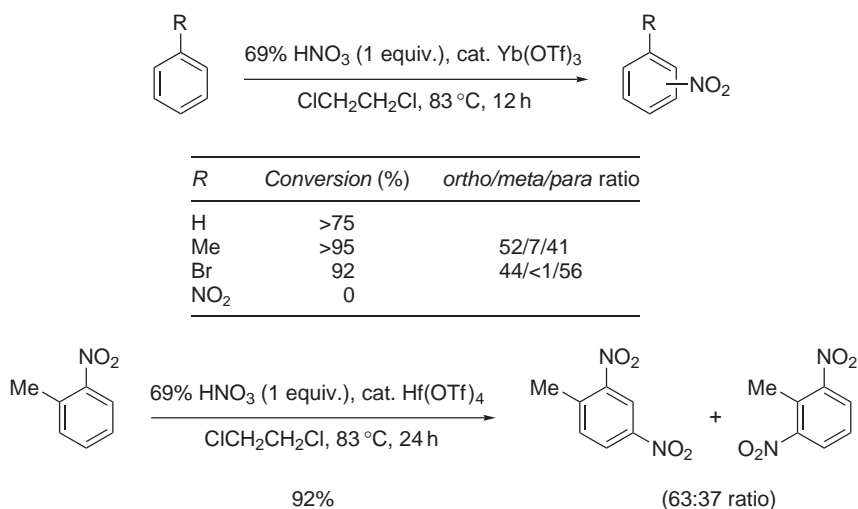


Bakke has reported new nitration procedures for deactivated aromatics including the difficult to effect direct *C*-nitration of pyridine and substituted pyridines. Using N₂O₅ in liquid sulfur dioxide followed by aqueous work-up [<1994ACS1001, 1995JCS\(P2\)1211>](#) or with N₂O₅ in nitromethane followed by treatment of the resultant *N*-nitropyridinium ion with aqueous sodium hydrogen sulfite [<1997S281, 1999ACS141>](#), moderate to good yields of 3-nitropyridines can be obtained (Scheme 79). A version of this method using NO₂/O₃ has also been reported [<1997TL5647, 2002H\(58\)301>](#).



Scheme 79

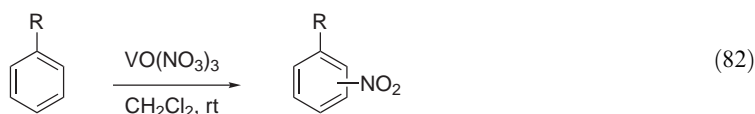
Lanthanide(III) triflates can be used as efficient and recyclable catalysts (1–10 mol.%) for atom-economic aromatic nitrations using a stoichiometric amount of 69% nitric acid in 1,2-dichloroethane at reflux (Scheme 80) [<1997CC613, 1999JCS\(P2\)867>](#). Ytterbium(III) triflate was



Scheme 80

found to be the most active catalyst of all lanthanide(III) triflates examined. A series of other metal salts were screened for catalytic activity and scandium(III) triflate was found to be of comparable activity to that of the corresponding ytterbium(III) salt. The only by-product of the reaction is water and the catalyst can be readily recovered by simple evaporation of the aqueous phase and reused. No dinitrated products are formed and, accordingly, the method is not effective for less reactive aromatics such as nitrobenzene and *o*-nitrotoluene. In these cases, hafnium(IV) and zirconium(IV) triflates are excellent catalysts (10 mol.%) for mononitration under the same conditions (Scheme 80) <1998TL1641, 1999JCS(P2)867>. Hafnium(IV) triflate and the ytterbium(III) and scandium(III) salts of triflic acid (TiF_3CH_3) are the most effective catalysts for nitration of electron-deficient fluoroarenes <2000SL57>. Very low catalyst loadings (0.02 mol.%) can be employed by performing the reaction with ytterbium(III) or scandium(III) perfluoroalkylsulfonates in 60% nitric acid without organic solvent <2002JFC(113)207>. 3-Substituted phenols can be regioselectively nitrated to give 3-substituted-5-nitrophenols in good yield, independently of the electronic character of the 3-substituent, by reaction with various lanthanide(III) nitrates in ethyl acetate at reflux <1997SC2793>.

Vanadium(V) oxytrinitrate is an easy-to-handle reagent for nitration of a range of substituted aromatic compounds under nonacidic conditions in dichloromethane at room temperature, affording almost quantitative yields of nitration products in most cases (Equation (82)) <1998JCS(P1)1589>.

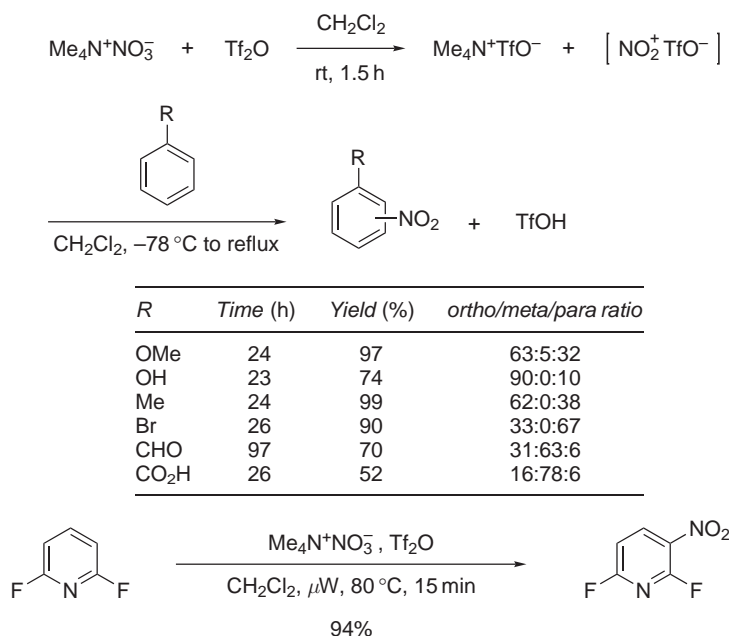


R	Time	ortho (%)	meta (%)	para (%)	2,4-Disub.(%)	Yield (%)
Me	6 min	35	2	41	19	>99
OH	0.5 min	32		9	51	93
NHAc	15 min	37		48		85
Cl	20 min	43		57		>99
CO ₂ Me	2 d	29	67	4		>99
CN	26 h					0

Strazzolini has described the preparation of dry solutions of nitric acid in dichloromethane by adding 96% sulfuric acid to potassium nitrate <2001TL1387>. The resultant solutions have been used for nitration of aromatics in 92–97% yields.

An improved procedure for the *in situ* preparation of nitronium triflate nitrating agent has been described by Shackelford employing tetramethylammonium nitrate and triflic anhydride in dichloromethane <2003JOC267>. The reagent efficiently nitrates a range of electron-rich and electron-deficient aromatic and heteroaromatic compounds with high regioselectivity and in high yields (Scheme 81). Purities of products after simple aqueous work-up are usually very high. The procedure is readily scalable and suitable for microwave-assisted heating. Microwave irradiation has proven to be very efficient for nitration of several heterocycles requiring only 0.5–6 minutes instead of 3–40 hours needed with conventional heating <1997IJC(B)1071>.

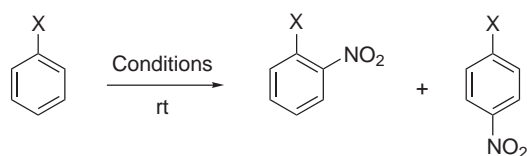
Especially convenient from an environmental point of view is the use of solid supported reagents, either as acid catalysts, nitrating agents or a combination of both. A further stimulus to the use of supported reagents is the possibility of influencing the regiochemical outcome of nitrations. Silica gel, clays and zeolites have been used as solid acid catalysts and supports for metal nitrates in aromatic nitration reactions. A high surface area Nafion[®]/silica nanocomposite has been developed by Harmer and shown to be an efficient acid catalyst to mono-nitrate benzene with nitric acid in 82% yield <1996JA7708>. Silica gel is an inexpensive solid support that has been exploited to adsorb sulfuric acid <1996TL513, 1999SC4187>, nitric acid <1996H(43)263>, or acetyl nitrate <1999T6733> for use in selective and efficient nitration reactions. Montmorillonite clay has been used in aromatic nitration reactions as acid catalyst <1998NJC339> and as solid support for nitrate salts such as ferric nitrate (“Clayfen”) <1984BSB961, 1985S909>, copper(II) nitrate (“Claycop”) <1985S909, 1995JOC3445, 1998T7843, 2001T1793>, ammonium nitrate (“Clayan”) <2003SC2497>, and bismuth(III) nitrate <2000TL8017>. This last supported nitrate is a particularly efficient aromatic nitration reagent (72–99% yields in 8–15 min at room temperature). Zeolites have been used as very efficient solid acid catalysts for aromatic nitrations



Scheme 81

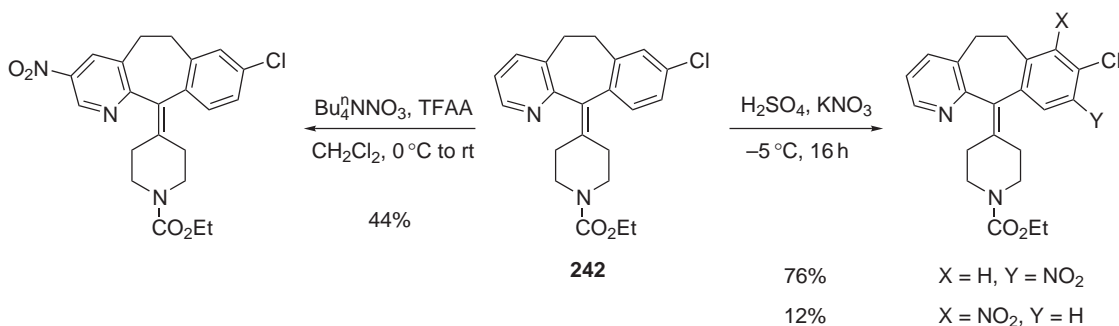
in combination with nitric acid <2000CC25>, nitric acid/acetic anhydride <1996CC469, 1998JOC8448>, nitric acid/trifluoroacetic anhydride <2000JCS(P1)2753>, dinitrogen tetroxide/air <2001CC2748>, nitrogen dioxide/ozone or molecular oxygen <2001TL4357, 2003OBC2326> and dinitrogen pentoxide <1999JCS(P2)1815, 2001JCS(P2)197>. Solid supported nitrating reagents usually afford higher regioselectivities than those obtained under analogous homogeneous conditions (Table 6) and reversal of isomer ratios are observed in some cases <2003OBC2326>. Improved *para*-regioselectivities are usually obtained using zeolites (and some clays <2002SC3565>) as catalysts which have shape-selective properties.

Table 6 Regioselectivity of nitration of toluene, phenol and chlorobenzene under classical homogeneous conditions and using solid-supported reagents

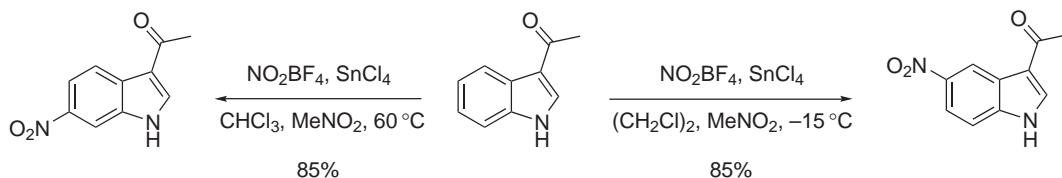


X	Conditions	Yield	ortho/para ratio	References
Me	NH ₄ NO ₃ , (CF ₃ CO) ₂ O	88	1.5	<1981JOC3056>
	HNO ₃ , Ac ₂ O, zeolite Hβ	>99	0.23	<1998JOC8448>
	N ₂ O ₄ , zeolite Hβ	76	1.1	<2001CC2748>
	NO ₂ , O ₂ , zeolite HZSM-5	82	0.08	<2001TL4357>
OH	AcONO ₂ , CHCl ₃	>99	1.8	<1999T6733>
	AcONO ₂ /SiO ₂ , CHCl ₃	>99	13.3	<1999T6733>
	Montmorillonite K10/Cu(NO ₃) ₂ , Ac ₂ O, CCl ₄	92	14.3	<1995JOC3445>
	Montmorillonite K10/Fe(NO ₃) ₃ , THF	80	0.95	<1984BSB961>
	Montmorillonite KSF/Bi(NO ₃) ₃ , THF	89	0.33	<2000TL8017>
Cl	NH ₄ NO ₃ , (CF ₃ CO) ₂ O	>99	0.25	<1981JOC3056>
	Montmorillonite K10/Cu(NO ₃) ₂ , Ac ₂ O, CCl ₄	98	0.15	<1995JOC3445>
	HNO ₃ , Ac ₂ O, zeolite Hβ	>99	0.075	<1998JOC8448>
	N ₂ O ₄ , zeolite Hβ	97	0.013	<2001CC2748>

Some interesting examples of regiochemistry control in aromatic nitration reactions under homogeneous conditions have been described. Thus, whereas classical nitration with $\text{KNO}_3/\text{H}_2\text{SO}_4$ of azatricyclic system **242** gives products mainly nitrated at the benzene ring, use of tetrabutylammonium nitrate/trifluoroacetic anhydride affords mainly nitration of the pyridine ring (Scheme 82) <1998JOC445>. An interesting temperature effect on the regioselectivity of nitration of 3-acetylindole has been observed by Ottoni. Using nitronium tetrafluoroborate in the presence of tin(IV) tetrachloride, 3-acetyl-5-nitroindole is selectively obtained when the reaction is performed at low temperature (-15 to -10°C), whereas at 60°C the corresponding 6-nitro isomer is exclusively formed (Scheme 83) <1999TL1117>.



Scheme 82

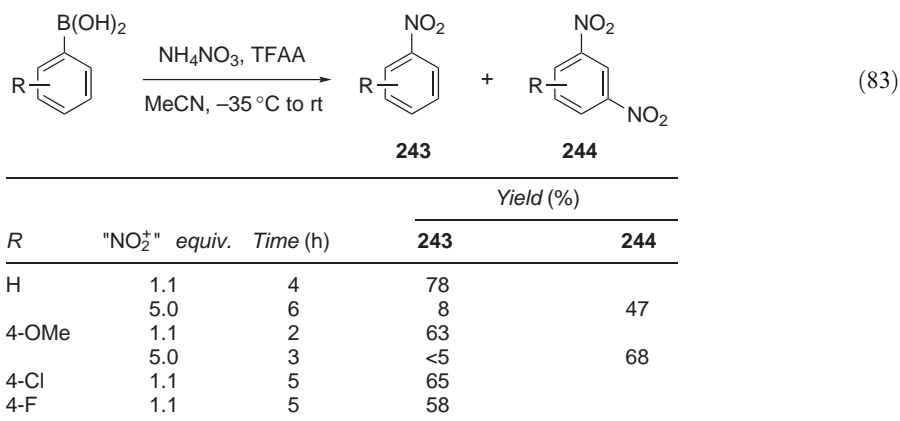


Scheme 83

New developments with respect to reaction media have been reported. Mononitration of phenol and substituted phenols can be accomplished in high yield and with good selectivity in a two-phase 1,2-dichloroethane/water system with dilute nitric acid (6%) using tetrabutylammonium bromide as phase-transfer catalyst <2003OPRD95>. Dilute nitric acid (5M) is also an effective nitrating agent when the reaction is performed in a cationic surfactant-based microemulsion system, which gives better *para*-selectivities than the corresponding reaction in a two-phase system (e.g., the *ortho/para* ratio for nitration of anisole is 10:90 in microemulsion versus 54:46 in a two-phase system) <2001MI(182)321, 2003TCC(227)53>. Perfluorocarbon solvents ("fluorous phase") are effective solvents in aromatic nitration reactions with nitric acid or dinitrogen pentaoxide, requiring lower temperatures and producing lower amounts of waste acid than traditional processes <2002GC275>. Use of fluorous phase in combination with ytterbium(III) or scandium(III) perfluoroalkylsulfonates as catalysts allows the nitration of aromatics to be performed with nitric acid at 60°C with very low catalyst loadings (0.05–0.1 mol.%) and the catalyst can be easily recovered and reused. Ionic liquids have been explored as solvents for electrophilic aromatic nitration, allowing easier product isolation, good solvent recycling, and a more efficient use of the nitrating agent than in analogous procedures with molecular solvents. Laali has investigated the potential utility of a series of ionic liquids with a variety of nitrating systems, observing that some common ionic liquids are unsuitable for this purpose due to their propensity to suffer nitration under the reaction conditions <2001JOC35>. Srinivasan has reported an efficient nitration of phenols with ferric nitrate using the ionic liquid 1,3-di-*n*-butylimidazolium tetrafluoroborate as solvent <2003SC961>. High *para*-selectivities are obtained under these conditions. The same authors have described the nitration of phenols in the ionic liquid ethylammonium nitrate in the presence of ferric nitrate or Montmorillonite K10-supported

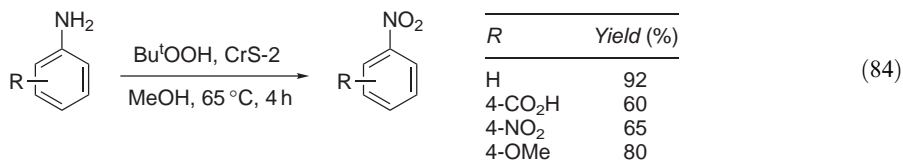
ferric nitrate (Clayfen) <2003MI41>. Ultrasound irradiation produced a significant rate enhancement as well as higher *para*-selectivities as compared to the corresponding reaction without ultrasound. Finally, Lancaster has described the nitration of a variety of aromatics in high yield and with high efficiency using $\text{HNO}_3/\text{Ac}_2\text{O}$ in 1-butyl-1-methylpyrrolidinium, an ionic liquid that is stable to nitration <2003CC2812>. Acetyl nitrate is probably completely dissociated in the ionic liquid to acetate and nitronium ions, making the nitrating reagent more reactive in the ionic liquid than in molecular solvents.

Arylboronic acids suffer a facile *ipso*-nitration upon treatment with trifluoroacetyl nitrate at low temperature to afford nitroarenes **243** in good yield in a completely regioselective way (Equation (83)) <2000SL1485>. Depending on the conditions, dinitrated products **244** can also be prepared.



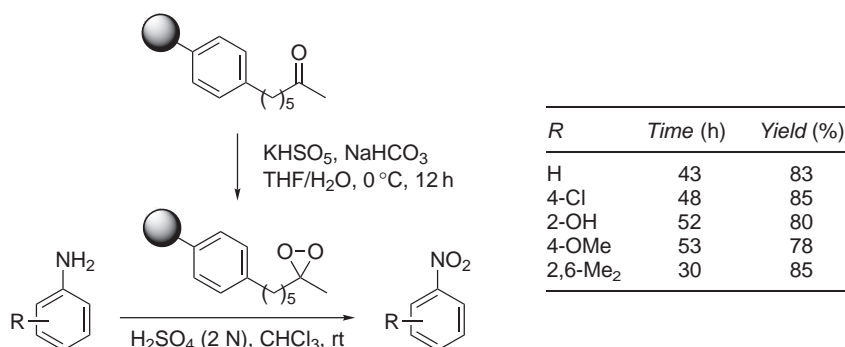
(ii) Oxidation of primary arylamines and aromatic nitroso compounds

The oxidation of aromatic primary amines to the corresponding nitro compounds can provide products that may otherwise be difficult to synthesize by direct aromatic electrophilic substitution. Such oxidations have been performed mainly with peracetic acid, sodium perborate and dimethyldioxirane (for electron-rich anilines) or with trifluoroperacetic acid and peroxydisulfuric acid (for electron-deficient anilines) <1991COS(7)735, B-2001MI007>. Hydroxylamines and nitroso compounds are common intermediates in most of these oxidation processes and, therefore, various side reactions can take place, such as formation of azoxy derivatives resulting from reaction between the former two intermediate products. A number of new selective oxidation methods have been described. The chromium zeolite CrS-2 is an efficient heterogeneous catalyst for the selective oxidation of primary arylamines to the corresponding aromatic nitro compounds with 70% *t*-butylhydroperoxide (Equation (84)) <1995CC1523, 1995T11305>. Diverse anilines with electron-donating and accepting substituents are oxidized to nitro compounds in good to excellent yields with *t*-butylhydroperoxide as the oxidant and $\text{Zr}(\text{O}i\text{Bu})_4$ as catalyst <1997JPR(339)335>. Several aminopyridines can be oxidized to the corresponding nitropyridines in moderate yield (41–47%) using this method.



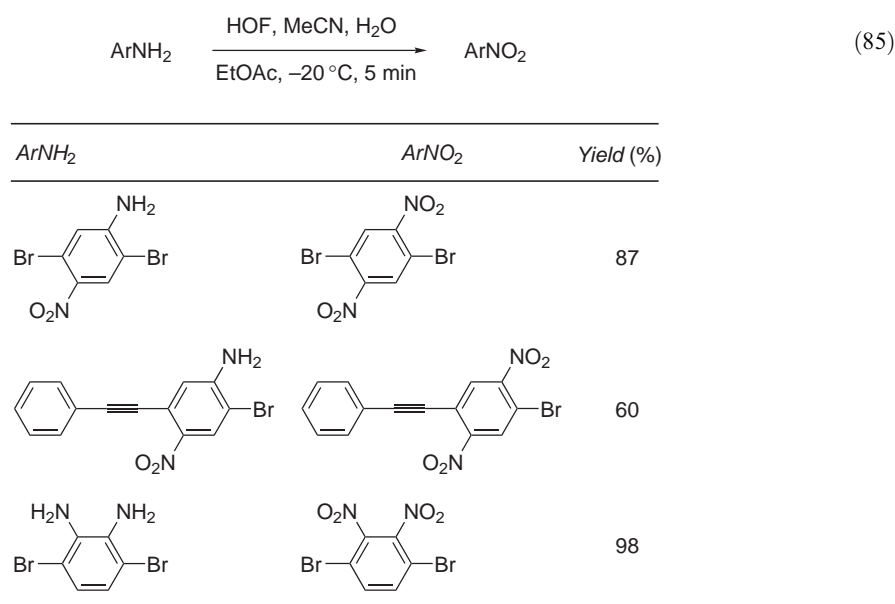
Methyltrioxorhenium catalyzes the oxidation of primary aromatic amines and nitroso compounds to the corresponding nitro derivatives with H_2O_2 at room temperature <1996TL805>. Azoxybenzene is formed as a by-product in the oxidation of aniline, and pyridine is oxidized to its *N*-oxide. Oxone[®] in 5–20% aqueous acetone buffered with sodium bicarbonate at 8 °C is a mild and selective system for the oxidation of anilines containing carboxylic acid and alcohol functionalities <1995TL2377>. Lower yields of nitro compounds are obtained in the absence of acetone, suggesting the competitive generation of dimethyldioxirane as a co-oxidant. A polystyrene-supported dioxirane has been described as an efficient and recyclable reagent for the

oxidation of diversely substituted anilines to nitro derivatives in near quantitative yields (Scheme 84) <1996MI(41)377>. Pyridine is oxidized to the corresponding *N*-oxide but 2-aminopyridine can be transformed to 2-nitropyridine in 80% yield with this method. Neumann has reported the preparation of an octafluoroacetophenone immobilized on silica as a heterogeneous catalysts for the oxidation of aromatic amines with aqueous hydrogen peroxide <2001CC487>. Aniline, alkyl-substituted anilines and halogen-substituted anilines yielded azoxy compounds as exclusive products in quantitative yields while anilines with hydroxyl or nitro substituents yielded the corresponding nitro derivatives in quantitative yield provided that the nitro group is not *ortho* to the amino substituent.



Scheme 84

The oxidation of electron-deficient anilines containing alkyne systems has been performed in good yield with HOF generated *in situ* in a fluorine–acetonitrile–water system at -20°C (Equation (85)) <2000OL3405>. Sudalai has described the preparation of a titanium superoxide radical ion as a novel heterogeneous catalyst for the oxidation of anilines to the corresponding nitro derivatives with 50% aqueous hydrogen peroxide <2001AG(E)405>. The catalyst is readily prepared by reacting 50% hydrogen peroxide with $\text{Ti}(\text{OPr}^i)_4$ in MeOH at room temperature. Electron-rich and electron-deficient anilines are oxidized at room temperature in 30–45 min with high selectivity and in 82–98% yield.

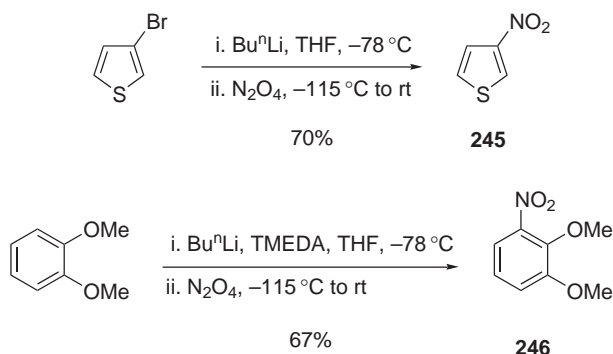


Electrophilic aromatic nitrosation (Section 2.15.9.1.2) is much more regioselective than nitration and, in view of the ease of oxidation of the nitroso product, offers an attractive two-step method (nitrosation followed by oxidation) for regioselective nitration. However, this

protocol is limited to aromatic substrates strongly activated to electrophilic substitution, such as phenols, aryl ethers, and alkylbenzenes. A wide variety of reagents can be used for the oxidation step (see <1997JCS(P2)1793>). Although mechanistically unclear, two methods described by Zolfigol for the one-pot nitration of phenols with NaNO_2 seem to correspond to this nitrosation–oxidation protocol. Both methods use wet SiO_2 as a heterogeneous acid catalyst in the presence of an oxidant, such as Oxone[®] <2001IJC(B)1191, 2001JCR(S)140> or trichloroisocyanuric acid <2003SL191>, in dichloromethane at room temperature affording moderate to high yields of nitrophenols.

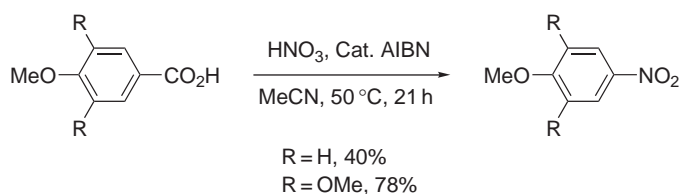
(iii) Other methods

Aryllithium compounds can be successfully nitrated by N_2O_4 in THF at -115°C (a critical effect of temperature on the outcome of the reaction has been observed) specifically at the position of lithiation in good to very good yields <1997JA1476>. The reaction is proposed to proceed via N_2O_4 oxidation of the anion to the radical followed by radical combination with NO_2 (or N_2O_4). This method is a highly convenient alternative to older methods available for the preparation of certain aryl and heteroaryl nitro compounds, such as 3-nitrothiophene **245** and 3-nitroveratrol **246** (Scheme 85).



Scheme 85

Electron-rich benzoic acids (and aromatic α,β -unsaturated carboxylic acids) suffer a facile nitrodecarboxylation upon treatment with nitric acid and catalytic AIBN in acetonitrile to yield nitroarenes in moderate-to-good yields in a completely regioselective way (Scheme 86) <2002OL3055>. The reaction is postulated to involve the generation of an acyloxy radical $\text{ArCO}_2\cdot$ followed by attack of an $\text{NO}_2\cdot$ radical.

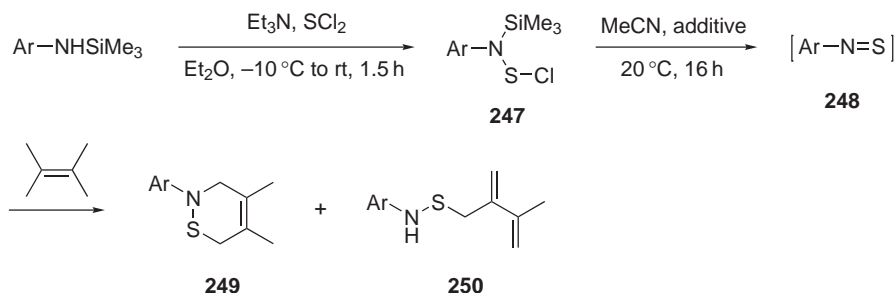


Scheme 86

2.15.9.4 Aryl Thionitroso Compounds

This section is an update on all new methods for the synthesis of aryl thionitroso compounds reported since the publication of COFGT (1995) <1995COFGT(2)737>. The chemistry of thionitroso compounds has been reviewed <1993RHA21, 1993SR293>.

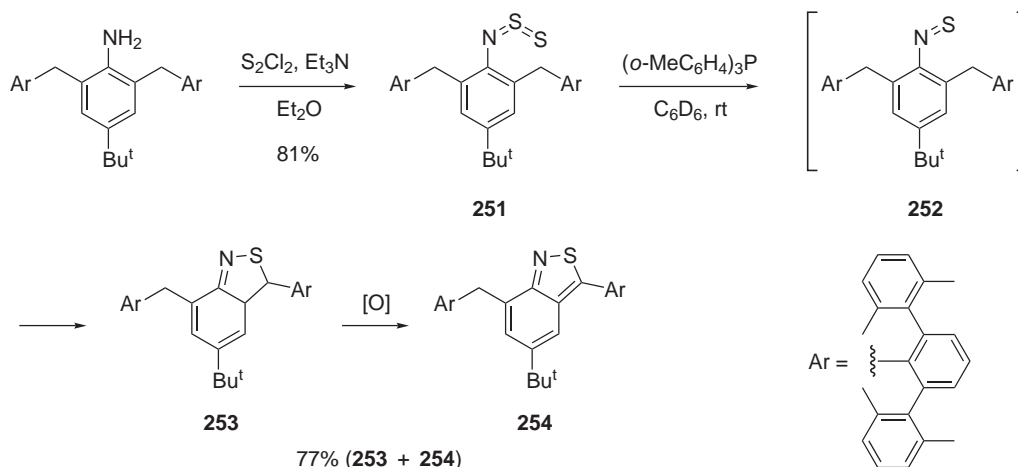
Very little progress has been made on the chemistry of this elusive group of compounds in the past decade, the interest being focused mainly on theoretical studies <1999JCS(P2)1249>. Bryce has described the transient generation of arylthionitroso compounds **248** (and alkylthionitroso compounds) from *N*-trimethylsilyl-*N*-chlorothioaryl(alkyl)amine precursors **247** by thermal fragmentation <1994TL5275> or by treatment with silver ions <1996JCS(P1)1825>, and their trapping with 2,3-dimethylbutadiene to afford Diels–Alder **249** and ene adducts **250** (Scheme 87). The reaction is more efficient and selective in the presence of silver ions.



Ar	Additive	Combined yield (%)	Isomer ratio 249/250
4-Br	None	50	25/75
	AgF	87	>95/5
2-Br	None	65	15/85
	AgF	80	>95/5
4-Me	None	55	60/40
	AgF	78	>95/5

Scheme 87

Goto and Okazaki have described the generation of a thionitrosoarene **252** by desulfuration of a stable *N*-thiosulfinylarylamine **251** bearing a bowl-type substituent (Scheme 88) <1998CL981>. The intermediate thionitrosoarene suffered an intramolecular cyclization with an *ortho*-alkyl substituent to afford a single diastereoisomer of 3,3a-dihydro-2,1-benzisothiazole **253** as a main product that partially oxidized to the isothiazole **254** upon purification.



Scheme 88

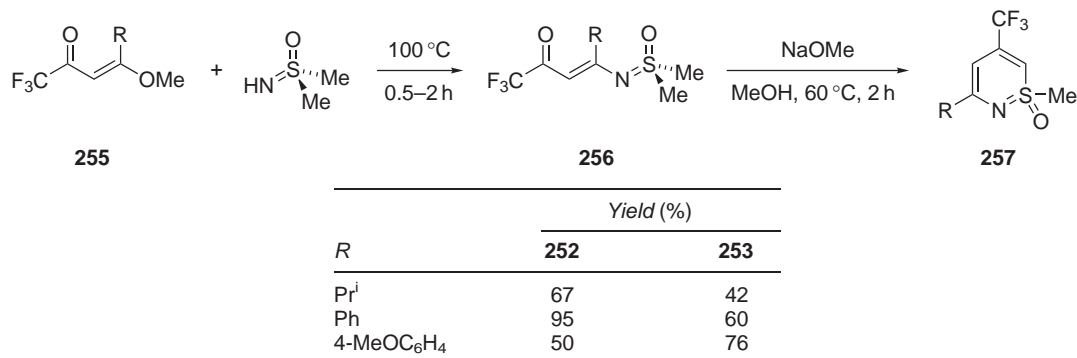
2.15.9.5 Sulfoximines

This section is an update on all new methods for the synthesis of vinyl and aryl sulfoximines that have been developed since the publication of COFGT (1995) <1995COFGT(2)737>. Two excellent

reviews on the structure, preparation, and synthetic applications of sulfoximines have been published <1999SR281, 2000S1>.

2.15.9.5.1 Vinyl sulfoximines

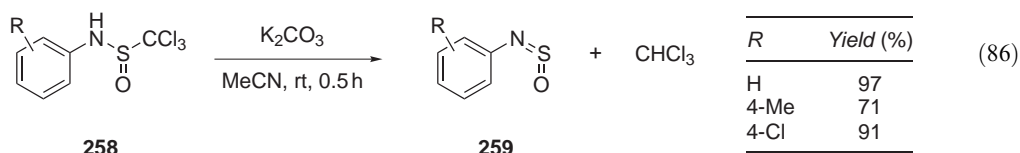
A series of *N*-vinyl sulfoximines **256** has been prepared in good yields by reaction of substituted 4-alkoxy-1,1,1-trifluoro-3-buten-2-ones **255** with *S,S*-dimethylsulfoximine in the absence of solvents (Scheme 89) <2000S1431>. Treatment of compounds **256** with base afforded 5-trifluoromethylated 1-methyl-1,2-thiazine 1-oxide derivatives **257** by intramolecular condensation.



Scheme 89

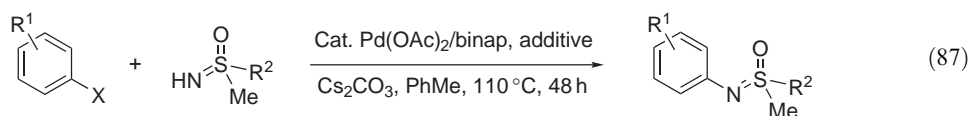
2.15.9.5.2 Aromatic sulfoximines

Braverman has described the preparation of aromatic *N*-sulfinylamines **259** in high yield from *N*-monosubstituted trichloromethanesulfinamides **258** by base-induced elimination of chloroform under mild conditions (Equation (86)) <1997TL487>. The starting trichloromethanesulfinamides **258** were readily prepared from the corresponding arylamines by reaction with trichloromethanesulfonyl chloride followed by oxidation of the resultant sulfenamides with MCPBA (Scheme 96).

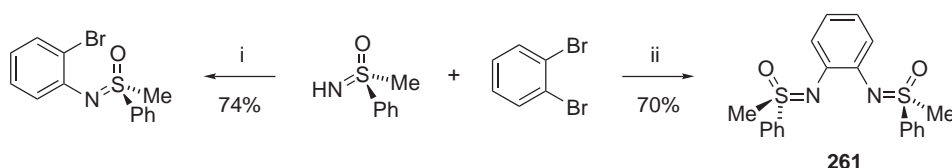
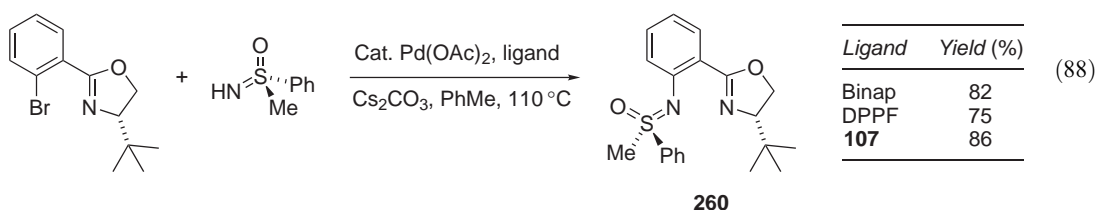


(86)

Bolm has described an efficient and versatile preparation of *N*-arylsulfoximines by palladium-catalyzed *N*-arylation of sulfoximines with aryl bromides and aryl iodides in the presence of chelating phosphanes (Equation (87)) <1998TL5731, 2000JOC169>. Aryl bromides with diverse substitution pattern were the more effective coupling partners, while aryl iodides required the use of lithium or silver salts as additives to ensure product formation in reasonable yields. The procedure has been successfully applied to the preparation of diastereoisomerically pure sulfoximines **260**, showing that the coupling reaction proceeds without racemization at sulfur (Equation (88)). The reaction of dibromobenzenes afforded monosulfonimidoyl arenes in all cases under these conditions (Scheme 90). However, employing a slightly modified protocol developed by Divers for bisamination of *o*-dibromobenzene that uses a different palladium source, stronger base and a higher temperature <2000TA1703>, the chiral *C*₂-symmetric bissulfoximine **261** could be smoothly obtained in good yield (Scheme 90) <2001JA3830>. Using this methodology, related *C*₂-symmetric <2003OL427> and *C*₁-symmetric bissulfoximines <2003CC2826> has been prepared and tested as chiral ligands for diverse metal-catalyzed enantioselective reactions.



X	R ¹	R ²	Additive	Yield (%)
Br	H	Me	None	86
Br	4-CO ₂ Me	<i>p</i> -Tol	None	88
Br	3-OMe	<i>p</i> -Tol	None	74
I	2-CO ₂ Me	Ph	LiBr	56
I	4-NO ₂	<i>p</i> -Tol	AgOTf	79
I	2-OMe	Ph	AgOTf	<2

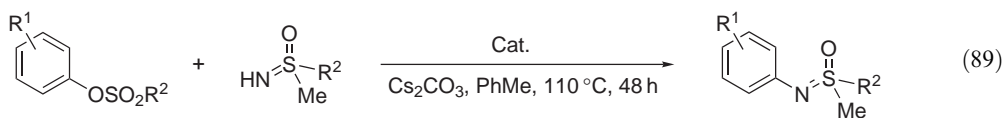


i. Cat. Pd(OAc)₂/binap, Cs₂CO₃, PhMe, 110 °C, 48 h

ii. Cat. Pd₂(DBA)₃/binap, NaOBu^t, PhMe, 135 °C, 10 h

Scheme 90

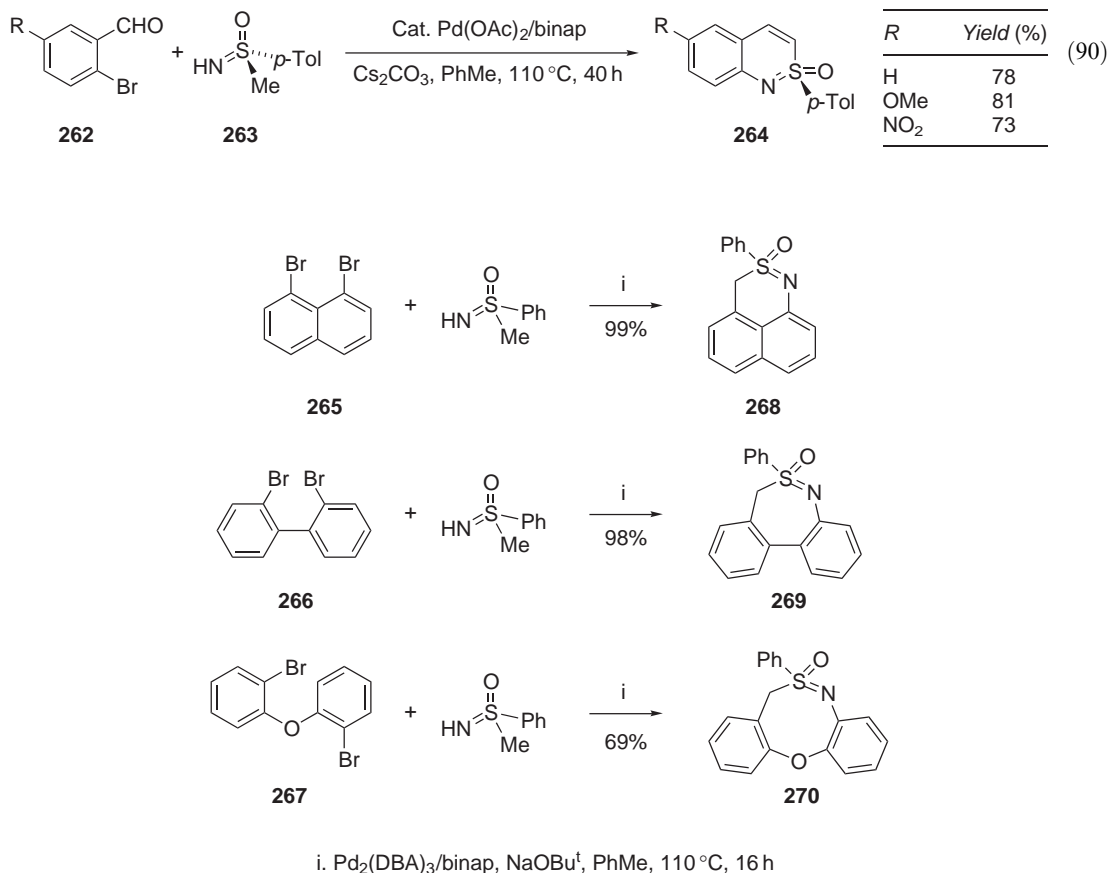
Bolm has extended this *N*-arylation methodology to aryl sulfonates (Equation (89)) <2000S911>. Thus, aryl triflates and, especially, aryl nonaflates were efficiently coupled with sulfoximines using palladium catalysis under the same conditions as aryl bromides. The less reactive aryl tosylates could also be used as coupling partners employing Ni(COD)₂/binap as catalyst affording moderate-to-good yields of *N*-arylated sulfoximines.



R ¹	R ²	Cat.	Yield (%)
4-Me	CF ₃	Pd(OAc) ₂ /binap	63
4-NO ₂	CF ₃	Pd(OAc) ₂ /binap	86
4-OMe	(CF ₂) ₃ CF ₃	Pd(OAc) ₂ /binap	97
4-Bu ^t	(CF ₂) ₃ CF ₃	Pd(OAc) ₂ /binap	76
4-Bu ^t	<i>p</i> -Tol	Ni(COD) ₂ /binap	41
4-CN	4-Bu ^t	Ni(COD) ₂ /binap	35

The intermolecular palladium-catalyzed *N*-arylation of sulfoximines can be coupled with an intramolecular ring-closure reaction to afford diverse heterocyclic systems in excellent yields. Thus, Harmata has developed a one-pot procedure for the preparation of enantiomerically pure benzothiazines **264** by palladium-catalyzed *N*-arylation of chiral sulfoximine **263** with *o*-bromobenzaldehydes **262** followed by an intramolecular condensation reaction (Equation (90))

<1999AG(E)2419>. More recently, Harmata has extended this approach to *o*-bromocinnamates although in this case the cyclization step, which is stereospecific, has to be induced in a second synthetic operation by treatment of the *N*-arylated sulfoximine with amide bases <2003JA5754>. While attempting to prepare bissulfoximines by double coupling of dibromoarenes **265–267**, Bolm reported another example of one-pot *N*-arylation of sulfoximines followed by cyclization (Scheme 91). Instead of the expected bissulfoximines, heterocycles **268–270** were obtained in very good yields. The authors have shown clear evidence that the second step is promoted by the palladium catalyst.



Scheme 91

2.15.9.6 *N*-Sulfonylamines

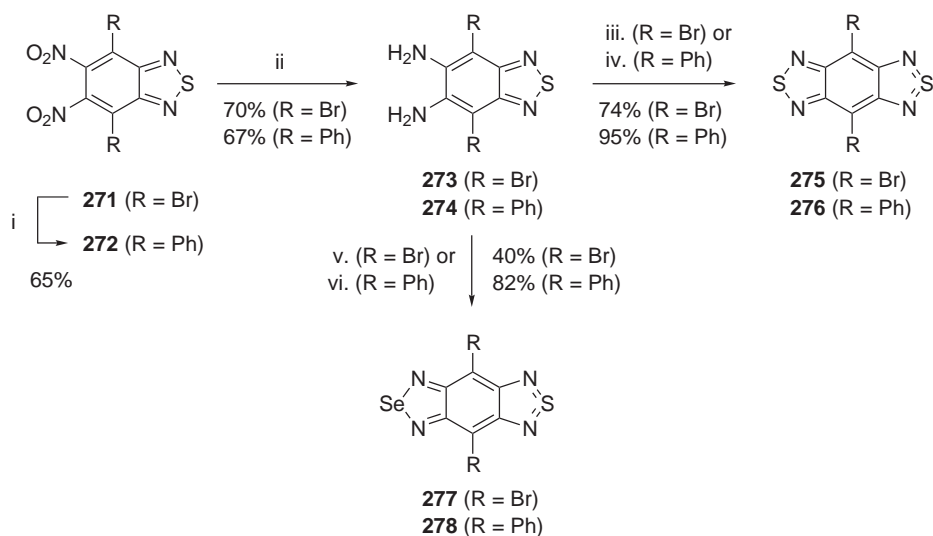
No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)737>.

2.15.9.7 Sulfurdiimides

This section is an update on all new methods for the synthesis of vinyl and aryl sulfurdiimides that have been developed since the publication of COFGT (1995) <1995COFGT(2)737>.

2.15.9.7.1 Vinyl sulfurdiimides

Yamashita has reported the preparation of nonclassical heterocycles **275–278**, with interesting optical and redox properties, starting from dibromodinitrobenzothiadiazole **271** (Scheme 92) <1994AG(E)1977, 1997T10169>. Stille coupling of dibromide **271** with phenyltributylstannane



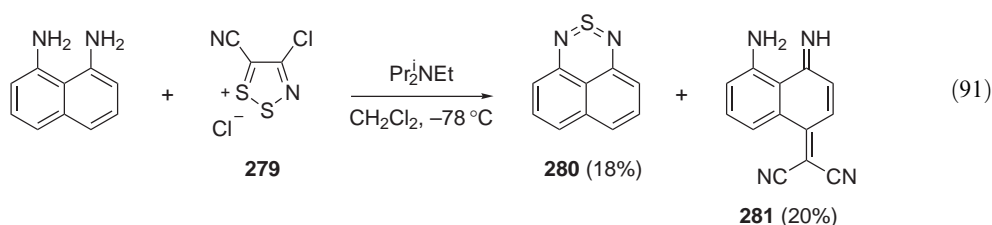
i. PhSnBu_3 , $\text{PdCl}_2(\text{PPh}_3)_2$, THF, 70°C , 4 h; ii. Fe, AcOH, 100°C , 1.5 h; iii. SOCl_2 , pyr, rt, 20 h;
 iv. PhNSO , TMSCl , pyr; v. SeO_2 , EtOH, 78°C , 24 h; vi. SeO_2 , EtOH/ H_2O , 78°C , 15 min.

Scheme 92

afforded the diarylated product **272**. Reduction of the dinitro derivatives **271** and **272** with iron dust in acetic acid gave diamines **273** and **274**, respectively. Subsequent reaction with thionyl chloride and with *N*-thionylaniline in pyridine afforded the heterocycles **275** and **276**. Alternatively, reaction of diamines **273** and **274** with selenium dioxide gave the corresponding selenium compounds **277** and **278**.

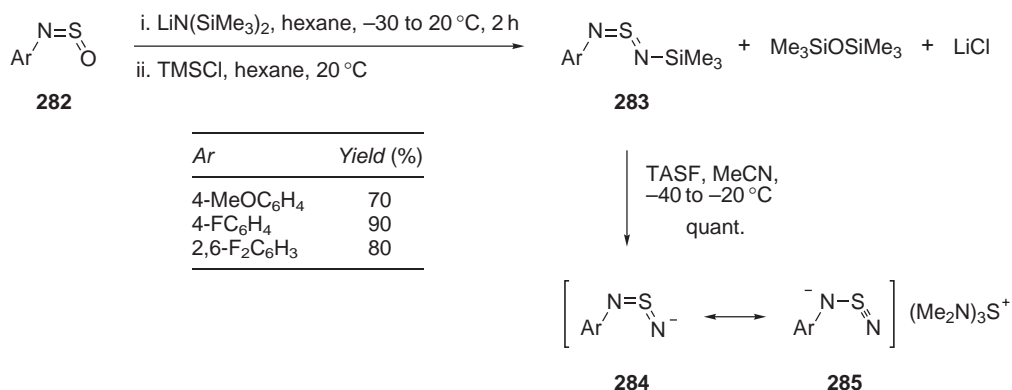
2.15.9.7.2 Aryl sulfurdiimides

Koutentis and Rees have isolated sulfurdiimide **280** in low yield by reaction of 1,8-diaminonaphthalene with 4-chloro-5-cyano-1,2,3-dithiazolium chloride **279** at low temperature (Equation (91)) <1999JCS(P1)111>. Elemental sulfur and quinomethane imine **281** are also formed in this reaction.

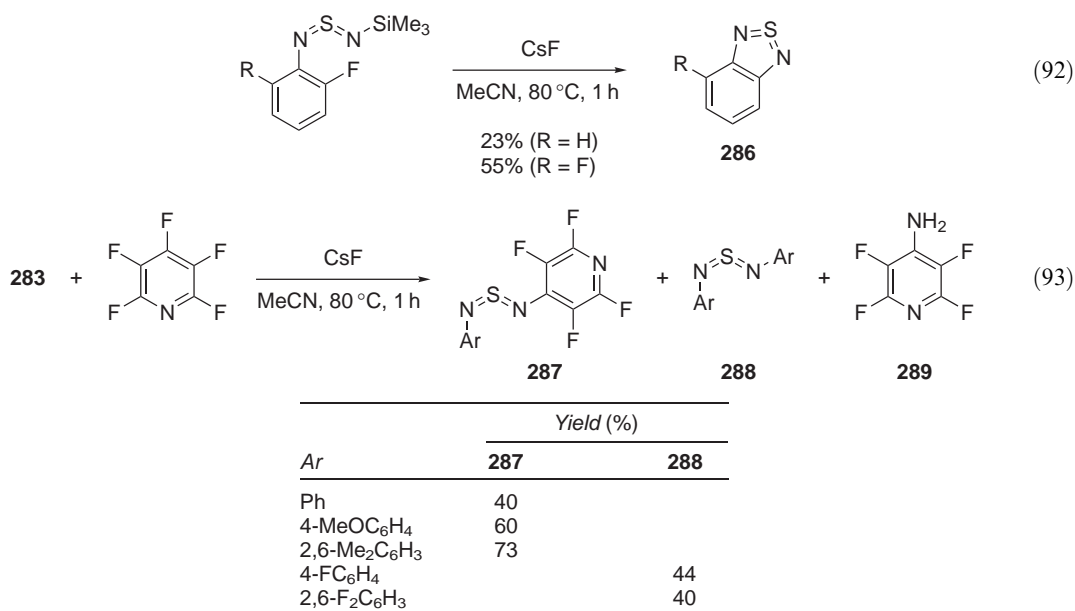


Zibarev has reported the synthesis of several acyclic and heterocyclic sulfurdiimides by both electrophilic and nucleophilic aromatic substitution reactions of *N*-aryl-*N'*-trimethylsilylsulfurdiimides **283**. The latter compounds are generally available from the corresponding thionylimides **282** and $\text{LiN}(\text{SiMe}_3)_2$, followed by reaction with TMSCl (Scheme 93) <1988ZOB465, 2001CEJ3504>. Sulfurdiimides **283** react with TASF $\{[(\text{Me}_2\text{N})_3\text{S}]^+[\text{Me}_3\text{SiF}_2]^- \}$ in acetonitrile at low temperature to give in quantitative yield the sulfurdiimide anions **284**, which are stable below -20°C and are better represented as the thiazylamide resonance form **285** according to structural and theoretical studies (Scheme 93) <1998CC991, 2001CEJ3504>. These anions suffer intramolecular nucleophilic aromatic substitution in systems with at least one *ortho* fluorine to afford 2,1,3-benzothiadiazole **286** (Equation (92)) <2001EJI2123, 2003EJI77>. Alternatively, intermolecular nucleophilic substitution takes place with some polyfluorinated arenes and heteroarenes to yield new sulfurdiimides **287** or symmetrical sulfurdiimides **288** and amine **289**, depending on the substitution pattern of the initial sulfurdiimide **283** (Equation (93)) <2001EJI2123>.

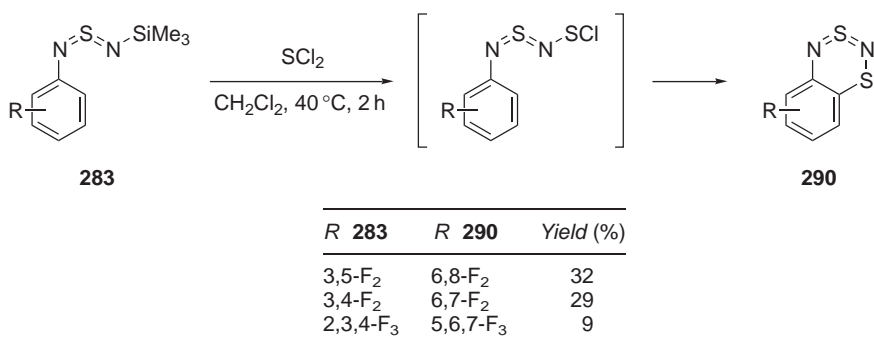
N-Adamant-1-yl-*N'*-polyfluoroaryl(heteroaryl) sulfur diimides are accessible from *N*-adamant-1-yl-*N'*-trimethylsilylsulfur diimide using a similar approach [<2002JFC165>](#). These nucleophilic aromatic substitution reactions seem to be restricted to arenes with fluorine substituents.



Scheme 93

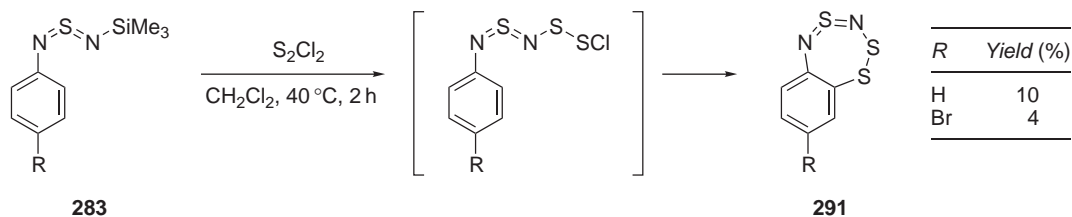


Zibarev has described improved reaction conditions for the electrophilic cyclization of sulfur diimide **283** promoted by SCl₂ to give 1,3,2,4-benzodithiadiazines **290** using substoichiometric amounts of SCl₂ (Scheme 94) [<2001HAC563, 2003EJ177>](#). This cyclization reaction has been



Scheme 94

extended to S_2Cl_2 to afford the previously unknown heterocyclic system 1,2,4,3,5-benzotrithia-diazepine **291** in very low yield (Scheme 95) <2001CC1774>.

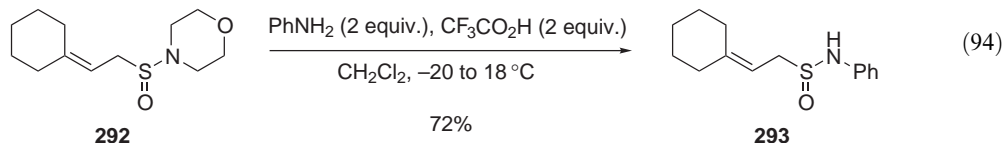


Scheme 95

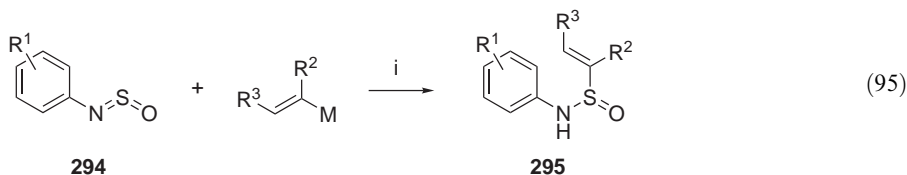
2.15.9.8 Sulfinamides

This section is an update on all new methods for the synthesis of aryl sulfinamides reported since the publication of COFGT (1995) <1995COFGT(2)737>.

Baudin and Julia have described the preparation of *N*-phenylsulfinamide **293** by a facile transamination of 4-sulfinylmorpholine **292** with aniline in the presence of TFA (Equation (94)) <1995BSF196>.



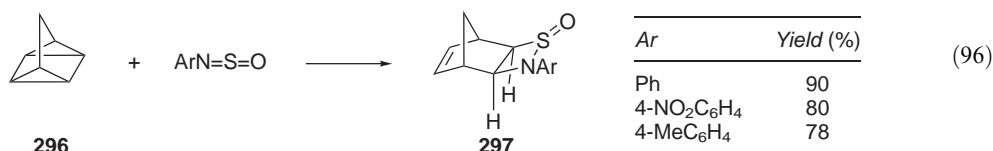
Addition of vinylic Grignard reagents or diisobutylalanes to *N*-sulfinylarenamines **294** affords substituted *N*-aryl alk-1-enesulfinamides **295**, which are useful starting materials for a new synthesis of indoles (Equation (95)) <1996BSF329>.



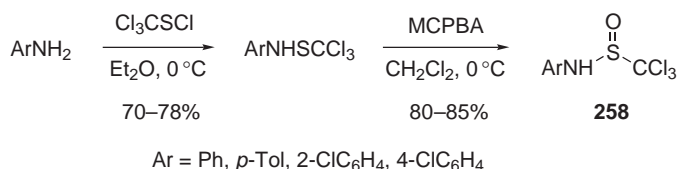
i. THF, -78°C to rt, 2 h ($M = \text{MgBr}$) or PhMe, 0°C to rt, 15 h ($M = \text{AlBu}_2^i$)

R^1	R^2	R^3	M	Yield (%)
H	H	H	MgBr	90
4-Me	H	Bu ⁿ	AlBu ₂ ⁱ	76
4-OMe	Ph	H	MgBr	93

Warrener and Amaraseka have reported the preparation of 1,2-thiazetidines-*S*-oxides **297** by cycloaddition of *N*-sulfinylarylamines with quadricyclane **296**, but the reaction conditions were not described (Equation (96)) <1997SL167>.

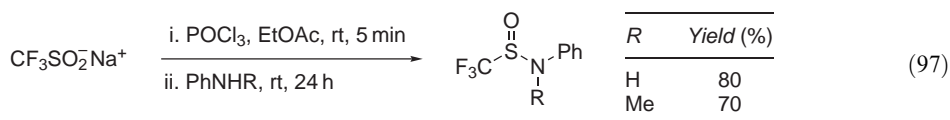


Trichloromethanesulfinamides **258** can be readily prepared from the corresponding arylamines by reaction with trichloromethanesulfonyl chloride followed by oxidation of the resultant sulfenamides with MCPBA (Scheme 96) <1997TL487>. Sulfinamides **258** suffer base-induced elimination of chloroform under mild conditions to afford *N*-sulfinylamines **259** (Equation (86)).

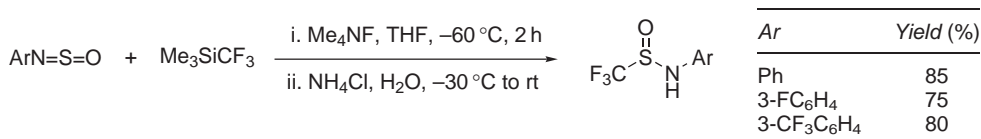


Scheme 96

Langlois has described the synthesis of trifluoromethanesulfinamides by reaction of sodium trifluoromethanesulfonate with phosphoryl chloride in EtOAc followed by addition of the corresponding amine (Equation (97)) <1999T7243>. Although the nature of the sulfinylating agent is not known, the best yields were obtained when the $\text{CF}_3\text{SONa}/\text{POCl}_3/\text{RNH}_2$ ratio was 2:1:1.

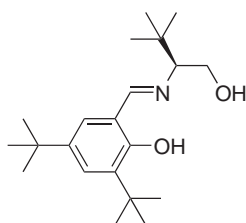
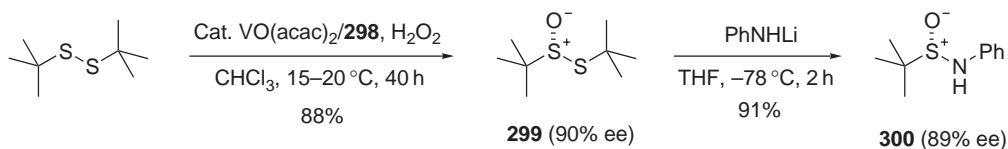


In an alternative approach, Yagulpolskii has reported a high-yield synthesis of perfluoroalkyl-sulfinamides by perfluoroalkylation of *N*-sulfinylamines with trimethyl(perfluoroalkyl)silanes in the presence of fluoride ions (Scheme 97) <2002TL3029>.



Scheme 97

Ellman has developed a method for the preparation of enantiomerically pure *t*-butanesulfinamides **300** (Scheme 98) <1998JA8011>. Thus, catalytic asymmetric oxidation of *t*-butyl disulfide with H_2O_2 catalyzed by $\text{VO}(\text{acac})_2$ and the chiral Schiff base **298**, affords *t*-butyl *t*-butathiosulfinate **299** with 91% enantiomeric excess in high yields on up to molar scale. Thiosulfinate **299** reacts readily and stereospecifically with a range of *C*- and *N*-nucleophiles to provide enantiomerically pure chiral sulfoxides, sulfinamides, and sulfinimines in good yield.



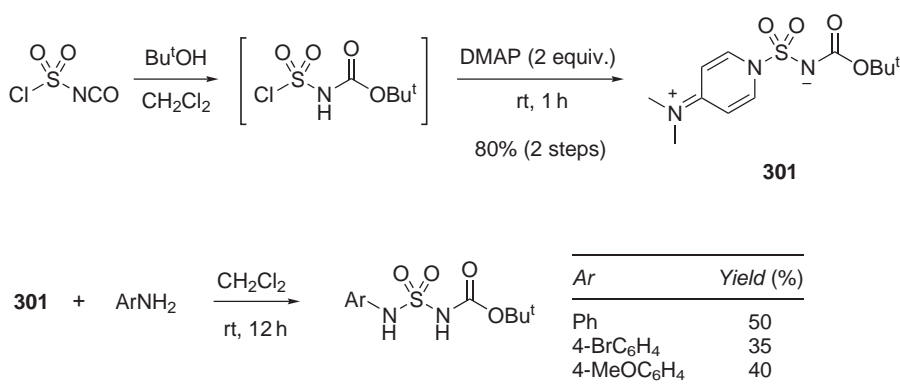
298

Scheme 98

2.15.9.9 Sulfamides

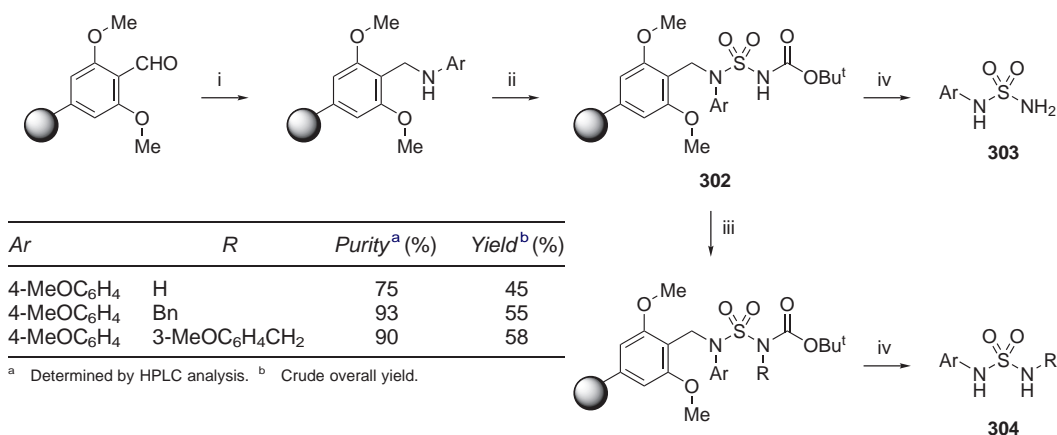
This section is an update on all new methods for the synthesis of aryl sulfamides that have been developed since the publication of COFGT (1995) <1995COFGT(2)737>. The applications of sulfamides to the synthesis of heterocyclic compounds have been reviewed <2000RCR221>.

Winum and Montero have reported the preparation of the new sulfamoylating reagent **301**, which is a crystalline colorless solid, nonmoisture sensitive, and stable at room temperature (Scheme 99) <2001OL2241>. Compound **301** reacts with primary and secondary alkylamines under very mild conditions to afford sulfamides in good yield. However, yields with arylamines are only moderate due to their low nucleophilicity and no improvement is observed under thermal conditions.



Scheme 99

Esteve and Vidal have applied this reagent **301** to solid-phase synthesis of sulfonamides (Scheme 100) <2002TL1019>. Thus, sulfamoylation of resin-bound (crosslinked polystyrene) amines affords bound *t*-BOC-protected sulfamides **302** that can be subsequently *N*-alkylated under Mitsunobu conditions. Simultaneous deprotection and cleavage of the products provides unsymmetrically substituted sulfamides **303–304**.

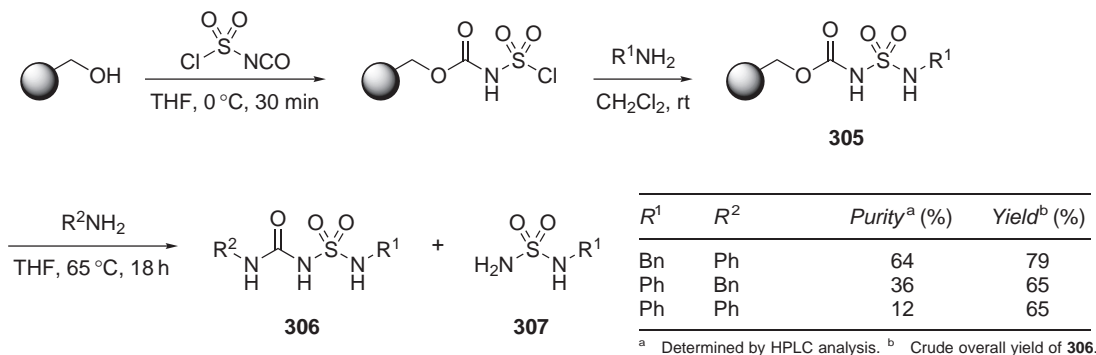


^a Determined by HPLC analysis. ^b Crude overall yield.

i. ArNH₂, NaBH₃CN, DMF/MeOH (8:2), rt, 18 h; ii. **301**, CH₂Cl₂, rt, 18 h; iii. 6 equiv. ROH/Bu₃P/1,1'-(azodicarbonyl)dipiperidine, DMF, rt, 18 h; iv. TFA/CHCl₃/H₂O (50:50:1).

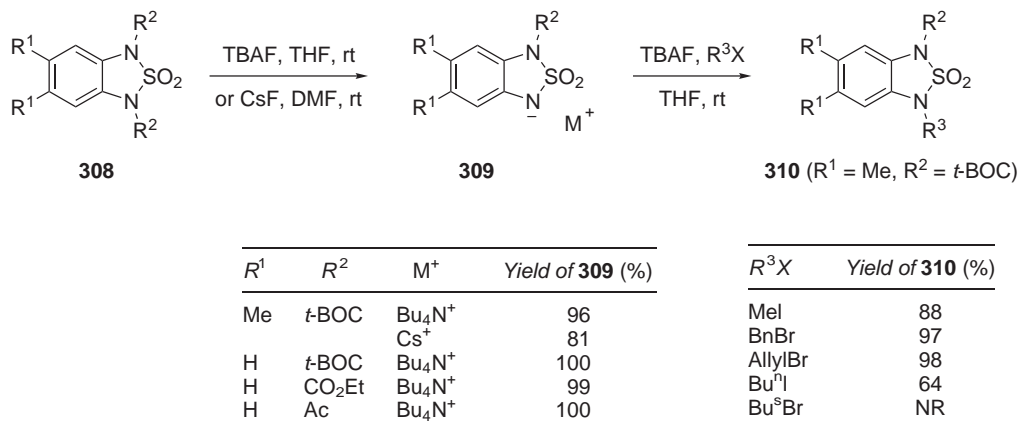
Scheme 100

In an approach to solid-phase synthesis of sulfonamides, Fitzpatrick and Rivero reacted Wang resin with chlorosulfonyl isocyanate followed by reaction with an amine to provide resin-bound aminosulfonyl carbamates **305** (Scheme 101) <1997TL7479>. Heating of carbamates **305** in THF with a second amine gives aminosulfonyl ureas **306** together with the corresponding sulfamide **307** as a minor impurity.



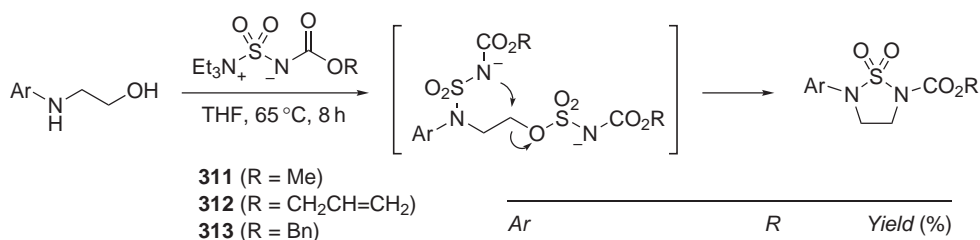
Scheme 101

Rebek has described a mild and efficient method for the selective monodeprotection of symmetric *N,N'*-diacylated aromatic sulfamides **308** using TBAF in THF or CsF in DMF at room temperature (Scheme 102) <2001OL4247>. The reaction seems to be general and is high yielding. The resultant highly stable anionic products **309** are excellent substrates for a variety of alkylation conditions and the monodeprotection and *N*-alkylation steps can be performed as a one-pot reaction to afford the monoalkylated products **310** in good yield with the exception of secondary alkyl halides that provided only traces of product.

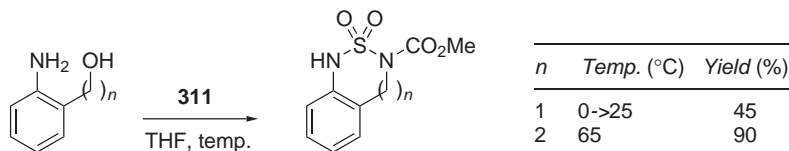


Scheme 102

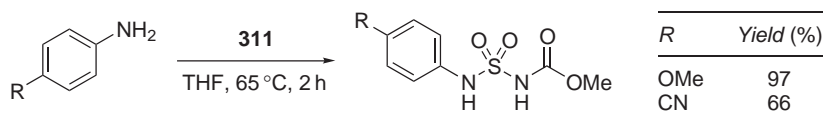
Nicolaou has reported a practical and high-yielding method for the one-step synthesis of nonsymmetrical cyclic sulfamides by reaction of 1,2-, 1,3- and 1,4-aminoalcohols with Burgess reagent **311** and related compounds **312**, **313**, having a similar zwitterionic structure as reagent **301** (Scheme 103) <2002AG(E)3866>. Subsequent deprotection using conventional procedures and/or substitution with appropriate electrophiles provides a general and efficient synthesis of diversely substituted cyclic sulfamides. Burgess reagent reacts smoothly with all types of amines, including arylamines, to afford nonsymmetrical linear sulfamides in excellent yields (Equation (98)) <2002AG(E)3866>.



Ar	R	Yield (%)
Ph	Me	92
Ph	CH ₂ CH=CH ₂	75
4-NO ₂ C ₆ H ₄	Me	82
3,4,5-(MeO) ₃ C ₆ H ₂	Me	69

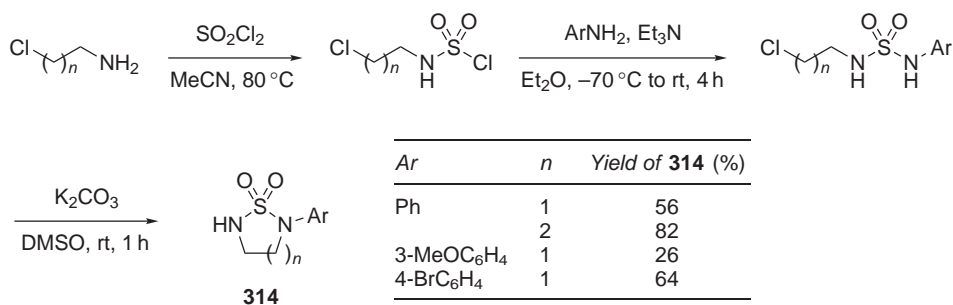


Scheme 103



(98)

Johnson has described an alternative approach to cyclic sulfamides **314** by reacting chloroalkylamines with sulfuryl chloride followed by addition of a primary aryl(alkyl)amine and subsequent ring closure upon treatment with K₂CO₃ in DMSO (Scheme 104) <2003TL5483>.

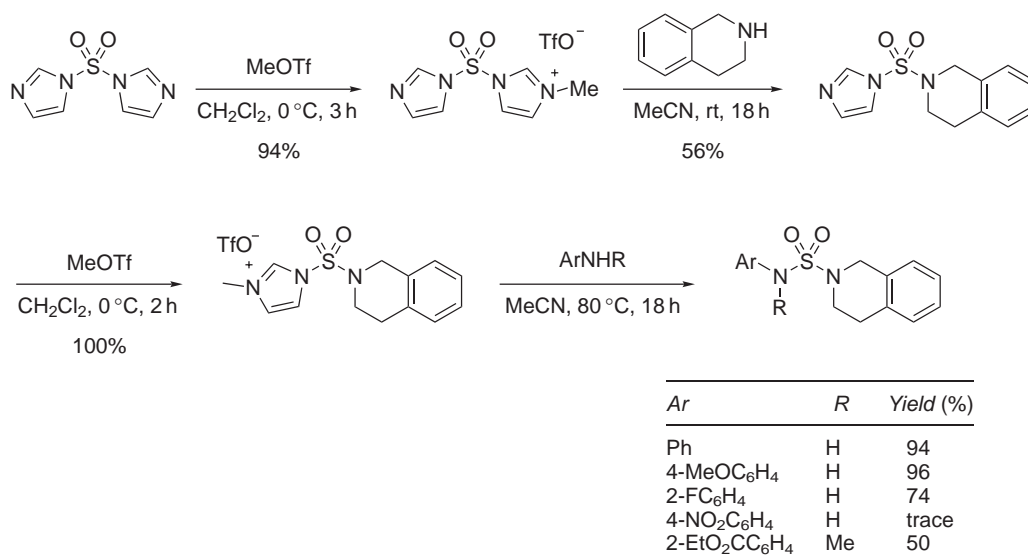


Scheme 104

Beaudoin has recently developed another approach to nonsymmetrical sulfamides using *N,N'*-sulfuryldiimidazole, which can be sequentially activated by alkylation with methyl triflate followed by nucleophilic displacement with a variety of alkyl- and arylamines (Scheme 105) <2003JOC115>.

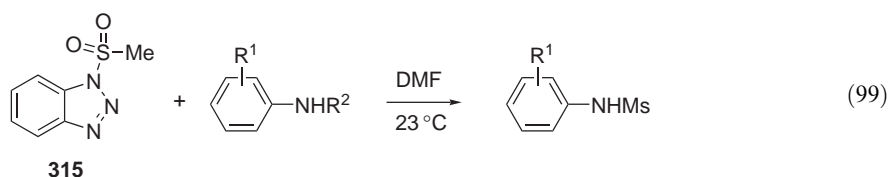
2.15.9.10 Sulfonamides

This section is an update on all new methods for the synthesis of aryl sulfonamides reported since the publication of COFGT (1995) <1995COFGT(2)737>.



Scheme 105

Kim has described the use of 1*H*-benzotriazol-1-yl methanesulfonate **315** for the selective mesylation of primary alkyl- or arylamino groups in the presence of hydroxyl and secondary amino groups (Equation (99)) <1999TL117>. The reagent is highly sensitive to steric and electronic properties of the amine.



<i>R</i> ¹	<i>R</i> ²	Time (h)	Yield (%)
H	H	22	85
4-MeOC ₆ H ₄	H	2	81
4-NO ₂ C ₆ H ₄	H	48	85 ^a
H	Me	120	83 ^a

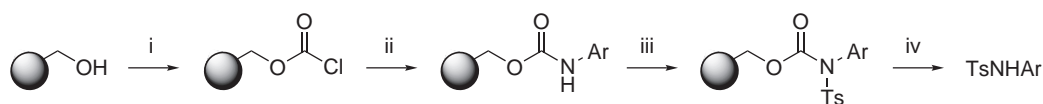
^a Yield of recovered starting amine.

Several methods have been developed for the solid phase synthesis of sulfonamides some of which include examples of *N*-aryl derivatives. Thus, Raju and Kogan use a Wang polystyrene resin to anchor amines through a carbamate linker. Deprotonation of the carbamate with NaH in DMA followed by addition of a sulfonyl chloride afforded the resin-bound sulfonamide that was released from the resin by basic hydrolysis (Scheme 106) <1997TL3373>. Fivush and Willson have described a related approach using AMEBA polystyrene resin, an acid sensitive solid support that contains a resin-bound *o*-methoxybenzaldehyde that allows the attachment of amines by reductive amination <1997TL7151>.

Sulfonamides can be *N*-arylated in solution in the presence of copper promoters or catalysts using a variety of reagents that include triarylbismuth <1996TL9013>, aryllead triacetates <1996JOC5865>, phenylboronic acids <1998TL2933> and aryl halides <2003TL3385> (Scheme 107). More recently, Combs and Rafalski have extended the *N*-arylation of sulfonamides to solid phase using arylboronic acids <2000JCO29>.

2.15.9.11 Aromatic Nitrosamines

This section is an update on all new methods for the synthesis of aromatic nitrosamines reported since the publication of COFGT (1995) <1995COFGT(2)737>.

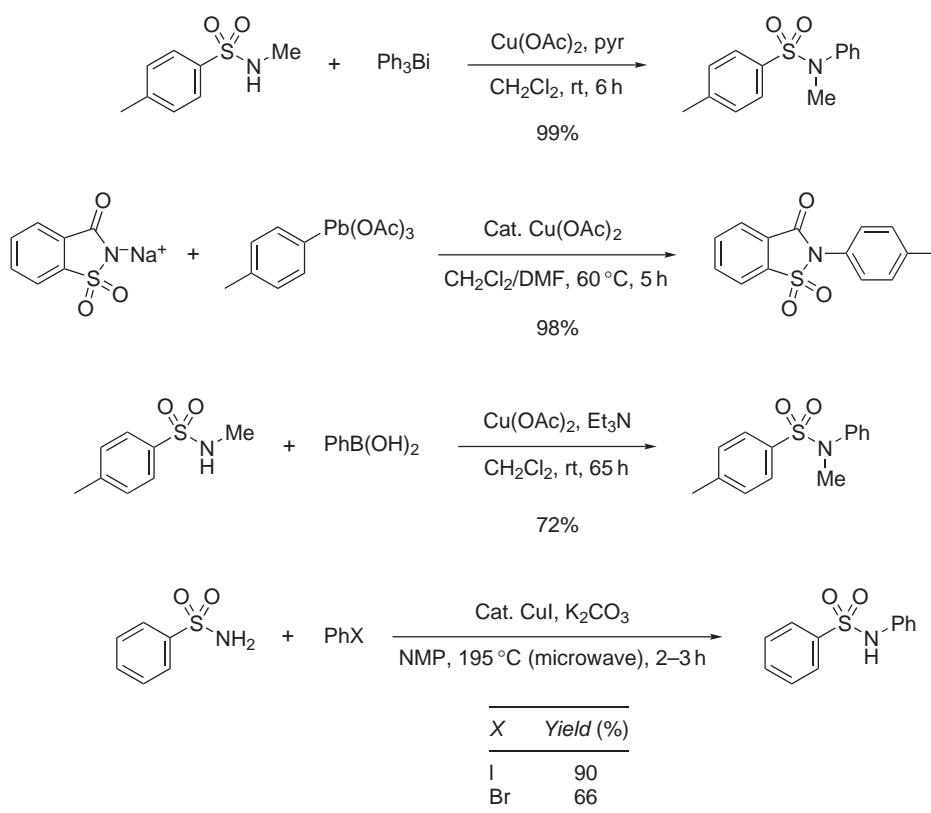


i. COCl_2 , PhMe/THF, rt, 8 h; ii. ArNH_2 , Pr_2NEt , THF, rt 8 h; iii. NaH, DMA, rt, 8 h, then TsCl; iv. LiOH, THF/ H_2O , rt, 54 h.

Ar	Purity ^a (%)	Yield ^b (%)
Ph	96	63
2-MeOC ₆ H ₄	88	48
4-NO ₂ C ₆ H ₄	50	45

^a Determined by HPLC analysis. ^b Crude overall yield.

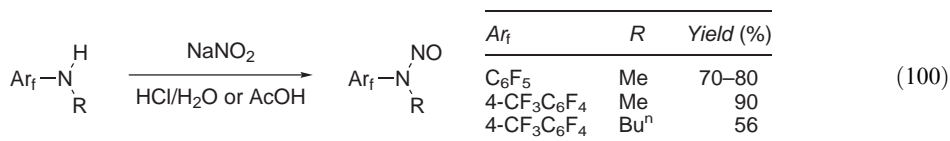
Scheme 106



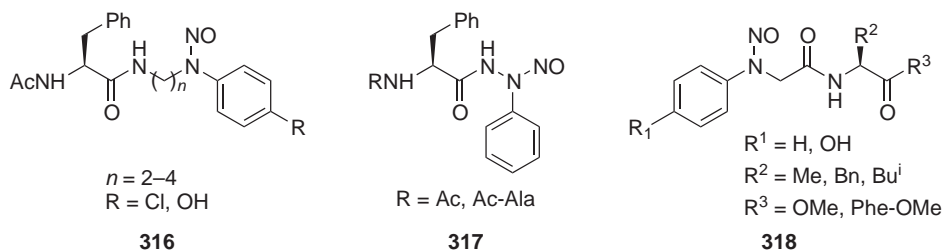
Scheme 107

Zolfigol has described several new procedures for the preparation of nitrosamines by selective *N*-nitrosation of dialkyl- or diarylamines with sodium nitrite in the presence of oxalic acid <1999SC905>, $\text{Mg}(\text{HSO}_4)_2$ or NaHSO_4 <2000SC2057>, periodic acid and wet silica <2001SC359>, KHSO_5 and wet silica <2001SC1161>, silica chloride (obtained by treating silica with thionyl chloride) <2002SC1809>, and silica sulfuric acid (obtained by treating silica with chlorosulfonic acid). The reactions are performed in dichloromethane at room temperature and yields for nitrosation of diarylamines are usually quantitative.

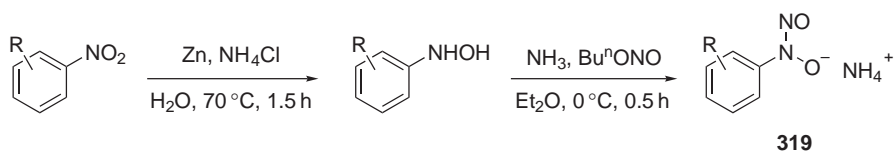
Platonov has reported the nitrosation of *N*-alkylperfluoroarylamines with nitrous acid to afford the corresponding nitrosamines (Equation (100)) <2002JFC(114)55>.



Wang has described the preparation of a series of peptidyl *N*-nitrosoanilines **316–318**, as examples of a novel class of cysteine protease inactivators, using standard *N*-nitrosation procedures [<1998JA3726>](#).



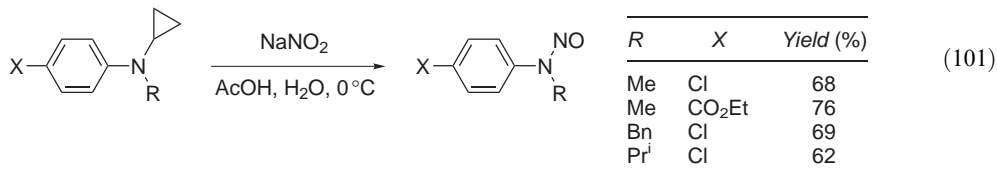
Balaban has reported the preparation of a series of novel *N*-nitroso-*N*-phenylhydroxylamines (cupferron) derivatives **319** as potential nitric oxide donors using a procedure that consists of the reduction of a nitroarene to the corresponding hydroxylamine derivative followed by *N*-nitrosation with an alkyl nitrite (Scheme 108) [<1998OPP439>](#).



R	Overall yield (%)
H	81
2-MeOC ₆ H ₄	25
4-ClC ₆ H ₄	84

Scheme 108

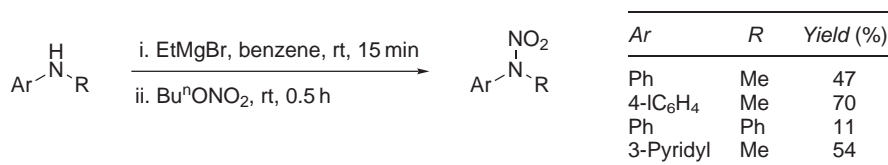
Loeppky and Elomary have studied the nitrosation of *N*-alkyl-*N*-cyclopropylaniline with nitrous acid in aqueous acetic acid. The compounds examined reacted rapidly to produce the corresponding *N*-alkyl-*N*-nitrosoanilines by cleavage of the cyclopropyl group from the nitrogen, independently of the nature of the alkyl substituent (Equation (101)) [<1998JA5193, 2000JOC96>](#). To explain these results, the authors propose a mechanistic hypothesis involving the formation of an amine radical cation.



2.15.9.12 Aromatic Nitramines

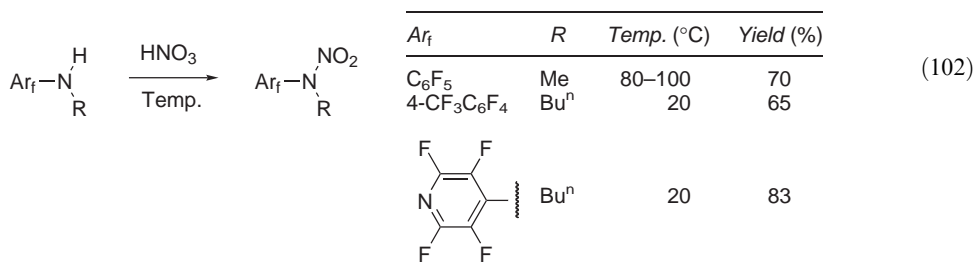
This section is an update on all new methods for the synthesis of aromatic nitramines that have been developed since the publication of COFGT (1995) [<1995COFGT\(2\)737>](#).

Secondary arylamines can be easily converted into the corresponding nitramines by reaction of *n*-butyl nitrate with the magnesium bromide salt of the starting amine (Scheme 109) <1994OPP337, 2000ZOR410>.



Scheme 109

N-Alkylperfluoroarylamines are readily transformed into the corresponding nitramines in good yield by reaction with nitric acid (Equation (102)) <2001JFC(109)131>.



2.15.9.13 Diazonium Salts

This section is an update on all new methods for the synthesis of vinyl and aryl diazonium salts that have been developed since the publication of COFGT (1995) <1995COFGT(2)737>. The chemistry of diazonium ions, one of the most versatile functional groups in organic chemistry, has been reviewed <B-1978MI247, B-1994MI005>.

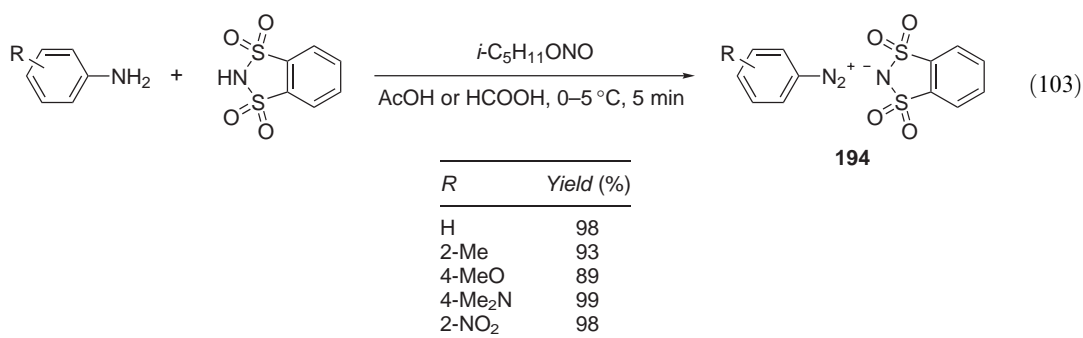
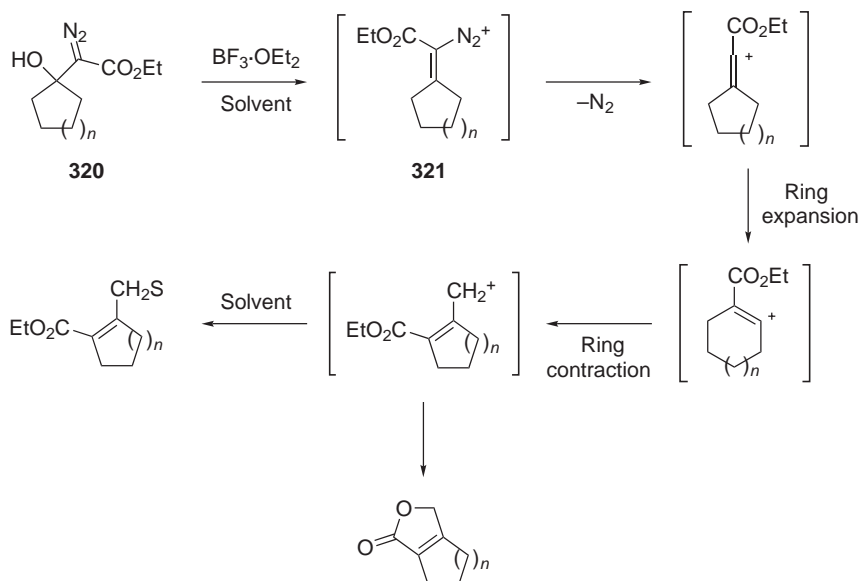
2.15.9.13.1 Alkenyl (vinyl) diazonium salts

Akenyl diazonium salts **321** have been proposed as intermediates in the reaction of α -diazo- β -hydroxy esters **320** with boron trifluoride etherate to afford an array of products through a carbocation reaction cascade, depending on the structure of the starting esters and the solvent (Scheme 110) <1996JA1>.

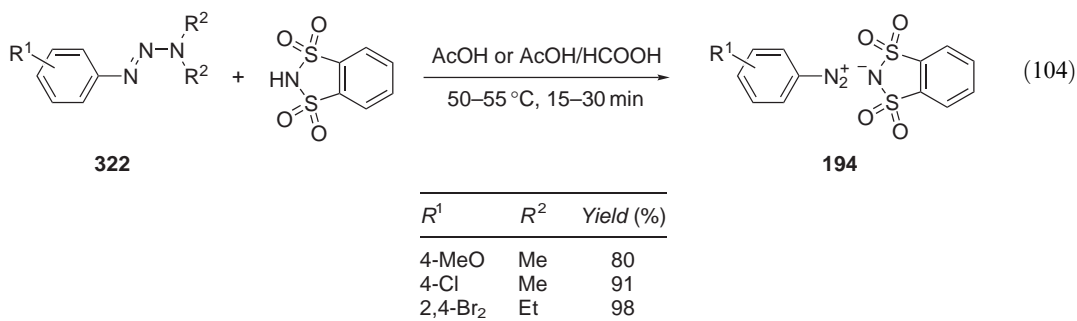
2.15.9.13.2 Aromatic diazonium salts

Aromatic diazonium ions participate in a number of important reactions, such as the Sandmeyer, Schiemann, Meerwein, Pschorr and Gomberg–Bachmann reactions, the formation of azo and triazine compounds (see Sections 2.15.8.2.2 and 2.15.8.4) and, more recently, the Heck reaction <2000CRV3009>.

Arene diazonium *o*-benzenedisulfonimides **194** (see Sections 2.15.8.2.2 and 2.15.8.4) are unusually stable in the dry state and can be readily obtained by diazotization of aromatic amines with isoamyl nitrite and *o*-benzenedisulfonimide in glacial acetic acid or formic acid at 0–5 °C (Equation (103)) <1998S1171>.



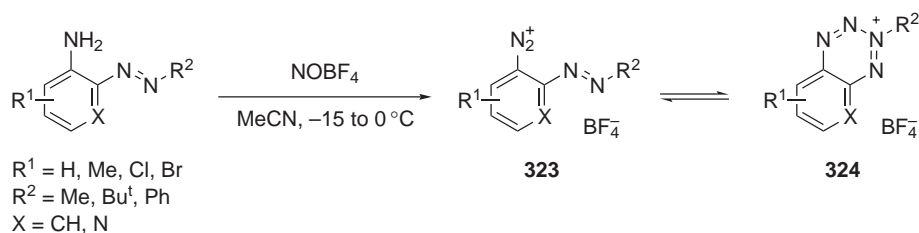
Arenediazonium salts **194** can also be prepared by treatment of 1-aryl-3,3-dialkyltriazenes **322** with a twofold excess of *o*-benzenedisulfonimide in glacial acetic acid or acetic acid-formic acid at 50–55 °C for 15–30 min (Equation (104)) <2001S2180>. On cooling the reaction mixture to 20 °C, compounds **194** precipitate and can be isolated in very high yield by filtration. In this context, triazenes **322** can be considered as a protected form of the diazonium group.



Colas and Goeldner have described a very mild procedure for the synthesis of crystalline arenediazonium trifluoroacetates under anhydrous conditions by diazotization of arylamines with isoamyl nitrite and TFA in CH₂Cl₂ or CH₂Cl₂/MeCN <1999EJO1357>. The products can be isolated in very high yields after precipitation with diethyl ether at low temperature. These diazonium salts are much more soluble in organic solvents than their tetrafluoroborate counterparts and have proved to be very efficient partners in several Pd-catalyzed Heck-type reactions.

Zhang has reported several procedures for the preparation of arenediazonium nitrates under anhydrous conditions by reaction of arylamines or arylureas with adducts of NO_2 with dioxane <2001OPP305, 2001SC329>, DMF <2001SC1243>, PEG <2002IJCB1531> and tributyl phosphate <2001MI101>. Arenediazonium nitrates and chlorides can be prepared in quantitative yield in the solid state by reaction of crystalline anilines with gaseous NO_2 or NOCl , respectively <1997JPR(339)256, 2002CEJ1395, 2003EJO1545>.

The diazotization of anilines bearing an *ortho*-alkylazo group results in formation of the benzenediazonium salts **323**, which exist in equilibrium with the 2-alkyl-1,2,3,4-benzotetrazinium salt cyclic isomers **324** (Scheme 111) <2002EJO3821>. This equilibrium is fast on the NMR timescale and only one set of signals is observed, even at low temperatures. The isomer ratio can be calculated from the observed averaged chemical shift values of representative NMR signals of the equilibrium mixture of isomers **323** and **324** and those corresponding to the pure cyclic and acyclic isomers measured in compounds that exist in a single isomeric form.

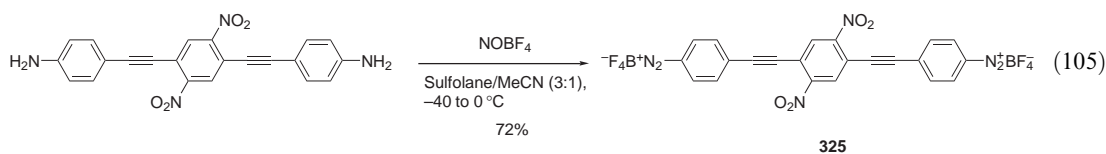


X	R ¹	R ²	Yield (%)	323/324 ratio ^a
CH	H	Bu ^t	93	30/70
CH	4-Br	Bu ^t	80	55/45
CH	H	Ph	61	5/95 ^b
CH	4,6-Br ₂	Bu ^t	80	0/100
N	H	Bu ^t	80	100/0

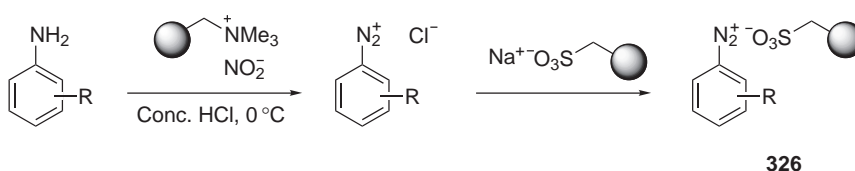
^a Obtained from ¹H NMR studies in $(\text{CD}_3)_2\text{CO}$ solution at 297 K. ^b At 273 K.

Scheme 111

Kosynkin and Tour have described the preparation of a series of phenylene ethynylene diazonium salts, e.g., **325**, for use in molecular electronic devices by reaction of the corresponding anilines with NOBF_4 in sulfolane–acetonitrile solvent (Equation (105)) <2001OL993>. Unlike acetonitrile alone, the sulfolane–acetonitrile system afforded good yields.



Arenediazonium salts have been prepared immobilized on solid supports using either covalent or ionic attachment. Covalently immobilized arenediazonium tetrafluoroborates have been obtained by reacting resin-supported anilines with isoamyl nitrite and $\text{BF}_3 \cdot \text{OEt}_2$ in dichloromethane at low temperature (see Section 2.15.8.4, Scheme 60) <1996JOC8160, 1999TL2105, 2000AG(E)3681, 2002BMCL1845, 2002TL9717>. Ionically immobilized diazonium salts **326** have been prepared using macroporous polystyrene ion-exchange resins and have subsequently been used in the synthesis of azo dye libraries (Scheme 112) <2002CC140>. Macroporous



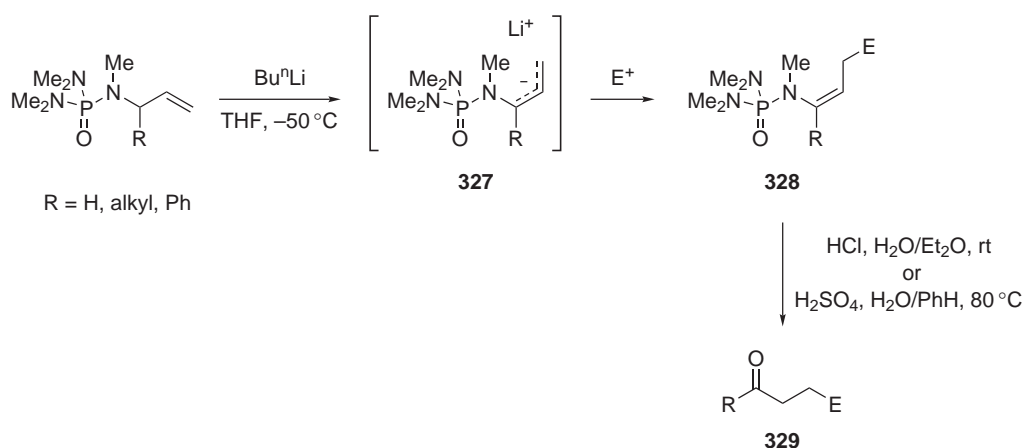
Scheme 112

polystyrene ion-exchange resin Amberlyst A-15 was employed as support, allowing the use of aqueous based chemistry. The free diazonium salt was first generated in solution using a polymer-supported nitrite and subsequent ion-exchange with excess Amberlyst A-15 afforded the resin-supported diazonium salt <2000GC43>.

2.15.10 N–P FUNCTIONS

This section is an update on all new methods for the synthesis of vinyl and aryl compounds containing an N–P function reported since the publication of COFGT (1995) <1995COFGT(2)737>.

Lithiation of (1-alkyl-2-propenyl)- or (1-phenyl-2-propenyl)-pentamethyl phosphoric triamides gives ambident anions **327** that undergo regioselective γ -reaction with various electrophiles, such as alkyl halides, aldehydes and dialkyl disulfides, to afford enephosphoramides **328** in good yields and with high *Z*-stereoselectivity (Scheme 113) <1994TL8381, 1999JOM(586)208, 2003T2101>. Acid hydrolysis of the adducts releases the corresponding carbonyl compound **329**. Thus, these anions can be used as new aldehyde or ketone homoenolate equivalents.

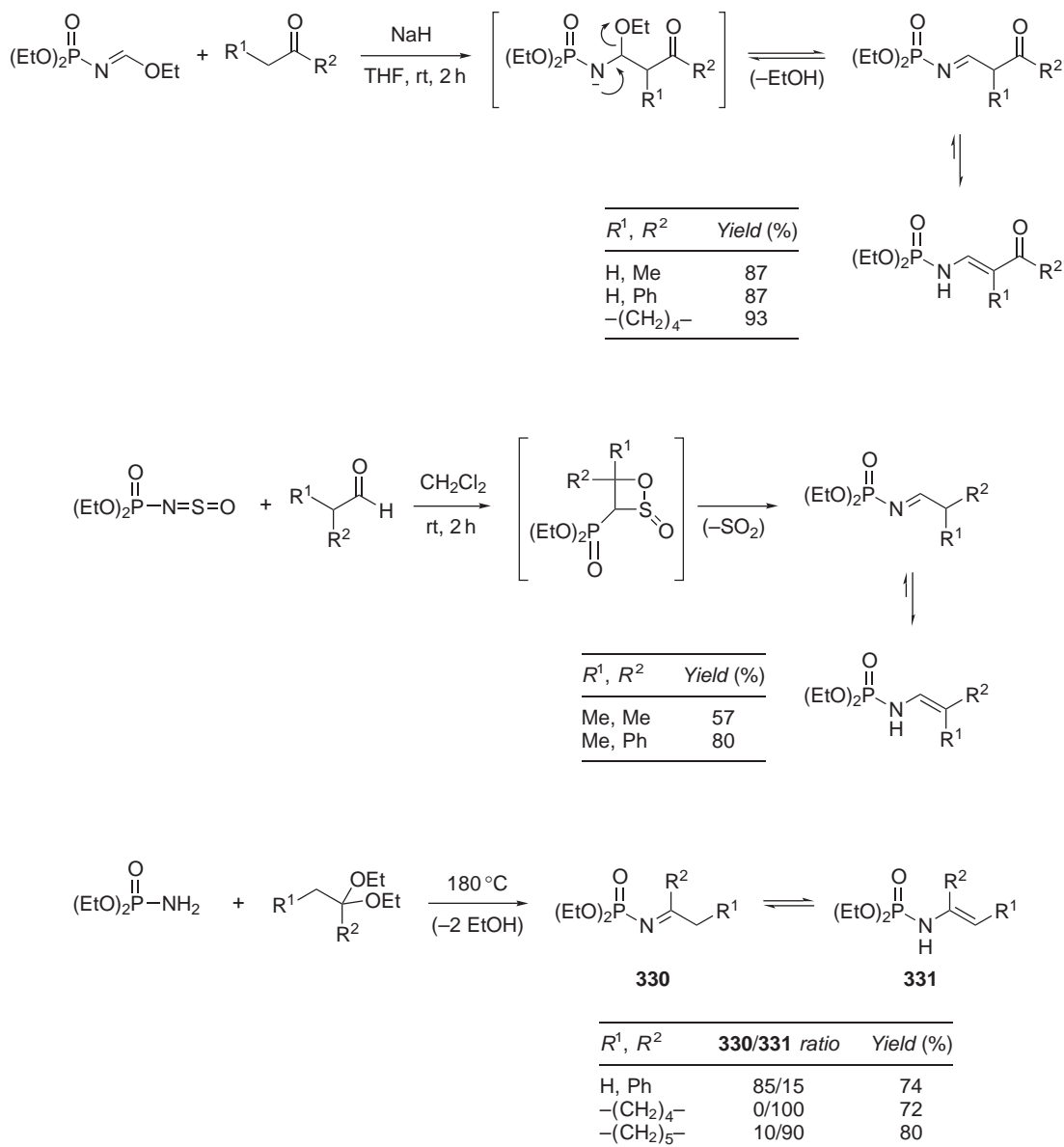


R	E ⁺	E	Yield (%)	
			328 (<i>E/Z</i> ratio)	329
H			98 (78/22)	87
Me	Mel	Me	100 (88/12)	87
Me	MeSSMe	MeS	64	51
Me	Pr ⁱ CHO	Pr ⁱ CHOH	75 (100/0)	
Pr	C ₅ H ₁₁ I	C ₅ H ₁₁	100 (100/0)	90
Ph	MeOCH ₂ Cl	MeOCH ₂	74 (100/0)	61

Scheme 113

Zwierzak has described three different routes to diethyl 1-alkenylphosphoramidates: (i) the aza-Claisen condensation of ethyl *N*-(diethoxyphosphoryl)formimidate with enolizable ketones, (ii) the reaction between diethyl *N*-sulfinylphosphoramidate and aliphatic aldehydes, and (iii) the reaction of diethyl phosphoramidate with ketone diethyl acetals under thermal conditions (Scheme 114) <2000T6299>. The products exist exclusively as the enamide tautomer **331**, with a few exceptions in which the imine tautomer **330** is also present in variable amounts.

Trimethoxy(1-phenylvinylimino)phosphorane **332** (X = OMe) and methoxydiphenyl(1-phenylvinylimino)phosphorane **332** (X = Ph) react with electron-deficient acetylenes to afford stable 1,2λ⁵-azaphosphinines **333** via a formal (stepwise) [4 + 2]-cycloaddition reaction, while trimethoxy(vinylimino)phosphorane **334** reacts with DMAD via a formal [2 + 2]-cycloaddition reaction to give functionalized butadienes **335** (Scheme 115) <1998H(48)1903>.



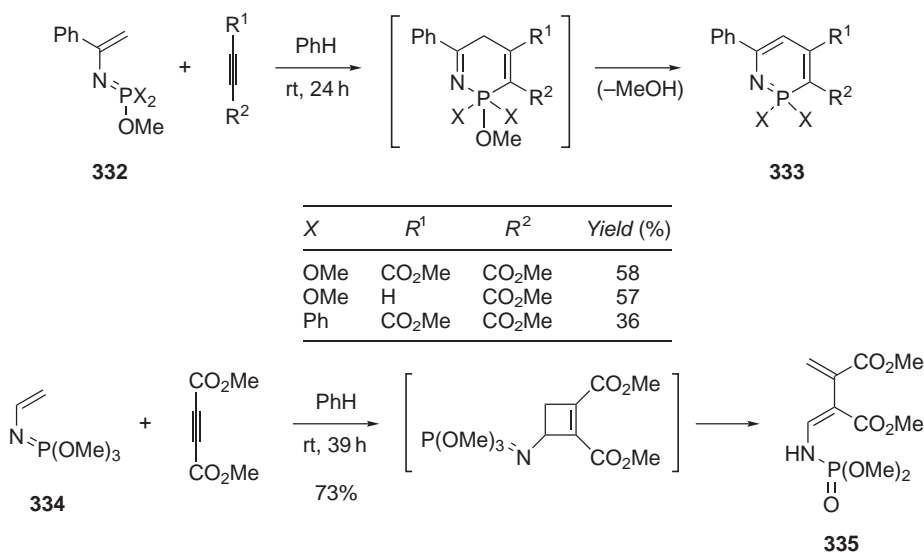
Scheme 114

The reaction of hexachlorocyclodiphosphazene **336** with primary arylamines affords bisphosphoranimine hydrochlorides **337**, which yield highly basic bisphosphoranimines **338** upon treatment with methanolic KOH (Scheme 116) <1994JCS(D)847>.

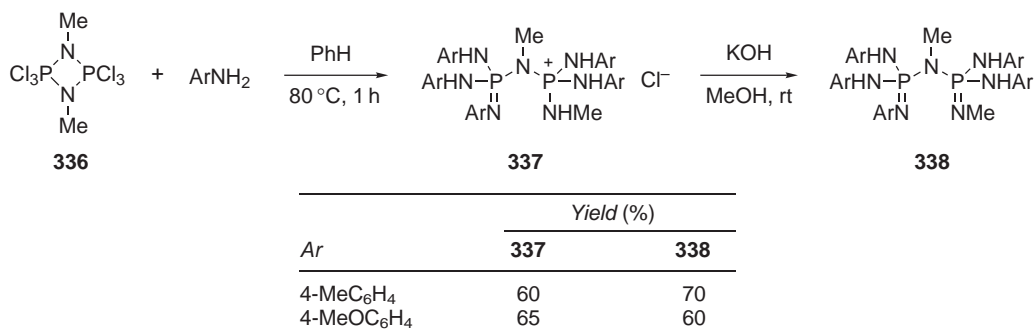
Wan and Modro have described the preparation of monocyclic **340** and bicyclic phosphoric triamides **341** by sequential cyclization of *N*-bis(2-chloroethyl)phosphoric triamides **339** (Scheme 117) <1996S1227>. Bicyclic phosphoric triamides **341** can be readily hydrolyzed under acidic conditions to provide bis(2-arylaminoethyl)amines in good yield <2000S1315>.

Iminophosphanes **343** can be prepared by *P*-alkylation of readily available *N,P,P*-trisubstituted aminophosphanes **342** with reactive alkyl halides and subsequent base-promoted dehydrohalogenation (Scheme 118) <2003SL801>.

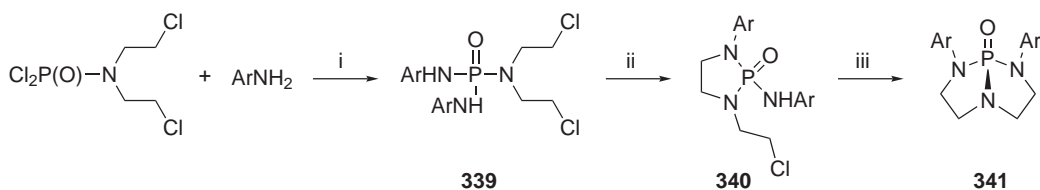
Niecke has described the synthesis and structure of the first imido(imino)phosphorane **346** and its isoelectronic oxygen derivative **348** (Scheme 119) <1995AG(E)460>. Thus, treatment of iminophosphoranes **344** with trimethylsilyl azide in the presence of one equiv. of MeOH affords the amino(azido)phosphanes **345**, which decomposes above 40°C with elimination of nitrogen followed by a 1,3-H shift to give the phosphoranes **346**. Thermal decomposition of products **346** gives the isomeric products **347** in quantitative yield via CH activation of an *ortho* *t*-butyl group



Scheme 115



Scheme 116



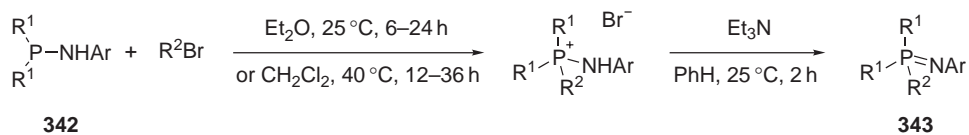
i. Et₃N, CH₂Cl₂, -20 °C to rt, 121 h; ii. NaOMe, MeOH, 0-5 °C to rt, 24 h; iii. NaH, Bu₄NBr, PhH, rt, 6 h.

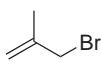
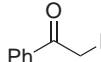
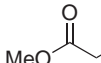
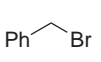
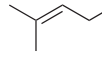
Ar	Yield (%)		
	339	340	341
Ph	74	95	90
4-MeOC ₆ H ₄	60	95	92

Scheme 117

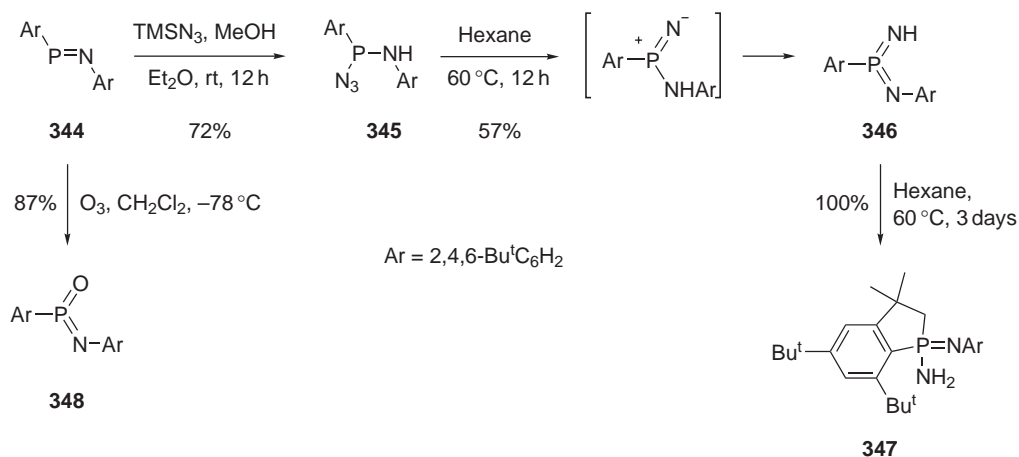
by the highly electrophilic *P*. The oxygen analogues **348** can be obtained by ozonization of the iminophosphoranes **344**.

A straightforward synthesis of highly stable phosphiranes **352** has been reported by Grützma-cher (Scheme 120) <1999AG(E)1623>. Starting from dibenzoannelated tropolone **349**, the amines **350** can be obtained which upon lithiation and subsequent reaction with PCl₃ afford

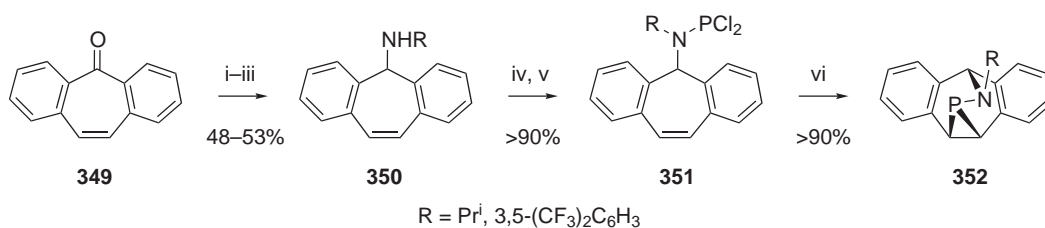


Ar	R ¹	R ²	Yield (%)	
			342	343
4-MeC ₆ H ₄	Ph		74	92
4-MeC ₆ H ₄	Ph		78	94
4-MeC ₆ H ₄	Ph		81	89
4-MeC ₆ H ₄	Pr ⁱ		81	92
Bn	Ph		83	90

Scheme 118



Scheme 119

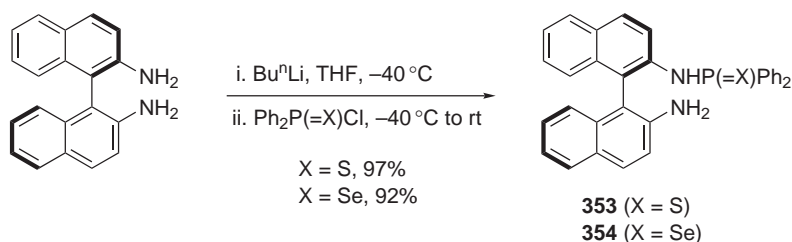


i. NaBH₄, MeOH; ii. SOCl₂, Δ, 3 h; iii. RNH₂, PhMe, rt; iv. BuⁿLi, Et₂O, -30 °C to rt; v. PCl₃, Et₂O, -20 °C; vi. Mg, PhMe, rt.

Scheme 120

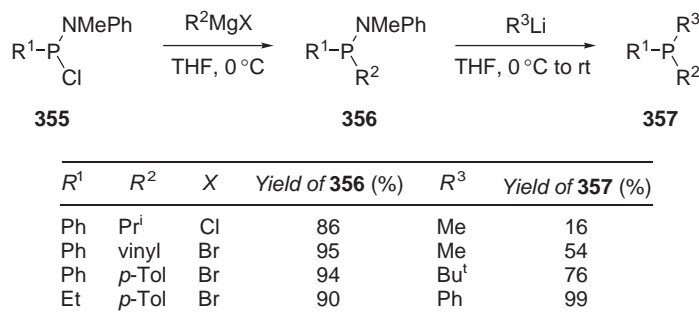
dichloroaminophosphanes **351** in very high yields. Treatment of the derivatives **351** with magnesium turnings affords phosphiranes **352** in excellent yield and in gram quantities via a formal [2 + 1]-cycloaddition of an R_2NP phosphinidene unit to the C—C double bond of the central seven-membered ring of the dibenzotropyliene unit. Platinum(0) complexes of these phosphiranes are active hydrosilylation catalysts <2000T143>.

Shis has reported that treatment of (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine with diphenylthiophosphinic chloride or diphenylselenophosphinic chloride using butyllithium as a base affords exclusively, for steric reasons, the monosubstituted products **353** and **354**, respectively (Scheme 121) <2000TA773, 2000TA835>. These compounds have been used as chiral ligands in metal-catalyzed enantioselective reactions.



Scheme 121

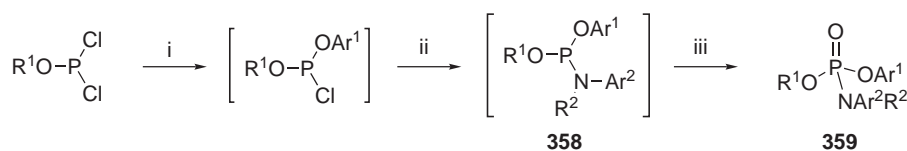
Singh and Nicholas have developed a new synthesis of unsymmetrical tertiary phosphines **357** by sequential alkylation of chloroaminophosphines **355** with Grignard and organolithium reagents (Scheme 122) <1998CC149>. The intermediate *N*-methyl-*N*-phenylaminophosphines **356** react extremely slowly with excess Grignard reagents at high temperature but rapidly with organolithium reagents.



Scheme 122

The reaction of nitroarenes with diethyl chlorophosphite in the presence of a tertiary amine at room temperature generates intermediate phosphoramidates that can be subsequently hydrolyzed *in situ* with HCl/MeOH to afford the corresponding arylamines in good overall yields (see Table 2) <1998JOC393, 2002JOC711>. *O*-Alkyl-*N,O'*-arylphosphoramidates **359** can be synthesized in a one-pot procedure, using the phosphite chemistry approach previously developed for other types of phosphoramidates, by reacting phenol and aniline derivatives with alkyldichlorophosphites to form phosphoramidites **358** followed by oxidation with MCPBA (Scheme 123) <1998T4223>.

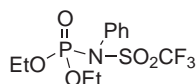
The new amide and peptide coupling reagent **360** can be readily prepared by successive treatment of trifluoromethyl sulfonanilide with sodium hydride in THF at room temperature (1 h) and then with diethyl chlorophosphate at room temperature (2 days) and purification by silica gel column chromatography <2000JCS(P1)2901>. Compound **360** has shown excellent performance in coupling of bulky amines and carboxylic acids as well as low racemization in peptide coupling.



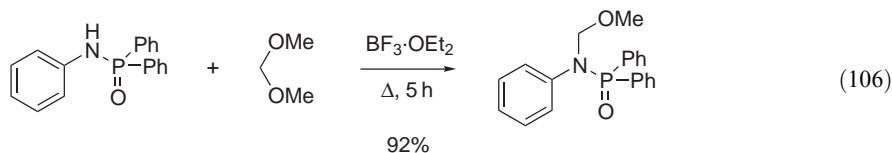
i. Ar^1OH , Pr_2NEt , Et_2O , -78°C , 4 h; ii. Ar^2NHR^2 , Et_2O , -78°C , 4 h; iii. *m*-CPBA, CH_2Cl_2 , $-40^\circ\text{C} \rightarrow \text{rt}$, 1 h.

R^1	Ar^1	Ar^2	R^2	Overall yield of 359 (%)
Me	4-BnO ₂ C-C ₆ H ₄	Ph	H	37
Me	H	Ph	Me	48
Bn	4-BnO ₂ C-C ₆ H ₄	Ph	H	45
Bn	H	Ph	H	58

Scheme 123

**360**

Secondary phosphamides, amides and sulfonamides can be efficiently *N*-alkoxymethylated by reaction of dialkoxymethanes in the presence of Lewis acids (Equation (106)) <2003SL372>.

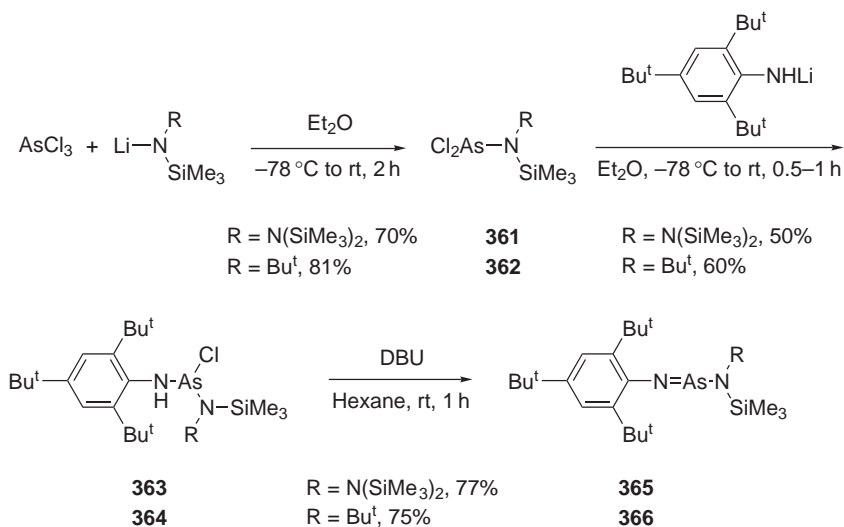


2.15.11 *N*-As, *N*-Sb, or *N*-Bi FUNCTIONS

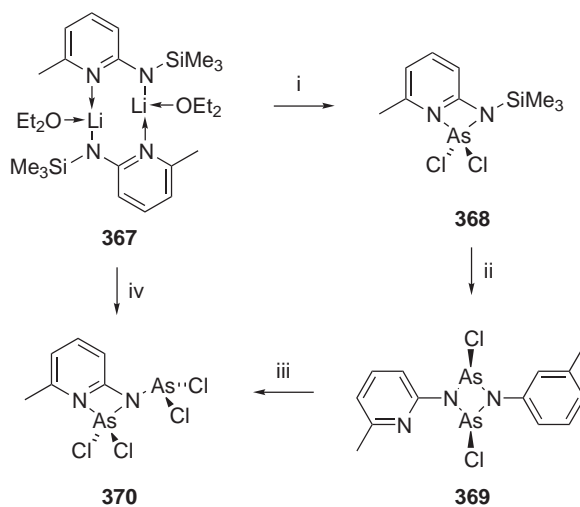
This section is an update on all new methods for the synthesis of vinyl and aryl compounds containing *N*-As, *N*-Sb, or *N*-Bi functions reported since the publication of COFGT (1995) <1995COFGT(2)737>.

Ross has reported a new route to iminoarsanes (Scheme 124) <2000EJI165>. Treatment of AsCl_3 with lithium tris(trimethylsilyl)hydrazide or lithium trimethylsilyl(*t*-butyl)amide affords hydrazinodichloroarsane **361** or aminodichloroarsane **362**, respectively. Reaction of these compounds with lithium (2,4,6-tri-*t*-butylphenyl)amide gives the hydrazinoaminochloroarsane **363** and bisaminochloroarsane **364**. Compounds **363** and **364** can be dehydrohalogenated by treatment with DBU to give hydrazinoiminoarsane **365** and aminoiminoarsane **366** in good yields.

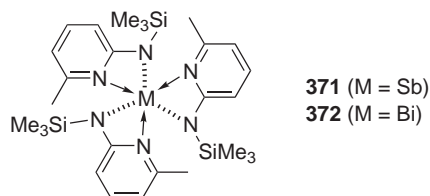
Raston has described the synthesis and structural characterization of amido-arsenic dichloride compound **368** from the reaction of lithium amide **367** and AsCl_3 , which can undergo further reaction via the elimination of Me_3SiCl to form the dimeric geminal amido-arsine **369** (Scheme 125) <2000JCS(D)1279>. The arsine rich geminal amido-arsine **370** can be prepared by reaction of compound **367** and four equivalents of AsCl_3 via the elimination of LiCl and Me_3SiCl . This compound can also be prepared through the redistribution reaction of the arsine **369** with 2 equiv. of AsCl_3 . Triamido-antimony **371** and -bismuth **372** complexes have also been prepared and structurally characterized by the reaction of three equiv. of compound **367** with 2 equiv. of MCl_3 ($\text{M} = \text{Sb}, \text{Bi}$).



Scheme 124



Scheme 125

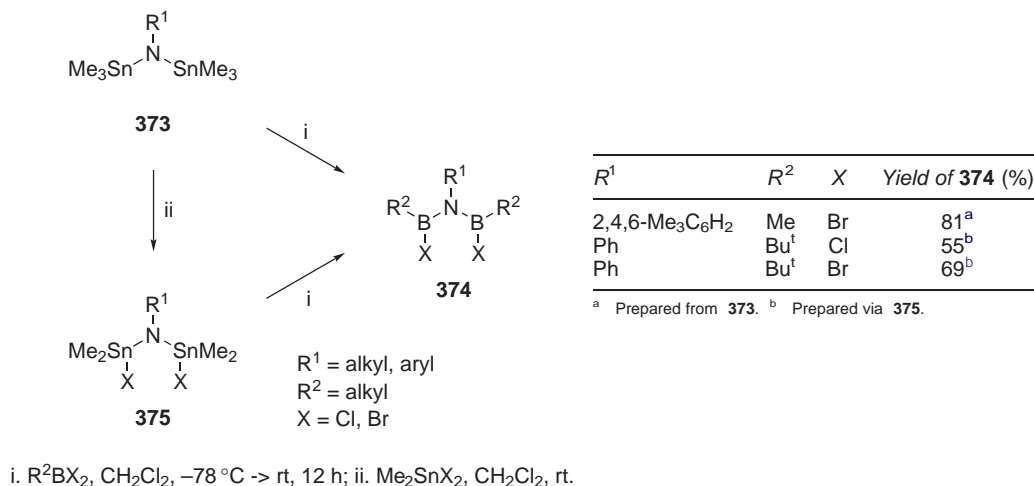


2.15.12 COMPOUNDS WITH AN N-METALLOID BOND

2.15.12.1 Compounds with a Boron—Nitrogen Bond

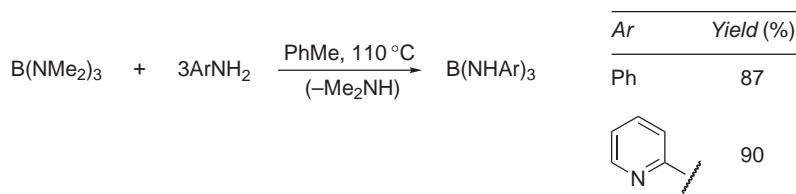
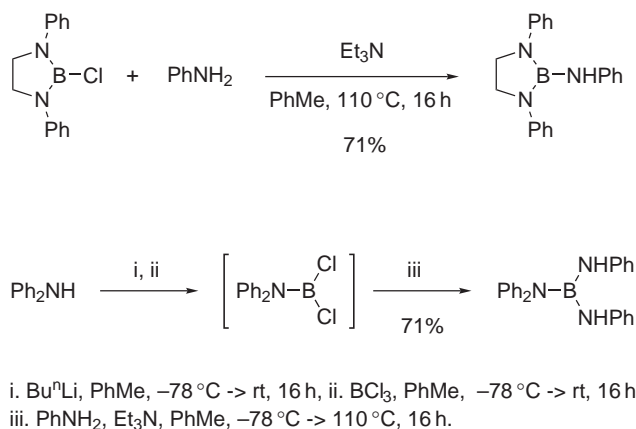
This section is an update on all new methods for the synthesis of vinyl and aryl compounds containing N—B function reported since the publication of COFGT (1995) <1995COFGT(2)737>.

Diborylamines $R^1\text{-N}(\text{BR}^2\text{X})_2$ (**374**; $X = \text{Cl}, \text{Br}$) can be obtained in very high yield by stannazane cleavage of distannylorganylamines **373** with alkyldihaloboranes $R^2\text{-BX}_2$ in a 1:2 molar ratio (Scheme 126) <1999EJI1765>. However, the presence of sterically demanding substituents R^1 and R^2 also causes C-Sn bond cleavage, resulting in low yields of the diborylamines **374**. The use of bis(dimethylhalostannyl)organylamines **375** as a nitrogen source suppresses C-Sn bond cleavage resulting in almost quantitative yields of diborylamines **374**.



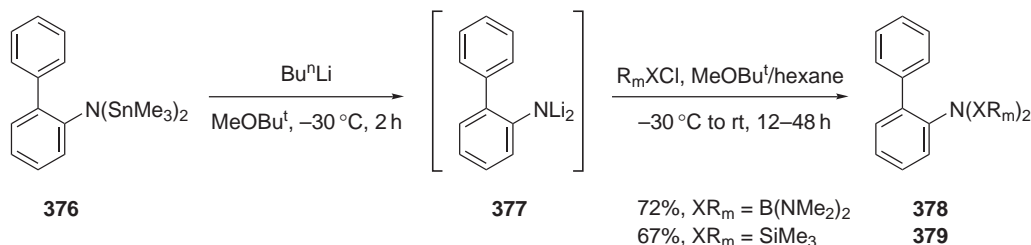
Scheme 126

Nöth and co-workers have prepared a series of new triaminoboranes in order to study their metallation to *N*-lithiotriaminoboranes <2002EJI1132>. The starting triaminoboranes were readily prepared by reaction of chloroboranes with amines in the presence of triethylamine or by aminolysis of $\text{B}(\text{NMe}_2)_3$ (Scheme 127). Competition between deprotonation, borate formation, and B-N bond cleavage was observed in the reaction of triaminoboranes with Bu^nLi , depending on the structure of the aminoborane and the solvent used.



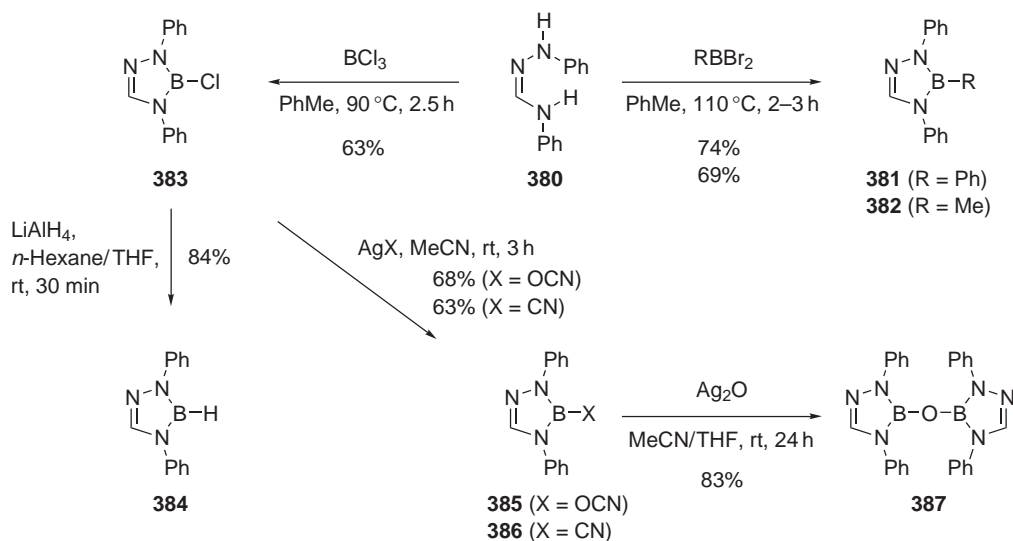
Scheme 127

2-Biphenylamine reacts with (dimethylamino)trimethylstannane in a 2:1 molar ratio to yield the distannylamine **376**. A stannazane cleavage reaction of amine **376** with Bu^nLi in MeOBu^t gives the extremely air and moisture sensitive (2-biphenyl)-*N,N*-dilithium amide **377** (Scheme 128) <2002EJI1040>. Both lithium in the amide **377** can be substituted by boryl or silyl groups to afford the diborylamine **378** or the disilylamine **379**, which are not easily accessible using other routes.



Scheme 128

Cyclocondensation of N^1,N^3 -diphenylformamidrazone **380** with dibromophenylborane, dibromo-methylborane, or boron trichloride yields the 3,4-dihydro-2,4-diphenyl-2*H*-1,2,4,3-triazaboroles **381–383** (Scheme 129) <1999EJI1193>. 3-Chloro-3,4-dihydro-2,4-diphenyl-2*H*-1,2,4,3-triazaborole **383** can be converted into 3,4-dihydro-2,4-diphenyl-2*H*-1,2,4,3-triazaborole **384** and the corresponding 3-cyano and 3-cyano derivatives **385** and **386** by treatment with LiAlH_4 , AgOCN , and AgCN , respectively. Reaction of the nitrile **386** with silver oxide affords the bis(1,2,4,3-triazaborolyl)oxane **387** in good yield.



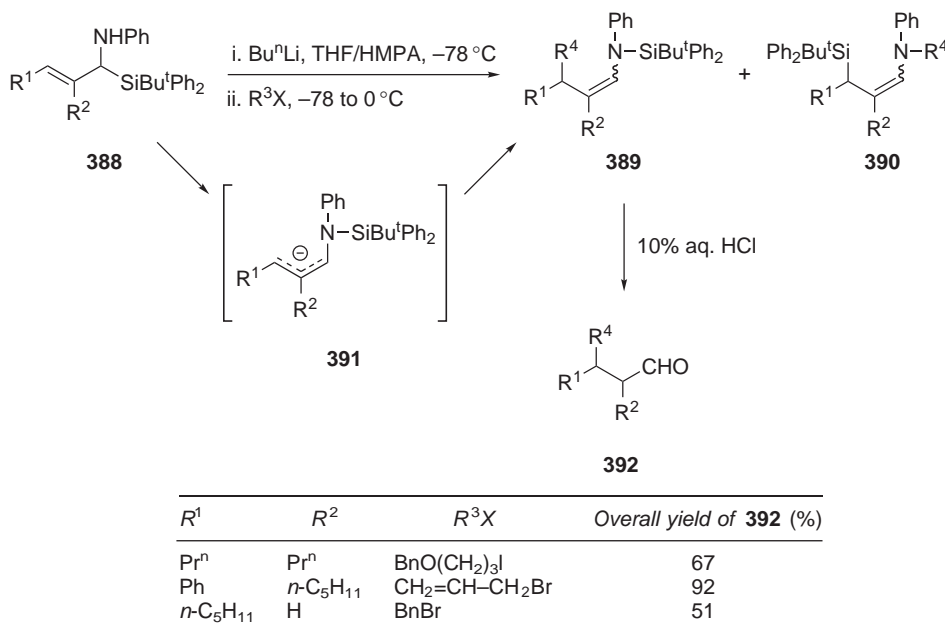
Scheme 129

2.15.12.2 Compounds with a Silicon–Nitrogen Bond

This section is an update on all new methods for the synthesis of vinyl and aryl compounds containing an N–Si function reported since the publication of COFGT (1995) <1995COFGT(2)737>. The chemistry of the compounds with silicon–nitrogen bonds has been reviewed recently <B-2001MI429>.

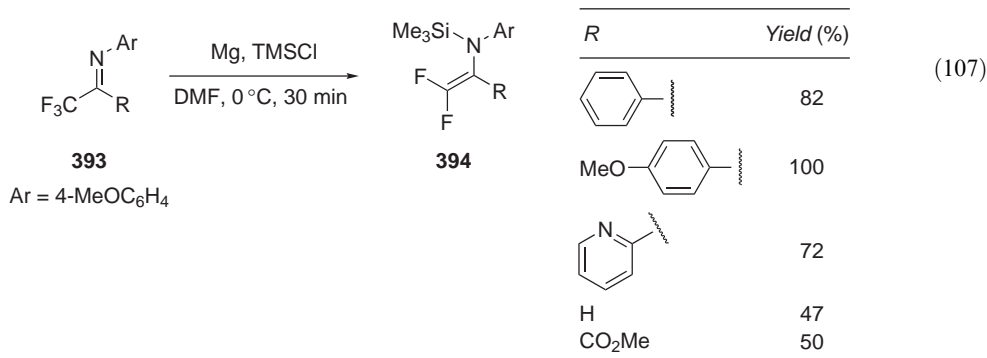
The most common method for the formation of Si–N bonds is the treatment of an NH functionality with an appropriate chlorosilane in the presence of a base. Numerous *N*-silylated arylamines have been prepared following this method in recent years and used as hindered ligands for diverse metal complexes (for a few selected examples, see <1995AG(E)2645, 1997JA12831, 2001JCS(D)972, 2001JCS(D)3179, 2002EJI1968, 2003EJI751>). New methods are described below.

Treatment of (α -silylallyl)amines **388** with Bu^nLi (2 equiv.) in THF/HMPA followed by addition of an alkyl halide affords *N*-silylenamines **389** where the alkyl group is introduced at the C_γ of the initial allylamine (Scheme 130) <1996JOC1196>. Without added HMPA, the corresponding *N*-alkylated enamine **390** is also formed as a minor product in the reaction. The reaction takes place via an aza-Brook rearrangement, where the silyl group of (α -silylallyl)amine **388** migrates from *C* to *N* generating an allyl anion **391**. Acid hydrolysis of the silylenamines **389** affords the corresponding aldehyde **392** in moderate-to-high overall yields.



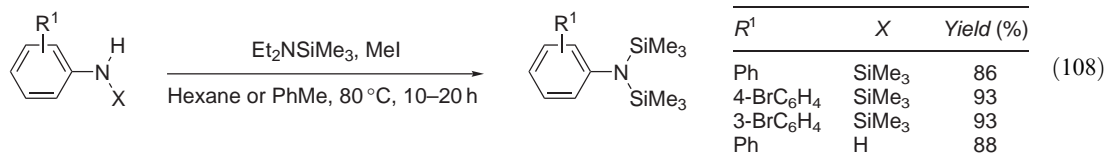
Scheme 130

N-Silylated difluoroenamines **394** can be prepared in moderate-to-high yield via the $\text{Mg}(0)$ -promoted selective C–F bond cleavage of aromatic and heteroaromatic trifluoromethyl imines **393** (Equation (107)) <2000TL7893>. This transformation can also be performed under electrochemical conditions <1998TL587>. Compounds **394** have been used as starting materials for the synthesis of 3,3-difluoroserine and cysteine derivatives.

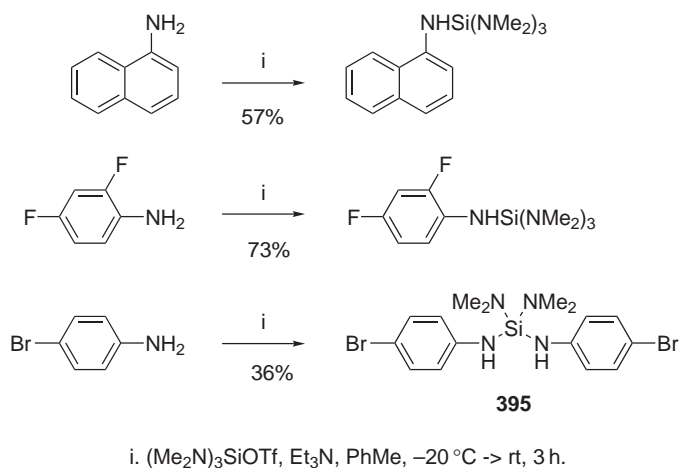


Aromatic and aliphatic *N,N*-bis(trimethylsilyl)amines are usually obtained by conversion of *N*–H to the corresponding metal amide and subsequent treatment with trimethylsilyl chloride (see Section 2.15.12.1, Scheme 128). Hamada has described a novel method that consists in the reaction of a primary alkyl or arylamine or its monotrimethylsilylated derivative with *N*-(trimethylsilyl)diethylamine and a stoichiometric amount of methyl iodide (Equation (108)) <1996JOM(510)1>. Allyl iodide, allyl bromide, and benzyl bromide were also effective in promoting the silylation reaction. *N,N*-Bis(trimethylsilyl)arylamines can also be prepared by

palladium-catalyzed amination of aryl halides with lithium bis(trimethylsilyl)amine <2001OL2729> (see Section 2.15.2.2.4, Scheme 31) or by direct nucleophilic aromatic substitution with this lithium reagent in the case of highly electrophilic aryl halides <1997JCS(D)2483>.

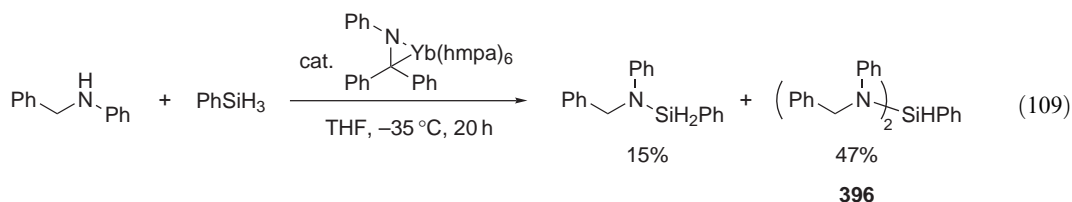


Several tetra(amino)silanes have been prepared by reaction of primary aromatic amines with tris(dimethylamino)silyl triflate in the presence of triethylamine (Scheme 131) <1997CB1167>. Products resulting from ligand redistribution, such as the diaryl derivative **395**, are formed in some cases. Tris(dimethylamino)silyl triflate can be readily prepared by treatment of Si(NMe₂)₄ with trifluoromethanesulfonic acid (2 equiv.) <1994JOM(467)31>.



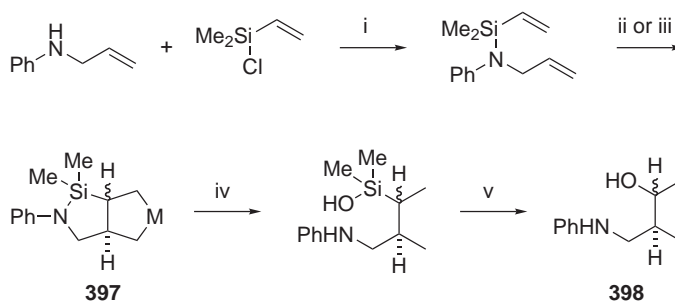
Scheme 131

Alkylaminosilanes can be prepared in good yields by dehydrogenative silylation of primary and secondary amines with triphenylsilane catalyzed by ytterbium–imine complexes [Yb(η^2 -Ph₂CNAr)- (hmpa)_n] <1999JOC3891>. However, whereas *n*- and *s*-alkylamines are readily silylated, *t*-alkylamines exhibit lower reactivities and aromatic amines are not silylated at all. Diphenyl and phenyl silanes are better silylating agents under these conditions, but diamino-silanes **396** are formed as major products (Equation (109)).



Whitby has cyclized 1,6- and 1,7-dienes and -enynes incorporating a silicon–nitrogen (or silicon–oxygen) link by reaction with zirconocene(1-butene) or diisopropoxytitanium(propene) to give metallabicycles **397**, which can be further elaborated by cleavage of the Si–C bond using Tamao oxidation to afford the alcohols **398** (Scheme 132) <1997SL1371>.

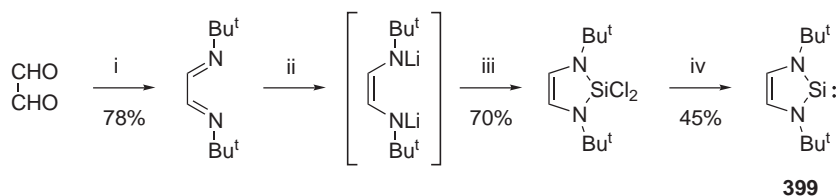
West has described the synthesis and reactivity of silylene **399**, the first stable silicon analog of Arduengo carbenes (Scheme 133) <1994JA2691, 1998JA12714, 1999JA9479>. Other stable silylenes has been reported <1995CC1931, 1996JOM(521)211, 1996PAC785, 1998CEJ541, 1998POL999, 2002AG(E)1290>.



i. Bu^nLi , THF, $-40^\circ\text{C} \rightarrow \text{rt}$, 1 h; ii. $\text{Cp}_2\text{ZrCl}_2 + 2\text{Bu}^n\text{Li}$, $-78^\circ\text{C} \rightarrow 20^\circ\text{C}$, 2 h;
 iii. $\text{Ti}(\text{OPr})_4 + 2\text{Pr}^i\text{MgCl}$, -40°C , 2 h; iv. H_2O , 20°C , 16 h; v. KHCO_3 , KF, H_2O_2 ,
 MeOH/THF, 20°C , 2–16 h.

M	Overall yield of 398 (%)	Threo/erythro
Threo:erythro	53	1/0
Threo:erythro	23	1/4.6

Scheme 132



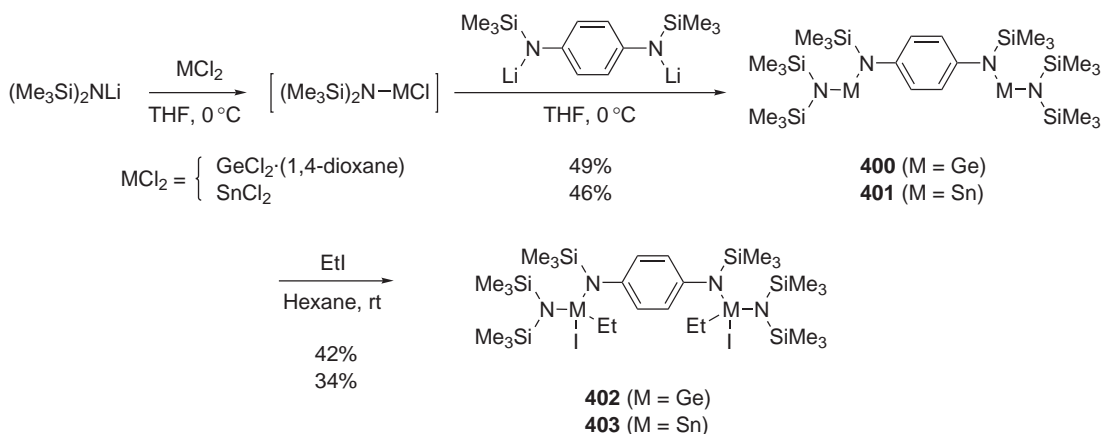
i. Bu^tNH_2 , H_2O , 0°C ; ii. Li, THF, $-78^\circ\text{C} \rightarrow \text{rt}$; iii. SiCl_4 , THF, rt; iv. K, THF, 80°C .

Scheme 133

2.15.12.3 Compounds with a Germanium—Nitrogen Bond

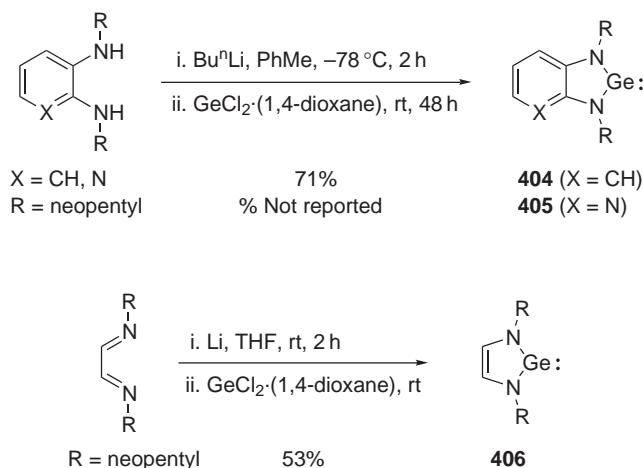
This section is an update on all new methods for the synthesis of vinyl and aryl compounds containing N—Ge function reported since the publication of COFGT (1995) <1995COFGT(2)737>.

The acyclic bisgermylene **400** and bisstannylidene **401** have been prepared by a one-pot, two-step ligand substitution reaction from gemanyl and tin dichloride, respectively (Scheme 134) <1994CL941>. Both products are stable at room temperature under argon and readily react with alkyl halides to give the corresponding oxidative addition products **402** and **403**.



Scheme 134

Heinicke has described the preparation of benzo-anellated cyclic germylenes **404** and **405**, respectively, by double lithiation of the corresponding aromatic *ortho*-diamines and subsequent reaction with $\text{GeCl}_2 \cdot (1,4\text{-dioxane})$ (Scheme 135) <1998CEJ541, 2001POL2215>. Analogously, the nonanellated 1,3,2-diazagermoline-2-ylidene **406** was obtained from *N,N'*-dineopentyl glyoxal diimine by reductive metalation with lithium metal followed by reaction with $\text{GeCl}_2 \cdot (1,4\text{-dioxane})$. Compounds **404**–**406** can be considered as germanium analogs of Arduengo carbenes.



Scheme 135

Three different routes for the *N*-germylation of *o*-(*N,N*-dimethylsulfonamido)phenylamine **407** have been compared <2003MI181>. Transamination with triethylgermyldimethylamine (Scheme 136; reagent i) requires an excess of reagent to give quantitative yields of the *N*-germylated product **408**. Dehydrochlorination with triethylgermyl chloride in the presence of Et_3N or DBU (Scheme 136; reagent ii) is not quantitative. Transmetalation (Scheme 136; reagent iii) is the best route to *N*-germylamines.



- i. $\text{Et}_3\text{GeNMe}_2$ (1 mole-equiv., 71%; 2 mole-equiv., 96%), 90°C , 2 h;
 ii. Et_3GeCl , Et_3N or DBU, 90°C , 2 h (70%); iii. (a) Bu^tLi , THF, $-78^\circ\text{C} \rightarrow \text{rt}$, 1 h,
 (b) Et_3GeCl (99%).

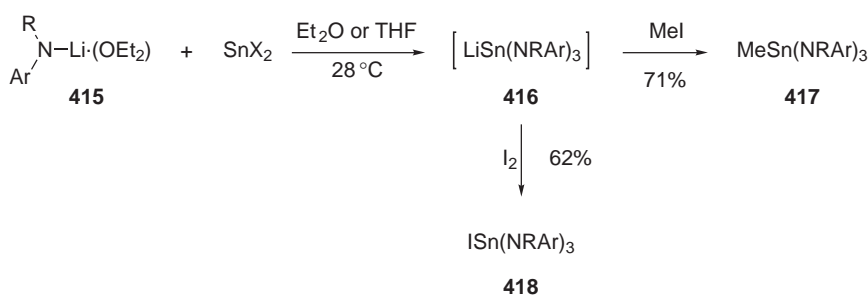
Scheme 136

Leung has reported the synthesis of the divalent group 14 metal complexes **409** containing 2,6-pyridyl-bridged bis(1-azaallyl) dianionic ligands by transmetalation of their alkali metal salts with $\text{GeCl}_2 \cdot (1,4\text{-dioxane})$, SnCl_2 and PbCl_2 (Equation (110)) <2003JCS(D)1505>. Related divalent germanium compounds with bidentate coordinating monoanionic β -diketiminate ligands have been described by Roesky <2001OM1190, 2002JA8542, 2002OM5216, 2003JCS(D)1094> and by Barrau <2003OM1106, 2003OM3143>.

2.15.13 COMPOUNDS WITH AN *N*-METAL BOND2.15.13.1 *N*-Sn, *N*-Pb, *N*-Hg, and *N*-Al Bonds

This section is an update on all new methods for the synthesis of vinyl and aryl compounds containing *N*-Sn, *N*-Pb, *N*-Hg, and *N*-Al functions reported since the publication of COFGT (1995) <1995COFGT(2)737>. Additional examples of synthesis of compounds with *N*-Sn and *N*-Pb functionalities can be found in Section 2.15.12.3.

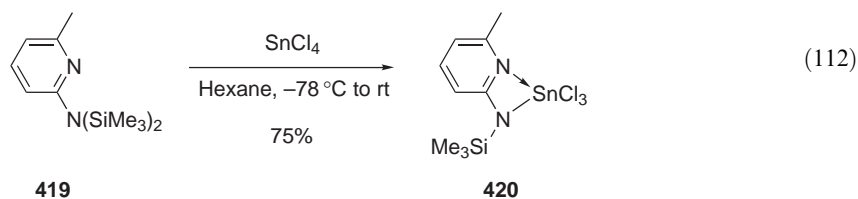
Reaction of an ethereal solution of tin(II) chloride or tin(II) iodide with 3 equiv. of a lithium *N*-*t*-butylanilide **415** affords the “ate” complexes **416**, which oxidatively add methyl iodide or iodine to generate the tin(IV) derivatives **417** and **418**, respectively (Scheme 138) <1995OM577>. In contrast, the reaction of the organotin halides PhSnCl₃ and MeSnCl₃ with LiNHPh in benzene or toluene leads to the formation of the nitrogen bridged polynuclear organotin compounds [(PhSn)₄(NPh)₅Cl₂] and [(MeSn)₄(NHPh)₄(NPh)₄], respectively <1999ZAAC735>.



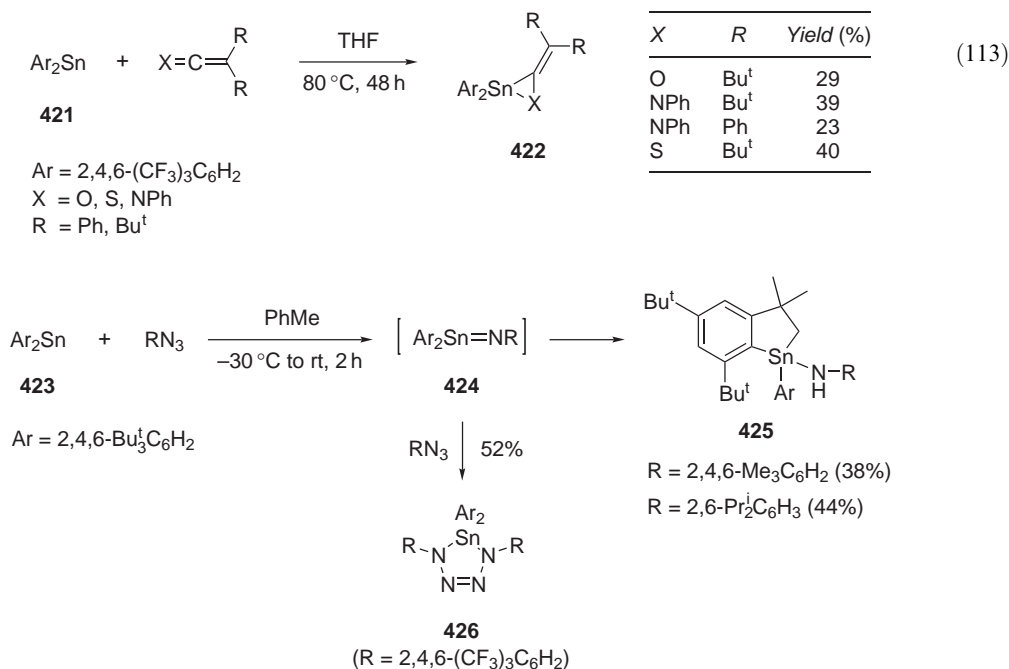
Scheme 138

Reaction of the lithium dianion of *meso*-tetra-*p*-tolylporphyrin and *meso*-tetrakis(*p*-*t*-butylphenyl)porphyrin with Ph₂SnCl₂ in CH₂Cl₂ gave 70–80% of the corresponding hitherto inaccessible *cis*-Ph₂Sn(porphyrins) <1996JA6082>. For comparison, the analogous *trans*-Ph₂Sn(porphyrins) can be readily prepared by reaction of Ph₂Mg with the corresponding *trans*-Cl₂Sn(porphyrins) in THF. Thus, the resulting stereochemistry is controlled by the choice of synthetic method and not by the nature of the central metal ion.

The amidotin trichloride derivative **420** can be readily prepared by reaction of the bis(trimethylsilyl) substituted amine **419** with tin(IV) tetrachloride at low temperature (Equation (112)) <2002NJC677>. In contrast, using the corresponding *N*-trimethylsilyl lithium amide as the source of the ligand leads exclusively to the 2:1 complex [6-(Me₃SiN)-2-Me-C₅H₃N]₂SnCl₂.

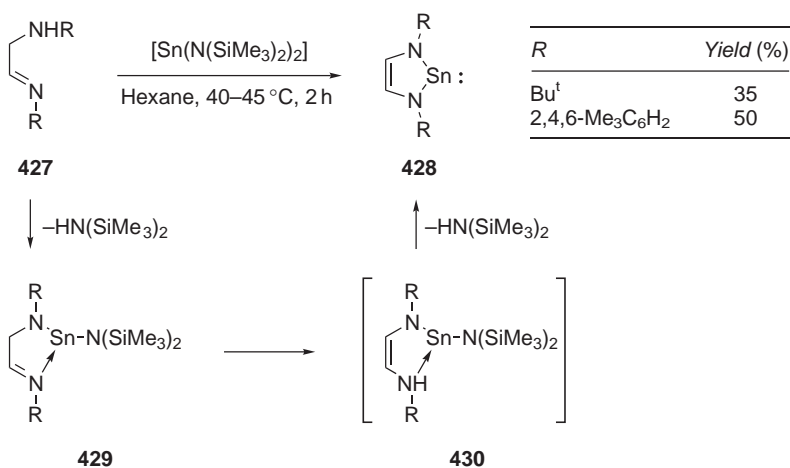


The stable diarylstannylene **421**, with the sterically and electronically stabilizing nonafluoromesityl substituent, readily undergoes cycloaddition reactions with various heterocumulenes, such as ketenes, keteneimines, and thioketenes, to give three-membered stannacycles **422** in moderate yield (Equation (113)) <1997JFC(84)29>. Similarly, the analogous diarylstannylene **423** reacts with mesityl and with 2,6-diisopropylphenyl azides via the stannanimines **424**, which rearrange by intramolecular addition of a C—H bond of one of the *ortho*-*t*-butyl groups across the Sn=N bond to give the stannaindan derivatives **425** (Scheme 139) <1999JOM(579)280>. However, treatment of this stannylene **423** with excess 3,5-bis(trifluoromethyl)phenyl azide affords the tetraazastannoline derivative **426** instead, presumably by a [3+2]-cycloaddition reaction of the azide to the stannanimine intermediate.

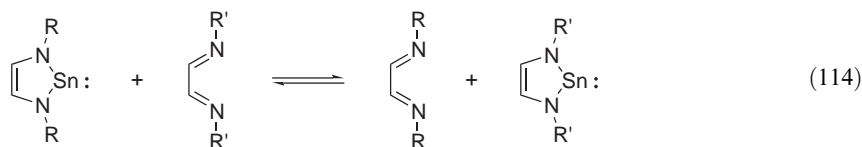


Scheme 139

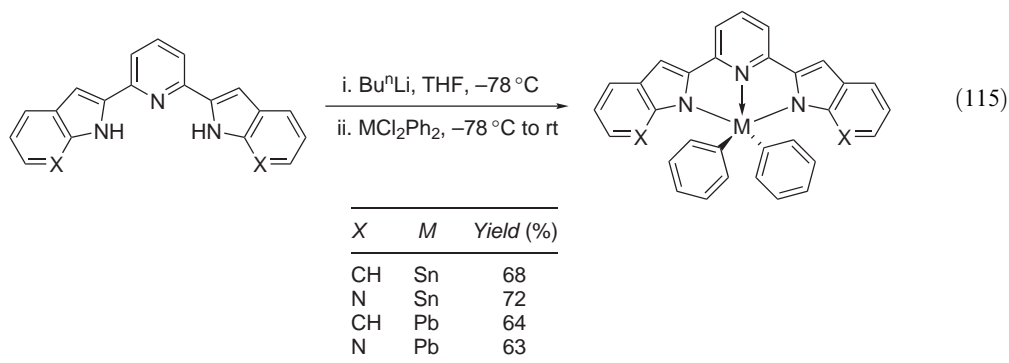
1,3,2- λ^2 -Diazastannoles **428**, which are tin analogs of Arduengo carbenes, can be prepared by transamination of [Sn(N(SiMe₃)₂)₂] with α -aminoaldimines **427** at 40–45 °C in nonpolar solvents (Scheme 140) <2002AG(E)1888>. The reaction is proposed to proceed through a multistep mechanism that involves initial condensation to give stannylenes **429**, 1,3-*H*-shift to afford intermediates **430**, and intramolecular elimination of HN(SiMe₃)₂ to produce the final products. Compounds **428** suffer a metathesis reaction with diazadienes to afford the complementary diazastannoles and diazadienes (Equation (114)). This behavior is unprecedented for the corresponding C, Si, and Ge analogs.



Scheme 140

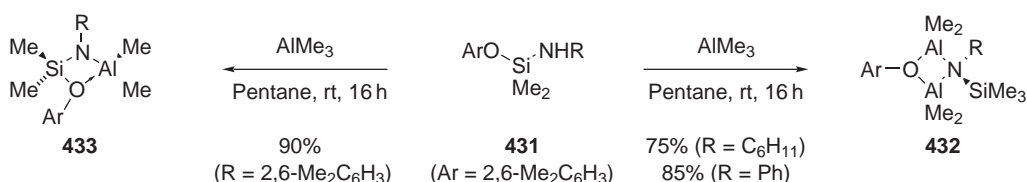


Five-coordinated Sn(IV) and Pb(IV) complexes of 2,6-bis(2'-indolyl)pyridine and 2,6-bis[2'-(7-azaindolyl)]pyridine have been synthesized by reaction of the dilithium salt of these ligands with an equimolar amount of MCl_2Ph_2 ($M = Sn, Pb$) (Equation (115)) <2003OM4070>.



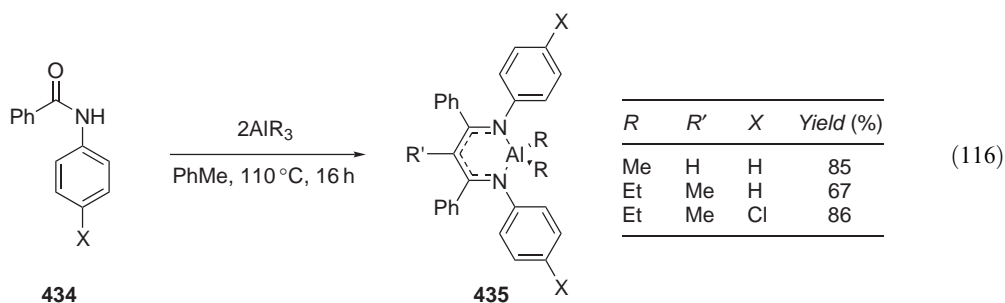
Ethynyl- and aryl-substituted porphyrins can be readily metallated with zinc(II), copper(II) or lead(II) by heating the corresponding porphyrin with either $Zn(OAc)_2$, $Cu(OAc)_2$ or $Pd(OAc)_2$ in DMF <2002T2415>.

Reaction of readily available (aryloxydimethylsilyl)amides (**431**, $Ar = 2,6-Me_2C_6H_3$; $R = C_6H_{11}$, Ph) with $AlMe_3$ in pentane at room temperature affords the unusual dinuclear aluminum complexes **432**, which contain both nitrogen- and oxygen-bridging groups (Scheme 141) <1999OM5713>. Conversely, the analogous reaction of (aryloxydimethylsilyl)amide (**431**, $Ar = R = 2,6-Me_2C_6H_3$) containing a bulkier *N*-substituent gives the monomeric *N,O*-chelated aluminum species **433**.



Scheme 141

The reaction of organoaluminum compounds with amides under various conditions has been studied by Lin <2001JCS(D)1359, 2002IC2987>. When benzanilides **434** are refluxed in toluene with two molar equivalents of AlR_3 , the aluminum diketimide compounds **435** are formed in good yield (Equation (116)).



Dimethylaluminum amides of arylamines, readily prepared by reaction of the appropriate amine with $AlMe_3$ in toluene, are highly efficient reagents for the conversion of $C=O$ into $C=NAr$ <2002CC2710>.

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1981HCA1208

1981JCS(P2)193
1981JOC3056
1981TI1453
1983CL927
1984BSB961
1985S909
1985ZOB466
1985ZOB2514
1986JOC5039
1986LA1456
1986OPP299
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1987TL887
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Biographical sketch



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2.16

Vinyl- and Arylphosphorus Derivatives

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Kyushu Institute of Technology, Kitakyushu, Japan

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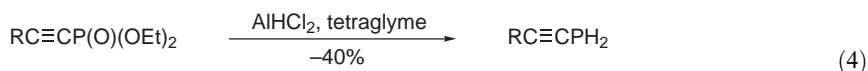
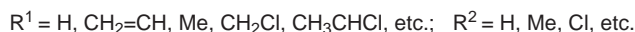
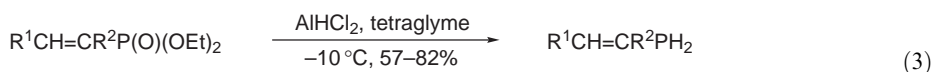
2.16.1 PHOSPHINES AND PHOSPHORANES

2.16.1.1 Phosphines

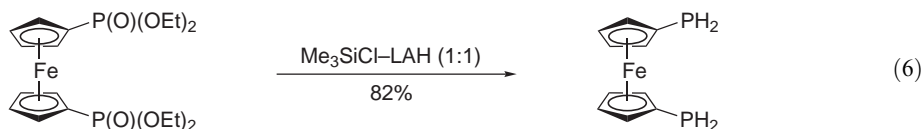
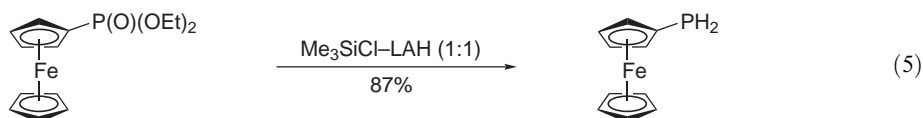
2.16.1.1.1 Primary phosphines

(i) *Reduction of arylphosphonous ($\text{ArP}(\text{OH})_2$) and arylphosphonic ($\text{ArP}(\text{O})(\text{OH})_2$) acids and their derivatives with LiAlH_4 (method A)*

As described in COFGT (1995) <1995COFGT(2)819>, a common synthetic method for primary arylphosphines has been by reduction of arylphosphonous dichlorides or aryl phosphonates with LiAlH_4 in ether or THF (Equations (1) and (2)). For selective reduction of the phosphorus moiety of alkenyl or alkynyl phosphonates, AlCl_2H , prepared *in situ* from LiAlH_4 (1 equiv.) and AlCl_3 (3 equiv.), is effective (Equations (3) and (4)). Reduction of these unsaturated phosphonates with LiAlH_4 results in undesirable alkylphosphines <2001HAC161>.



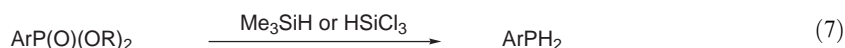
For transformation of aryl or ferrocenyl phosphonates to the corresponding primary phosphines, reduction with a LiAlH_4 – TMSCl (1:1) system is also useful (Equations (5) and (6)) <2002JOM(656)120>.



Since primary phosphines are very sensitive to air, all reactions must be performed in dry solvents under oxygen-free N_2 or Ar. From the viewpoint, for instance, of stabilization of primary phosphines and the application of their metal complexes, the development of primary arylphosphines containing bulky groups at the adjacent positions has particularly been studied.

(ii) *Reduction of arylphosphonous dichlorides (ArPCl_2) and aryl phosphonates ($\text{ArP}(\text{O})(\text{OR})_2$) with hydrosilanes (method B)*

Similar to LiAlH_4 , hydrosilanes, such as Me_3SiH , HSiCl_3 , are often utilized for reduction of arylphosphonous dichlorides or aryl phosphonates leading to primary arylphosphines (Equation (7)).



(iii) *Miscellaneous methods*

Although reduction of alkylphosphonous dicyanide, easily prepared from RPCl_2 and Me_3SiCN or AgCN , with hydrogenzirconocene chloride (Schwartz's reagent) is utilized for the synthesis of primary alkylphosphines, application of this method to arylphosphonous dicyanides leads only to arylphosphinous cyanide (Equation (8); see Table 1) <2001OM25>.

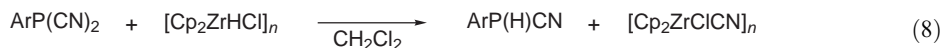


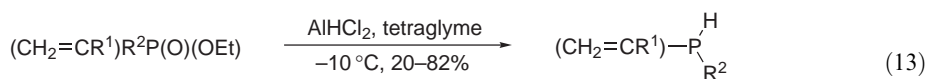
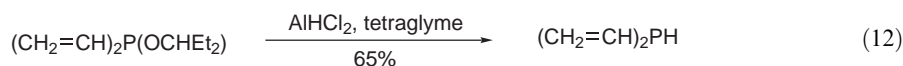
Table 1 Synthesis of primary phosphines (ArPH_2)

Entry	Method	Ar	Yield (%)	References
1	A	2-(Bu^tSCH_2) C_6H_4	64	<2000JOC900>
2	A	2-(H_2N)Naphthyl	90	<1995BSF729>
3	A	2,3,5,6-(4- $\text{Bu}^t\text{C}_6\text{H}_4$) $_4$ -4-(PH_2) C_6	94	<2000IC3860>
4	A	2,6-(F_3C) $_2\text{C}_6\text{H}_3$	63	<2002AG(E)1193>
5	A	2- Pr^i -4,6- $\text{Bu}^t_2\text{C}_6\text{H}_2$	82	<2001HAC418>
6	A	2,6-(Et_2NCH_2) $_2$ -4- $\text{Bu}^t\text{C}_6\text{H}_2$	45	<1999BCJ1335>
7	A	2,6-($\text{Pr}^i_2\text{NCH}_2$) $_2$ -4- $\text{Bu}^t\text{C}_6\text{H}_2$	26	<1999BCJ1335>
8	A	2,6-(2,4,6- $\text{Pr}^i_3\text{C}_6\text{H}_2$) $_2\text{C}_6\text{H}_3$	61	<2000JOM(609)152>
9	A	2,4,6- $\text{Bu}^t_3\text{C}_6\text{H}_2$	63	<2001HAC418>
10	A	9-Anthryl	83	<1999OM4222>
11	A	$\text{CH}_2=\text{CH}$	76	<2001HAC161>
12	A	$\text{CH}_2=\text{CMe}$	82	<2001HAC161>
13	A	$\text{HC}\equiv\text{C}$	40	<2001HAC161>
14	B	3,5- $\text{Cl}_2\text{C}_6\text{H}_3$	47	<2002HCA1140>
15	B	3- Cl -5-(H_2P) C_6H_3	35	<2002HCA1140>
16	B	3,5-(H_2P) $_2\text{C}_6\text{H}_3$	25	<2002HCA1140>

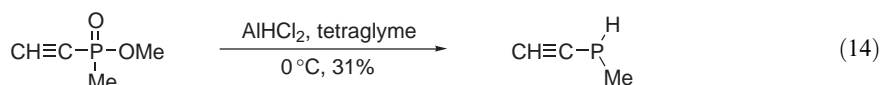
2.16.1.1.2 Secondary phosphines

(i) Reduction of arylphosphinous ($ArRPX$) or arylphosphinic ($ArRP(O)X$) halides, esters, and amides with $LiAlH_4$ (method A)

Similar to the synthesis of primary phosphines, lithium aluminum hydride has been widely utilized as a reducing agent of arylphosphinous acids <1998HAC183>, arylphosphinous or arylphosphinic chlorides <1996JFC(76)29, 2000OM2090, 2000EJO3497, 1997JOM(529)59> or esters <1995COFGT(2)819> and amines <1995COFGT(2)819> to synthesize secondary phosphines (Equations (9)–(11)), but is not applicable to reduction of the corresponding alkenyl or alkynyl derivatives. The use of $AlCl_2H$ solves this problem and leads to the corresponding alkenyl- or alkynylphosphines in good-to-moderate yields (Equations (12)–(14)) <2001HAC161>.

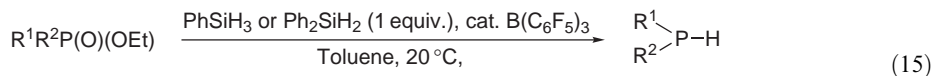


$R^1 = H, Cl; R^2 = Me, \text{ allyl, Bn, Ph}$

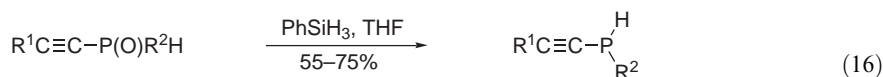


(ii) Reduction of arylphosphinous ($ArRPOH$) or arylphosphinic ($ArRP(O)OH$) acids and their derivatives with hydrosilanes (method B)

The reduction of phosphinous or phosphinic acids and their chloride or ester derivatives with various types of hydrosilanes such as phenyl silane, diphenyl silane, and trichlorosilane is one of the commonly used methods for the synthesis of secondary phosphines (Equations (15) and (16)) <2002TL5569, 2001HAC161, 2002JOM(643–644)342>.



$R^1 = CH_2=CH, Ph, \text{ etc.}; R^2 = Bn, \text{ alkyl, etc.}$

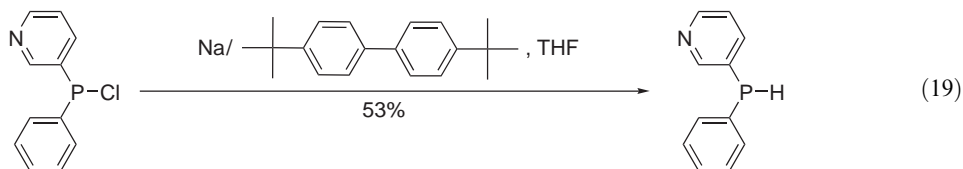
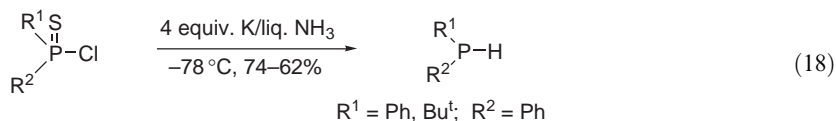
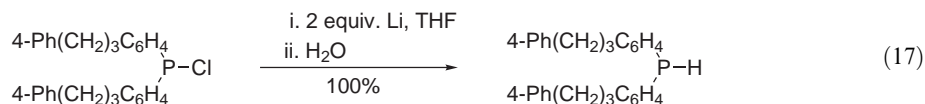


$R^1 = H, Ph; R^2 = Et, Pr^i, Bu^t, Ph$

(iii) Hydrolysis (or alcoholysis) of metal phosphides (method C)

The synthesis of secondary arylphosphines via hydrolysis of metal arylphosphides has usually been limited to application in the synthesis of symmetrical diarylphosphines due to the availability of starting triarylphosphines or diarylphosphinous halides (Equation (17)) <1997JMOC(124)21>.

However, treatment of unsymmetrical arylphosphinous chlorides or arylthiophosphinic chlorides with K/liq. NH₃ (or Na/4,4'-di-Bu^t-1,1'-biphenyl) provides the expected unsymmetrical arylphosphines (Equations (18) and (19)) <2002HAC330, 1997OM3027>.



Important applications of method C include synthesis of chiral secondary phosphine boranes via asymmetric reductive cleavage of chiral tertiary phosphine boranes with lithium naphthalenide (Equations (20) and (21); see Table 2) <2000JOC2337, 2001JOC1514>.

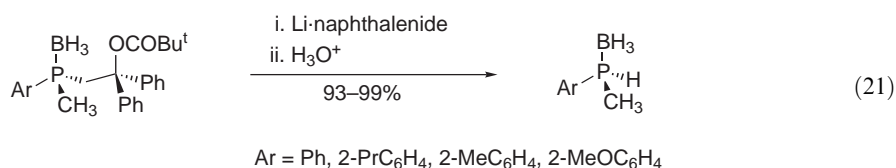
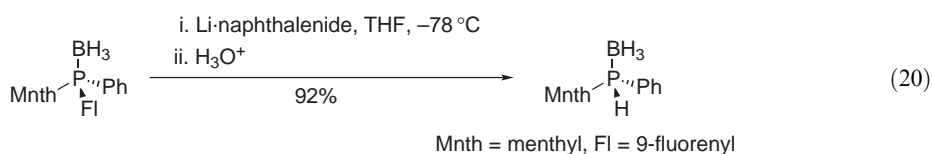


Table 2 Synthesis of secondary phosphines (ArRPH)

Entry	Method	Ar	R	Yield (%)	References
1	A	2-(MeO)C ₆ H ₄	(Me ₃ Si) ₂ CH	72	<2000OM2090>
2	A	2,3-(MeO) ₂ C ₆ H ₃	(Me ₃ Si) ₂ CH	70	<2000OM2090>
3	A	2-HO-3,5-Bu ₂ C ₆ H ₂	Ph	40	<1998HAC183>
4	A	2,6-(Me ₂ NCH ₂) ₂ C ₆ H ₃	Ph	68	<1997JOM(529)59>
5	A	C ₆ F ₅	Ph	<70	<1996JFC(76)29>
6	A	C ₆ F ₅	C ₆ F ₅	<66	<1996JFC(76)29>
7	A	Ph	3-(Ph(H)PCH ₂)C ₆ H ₄	46	<2000EJO3497>
8	A	Ph	Ph(Ph ₃ P)C	89	<1998EJI381>
9	A	H ₂ C=CH	H ₂ C=CH	65	<1996OM3466>
10	A	H ₂ C=CH	Bn	82	<2001HAC161>
11	A	3,5-(CF ₃) ₂ C ₆ H ₃	3,5-(CF ₃) ₂ C ₆ H ₃	77	<2002JFC(117)121>
12	A	HC≡C	Me	31	<2001HAC161>
13	B	PhC≡C	Pr ⁱ	70	<2002JOM(643-644)342>
14	B	Ph	PhC≡C	75	<2001HAC161>
15	B	Ph	HC≡C	75	<2001HAC161>
16	C	Ph	Ph	62	<2002HAC330>
17	C	Ph	Bu ^t	74	<2002HAC330>
18	C	Ph	Pyr	53	<1997OM3027>
19	C	4-(Ph(CH ₂) ₃)C ₆ H ₄	4-(Ph(CH ₂) ₃)C ₆ H ₄	100	<1997JOC(124)21>

2.16.1.1.3 Tertiary phosphines

(i) Reaction of arylphosphinous ($ArRPX$), or arylphosphonous ($ArPX_2$) halides, or phosphorus trihalides, or their ester derivatives with Grignard, organolithium, or organometallic reagents (method A)

This method is normally used for the synthesis of various tertiary phosphines (Equations (22)–(24); see Table 3) <2000MI3806, 1997JOM(529)59, 2002TL4977>.

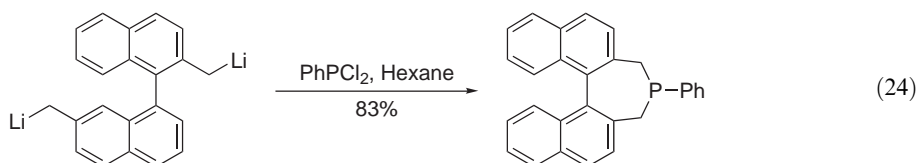
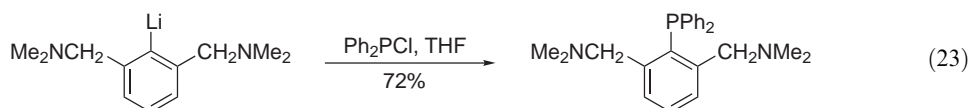
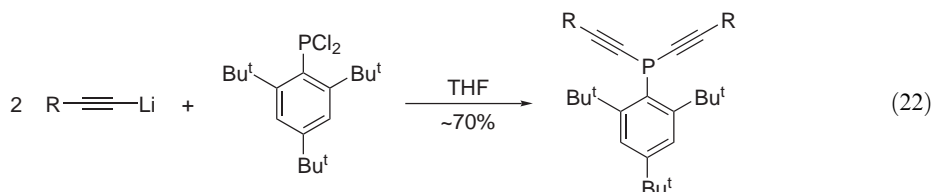
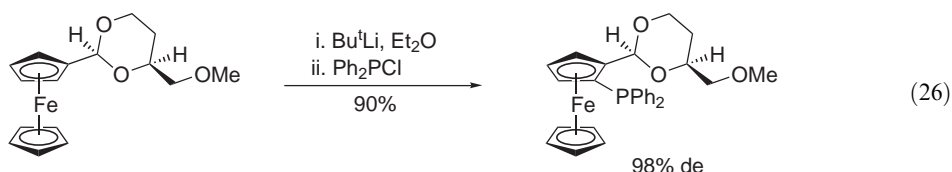
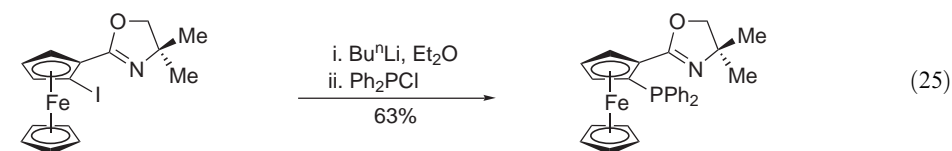


Table 3 Synthesis of tertiary phosphines (ArR^1R^2P)

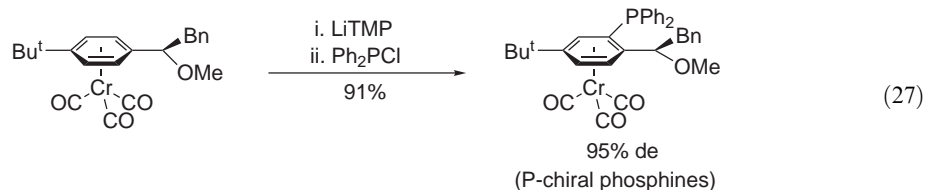
Entry	Method	Ar	R^1	R^2	Yield (%)	References
1	A	Ph	2-Furyl	2-Furyl	77–80	<2002T2551>
2	A	Ph	Ph	$\text{CF}_2=\text{CF}$	80	<1999JCS(D)427>
3	A	3,5- $(\text{CF}_3)_2\text{C}_6\text{H}_3$	3,5- $(\text{CF}_3)_2\text{C}_6\text{H}_3$	$\text{CH}_2=\text{CH}$	47	<2002JFC(117)121>
4	A	Ph	$\text{CF}_2=\text{CF}$	$\text{CF}_2=\text{CF}$	61	<1999JCS(D)427>
5	A	$\text{CF}_2=\text{CF}$	$\text{CF}_2=\text{CF}$	$\text{CF}_2=\text{CF}$	24	<1999JCS(D)427>
6	A	9-Anthryl	9-Anthryl	9-Anthryl	59	<2002JOM(646)277>
7	A	1-Naphthyl	Bu^t	Bu^t	75	<2002JOM(643–644)68>
8	A	Ph	2-Py	2-Furyl	33	<2001JMOC(168)75>
9	A	Ph	Menthyl	Fluorenyl	55	<2000JOC2337>
10	A	2- $(\text{Me}_2\text{NCH}_2)\text{C}_6\text{H}_4$	2- $(\text{Me}_2\text{NCH}_2)\text{C}_6\text{H}_4$	Me	65	<2001OM648>
11	C	Ph	Ph	1-Naphthyl	91	<2003JOC4590>
12	C	Ph	Ph	2-MeC ₆ H ₄	76	<2003JOC4590>
13	C	Ph	Ph	2,4,6-Me ₃ C ₆ H ₂	70	<2003JOC4590>
14	C	Ph	Ph	4- $(\text{Ph}_2\text{P})\text{C}_6\text{H}_4$	71	<2003JOC4590>
15 ^a	A	Ph	Ferrocenyl	Bu^n	90	<2003JOC156>
16 ^a	A	Ph	Ferrocenyl	2-PhC ₆ H ₄	69	<2003JOC156>
17	M	Ph	2-Py	2-Py	68	<1999JOM(584)387>
18	M	Ph	Ph	2-Thienyl	65	<1999JOM(584)387>

^a As P-chiral phosphine boranes.

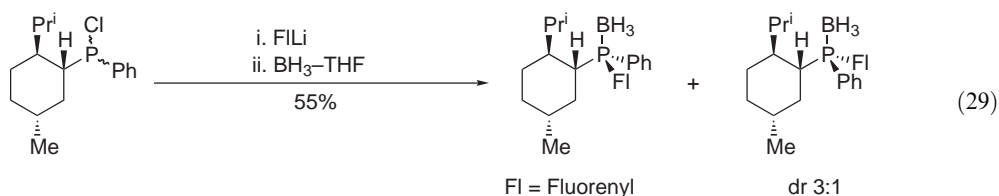
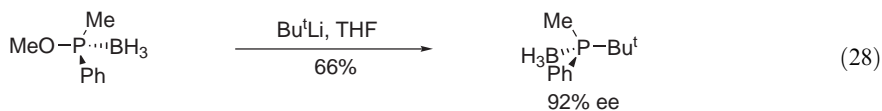
Recent studies have been directed to regio- or stereoselective lithiation using the attached functional group or chiral auxiliary, and subsequent reaction with halophosphines to form functionalized, enantioselective, or diastereoselective tertiary phosphines. Thus, ferrocenyl complexes bearing chiral functionalities such as acetals <1997JOC6733, 2002OM4552>, oxazolines <1997JOM(545–546)381, 1996TL6137, 1995SL79, 2001JOM(637–639)99>, amines <1996JOC1172, 1996JOM(508)209, 1996JA685, 1995TA2495, 1999TA4369, 2002OM1766, 2001JOC8912>, a sulfonate <2002OL1935>, or a sulfoxide <1998T7301> give high enantioselective or diastereoselective ferrocenyldiphenylphosphines via selective ortholithiation-electrophilic Ph_2PCl quenching sequences (Equations (25) and (26)) <2002JOC4684, 1997JOC6733>.



In (arene)tricarbonylchromium(0) complexes also bearing chiral functionalities similar selective lithiation and subsequent coupling with arylphosphinous chlorides have been found to give chiral tertiary phosphine complexes (Equation (27)) <2002T4617, 2001CC1070, 1995JOM(503)143>.

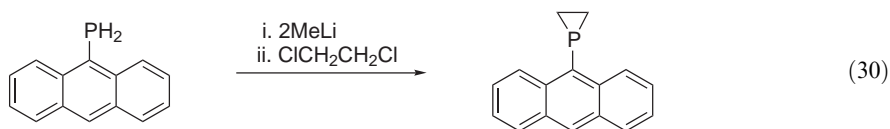


Tertiary phosphines possessing chirality at a P atom have been synthesized by the nucleophilic substitution at the P atom of chiral phosphinite boranes or the reaction of phosphinous chlorides bearing chiral functionalities with organolithium compounds (Equations (28) and (29)) <2002JOC5239, 2000JOC2337>.



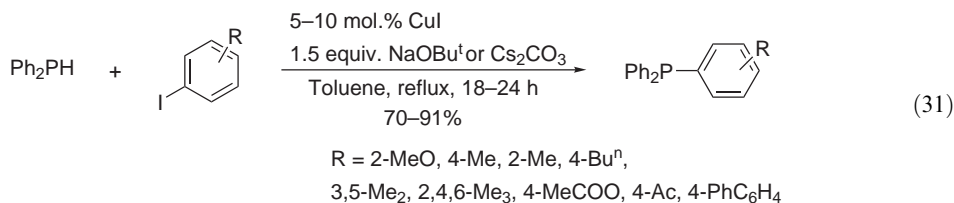
(ii) Reaction of metal arylphosphides with aryl or alkyl halides (method B)

Preparation of metal diarylphosphides and their reaction with aryl or alkyl halides to produce tertiary phosphines was described in COFGT (1995) <1995COFGT(2)819>. Similar reactions of dimetal arylphosphides, prepared from primary phosphines and alkyllithiums (2 equiv.), with aryl or alkyl halides lead to tertiary phosphines (Equation (30)) <1999OM4222>.



(iii) Copper-catalyzed reaction of diarylphosphines with aryl iodides (method C)

Various tertiary arylphosphines are prepared not only by reaction of metal diarylphosphides with electrophiles such as aryl or alkyl halides <1995COFGT(2)819> or oxiranes <2002JFC(117)121> but also by coupling diarylphosphines with aryl iodides with catalytic amounts of CuI in the presence of a base (NaOBu^t, K₂CO₃, or Cs₂CO₃) (Equation (31)) <2003JOC4590>.



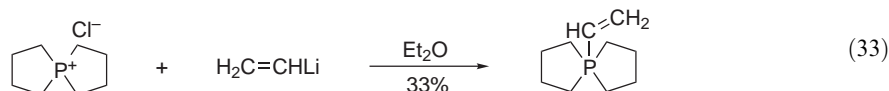
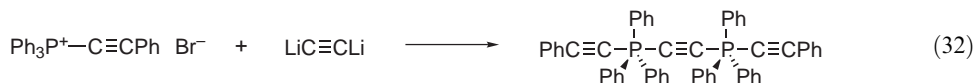
(iv) *Miscellaneous methods*

Nickel-catalyzed electrochemical coupling between diarylphosphinous halides and aryl or heteroaryl halides in the presence of NiBr₂bpy (0.1 equiv.) is useful for the preparation of triaryl or diaryl(heteroaryl)phosphines <1999JOM(584)387>.

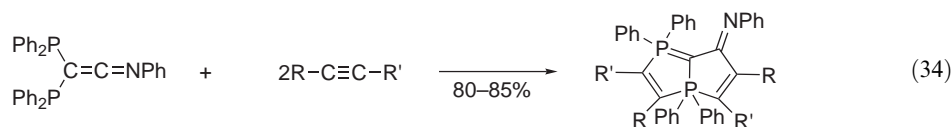
2.16.1.2 Phosphoranes

2.16.1.2.1 Pentaorganophosphoranes

Pentaorganophosphoranes are usually prepared by the reaction of tetraorganophosphonium salts with organolithiums (Equations (32) and (33)) <1993TL839, 2002JA6126>.

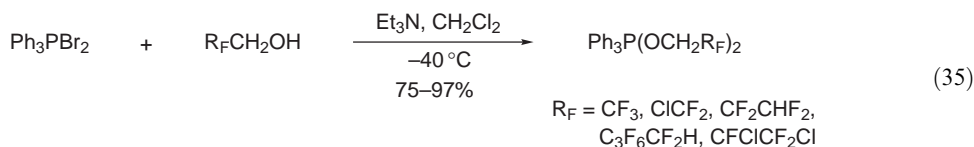


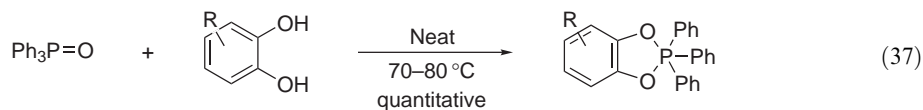
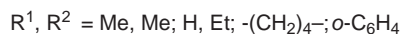
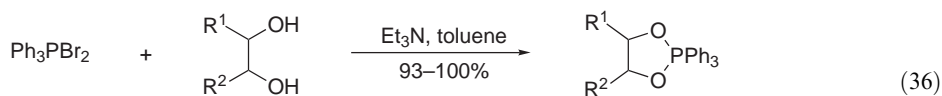
Little else is known about the synthesis of pentaorganophosphoranes. As a special case, 1λ⁵,3λ⁵-diphospholes containing the phosphorane unit have been synthesized by two consecutive [3+2]-cycloaddition reactions of a diphenyl keteneimine with 2 equiv. of an electron-poor alkyne (Equation (34)) <2002MI3872>.



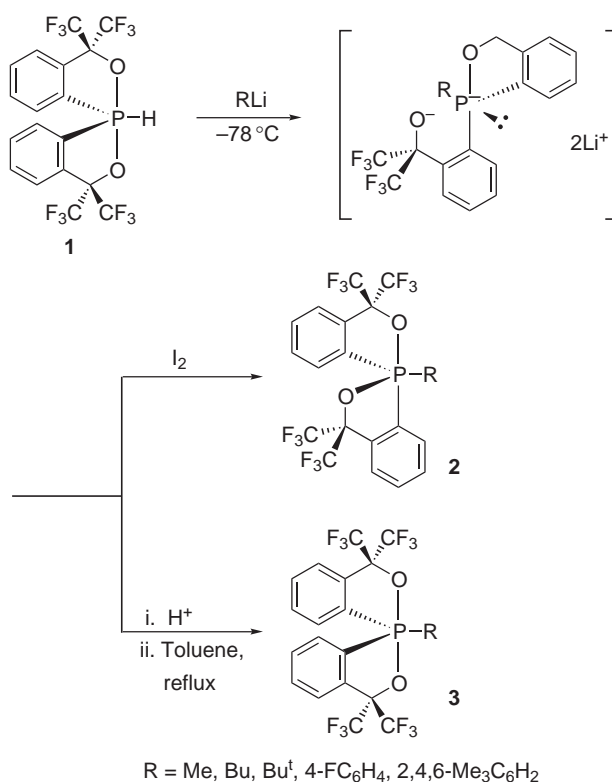
2.16.1.2.2 Dialkoxytriorgano- and alkoxytetraorganophosphoranes

Simple acyclic or cyclic dioxaphosphoranes are prepared by reaction of dibromotriphenylphosphorane with primary or secondary alcohols, cyclic alcohols, and pyrocatechol (Equations (35) and (36)) <1995JOC5696, 1996SL1123> in the presence of tertiary amines. Simply heating a mixture of triphenylphosphine oxide and *ortho*-dihydroxyaromatic compounds such as 1,2-dihydroxybenzenes and 2,3-dihydroxynaphthalene also leads to phenylenedioxy- or naphthylenedioxy triphenylphosphoranes in quantitative yields (Equation (37)) <2001MI1545>.



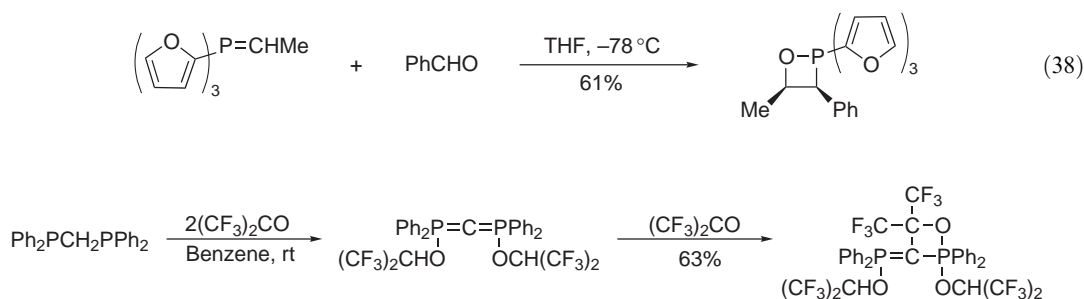


Compared with studies of the synthesis of simple acyclic or cyclic dioxaphosphoranes, spirocyclic dioxaphosphoranes have been extensively studied owing to their interesting molecular structure, fluxional rearrangements, steric effects, stereochemistry, etc. [<2002JA13154, 1996JA12866, 1997TL547, 1996TL8409, 1998JA6848>](#). Selective synthesis of spirocyclic dioxaphosphoranes containing O-equatorial (O-*cis*) **2** or O-apical (O-*trans*) **3** configurations has been made by the reaction of P-H phosphorane **1** with RLi, followed by treatment with I₂ or by heat after neutralization (Scheme 1).



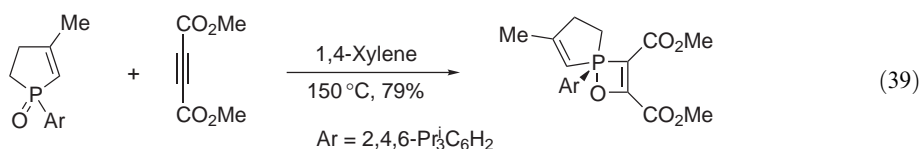
Scheme 1

1,2-Oxaphosphetanes are well known as reactive intermediates in the Wittig reaction. Accordingly, great attempts at their isolation or detection by NMR spectroscopy have been made. In the Wittig reaction of tri(2-furyl)phosphonium ylides with aromatic aldehydes, or of a carbodiphosphorane with hexafluoroacetone, the stable monocyclic oxaphosphetanes have been successfully isolated (Equation (38)) [<2002EJO1143>](#), (Scheme 2) [<2001EJI2377>](#).

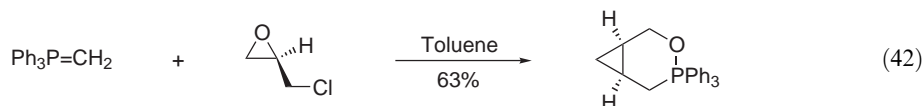
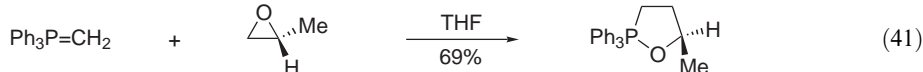
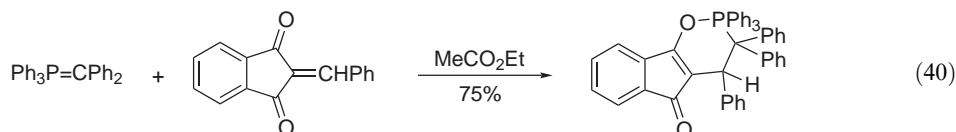


Scheme 2

The spiro derivatives of 1,2-oxaphosphetes possessing greater ring strain have been synthesized in good yield by [2 + 2]-cycloaddition of cyclic phosphine oxides with dimethyl acetylenedicarboxylate (Equation (39)) <2000T4823>.



Reactions using phosphonium ylides are also useful for the preparation of alkoxytetraorgano-phosphoranes such as oxaphosphinins and oxaphospholanes other than oxaphosphetanes. For examples, the reactions of benzyldenetriphenylphosphorane with α,β -unsaturated carbonyl compounds and of methylenetriphenylphosphorane with oxiranes result in oxaphosphinins (Equation (40)) <1997HAC157> and oxaphospholanes (Equations (41) and (42)) <1998T4243, 2002JOC286>, respectively.



2.16.2 PHOSPHORUS HALIDES

2.16.2.1 Arylphosphonous Dihalides (Aryldihalophosphines) (ArPX₂)

Although arylphosphonous dichlorides are usually prepared by the Friedel–Crafts reaction of phosphorus trichloride with aromatic hydrocarbons in the presence of AlCl₃, the synthesis of functionalized arylphosphonous dichlorides free from contamination of isomers is achieved by treatment of aryl(bis(diethylamino))phosphines, which are prepared by the reaction of aryl-lithiums (or Grignard reagents) with ClP(NEt₂)₂, with dry HCl (Method A) (Equation (43); see Table 4) <2003MM291>.

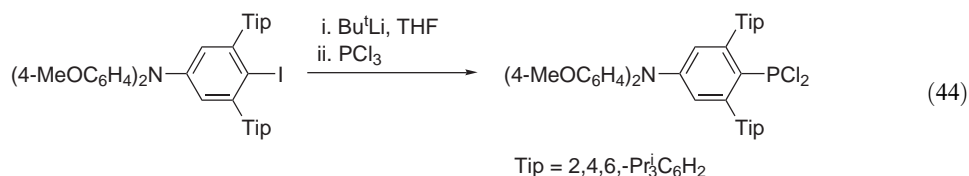


Table 4 Preparation of aryl- and alkenyl- or alkynylphosphonous dihalides (ArPCl₂)

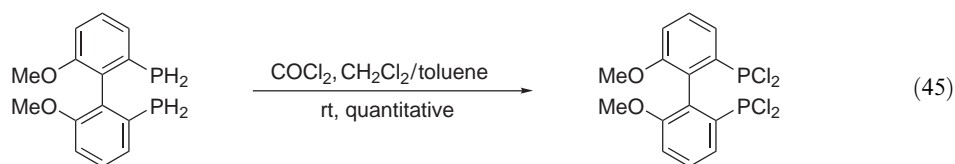
Entry	Method	Ar	Yield (%)	References
1	A	4-Bu ⁿ C ₆ H ₄	75	<2003MM291>
2	A	4-(C ₁₂ H ₂₅)C ₆ H ₄	84	<2003MM291>
3	A	Ph	No data	<2002TL5075>
4	A	2,4,6-Me ₃ C ₆ H ₂	No data	<2002TL5075>
5	A	2-(Ph ₂ P)C ₆ H ₄	95	<1999TA2129>
6	B	2-(PhOCH ₂)-4,6-Bu ^t ₂ C ₆ H ₂	No data	<2002TL7953>
7	B	2,6-(2,4,6-Me ₃ C ₆ H ₂) ₂ C ₆ H ₃	No data	<1996MI369>
8	B	2,3,5,6-Bu ^t ₄ -4-(Cl ₂ P)C ₆	56	<2000IC3860>
9	B	9-Anthryl	80	<1999OM4222>
10	B	2,4,6-(F ₃ C) ₃ C ₆ H ₂	42	<2001EJ1729>
11	A	PhC≡C	No data	<2002TL5075>
12	A	(2,4,6-Me ₃ C ₆ H ₂)C≡C	No data	<2002TL5075>
13	M ^a	CH ₂ =C=CH	23	<1999OM5259>
14	M ^a	CHCl=CPh	39	<2001MI813>
15	M ^a	4-(Ph ₂ N)C ₆ H ₄	87	<1999MI161>

^a Miscellaneous method.

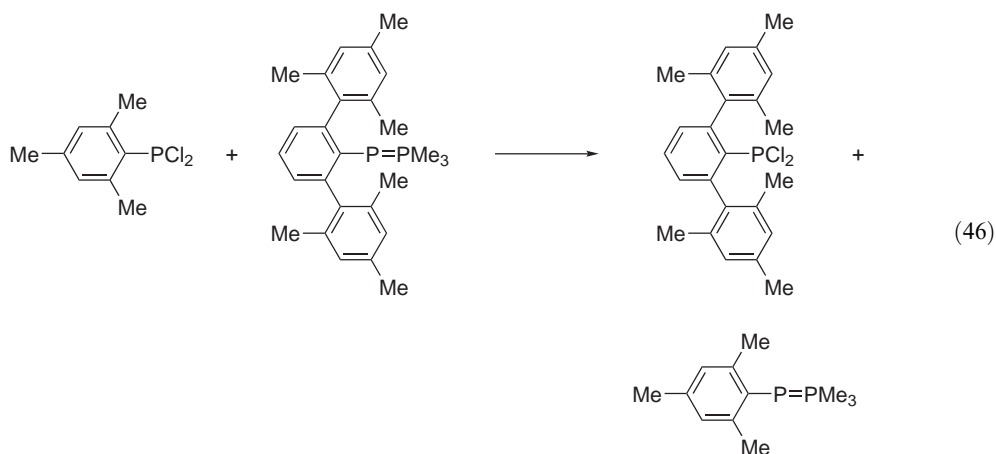
Sterically hindered arylphosphonous dichlorides are prepared from the corresponding aryllithiums (or Grignard reagents) and PCl₃ (method B) (Equation (44)) <2002HCA3842, 2002TL7953, 1996MI369>.



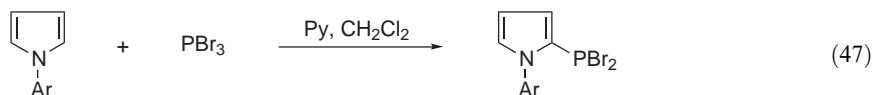
Although not in common use, chlorination of primary phosphines with phosgene leads to arylphosphonous dichlorides (method C) (Equation (45)) <2002OM7>.



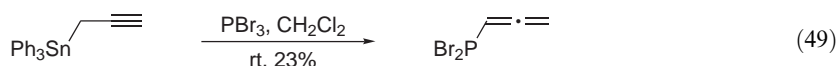
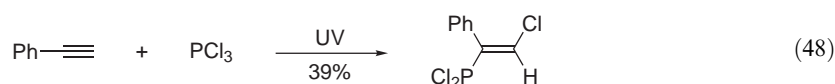
As shown below, various preparative methods for aryl- or alkenylphosphonous dihalides have been reported. Synthesis of sterically hindered arylphosphonous dichlorides is also achieved by an unusual intermolecular chlorine atom transfer process between diphosphenes and arylphosphonous dichlorides (Equation (46)) <2003JA40>.



The direct reaction of arylamines such as triphenylamine <1999MI161> or heteroaromatic compounds, e.g., pyrroles <2002HAC223>, furans <2001CHE1181>, thiophenes <2001CHE1181>, or phospholes <2002JOM(643–644)32>, with phosphorus tribromide (or phosphorus trichloride) in the presence of pyridine (and/or triethylamine) leads to regioselective dibromo(or dichloro)phosphination products (Equation (47)).

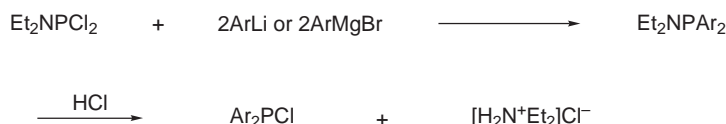


Alkenylphosphonous dichlorides and allenylphosphonous dibromides are obtained by regio- and stereospecific addition of phosphorus trichloride to alkynes under UV irradiation and by reaction of propargylstannanes with phosphorus tribromides (Equations (48) and (49)) <2001MI813, 1999OM5259>.



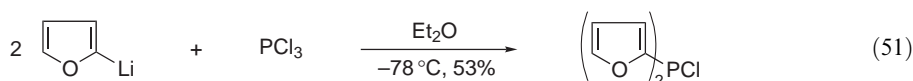
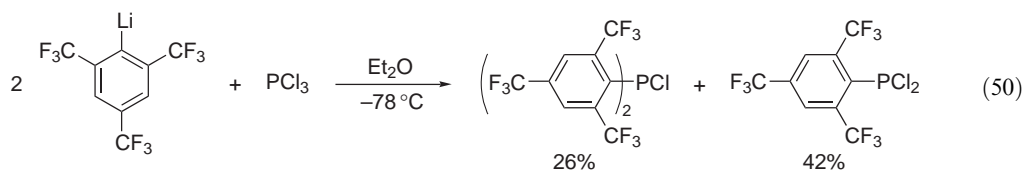
2.16.2.2 Diarylphosphinous Halides (Diarylhalophosphines) (Ar_2PX)

In general, diarylphosphinous halides are synthesized by methods similar to those of arylphosphonous halides. Reaction of Et_2NPCI_2 with 2 equiv. of aryllithium (or arylmagnesium bromide) gives intermediate diaryl(diethylamino)phosphines, and subsequent treatment with HCl in ether (or THF) leads to diarylphosphinous halides (method A) (Scheme 3) <2001HCA3105>.

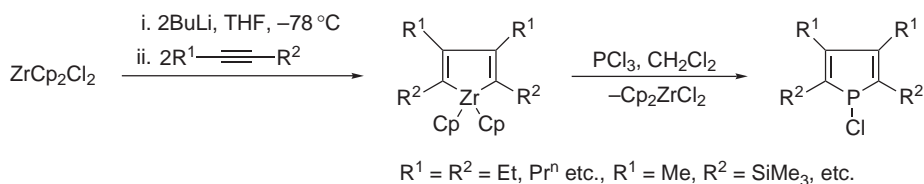


Scheme 3

Diaryl or heteroarylphosphinous halides are also prepared by the reaction of 2 equiv. of an aryllithium or heteroaryllithium with 1 equiv. of a phosphorus trihalide at low temperature (method B) (Equations (50) and (51)) <2001EJI1729, 2001TA263>.



1-Chlorophospholes, which are examples of cyclic phosphinous halide species, are made in good yield by treatment of bis-(cyclopentadienyl)-1-zirconacyclopenta-2,4-dienes with phosphorus trichloride (Scheme 4) <2002NJC1378, 2002OL1245, 2001ZAAC1741>.



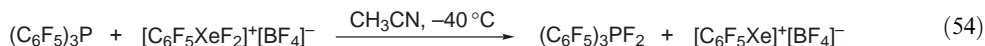
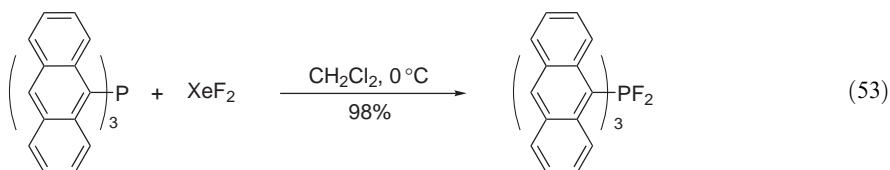
Scheme 4

2.16.2.3 Arylhalophosphoranes

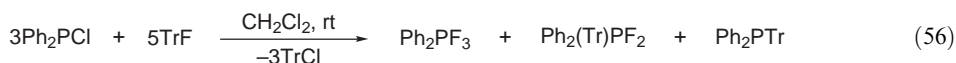
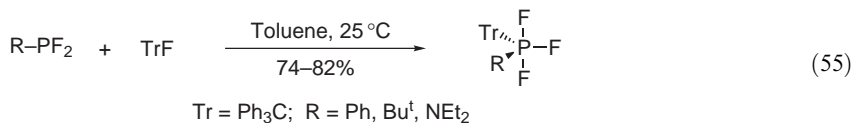
Although triphenylphosphine dichloride is generally prepared by the direct reaction of triphenylphosphine with dichlorine in a 1:1 stoichiometric ratio, the structure is very delicate and dependent upon the solvent used in the reaction. To obtain five-coordinate dichlorotriphenylphosphorane, which retains a trigonal bipyramidal structure and not the ionic structure, the reaction is required to be carried out in a nonpolar solvent or less polar solvent (Equation (52)) <1998CC921>.



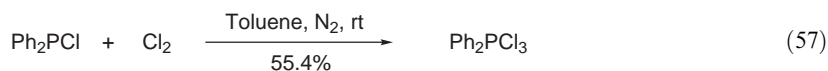
In comparison with dichlorotriarylphosphorane, there is little limitation on the solvent used in preparations of the corresponding difluorophosphoranes, since they retain a pentacoordinate structure in aprotic polar solvents such as dichloromethane. Preparation of difluorotriaryl- or difluorodiarylvinylphosphoranes is generally performed by treatment of the phosphines with xenon difluoride in dichloromethane or chloroform (Equation (53)) <2002JOM(646)277, 2001JFC(112)35>. Difluorotriarylphosphoranes are also prepared by oxidation of the phosphines with an aryldifluoroxenonium(IV) salt (Equation (54)) <2000AG(E)391>.



Trityl fluoride (trityl = triphenylmethyl) is sometimes effective as a fluorinating agent of phosphorus compounds to give fluorophosphoranes. For example, air-stable aryltrityl or alkyltrityl trifluorophosphoranes are obtained by the oxidative addition of trityl fluoride to difluorophosphines (Equation (55)) <1999ZAAC1278>. The reaction between trityl fluoride and diphenylphosphinous chloride provides fluorophosphoranes via halogen exchange reaction (Equation (56)) <1998JFC(92)173>.



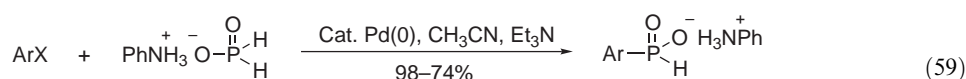
The corresponding five-coordinate neutral trichlorodiphenylphosphorane is simply prepared by injection of chlorine gas into a solution of diphenylphosphinous chloride in toluene (Equation (57)) <1999IC2524>.



2.16.3 COMPOUNDS WITH A P—O BOND

2.16.3.1 Arylphosphonous (ArP(OH)₂) and Unsaturated Phosphonous Acids, and Their Derivatives

As described in COFGT (1995) <1995COFGT(2)819>, arylphosphonous acids (ArP(OH)₂) normally exist as arylphosphinic acids (ArPH(O)(OH)). Accordingly, free acids containing a single C—P bond are similarly termed phosphinic acids. Arylphosphinic or alkenylphosphinic acids are commonly synthesized via hydrolysis of the corresponding phosphonous dichlorides with small amounts of water under mild conditions (Equation (58)), since the phosphonous dichlorides are available or accessible to some extent (Section 2.16.2.1). However, this method is often limited in the functionality and the yield of the starting phosphonous dichlorides. These disadvantages have been overcome by palladium-catalyzed cross-coupling reactions of anilinium hypophosphite with aryl or alkenyl halides. Various monoaryl-substituted phosphinic acids can be prepared in high yields by the reaction of functionalized aryl iodides (or aryl bromides) with anilinium hypophosphite in the presence of a catalytic amount of palladium(0) catalyst and excess triethylamine (3 equiv.) (Equation (59)) <2001JA510>.



Ar = Ph, 2-MeC₆H₄, 4-MeC₆H₄, 4-O₂NC₆H₄, 4-MeOC₆H₄, 2-Naphthyl, etc.

Similar cross-coupling reactions of anilinium hypophosphite with alkenyl bromides and triflates result in monosubstituted phosphinic acids in good yields (Equation (60); see Table 5) <2002JOM(653)252>. This methodology was effective in the synthesis of some of GABA analogs (Scheme 5).

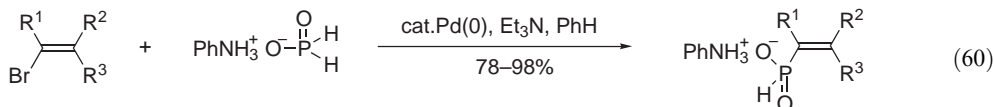
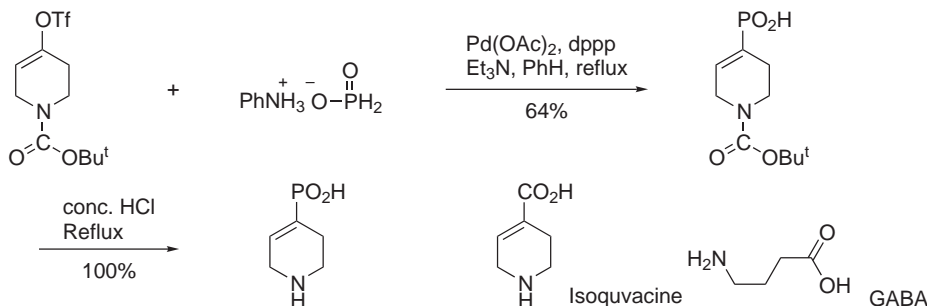


Table 5 Synthesis of alkenylphosphinic acids

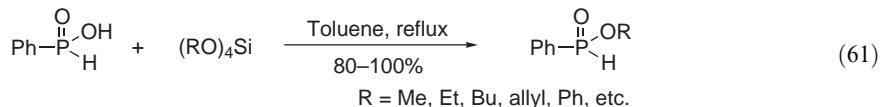
R ¹	R ²	R ³	Yield (%)
Ph	H	H	98
Hex	H	H	85
H	Ph	H	94
H	Me	Me	78
—(CH ₂) ₄ —		H	96

Source: <2002JOM(653)252>.

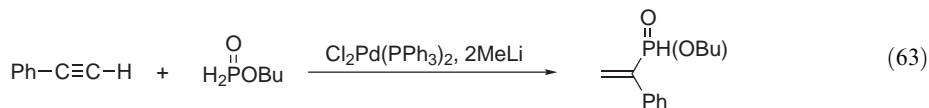
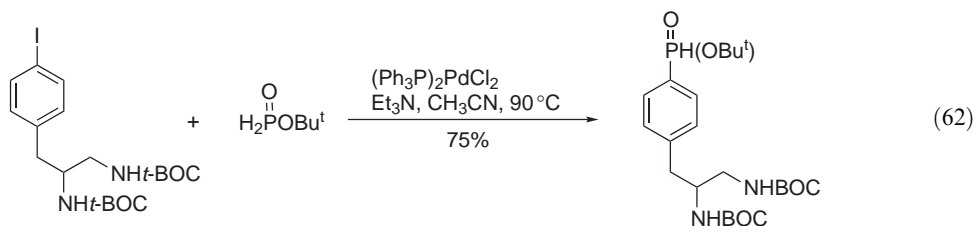


Scheme 5

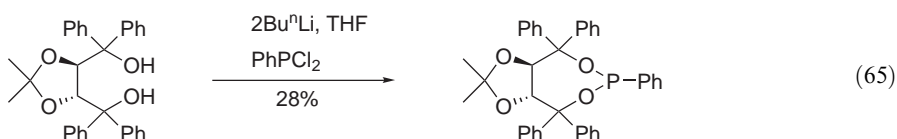
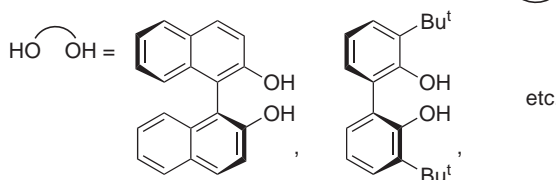
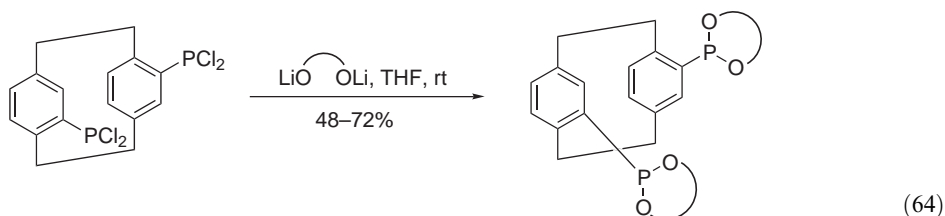
Preparation of monosubstituted phosphinic acid esters has often been performed via esterification of the phosphinic acids with diazoalkane, carbodiimide/alcohol, RCOCl /alcohol, etc. <1995COFGT(2)819>. These existing methods contain some problems such as selectivity, inconvenience, or limitations. To avoid these disadvantages, an esterification method of phosphinic acids utilizing orthosilicates has recently been developed (Equation (61)) <2000OL3341>. When the corresponding orthosilicate is not available, reflux of a mixture of a phosphinic acid, an alcohol, and tetraphenoxysilane in toluene gives the desired ester via transesterification.

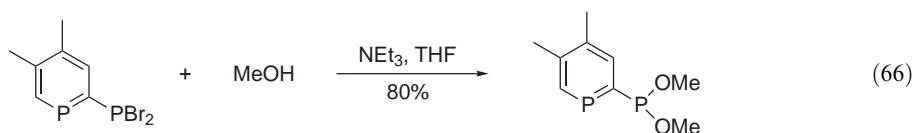


As described for the palladium-catalyzed reaction of aryl or alkenyl halides with anilinium hypophosphites, monosubstituted phosphinic acid esters are produced directly by palladium-catalyzed cross-coupling reactions of aryl iodides with hypophosphorus acid esters (Equation (62)) <1996TL425>. Alkenes and alkynes undergo palladium-catalyzed addition of hypophosphorus acid esters to provide regioselectively controlled alkyl- or alkenylphosphinic acid esters in excellent yields (Equation (63)) <2002JA9386>.

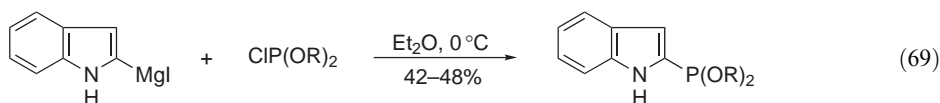
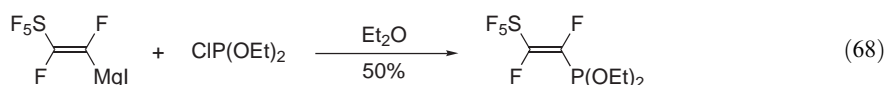
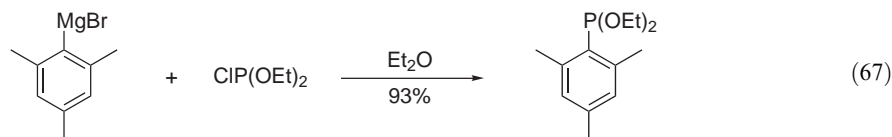


Chiral dialkyl arylphosphonites as well as chiral tertiary arylphosphines have often been utilized in recent years as ligands of metal complex catalysts for catalytic asymmetric synthesis. Accordingly, various types of the chiral phosphonites have been actively developed. The dialkyl or cyclic phosphonites are normally prepared by treatment of the phosphonous dichlorides with 2equiv. of alcohol or 1equiv. of glycol in the presence of base (Equations (64)–(66)) <2001OL3687, 2000EJO4011, 2001OM2966, 1996OM1597>.





Alternatively, the dialkyl aryl- and vinylphosphonites are provided by the action of aryl- and vinylmagnesium halides (or the corresponding organolithiums) on dialkyl phosphorochloridites (Equations (67)–(69)) [<2001T10299, 2001HAC300, 1997HAC467, 2001MI1033>](#).

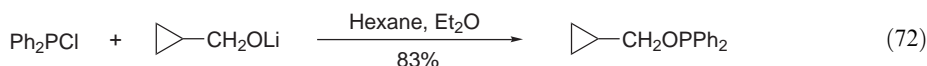
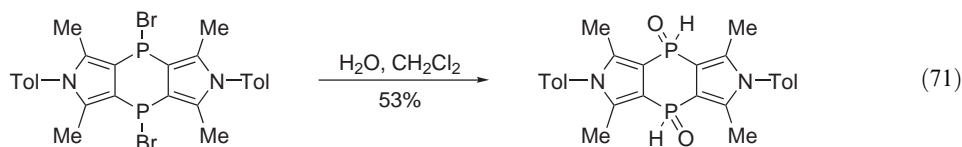
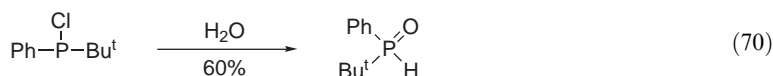


2.16.3.2 Arylphosphinous Acids (ArRPOH) and Their Derivatives

Diarylphosphinous acids (Ar₂POH) and diarylphosphine oxides (Ar₂P(O)H) are in tautomeric equilibrium.

2.16.3.2.1 Diarylphosphinous halides with water or alcohols

Diarylphosphinous halides show similar chemical properties toward water (Equations (70) and (71)) [<2000EJO3205, 2002HAC46>](#) and alcohols (Equation (72)) [<2003JA886>](#) as those of arylphosphonous dihalides.



2.16.3.2.2 Dialkyl phosphonates with Grignard reagents

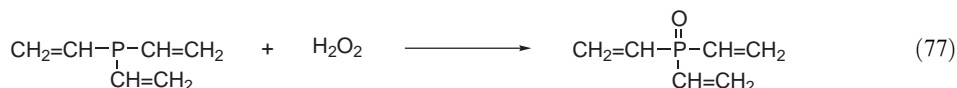
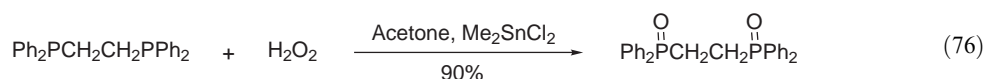
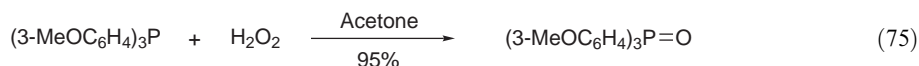
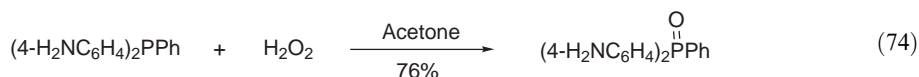
The conventional method for preparation of secondary phosphine oxides is via the reaction of dialkyl phosphonates with 3 equiv. of a Grignard reagent (or organolithium) followed by hydrolysis (Equation (73)).



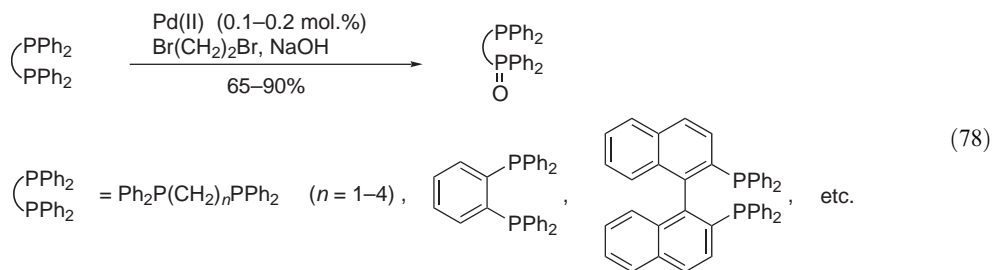
2.16.3.3 Tertiary Arylphosphine Oxides

2.16.3.3.1 Oxidation of tertiary phosphines (method A)

The oxidation of tertiary phosphines with oxidizing agents is still one of the most useful methods for the preparation of tertiary phosphine oxides. Of a wide variety of oxidizing agents, hydrogen peroxide is frequently utilized as oxidant (Equations (74)–(77)) <1995JOC3499, 2002EJO269, 2000CC1901, 2003OM145>.

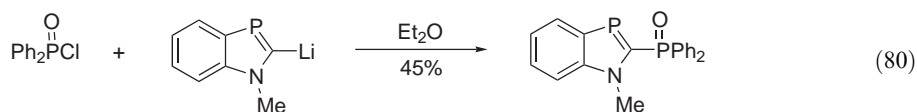
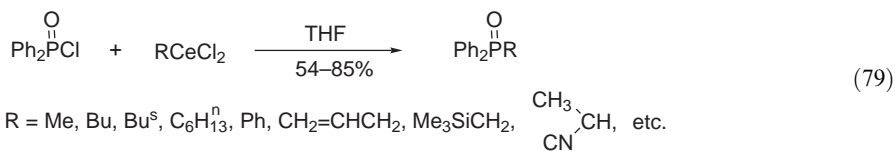


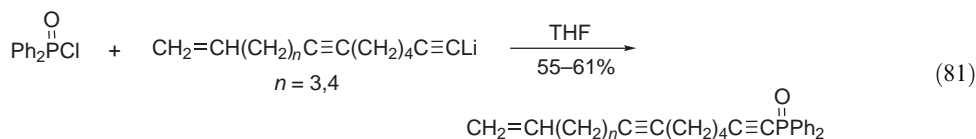
In addition to hydrogen peroxide, oxidizing agents such as air <1999JMO(148)17>, KMnO_4 <1995JOC3499>, pyridine *N*-oxides/oxorhenium(V) catalysts <2000OL3525, 2001IC2437>, and triarylbismuthane oxide <2001JA6443> are also useful for the preparation of tertiary phosphine oxides. However, these oxidizing agents are nonselective to oxidation of bisphosphines. The highly selective synthesis of bis-phosphine monoxides has been achieved by treatment of the corresponding bis-phosphines with catalytic amounts of a Pd(II) salt in the presence of dibromomethane and alkali (Equation (78)) <2001OM3950>.



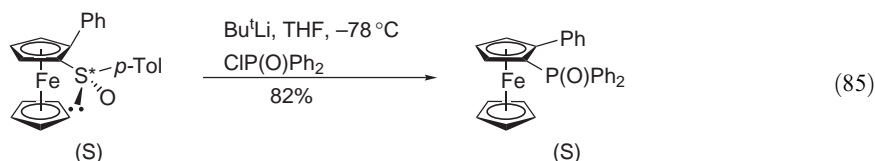
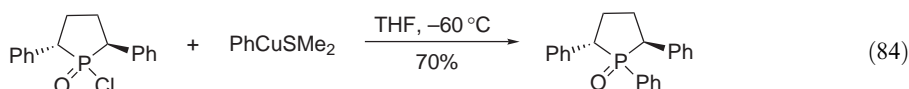
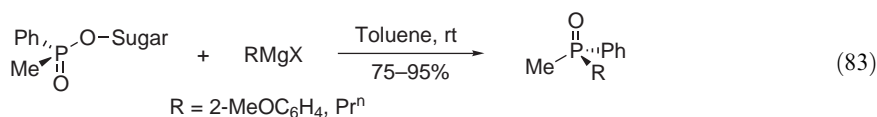
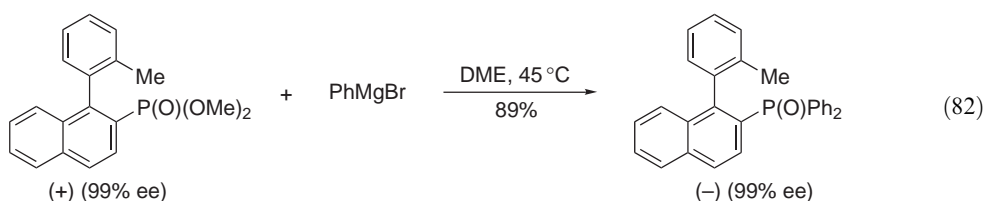
2.16.3.3.2 Phosphorus halides or esters with organometallic reagents

Tertiary phosphine oxides are also produced from the reaction of phosphorus oxyhalides, phosphonic dihalides, or phosphinyl halides (Equations (79)–(81)) <1999EJO2299, 2002OM912, 2003JOC378>, or their esters, with organometallic reagents such as Grignard and organolithium reagents.

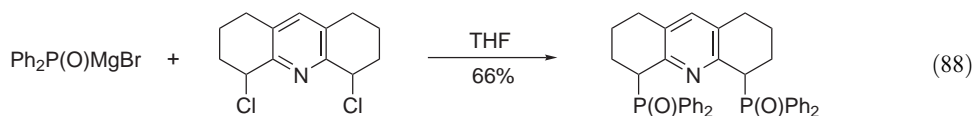
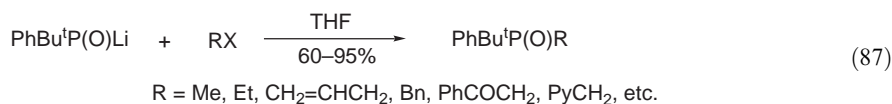
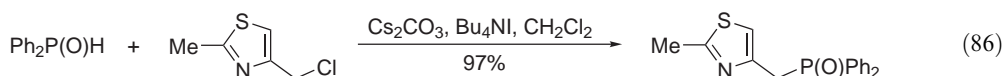




Recent interest in this area has been focused on the development of chiral tertiary phosphine oxides which are one of the key precursors for the preparation of chiral tertiary phosphine ligands for asymmetric catalytic synthesis. In order to realize this, two ways of using chiral phosphonic acid esters (or phosphinate esters possessing chirality at a P atom, i.e., P-chiral phosphinate esters) and chiral organolithium reagents as chiral auxiliaries have been studied. Reaction of axially chiral biaryl phosphonate esters [<2000JA12051>](#), P-chiral phosphinate esters [<1996TA3353, 1997JOM\(529\)435>](#) or P-chiral phosphinyl chlorides [<2002T5895>](#) with Grignard (or organolithium) reagents leads to the corresponding axially chiral phosphine oxides or P-chiral phosphine oxides in high optical yields. Treatment of achiral diarylphosphinyl chlorides with chiral *ortho*-functionalized ferrocenyllithium reagents [<2002JOC7982>](#) also produces chiral phosphine oxides ([Equations \(82\)–\(85\)](#)).

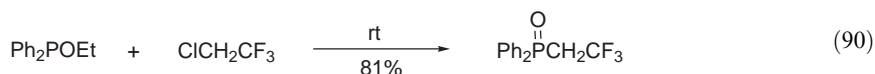
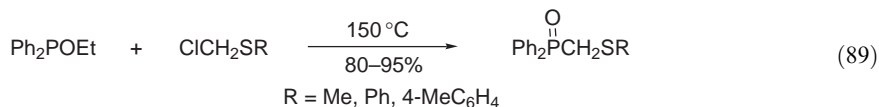


The reaction of diarylphosphinic acid alkali metal salts with alkyl halides is often useful for the preparation of tertiary phosphine oxides of the type $\text{Ar}_2\text{P}(\text{O})\text{R}$ ([Equations \(86\)–\(88\)](#)) [<2000OL1633, 2000EJO3205, 2000IC4591>](#).



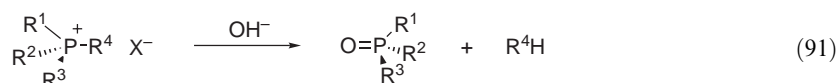
2.16.3.3 Michaelis–Arbuzov reaction of phosphinic acid esters with alkyl halides

The Michaelis–Arbuzov reaction of phosphinic acid esters with alkyl halides to prepare tertiary phosphine oxides is mainly applied to the cases using reactive alkyl halides as alkylating agents to avoid the alkyl halide reacting again with the starting esters (Equations (89) and (90)) <1997T10527, 2002JOC3156>.

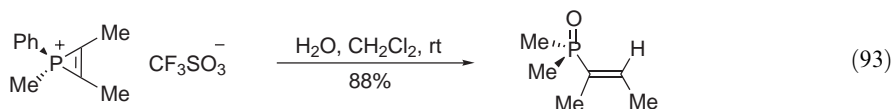
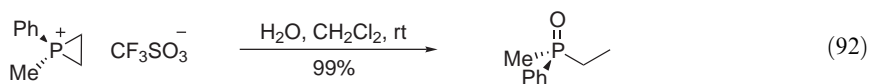


2.16.3.4 Hydrolysis of phosphonium salts

The alkaline hydrolysis of phosphonium salts leads to phosphine oxides with inversion of configuration at phosphorus (Equation (91)).

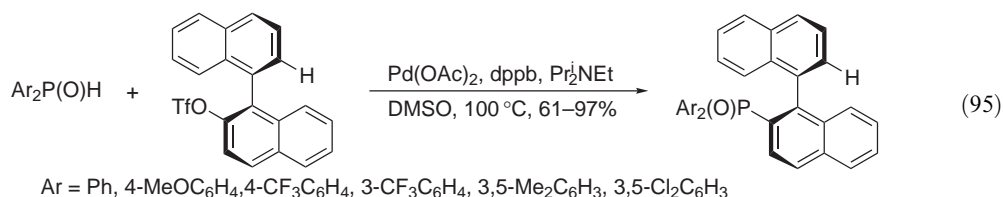
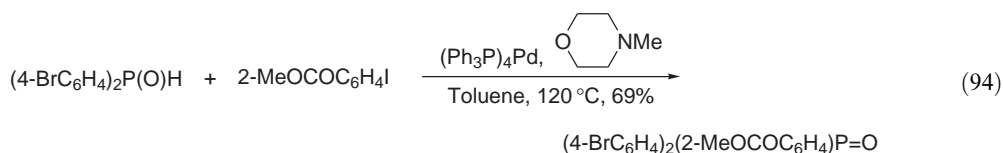


The strained phosphiranium and phosphirenium salts undergo ring opening with water to give the corresponding ethyl- and vinylphosphine oxides (Equations (92) and (93)) <1997JOM(529)189>.



2.16.3.5 Palladium-catalyzed reaction of alkenyl or aryl bromides with secondary phosphine oxides

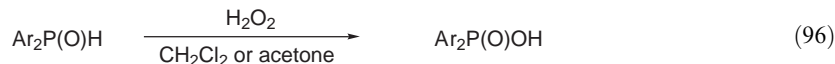
Preparation of tertiary phosphine oxides via palladium-catalyzed reaction of alkenyl or aryl bromides with secondary phosphine oxides in the presence of tertiary amines and a catalytic amount of Pd(0) catalyst is becoming increasingly important due to the simplicity and effectiveness of its use (Equations (94) and (95)) <1997JOM(529)189>.



2.16.3.4 Arylphosphinic Acids (ArRP(O)OH) and Their Derivatives

2.16.3.4.1 Oxidation of secondary phosphines or phosphine oxides

This method (Equation (96)) is the conventional method for the synthesis of simple diarylphosphinic acids, since diarylphosphines or diarylphosphine oxides are easily prepared as described in Section 2.16.3.2.

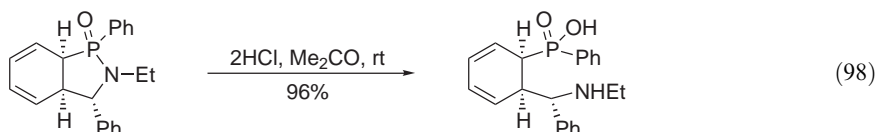


2.16.3.4.2 Hydrolysis of arylphosphinyl halides ($\text{Ar}_2\text{P(O)Cl}$) or arylphosphinic amides ($\text{Ar}_2\text{P(O)NR}_2$)

Diarylphosphinyl halides show similar chemical properties toward water as those of diarylphosphinous halides (Equation (97)).



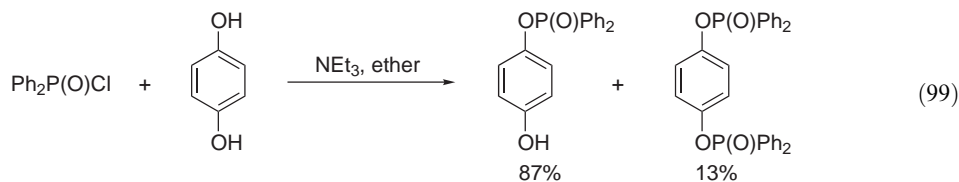
Cyclic arylphosphinic amides (1-aza-2 λ^5 -phosphole 2-oxides) also undergo hydrolysis in aqueous acetone to give γ -aminoarylphosphinic acids (Equation (98)) <2002JOC3852>.

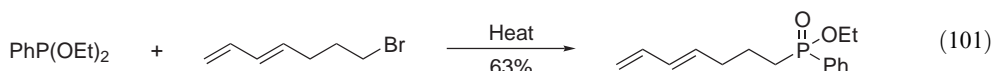


2.16.3.4.3 Arylphosphinic acid derivatives

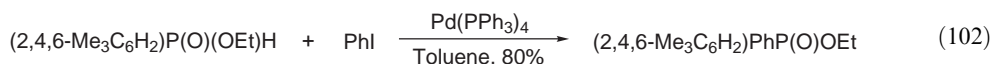
A wide variety of methods for the preparation of aryl- or alkenylphosphinic acid esters have been developed. These are: (i) reaction of arylphosphinic chlorides with alcohols in the presence of tertiary amines <1996TA3353, 2002HAC126>; (ii) alcoholysis of arylphosphinic amides under acidic conditions <1997JOM(529)435>; (iii) the Arbuzov reaction of dialkyl aryl phosphonites with alkyl halides <2002MI486, 2002JOC6174, 2002BMC41> or the intramolecular Arbuzov rearrangement of dialkyl aryl phosphonites initiated by anodic oxidation <1996TL1625>; (iv) palladium-catalyzed reactions of alkenyl or aryl bromides (or iodides) with monoalkyl or monoaryl phosphonites <2001T10299, 1998MI(357)227, 1996BMCL2073, 2001JCS(P1)2389>; (v) palladium-catalyzed hydrophosphinylation of alkynes with aryl phosphinates <2002JA3842>; (vi) the Horner–Emmons reaction of phosphinyl methyl phosphonates with aldehydes <2002JOM(662)83>; (vii) phosphorylation of alcohols and phenols by phenylmethylenephosphine oxide <1998JOM(570)49, 2001MI1737, 2002HAC626>; (viii) the reaction of chloroalkenes with a phosphinidene–pentacarbonyltungsten complex $[\text{PhP-W(CO)}_5]$, followed by an oxidative decomplexation with trimethylamine oxide <2000JOC652>; and (ix) miscellaneous methods <2001TL6121, 2001EJO911, 2002JOC4407, 2003BMC427>.

Methods 1–3 are conventionally used for the preparation of phosphinic acid esters (Equations (99)–(101)) <2002HAC126, 1997JOM(529)435, 2002JOC6174>.

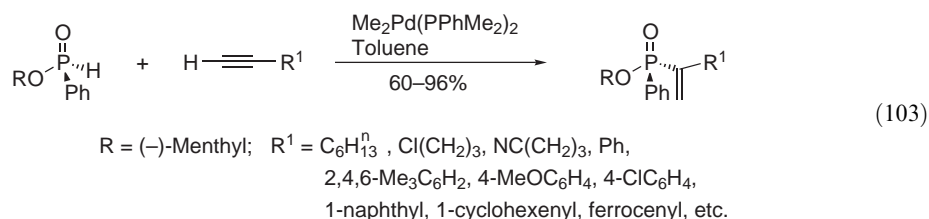




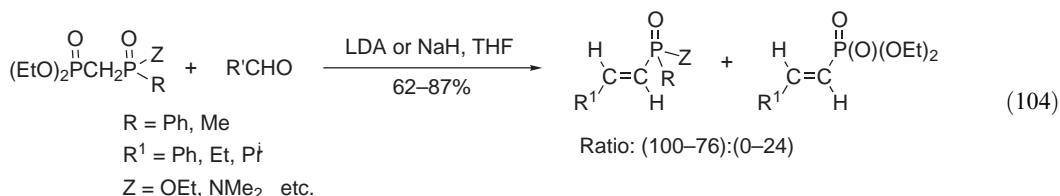
Palladium-catalyzed cross-coupling (method 4) has recently become an important tool for the preparation of arylphosphinic acid esters as well as the arylphosphonous acid esters and tertiary arylphosphine oxides described in Sections 2.16.3.1 and 2.16.3.3.5 (Equation (102)) <2001T10299>.



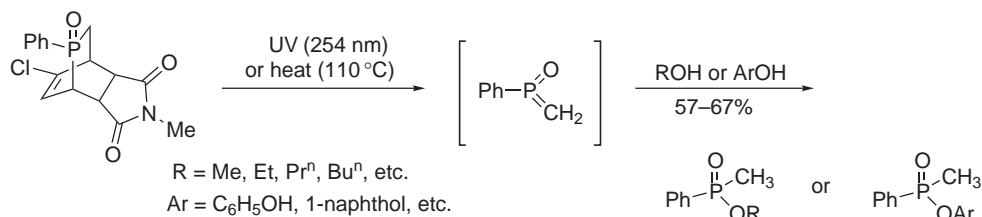
In addition, palladium-catalyzed hydrophosphinylation of a variety of alkynes with menthyl phenyl phosphinate takes place stereospecifically to give vinyl phosphinates in high yields with retention of configuration at phosphorus (method 5) (Equation (103)).



Although method 6 is also applicable to the preparation of chiral vinyl phosphinates and vinylphosphinic amides, the vinylphosphinic derivatives are not avoided, thus contaminating the product with undesired vinyl phosphonates (Equation (104)) <2002JOM(662)83>.



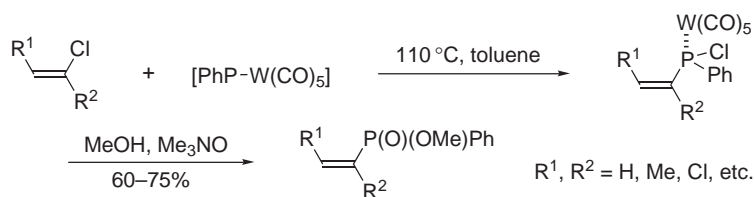
Phenylmethylenephosphine oxide, generated *in situ* by UV light-mediated photolysis <1998JOM(570)49> or thermolysis <2001MI1737> of the 2-phosphabicyclo[2.2.2]octane framework, is easily trapped with alcohols or phenols to afford phosphinic acid esters (method 7) (Scheme 6).



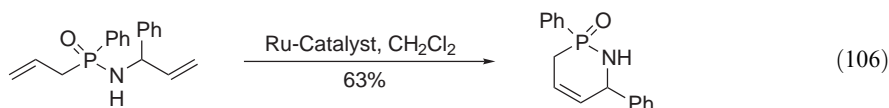
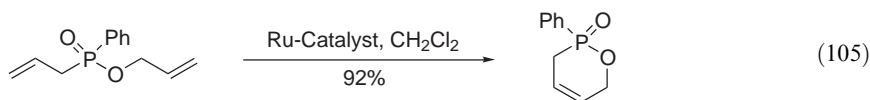
Scheme 6

A new route to vinylphosphinic acid esters via formal insertion of phosphinidenes into the carbon–chlorine bond of chloroalkenes with retention of the alkene stereochemistry as shown in Scheme 7 has recently been developed (method 8).

As a further example of the efficient synthesis of phosphinic acid derivatives utilizing organo-metallic reagents, ring-closing metathesis of dienes in the presence of Grubbs' catalyst for the synthesis of cyclic phosphinic acid esters and amides has been reported to afford [1,2]oxaphosphine 2-oxides and 1*H*-[1,2]azaphosphinine 2-oxides in high yields (Equations (105) and (106)) <2000T2053>.



Scheme 7



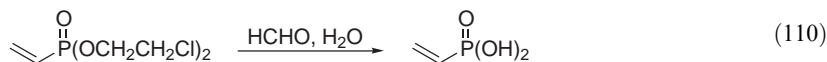
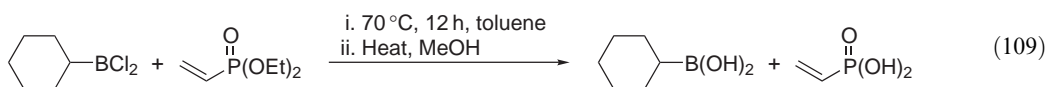
2.16.3.5 Arylphosphonic Acids (ArP(O)(OH)_2) and Unsaturated Phosphonic Acids, and Their Derivatives

2.16.3.5.1 Hydrolysis of phosphonic halides, esters, amides, and aryltrichlorophosphonium salts (method A)

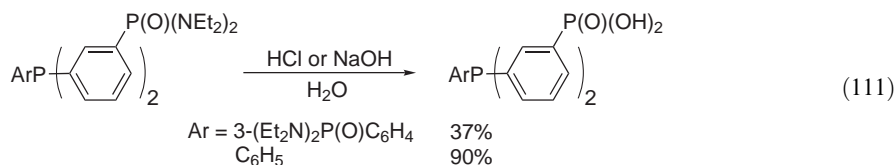
Arylphosphonic chlorides and alkenylphosphonic chlorides easily hydrolyze in water solution to the corresponding phosphonic acids (Equation (107)) <1995COFGT(2)819>.



Hydrolysis of arylphosphonic esters is catalyzed by acids or bases <1995COFGT(2)819>. A more convenient procedure for the hydrolysis is stirring the substrate with HCl in water (Equation (108)) <2002TL7659, 2002HCA1140, 1999BMCL1443, 1995S539>. Diethylvinylphosphonate is deprotected by organoboranes under mild conditions (Equation (109)). The bis-(β -chloroethyl) ester of vinylphosphonic acid hydrolyzes in the presence of formaldehyde (50–200 mol.%) and vinylphosphonic acid (1–10 mol.%) (Equation (110)) <2003PCT016319>.

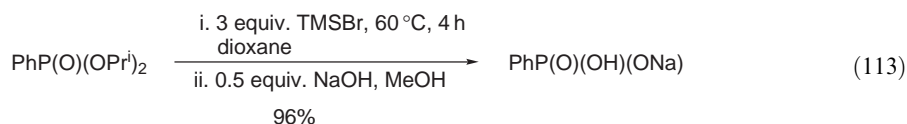
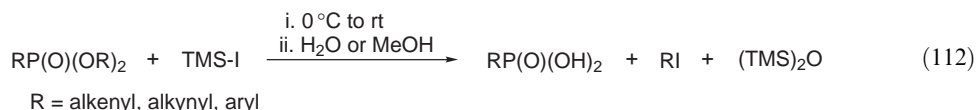


Arylphosphonic amides undergo acid-catalyzed hydrolysis under rather mild conditions (Equation (111)) <2001TL5373, 1999ZAAC707>.



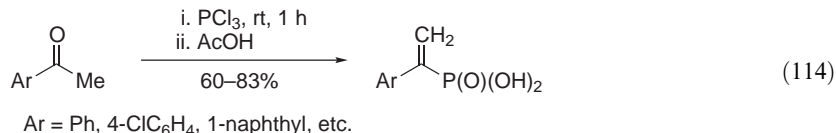
2.16.3.5.2 Dealkylation of phosphonic acid esters with iodotrimethylsilane (method B)

Iodotrimethylsilane cleaves alkyl groups in phosphonic acid dialkyl esters yielding bis-(trimethylsilyl) esters, which are easily hydrolyzed to phosphonic acids (Equation (112)) <2002TL4017, 2002TA961, 2000BMCL1241, 1995COFGT(2)819>. However, iodotrimethylsilane is not suitable for the substrates containing labile functional groups. Bromotrimethylsilane is a more general reagent for removal of alkyl esters of phosphonic acids <2002HAC654, 2002T7573, 2002JOC8191, 2001EJO477, 1996TL4701>. It cleaves isopropyl esters efficiently and chemoselectively if used in excess in dioxane (Equation (113)) <1995TL6759>. Chlorotrimethylsilane is used mainly for dealkylation of more labile dimethyl phosphonates <1995JOC74>. Following an efficient modification of the methodology with chlorotrimethylsilane, chlorotrimethylsilane in chlorobenzene has been developed as a reagent that readily cleaves diethyl vinyl phosphonates in high yield in the presence of a wide variety of functional groups <2001MI1299>.



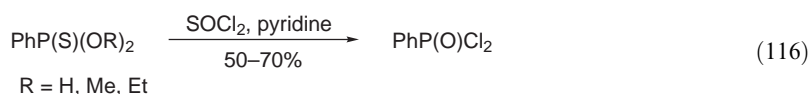
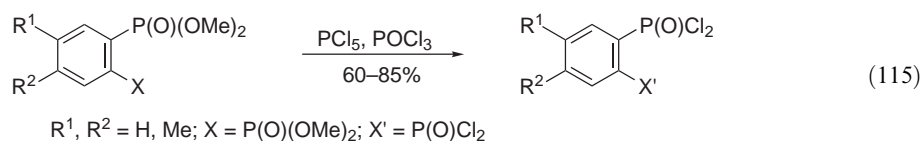
2.16.3.5.3 Miscellaneous methods

1-Arylethenylphosphonic acids are prepared by phosphorylation of acetylenes with phosphorus trichloride in the presence of glacial acetic acid (Equation (114)) <2002MI573>.

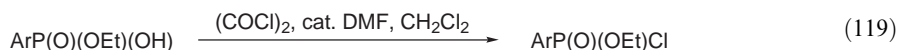
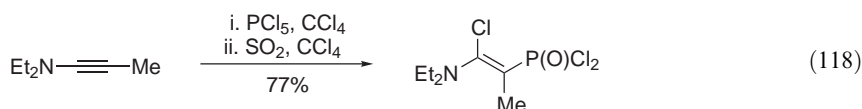
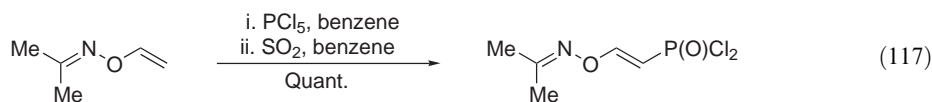


2.16.3.5.4 Phosphonic acid derivatives

Arylphosphonic dichlorides are generally prepared by treatment of the phosphonic acid with PCl₅ or SOCl₂, or by oxidation of arylphosphorus dichlorides <1995COFGT(2)819>. Arylphosphonic acid dimethyl esters are transformed to arylphosphonic dichlorides on treatment with PCl₅–POCl₃ (Equation (115)) <2001MI1821>. Treatment of phenylthiophosphonic acid or its dialkyl esters with thionyl chloride in the presence of pyridine gives phenylphosphonic dichloride (Equation (116)) <2002PS(177)1093>.



Alkenylphosphonic dichlorides are prepared by the addition of phosphorus pentachloride to alkene <2001MI979> or alkyne <1996MI1054>, with subsequent reaction with sulfur dioxide (Equations (117) and (118)). Aryl phosphonochloridates are obtained by treatment of monoalkyl aryl phosphonates with oxalyl chloride (Equation (119)) <2000OL3887>.

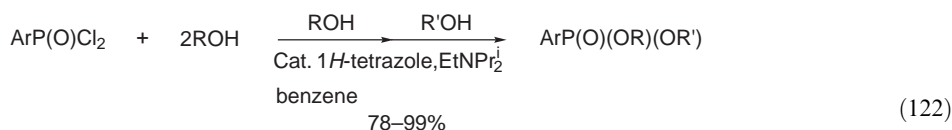
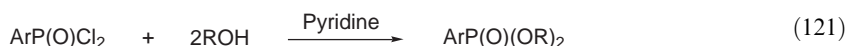


Monoalkyl aryl or alkenyl phosphonates are prepared by monoalkylation of the phosphonic acids <1995COFGT(2)819>, partial alkaline hydrolysis <2002T7573, 2001BMC395>, or monodealkylation <2002OL1687, 2001OL1597, 2001PS(174)1, 1998S381> of the dialkyl phosphonates (Equation (120)).

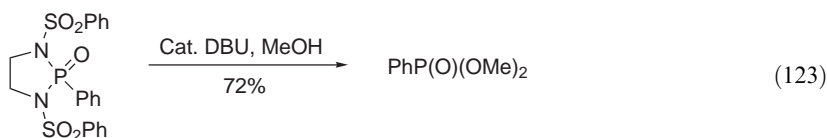


Phosphonic acid esters are prepared by the following methods: (i) alcoholysis of phosphonic dichlorides or active phosphonic esters; (ii) *O*-alkylation of phosphonic acids or their monoesters; (iii) the Arbuzov reaction or the Arbuzov type reaction of aryl halides with trialkyl phosphites; (iv) the reaction of dialkyl phosphorochloridates with organometallic reagents; (v) the Michaelis–Becker reaction or the Michaelis–Becker type reaction of dialkyl phosphonate ions with aryl halides; (vi) the palladium-catalyzed reaction of aryl halides with dialkyl phosphites; and (vii) oxidation of phosphonous acid diesters.

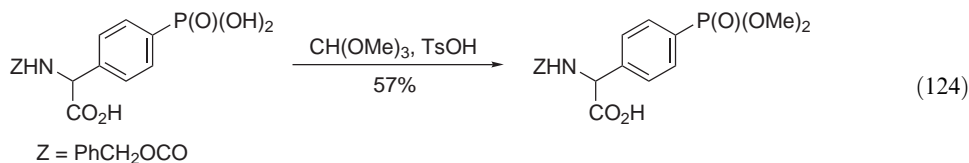
The most useful method for the preparation of dialkyl aryl, alkenyl, or alkynyl phosphonate is esterification of the corresponding phosphonic dichlorides with alcohols in the presence of tertiary amines (Equation (121)) <1995COFGT(2)819>. 1*H*-Tetrazole selectively catalyzes mono addition of alcohols to phosphonic dichlorides such that mixed phosphonate diesters can be prepared in high yield (Equation (122)) <2002TA1965, 2001BMC395, 1996JOC5686, 1993T363>. 2-Oxo-1,3-disulfonyl-1,3,2-diazaphospholidines undergo alcoholysis to give phosphonate diesters (Equation (123)) <2001JHC475>.

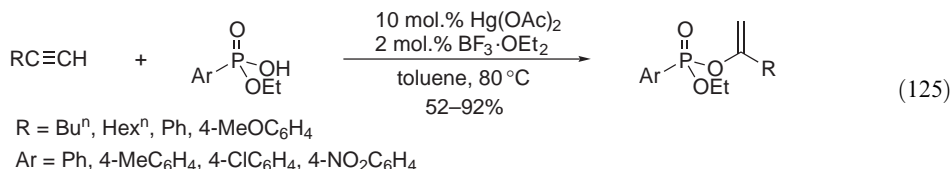


ROH = PhCH₂OH, PhCH(CH₃)OH, cyclohexanol, menthol, testosterone, etc.
R'OH = MeOH, PrⁱOH, PhCH₂OH, etc.

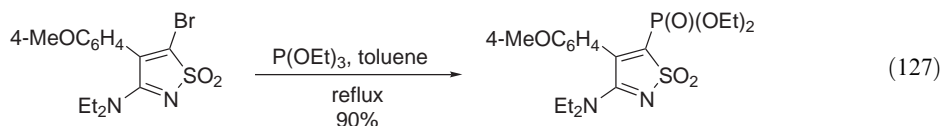
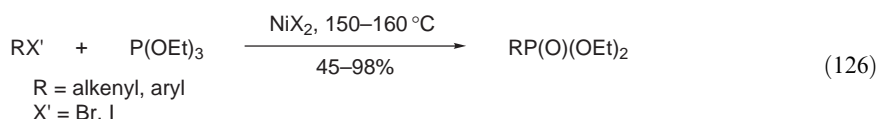


O-Alkylation of phosphonic acids or their monoesters gives the corresponding phosphonic acid esters. Arylphosphonic acids are converted into a dimethyl phosphonate upon treatment with CH(OMe)₃ and TsOH (Equation (124)) <2000BMCL1241>. Vinyl aryl phosphonates are prepared by the addition of monoesters of phosphonic acid to alkynes in the presence of Hg(OAc)₂/BF₃·OEt₂ (Equation (125)) <2003S205>.

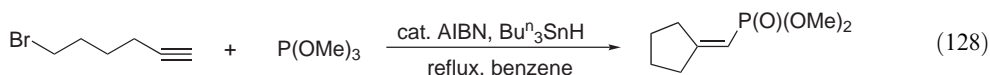




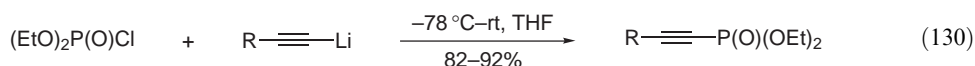
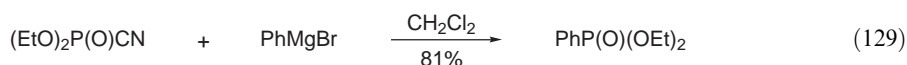
Reaction of aryl or alkenyl halides with trialkyl phosphites does not proceed under simple Arbuzov reaction conditions. However, the reaction in the presence of nickel chloride or bromide takes place to give dialkyl aryl or alkenyl phosphonates (Equation (126)) <2001T9963, 2001TL4115, 1999TL569, 1999S264, 1995COFGT(2)819>. Activated aryl or alkenyl halides undergo the Arbuzov reaction without nickel catalyst to afford dialkyl phosphonates (Equation (127)) <2001T5455, 1998PS(141)135, 1999MI428, 1999MI768, 1995PS(101)67, 1995JHC299>.



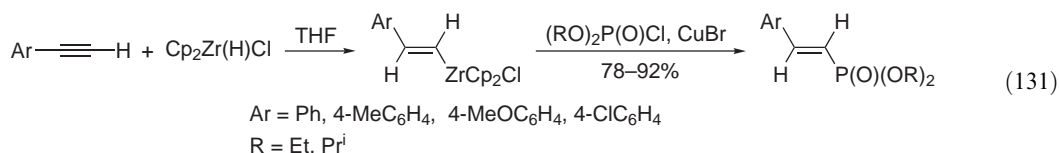
Generation of alkenyl radicals in the presence of trialkyl phosphite gives dialkyl aryl or alkenyl phosphonates (Equation (128)) <1999JA6088>.



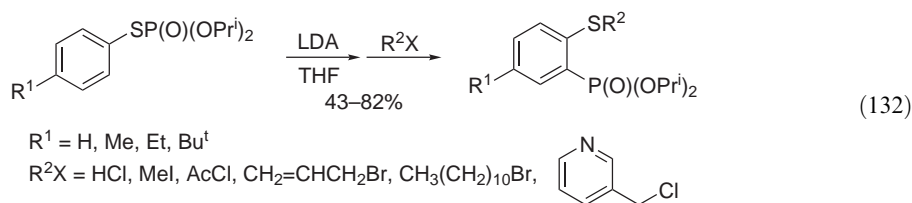
The reaction of dialkyl phosphorochloridates with organolithium or Grignard reagents is a very simple method for preparing dialkyl phosphonates, although this procedure does not give high yields <2002JCS(D)2591, 2001HAC300, 2001MI1371, 1995COFGT(2)819>. The use of diethyl cyanophosphonate instead of diethyl phosphorochloridate provides diethyl aryl phosphonates in high yield (Equation (129)) <1999SC3021>. Reaction of diethyl chlorophosphonate with phenyl-cerium compound gives diethyl phenyl phosphonate in higher yield compared to the reaction with a Grignard reagent <1999EJO2299>. Alkynyl phosphonates are prepared from diethyl phosphorochloridate and alkyllithiums (Equation (130)) <1997SC3171>.



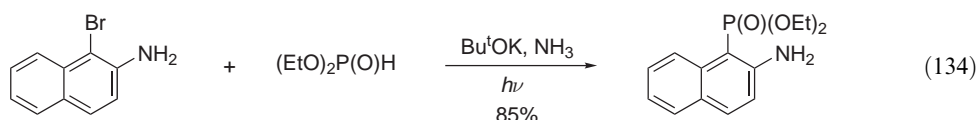
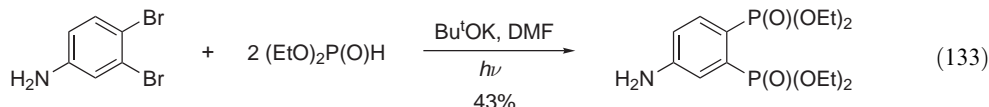
Terminal aromatic acetylenes react with Schwartz reagent to give alkenylzirconocenes, which are reacted with dialkyl chlorophosphates in the presence of cuprous bromide to afford (*E*)-aryl vinyl phosphonates in good yields (Equation (131)) <1999SL721>.



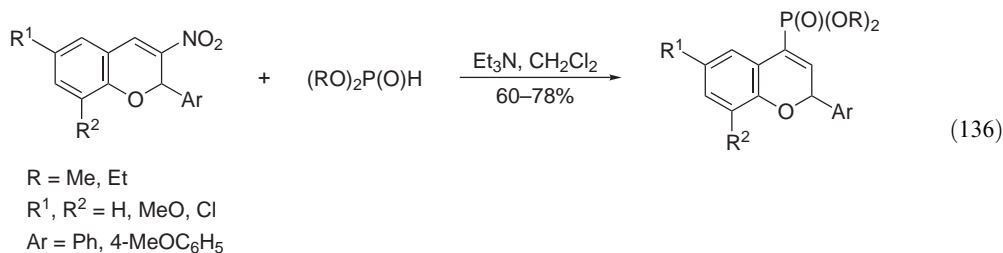
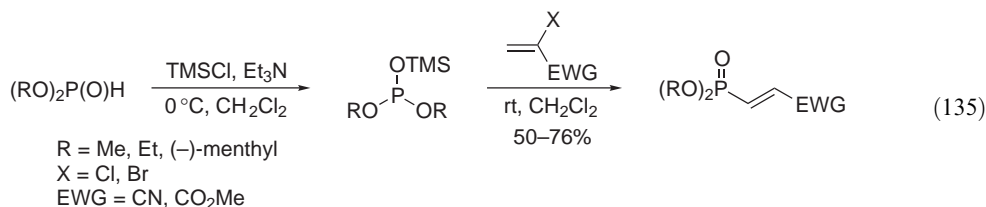
o-Lithio-*S*-arylphosphorothiolates undergo an S—C migration of the phosphoryl group to afford *o*-mercaptoaryl phosphonates (Equation (132)) <1996BSF951>.



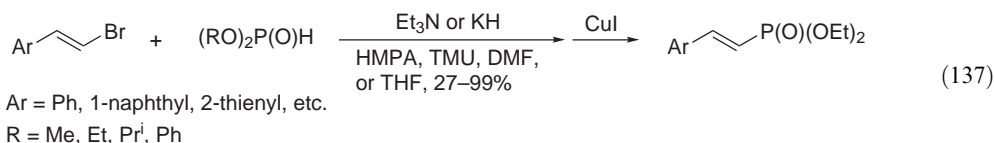
The Michaelis–Becker reaction is an important method for the preparation of dialkyl phosphonates, but this reaction is not applicable to the formation of sp^2 hybridized C–P bonds. Under photoirradiated conditions, however, various aryl bromides react with dialkyl phosphite salts (Equations (133) and (134)) <1999S1368, 1995BSF729, 1995COFGT(2)819>.



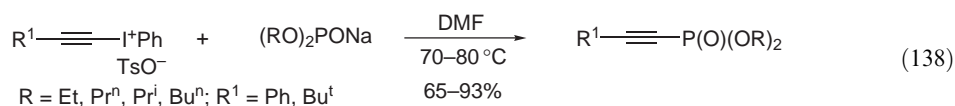
Dialkyl phosphites add to alkenes bearing both an electron-withdrawing group and a leaving group without photoirradiation to give dialkyl phosphonates (Equations (135) and (136)) <1998TL433, 1997JHC1243>.



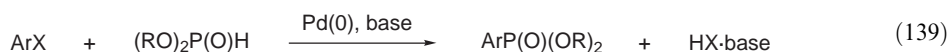
Cuprous iodide promotes the substitution reactions of aryl or alkenyl bromides with dialkyl phosphonates. These reactions show significant solvent effects and only proceed smoothly in solvents with a strong coordinating ability, like HMPA, TMU (tetramethylurea), DMF, and DMSO (Equation (137)) <1998JCS(P1)2953>.



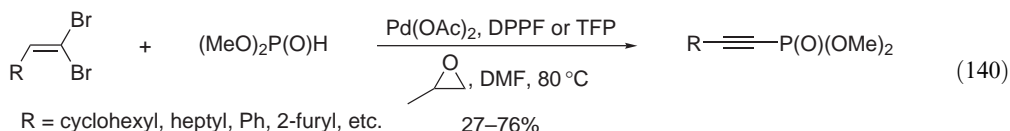
Reaction of sodium dialkyl phosphonate with alkynylphenyliodonium tosylates gives dialkyl alkynyl phosphonates (Equation (138)) <1998SC175>.



The palladium-catalyzed coupling of aryl or alkenyl halides with dialkyl phosphites is important, since this synthetic method has the advantages of wide applicability, good yields, selectivity, availability of starting reagents, and simple experimental operations (Equation (139)) <1998JCS(P1)2083, 1995MI791, 1995COFGT(2)819>. Aryl or alkenyl perfluoroalkansulfonates also undergo coupling to give the corresponding phosphonates <2003IC516, 2001JOC348, 2001BMCL777, 2000JFC(101)305>. Several modifications of standard conditions (Pd(0), triphenylphosphine, triethylamine, DMF) have been reported. The use of the catalyst generated *in situ* from 1,10-bis-(diphenylphosphino)ferrocene and palladium acetate in THF improves the rate of the coupling reaction <2000OL3887, 2000TL4513>. In certain instances, the switch from triethylamine to DABCO gives good results <2002TL7659>. Use of propylene oxide suppresses the decomposition of dialkyl phosphites in the presence of amine base <2001OL2765, 2000TL4513>. Under microwave irradiation the reaction rate is increased, although the yields are comparable <1997PS(130)59>. Treatment of dialkyl phosphites with diaryliodonium salts in the presence of palladium catalyst gives dialkyl aryl phosphonates in good yields <2001SC3289>.



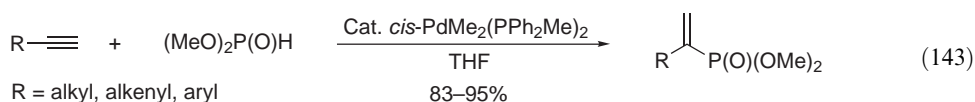
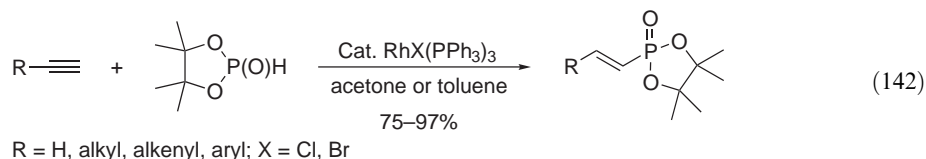
Treatment of 1,1-dibromo-1-alkenes with dialkyl phosphonates in the presence of Pd(OAc)₂–DPPF or TFP (tris(2-furyl)phosphine) and propylene oxide gives alkynyl phosphonates (Equation (140)) <2000OL3873>.

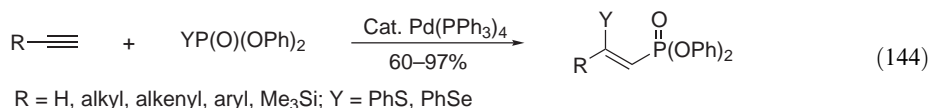


For the preparation of dialkyl aryl or alkenyl phosphonates via the oxidation of the corresponding phosphonites, oxidants used on other trivalent phosphorus compounds are also applicable (Equation (141)). Dialkyl phosphonites can be oxidized with I₂/NaOEt <1998T10111>, Bu^tOOH <2000TL8635, 1997JA9137, 1995JOC7390>, H₂O₂ <2002TL8665>, or MnO₂ <1995COFGT(2)819>.

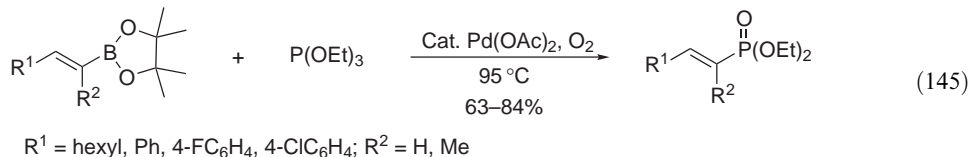


Rhodium-catalyzed phosphorylation of terminal alkynes via oxidative addition of dialkyl phosphites gives alkenyl phosphonates by regioselective attack of the phosphorus at the external carbon of the triple bond (Equation (142)) <2001AG(E)1929>. Palladium-catalyzed hydrophosphorylation of terminal alkynes leads to dialkyl alkenyl phosphonates with a complete regiochemical reversal to its rhodium-catalyzed counterpart (Equation (143)) <1996JA1571>. Palladium complexes catalyze the addition of a thiophosphate or a selenophosphate to terminal alkynes to produce (*Z*)-1-phosphoryl-2-thio- or (*Z*)-1-phosphoryl-2-selenoalkenes with high regio- and stereoselectivity (Equation (144)) <1999CL863, 1996JA7000>.

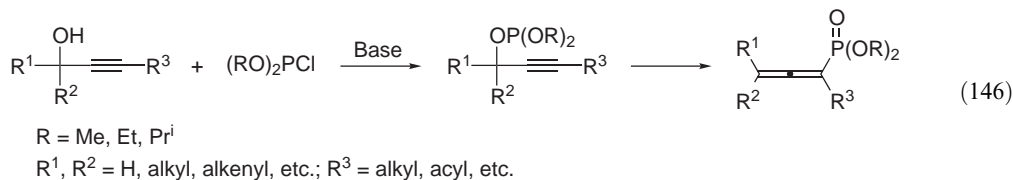




Palladium-catalyzed reaction of vinylboronate esters with triethyl phosphite gives alkenyl phosphonates stereospecifically (Equation (145)) <2003OL729>.



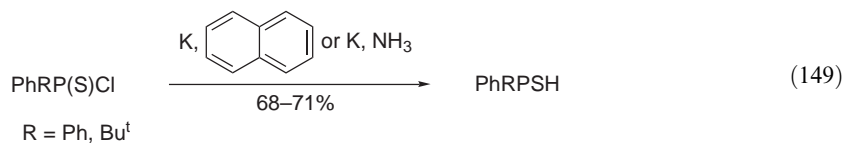
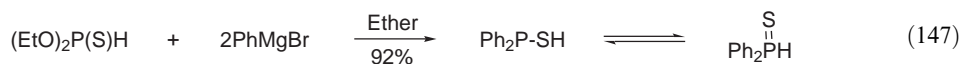
Phosphorylated allenes are prepared from propargyl alcohols via Horner–Mark [2,3]-sigmatropic rearrangement of the unstable phosphites generated *in situ* by reaction of dialkyl chlorophosphites with amine base (Equation (146)) <2002S1829, 1998PS(134/135)193, 1998PS(134/135)187, 1999EJO2367, 1998T1457>.



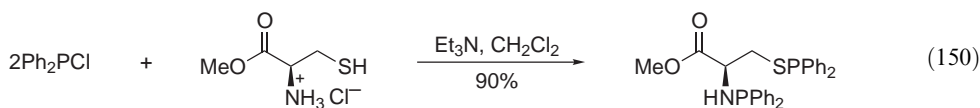
2.16.4 COMPOUNDS WITH A P–S BOND

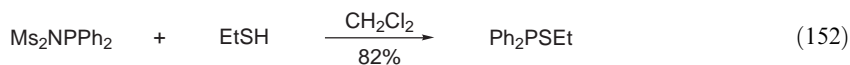
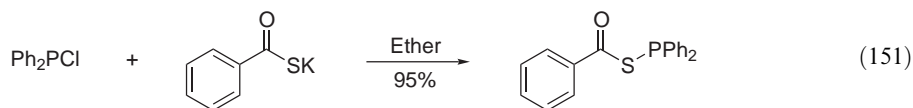
2.16.4.1 Arylthiophosphinous Acids (Ar₂PSH) and Their Derivatives

Arylthiophosphinous acids probably exist as diarylphosphine sulfides. Arylthiophosphinous acids are prepared by phenylation of thiophosphonic acid esters, phosphination of hydrogen sulfide (Equations (147) and (148)) <1995COFGT(2)819>, or by reduction of thiophosphinic acid chlorides with alkali metals (Equation (149)) <2002HAC330>.



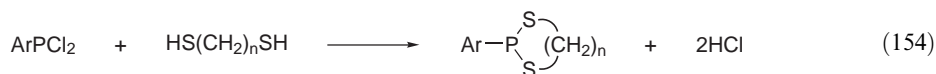
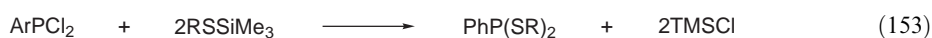
Reaction of diphenylphosphinous chloride with thiols, alkali metal thiocarboxylate, or alkali metal dithiocarboxylate gives diphenylthiophosphinous acid esters, acylthiodiphenylphosphines, or thioacylthiodiphenylphosphines, respectively (Equations (150) and (151)) <2001JCS(D)3598, 2000BCSJ1243>. *N,N*-Disulfonylated aminophosphines also react with thiols to afford diphenylthiophosphinous acid esters (Equation (152)) <2000ZAAC793>.





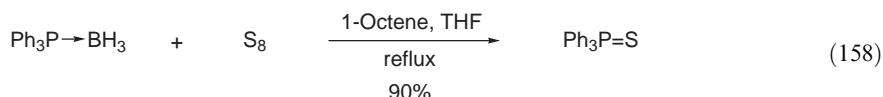
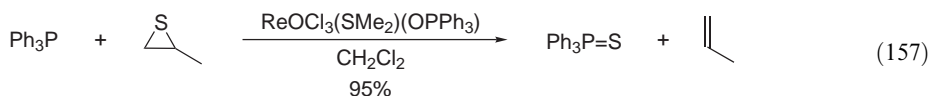
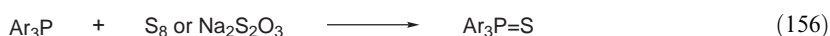
2.16.4.2 Arylthiophosphonous Acids (ArP(SH)₂) and Their Derivatives (ArP(SH)(Hal), etc.)

Aryl dithiophosphonous acid diesters are prepared by the reaction of arylphosphonous dihalides with alkylthiotrimethylsilanes or alkane dithiols (Equations (153) and (154)) <1996OM1597, 1995COFGT(2)819>. Reaction of alkali metal thio- or dithiocarboxylates with phenylphosphonous chloride gives bis-(acylthio)phenylphosphines or phenylbis-(thioacylthio)phosphines, respectively (Equation (155)) <2000BCSJ1243>.

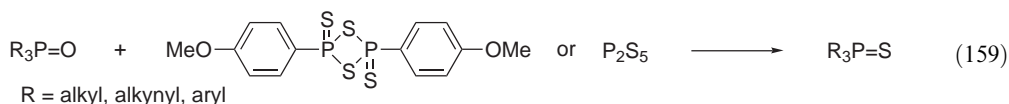


2.16.4.3 Arylphosphine Sulfides (ArR¹R²P=S)

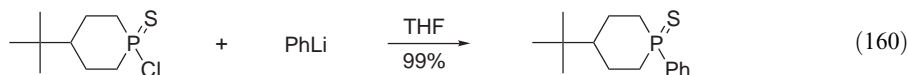
Useful methods for the preparation of tertiary phosphine sulfides are the direct reaction of phosphines with elemental sulfur <2003OM1494, 2002ICA(338)219, 2002ICA(330)38, 1998PS(139)209, 1998AJC667> or sodium thiosulfate <1996AG(E)902> (Equation (156)). These methods are applicable to the synthesis of aryl- or alkenylphosphine sulfides. Using rhenium-catalyzed sulfurization, phosphines, phosphites, and hexamethylphosphorus triamides are sulfurized with thiiranes in high yields (Equation (157)) <1997TL7701>. Organophosphorus borane complexes are transformed into the corresponding phosphine sulfides in high yields on treatment with elemental sulfur and 1-octene (Equation (158)) <2001TA1441>.



Reaction of Lawesson's reagent <2003JOC378, 1999EJO665> or phosphorus pentasulfide <2002TL8515> with phosphine oxides provides the corresponding phosphine sulfides (Equation (159)).

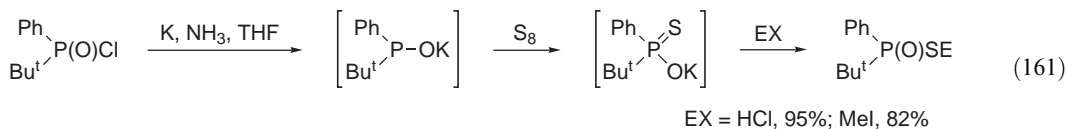


Treatment of 4-*t*-butyl-1-chlorophosphorinane-1-sulfide with phenyllithium gives 4-*t*-butyl-1-phenylphosphorinane 1-sulfide (Equation (160)) <1995PS(103)137>.

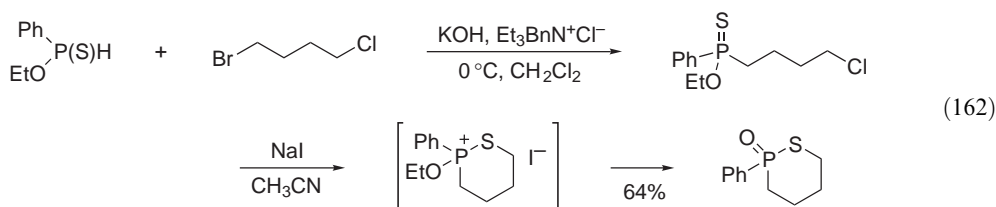


2.16.4.4 Arylthiophosphinic Acids and Their Derivatives ($\text{Ar}_2\text{P}(\text{S})(\text{OH})$, $\text{Ar}_2\text{P}(\text{O})\text{SH}$, $\text{Ar}_2\text{P}(\text{S})\text{SH}$, $\text{Ar}_2\text{P}(\text{S})\text{Hal}$)

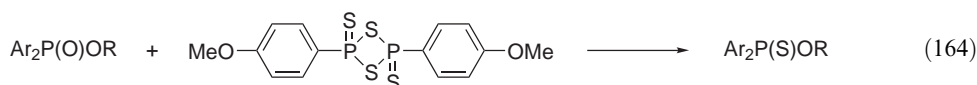
Reduction of *t*-butylphenylphosphinic chloride with potassium in liquid ammonia, followed by treatment with elemental sulfur and aqueous hydrogen chloride or iodomethane, gives *t*-butylphenylthiophosphinic acid or its *S*-methyl ester (Equation (161)) <2002HAC330>. *t*-Butylphenylthiophosphinic acid is resolved into the enantiomers by fractional crystallization of the diastereomeric salts formed with chiral methylbenzylamine <2000EJO3205>.



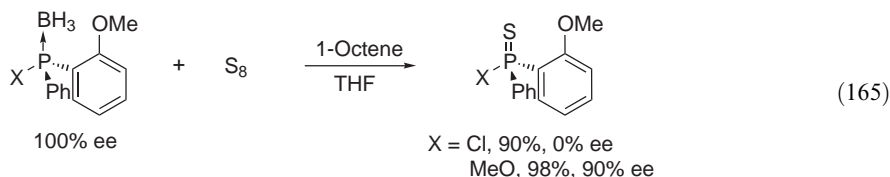
Intramolecular *S*-alkylation of chloroalkyl-substituted thiophosphinic acid *O*-esters proceeds in the presence of sodium iodide to afford cyclic thiophosphinic acid *S*-esters (Equation (162)) <2002HAC1, 2001MI359>.



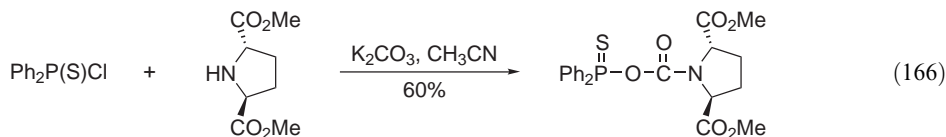
Thiophosphinic acid *O*-esters are prepared from phosphinous acid esters by treatment with elemental sulfur (Equation (163)) <2002TL9299, 2002JCS(D)4617, 2002JA7674, 2001SL860, 2000PS(162)1, 1998PS(139)209>, or from phosphinic acid esters by treatment with Lawesson's reagent (Equation (164)) <1995PS(102)185>.



Sulfurization of diarylchlorophosphine-borane or diarylphosphinous acid ester-borane complexes with elemental sulfur gives the corresponding thiophosphinic chlorides or thiophosphinic acid *O*-esters, respectively (Equation (165)) <2001TA1441>.

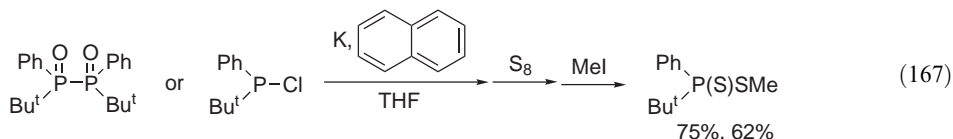


Reaction of diphenylthiophosphinic chloride with secondary amines in the presence of potassium carbonate produces unexpected carbon dioxide-inserted carbamic diphenylthiophosphinic anhydrides (Equation (166)) <2000JOC3443>.

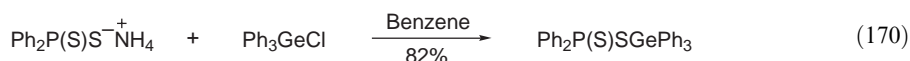
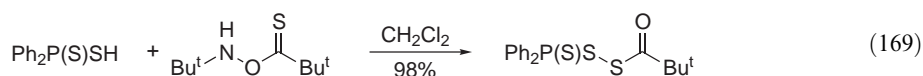
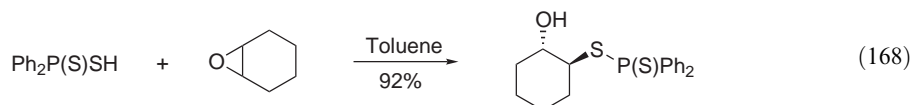


Reduction of bis-[(*t*-butylphenyl)phosphino]phosphinic anhydride or *t*-butylphenylchlorophosphine with potassium naphthalenide, followed by treatment with elemental sulfur and iodomethane gives *t*-butylphenyldithiophosphinic acid methyl ester (Equation (167)) <2000PS(161)39>.

Sequential treatment of *t*-butylphenylthiophosphinic chloride with potassium in liquid ammonia, elemental sulfur, aqueous hydrogen chloride or iodomethane gives *t*-butylphenyldithiophosphinic acid or its methyl ester, respectively <2002HAC330>.

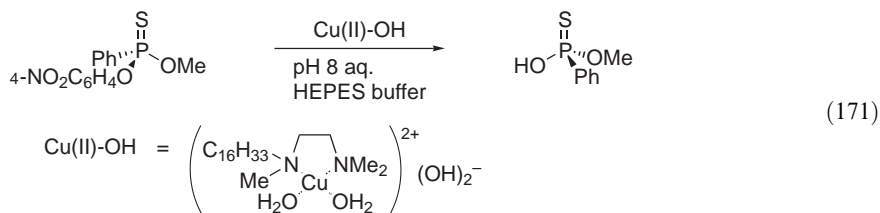


Aryldithiophosphinic acids are converted into their derivatives on treatment with electrophiles, such as epoxides, *O*-thioacylhydroxylamines, and chlorotriphenylgermane (Equations (168)–(170)) <2002TL7609, 2002JCS(P2)1747, 1995POL2231>.

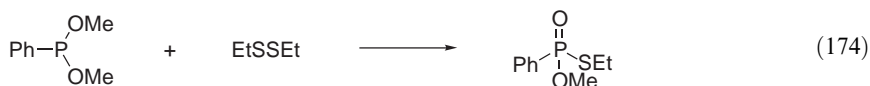
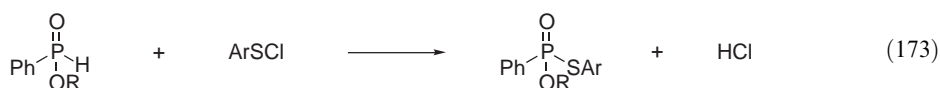
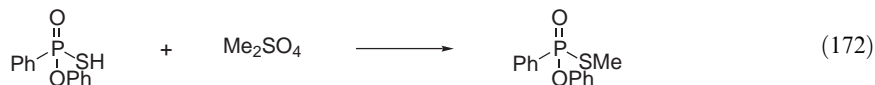


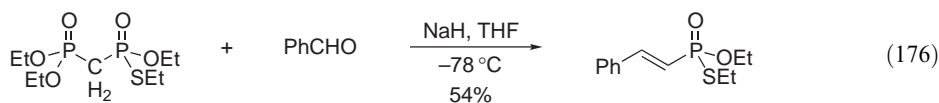
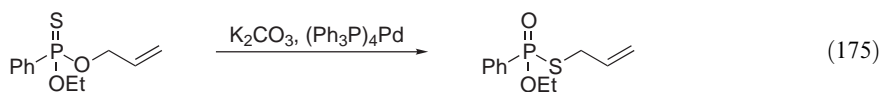
2.16.4.5 Arylthiophosphonic Acids and Their Derivatives (ArP(S)(OH)₂, ArP(O)(OH)SH, ArP(O)(SH)₂, ArP(S)OH(SH), ArP(S)(Hal)₂)

The copper metallomicellar hydrolysis of *O*-methyl *O*-4-nitrophenyl phenylthiophosphonate into phenylthiophosphonic acid *O*-ester takes place with effectively complete inversion at phosphorus (Equation (171)) <2002OL1835>.

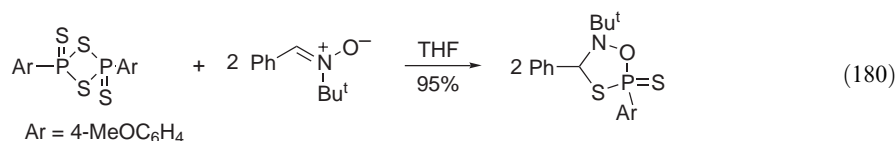
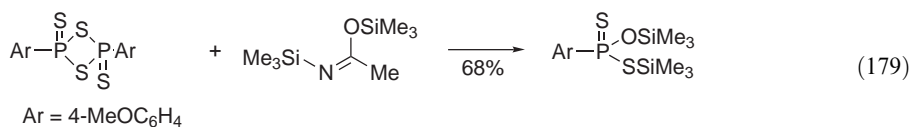
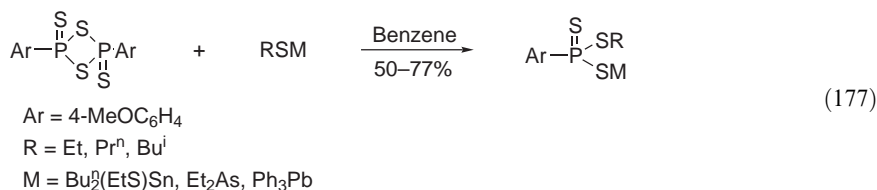


There are many methods for the preparation of arylthiophosphonic acid *O,S*-diesters, which include alkylation of arylthiophosphonic acid *O*-esters, sulfenylation of phenylphosphinic acid *O*-esters or phenylphosphonous acid esters, and isomerization of phenylphosphonothioic acid *O,O*-diesters (Equations (172)–(175)) <1995COFGT(2)819>. Vinylthiophosphonic acid *O,S*-diesters are prepared by a regioselective Horner–Emmons olefination using alkylidene diphosphorylated reagents, such as dialkyl [(ethoxyethylthio)phosphinyl]methyl phosphonate (Equation (176)) <2002JOM(662)83>.

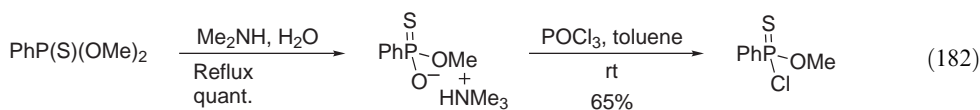
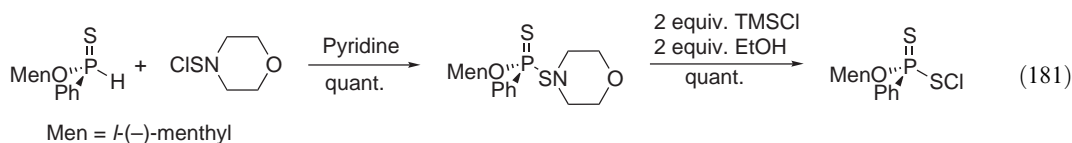




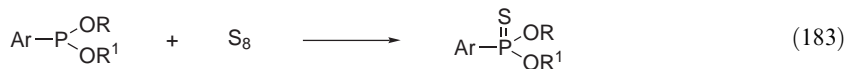
Lawesson's reagent and its homologs undergo ring opening on treatment with nucleophiles. Reaction with tin, arsenic, or lead alkylthiolates gives the corresponding salts of alkyl 4-phenyl-trithiophosphonic acid monoesters (Equation (177)) <2001MI485, 1997MI1648, 1996MI518>. Reaction with oxygen nucleophiles affords arylthiophosphonic acid *O*-esters or their derivatives (Equation (178)) <2000MI129, 2000PS(167)117, 2000PS(157)1, 2000PS(157)145, 2000EJI2239, 1997PS(126)137>. *O,S*-Disilyl dithiophosphonates are prepared from Lawesson's reagent and disilylacetamide (Equation (179)) <2000HAC276>. 1,3-Dipolar cycloaddition of Lawesson's reagent with nitrones gives oxathiazaphospholidines (Equation (180)) <1995JOC3904>. Phenylthiophosphonous acid *O,S*-diesters are formed by sulfurization of phenylthiophosphonous acid *O,S*-diesters with sulfur <1995JOC7390>.



Reaction of a phenylthiophosphonous acid *O*-ester with aminosulfonyl halides gives the corresponding thioxophosphoranesulfonyl amide, which is converted into a thioxophosphoranesulfonyl chloride on treatment with chlorotrimethylsilane and ethanol (Equation (181)) <1998T9731>. Chlorination of ammonium salts of phenylthiophosphonic acid *O*-esters with phosphorus oxychloride gives phenylthiophosphonic acid chloride *O*-esters (Equation (182)) <1998SC2769>.

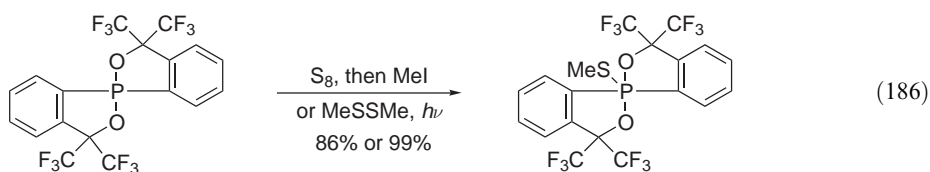
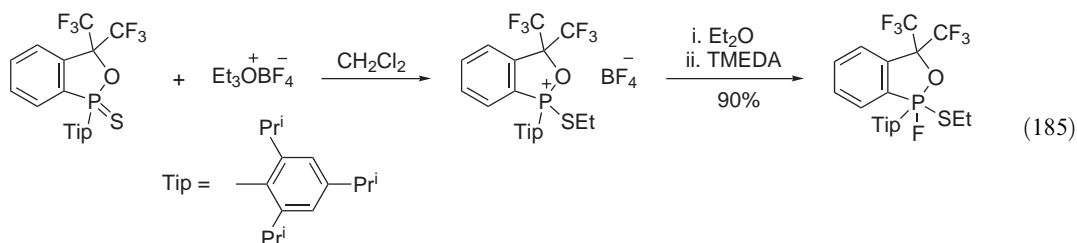


Arylthiophosphinic acid *O,O*-diesters are mainly prepared by sulfurization of arylphosphonous acid diesters with sulfur (Equation (183)) <2002T8489, 2002CC432, 2001HAC300, 1995JOC7390> or by sulfurization of arylphosphonic acid diesters with Lawesson's reagent or phosphorus pentasulfide (Equation (184)) <2001BMC395, 1999S2071>. Treatment of Lawesson's reagent with cyclic diols gives 4-methoxyphenylthiophosphinic acid *O,O*-diesters <2002SC1415, 2001MI37, 2000PS(164)11, 2000PS(156)173>.



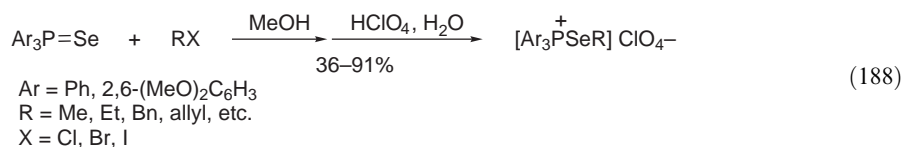
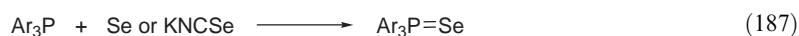
2.16.4.6 Arylphosphorane Compounds with Sulfur Functions

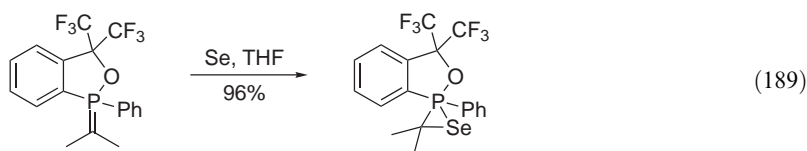
S-Alkylation of a cyclic thiophosphinate bearing the Martin ligand with triethyloxonium tetrafluoroborate gives the corresponding phosphonium salt, which is converted into (ethylthio)fluorophosphorane by the addition of ether (Equation (185)) <2002CL268>. 1-Hydrospirophosphoranes are converted to 1-alkylthio spirophosphoranes by sulfenylation using elemental sulfur and methyl iodide <2002JOM(643–644)441>, or photoreaction with alkyl disulfide (Equation (186)) <2001JOC6181>.



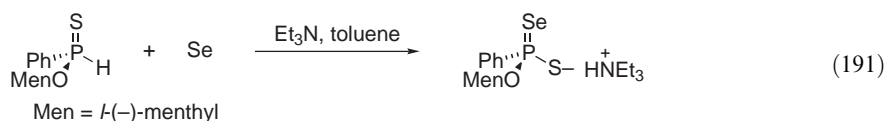
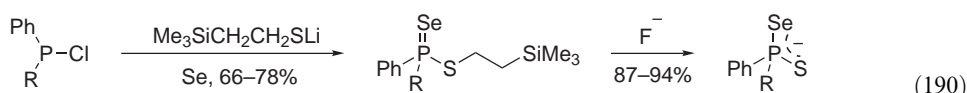
2.16.5 COMPOUNDS WITH A P—Se AND/OR A P—Te BOND

Phosphine selenides are prepared by selenation of the corresponding phosphines with elemental selenium <2003OM145, 2002OM4611, 1996BCJ655, 1995CB365> or potassium selenocyanate <2001MI259> (Equation (187)). Reaction of triarylphosphine selenides with alkyl halides gives alkylselenophosphonium salts (Equation (188)) <1996BCJ655>. Treatment of a phosphorus ylide with elemental selenium affords the selenaphosphirane, which is highly moisture sensitive (Equation (189)) <2002JA9706>.

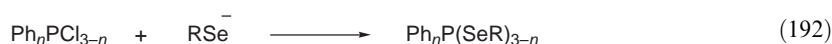




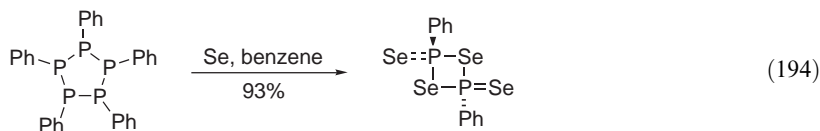
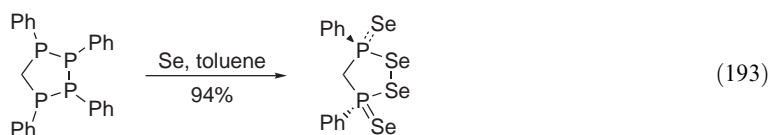
Reaction of diphenylphosphinous chloride with elemental selenium and lithium 2-(trimethylsilyl)ethanethiolate gives *S*-2-(trimethylsilyl)ethyl selenothiophosphinate, which is converted into selenothiophosphinic acid salts on treatment with ammonium or alkali metal fluorides. Alkylation of the salts proceeds at the selenium atom, whereas acylation occurs at the sulfur atom (Equation (190)) <2002CL914>. Addition of elemental selenium to phenylthiophosphinous acid *O*-esters leads to phenylselenophosphonothioic acid *O*-esters (Equation (191)) <1995HAC365>.



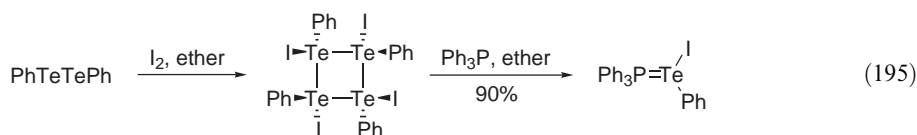
Diphenylphosphinous chloride or phenylphosphonous dichloride reacts with selenium nucleophiles to afford diphenylselenophosphinous or phenylselenophosphonous acid Se-esters, respectively (Equation (192)) <2002JOC5257, 2001EJI1983, 1995H889>.



Selenation of cyclopentaphosphines or cyclomonocarbatetraphosphines with elemental selenium affords five- and four-membered heterocycles (Equations (193) and (194)) <2001CC2288, 2001ZAAC1269>.



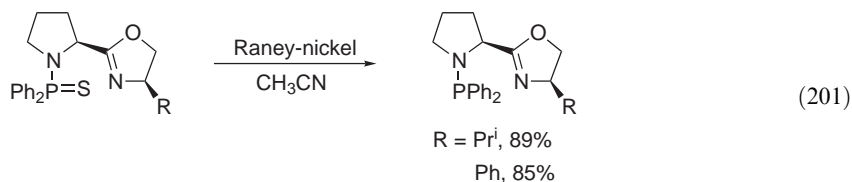
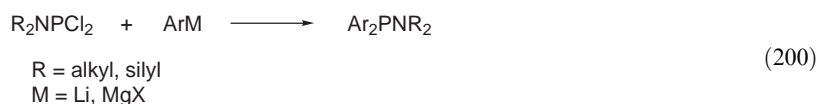
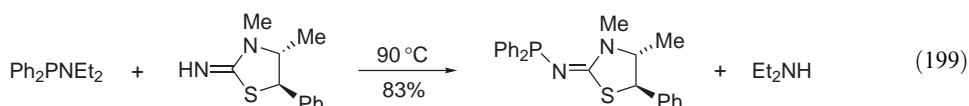
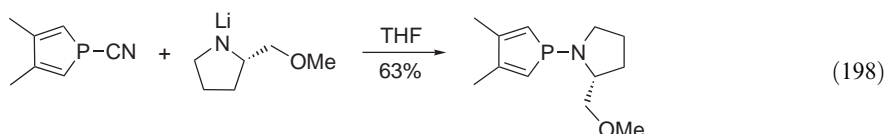
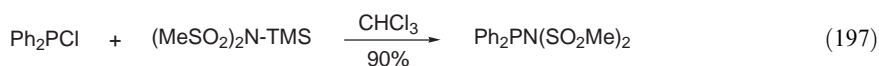
The reaction of Na[Ph₂PNPPH₂] with elemental tellurium in the presence of TMEDA produces [[Na(TMEDA)][(TePPh₂)₂N]}₂ as moisture-sensitive crystals <2002AG(E)3468>. Ph₄Te₄I₄, which is prepared from diphenyl ditelluride and iodine, reacts with triphenylphosphine to produce Ph₃PTe(I)Ph (Equation (195)) <2000AG(E)1796>.



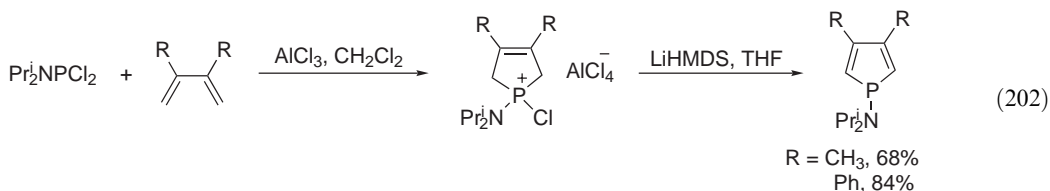
2.16.6 COMPOUNDS WITH A P—N BOND

2.16.6.1 Amides of Arylphosphinous Acid (Ar_2PNR_2 , ArPHNR_2)

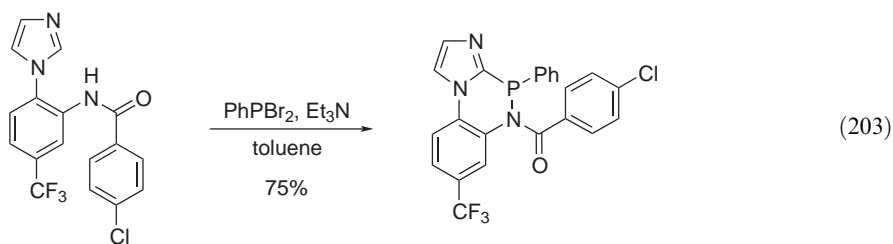
A useful method for the preparation of arylphosphinous amides is amination of phosphinous halides <2002TL6803, 2002OM4241, 2001JCS(D)3598, 2001JCS(D)3421, 2001NJC824, 2000ZAAC793, 1995COFGT(2)819>, phosphinous cyanides <2002TA1097>, or phosphinous amides <2001ZAAC1846> (Equations (196)–(199)). Reaction of aminochlorophosphines with Grignard or organolithium reagents gives the corresponding arylphosphinous amides (Equation (200)) <2002AG(E)3897, 2002T2551, 2002JCS(D)513, 2002JOM(646)223, 1998CC149>. Reduction of arylthiophosphinic amides with Raney nickel provides arylphosphinous amides (Equation (201)) <2002TL2811>.



Dichloro(diisopropylamino)phosphine reacts with 1,3-butadienes in the presence of AlCl_3 to afford quantitatively the corresponding 3-phospholenium cations, and subsequent dehydrohalogenation with LiHMDS gives the corresponding phospholes (Equation (202)) <2002EJO675>.

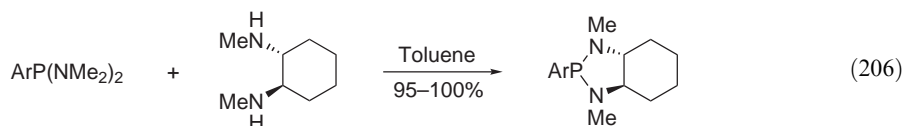
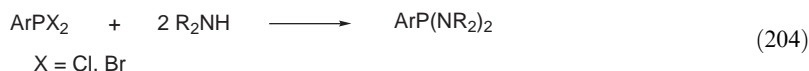


4,5-Dihydrobenzo[e]imidazo[2,1-c][1,4,2]diazaphosphinine is prepared by the direct phosphorylation of 1-(4-chlorophenylcarboxamido)-2-(1*H*-1-imidazolyl)-5-trifluoromethylbenzene with dibromophenylphosphine (Equation (203)) <2002HAC84>.



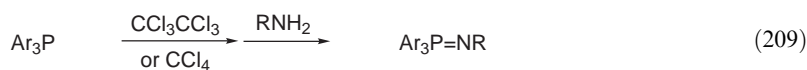
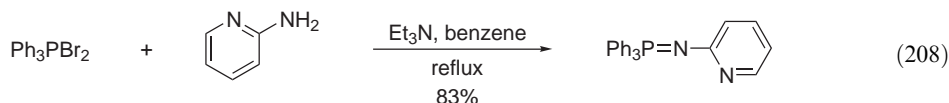
2.16.6.2 Amides of Arylphosphonous Acid ($\text{ArP}(\text{NR}_2)_2$, $\text{ArP}(\text{SR})\text{NR}_2$, $\text{ArP}(\text{NR}_2)\text{Hal}$)

Typical methods for the preparation of arylphosphonous acid diamides include amination of aryldihalophosphines <2002JCS(D)1093, 2002JOM(643–644)32, 1999OM3138, 1998TA927> or aryldimethylaminophosphines <1999JOC9735, 1997CC1053>, and reaction of Grignard reagents or aryllithium reagents with diaminohalophosphines <2002TL4025, 2002JOM(643–644)237, 2002JOM(643–644)68, 2001TA1159> (Equations (204)–(206)). Arylphosphonous amide halides are prepared by the reaction of aryldihalophosphines with an equimolecular amount of amines <2001PCT0179213, 2001ZN(B)812>.



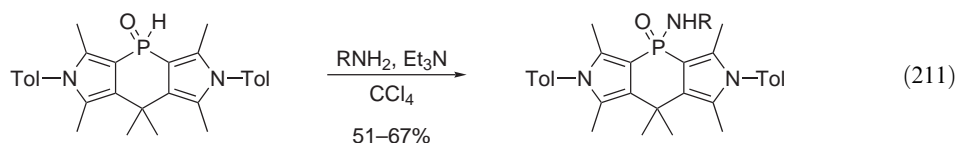
2.16.6.3 Arylphosphine Imides ($\text{Ar}_3\text{P}=\text{NR}$)

Triarylphosphine imides are well known as aza-Wittig reagents, which are synthetically versatile for the preparation of imines, amines, and nitrogen heterocycles. Phosphine imides are prepared according to the following methods: (i) reaction of phosphines with organic azides (Equation (207)) <2002EJO3801, 2002T2569, 2001TL605, 2000PS(167)275, 2000S2085>; (ii) reaction of phosphine dihalides with amines (Equation (208)) <2002JOC7797>; (iii) reaction of phosphines and polyhalogenoalkanes with amines (Equation (209)) <2000MI421, 1998S1467, 1995TL59>; and (iv) reaction of phosphines and diethyl azodicarboxylate or dimethyl acetylenedicarboxylate with amines (Equation (210)) <2001EJO1449, 2002T7213, 1995TL7881>. *N*-Unsubstituted triphenylphosphine imide is prepared by treatment of triphenylphosphine oxide with triflic anhydride followed by addition of ammonia <1995S1496>. *N*-Benzyltriphenylphosphine imides are prepared by deprotonation of benzylaminotriphenylphosphonium bromides with sodium amide <1998MI879>.

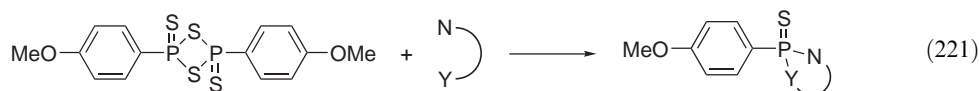


2.16.6.4 Amides of Arylphosphinic Acids ($\text{Ar}_2\text{P}(\text{O})\text{NR}_2$, $\text{Ar}_2\text{P}(\text{Se})\text{NR}_2$)

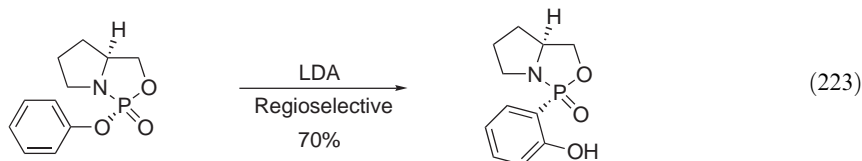
Arylphosphinic amides are generally prepared by the Todd–Atherton reaction (Equation (211)) <2000HAC107>, reaction of arylphosphinic halides with amines (Equation (212)) <1999TA3319>, or oxidation of arylphosphinous amides (Equation (213)) <2002JOC3852, 2002EJO675, 2001TA1441, 1995TL3921>. Arylthiophosphinic amides <2002TL2811, 2001TA1441, 2000TA773> and arylsele-nophosphinic amides <2003MI78, 2002EJI2408, 2000TA835> are prepared in a similar manner.



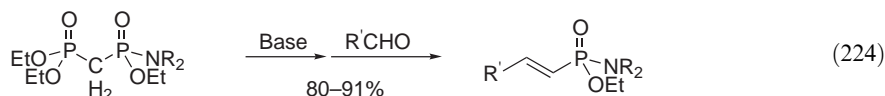
Reaction of Lawesson's reagent with substrates containing two nucleophilic functional groups, such as diamines, aminoalcohols, α -hydroxynitriles, or α -aminonitriles, gives cyclic arylthiophosphonic amides <2000PS(164)11>, aryl phosphoramidodithionates <2000PS(164)11>, aryl phosphoramidodithioates <2002S2527>, or arylthiophosphonic amides <2001S2445>, respectively (Equation (221)). The reaction with monoamines affords aryl phosphoramidodithioates <2000EJ12239>. Phosphoramidates are converted into phosphoramidodithionates on treatment with Lawesson's reagent (Equation (222)) <2001TL4313>.



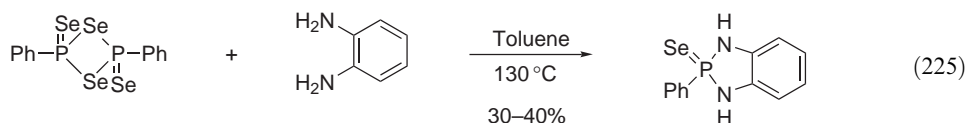
Chiral (*o*-hydroxyaryl)oxazaphospholidine oxides and (*o*-hydroxyaryl)diazaphospholidine oxides are synthesized by aromatic anionic O—C rearrangement (Equation (223)) <2000EJO3313, 2000T595>.



Vinyl phosphoramidates are prepared by a regioselective Horner–Emmons olefination using alkylidene diphosphorylated reagents (Equation (224)) <2002JOM(662)83>.



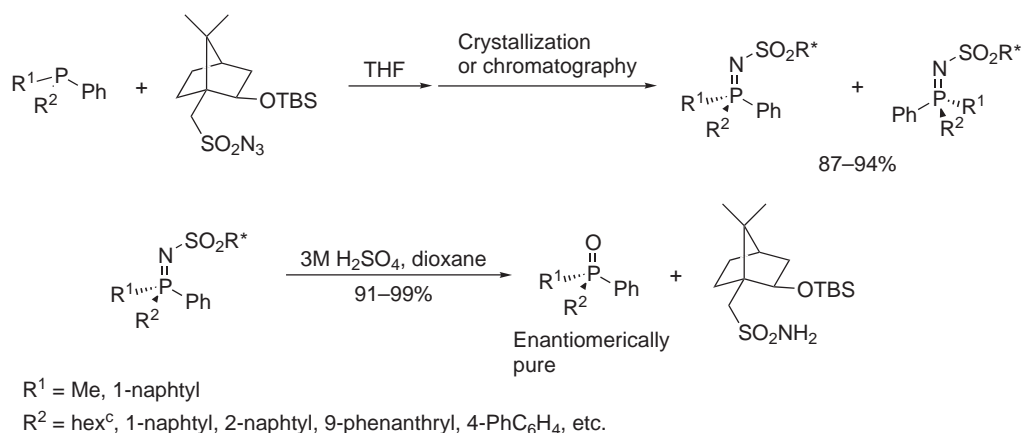
Treatment of 2,4-diphenyl-1,3-diselenadiphosphetane-2,4-diselenide, a selenium analogue of Lawesson's reagent, with 1,2-phenylenediamine or 2-aminophenol gives a cyclic arylselenophosphonic amide or an aryl selenophosphoramidate, respectively (Equation (225)) <2001JOM(623)116>.



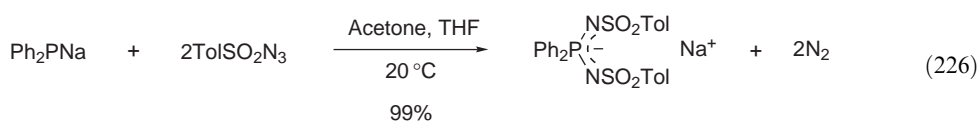
2.16.6.6 Arylphosphorus Compounds Incorporating an NY Function

2.16.6.6.1 $Y=S$: $\text{Ar}_2\text{P-N=S}$, $\text{Ar}_2\text{P=N-S}$, etc.

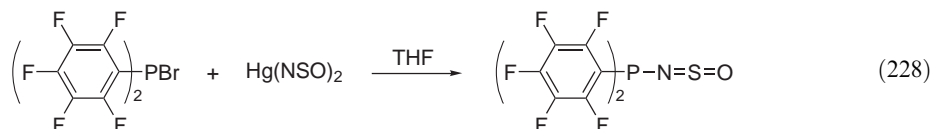
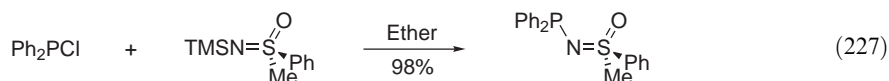
The simplest and most convenient method for the synthesis of *N*-sulfonyl phosphine imides is the Staudinger reaction of tertiary phosphines with sulfonyl azides. Optical resolution of racemic phosphines is achieved by exploiting the reaction with enantiopure sulfonyl azides (Scheme 8) <2001JOC7478>. The reactions of tertiary phosphines with *N,N*-dichloroperfluoroalkanesulfonamides in the presence of zinc powder <1997IC4909> or the reaction with (tosyliminoiodo)arenes <1999JA7164> also give the corresponding *N*-sulfonyl phosphine imides. Treatment of triarylphosphines with sulfonamides or sulfinamides in the presence of diethyl azodicarboxylate affords *N*-sulfonyl or *N*-sulfinyl triarylphosphine imides <2002IC1940, 2001EJO1449>, respectively. Condensation of the *N*-trimethylsilyl phosphine imide with benzenesulfonyl chloride in the presence of sodium fluoride and a catalytic amount of 18-crown-6 gives *N*-benzenesulfonyl triphenylphosphine imide <2000JCS(P1)515>. Stabilized diamminophosphonium diaza-ylides are synthesized from sulfonyl azides by Staudinger reaction with sodium diphenylphosphide (Equation (226)) <2001S69>.



Scheme 8



Reaction of arylphosphinous chloride with *N*-(trimethylsilyl)sulfoximides or mercuric sulfinylamides gives *N*-diphenylphosphinyl sulfoximides (Equation (227)) <2001TA1255> or arylphosphinous *N*-sulfinylamides (Equation (228)) <1999JFC(96)147>, respectively.



2.16.6.6.2 $Y=N$: $Ar_2P-N=N-R$, $Ar_2P-N=N=N$

Phosphazides lose nitrogen at room temperature to give the corresponding phosphine imides (Staudinger reaction). Isolable phosphazides are formed from sterically hindered azides (Equation (229)) <2002AG(E)1205, 1998EJO121, 1996T9629>. Treatment of triphenylphosphine with 1,2,4-triazine azides also gives isolable phosphazides <1999PS(139)163>.

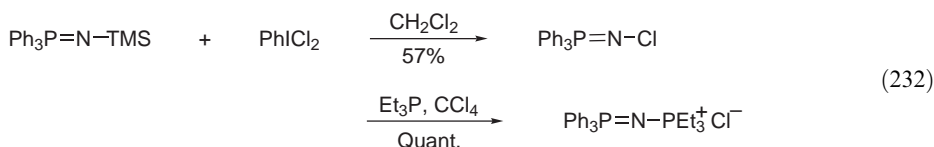
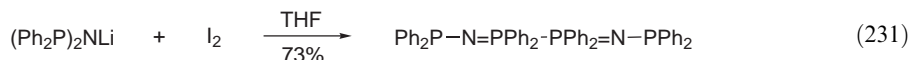
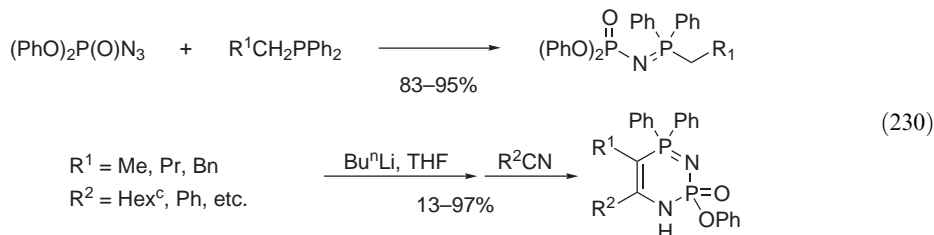


2.16.6.6.3 $Y=P$: $Ar_2P-N=P$, etc.

Cyclophosphazenes are well-known heterocycles bearing $P-N=P$ bonds, and their syntheses and chemistry have been reviewed <2001MI1, 1997JCS(P2)15, 1995COFGT(2)819>.

Staudinger reaction of phosphoryl azides with phosphines gives *N*-phosphorylphosphine imides <2003IC3293, 1999EJ1601>. The reaction of lithiated (*N*-diphenylphosphoryl)phosphine imides with nitriles affords 1,2-dihydro-1,3-diaza-2,4-di-phosphorine 2-oxides (Equation (230)) <2002T2569>. Treatment of phosphine imides with phosphinous chlorides provides *N*-phosphinousphosphine imides <2001OM2303, 1996HAC403>. Oxidation of lithium bis-(diphenylphosphanyl)amide affords an *N*-phosphinousphosphine imide bearing a $P-P$ bond (Equation (231))

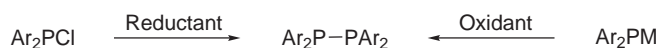
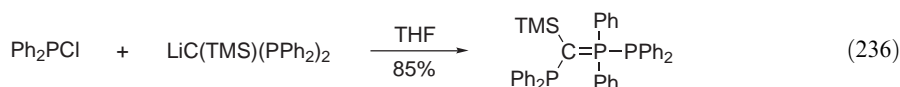
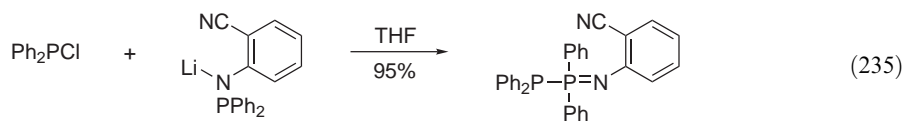
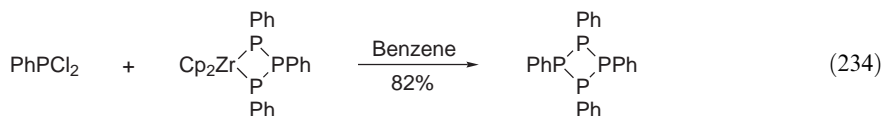
<1995CC37>. *N*-Chlorotriphenylphosphine imine, which is prepared from *N*-trimethylsilyltriphenylphosphine imine and phenyliodine dichloride, reacts with phosphines forming iminophosphonium salts (Equation (232)) <1999ZAAC633>.



2.16.7 COMPOUNDS WITH A P—P, P—As, P—Bi, OR P—Sb BOND

2.16.7.1 Arylphosphorus Compounds with a P—P Bond

Compounds with a P—P bond, such as diphosphines, are prepared by the reaction of arylphosphorus chlorides with metalated arylphosphines (Equation (233)) <2001JOM(630)193, 2000HAC512, 1996HAC239, 1995OM944>. Triphosphanato metallacycles ($\text{Cp}_2\text{Zr}(\text{PPh})_3$) react cleanly with phenylphosphonous dichloride to yield tetraphenylcyclobutaphosphanes (Equation (234)) <1997OM365>. Treatment of a phosphinoamide anion or a diphosphio(silyl)methyl anion, which reacts as a methylenephosphide anion or an iminophosphide anion, with diphenylphosphinous chloride leads to P—P bond formation (Equations (235) and (236)) <2003IC2125, 1997JOM(529)151>. Reductive coupling of phosphorus chlorides <2001ZAAC1741, 1997CB819> or oxidative coupling of phosphines or metalated phosphines <2002JOM(656)43, 2002OL761, 2000ZAAC1121, 1996PS(117)189> also give diphosphines (Scheme 9).

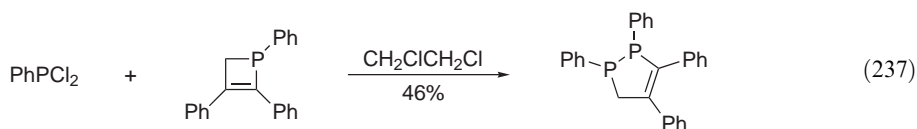


Reductant: Ca, Mg

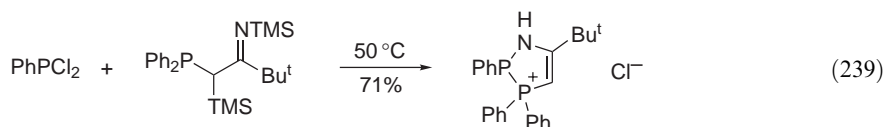
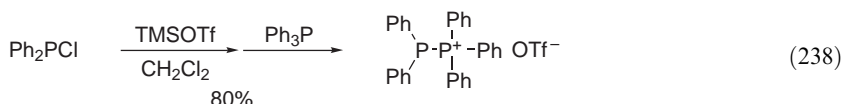
Oxidant: PbI_2 , $\text{Ni}(\text{PPh}_3)_2\text{Br}_2$, BiCl_3 , $\text{CH}_2\text{BrCH}_2\text{Br}$

Scheme 9

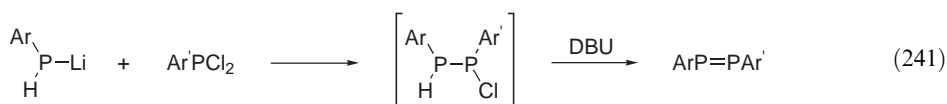
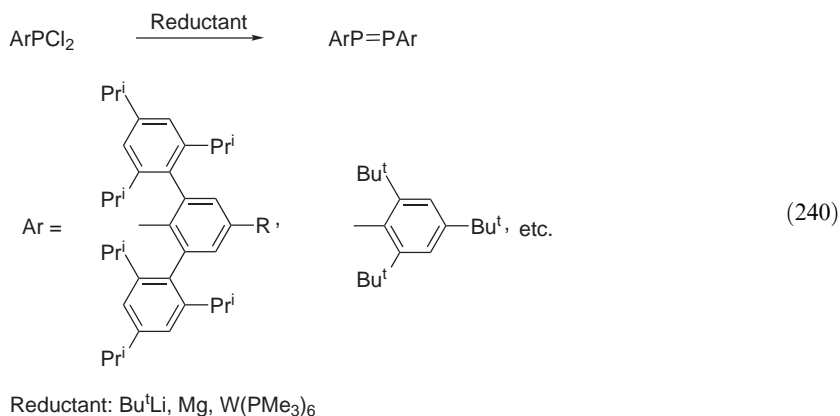
Treatment of 1,2-dihydrophosphetes with phosphorus chlorides gives 1,2-diphosphacyclopent-3-enes (Equation (237)) <1995AG(E)590>.



Addition of phosphines to electron-deficient phosphinic centers provides phosphinophosphonium salts (Equation (238)) <2001JA7947, 1996IC5460, 1995TL2085>. Treatment of $\text{Me}_3\text{SiN}=\text{C}(\text{Bu}^t)\text{CH}(\text{R})\text{PPh}_2$ with phosphorus chlorides gives the cyclic phosphinophosphonium chlorides (Equation (239)) <1999JOM(580)386>. *P*-Aminodiphosphanes react with triphenylphosphine in the presence of trifluoromethylsulfonic acid to afford diphosphanophosphonium salts <1995CC1383>.

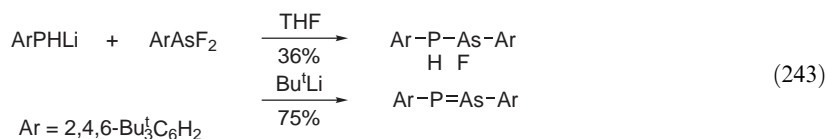
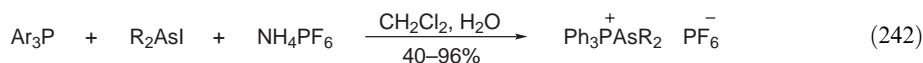


Isolation of diphosphenes is possible when they are kinetically stabilized by using bulky substituents. A typical method for the synthesis of symmetrical diphosphenes is reductive coupling of arylphosphonous dichlorides (Equation (240)) <2002HCA3842, 2002JOM(646)255, 1995CC2429>. Unsymmetrical diphosphenes are prepared by the reaction of arylphosphonous dichlorides with metalated primary arylphosphines and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Equation (241)) <2002IC5296, 2001HAC418, 2002TL119>. Reduction of arylphosphonous dichlorides by zinc and trimethylphosphine leads to phosphanylidene phosphoranes <2002EJI2779>.



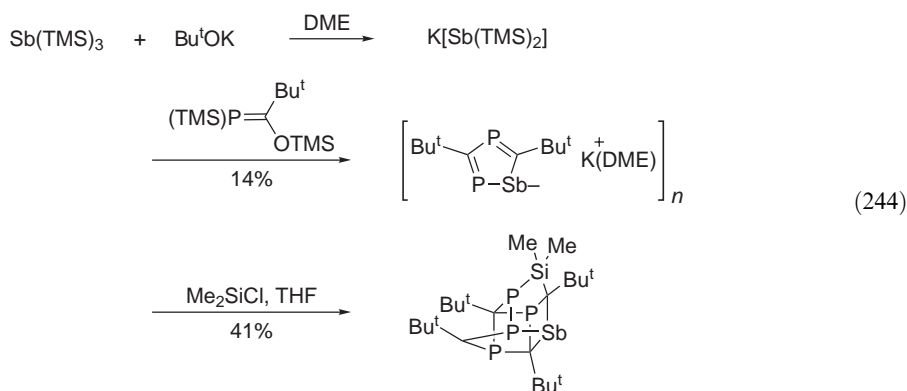
2.16.7.2 Arylphosphorus Compounds with a P—As Bond

Treatment of arsenious iodides with phosphines in the presence of aqueous ammonium hexafluorophosphate gives the corresponding phosphine-stabilized arsenium salts (Equation (242)) <2002IC6380>. The reaction of arsenious difluoride with lithiated phosphines followed by Bu^tLi affords the phospharsenes (Equation (243)) <2001JOM(619)275>. Arsenic(III) halides react with 1 M equivalent of 1,2-phenylenediphosphine to give cyclic phosphine complexes with arsenic halides <2002JCS(D)1188>.



2.16.7.3 Arylphosphorus Compounds with a P—Sb Bond

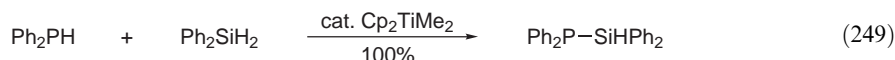
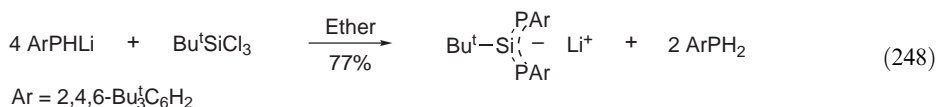
Diphosphastibolyl-potassium complex is prepared from the reaction of $\text{K}[\text{Sb}(\text{SiMe}_3)_2]$ with the phosphaaalkene $(\text{Me}_3\text{Si})\text{P}=\text{C}(\text{Bu}^t)(\text{OSiMe}_3)$. The reaction of 2 equiv. of this complex with dichlorodimethylsilane affords a hexahetero-cage compound (Equation (244)) <2001JOM(622)61>.



2.16.8 COMPOUNDS WITH A P—METALLOID BOND

2.16.8.1 Arylphosphorus Compounds with a P—Si Bond

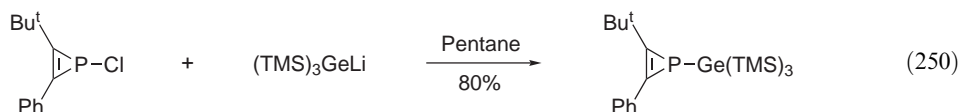
Arylbis-(trialkylsilyl)- or aryl(trialkylsilyl)- or diaryl(trialkylsilyl)phosphines are readily synthesized by the reaction of the corresponding dialkali metal or monoalkali metal arylphosphides with trialkylchlorosilanes (Equations (245)–(247)) <2001OM4565, 1995COFGT(2)819>. *Trans*-silylation of diorgano(trimethylsilyl)phosphines with tetrachlorosilane affords diorgano(trichlorosilyl)phosphines <2000ZN(B)953>. Trichlorosilanes react with a fourfold excess of lithium arylphosphides followed by hydrolysis to give phosphinosilaphosphenes (Equation (248)) <1998OM2425>. Heterodehydrocoupling between silanes and diphenylphosphine proceeds in the presence of titanocene catalyst to give the corresponding silylphosphines (Equation (249)) <1998JA12988>.



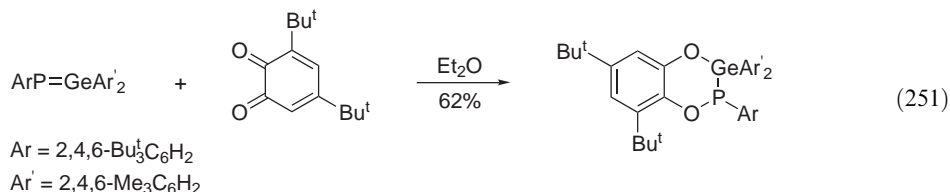
Reaction of phosphanylidene phosphoranes ($\text{ArP}=\text{PMe}_3$) with trimethylsilyl triflate produces *P*-(trimethylsilyl)diphosphonium salts <2000JOM(608)12>.

2.16.8.2 Arylphosphorus Compounds with a P—Ge Bond

Alkylgermyl- or arylgermylphosphines are prepared in a similar method to silylphosphines (Section 2.16.8.1) by the reaction of lithium phosphides with germyl halides <2002IC3084, 1995COFGT(2)819>. Reaction of 1-chloro-1*H*-phosphirenes with tris-(trimethylsilyl)germyl-lithium gives 1-germyl-1*H*-phosphirenes (Equation (250)) <1997CB711>.



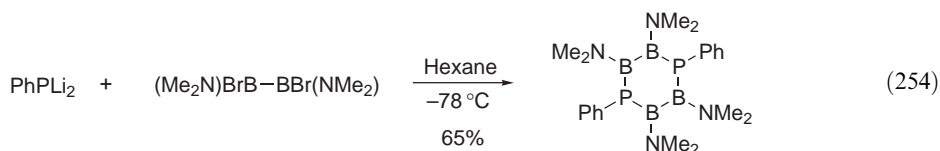
Stable germaphosphenes <1996MI199, 1990CRV283> react with *o*-quinones to afford six-membered-ring heterocycles (Equation (251)) <1995OM1954>.



2.16.8.3 Arylphosphorus Compounds with a P—B Bond

The best-known compounds having P—B bonds are phosphine–borane complexes. Trivalent phosphorus compounds in low oxidation states are more or less air sensitive. Moreover, P-chiral phosphines are prone to racemize. These problems can be overcome by complexation of the phosphines with boranes. The complexes are air stable and their racemization is completely prevented. They are prepared by the reaction of the corresponding phosphine with borane–dimethylsulfide complex or borane–THF complex. The synthesis and reactivities of phosphine–borane complexes have been reviewed by several groups <1999T1197, 1998S1391>.

Borylphosphines are prepared by the reaction of boron halides with metalated phosphines or with phosphines in the presence of an amine (Equations (252) and (253)) <2002AG(E)174, 1997CB1677, 1995COFGT(2)819>. Reaction of dilithium phenylphosphide with diborane derivative B₂(NMe₂)₂Br₂ affords a P₂B₄ six-membered compound (Equation (254)) <1995ZAAC1993>.



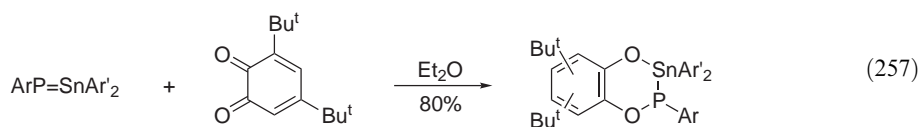
2.16.9 COMPOUNDS WITH A P—METAL BOND

2.16.9.1 Arylphosphorus Compounds with a P—Sn Bond

Stannylphosphines are prepared by the reaction of tin halides with metalated phosphines or with phosphines in the presence of an amine (Equations (255) and (256)) <2002IC3084, 2002JOM(646)113, 1995COFGT(2)819>.

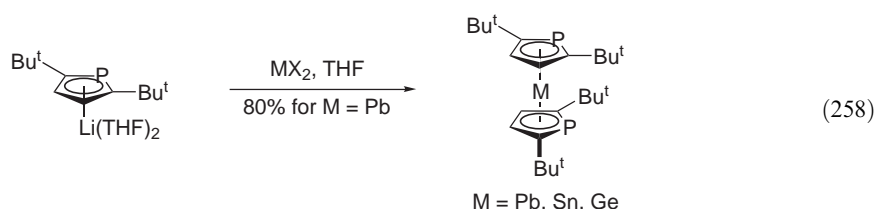


Stable stannaphosphenes <1994OM2787> react with *o*-quinones to afford six-membered-ring heterocycles (Equation (257)) <1995OM1954>.



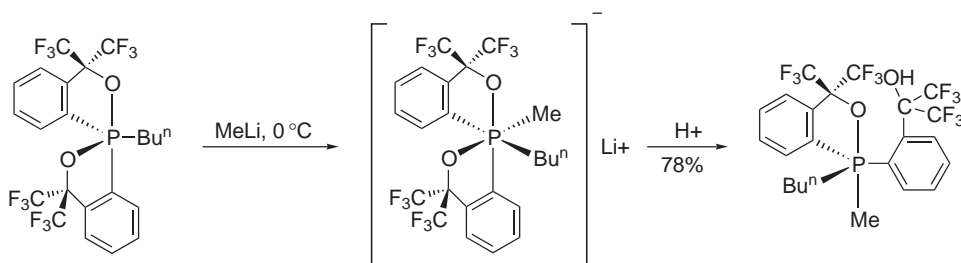
2.16.9.2 Arylphosphorus Compounds with a P—Pb Bond

Although synthesis of arylphosphorus compounds with a P—Pb σ -bond via the reaction of alkali metal arylphosphides with organolead chlorides has been established, the chemistry of π -complexes of phosphorus compounds with lead will hereafter be increasingly studied. For example, treatment of a THF solution of lithium 2,5-di-(*t*-butyl) phospholyl with MX_2 ($\text{M} = \text{Pb}, \text{Sn}, \text{Ge}$) produces air- and moisture-sensitive phospholyl sandwich complexes containing group 14 elements in good yields (Equation (258)) <1999CC1273>.

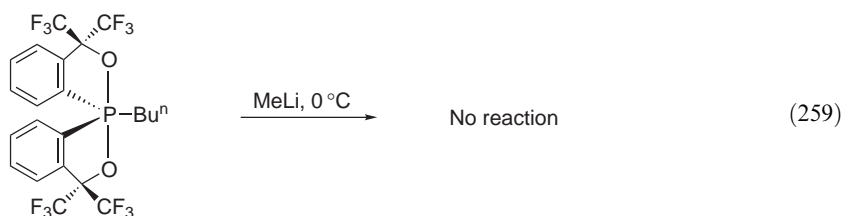


2.16.10 HEXAVALENT PHOSPHORUS COMPOUNDS

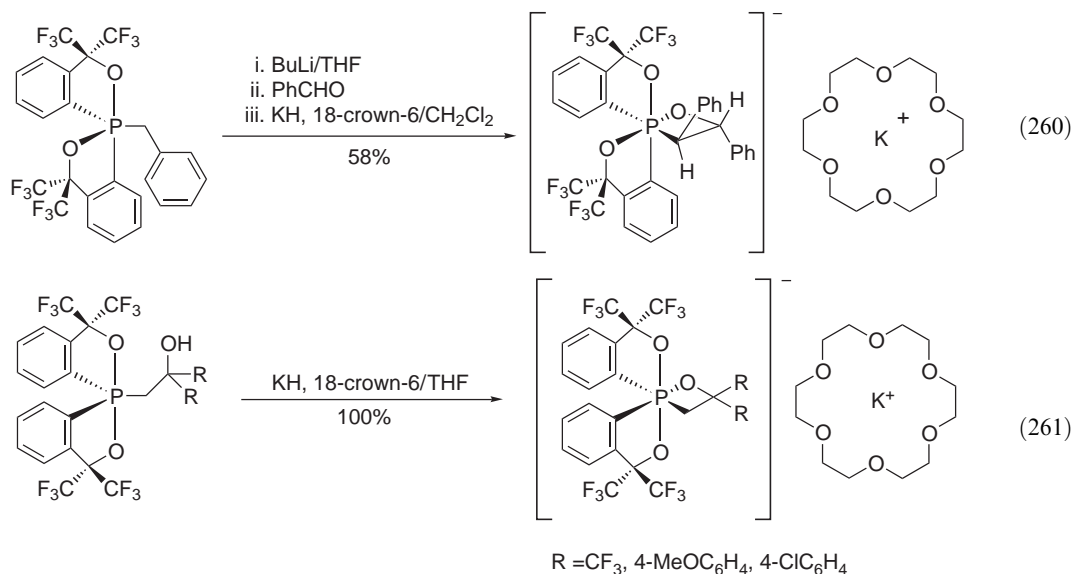
As a representative synthetic method for hexacoordinated phosphorus compounds, the method via the reaction of phosphoranes with nucleophiles is well known <1995COFGT(2)819>. To examine the relationship between the structures and the reactivities of phosphoranes, synthesis of hexavalent phosphorus compounds from phosphoranes and nucleophiles has recently been of great interest to chemists. *O*-*cis*-Spirophosphoranes having an apical-carbon-equatorial-oxygen configuration in a five-membered ring show higher reactivity toward nucleophiles than the corresponding *O*-*trans* isomeric spirophosphoranes having an apical-oxygen-equatorial-carbon configuration. Thus, *O*-*cis*-spirophosphoranes react with nucleophiles such as MeLi or $\text{Bu}_4\text{N}^+\text{F}^-$ to produce hexacoordinate phosphorus intermediates which are observed by NMR spectroscopy but not isolated (Scheme 10), while similar reaction using the corresponding *O*-*trans* isomers did not give the hexavalent phosphorus derivatives (Equation (259)) <2002JA13154>.



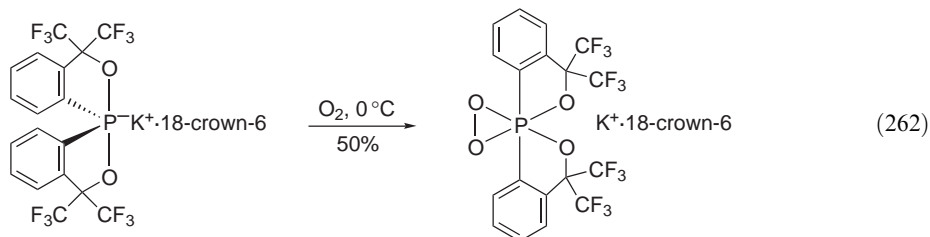
Scheme 10



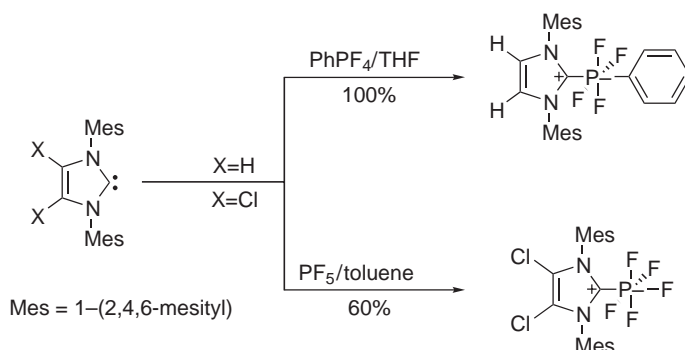
The hexavalent phosphorus compound derived from the reaction of the benzylic anion from *O*-*cis*-benzylspiroposphorane with benzaldehyde can be isolated as stable crystals (Equation (260)) <2002JA13154>. Similar treatment of the β -hydroxyalkylphosphoranes with KH in the presence of 18-crown-6 ether gave the hexacoordinate 1,2-oxaphosphetanes, which are stable in solution at room temperature (Equation (261)) <1997TL547, 1997TL551>. Some of these hexavalent phosphorus compounds on heating give Wittig-type olefination products.



Akiba and co-workers have recently succeeded in isolating a novel hexacoordinated phosphorus species bearing two Martin ligands and a P—O—O three-membered ring, which is formed by the reaction of potassium 10-P-4 phosphoranide with oxygen (Equation (262)) <1999JA6958>.

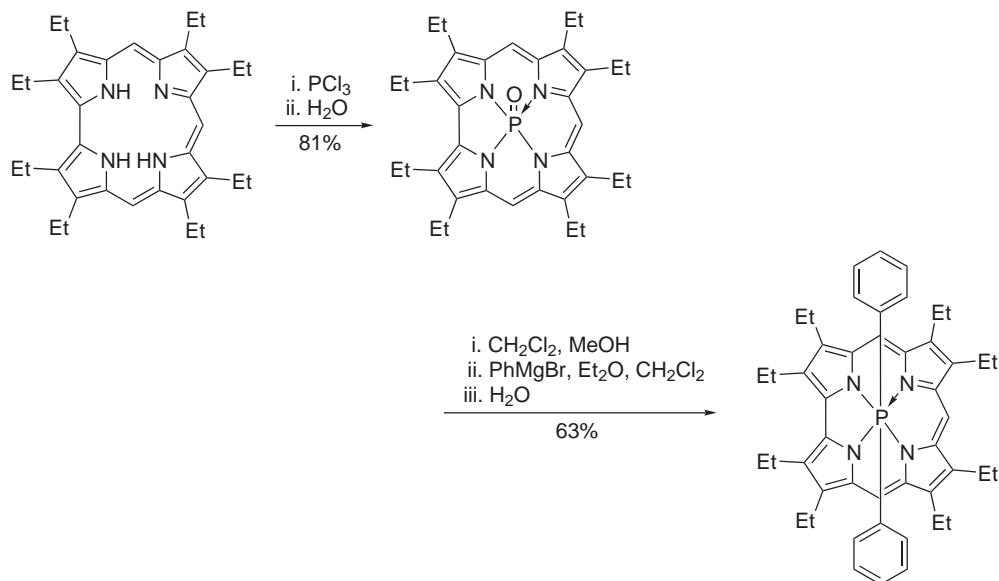


Hexacoordinate phosphorus compounds are also formed by the direct reaction of the stable carbene species imidazol-2-ylidene with phenyltetrafluorophosphorane or phosphorus pentafluoride (Scheme 11) <1997JA3381, 2000M251>. These compounds have internal zwitterionic structures with imidazolium ion character and a pentavalent phosphorus anion bonded to C-2, and show octahedral geometry at the phosphorus center.



Scheme 11

Another type of hexavalent phosphorus compound (phosphorus octa-ethylcorroles) with a variety of axial ligands has recently been developed <2000IC5675>. For example, treatment of the oxo phosphorus octa-ethylcorrole ((OEC)P=O), derived from the reaction of PCl_3 with octa-ethylcorrole, with excess phenylmagnesium bromide leads to diphenylphosphorus octaethylcorrole ((OEC)PPh₂) (Scheme 12).



Scheme 12

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1995CB365
1995CC37

1995CC1383
1995CC2429
1995COFGT(2)819

1995H889
1995HAC365
1995IC5003

1995JHC299
1995JOC74

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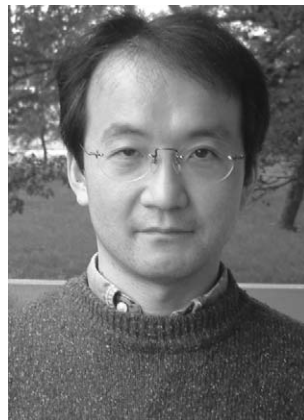
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2.17

Vinyl- and Arylarsenic, -antimony, and -bismuth Compounds

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2.17.1 ARSINES AND ARSORANES AND THEIR ANTIMONY AND BISMUTH ANALOGS

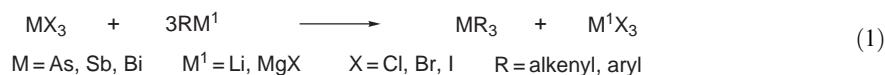
The field of organoarsenic, organoantimony, and organobismuth chemistry has seen considerable progress since publication of COFGT (1995) <1995COFGT(2)871> primarily through the introduction of more sophisticated methodology and reagents. Authoritative chemical reviews were given previously in monographs <B-1994MI217-01, B-1979MI217-01, 1978HOU(13)1, B-1970MI217-01>, in general reviews <1982COMC-I(2)863, B-1975MI217-01>, and specialized reviews. More recently, methods for the synthesis of arsenic compounds and the preparation and applications of antimony compounds have been published in the "Science of Synthesis" series <2002MI217-01, 2002MI217-02>. Organo-As, -Sb, and -Bi compounds have been reviewed in the monographs by Norman <B-1998MI217-01> and Lloyd and Gosney <B-1994MI217-01>, and a review of organo-Bi compounds has also appeared in monograph form <B-2001MI217-01>. The chemistry of the whole of groups 13–15, including the higher homologs of group 15, antimony and bismuth, was comprehensively reviewed by Schulz <2001CCR(215)1>, and the organic chemistry of arsenic was reviewed along with that of phosphorus, sulfur, selenium, tellurium, and silicon by Fletcher <2002AR(B)(98)61>.

The sections of this chapter are organized along the lines of the corresponding chapter in COFGT (1995), but where there has been little or no activity since the 1990s the relevant subsections have been omitted. Concomitantly, where new activity has appeared, new subsections have been defined.

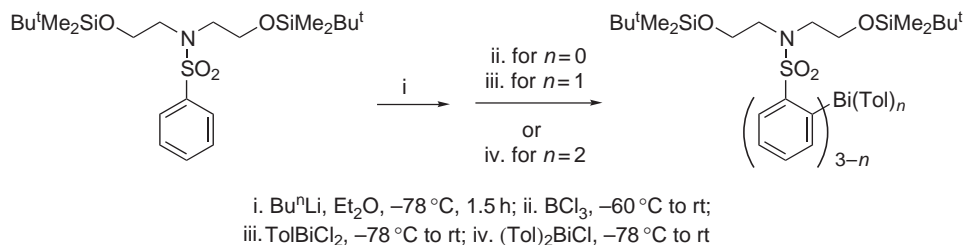
2.17.1.1 Organometal(III) and (V) Compounds through Carbon–Metal Formation

2.17.1.1.1 Transmetalation

Treatment of arsenic, antimony, and bismuth trihalides with organometallic reagents (Equation (1)) remains the most widely used synthetic method for the preparation of organometal(III) derivatives, including heteroaromatic <1996JOM(506)19, 2001JOM(634)5> and dimetallic <2003POL211> derivatives.



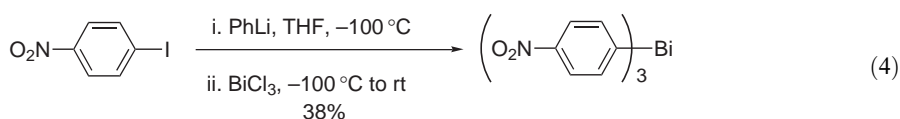
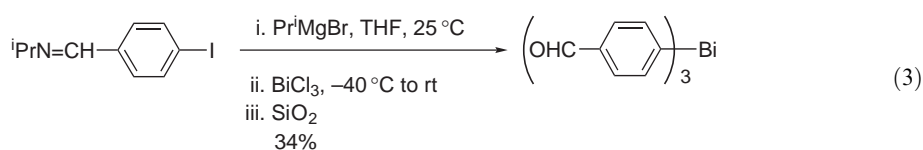
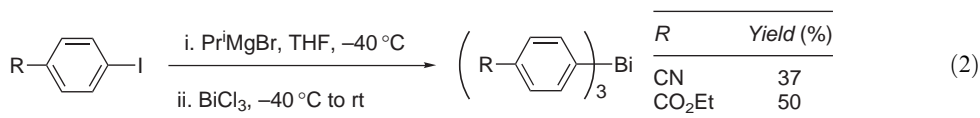
Recently, *o*-lithiation, as well as halometal exchange, has featured as a route to the organo-Mg and organo-Li intermediates <1993JCS(P1)2969, 2002CPB1404>, and this synthetic method has afforded neutral, water-soluble compounds through final deprotection of phenolic or alcohol substituents (Scheme 1) <1998JCS(P1)2511>.



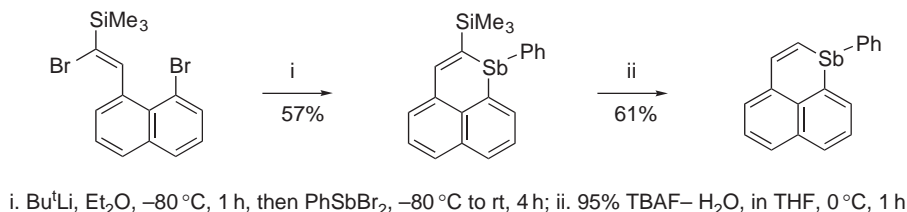
Scheme 1

Organo-Mg and organo-Li reagents are difficult to stop at monosubstitution and are best used to prepare triorganometal derivatives from MX₃ (M = As, Sb, Bi; X = Cl, Br, I). Steric crowding in the organic unit can limit the reaction to mono- and disubstitution <1989JOM(366)73, 1999JA3357, 1992BCJ(65)3504>. In the latter case, subsequent use of less hindered organo-Li reagents has provided several crowded alkyl-, alkenyl-, and alkynyldiarylbismuthines. Notably,

some of the most crowded triaryl metals on record have been synthesized by the reaction of 2,4,6-triisopropylphenylcopper(I) with the corresponding MX_3 derivative ($\text{M} = \text{As}, \text{Sb}, \text{Bi}$) <2002JA14830>. Preparation of organo-Li reagents by halometal exchange in THF solvent and their use at low temperature <1996OM5613> has given improved yields over oxidative insertion chemistry in Et_2O <1941JA207> in the synthesis of amino-substituted triaryl-Bi compounds. Equally, halometal exchange of iodoarenes with isopropyl-Mg or Ph-Li provides easy routes to triarylbi-muthanes, with arene groups each bearing a *para*-accepting substituent; these substances are inaccessible by conventional Grignard methods (Equations (2)–(4)) <2000S1208>. Highly crowded tri(9-anthryl)bismuthine derivatives have been synthesized by this route <2002OM2555>.

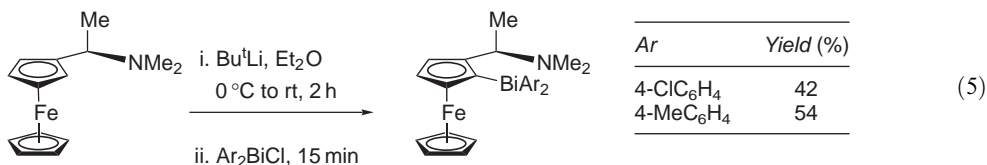


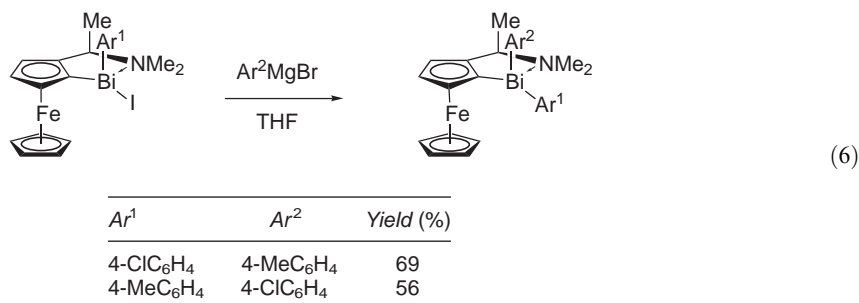
1-Stibaphenalenenes, the first examples of heterophenalenenes, have also been prepared in moderate yield using the direct organo-Li substitution route, following halometal exchange, through displacement of stibine halide groups (Scheme 2) <2001CL554>.



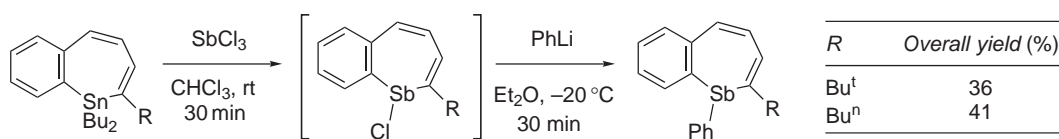
Scheme 2

ortho-Lithiated benzylamines have also provided unsymmetrical and chiral triorganobismuthines <1993JCS(P1)2969>, including ferrocenyl derivatives (Equation (5)) <1996CC1693, 1998OM1711> and triorganobisstibines <2002CPB1404>. Indeed, substitution at the chiral bismuth center of optically pure diastereomeric iodobismuthanes bearing an intramolecular Bi–N coordination bond in such a ferrocene molecule by aryl Grignard reagents has provided triarylbi-muthanes with inversion of configuration (Equation (6)) <2000JOM(611)100>. Some care needs to be taken in the manipulation of the resulting triarylbi-muthanes. They are configurationally stable in refluxing toluene but suffer disproportionation, with intermolecular exchange of aryl groups, upon chromatography on silica gel.

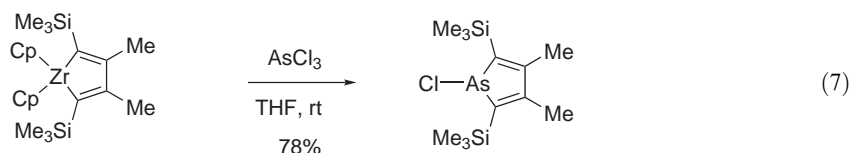




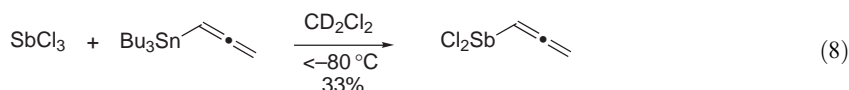
Since the publication of COFGT (1995) <1995COFGT(2)871>, where less reactive organo-metallic derivatives of Hg, Cd, Sn, Si, and Zr were described to introduce aryl and alkenyl groups to As, Sb, and Bi, organo-Sn reagents have seen repeated use <1994OM1525, 1995IC1466, 2001OM2109>, including for the first synthesis of 1-benzostibepines through aryl and alkenyl transfer (Scheme 3) <1998CC767>. The immediate benzostibepine chlorides were unstable and were immediately converted into triorgano-Sb derivatives through conventional treatment with MeLi and PhLi. Similar transmetalation using organo-Zr reagents yields arsacyclopentadienides (Equation (7)) <1999OM2491>.



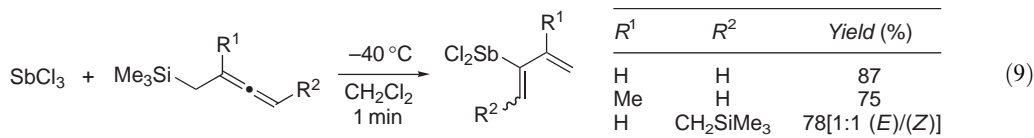
Scheme 3



Allenyltri-*n*-butylstannane reacts with AsCl₃ and divinyl-SbCl at low temperatures (−80 to −20 °C) to give the corresponding propargylic haloarsine and triorganostibine, but gentle warming to room temperature provides near quantitative conversion to the isomeric allenyldichloroarsine and -divinylstibine <1999OM5259>. Reaction with the stronger Lewis acid SbCl₃ proceeds directly to the corresponding allenyldichlorostibine (Equation (8)).



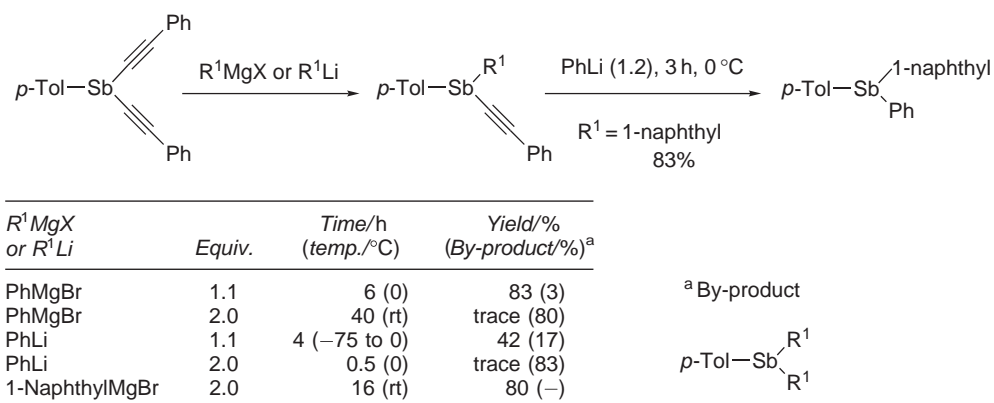
The reaction of β -allenyl silanes with SbCl₃ and SbCl₅ gives practical yields of the corresponding buta-1,3-dien-2-yl halostibine derivatives (Equation (9)) through ligand exchange <2002CC644>.



Methods for synthesis of pentaorganometal(V) compounds have seen little improvement, and the favored method still remains the reaction of organo-Li reagents with R₃MX₂.

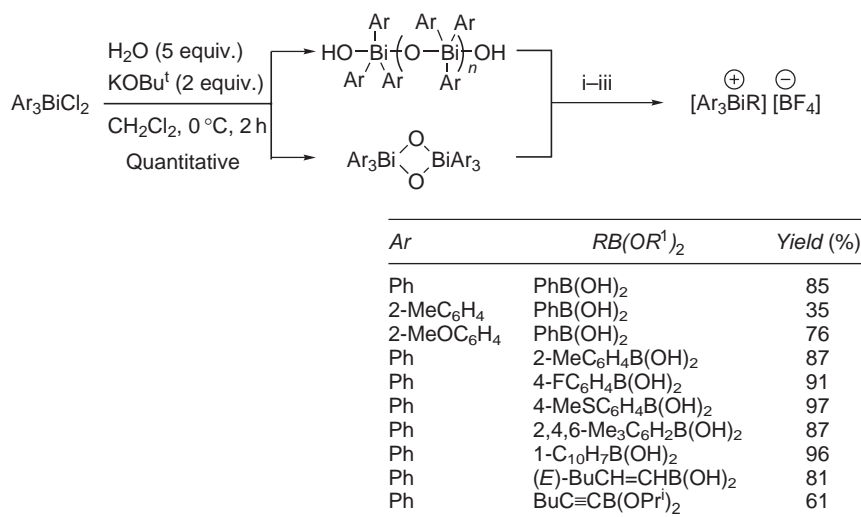
While the most convenient method for the preparation of many group 15 mixed organometallic compounds is through stepwise nucleophilic displacement of halogens from R_nMX_{3-n}, the method is unsatisfactory in all but hindered cases using Grignard or organo-Li reagents <1992BCJ(65)3504, 1995CL959, 1995JOM(485)141, 2002JA14830> because of the high susceptibility of the halides to

substitution. One approach to overcoming this shortcoming is the use of less reactive organometallic reagents. Another method has been the stepwise displacement of the more moderate ethynyl leaving group, which has given high yields of unsymmetrical triorgano-Sb compounds (Scheme 4) <2000SL1503>.



Scheme 4

Triarylbiomuth(V)-oxo and -hydroxo compounds are easily prepared in quantitative yield from Ar_3BiCl_2 <2001JA6443> and react efficiently with organoboronic acids and esters ($\text{RB}(\text{OR}^1)_2$) (R = aryl, alkenyl, and alkynyl) in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to afford the corresponding bismuthonium salts $[\text{Ar}_3\text{Bi}^+\text{R}] \text{BF}_4^-$ under mild conditions (Scheme 5) <2002S631>. The efficiency of this method is comparable to that using Ar_3BiF_2 <2000CC2233, 1998OM4332, 1999OM5668>.

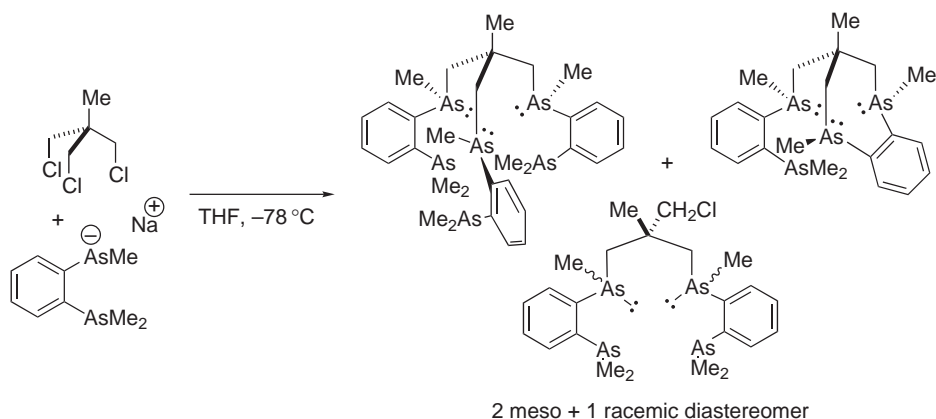


i. $\text{BF}_3 \cdot \text{OEt}_2$ (2 equiv.), $\text{RB}(\text{OR}^1)_2$, CH_2Cl_2 , rt, 2 h; ii. NaBF_4 , H_2O

Scheme 5

2.17.1.1.2 Halogen-metal exchange

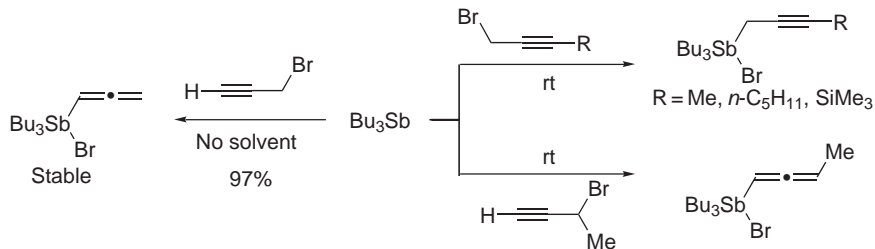
The reagent prepared from elemental As and Sb with Na or K metal in liquid NH_3 is capable of reacting with aryl halides under irradiation by light to form symmetrical triaryl derivatives. Meanwhile, alkali metal salts of diorganoarsines and -stibines, generated in a similar manner from the corresponding metal hydride and alkali metal, are able to displace the halide ion from alkenyl and aryl halides to provide mixed triorganyl derivatives. These approaches operate through an $\text{S}_{\text{RN}}1$ mechanism, but are dated and have seen little use since the 1990s. One application involving alkylation has been the preparation of chiral multidentate tertiary arsine ligands (Scheme 6),



Scheme 6

following which the ligands were isolated as their cobalt salt complexes and the structures confirmed by X-ray crystallography [<2000JCS\(D\)3603>](#). The yields of individual isolated complexes were very small but by increasing the proportion of the arsenide reagent (from 3 to 5 equiv.) formation of the bidentate ligand was avoided.

An interesting variant on the halogen–metal exchange approach has been the reaction of Bu_3Sb with propargyl bromide. The resulting allenyltributylstibonium bromide, which is normally inert toward aldehydes, reacts readily with them after conversion to pentaorganyl-Sb(V) reagents [<1994JOM\(471\)77>](#). This synthesis has limitations because of the perennial problem of allene–alkyne isomerism. Interestingly, the reaction of Bu_3Sb with 1-bromo-2-butyne gave the corresponding alkynyl derivative, but treatment with 3-bromo-1-butyne again provided the allenyl derivative (Scheme 7). The subsequent reaction of these products with Bu^nLi and then aldehydes has been examined.

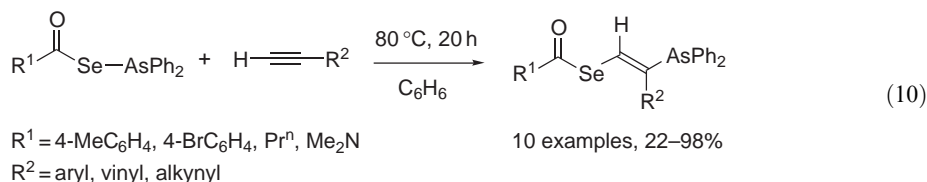


Scheme 7

2.17.1.1.3 Reaction of organometallic reagents with arenes and alkynes

The reaction of arsenic halides and oxygen derivatives with alkenes and aromatic substrates is a successful route to the products of electrophilic substitution. Unactivated substrates require Lewis acids or other catalysis. The addition of alkyl-, alkenyl-, and aryl-As and -Sb to alkynes also serves as a useful means of preparing mainly (*Z*)-1,2-disubstituted alkenes. Products of single or double *anti*-addition are obtained depending upon the bulk of the alkyne, and the reaction can provide a route to heterocycles.

An extension of this general approach, selenoarsenation of alkynes, has been reported for the first time [<1995OM4975>](#). The reaction using conjugated alkynes gives the corresponding (*E*)-alkenyl derivatives in 40–90% isolated yield with complete regio- and stereoselectivity (Equation (10)).

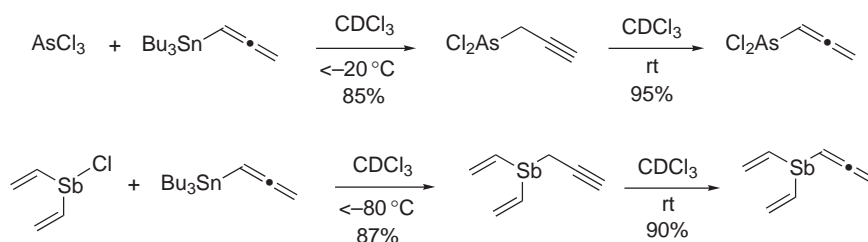


2.17.1.2 Organometal(III) and (V) Compounds through Modification of Existing Organic Groups

2.17.1.2.1 Thermal processes: cycloaddition and thermal rearrangements

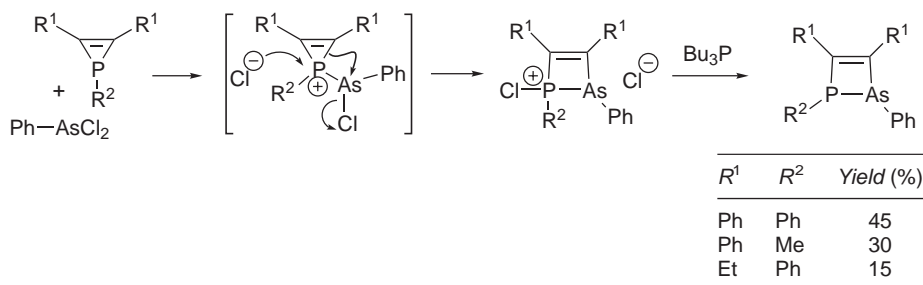
Vinyl-As, -Sb, and -Bi derivatives are generated through Diels–Alder reactions of heterobenzenes with alkenes and alkynes, but there are reactivity differences. The basis of these differences has been studied by PM3 semiempirical molecular orbital and higher molecular orbital methods <2001RRC(45)1021>. The results indicate that the reactions are under thermodynamic rather than kinetic control.

Allenyl-As and certain allenyl-Sb compounds can be prepared in high yield through very mild thermal induced rearrangement of the corresponding propargyl derivatives (Scheme 8; compare with Equation (8)) <1999OM5259>. An earlier report of the synthesis of allenyldichloroarsine <1995IC5694> failed to detect the propargylic intermediate. It is interesting that with AsCl_3 the propargylic intermediate was isolable while the more Lewis acidic metal halide SbCl_3 yielded the allenyl derivative directly at temperatures as low as -80°C .



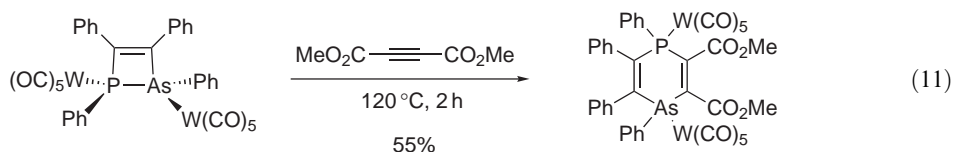
Scheme 8

1,2-Dihydro-1,2-arsaphosphetes have been prepared in modest but acceptable overall yields from phosphirenes and dichlorophenylarsine (Scheme 9) <1993BSF(130)521>. The mechanism of the reaction probably involves initial arsenylation of phosphorus followed by a ring expansion initiated by the nucleophilic attack by Cl^- at phosphorus.



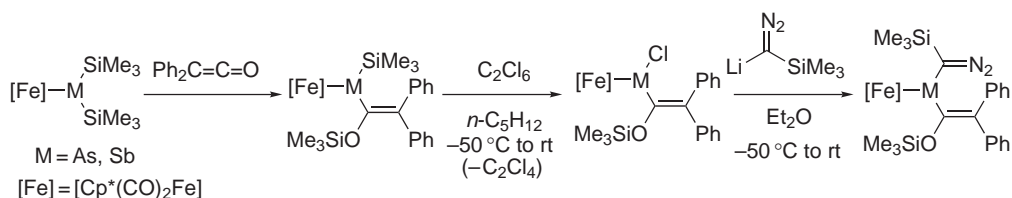
Scheme 9

A 1,4-dihydro-1,4-arsaphosphinine has been prepared in good yield as its ditungsten derivative by the treatment of di(tungstenpentacarbonyl) derivative of a 1,2-dihydro-1,2-arsaphosphete (Equation (11)) <1993BSF(130)521>. Dimethyl acetylenedicarboxylate participates in what is probably a cycloaddition reaction with the acyclic 1-arsa-4-phosphadiene tautomer of the arsaphosphete.



Ferriodisilylarsanes and -stibanes react with carboxylic acid chlorides to yield ferriarsaalkenes <1996AG(E)271, 1996CB(129)367>, which are the topic of Chapter 3.13, and ferriodisilylarsastibanes <2000ZAAC(626)412>, which are referred to in Chapter 5.23. They react with

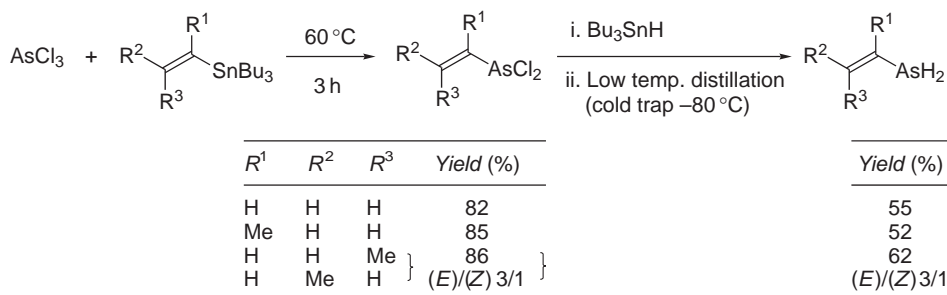
diphenyldiketene to generate useful alkenyl-As and -Sb intermediates (Scheme 10) <2002JOM(643-644)81>.



Scheme 10

2.17.1.3 Organometal(III) Compounds through Reductive Processes

Primary and secondary aryl- and vinyl-As, -Sb, and -Bi are usually prepared from the corresponding halo derivatives by the reductive methods. Chemoselective reducing agents are typically Bu_3SnH (Scheme 11) and this reagent has been used to prepare both primary and secondary vinylarsines <1994OM1525> and vinyl- and alkynylstibines <1995IC(34)1466>.

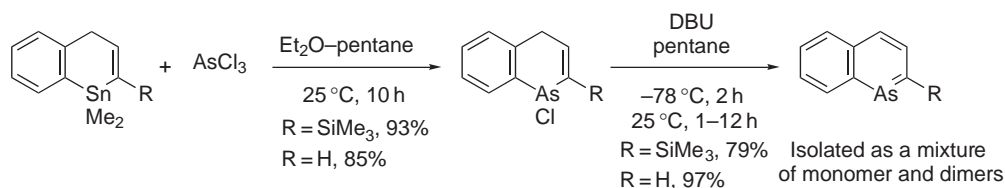


Scheme 11

Triaryl-Sb(III) compounds have been prepared reductively from the corresponding oxides (R_3SbO ; $\text{R} = \text{Ph}$, 4-MeC₆H₄, 2,4,6-Me₃C₆H₂) by the treatment with SmI_2 in HMPA-THF <1995MI331>, but the method has not been used widely.

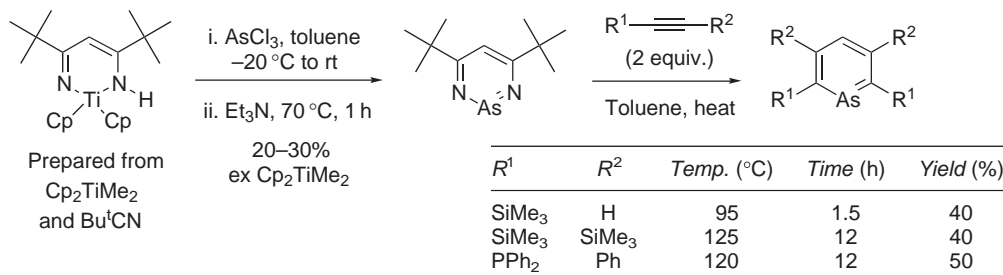
2.17.1.4 Heteroaromatic Compounds of Arsenic, Antimony, and Bismuth

The chemistry of group 15 heterobenzenes is well known <1982TCC125, 1996CHC(II)(6)1073, B-1998MI217-02>, including their proton affinities <1995MI51>, aromaticity studies through photoelectron spectroscopy <1995JST(347)57>, and participation in Diels-Alder chemistry <1996MI217-01, 2001RRC(45)1021>. Their synthesis is often achieved through twofold hydrostannylation of diynes followed by the transmetalation of the intermediate dihydrostannin and dehydrohalogenation <1969AG(E)991, 1971JA3293>. The recent synthesis of 1-arsanaphthalene (Scheme 12) <2001OM2109> is illustrative of the method. It relies upon chemistry that was described in Scheme 2 to prepare the 1,4-dihydrostannanaphthalene and is amenable to scale up.



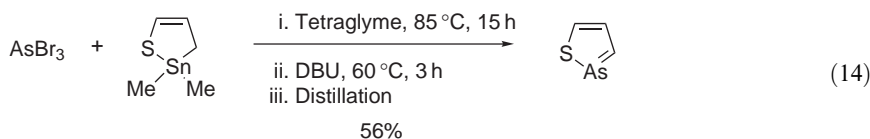
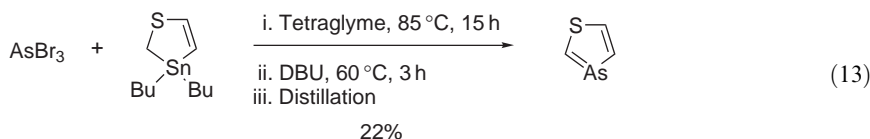
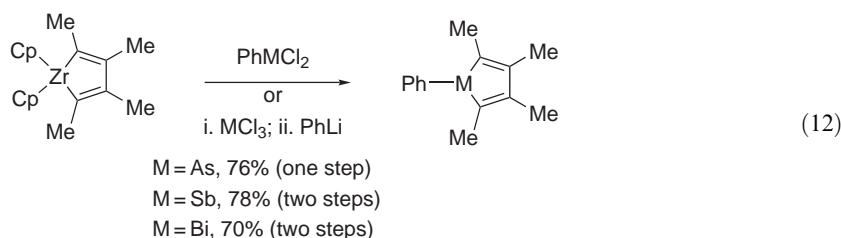
Scheme 12

It is interesting that alkyl-substituted 1,3,2-diazaarsinines have also been prepared by transmetallation from the corresponding diazatitanacycles, and these undergo twofold thermal cycloaddition reactions with acetylenes to give arsabenzenes (Scheme 13) <1997OM4089>.



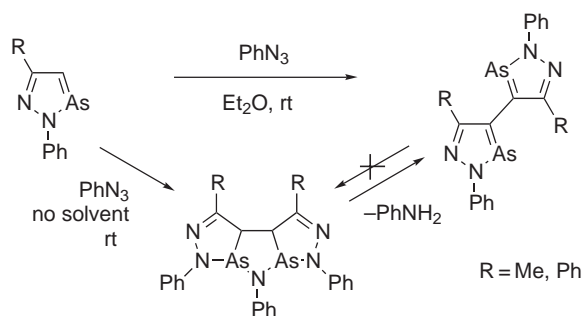
Scheme 13

Nonbenzenoid heteroaromatics have attracted interest because of their importance in industry as electronic material precursors. They are usually prepared in highly substituted form and can be obtained in a single step or through the halometalloycycle by subsequent substitution (Equation (12)) <1988JA2310>. Five-membered heteroaromatics containing bismuth have been reviewed <1995AG(E)295>. 1,3-Thiarsole itself has been obtained, albeit in low yield, from a 2,3-dihydro-1,3-thiastannane by the transmetallation followed by the treatment with DBU (compare Scheme 12) and direct distillation from the reaction mixture (Equation (13)) <1999CC1283>. The isomeric 1,2-thiarsole has been prepared in significantly higher yield by the same method through the use of a 2,2-dimethyl-1,2-thiastannole precursor (Equation (14)) <2000JA7012>.

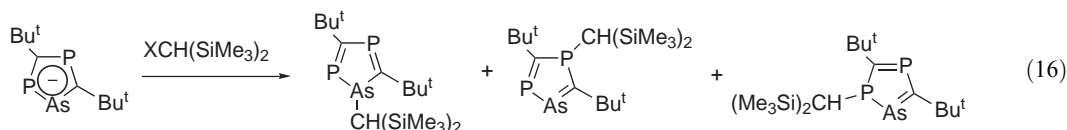
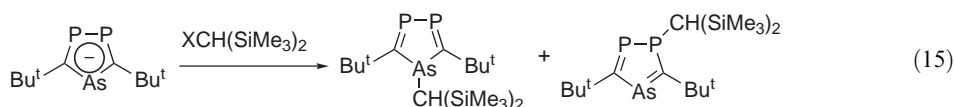


In another report, 2*H*-1,2,3-diazaarsoles were found to react with phenyl azide to give a range of crystalline products, dependent upon reaction conditions <1996HAC123>. At room temperature in Et_2O a product of oxidative coupling was observed, probably through a cycloaddition process involving the phenylnitrene (Scheme 14).

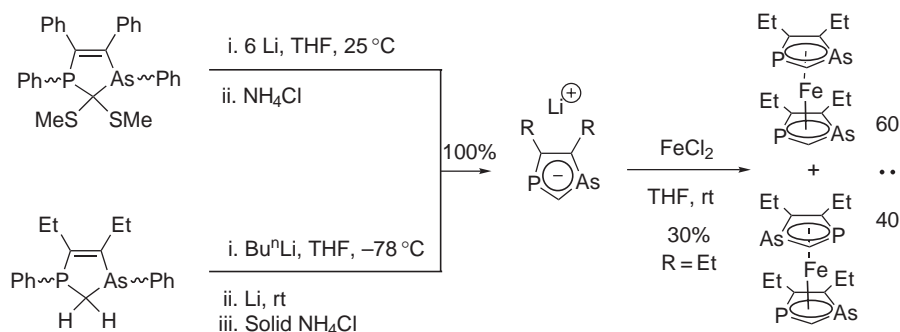
The synthesis of two new arsadiphospholes through alkylation of the corresponding arsadiphosphacyclopentadienyl anions has been reported <2002MI217-03>, and it appears from *ab initio* calculations at the MP2/6-31 G(d) level that the distribution of observed isomeric products corresponds to that expected from the thermodynamic control of product formation (Equations (15) and (16)).



Scheme 14



1,3-Arsaphospholides have been prepared through reductive cleavage of the two exocyclic P—Ph and As—Ph bonds of 1,3-diphenyl-1,3-arsaphospholenes. Where the latter heterocycles also contain a 2,2-dithioacetal group, the reductive desulfurization occurs concomitantly, but when the 2-position of the heterocycle is unsubstituted, reduction is only successful if the heterocycle is first treated with Bu^nLi . The 4,5-diethyl-substituted arsaphospholide has also provided 1,1'-diarsa-3,3'-diphosphoferrocene upon reaction with FeCl_2 although the corresponding 4,5-diphenyl derivative reacts very sluggishly in ferrocene formation (Scheme 15) <1993BSF(130)521>.



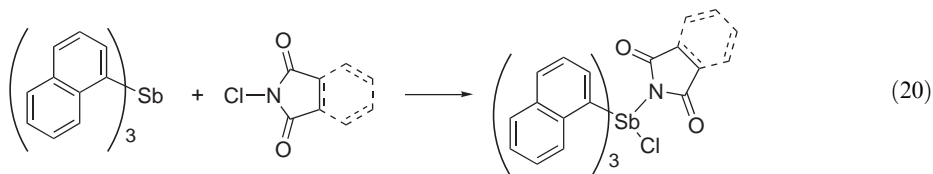
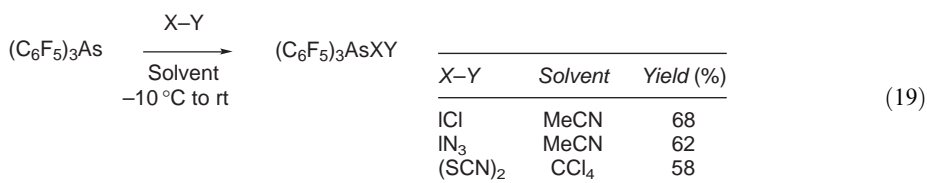
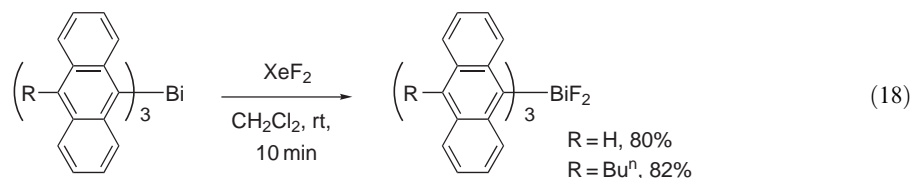
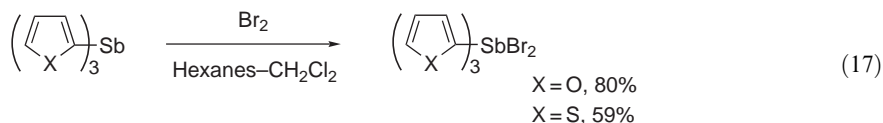
Scheme 15

2.17.2 ARSENIC HALIDES AND THEIR ANTIMONY AND BISMUTH ANALOGS

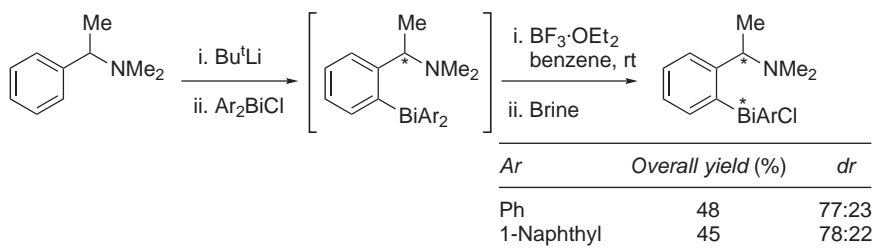
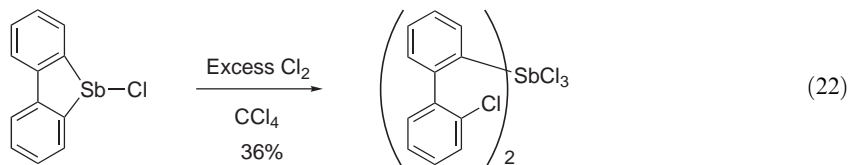
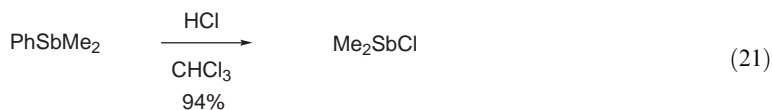
2.17.2.1 Halogenation of Arsines, Stibines, and Bismuthines

The preparation of R_3MX_2 (R = alkenyl, aryl; M = As, Sb, Bi; X = F, Cl, Br, I) continues to be achieved efficiently by direct halogenation of R_3M . Thermal stability decreases in the order $\text{F} > \text{Cl} > \text{Br} > \text{I}$. The method is equally applicable to heteroaryl-M compounds (Equation (17)) <2001JOM(634)5>. Ph_3BiF_2 <1994PS(92)225> and $\text{N}_3\text{CF}_2\text{CF}_2\text{CO}_2\text{Me}$ <1999PS(149)75> serve as novel reagents for the oxidative fluorination of group 15 and 16 elements, including Sb(III) compounds. Recently used halogenating agents have also included XeF_2 (Equation (18)) <1997ZAAC(623)122, 2002OM2555>, SO_2Cl_2 <1988TL3817, 1994AG(E)976>, CuBr_2

<2002MI217-04>, CuCl_2 <2002ZOB(E)392>, and TeCl_4 <1998JCS(P1)2511, 2002SRI399>. Interhalogens and halopseudohalogens $\text{I}-\text{X}$ ($\text{X} = \text{Cl}, \text{Br}, \text{N}_3, \text{NCO}$, and imides) have provided equivalent species (Equations (19) and (20)) <2002SRI399, 2003JFC(122)165>, but halogenation and halopseudohalogenation have limitations. For example, attempts to oxidize $(2,6\text{-F}_2\text{C}_6\text{H}_3)_3\text{Bi}$ with a variety of reagents, including IF_5 <1986JFC(34)129>, have been complicated by halo-demetalation <1997ZAAC(623)122>.



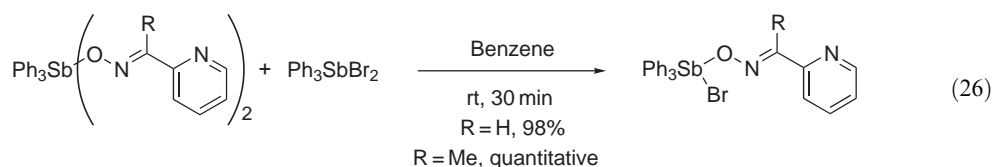
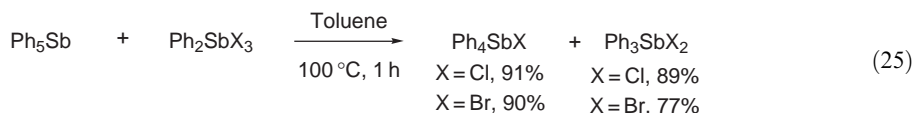
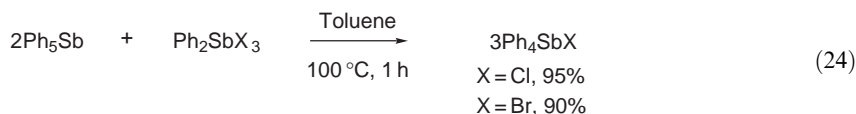
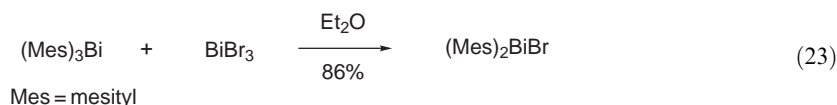
Halodearylation can provide a useful route to both alkyl <2000ZAAC(626)1137> and aryl halometal <1994JOM(480)227> compounds (Equations (21) and (22)), and has been the basis of interesting studies of asymmetric induction at Bi (Scheme 16) <1993JCS(P1)2969>, following which the first optically pure diastereomeric iodo organobismuthane, a ferrocenyl derivative, was characterized <1998OM1711>. The reaction can proceed with surprising ease and, in a negative sense, prevented halogenation of $(2,6\text{-F}_2\text{C}_6\text{H}_3)_3\text{Bi}$ by Br_2 , I_2 , ICl , and IF_5 <1997ZAAC(623)122>.



Scheme 16

2.17.2.2 Disproportionation and Transmetallation Reactions

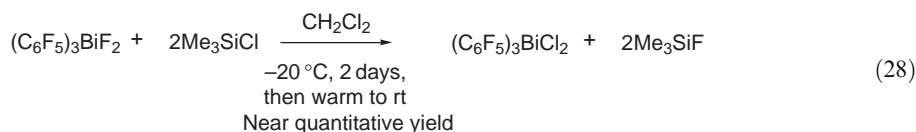
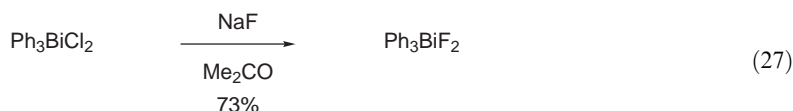
One of the most convenient methods of preparing halogen derivatives RMX_2 and R_2MX ($\text{M} = \text{As}, \text{Sb}, \text{Bi}$; $\text{R} = \text{aryl and vinyl}$) in high yield is through disproportion reactions of R_3M and MX_3 . The method is most often used to prepare Bi derivatives (Equation (23)) <1994JOM(470)93>, but is also suited to the preparation of Sb(III) <2001ZAAC(627)699> and Sb(V) compounds (Equations (24) and (25)) <2003MI217-01>. In the Sb series it has also been used to redistribute oxygen and halogen substituents (Equation (26)) <2002POL2387>.



Related transmetallation reactions also allow Ph_3BiF_2 to serve as a mild reagent for oxidative fluorination of R_3Sb <1994PS(92)225>.

2.17.2.3 Displacement Reactions

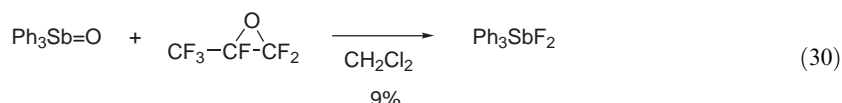
Nucleophilic substitution procedures such as the Finkelstein reaction allow halogens to be interchanged by displacement reactions (Equation (27)) <2002ZOB(E)44, 1993JOM(455)185, 1993JCS(P1)2969>. Judicious choice of reagent can lead to products through displacement of halides in the opposite sense (Equation (28)) <1997JFC(84)69>.



Bromination of $(\text{Ph}_2\text{As})_2\text{O}$ has been reported to cleave the oxobridge with the formation of a new organoarsenic(V) bromide (Ph_2AsBr_3) albeit in unspecified yield (Equation (29)) <2000MI217-01>. Similar cleavage of catechol derivatives with alcoholic HCl provides an alternative route to Ph_3SbCl_2 <1995IZV748>. Fluorinative displacement of oxygen in Sb(V) and Bi(V) oxides has also been achieved in low yield using hexafluoropropene oxide as the fluorinating agent (Equation (30)) <1998IZV(E)1609>.

2.17.2.4 Reductive Halogenation of Arsonic and Arsinic Acids and Their Antimony and Bismuth Analogs

Halogenation of both As(III) and As(V) oxide derivatives and their Sb analogs provides halo derivatives through cleavage of As—O bonds. In the example in Equation (29), the reaction proceeds through a further subsequent bromination <2000MI217-01>. Substitutive halogenation of Sb(V) and Bi(V) oxygen-containing compounds using hexafluoropropene oxide has also provided low yields of the corresponding difluoro derivatives (Equation (30)) <1998IZV(E)1609>.



2.17.3 ARSENIC COMPOUNDS WITH AN As—O BOND AND THEIR ANTIMONY AND BISMUTH ANALOGS

2.17.3.1 Preparation through Metal—Carbon Bond Formation

A range of alkyl and aryl organoarsenic and -arsinic acids, particularly those containing organofluorine substituents, has been synthesized as potential ligands for the purpose of *f*-transition metal ion extraction (Figure 1) <1996MI217-02>. This literature study does not always report yields, but provides an excellent overview of the methods available for the preparation through formation of the As—C bond. These methods are not all suitable for the organofluorine derivatives that were sought, and have not been transported to the Sb and Bi analogs.

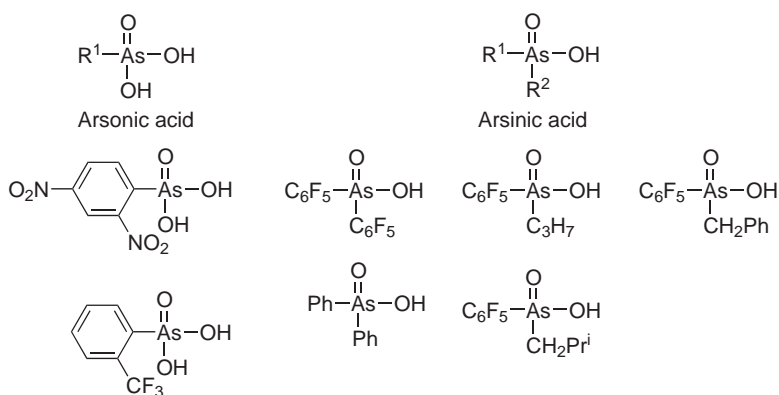
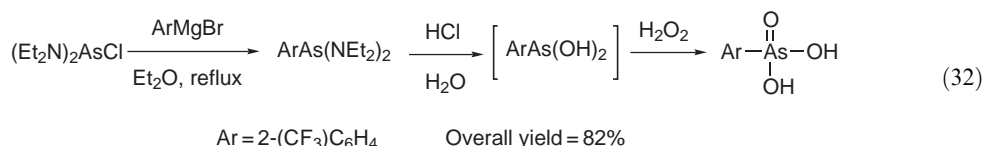
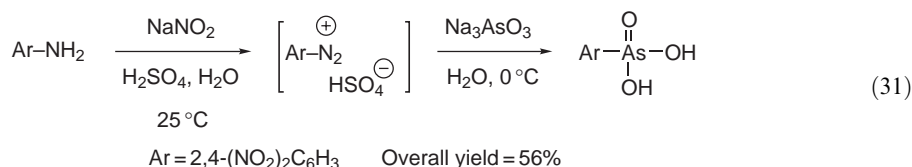
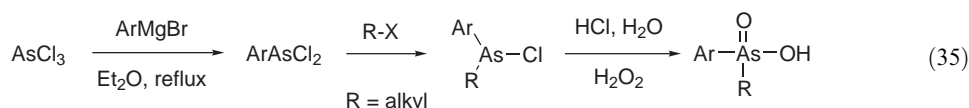
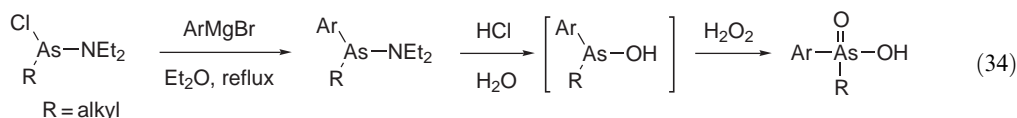
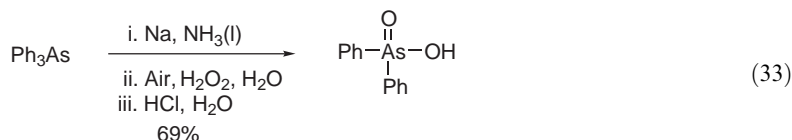


Figure 1

A well-established, general synthesis of arylarsonic acids is through the reaction of diazonium salts with Na_3AsO_3 ; this is the Bart reaction (Equation (31)) <1922LA(429)96>. This method has been used elsewhere to prepare phenolic arsonic acids <1997MI217-01, 1997MI217-02>. An alternative approach involving nucleophilic arylation of $(\text{Et}_2\text{N})_2\text{AsCl}$ <1968JOM(12)377>, followed by hydrolysis and oxidation (Equation (32)) is relatively general and provides high yields. As a word of caution, this method was applied to the synthesis of $\text{C}_6\text{F}_5\text{AsO}_3\text{H}_2$ but inexplicably the intermediate $\text{C}_6\text{F}_5\text{As}(\text{NET}_2)_2$ underwent conversion to $(\text{C}_6\text{F}_5)_2\text{AsO}_2\text{H}$ upon hydrolysis and oxidation.



One approach to organoarsinic acids is exemplified in the synthesis of $\text{Ph}_2\text{AsO}_2\text{H}$, which proceeds efficiently from Ph_3As through reductive dearylation followed by oxidation (Equation (33)). More directed syntheses that have provided mixed alkyl-/aryl arsinic acids are illustrated in Equations (34) and (35). The former method appears to be influenced by the steric effects through substituents in the Grignard reagent while the latter method works best with active alkylating agents, such as benzyl halides <1996MI217-02>.

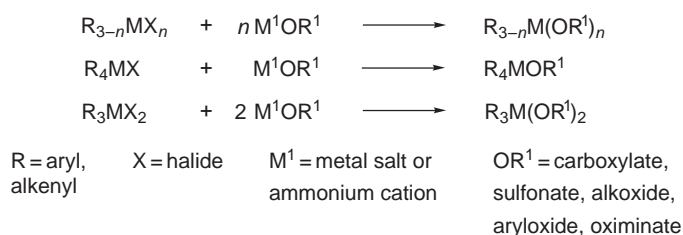


In other recent research, arylarsonic acids have been synthesized from smaller, preformed amino-arylarsonic acids for screening as potential antileukemic agents <2003BMC581>. Diastereomeric arsinites $[\text{ArRAsOR}^*]$ have also been prepared in 30 and 50% de from homochiral precursors $[\text{ArAs(OR}^*)_2]$ through displacement of menthyloxy substituents <1995ZN(B)339>.

2.17.3.2 Formation of Metal—Oxygen Bonds by Substitution Reactions

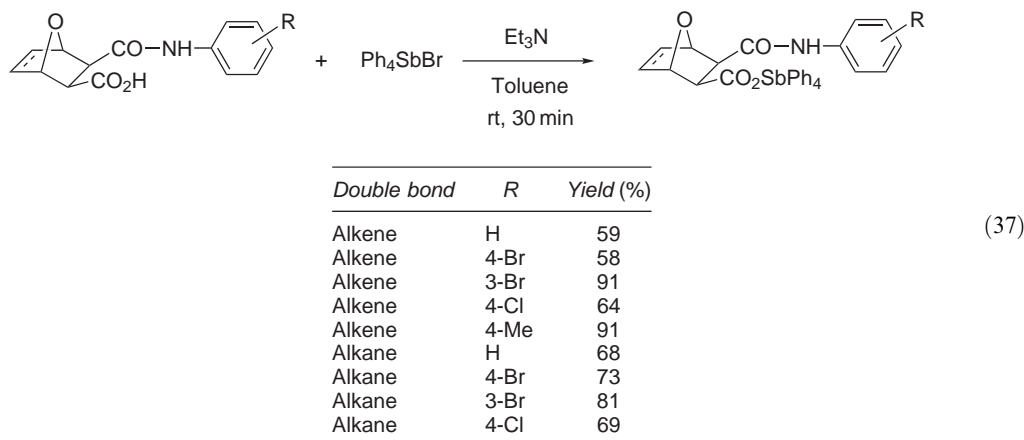
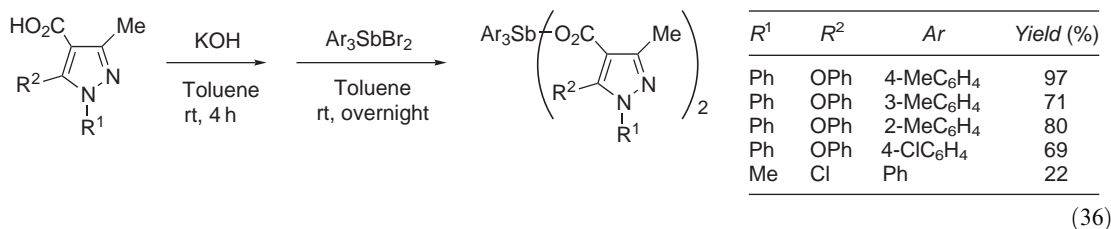
The synthesis of metal(III) and (V) carboxylates, sulfonates, alkoxides, aryloxides, and oximates is most often and easily carried out by reactions that involve nucleophilic substitution. The leaving groups are usually halides (Scheme 17).

Many procedures have used traditional alkali metal carboxylate salts in hot solvents to achieve substitution <1993PIA(A)(59)309, 1997ZAAC(623)122, 2001MI217-02, 2001MI217-03, 2002SRI449, 2002SRI569>. One recent example has produced triarylsantimony dipyrazolecarboxylates that have



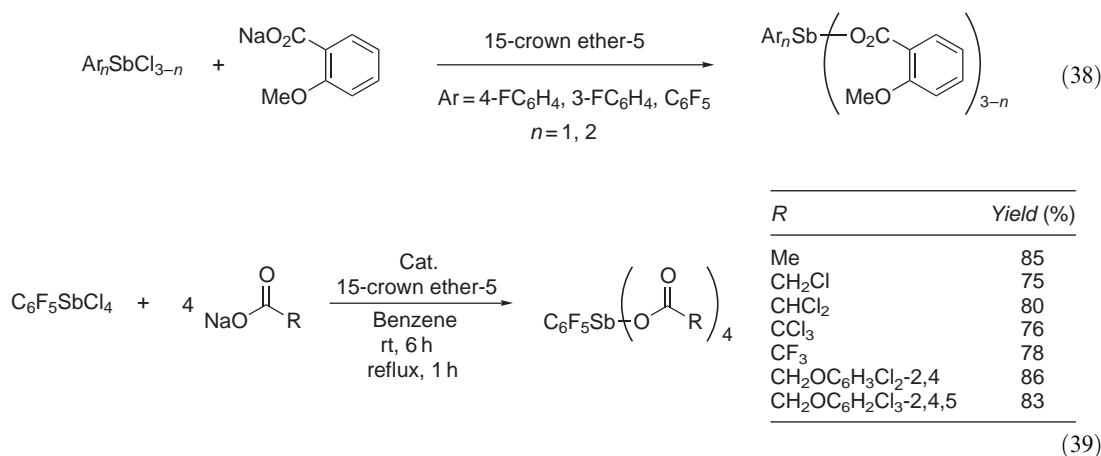
Scheme 17

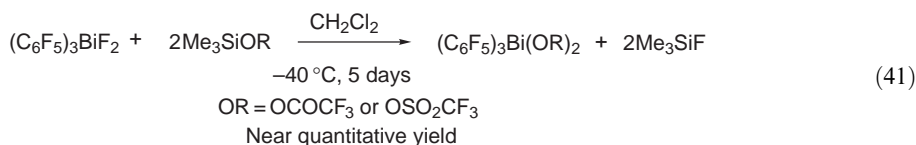
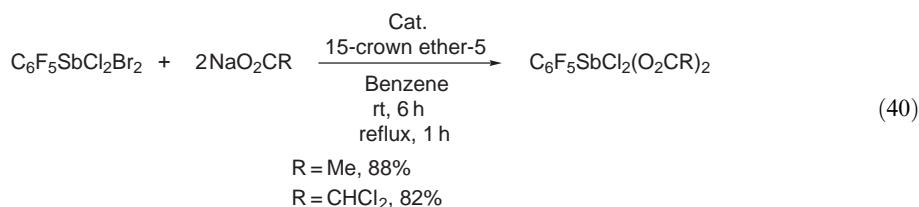
shown antibacterial activity (Equation (36)) <2002HAC299>. Others have used the carboxylic acids themselves in the presence of Et₃N <1993JFC(64)107, 1994IJC(A)687>, including one that has yielded candidates for antitumor activity testing (Equation (37)) <2001MI217-04>.



Nitrite and nitrate derivatives—Ph₃Sb(ONO)₂, Ph₃Bi(ONO)₂, and Ph₃Bi(ONO₂)₂—which have metal—oxygen bonds, have been prepared in 91, 86, and 77% yield by the treatment of Ph₃SbBr₂ and Ph₃BiCl₂ with NaNO₂ and AgNO₃, respectively <2002MI217-05, 2003MI217-02>. An alternative approach to Ph₄SbNO₂ (90%) involves metathesis through the treatment of Ph₅Sb with Ph₃Sb(NO₂)₂ <2002MI217-05>.

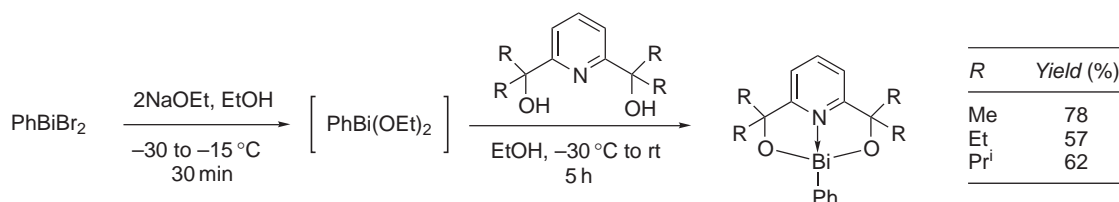
Alkali metal carboxylates have also been used in the presence of appropriate crown ethers under phase-transfer conditions (Equations (38) and (39)) <1993JFC(64)107, 2000SRI(30)909, 2002JFC(113)155> to aid the reaction, and in this situation one can also obtain selectivity between halides (Equation (40)) <2002JFC(113)155>. Others have used a combination of fluoride leaving groups and Me₃SiOR¹ reagents (Equation (41)) <1997JFC(84)69> to drive reactions to completion (compare Equation (28)). It should be noted that organo-Bi compounds with highly fluorinated aryl groups are much more sensitive to heat than their nonfluorinated counterparts, to the extent that (C₆F₅)₃Bi(O₃SCF₃) decomposes readily below room temperature.





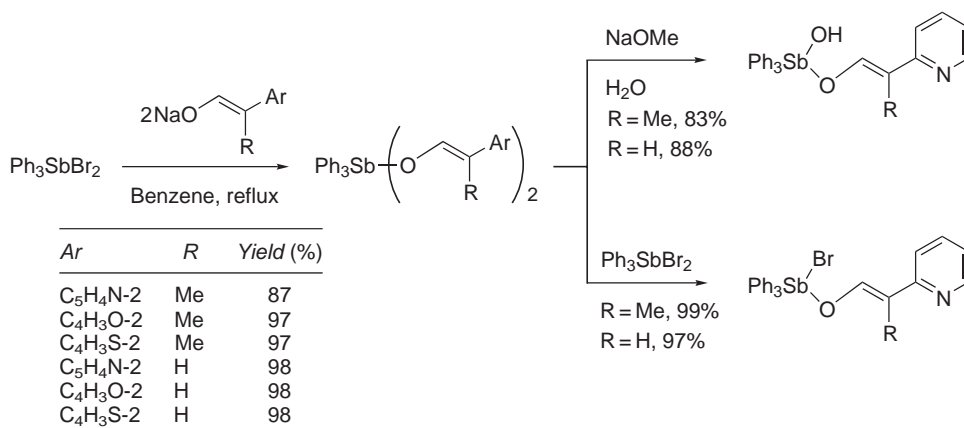
The introduction of weak nucleophiles such as CF_3SO_3^- and CF_3CO_2^- by the nucleophilic substitution is rare; it has been aided by the use of silver salts <1997ZAAC(623)122>.

Hydroxide, alkoxides, and aryl oxides provide good yields without the need for crown ethers or other promoters <2002SRI399, 1997PS(128)19, 2000OM931>. In one reported attempt to prepare $\text{PhBi}(\text{OR})_2$ derivatives bearing pyridinedimethoxide ligands, direct displacement of bromide from PhBiBr_2 was unsatisfactory. A practical solution came in the form of ligand exchange from $\text{PhBi}(\text{OEt})_2$ <1976ZAAC(423)40>, which was generated *in situ* from the corresponding dibromide (Scheme 18) <2000OM931>. Substitution by alkoxides at As has also been observed in certain halogenated arsenic heterocycles <1994JOM(467)57>. It should be noted in dealing with substitution by phenols that pentachlorophenol itself has led to the first reported cleavage of Sb—C and Bi—C bonds of triaryl-Sb and -Bi compounds by such reagents <1994IJC(A)687, 1997PS(128)19>.



Scheme 18

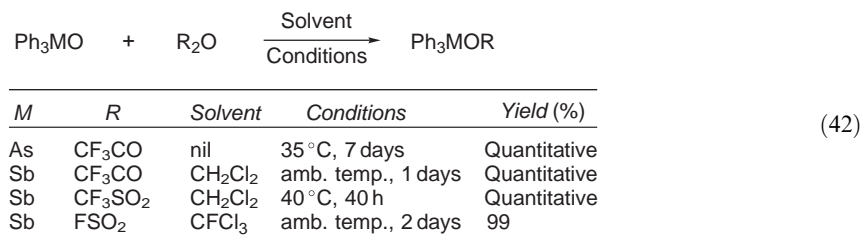
Triphenylstannoxide has been used as nucleophile in halide displacement, without catalysis, but displacement of a fluoride leaving group gave a much better yield and purity of product than the other halides <2000MI217-02>. Internally functionalized oximes can also be prepared by the substitution of halide ion (Scheme 19) <2002POL2387, 2002JOM(645)118, 2002SRI449,



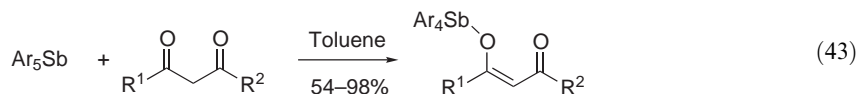
Scheme 19

2002SRI569>. As observed in Scheme 18, ligand exchange can also be used to prepare compounds with mixed oxygen ligands, as through hydrolysis with NaOMe/H₂O. Exchange can also take place between oxygen and halogen (Scheme 19).

In some cases, it is more convenient to utilize metal oxides (Ph₃M=O; M = As, Sb, Bi), in acylation or sulfonylation processes <1995JFC(70)237> and this process has yielded fluoro-sulfonate derivatives (Equation (42)).

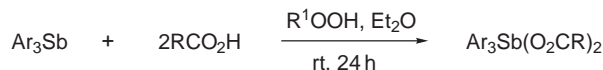


Aryl-Sb and -Bi reagents have found much use in C-arylation processes in organic synthesis. The corollary to this reaction has been the preparation of Ph₄Sb-β-diketonates in good-to-excellent yields from Ph₅Sb (Equation (43)) <2000ZOB(E)696, 2003MI217-03> through dearylation. Similar Sb—C and Bi—C bond cleavage takes place in the reaction of Ph₃M (M = Sb, Bi) with aryl oxides <1994IJC(A)687> and mesitylchlorostibines with catechols <1997PS(128)19> to yield triorganometals.



2.17.3.3 Formation through Oxidative Processes

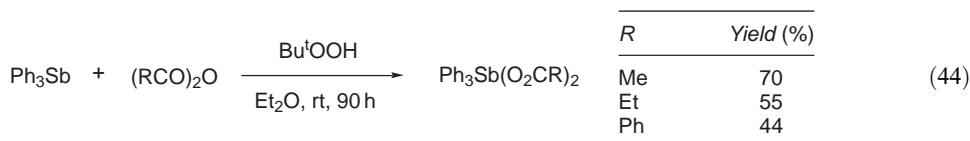
Treatment of R₃M with stoichiometric quantities of oxygen nucleophiles in the presence of oxidants, such as peroxides and HIO₄, has been an alternative source of M(V)–O derivatives. This approach is illustrated by the oxidation of Ph₃Bi in toluene at –78 °C. The reaction with ozone unexpectedly gave 33% yield of Ph₃Bi(O₂CH)₂, which serves as a precursor in exchange reactions with other carboxylate reagents <1993JCS(P1)2411>. The route has been particularly well studied in the Sb series with carboxylic acid nucleophiles (Scheme 20) <2003JOM(667)176>, where the products have been examined as Pd-catalyzed C-arylating agents for unsaturated compounds. The oxidants H₂O₂ and Bu^tOOH give similar yields.



Ar	RCO ₂ H	Yield (%) with	
		R ¹ = Bu ^t	R ¹ = H
Ph	HCO ₂ H	58	
Ph	AcOH	90	85
Ph	EtCO ₂ H	76	78
Ph	CF ₃ CO ₂ H	85	
Ph	PhCO ₂ H	80	77
4-MeC ₆ H ₄	AcOH		80
3-MeC ₆ H ₄	AcOH		68
2-MeC ₆ H ₄	AcOH	71	
2,4,6-Me ₃ C ₆ H ₂	AcOH	48	
4-MeOC ₆ H ₄	AcOH	84	

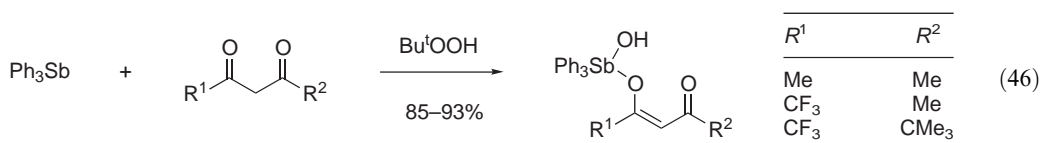
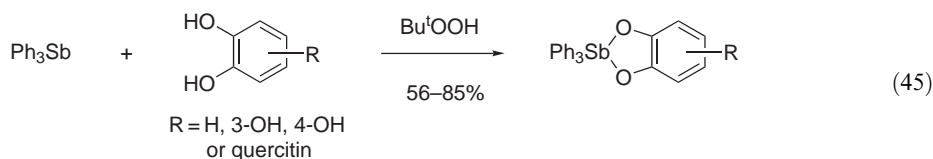
Scheme 20

Variants of this oxidative scheme have been successful. Carboxylic anhydrides can be used in place of carboxylic acids, but the reaction is more sluggish than with acids (Equation (44)) <2003JOM(667)176>. The reaction has also been successful where Ar = C₆F₅ with HIO₄ as the oxidant <1993JFC(64)107>.

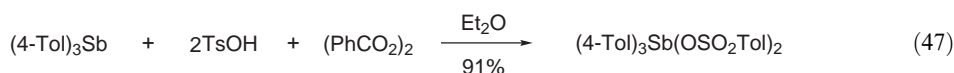


Furthermore, Ph₃Sb(OAc)₂ and Ph₃Bi(OAc)₂ have been obtained in 50–94% yield by the treatment of Ph₃M (M = Sb, Bi) with equimolar quantities of Bu^tOOAc and AcOH or Ac₂O in toluene <1995IZV964>.

The process is not restricted to carboxylic acids, and modification of the method to include phenol, 4-nitrophenol, and 2,4,6-tribromophenol provides the diaryloxy derivatives <2001ZOB(E)983, 2002MI217-06>. Catechol-like nucleophiles have enabled Ph₃Sb to be converted into dioxastibolanes (Equation (45)) <1996ZOB1498, 1995IZV748> and dimeric macrocycles, while the uses of alkanediols <1995ZOB797> and β-diketones (Equation (46)) <1994IZV1302, 1998MI217-03> have also been reported. The reaction of catechol derivatives, e.g., Equation (45), probably proceeds through initial oxidation of the phenols since o-quinones have also given cyclic 1,3,2-benzodioxarsoles <1997PS(126)75>.



The method can be extended to the preparation of ditosylates through the use of (PhCO₂)₂ as the oxidant, as illustrated in Equation (47) <2002ZOB(E)229>.



2.17.3.4 Formation through Disproportionation

A common method of preparing primary and secondary metal halides is through disproportionation (see Section 2.17.2.2). Treatment of Ph₃Sb(OAr)₂ (Ar = Ph, 4-NO₂C₆H₄) with Ph₅Sb has also provided access to aroxytetraaryl derivatives (Ph₄SbOAr) of antimony <2001ZOB(E)983>.

2.17.4 ARSENIC, ANTIMONY, AND BISMUTH COMPOUNDS WITH THE HETEROATOM BONDED TO OTHER CHALCOGENS

Metal–chalcogenides, particularly sulfur-bonded compounds, are of interest because of their biological activities and applications in agriculture. The chemistry of cyclic polychalogenides containing heavier main-group elements, including those from group 15 and paying particular attention to the use of 2,4,6-tris[bis(trimethylsilyl)methyl]phenyl (Tbt) as an effective steric protection group, has been reviewed <2001PS(168-169)41>. Most methods of synthesis involve indirect methods of displacement or oxidation to introduce the metal–chalcogenide bond rather than the formation of metal–carbon bonds.

2.17.4.1 Preparation of Organometal(III) Derivatives through Nucleophilic Displacement Reactions

Sulfur-bound derivatives of arsenic, antimony, and bismuth(III) have received the most attention of all the chalcogenides other than oxygen. Arsenic and antimony derivatives are readily prepared from R_2MX and RMX_2 (R = aryl; X = halogen, OR^1 , NR^1_2 ; R^1 = lower alkyl) through the direct displacement by thiolate and dithiocarbamate nucleophiles. Such reactions have been used to prepare sterically hindered bifunctional tetradentate ligands (Equation (48)) <2000MI217-03>, and the first neutral and dianionic organoantimony(III) dithiolene complexes (Figure 2) <2001IC2570, 2003OM2042>.

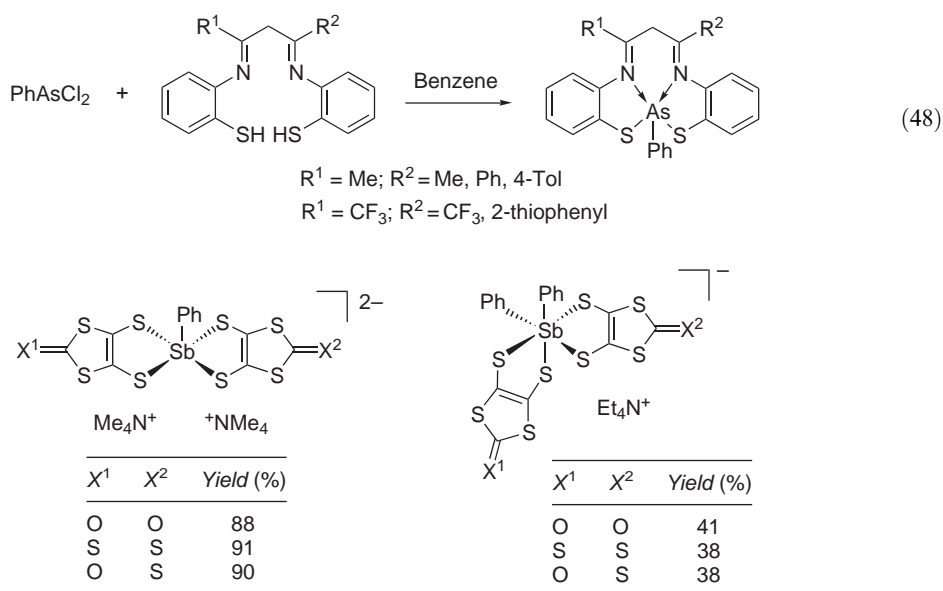
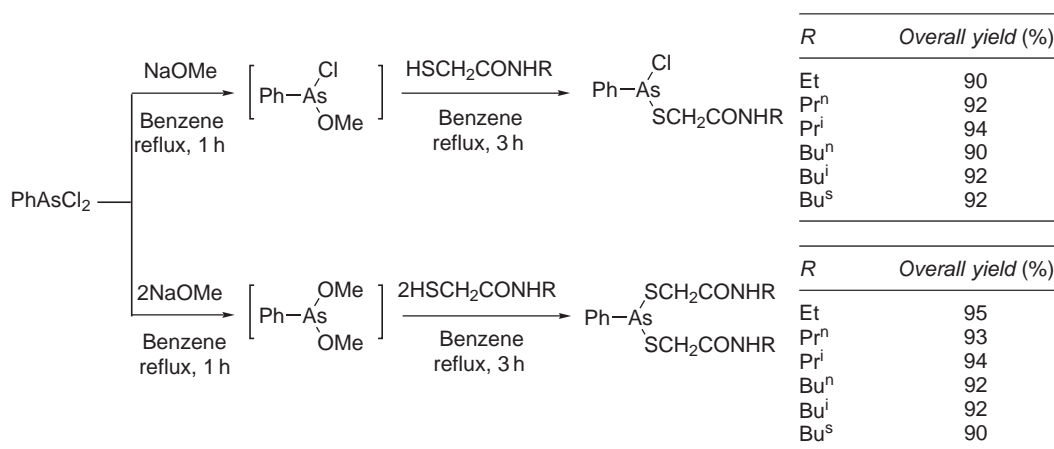


Figure 2

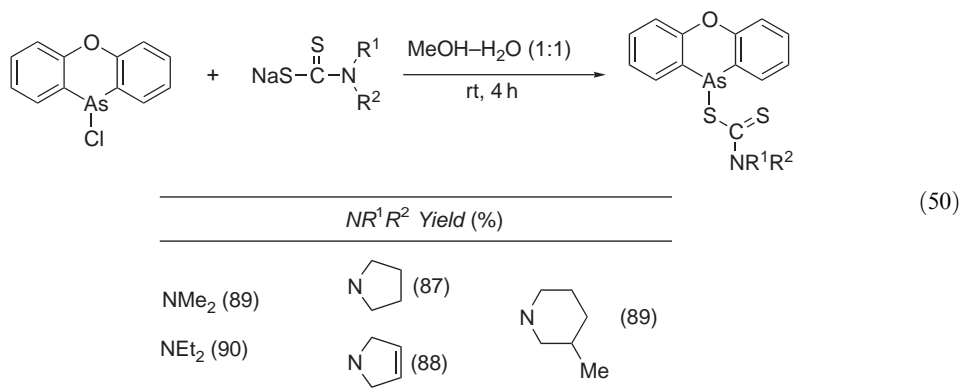
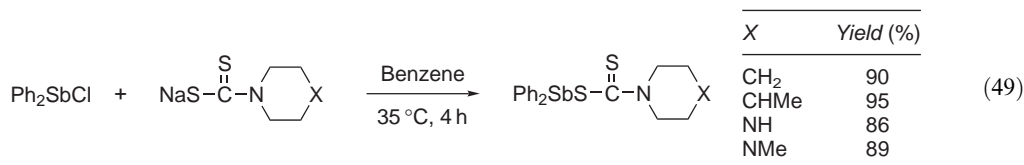
High yields of single and twofold substitution have been achieved using mercaptoacetamide as nucleophile (Scheme 21) <1993IJC(A)435>. Notably, in a competitive situation, methoxide is displaced in preference to chloride under identical conditions.



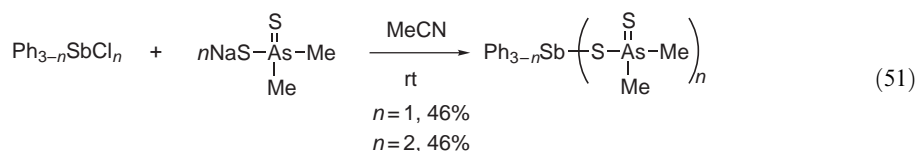
Scheme 21

Products of single dithiocarbamate substitution have been prepared under anhydrous conditions in benzene (Equation (49)) <1994PS(86)197, 1995PS(107)13>, wherein the inorganic by-product separates from solution, and in aqueous MeOH (Equation (50)) <1995JOM(493)61>.

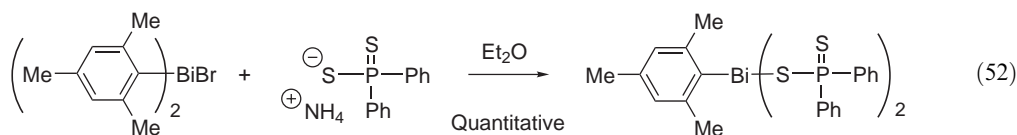
whereupon the products are precipitated. In appropriate cases, twofold substitution can also take place by the adjustments in stoichiometry <1995PS(107)13>.



Similar reactions in MeCN have yielded phenylantimony(III) and diphenylantimony(III) dimethyl dithioarsinate derivatives (Equation (51)) <1994JOM(469)45>.

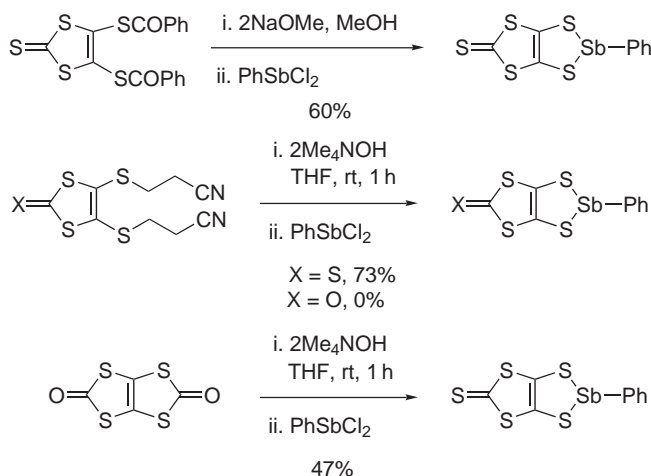


Caution must be exercised with Bi compounds in these transformations. Treatment of sterically hindered (mesityl)₂BiBr with an equimolar quantity of NH₄S₂PPh₂ leads to Bi—C bond cleavage to give (mesityl)Bi(S₂PPh₂)₂ in quantitative yield based on thiolate (Equation (52)) <1994JOM(470)93>.



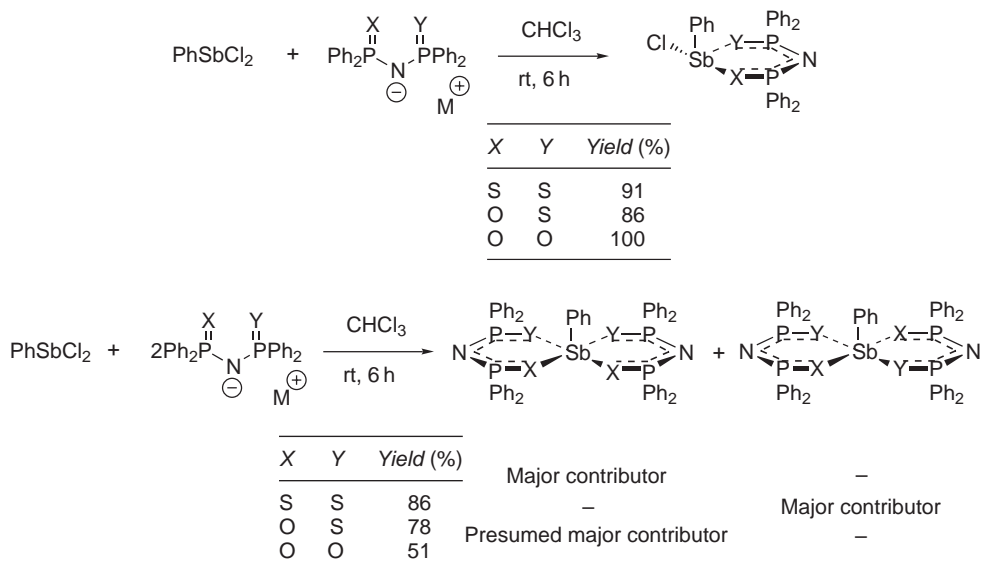
A nucleophilic substitution approach has been successful in a synthesis of the first organo-Sb(III) dithiolene complex (Scheme 22) <2001IC2570>. Rapid addition of PhSbCl₂ to the thiolate salt after its generation *in situ* from a bis(thiobenzoate) precursor is critical in obtaining high yields of the product. The strategy has been extended to the use of cyanoethyl-protected thiol precursors but where these fail in the oxo analog, due to competitive reactions at the carbonyl group, a different precursor (1,3,4,6-tetrathiapentalene-2,5-dione) has been more successful using the same reagents (Scheme 22) <2003OM2042>.

Treatment of PhSbCl₂ with two molar equivalents of the dianionic ligands used in Scheme 22 has given structurally related dianionic Sb(III) complexes in high yields (Figure 2) while subsequent treatment of the dianionic complexes from Et₄N⁺ salts of the precursors with more PhSbCl₂ has given monoanionic Sb(V) complexes in moderate yields <2003OM2042>. It is reassuring that stepwise addition of complementary thio and oxo ligands has provided access to the corresponding species with mixed ligands in comparable yields to those with identical ligands.



Scheme 22

Access to oxygen- and sulfur-bound diphosphinic acid ligands is provided by a similar route (Scheme 23) <2002JOM(642)113>. Changes in stoichiometric yield products that have largely trivalent structures in which the second phosphorus ligand contributes a weak noncovalent bond. Two X-ray crystal structures of derivatives bearing two diphosphinic acid ligands show that the stronger covalent bonds lie in a *cis* configuration.

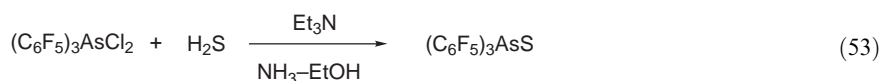


Scheme 23

It should be noted that completely parallel behavior is not found in the case of thiocyanate ligands. First, it has not been possible to prepare $\text{PhSb}(\text{SCN})_2$ from PhSbCl_2 by treatment with thiocyanate salts. Treatment of PhSbCl_2 with KSCN (1–2 equiv.) in MeCN instead affords $\text{K}[\text{SbPh}(\text{SCN})_3]$ (37% yield from 2 equiv.) and unreacted PhSbCl_2 <1995JCS(D)1173>. An increase in the amount of KSCN (3–4 equiv.) does not increase the yield but gives the tetra-thiocyanate salt, $\text{K}_2[\text{SbPh}(\text{SCN})_4]$ in up to 88% yield. While Ph_2SbSCN and Ph_2BiSCN have both been prepared <1995JCS(D)377, 1995JCS(D)383>, they exist in polymeric form with thiocyanate bridges between pairs of group 15 metals. Curiously, the orientation of every third bridging group is reversed. Treatment of Ph_2SbSCN with KSCN in MeCN provides $\text{K}[\text{SbPh}_2(\text{SCN})_2]$ in 77% yield, but excess KSCN does not yield higher salts <1995JCS(D)1173>.

2.17.4.2 Preparation of Organometal(V) Derivatives through Displacement and Disproportionation Reactions

The preparation of Ph_3AsS can readily be achieved in a substitutive manner by the treatment of Ph_3SbCl_2 with H_2S in NH_3 solution (Equation (53)) <2003JFC(122)165>. This is in contrast to the treatment of TbtMCl_2 ($\text{Tbt} = 2,4,6\text{-tris[bis(trimethylsilyl)methyl]phenyl}$; $\text{M} = \text{Sb, Bi}$) with Li_2Se , which yields heterocyclic products, the corresponding triselenatristibane and -tribismuthane (see Equation (64), Section 2.17.6.1) <2002BCJ661>.



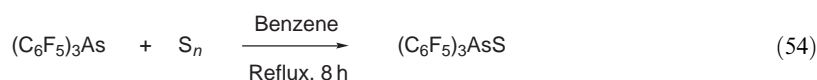
Substitution can also take place in less halogenated Sb derivatives. Thus, the preparation of $\text{Ar}_4\text{SbSC(S)NR}_2$ ($\text{Ar} = \text{Ph, Tol}$; $\text{R} = \text{Me, Et}$) has been achieved in high yield from Ar_4SbCl through the treatment with NaSC(S)NR_2 in H_2O <2002ZOB(E)1379, 2003MI217-04>. Substitution takes place readily in this case, but the method has limitations. When Ph_3SbCl_2 was treated with NaSC(S)NEt_2 in toluene at 100°C reductive dehalogenation occurred to give Ph_3Sb <2002ZOB(E)1379>.

Arsenic(III) thioxide derivatives can also be prepared through singular displacement of OR substituents from PhAs(OR)_2 ($\text{R} = \text{Me, Et}$) by the treatment with Lawesson's reagent <1997PS(126)137>.

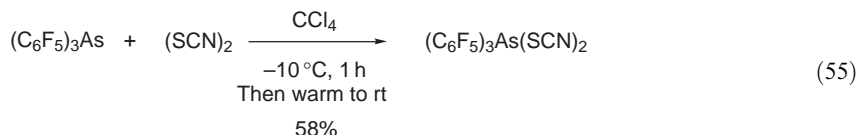
In an alternative to displacement, $\text{Ph}_4\text{Sb(SCN)}$ has been synthesized in 68% yield through the disproportionation between Ph_5Sb and $\text{Ph}_3\text{Sb(SCN)}_2$ in toluene <1996ZOB1755>. Anionic secondary organo-Sb(V) dithiolene salts (Figure 2) have also been synthesized through a disproportionation process from PhSbCl_2 <2003OM2042>.

2.17.4.3 Preparation of Sulfur, Selenium, and Tellurium Derivatives by Oxidative Processes

Oxidative approaches to organo-Sb(III) and (V) chalcogen derivatives have been described <1985POL251>, but corresponding treatment of As species is less well known. Since the publication of COFGT (1995) <1995COFGT(2)871>, the preparation of $(\text{C}_6\text{F}_5)_3\text{AsS}$ has been achieved by the treatment of $(\text{C}_6\text{F}_5)_3\text{As}$ with elemental sulfur (Equation (54)) <2003JFC(122)165>, although there is no reaction between tris(perfluoroalkyl)Sb and sulfur. This oxidative synthesis adds to the substitution method from $(\text{C}_6\text{F}_5)_3\text{AsCl}_2$ with H_2S in ammoniacal solution <2003JFC(122)165>.

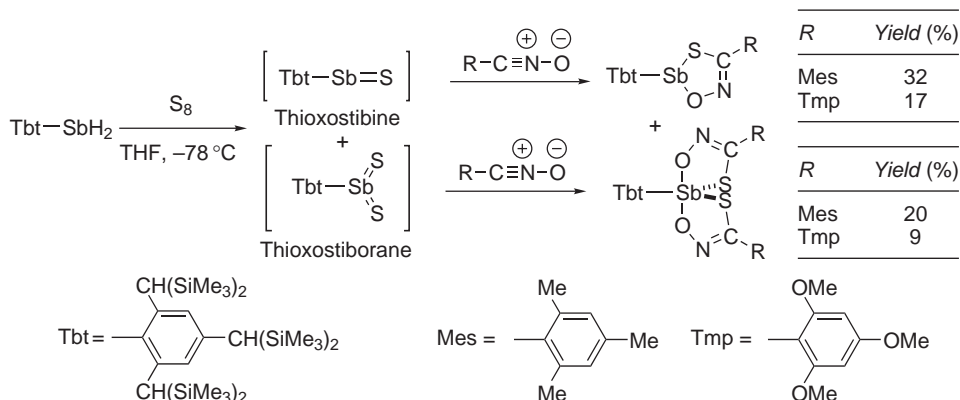


The derivative $(\text{C}_6\text{F}_5)_3\text{As(SCN)}_2$ has been prepared by oxidative addition of $(\text{SCN})_2$ to $(\text{C}_6\text{F}_5)_3\text{As}$ (Equation (55)) <2003JFC(122)165>.



A thioxostibine and/or dithioxostiborane have been implied as intermediates in the reaction of highly crowded aryl-SbH₂ with S_8 to give Sb-containing cyclic polysulfides (analogous to the selenium heterocycles described in Equation (64)) <1995CL959>. More recently these novel $\text{Sb}=\text{S}$ classes of compounds have been trapped through [2 + 3]-cycloaddition with nitrile oxides (Scheme 24) <2001HAC244>.

A complementary study to that shown in Equation (49) has revealed that tetradentate aroyl-pyruvate-derived Schiff bases can react with equimolar quantities of Ph_3Sb . These reactions proceed by dearylation to yield PhSb(III) dithiolato derivatives with structures that are penta-coordinate around Sb <2002PS(177)2813>.

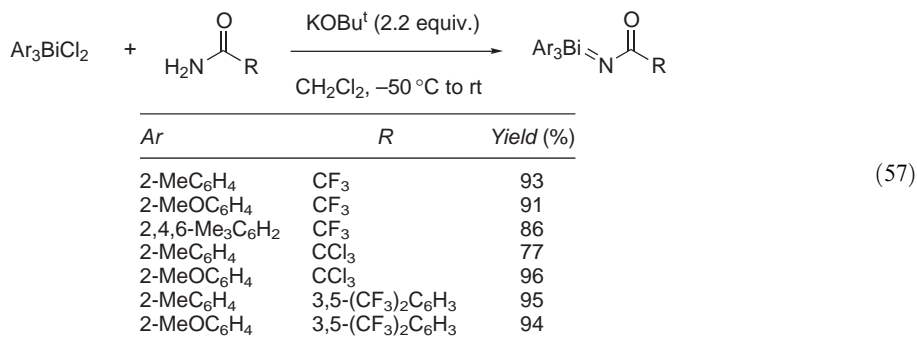
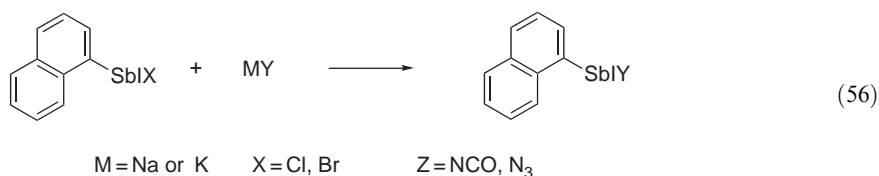


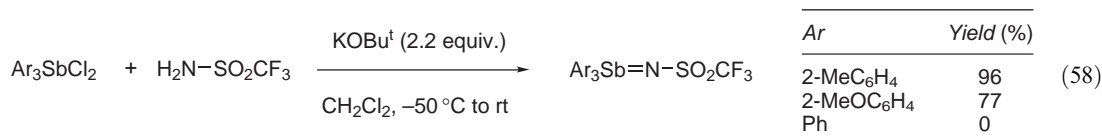
Scheme 24

2.17.5 ARSENIC COMPOUNDS WITH AN As—N BOND AND THEIR ANTIMONY AND BISMUTH ANALOGS

2.17.5.1 Preparation by Displacement of Halide and Halide Equivalents from the Metal

The most versatile approach to the synthesis of organometal(III) and (V) amides has been through the reaction of organometal halides with nitrogen nucleophiles. Traditional nucleophilic reagents have included primary and secondary amines, most successfully as their amide salts, but alkali metal isocyanates and azides [<2002SRI399>](#), imidodiphosphinic acid derivatives (Scheme 23) [<2002JOM\(642\)113>](#), and dithiocarbazate reagents [<2000PS\(166\)125>](#) have emerged as reagents in recent years. 1-Naphthyl-SbCl₂ can undergo twofold displacement of halide with isocyanate and azide nucleophiles while the corresponding -SbCl and -SbBr compounds can yield products of monosubstitution. In these cases, displacement of Cl and Br occurs in preference to displacement of I (Equation (56)) [<2002SRI399>](#). Carboxamide (Equation (57)) [<2001JA10954>](#) and sulfonamide reagents (Equation (58)) [<2000IC1340, 2002IC1940>](#), in the presence of a base, afford high yields of substituted iminostibanes and -bismuthanes, but the products are extremely sensitive to hydrolysis and decomposition unless the aryl groups attached to the metal have at least one *ortho*-substituent. This has been confirmed by synthesis of the materials by independent methods (see Section 2.17.5.2).

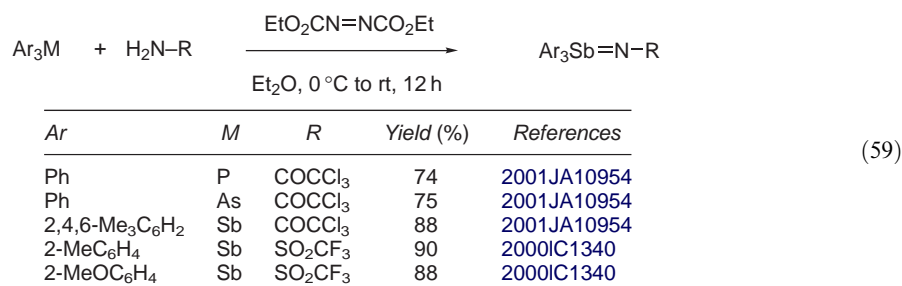




2.17.5.2 Preparation by Formation of Metal–Nitrogen Bonds through Oxidative Processes

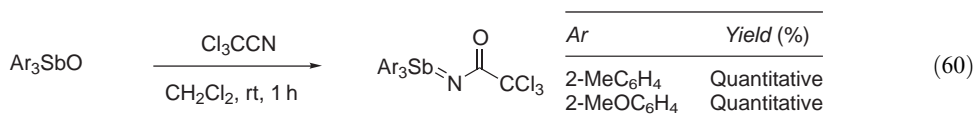
Trinaphthyl-Sb(V) compounds containing succinimide and phthalimide ligands have been prepared readily by an oxidative route through the treatment of (1-naphthyl)₃Sb with *N*-chlorosuccinimide and *N*-chlorophthalimide (see Equation (20), Section 2.17.2.1) <2003JFC(122)165>. Oxidative methods have been used to prepare azaarsane derivatives through the reaction of 2*H*-1,2,3-diazaarsoles with PhN₃ (see Scheme 14, Section 2.17.1.4) <1996HAC123>.

Iminoarsines and -stibines can be prepared in workable yields through the oxidative condensation of triaryl metals with primary amides and sulfonamides in the presence of diethyl azodicarboxylate (Equation (59)) <2000IC1340, 2001JA10954>.

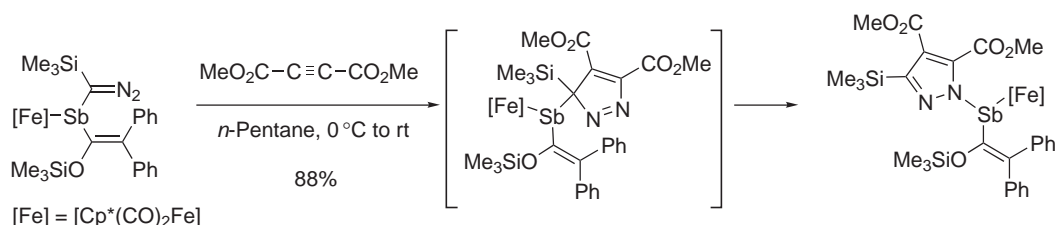


2.17.5.3 Preparation by Formation of Metal–Nitrogen Bonds through Rearrangement Processes

Iminostibine(V) derivatives can be prepared in high yield from the corresponding organostibine oxide through a condensation (involving rearrangement) with Cl₃CCN (Equation (60)) <2001JA10954>.



A rather specialized, but potentially general and interesting synthesis of *N*-bound pyrazolyl derivatives of alkenyl-Sb has involved a tandem cycloaddition-rearrangement process starting from diazoalkane precursors (Scheme 25; see also Scheme 10, Section 2.17.1.2) <2002JOM(643-644)81>.



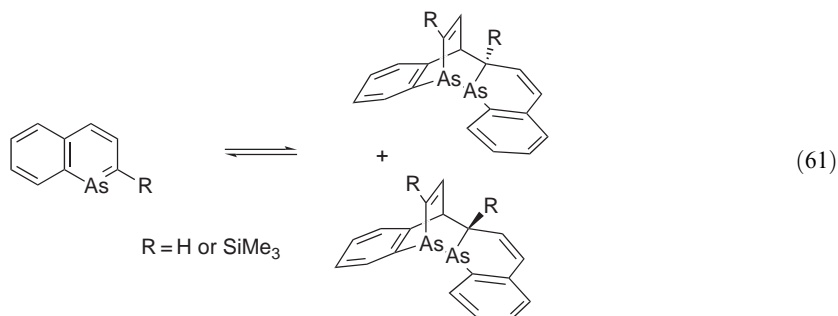
Scheme 25

2.17.6 ARSENIC, ANTIMONY, AND BISMUTH COMPOUNDS WITH THE HETEROATOM BONDED TO OTHER GROUP 15 ELEMENTS

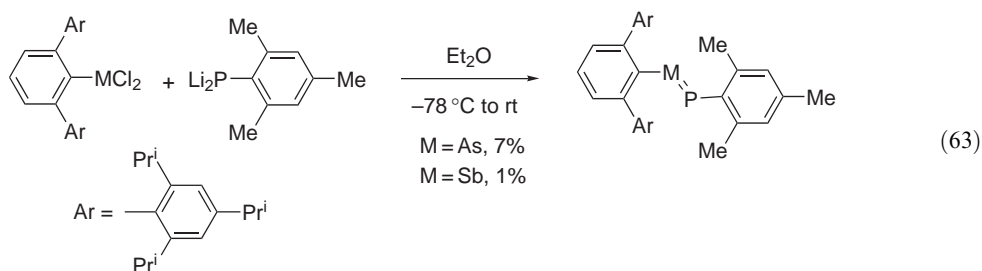
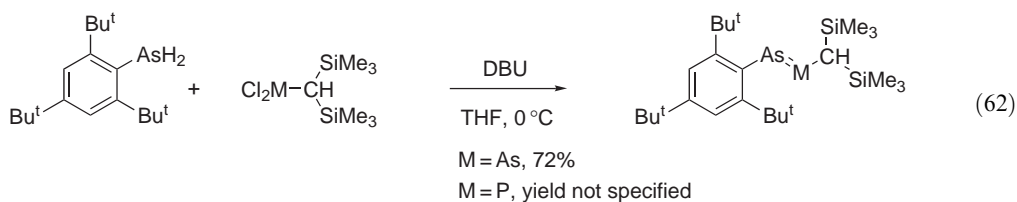
2.17.6.1 Organodiarsines, -distibines, and -dibismuthines

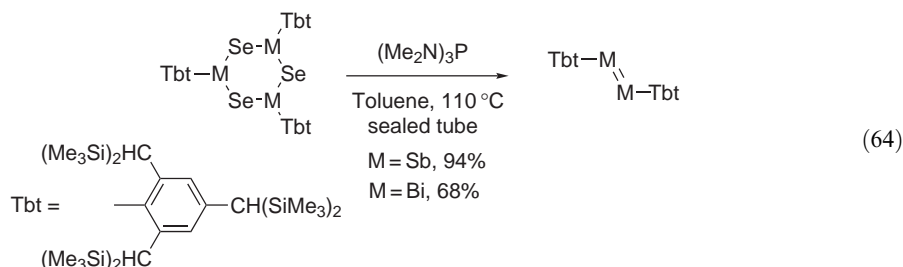
Synthesis of symmetrical $R_2M=MR_2$ ($M = As, Sb, Bi$; $R =$ alkenyl, aryl) compounds, which can be derived through the treatment of R_2MLi with an oxidant or from R_2MX ($X =$ halogen) by treatment with Mg , Al , or Cp_2Co , were described in COFGT (1995) <1995COFGT(2)871>.

Unsymmetrical $As-As$, $Sb-Sb$, and $Bi-Bi$ compounds have also been observed in equilibrium in solution with heteroaromatic compounds and arise through a Diels–Alder dimerization of 1-arsanaphthalenes (Equation (61)) <2001OM2109> and stibabenzene and bismabenzene <1982JA5693>.

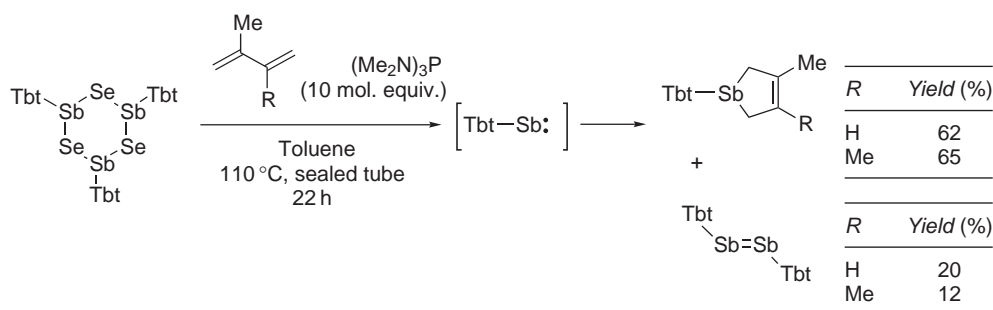


Syntheses of stable $RM=MR$ ($M = As, Sb, Bi$; $R =$ aryl) compounds are also of interest, but have been more elusive and have resulted where there is kinetic stabilization of the species through extreme steric crowding <1999JA3357>. The first compound with an unsupported $As-As$ double bond was unsymmetrical and prepared from a monoarylsarsane (Equation (62)) <1983JA5506, 1985JCS(D)383>. There have been similar approaches to unsymmetrical, hindered monoaryl- As and $-Sb$ compounds with double bonds to P , but the yields have been extremely low (Equation (63)) <1998CC1979, 1997CL855, 1984IC2582, 1983CC881>. Steric crowding is provided very effectively when $R = Tbt$ (2,4,6-tris[bis(trimethylsilyl)methyl]phenyl), and it is through this device that a much improved synthesis of symmetrical distibine <1998JA433> and dibismuth <1997SCI(277)78, 1997PS(124)371> compounds with unsupported double bonds has been developed through a deselenation of a triselenatristibane (Equation (64)) <2002BCJ661>. It should be noted that this process failed to yield evidence of the intermediate arylstibinidene through desulfurization of the corresponding trithiatristibane.





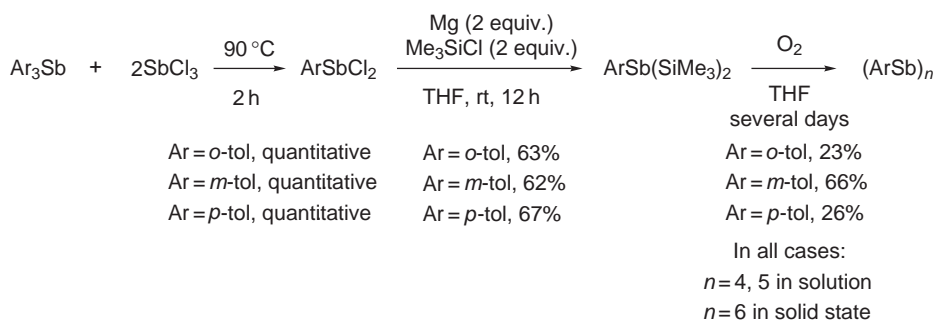
The same symmetrical distibine has since been isolated, albeit in low yield, as evidence for the generation of a stibinidene ($\text{Tbt}-\text{Sb}:$; $\text{Tbt} = 2,4,6\text{-tris[bis(trimethylsilyl)methyl]phenyl}$) during deselenation of a 1,3,5-triseleno-2,4,6-tristibane with $(\text{Me}_2\text{N})_3\text{P}$ (HMPT) in the presence of 1,3-butadienes (Scheme 26) <2001CL42>.



Scheme 26

2.17.6.2 Cyclopolyantimony Compounds

Organoantimony rings $(\text{RSb})_n$ that are not protected by bulky substituents readily take part in ring–ring equilibria. The extent to which this takes place has been examined in the solid state <1985AG(E)72, 1986ZN(B)327> and in solution <1989CB(122)473>, but the ring size can be different across these states and the compounds previously studied have not existed in both states. A German group has prepared a series of tolylantimony compounds (Scheme 27) <1995CB(128)599>, for just this purpose, by mild oxidation of bis(trimethylsilyl)antimony derivatives <1986ZN(B)321, 1989PS(44)129>.



Scheme 27

2.17.7 ARSENIC, ANTIMONY, AND BISMUTH COMPOUNDS WITH THE HETEROATOM BONDED TO A METALLOID

No significant new work has been reported in this area since the publication of COFGT (1995) <1995COFGT(2)871>. Silicon derivatives of ferric-As and -Sb reagents have been described in Scheme 10 <2002JOM(643-644)81>, and trimethylsilyl-Sb and -Bi compounds are implied

as intermediates in the preparation of halogen-metal derivatives, as in Equation (28) <1997JFC(84)69>. Triisopropylsilicon-As reagents are also used in the preparation of calcium and strontium bis(arsolide) complexes in Section 2.17.8 <2000EJI2173>.

2.17.8 ARSENIC, ANTIMONY, AND BISMUTH COMPOUNDS WITH THE HETEROATOM BONDED TO A METAL

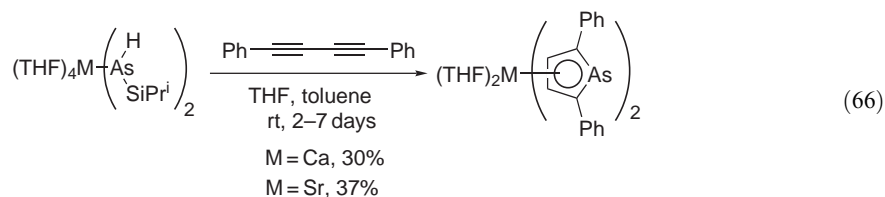
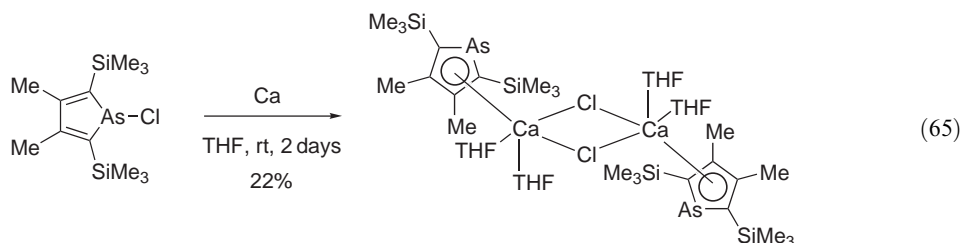
2.17.8.1 Alkali Metal Derivatives

Alkali metal derivatives of organo-As, -Sb, and -Bi compounds can be prepared by a variety of reductive metallation reactions from R_3M , R_2MX , R_2MH (R = aryl; M = As, Sb, Bi; X = halogen) and deprotonation reactions from RMH_2 (R = aryl; M = As, Sb) as has been illustrated in earlier sections and outlined in COFGT (1995) <1995COFGT(2)871>. A method for the preparation of antimonide and bismuthide salts has been reported in the Russian patent literature <1999URP>. Coordinating solvents can influence the σ or π nature of bonding <1991CB2453>.

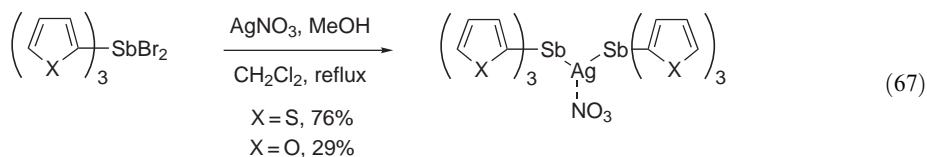
2.17.8.2 Transition Metal Derivatives

Ligand exchange has provided a number of transition metal (W, Cr, Mn, Ru) complexes of 1-substituted 2,3,4,5-tetramethylarsoles, which appear to have σ metal-As bonds because they undergo Diels-Alder cycloaddition with DMAD <1994JOM(467)67>. In contrast, a 1-arsanaphthalene yielded a crystalline π -complex (97% yield) when treated with $Mo(CO)_3Py_3$ and $BF_3 \cdot OEt_2$ <2001OM2109>.

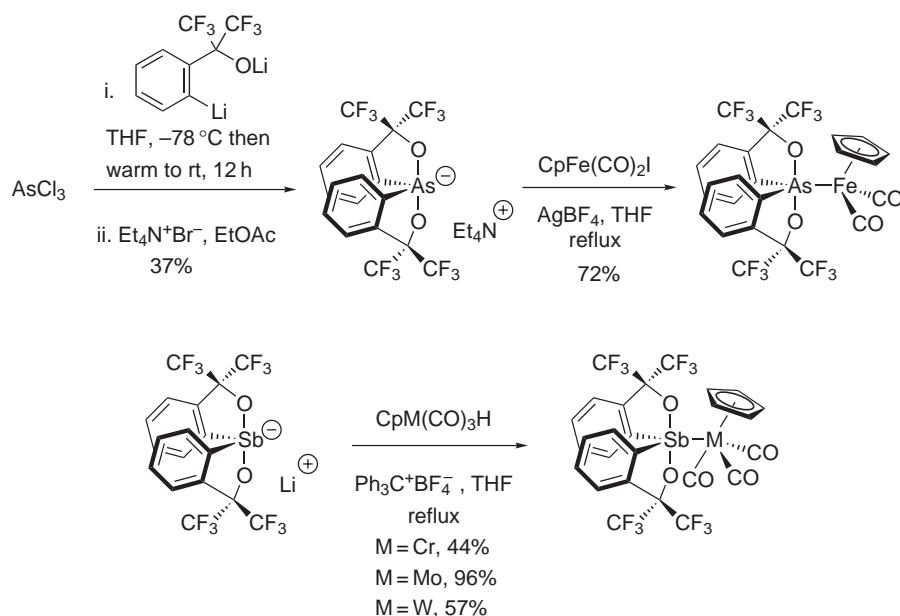
Heteroleptic n^5 -bonded arsolide complexes of calcium have been prepared by the reduction of 1-chloroarsoles (Equation (65)) <1999OM2491>. In contrast, Ca and Sr bis(arsolide) complexes have been synthesized by the treatment of the corresponding triisopropylsilyl arsanides with diphenylbutadiyne in a solvent mixture of toluene and tetrahydrofuran (Equation (66)) <2000EJC2173>.



Silver(I) trithiophenyl- and trifuranyl-Sb complexes ($[R_3Sb]_2AgNO_3$; R = 2-thiophenyl, 2-furanyl) have been prepared (76 and 29% yield, respectively) through the treatment of the corresponding Sb(V) dibromide with $AgNO_3$ (Equation (67)) <2001JOM(634)5>. The complexes are sensitive to moisture, light, and air to varying degrees although the products of decomposition have not been characterized.



Hypervalent arsorane and stiborane compounds with metal–transition metal bonds have been prepared in good yield through reaction of the Et_4N arsoranide and Li stiborane salts with $\text{CpFe}(\text{CO})_2\text{BF}_4$ <2000HAC42> and $\text{CpM}(\text{CO})_3\text{BF}_4$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) <2000OM5134, 1999CL783>, respectively (Scheme 28).



Scheme 28

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2.18

Vinyl- and Arylsilicon, germanium, and boron Compounds

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2.18.1 BORON DERIVATIVES

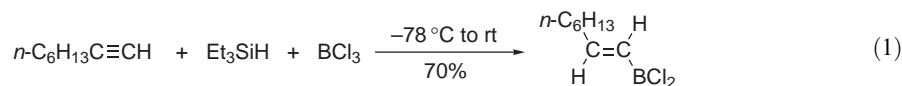
Organoboranes are widely used synthetic reagents and interest in their synthesis and transformations is continuing. Since the publication of COFGT (1995) <1995COFGT(2)899>, several books and reviews related to alkenyl- and arylboranes have been published <B-1995COMCII191, B-1995MI001, B-1997MI163, 1997MI121, 1997RHA271, 1997T4957, B-1998MI141, 2000CRV3221, B-2001MI002, B-2002MI465, 2002TCC11, B-2002MI249, 2002T9633, B-2003MI003>.

2.18.1.1 Alkenylboron Compounds

2.18.1.1.1 Hydroboration of alkynes

(i) Uncatalyzed hydroboration

Hydroboration of alkynes with various borane derivatives provides direct access to alkenylboranes. New approaches to hydroborating agents exhibiting high reactivity or selectivity have been developed. Thus, the reduction of a boron–halogen bond with di- and trialkylsilanes provides a highly convenient method for the formation of a B–H bond. Dichloroborane, generated in this way from boron trichloride in nonethereal solvents, hydroborates both terminal and internal alkynes to give the corresponding (*E*)- and (*Z*)-alkenyldichloroboranes, respectively (Equation (1)) <1995OM4157, 1996MI705, 1999JOM(580)354>.



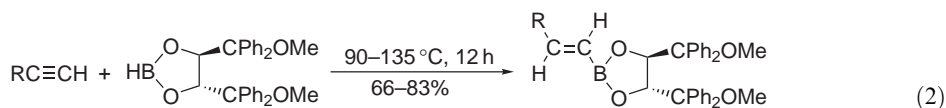
Competing chloroboration of internal alkynes can be circumvented by the use of diethylsilane <1996MI705>. Hydroboration of 1-dichloroboryl-2-trimethylsilylacetylene with dichloroborane produced 1,1-bis(dichloroboryl)-2-trimethylsilylethene and dihydroboration products <2002EJI1293>.

Bis(pentafluorophenyl)borane is generated in the same way by the reduction of bis(pentafluorophenyl)chloroborane with dimethylchlorosilane <1998OM5492>. Alternatively, it can be generated by prolonged heating of tris(pentafluorophenyl)borane with triethylsilane at 60 °C in benzene. Stepwise hydroboration of 1-alkynes is possible, and the reaction with internal alkynes stops at the monohydroboration stage. Chemo- and regioselectivity of the reagent is comparable to 9-borabicyclo[3.3.2]decane (9-BBN-H) <1995AG(E)809, 1998OM5492>. 10-Trimethylsilyl-9-borabicyclo[3.3.2]decane (10-TMS-9-BBD) is another new hydroborating agent differing from 9-BBN-H in the clean monohydroboration of 1-alkynes. This reagent also monohydroborates enynes <B-2000MI472>.

Several new highly selective alkoxy derivatives of thexylborane have been prepared (Thx(RO)BH; Thx = 2,3-dimethyl-2-butyl, R = Et, Prⁱ, Buⁱ, Bu^s, Bu^t, Ph) <1996MI892>.

Radical effects in the hydroboration with catecholborane have been reported for the first time <1996MI705>. Thus, the reaction with 3-hexyne produced more *anti*- than *syn*-addition product: this result is totally opposite to the stereoselective *syn*-addition of catecholborane to internal alkynes reported previously. The amount of (*E*)-isomer increased to >90% in the presence of AIBN. However, it should be noted that heat or radical catalysis isomerize the (*Z*)- to the (*E*)-isomer.

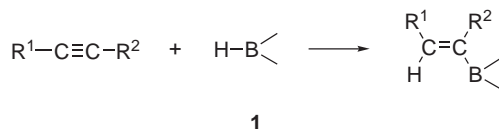
New enantiomerically pure 1,3,2-dioxaborolanes have been developed and employed for the hydroboration of alkynes. Stable, enantiomerically pure alkenylboronic esters can be prepared (Equation (2)) <1998CC2651, 2000JCS(P1)4293>.



R = Buⁿ, *n*-C₅H₁₁, Ph, TBDPSOCH₂, TBDMSOCH₂, TBDPSO(CH₂)₃

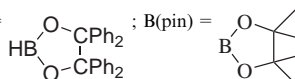
Various functionalized alkynes have been hydroborated (Table 1) and the organoboranes produced serve as intermediates for further transformations. 1,3-Dienylboronates and borates,

Table 1 Hydroboration of functionalized alkynes with dialkylboranes and dialkoxyboranes



R ¹	R ²	H—B<	Product		References
			B<	Yield (%)	
(CH ₂) ₈ COMe, (CH ₂) ₈ COEt, (CH ₂) ₈ CHO, (CH ₂) ₃ COPh	H	(<i>c</i> -Hex) ₂ BH ^a	B(<i>c</i> -Hex) ₂	50–94 ^b	<1997TL7681, 1998CJC800>
<i>n</i> -C ₅ H ₁₁ , Cl(CH ₂) ₃ , Ph	P(O)(OEt) ₂	PBH ^a	B(pin) ^a	38–72 ^b	<2001TL8059>
R ₃ Sn R = Ph, Bu ⁿ	H	9-BBN-H	9-BBN	>87 ^b	<2002JCR(S)190>
MeSe	H	9-BBN-H	9-BBN	>87 ^b	<1997CSR345>
RSe	H	(<i>c</i> -Hex) ₂ BH	B(<i>c</i> -Hex) ₂	97–99 ^b	<1997SC231>
R = Me, Et, Pr ⁱ , <i>n</i> -C ₅ H ₁₁ , <i>n</i> -C ₆ H ₁₃ , (<i>c</i> -Hex), Ph	TeR	(<i>c</i> -Hex) ₂ BH	B(<i>c</i> -Hex) ₂	9–82 ^b	<2000SC1903>
Et, Bu ⁿ	R = Bu ⁿ , Ph, CH ₂ OMe	(<i>c</i> -Hex) ₂ BH	B(<i>c</i> -Hex) ₂	60–81 ^b	<1997SL891>
RSe	RSe	(<i>c</i> -Hex) ₂ BH	B(<i>c</i> -Hex) ₂	60–81 ^b	<1997SL891>
R = Et, Bu ⁿ , <i>n</i> -C ₅ H ₁₁ , <i>n</i> -C ₆ H ₁₃ , (<i>c</i> -Hex), Ph	X	Sia ₂ BH	BSia ₂	>93 ^b	<1995JCS(P1)2955>
Bu ⁿ , Bu ^t	X = Cl, Br, I	9-BBN-H	9-BBN	~99 ^b	<1997SC567>
TBSOCH ₂	H	Ph-PBH ^a	B(pinPh)	43	<2003SL91>
	H	Ipc ₂ BH	B(pinPh) ^c	43	<2003SL91>
	H	Ipc ₂ BH	B(pinPh) ^c	24	<2003SL91>
CH ₂ =CHMe	H	CBH ^a	BO ₂ C ₆ H ₄	^d	<1996TL6699>

^a (*c*-Hex)₂BH = dicyclohexylborane; PBH = pinacolborane; Ph-PBH =



4

5

Sia₂BH = bis(3-methyl-2-butyl)borane; ^b Used *in situ* for further transformations. Yield of the transformation product. ^c The hydroboration product was transformed into boronic ester. ^d Yield not specified.

including chiral derivatives, are readily prepared from enynes and find applications in the Diels–Alder reaction <1996TA2523, 1999H703, 1999TL1295, B-2000MI464>.

(ii) Catalytic hydroboration

A number of reviews of this area have been published since 1994 <1995MI95, 1997AG(E)2441, 1997T4957, B-1998MI141, 1998MI63, 1999MI788, B-2001MI002, 2002MI(818)334>. Transition metal-catalyzed hydroboration of alkynes continues to be an area of active research. Catecholborane and pinacolborane are used as hydroborating agents. New catalysts and reaction media have been described. Representative examples are shown in Table 2. Selective hydroboration of enynes at the triple bond with catecholborane produces the corresponding dienylboronates <1999CCC1049, B-2000MI464>.

Earlier mechanistic proposals have been supported by more experimental evidence. This shows that boryl complexes model single steps of the catalytic cycle, which involve insertion of the coordinated multiple bond into a metal–hydrogen bond and reductive elimination of alkyl- or alkenylborane <1999AG(E)1110>. However, direct addition of a B–H bond to the coordinated multiple bond in hydroborations catalyzed by titanium complexes <1995JA6615, 1997JA2743>, hydrozirconation of an alkyne by the catalyst HZrCp₂Cl <1995OM3127, 1996OM5155>, and ethyne insertion into an Ru–B bond forming a vinyl compound <1997OM5499, B-2000MI379>, have been observed.

Rhodium- and nickel(II)-catalyzed hydroboration of terminal alkynes with pinacolborane is accelerated in ionic liquids. For example, the reaction carried in 1-butyl-3-methylimidazolium chlorozincate in the presence of Wilkinson's catalyst at 40 °C was complete in less than 2 h in quantitative yield <2002MI(818)334>. Recycling of the catalyst solution resulted in lower catalyst activity but with a significant increase of regioselectivity. In fluorous media catalyst immobilization was achieved by transforming [RhCl(cod)]₂ into ClRh{[P(CH₂)₂(CF₂)₅CF₃]₃}₃, soluble in CF₃C₆F₁₁ and stable to 300 °C but insoluble in most organic solvents. Hydroboration of alkynes with catecholborane and pinacolborane in CF₃C₆F₁₁ solution produced alkenylboranes in 88–89% yield (Table 2), with high TON numbers and loss of only 4.5–2.2 ppm rhodium/mole of the product <1999JA2696>.

Unusual iridium- and rhodium-catalyzed *anti*-hydroboration of terminal alkynes with catecholborane leads to (*Z*)-1-alkenylboronates (Table 2). The presence of more than 1 equiv. of triethylamine is necessary to achieve high selectivity.

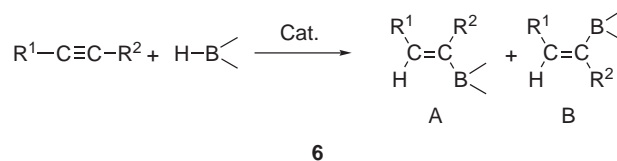
Dehydrogenative borylation is sometimes a side reaction in catalytic hydroboration of alkenes with catecholborane. Exchanging catecholborane for isoelectronic 1,3,2-benzodiazaborole results in acceleration of the side reaction which becomes the main pathway leading to the formation of a vinyl derivative in the reaction with ethene <1997AG(E)2441, 1997JA2743>.

New aspects of hydroboration with catecholborane have been reported. Thus, certain dialkylboranes, e.g., dicyclohexylborane, catalyze hydroboration of alkynes with an equimolar amount of the reagent in THF producing the 2-alkenyl-1,3,2-benzodioxaborole under mild conditions <1995SC1957>. A similar catalytic effect of dicyclohexylborane was observed in the hydroboration of 1-halo-1-alkynes with 9-BBN-H producing *B*-[(*Z*)-1-halo-1-alkenyl]-9-BBN <1997SC567>. It should be noted that copper-catalyzed reaction of bis(pinacolato)diboron with 1-alkynes followed by hydrolysis of the organocopper intermediate leads to either 1-boryl-1-alkenes or 2-boryl-1-alkenes <2001JOM(625)47>.

2.18.1.1.2 Haloboration of alkynes

Haloboration and related reactions have been reviewed since the publication of COFGT (1995) <1995MI77, B-1997MI163, 1997RHA271, B-2003MI9> (experimental procedures are described). Haloboration is an *anti*-Markovnikov *syn*-addition of a boron–halogen bond to a C–C multiple bond. The reaction, extensively studied by Suzuki and co-workers <B-2003MI9>, is limited to terminal alkynes and allenes. Boron tribromide and *B*-bromo-9-borabicyclo[3.3.1]nonane (*B*-Br-9-BBN) are the most commonly used and readily available reagents. Chloro- and iodo-analogs can also be used and the order of reactivity is *B*-I-9-BBN, BBr₃ > BCl₃ > *B*-Br-9-BBN >> *B*-Cl-9-BBN. The boron atom is placed at the terminal position (Equation (3)). Functional groups such as aldehydes, ketones, esters and halogens are tolerated. Competitive hydroboration/chloroboration was observed in the reaction of

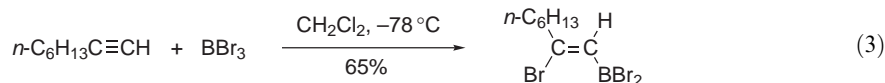
Table 2 Catalytic hydroboration of alkynes with catecholborane (CBH) and pinacolborane (PBH)



R^1	R^2	$H-B<$	Catalyst	Product		References
				Yield (%)	A:B	
Et, Ph, Bu ^t , <i>c</i> -C ₅ H ₉ , <i>n</i> -C ₆ H ₁₃ , Me ₃ Si	H	PBH	HZrCp ₂ Cl 5 mol.%, CH ₂ Cl ₂ , rt	75–95	>95:5	<1995OM3127>
<i>n</i> -C ₆ H ₁₃ , Ph, Cl(CH ₂) ₃ , Pr ⁱ	H	PBH	Rh(CO)(PPh ₃)Cl 3 mol.%, CH ₂ Cl ₂ , rt,	99	99:1	<1996TL3283>
Ph, Cl(CH ₂) ₃ , Pr ⁱ , <i>n</i> -C ₆ H ₁₃ , Bu ⁿ , <i>c</i> -Hex, Ph	H	PBH	NiCpPPh ₃ Cl	99	99:1	
	H	CBH	NiCl ₂ (DPPE) 1 mol.%, THF, rt, 3–6 h	81–89	>98:2	<2000MI765>
Et	Et	CBH	6 h	65	>99:1	
BrCH ₂ CH ₂ ^a , MeOCH ₂ CH ₂ , AcOCH ₂ CH ₂ , Me ₃ Si	H	CBH	3 h	50	98:2	
CH ₂ =CH, CH ₂ =CMe, 1-cyclohexen-1-yl	H	CBH	NiCl ₂ (DPPE) 1 mol.%, THF, rt, 8 h	54–87	>95:5	<1999CCC1049>
(pin)BC≡C(CH ₂) _n <i>n</i> = 1, 2 ^f	H	PBH	HZrCp ₂ Cl 5 mol.%	94–95	^b	<B-1997MI104, 1997JOC8907>
<i>n</i> -C ₆ H ₁₃ ,	H	CBH	[Rh(cod)Cl] ₂ -4PPri ⁱ ₃ 3 mol.%,	74	1:99	<2000JA4990>
Me ₃ Si	H	CBH	Et ₃ N, rt, 1–4 h		2:98	
Bu ^t	H	PBH	[Ir(cod)Cl] ₂ -4PPri ⁱ ₃ 3 mol.%, Et ₃ N, rt, 1–4 h	71	3:97	
Bu ⁿ , 4-Tol,	H	CBH	Cp ₂ Ti(CO) ₂ 4 mol.%	96–97	^b	<1996JA1696>
Ph	Ph		Et ₂ O, rt, 2 h	~91	^{b, c}	
Bu ⁿ , Ph,	H	CBH	ClRh{[P(CH ₂) ₂ (CF ₂) ₅ CF ₃] ₃ } ₃ 0.19 mol.%, CF ₃ C ₆ F ₁₁ , 0.5 h,	88–89	^{b, d}	<1999JA2696>
Ph	H	PBH	40 °C, 12 h	90	95:5	
MeSe	H	CBH	Pd(PPh ₃) ₄	>74	^{b, e}	<1997JCR(S)62>

^a In benzene. ^b Product A. ^c Yield of the oxidation product. ^d Very small amount unspecified regioisomers observed spectroscopically. ^e Used *in situ* for further transformation. Yield of the transformation product. ^f (pin)B = << S005 here >>.

propyne and 1-butyne with boron trichloride-trimethylsilane when excess of boron trichloride was used <2002ZN(B)295>. The corresponding bis(2-chloro-1-alkenyl)chloroboranes and tris(2-chloro-1-alkenyl)boranes were formed as by-products.

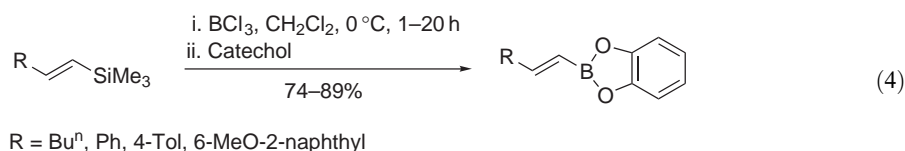


In contrast to terminal alkynes, acetylene reacts with boron tribromide to give the *anti*-addition product, presumably due to the isomerization of the initially formed less stable *syn*-addition product <B-2003MI9>. A detailed experimental procedure for the bromoboration of allene with boron tribromide has been published <1997OSI29>. Both (*E*)- and (*Z*)-bromoboration products have been prepared and utilized for the cross-coupling reaction with the alkenylzinc compounds producing 1,3-dienylboronates <B-2000MI464>, which can be transformed into the corresponding borates, including chiral derivatives <1999H703>.

2.18.1.1.3 Alkenylboranes from alkenyl metals

The classical synthesis of alkenylboranes by the reaction of organometallics with boron alkoxides and halides is widely used. For example, bis(trifluoromethyl)trifluoro-ethenylborane <2000JOM(604)43>, *B*-allenyl-10-TMS-9-BBD <B-2000MI472>, dibromovinylborane <1999JOM(580)354>, 2-substituted cycloalken-1-yl- and 3-alkoxyalkenylboronic acid pinacol esters, which are convenient precursors of (*Z*)-2-substituted organoboranes <2002OL2861>, and 2,5-dihydroxyboryl-1,1-dibutyl-3,4-diphenyl-1*H*-silole <2000AG(E)1695> have been prepared by this method. However, when highly pure 1-alkenylboranes are required, the method may suffer from the formation of small amounts of stereoisomers and di- or trialkenylboranes.

A convenient transformation of 1-alkenylsilanes into the corresponding 1-alkenylboronates has been achieved by the reaction with boron trichloride (Equation (4)) <1995CC2523>.

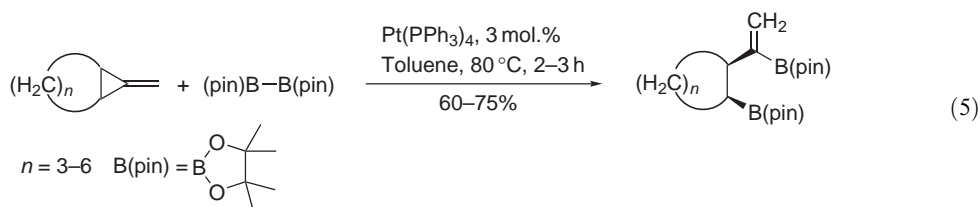


2.18.1.1.4 Addition of B element bonds to C—C multiple bonds

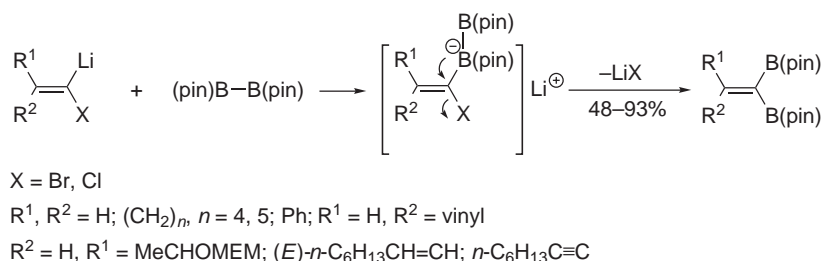
Transition metal-catalyzed boron-element bond addition to multiple C—C bonds is an area of active current research, which has been reviewed <1998CRV2685, 1998MI63, 1999CC395, 1999CRV3435, 2000CRV3221, 2000JOM(611)392, 2001CCR(223)1, 2002YGK826, 2003JOM(680)43, B-2003MI92>. The additions leading to alkenylboranes involve such bonds as B—B (diboration) <1996JA6331, 1996OM5137, 1997JOC7076, 1998JCS(D)301, 1998TL2357, 2000JOM(611)392, B-2003MI92>, B—Si (silaboration) <1996CC2777, 1997CC1229, 1998OM5233, 2000JP159778, 2000CRV3221, 2003JOM(680)43>, B—Sn (stannaboration) <1996OM5450, 1997OM5389, 1999CC1863, 2003JP26692>, B—Ge (germaboration) <1998OM5233, 2000CRV3221> and B—S (thiaboration) <1993JA7219>.

Diboration of alkynes catalyzed by platinum(0) or rhodium(I) complexes provides direct access to 1,2-bis(boryl)alkenes. Tetraalkoxydiboranes are most often used as the boron reagents. The catalytic cycle involves an oxidative addition-insertion-reductive elimination sequence <1996OM713, 1996OM5137, 1997CC689, 1998OM742, 2001CCR(223)1, 2001JCS(D)1650>.

1,2-Diborylated alkenes are readily produced from alkynes in high yield by this methodology <2000JOM(611)392, B-2003MI92>, whereas monoborylated alkenes are produced from 1-alkynes in the presence of copper catalyst <2001JOM(625)47>. Tetraborylated ethene was prepared from catechol-substituted diborylacetylene <1999EJ11693>. Diboration of allenes provides products having both alkenyl and allylic borane moieties <1998TL2357, 1999CC395, 2001JA761>. Strained C—C single bonds also undergo the reaction. For example, methylenecyclopropanes react with bis(pinacolato)diboron producing the corresponding 2,4-bis(boryl)-1-butenes (Equation (5)) <1999SL1790>.

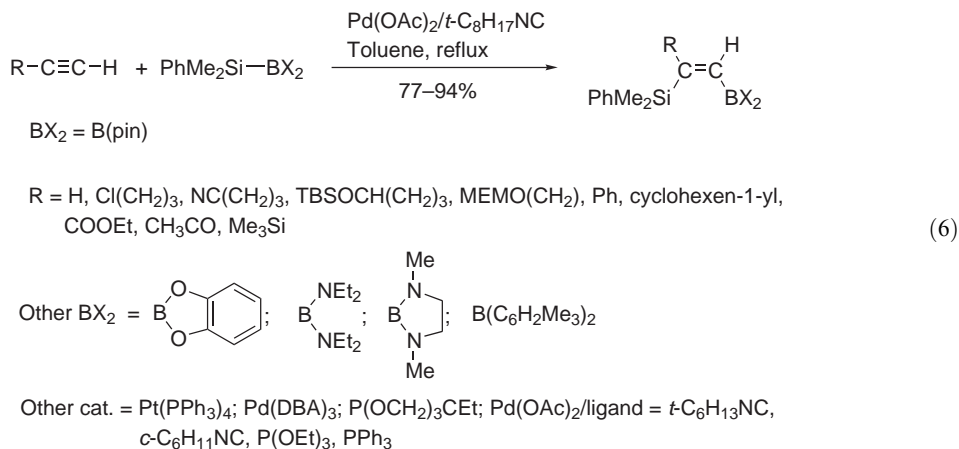


Uncatalyzed *gem*-diboration of 1-halo-1-lithioalkenes, alkylidene-type carbenoids generated from 1,1-dihaloalkenes, proceeds via a well-known 1,2-migration from the negatively charged boron of the intermediate “ate” complex (Scheme 1) <2001AG(E)790, 2001YGK1062, 2002T6381>.

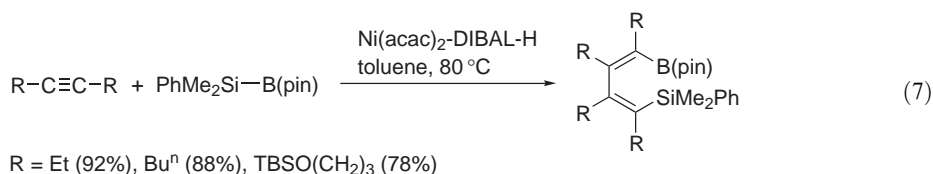


Scheme 1

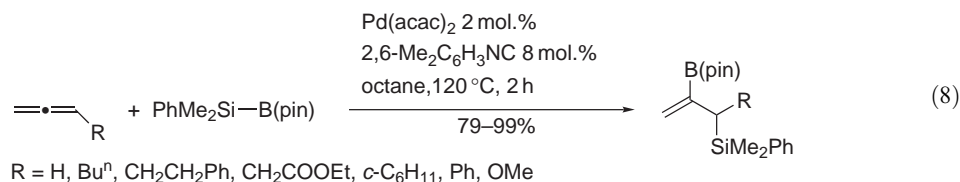
Silaboration of terminal and internal alkynes, catalyzed by palladium and platinum complexes, is a *syn*-addition proceeding with high regioselectivity (Equation (6)) <1996CC2777, 1997CC1229, 1999T8787, 2000CRV3221, 2002JOM(646)179>.



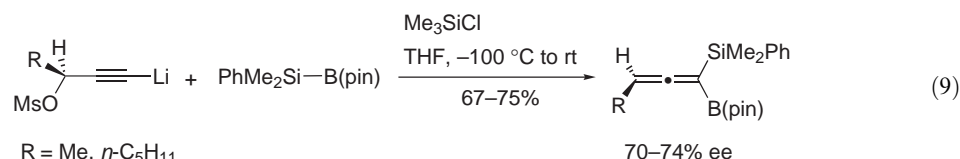
Silaboration of acetylene and trimethylsilylacetylene leads to the corresponding (*E*)-isomers. Diynes can be transformed into mono- and disilaboration products <1997CC1229>. However, intra- and intermolecular silylboration dimerization and carbocyclization, depending on the reagent and catalyst, can lead to silylated dienyboranes (Equation (7)) <1997CC1229, 1998OM5233>. Silylated alkenylborane carbocyclization products are formed from enynes <1997CC1229>.



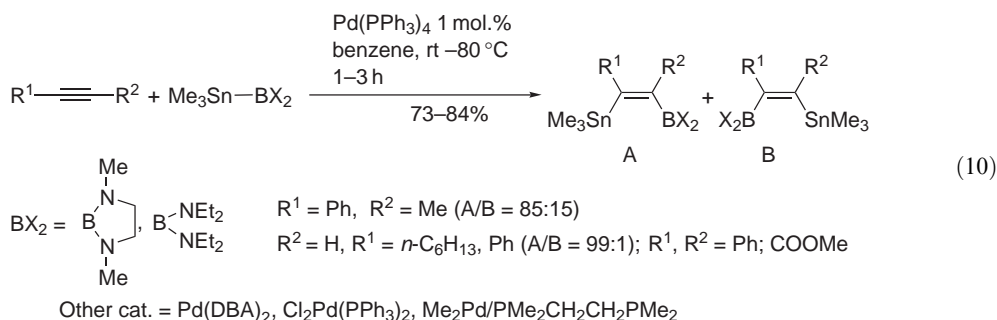
β -Borylallyl silanes are formed by palladium-catalyzed silaboration of allenes. Notably, the more substituted double bond of the terminal allene is involved in the addition with exclusive placement of the boron atom at the central carbon atom of the allene (Equation (8)) <1999SL1567, 2001JA4601, 2003JOM(680)43>. However, (perfluorohexyl)allene undergoes the reaction exclusively at the terminal double bond <1999SL1567, 2003JOM(680)43>, and placement of boron at either the terminal or the internal position depending on catalyst has been observed <2000JOM(611)403>. The reaction is also catalyzed by palladium complex—etpo ($\text{Pd}_2(\text{dba})_3/\text{etpo}$; dba = dibenzylideneacetone, etpo = 4-ethyl-2,6,7-trioxa-1-phospha-bicyclo[2.2.2]octane) <1999CC1863>.



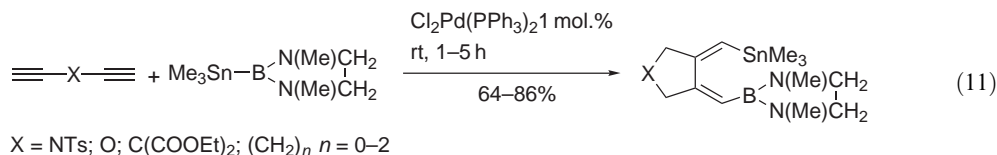
In a manner similar to *gem*-diboration (Scheme 1), uncatalyzed *gem*-silaboration of alkylidene-type carbenoids affords 1-boryl-1-silylalkenes <2001AG(E)790, 2002T6381>. Silaboration of α -chloroallyllithiums produces 1-boryl-1-silyl-2-alkenes which serve as reagents for stereodivergent allylation leading to 4-oxy-(*E*)-alkenylboronates and 4-oxy-(*Z*)-alkenylsilanes <2001YGK1062>. 1,1-Diboryl- and 1,1-borylsilyl-1,3-dienes are also available using this methodology <2001AG(E)790, 2001YGK1062>. *gem*-Silaboration of properly substituted alkynylidene-type carbenoids leads to 1-boryl-1-silylallenes. Enantiomerically enriched products (70–74% ee) have been prepared from mesylates of optically active propargylic alcohols (Equation (9)) <2003OL225>.



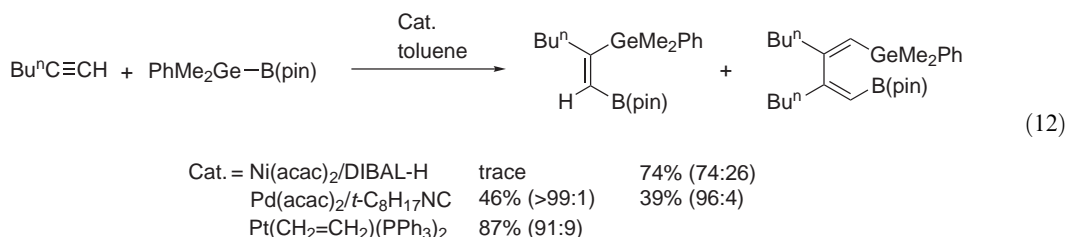
Palladium-catalyzed stannaboration of alkynes is a *syn*-addition of a B—Sn bond proceeding under mild conditions with high regioselectivity placing the B at the less hindered position (Equation (10)) <1996OM5450>.



1-Boryl-4-stannyl-1,3-dienes are produced under mild conditions by the palladium-catalyzed reaction of 1-alkynes with 1,3-dimethyl-2-trimethylstannyl-1,3,2-diazaborolane <2003JAP26692>. In contrast to silaboration, 1,2-dienes react with the reagent to give 1:2 telomers having both vinyl—Sn and allyl—B moieties <1999CC1863>. Boryl stannylation cyclization of diynes and enynes provides a versatile method for synthesizing 1-borylmethyldiene-2-stannylmethylidenecycloalkanes and (*Z*)-borylmethylidene-2-(stannylmethyl)cycloalkanes, respectively. Even a strained cyclobutane ring is readily formed. Functional groups, such as ether, sulfonamide or ester, are tolerated (Equation (11)) <1997OM5389>.



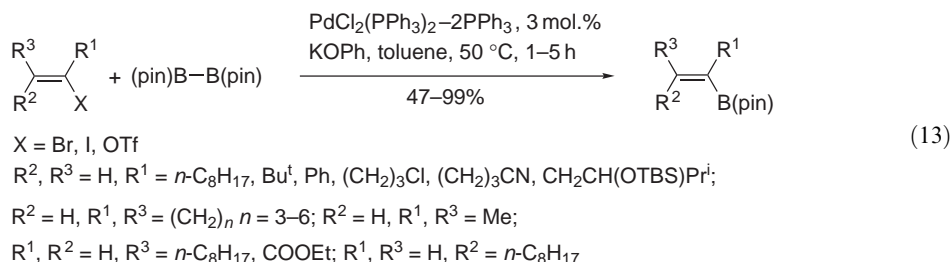
The ratio and regioselectivity of 1,1-germaboration and germaborative dimerization of 1-alkynes depends on the catalyst (Equation (12)) <1998OM5233, 2000CRV3221>.



(Organothio)boranes, readily available by uncatalyzed and catalyzed reactions of dialkylboranes with alkyl- and arylthiols <B-2003MI9>, undergo palladium(0)-catalyzed addition to terminal alkynes producing (*Z*)-(2-organothio)alkenylboranes <1993JA7219>.

2.18.1.1.5 Cross-coupling of boron compounds with alkenyl derivatives

The palladium-catalyzed cross-coupling reaction of bis(pinacolato)diboron with 1-alkenyl halides and triflates provides a one-step procedure for the synthesis of 1-alkenylboronic esters in high yield with complete retention of configuration of the double bond. 1-Alken-2-ylboronates and 1-cycloalkenylboronates, which are difficult to prepare via hydroboration, can be synthesized (Equation (13)) <2000CL126, 2002JA8001>. Proper choice of base and solvent is essential to avoid the formation of side products, and bromides and triflates are preferred over iodides. 1-Cyclohexenylboronates <2002JA8001> and β -boryl- α,β -unsaturated esters, amides, and ketones have been synthesized from the corresponding triflates <2002SL1880>. β -Boryl- α,β -unsaturated compounds, which can also be prepared via hydroboration of propiolic acid esters and by multistep procedures <B-2000MI464>, are valuable synthetic intermediates for the Diels–Alder reaction <B-2000MI464>, other cycloadditions, 1,4-additions <1998TL8513, 2000TL4229, 2000TL4235> and radical additions <1995T6999>.

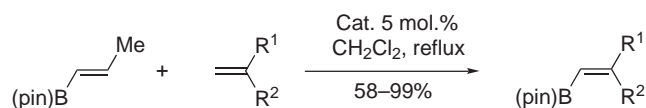


The cross-coupling reaction of pinacolborane with various alkenyl iodides and triflates in the presence of triethylamine and a catalytic amount of PdCl₂(DPPF) and AsPh₃ affords the corresponding alkenylboronates in good yield <2000S778>.

2.18.1.1.6 Alkenylboranes from organoboranes

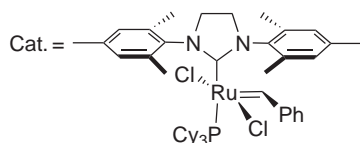
(i) Metathesis of alkenylboronates

The emergence of new transition metal catalysts for metathesis has greatly expanded its scope and utility, and the subject has been reviewed <2001ACR18, B-2003MI004, 2003AG(E)1900>. Cross-metathesis (CM) offers an attractive alternative to alkyne hydroboration for the synthesis of alkenylboronates. β,β -Disubstituted alkenylboronates, which are not available by hydroboration, can also be prepared. The reaction involves ruthenium-catalyzed olefin cross-metathesis of 1-propenylboronic acid pinacol ester and various 1-alkenes, including functionalized and 1,1-disubstituted alkenes, protected (*Z*)-but-2-en-1,4-diol and (*Z*)-but-2-en-1,4-diamine. Vinyl- and 1-propenylboronic acids can also be used but are less convenient due to oligomerization and partial hydration (Equation (14)) <2000JA58, 2003JOC6031>.

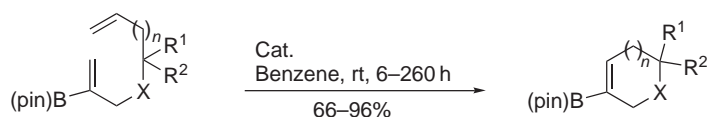


$\text{R}^2 = \text{H}$; $\text{R}^1 = n\text{-alkyl}$, Me_3SiCH_2 , $\text{Pr}_3^i\text{SiCH}_2$, $(\text{CH}_2)_4\text{OAc}$, $c\text{-C}_5\text{H}_9$, $\text{Me}_2(\text{OH})\text{C}$, $(\text{CH}_2)_2\text{OBz}$, Ph , $o\text{-BrC}_6\text{H}_4$, $o\text{-NO}_2\text{C}_6\text{H}_4$, $\text{R}^1, \text{R}^2 = (\text{CH}_2)_n$, $n = 4, 5$

(14)

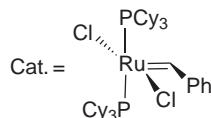


The methodology has also been applied to the synthesis of cyclic alkenylboronates by ring-closing metathesis of acyclic boronates (Equation (15)) <1998JA7995>.



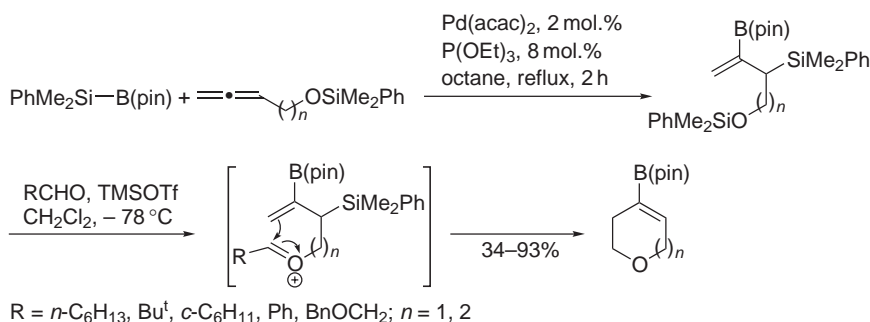
$\text{X} = t\text{-BOCN}$; O ; CH_2 ; CHOBn or CHOTBS
 $\text{R}^1, \text{R}^2 = \text{H}, \text{Me}, \text{Ph}$; $n = 0-2$

(15)



(ii) Allylation of aldehydes and acetals with β -borylallyl silanes

Lewis acid-promoted reactions of β -borylallyl silanes with aldehydes and acetals produce functionalized alkenylboronates, including cyclic structures (Scheme 2) <2001JA4601>. This approach is complementary to the synthesis of cyclic alkenylboronates by metathesis.



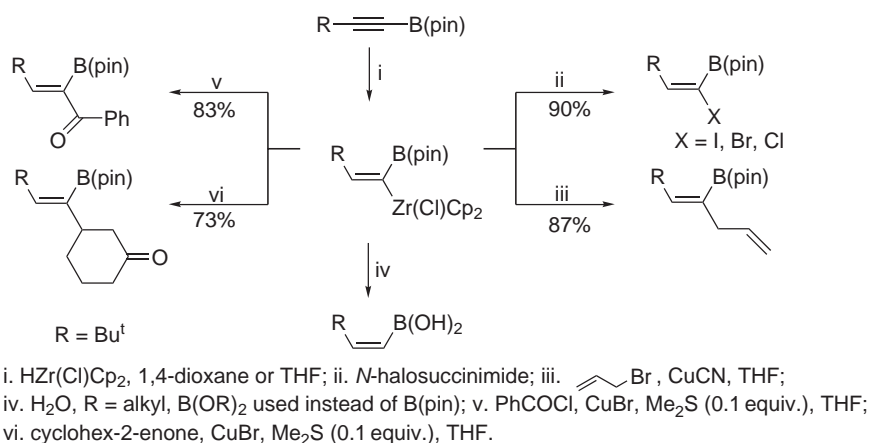
Scheme 2

Similarly, the allylation of aldehydes with 1-boryl-1-silyl-2-alkenes leads stereoselectively to homoallylic hydroxyalkenylboronates <2001AG(E)4283>.

(iii) From 1-alkynylboronates

Hydrozirconation of 1-alkynylboronates with $\text{HZr}(\text{Cl})\text{Cp}_2$ in 1,4-dioxane or THF is a stereoselective *syn*-addition producing (*E*)-1,1-borylzirconocene alkenes. The reaction is not sensitive to many

functional groups. The more reactive C—Zr bond can be transformed into (*Z*)-alkenylboronates by hydrolysis and into functionalized derivatives by reaction with electrophiles (Scheme 3) <1994JA10302, 1994JOC6871, 1996TL567, 2000CRV2887>.

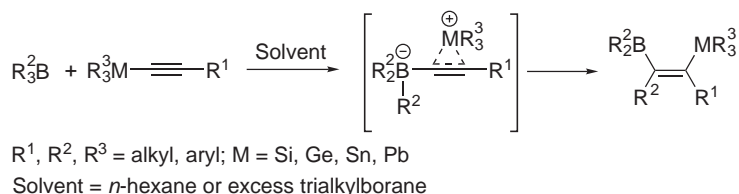


Scheme 3

Zirconocene-mediated cyclization of α,ω -diborylenynes provides access to 1-borylmethylidene-2-borylmethylcycloalkanes <B-1997MI104>. The methodology has been applied to the synthesis of natural products, e.g., chokols <1996MI267, 1996TL2735> and temarotene <1995JOC3276>. Hydrostannation of alkynyldiaminoboranes affords (*E*)- or (*Z*)-1-trialkylstannyl-2-diaminoborylalkenes depending on conditions. The palladium-catalyzed cross-coupling of alknyediaminoboranes leads to stereodefined (*E*)- or (*Z*)-alkenylboronic esters <1996SL377>. Hydroboration-protonolysis of alkynylborinates with certain dialkylboranes, e.g., dicyclohexylborane, provides access to (*Z*)-alkenylborinates <1995TL6847>.

(iv) 1,1-Organoboration

1,1-Organoboration products are formed by the reaction of trialkylboranes with acetylenic derivatives of the elements of group 14 (Scheme 4) <1995CCR(145)125>.



Scheme 4

The reactivity order of alkynyl metal compounds is $\text{Pb} > \text{Sn} > \text{Ge} > \text{Si}$. The reaction with alkynyllead compounds proceeds at -78°C and the products are unstable, whereas alkynylsilanes require prolonged heating at 100°C . *syn*-Addition of the boron and metal groups is preferred. The yields are variable and mixtures of products are often formed.

The reaction with triallylborane affords a mixture of 1,1- and 1,2-allylboration products <1999JOM(580)234>. The 1,1-allylboration is much faster than 1,1-organoboration with trialkylboranes, and its rate increases further when acetylenes containing silicon hydrides are used as starting materials, e.g., bis(dimethylsilyl)acetylene reacts at room temperature <1999AG(E)124>. Boraheterocycles are also produced by the reaction of trialkylboranes and triallylborane with the above mentioned acetylenic derivatives of silicon and tin <B-2000MI434>.

Alternatively, organometallic-substituted alkenylboranes can be prepared by the treatment of alkynyl “ate” complexes which are well known with electrophiles inducing 1,2-migration from the negatively charged B. Their rich chemistry, involving transformations to other alkenyl and boraheterocyclic products, has been reviewed <B-1997MI73>.

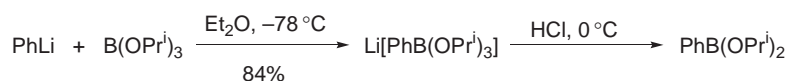
(v) *The cross-coupling of 1,2-bis(boryl)-1-alkenes*

The diboration products of 1-alkynes with bis(pinacolato)diboron undergo highly regio- and stereoselective cross-coupling with alkenyl, allylic, aryl and benzyl halides at the terminal position producing the corresponding (*E*)-(1-alkyl-1-alkenyl)boronates <1996CL1117, 2000JOM(611)392>. The reaction is synthetically equivalent to carboboration of alkynes.

2.18.1.2 Arylboron Compounds

2.18.1.2.1 Arylboranes from aryl metals

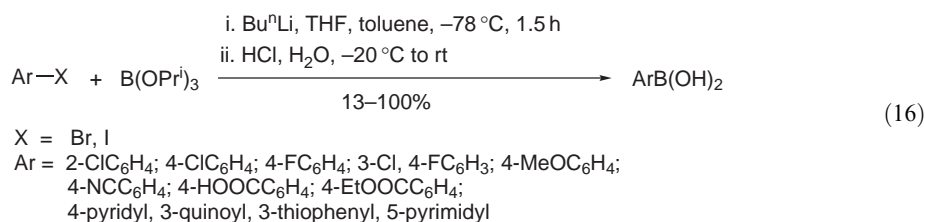
The transmetallation reaction of organometallics, usually aryllithium, magnesium, or tin compounds, with boron alkoxides and halides is the classical method for the synthesis of arylboron compounds. The methodology is widely used and is described in COFGT (1995) <1995COFGT(2)899> and in recent monographs and reviews <B-1995COMCH191, B-1995MI001, B-1997MI345, B-2002MI465, B-2003MI003>. The choice of reagents depends on several factors, such as stability of organometallic reagents and intermediate “ate” complexes, reactivity of boron reagents and solvent. Clean formation of the desired product requires careful control of reaction conditions. Synthesis of boronic acids and esters via organolithium reagents has been reviewed <1990CRV879>. Triisopropoxyborane is often the reagent of choice for this transformation (Scheme 5) <1983OM1316>. Chiral binaphthylboronic acids have been prepared in this way <1997CB923>. A large excess of trimethoxyborane is necessary to suppress side reactions.



Scheme 5

Various boronic acid derivatives of pyrrole <1999EJI399>, indole <2002JOC7551>, furan <2001OL3991, 2003OBC1447>, benzo[*b*]thiophene <2002EJO2524>, halopyridines <2002JOC7541, 2002T3323, 2002T4369, 2003JOC3352> and substituted benzenes <1998JOC2054, 1999JOM(581)82, 2001OL1435>, have been prepared by a regioselective metal exchange using BuⁿLi or directed *ortho*-lithiation with LDA and subsequent quenching with trialkoxyborane.

The *ortho*-lithiation reaction, where a functional group attached to pyridine ring is used to direct a regioselective deprotonation, is widely used for functionalization of the ring, and has been reviewed <2001T4059>. *In situ* formation of aryllithium is a useful alternative to improve yield <2002JOC7551, 2002UKZ54> when the reagent is unstable or reactive functional groups are present (Equation (16)) <2002JOC5394>. The reaction is independent of temperature and works even at 0 °C although with somewhat lower yields. A nonaqueous work-up can be employed for direct isolation of arylboronates <2002JOC1041>.

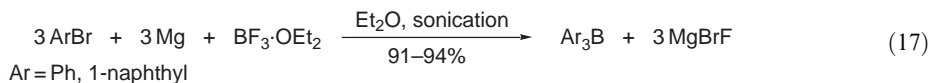


Aryl Grignard reagents are also useful for the synthesis of arylboronic acids when the reagent can be readily generated <1994JA7597, 1999JOC8495, 2002MI479, 2003PAC1349>. An electrochemical variant of the reaction has been developed <2002NJC373, 2003C185>. Other organometallics are employed less frequently. Tin–boron and mercury–boron exchange has been used for the preparation of dichloro- and dibromo(pentafluorophenyl)borane <2000JOM(598)127>, and tin–boron exchange was used to prepare 1-methyl-2,5-dihydroxyborylpyrrole <1999EJI399>.

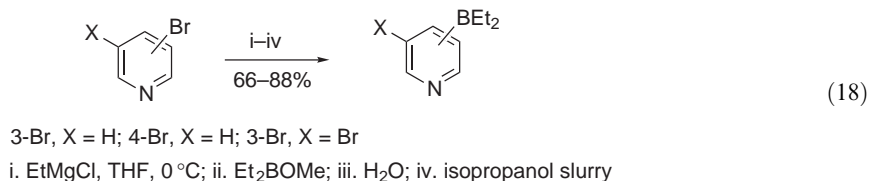
Alternatively, aryldifluoroboranes are conveniently generated from the corresponding potassium aryltrifluoroborates, which are readily available by the reaction of arylboronic acids with potassium hydrogen fluoride <1995JOC3020, 2000JOM(598)127>. The use of haloboranes and aryl Grignard <B-2002MI474> or aryltin compounds <1995AG(E)809> also provides the corresponding diarylhaloboranes and diarylaminoboranes.

Arylboronic acids can be prepared by the same transmetallation methodology when the reaction of aryllithium or Grignard reagents with trialkoxyboranes is carried out in a 2:1 molar ratio <2002MI501> or by the reaction with arylboronates, providing access to products with mixed aryl groups.

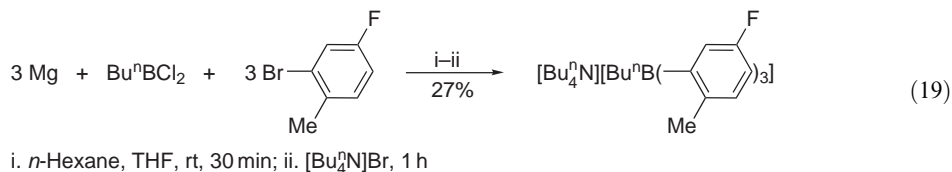
Triarylboranes are obtained from aryl Grignard reagents and trialkoxy- or trihaloboranes. A side reaction is the formation of tetraarylborates, which can be suppressed by *in situ* formation of the Grignard reagent aided by sonication (Equation (17)) <1986JOC427>. The reaction is solvent dependent, and tetraarylborates are obtained in THF <1986OM391>.



The above procedure (Equation (17)) did not work when lithium was used instead of magnesium. However, aryllithiums, formed by lithium–halogen exchange, are useful for the synthesis of alkylarylboranes, e.g., dialkylpyridylboranes <2001TL2093>. Low temperatures are necessary to avoid decomposition of pyridyllithium. A practical alternative is to use more stable Grignard reagents, generated by the entrainment method, providing access to reagents difficult to generate directly from halides (Equation (18)) <2002SL273>.



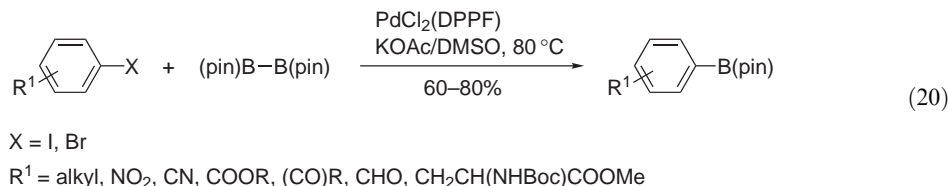
In a search for novel mono- and bidentate organoboron, Lewis acids aryl-diethylboranes were prepared by tin–boron exchange <1998EJI761>. When borane-THF is used for the exchange, the corresponding boronic acids are obtained <2000JOM(613)236, 2002OM4886>. The interest in new Lewis acids, as co-catalysts for metallocene-based polymerization of alkenes and for other synthetic applications, resulted in new approaches to pentafluorophenylboranes <1995AG(E)809, 1997CSR345, 1998WOP9822470, 1998WOP9822475, 1999EJO527, 2002JFC1>. Other symmetrical and mixed arylborates have been prepared from boron alkoxides and halides using either preformed or *in situ* generated Grignard reagents (Equation (19)) <2002MI501, 2002JP226486>.



2.18.1.2.2 Cross-coupling of boron compounds with aryl derivatives

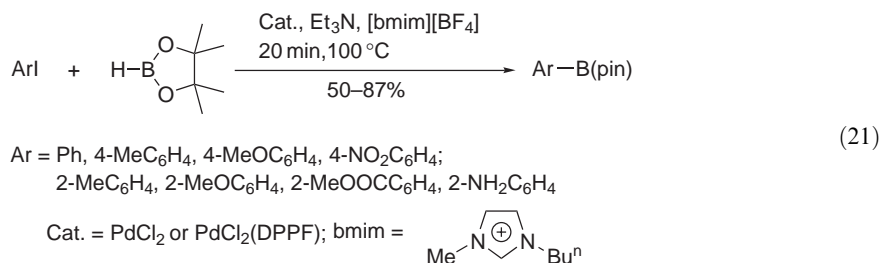
Arylboronic esters can be prepared directly from aryl halides and triflates <1995JOC7508, 1997JOC6458, 1997TL3447, 1998JOC7529, 1998JOC8019, 1999TL213, 2000JOM(611)392> or aryl diazonium tetrafluoroborates <1997TL1197, 2000AG(E)1066, 2000TL8683, 2001JOC7148> by palladium-catalyzed cross-coupling reactions with bis(pinacolato)diboron and other

tetraalkoxydiborons (Equation (20)). Noteworthy is the use of triflates and aryl diazonium salts, since a wide range of phenols and amines are available as substrates. This reaction can be conveniently carried out in ionic liquids <2002JOM(657)129>. Aryl chlorides, which are less reactive than aryl bromides and iodides, can also be used as substrates <2001T9813, 2002OL541>. Bis(pinacolato)diboron is commercially available and its synthesis both on a laboratory and larger scale has been described <1996CEN41, 2000OS176>. Other tetraalkoxydiborons are also used <B-2000MI391, 2001SL266>.



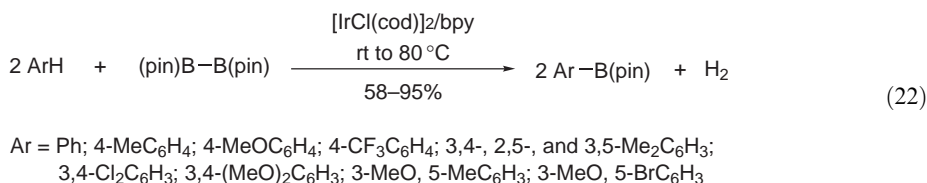
A convenient modification of the procedure is substitution of palladium(II) acetate (a ligandless catalyst) for PdCl₂(DPPF). This provides products of high purity that are simple to isolate and thus makes possible large-scale preparations <2003JOC3729>. Boronates prepared by this procedure can be used without isolation for Suzuki–Miyaura cross-coupling reaction with aryl halides to prepare biaryls.

A further improvement is the possibility of using more readily available pinacolborane for the cross-coupling. It reacts with aryl halides and triflates in the presence of base and a catalytic amount of PdCl₂(DPPF) producing arylboronates under very mild conditions, so that several functional groups are unaffected <1999TL213, 2000JOC164, 2000JOC9268, 2000BCJ231>. The yield and product distribution are influenced by the base, and tertiary amines are preferred. Bis(diphosphaferrocenyl)palladium(II) chloride <2001JOM(640)197> and cyclic rigid palladium complexes <2002CC1566> are also highly effective catalysts. The reaction carried in ionic liquids, e.g., [bmim]BF₄, is completed in a short time and the catalyst can be recycled (Equation (21)) <2003OBC3274>.



2.18.1.2.3 Borylation of arenes

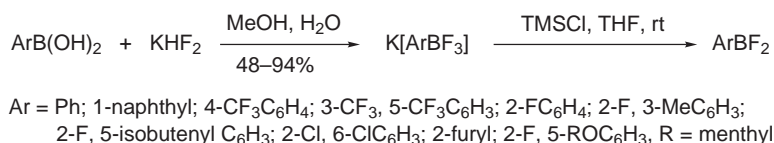
A direct synthesis of boronic acids by iridium-catalyzed borylation of arenes and heteroarenes with bis(pinacolato)diboron has been reported under mild conditions (Equation (22)) <2002AG(E)3056, 2002JA390, 2002TL5649>.



Alternatively, classical electrophilic borylation of aromatic rings with trihaloboranes leads to aryl dihaloboranes, which can be transformed readily into boronic acids and esters <1998JHC887>.

2.18.1.2.4 Arylboranes from organoboranes

Potassium aryl trifluoroborates, emerging as valuable synthetic reagents, can be readily prepared by the reaction of arylboronic acids with potassium hydrogen fluoride (Scheme 6) <1995JOC3020, 2000JOM(598)127>. Potassium aryl trifluoroborates are air stable, water soluble and do not form anhydrides and are compelling alternatives to boronic acids in organic transformations, e.g., the Suzuki–Miyaura cross-coupling <1998TL5045, 1999SC2457, 2002OL1867, 2002TL8111, 2003JOC4302> and rhodium-catalyzed C–C bond forming reactions <1999OL1683>.



Scheme 6

2.18.2 SILICON DERIVATIVES

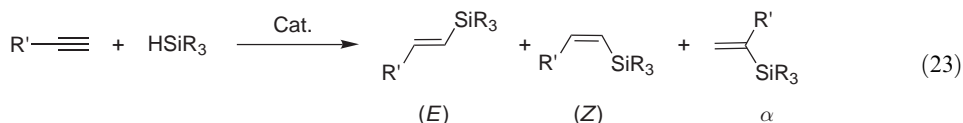
2.18.2.1 Alkenylsilanes

2.18.2.1.1 Vinylsilanes from alkynes

Vinylsilanes are a class of organosilicon reagents commonly used in organic synthesis <B-2002MI713, 2003ACA75>. Many efficient stereo- and regioselective methodologies for synthesis of vinylsilanes involving classical stoichiometric routes from organometallic reagents and, more recently, transition metal-catalyzed transformations of alkynes, silylalkynes, alkenes and other silicon derivatives have been reported. Main pathways to vinylsilanes are described in the following sections.

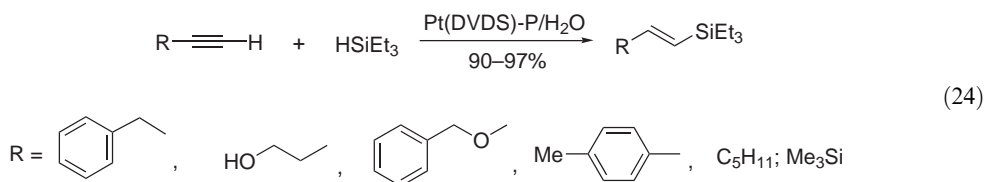
(i) Hydrosilylation of alkynes

Hydrosilylation of 1-alkynes, usually catalyzed by transition metal complexes, is the most versatile method for preparing 1-alkenylsilanes but the reaction often gives a mixture of three isomers (Equation (23)) <B-1993MI005, B-1996MI487, B-1998MI029, 1999AOC197, B-2000MI4, 2002MI155, B-2002MI491>.

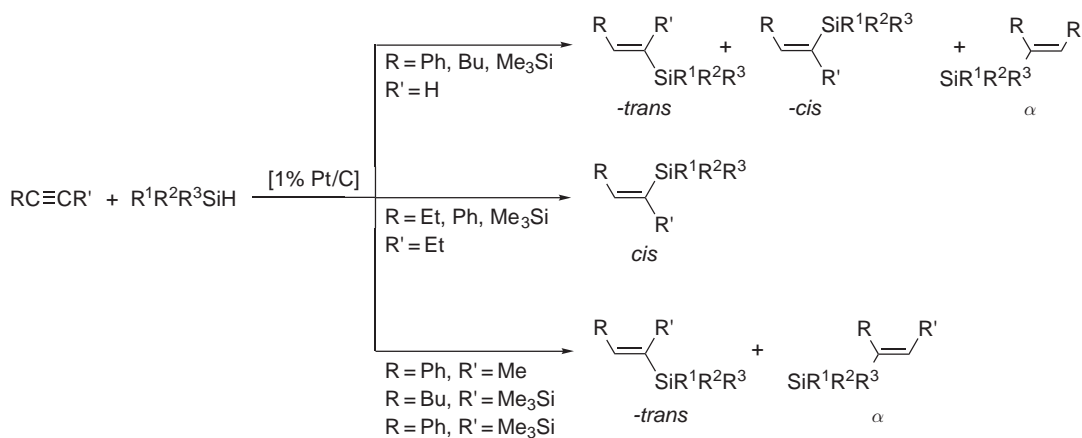


The product distribution is found to vary considerably with the nature of the catalyst and substrates and also with specific reactions conditions. In general, platinum and rhodium complexes with tertiary organic bases catalyze *syn*-addition across the C–C triple bond to yield β -adducts with the *trans*-configuration <B-1993MI005> but are usually accompanied by other isomers. Considerable effort has recently been devoted to the improvement of the selectivity, which depends on many factors, e.g., substituents on the alkyne and hydrosilane, the catalyst, the reaction temperature and the solvent.

A highly regio- and stereoselective hydrosilylation of terminal alkynes with triethylsilane catalyzed by Pt(DVDS)P [P = (bis(diphenylphosphinomethylene)butylamine)] under ambient conditions has been reported recently to give near quantitative yields and 100% stereoselectivity of various (*E*)-vinylsilanes (Equation (24)) <2003CC1668>.



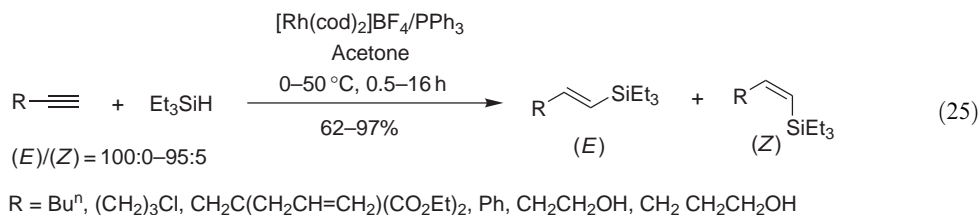
Excellent yields of vinylsilanes (>85%) can be achieved by using Pt/C which provides a significant cost advantage over homogeneous platinum complexes [<2002JOM\(645\)1>](#). The selectivity of the products depends on the silane. Chlorosilanes usually produce a single vinylsilane, while alkoxy-silanes and alkylsilanes yield a mixture of two or more isomeric vinylsilanes. Exclusive formation of *cis* isomers occurs in the hydrosilylation of symmetrical internal alkynes whereas unsymmetrical internal alkynes give a mixture of α - and β -(*trans*) products ([Scheme 7](#)).



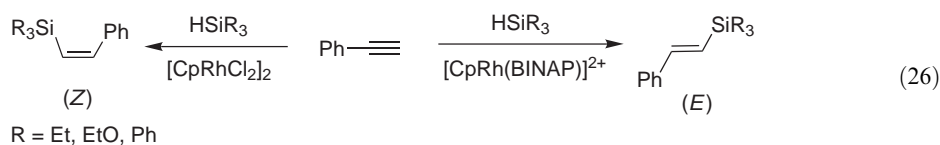
Scheme 7

Cationic rhodium complexes catalyze the hydrosilylation of 1-alkynes to give (*E*)-vinylsilanes as the major product, whereas neutral rhodium compounds lead to predominantly (*Z*)-vinylsilanes [<1995JOC3045, 2002OM1743>](#).

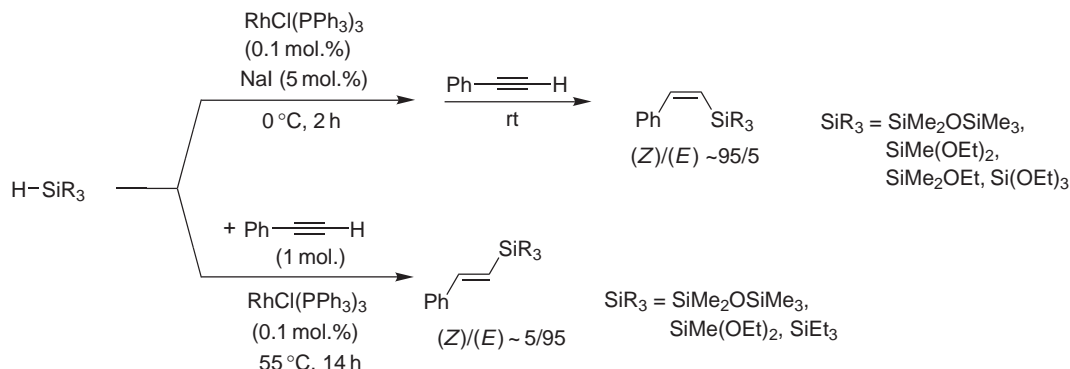
Rh(cod)₂BF₄/2PPh₃ catalyzes hydrosilylation of a wide range of 1-alkynes with triethylsilane. The reaction of propargylic alcohols with triethylsilane gives ethyl silyl allylic alcohols with high selectivities and excellent yields and can be carried out without protecting the alcohol functionality ([Equation \(25\)](#)) [<1995JOC3045>](#).



Also, the Rh(III) cationic complex Cp^{*}Rh(BINAP)²⁺(SbF₆)₂ [BINAP = 2,2'-bis(diphenylphosphino)-1,1'-biphenyl] promotes *syn*-addition of HSiEt₃, HSi(OEt)₃, and HSiPh₃ to phenylacetylene to yield the β -(*E*)-isomer, whereas Cp^{*}RhCl₂ catalyzes *anti*-addition to give the β -(*Z*)-isomer ([Equation \(26\)](#)) [<2002OM1743>](#).

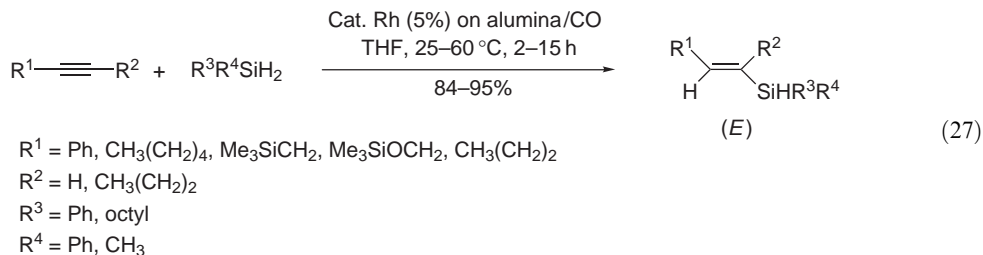


Whereas the $\text{Rh}(\text{I})(\text{PPh}_3)_3$ catalyst generated *in situ* by premixing the complex with hydrosilane, gives (*Z*)-alkenylsiloxanes, a direct reaction carried out with successive addition of all reagents affords the (*E*)-products (Scheme 8) <1998CL443>.

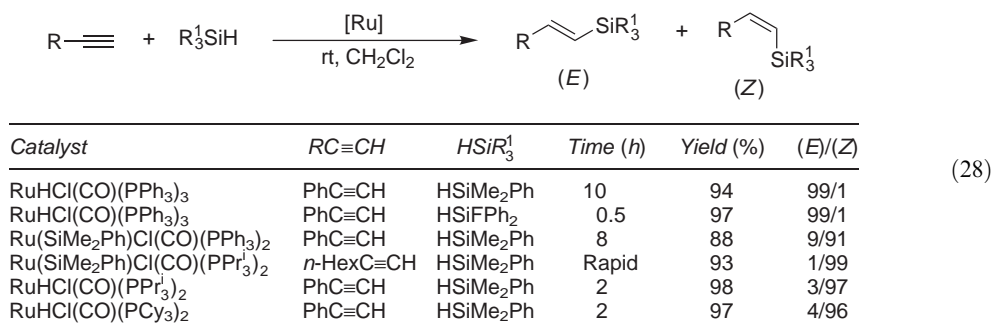


Scheme 8

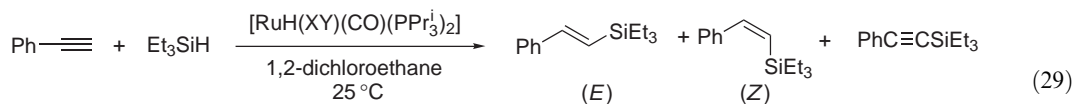
Rhodium on alumina in a CO atmosphere catalyzes the addition of PhMeSiH_2 and Ph_2SiH_2 to alkynes to yield (*E*)-vinylsilanes with high yields (>90%) and selectivities (Equation (27)) <2002MI41>.



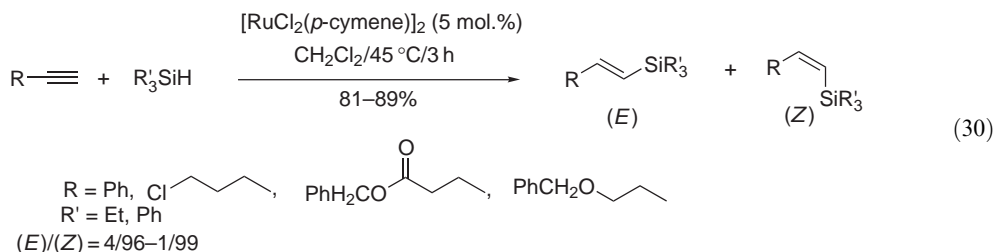
Ruthenium complexes are known to be generally less reactive in hydrosilylation than platinum and rhodium complexes but this property has been developed into very selective catalyst systems. $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ directs the hydrosilylation of terminal alkynes ($\text{RC}\equiv\text{CH}$; $\text{R} = \text{Ph}$, *para*-tolyl, *c*-hexyl, *n*-hexyl) with hydrosilanes (HSiMe_2Ar) stereoselectively giving (*E*) $\text{RCH}=\text{CHSiMe}_2\text{Ar}$ (>99%) while $\text{Ru}(\text{SiMe}_2\text{Ph})\text{Cl}(\text{CO})(\text{PPr}_3)_2$ results in formation of the (*Z*)-isomer with 91–99% selectivity (Equation (28)) <2002JOM(645)192>.



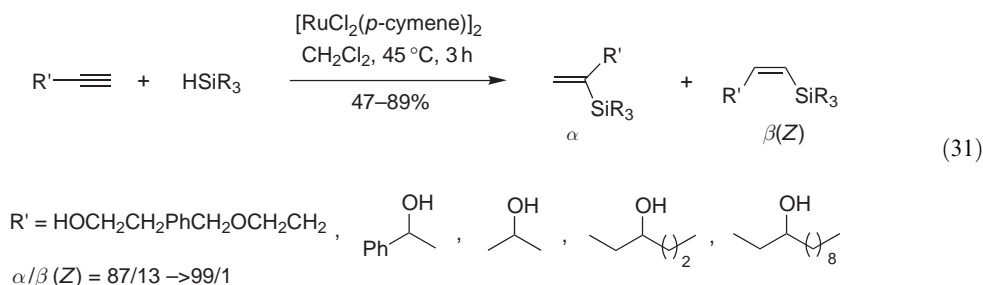
$\text{Ru}(\text{SiMe}_2\text{Ph})\text{Cl}(\text{CO})(\text{PPr}_3)_2$ has been found to be the most efficient ruthenium catalyst for the hydrosilylation of phenylacetylene. Other ruthenium complexes, e.g., $\text{RuH}(\text{XY})(\text{CO})(\text{PPr}_3)_2$ ($\text{XY} = \text{Cl}$, acetate, acac) (Equation (29)) <2002OM4027> and $\text{RuCl}_2(p\text{-cymene})$ (Equation (30)) <2000OL1887>, have been reported for stereoselective production of (*Z*)-vinylsilanes.



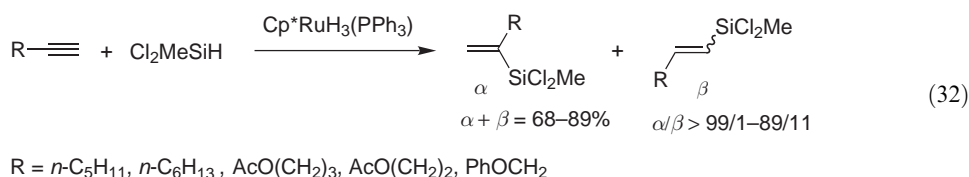
XY = Cl, acetate, (Z)/(E) PhC≡CSiEt₃ 97/2/1–100/0/0, time to yield 100%, 1–1.5 h



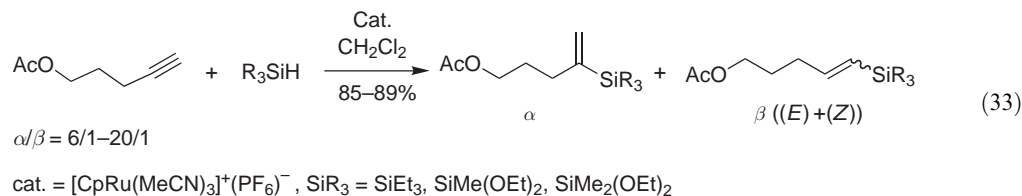
Recent reports also describe the selective formation of internal adducts in ruthenium-catalyzed reactions, either by functional group directed addition of trialkyl- and trialkoxysilanes <2000OL1987, 2002JOM(645)192> or by a more general Markovnikov addition <2001JA12726>. If alkynes having a hydroxyl group at the β -position to the triple bond are used as substrates, then α -vinylsilanes are generated in good yield (47–89%) and excellent selectivity (87/13–99/1) (Equation (31)) <2000OL1887>.



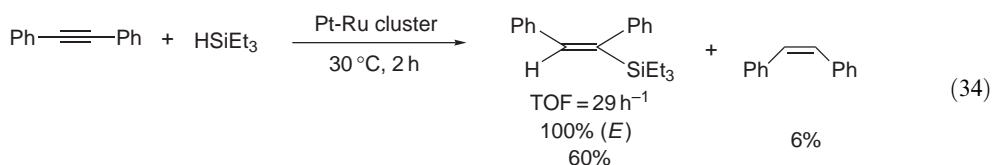
In the presence of Cp*RuH₃(PPh₃), the hydrosilylation of 1-alkynes by methyldichlorosilane proceeds regioselectively affording preferentially the internal α -product (Equation (32)) <2002OL2825>.



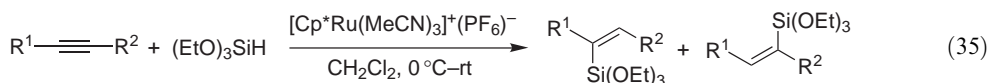
The cationic ruthenium complex [CpRu(MeCN)₃]⁺PF₆[−] catalyzes the hydrosilylation of alkynes with triethylsilane in good yield (Equation (33)) <2001JA12726>.



The platinum–ruthenium cluster complex [Pt₃Ru₆(CO)₂₀(μ_3 -PhC₂Ph)(μ_3 -H)(μ -H)] is an effective catalyst precursor for the highly selective catalytic hydrosilylation of diphenylacetylene with triethylsilane (Equation (34)) <1998OM2567>.

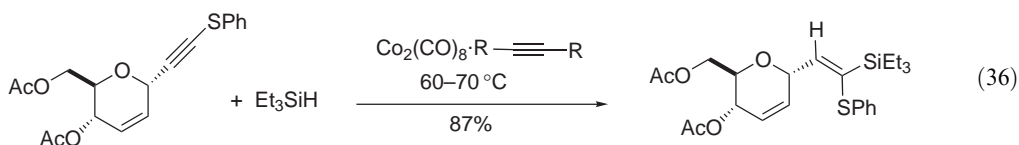


The hydrosilylation of unsymmetrical alkynes with triethoxysilane gives vinylsilanes as a mixture of (*Z*)-regioisomers (Equation (35)) <2003JA30>.

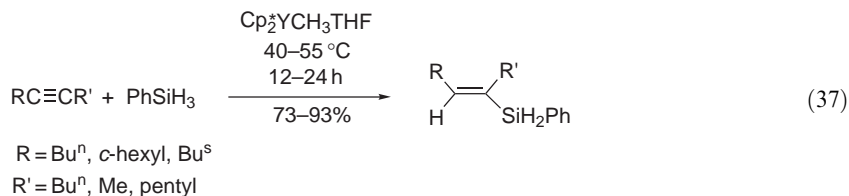


Hydrosilylation of cycloalkynes catalyzed by [Cp*Ru(MeCN)₃]PF₆ also proceeds chemo- and stereoselectively (particularly with (EtO)₃SiH) to provide good-to-excellent yields favoring *anti*-addition <2002CC2182>.

Octacarbonyldicobalt complexes of alkynes also catalyze effectively the hydrosilylation of internal alkynes. The regioselectivity is extremely high with phenylthioalkynes (Equation (36)) <1999TL6927, 1998TL2609>.



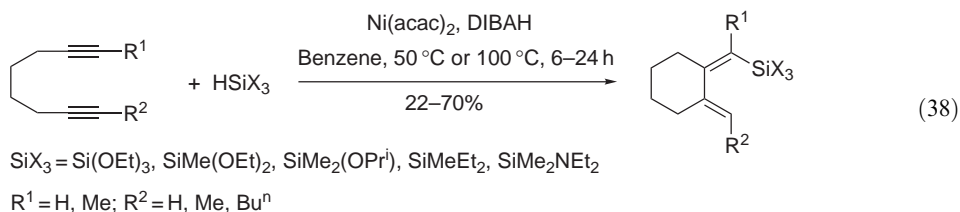
A less active but highly regioselective catalyst for hydrosilylation of unsymmetrical internal alkynes with phenylsilane is the organoytrium complex Cp₂*YCH₃THF. This gives exclusively the product having the silyl group on the less hindered carbon of the alkyne with good isolated yields (73–93%) (Equation (37)) <1995OM4570>. A variety of functional groups, e.g., halides, amines, protected alcohols, and trisubstituted alkenes, are unaffected by the reaction conditions.



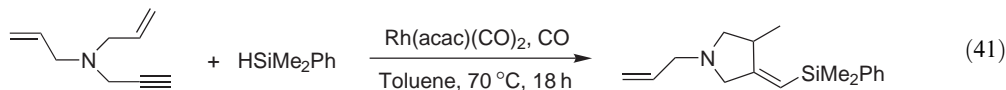
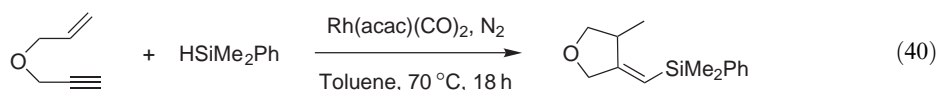
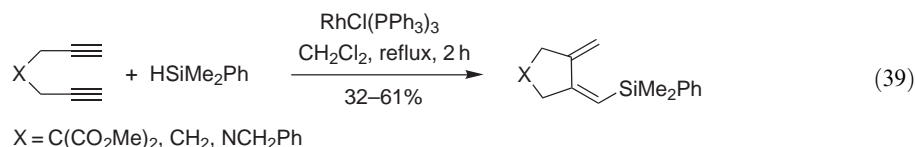
Lewis acids such AlCl₃ or EtAlCl₂ catalyze the hydrosilylation of 1-alkynes to produce predominantly the corresponding (*E*)-vinylsilane in high yield <1996JOC7654, 1999JOC2494>.

(ii) Cyclization of dialkynes and alkenynes via hydrosilylation

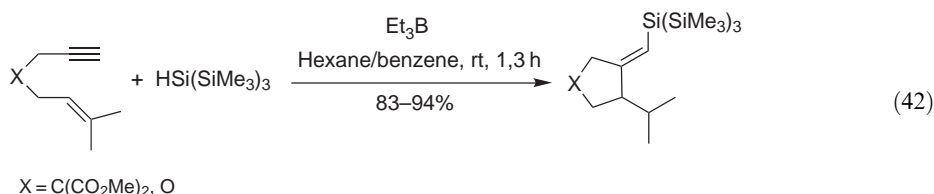
Dialkynes with propargylic substitution in the presence of Pt, Rh and Ni complexes react with hydrosilanes to form cyclic vinylsilanes in good yield and with high stereoselectivity. Ni(0) complexes catalyze the reaction of 1,7-diynes to silylated (*Z*)-1,2-dialkylidenecyclohexanes (Equation (38)) <1989JA6478>.



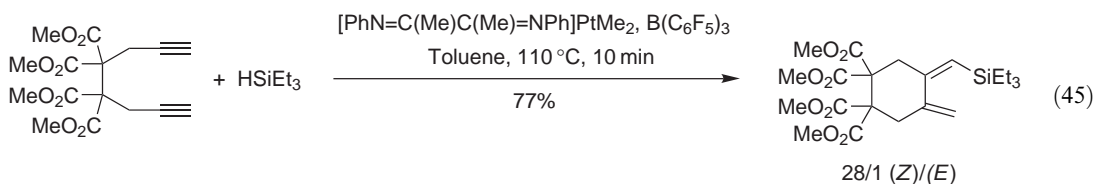
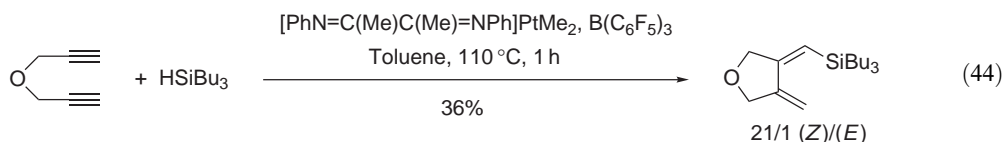
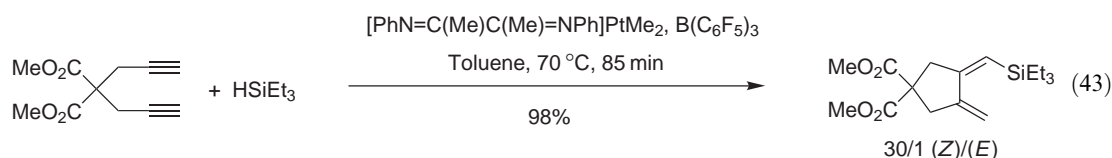
Rhodium complexes catalyze the hydrosilylative cyclization of: (i) 1,6-diynes to form predominantly (*E*)-1,2-dialkylidenecyclopentanes (Equation (39)) <1998TL7325> and (ii) 1,6-enynes to give monoalkylidenecyclopentanes (Equations (40) and (41)) <1992JA6580>.



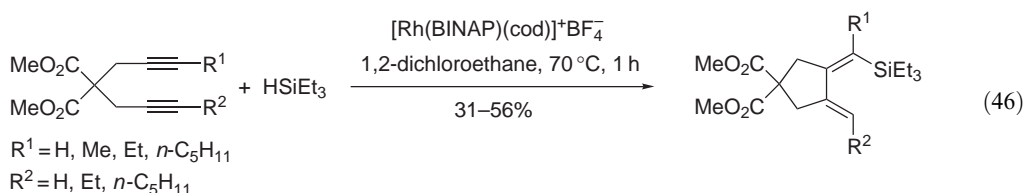
Functionalized alkylidenecyclopentanes can also be obtained by radical-induced cyclization-hydrosilylation (Equation (42)) <1993BCJ2348>.

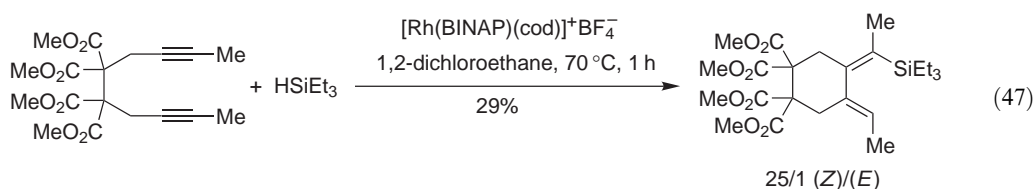


On the other hand, in the presence of a platinum complex with $\text{B}(\text{C}_6\text{F}_5)_3$, a large variety of 1,6-diynes, including esters, sulfones, amides, ketones, acetals, and silyl ethers, undergo facile cyclization-hydrosilylation to form silylated 1,2-dialkylidenecyclopentanes (Equations (43) and (44)). When a 1,7-diyne was used, the corresponding cyclohexane derivatives were formed (Equation (45)) <2002JOC2778>.



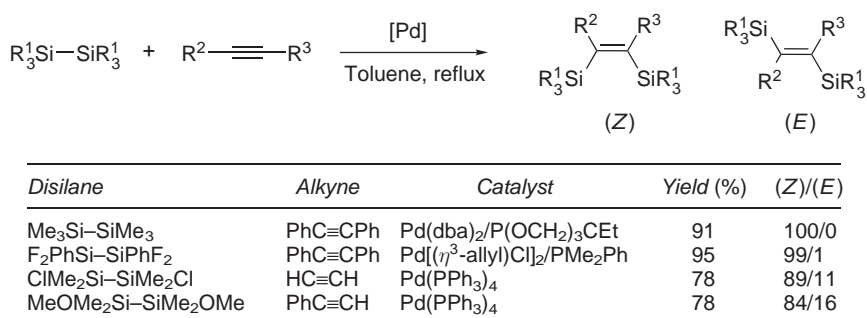
Similarly, a cationic rhodium complex catalyzes the cyclization-hydrosilylation of 1,6-diynes and 1,7-diynes having internal alkynes to form silylated 1,2-dialkylidenecycloalkanes in moderate-to-good yield and with high diastereoselectivity (Equations (46) and (47)) <2002OM5666>.





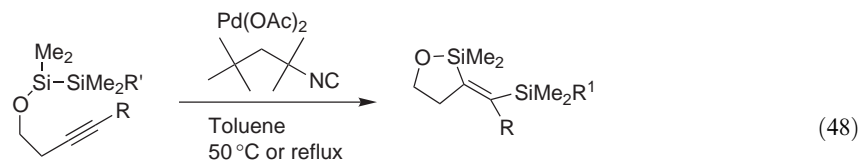
(iii) Bissilylation of alkynes

The addition of substituted disilanes to alkynes is an exothermic process that provides an attractive regioselective route to functionalized organosilicon compounds (Scheme 9). The reactivity of organosilanes in this reaction, which is catalyzed mostly by Pd complexes, is enhanced by electronegative substituents on silicon and is comparable with that of strained cyclic Si—Si bonded compounds. A large variety of stereo- and regioselectively functionalized unsaturated organosilicon compounds have been formed via this route <2000MI527>. This reaction has been comprehensively reviewed <1995CRV1317, 1995CRV1351>. Selected data on bissilylation of simple alkynes in the presence of a Pd catalyst are presented in Scheme 9 <1995CRV1351>.

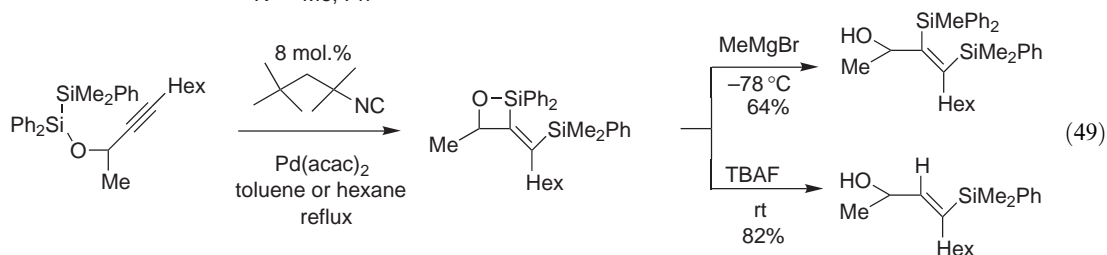


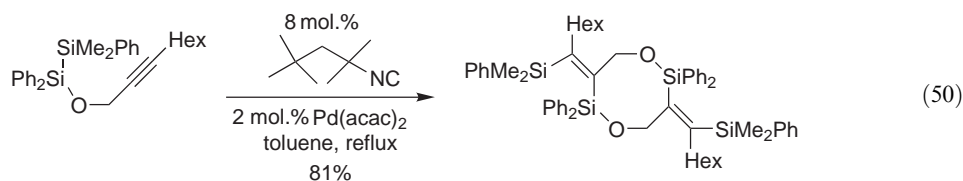
Scheme 9

Disilanyl ethers of homopropargylic alcohol having internal C—C triple bonds undergo intramolecular bis-silylation to give cyclic silolanes in good yield (Equation (48)) <1999JOM(576)300>. However, a disilanyl ether derived from 3-decyn-2-ol undergoes intramolecular addition to the Si—Si bond to give a four-membered ring, which can be cleaved by a Grignard reagent or undergo protodesilylation (Equation (49)) <1996JOC4884, 1998JA1930, 1999JOM(576)300> or, in another derivative, can dimerize (Equation (50)).



R = H, Me, Ph, SiMe₃, CO₂R, CH₂=CH₂, etc.
R¹ = Me, Ph

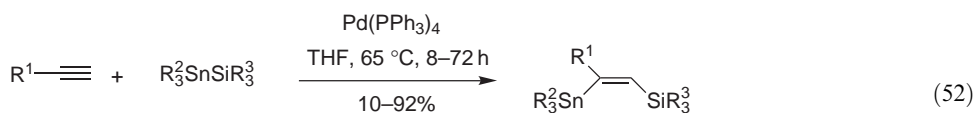
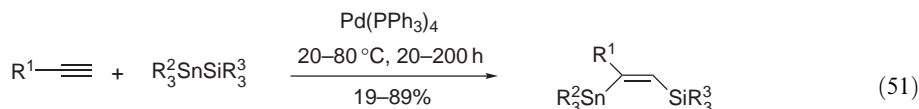




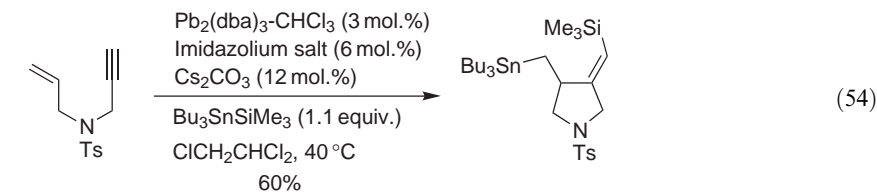
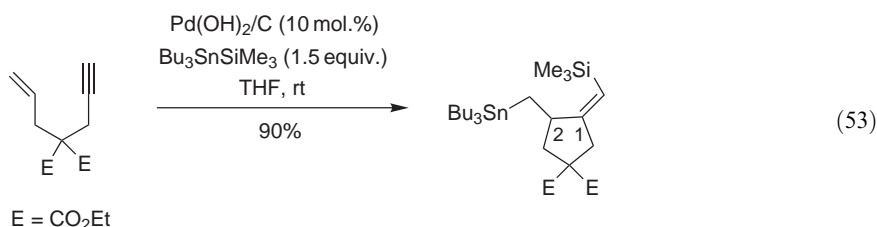
(iv) *Silylmethallation of alkynes*

Addition of a bimetallic reagent to a multiple bond (often catalyzed by transition metals) has been of great interest during the 1990s because the new metal–carbon bonds can be utilized in further transformations <1999CRV3435>. For the synthesis of vinylsilanes, one of the components should be Sn, Cu, Mg, Zn, B, Al, Mn, or Ti.

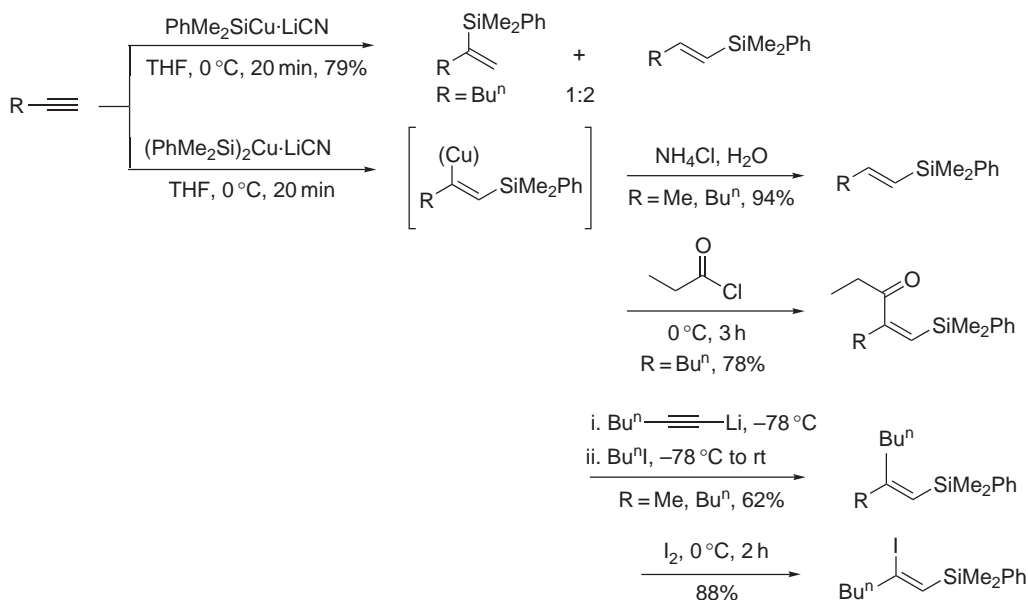
Silylstannylation. Terminal alkynes react efficiently with trialkylstannyltrialkylsilanes to produce (*Z*)-1-silyl-2-stannyl alkenes in good yield and with high regio- and stereoselectivity (Equations (51) and (52)) <1995COFGT(2)899>.



Recently bismetallation–cyclization between two multiple bonds has achieved special importance in synthesis. The Pd(0)-imidazolium salt catalyzed cyclization of enynes in the presence of $\text{Bu}_3\text{SnSiMe}_3$ proceeds under optimum conditions giving products having both vinylsilane and homoallylstannane functions in moderate-to-good yield (Equations (53) and (54)) <2001OM1907, 2003MI488>.

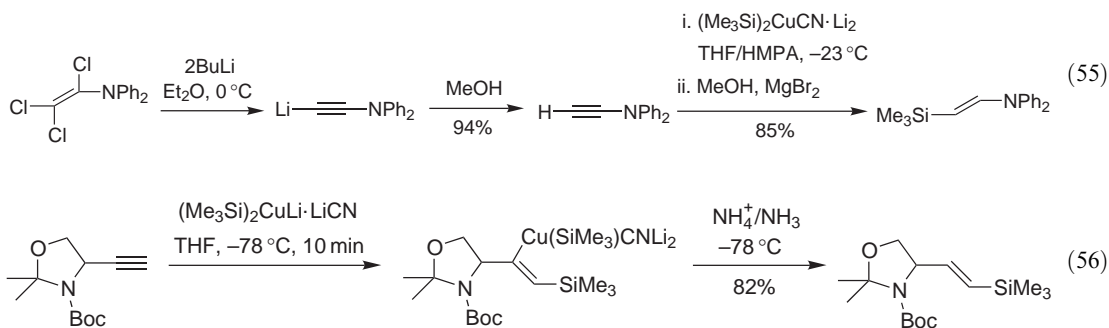


Silylcupration. Silylcupration, a reaction revealed by Fleming and co-workers <1997CRV2063>, is the stereospecific *syn*-addition of silylcopper reagents to terminal alkynes. This can be followed by protonation of the vinylcuprate intermediate or by reaction with carbon electrophiles. These reagents include $(\text{PhMe}_2\text{Si})_2\text{CuLi-LiCN}$ <1998TL9545>, $\text{PhMe}_2\text{Si(Me)CuLi-LiCN}$ and $\text{PhMe}_2\text{SiCuLiCN(Me}_3\text{Si)}_2\text{CuLi-LiCN}$ (Scheme 10) <1993TL3311, 1998TL9545>.

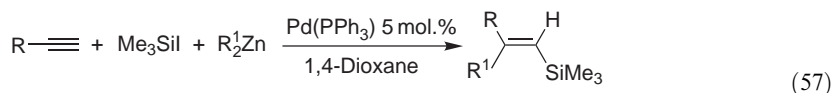


Scheme 10

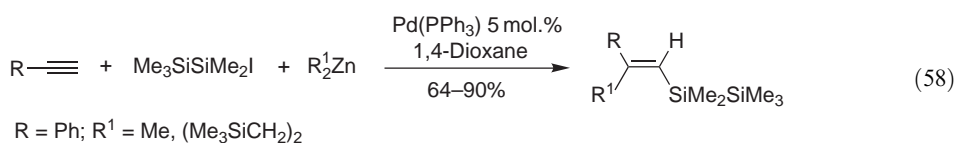
This protocol can also be used for the synthesis of functionalized vinylsilanes from propargylamines <1995COFGT(2)899>, *N*-phenyl-*N*-ethynylaniline and ethyloxazolidine (Equations (55) and (56)) <1993TL3311, 1998TL9545>.



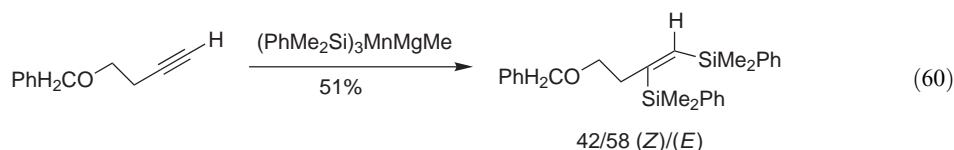
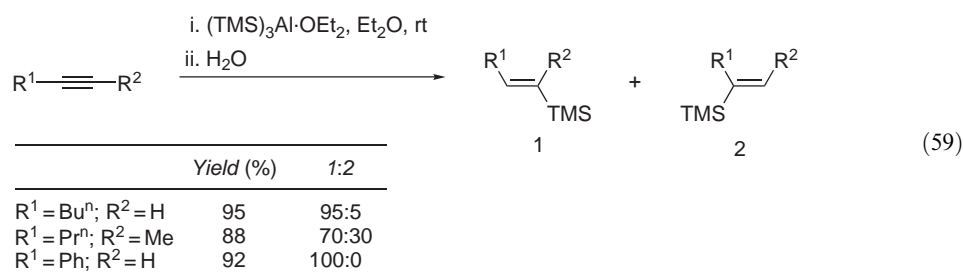
Palladium-catalyzed coupling of alkynes with iodotrimethyl silane. The reaction of terminal alkynes with Me_3SiI and an organozinc reagent in the presence of $\text{Pd}(\text{PPh}_3)_4$ results in addition of the TMS group and an alkyl group of the organozinc reagents to the acetylene. In all cases the TMS group is added to the terminal C of the acetylene. Both aromatic and aliphatic terminal alkynes undergo this coupling reaction with high regio- and stereoselectivity (Equation (57)) <1995JOC1834, 1999JOC7675>. This protocol can also be used for synthesis of functionalized vinyldisilanes (Equation (58)).



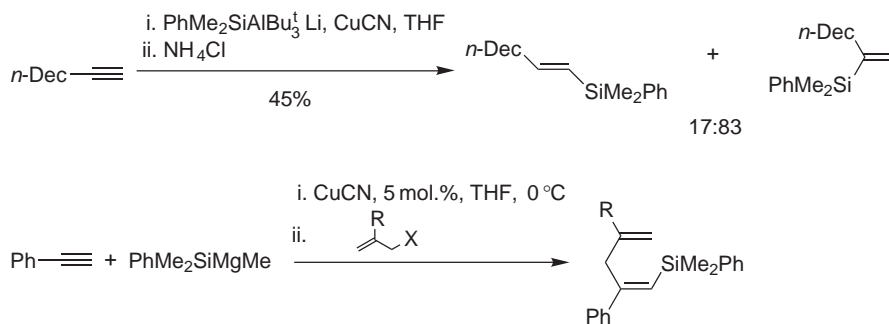
$\text{R} = \text{Ph}; \text{R}' = \text{Me, Et, Bu}; 61\text{--}90\%$
 $\text{R} = \text{C}_6\text{H}_{11}; \text{R}' = \text{Me, Et, Bu}; 48\text{--}73\%$



Addition of silylmagnesium, -aluminum, -manganese and -boron reagents. Tris(trisubstituted-silyl)metal compounds react with alkynes by transfer of all the three silyl groups to produce vinylsilanes after protonolysis. The reaction proceeds via a clean *syn*-addition and with high regioselectivity (Equation (59)) <1995COFGT(2)899> and (Equation (60)) <1997T5061>.



Monosilylmetallation reagents also add to terminal alkynes in the presence of a transition metal catalyst and produce vinylsilanes with high regio- and stereoselectivity (Scheme 11) <1995COFGT(2)899, 2002JOC2136>.

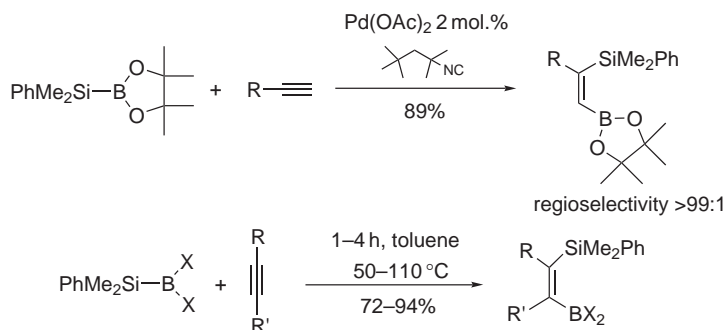


Scheme 11

Silylboration of alkynes (1-octyne, terminal alkynes, internal alkynes) catalyzed by palladium and platinum complexes is also a very efficient regio- and stereoselective route to (*Z*)- β -silyl-vinylboranes. The reaction is successfully catalyzed by palladium and platinum complexes mainly with phosphorus ligands (Scheme 12) <1996CC2777, 1998JOC6096, 1999T8787>.

(v) Carbosilylation of alkynes

Various types of silylated 1,4-dienes have been prepared recently via the Lewis acid-catalyzed allylsilylation of unsaturated alkynes (Equation (61)) <1996JOC4874, 1997JA6781, 1999SL519>. HfCl_4 catalyzed addition of substituted allylsilanes to phenylacetylene occurs smoothly at 0°C affording the corresponding adducts (Equation (62)) <1997JA6781>. The first carbosilylation of phenylacetylene with propargylsilanes afforded 1,4-enynes in a moderate yield (Equation (63)) <2000TL4499>.



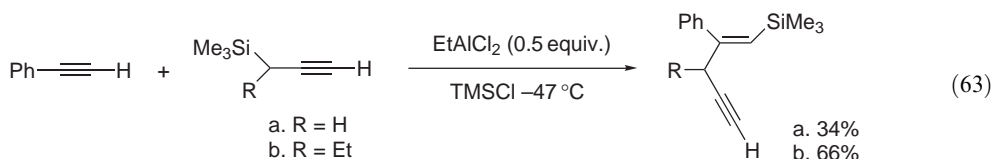
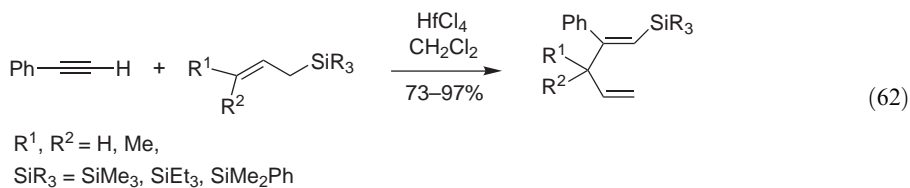
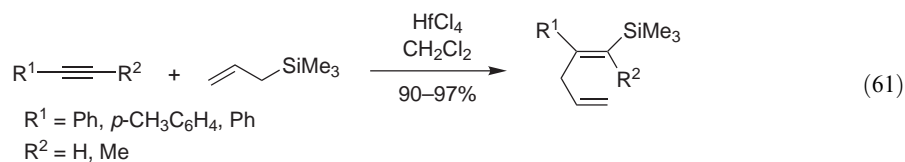
X = NEt₂, BuⁱCH₂CMe₂NC, (–OCMe₂CMe₂O–)

Cat. = Pd(OAc)₂/BuⁱCH₂CMe₂NC, Pd(OAc)₂/*c*-HexNC, Pd₂(dba)₃CHCl₃/P(OEt)₃, PdCl₂(PPh₃)₂, RhCl(PPh₃)₃, Pt(PPh₃)₄

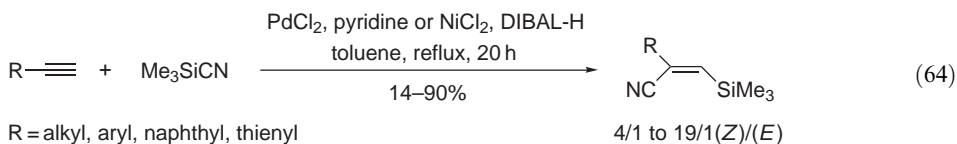
R = Ph, Bu, Me₃Si, CH₃CO, H

R' = Ph, Me, Bu

Scheme 12



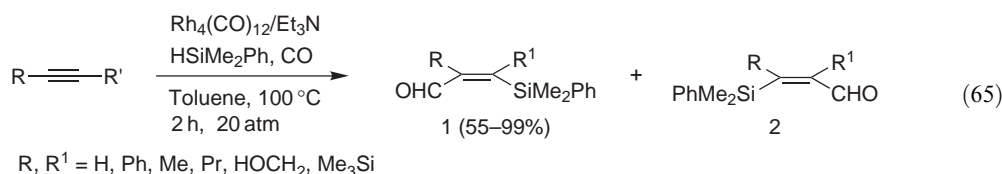
The addition of Me₃SiCN to alkynes gives β-silylacrylonitriles with fair to good (*Z*)-stereoselectivity (Equation (64)) <1995COFGT(2)899>.



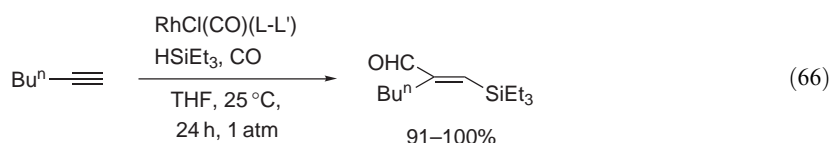
(vi) Silylcarbonylation of alkynes

Silylformylation of alkynes. The silylformylation of alkynes as a method of regio- and stereoselective synthesis of (*Z*)-3-silyl-2-alkenals in high yield has been independently reported by the Ojima and Matsuda groups <1990JA6120, 1991OM38>. Recent advances include the application of this reaction to the synthesis of 4-silyl-1-aza-1,3-butadienes, β-substituted-(*E*)-crotylsilanes and pyrrolizidine alkaloids <1995TL8723, 1998T4493>, and the extension of the reaction to silylcarbocyclization and silylcarbocyclization of triynes <1999JA3230> and silylhydroformylation reactions <1994OM1586>. The catalysts usually employed are Rh₄(CO)₁₂ <1990JA6120, 1997OM4327, 2003JOC9292> or Rh₂Co₂(CO)₁₂ <1991OM38, 1999AOC197>. The zwitterionic Rh(cod)(BPh₄) has also been used <1995JA4419, 1998T4493> but the best results have been obtained with Rh₂(pfb)₄ (pfb = perfluorobutyrate) under mild conditions <1993OM11,

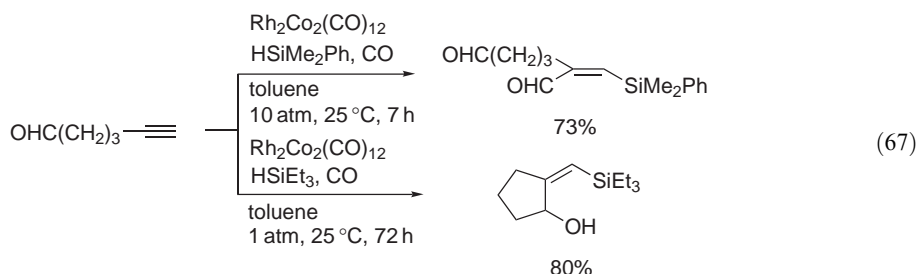
1994OM1081, 1995TL8723>. However, internal alkynes appear to be better served by the $\text{Rh}_4(\text{CO})_{12}$ catalyst (Equation (65)).



Espinet has reported that rhodium(I) complexes with P or N donor ligands effectively catalyze silylformylation. Rhodium(I) compounds of the type $\text{RhCl}(\text{CO})(\text{L-L}')$ [$\text{L-L}' = \text{P}(\text{bzN})\text{Ph}_2$, $\text{P}(\text{bzN})_2\text{Ph}$, $\text{P}(\text{bzN})_3$, PePy , PePy_2 , ($\text{bzN} = 2$ -(dimethylaminomethyl) phenyl; $\text{PePy}_n = \text{P}(\text{CH}_2\text{CH}_2\text{-Py})_n\text{Ph}_{3-n}$; $\text{Py} = 2$ -Pyridyl; $n = 1, 2$)] are effective catalysts for silylformylation of 1-hexyne under a CO atmosphere in THF (Equation (66)) <2001TL5697>.

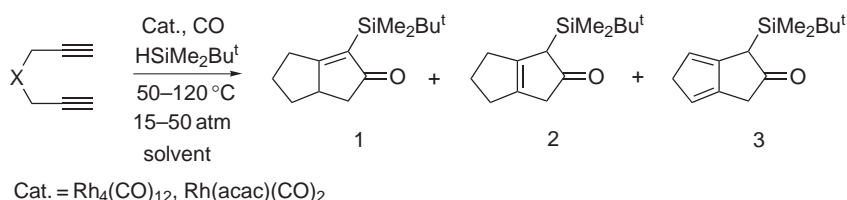


Silylformylation of the acetylene functionality was observed in the reaction of 5-hexynyl-1-ol <1994JA3643> but, depending on the reaction conditions, it was also possible to obtain products of silylcyclocarbonylation (Equation (67)).



When optically active acetylenes are treated with Me_2PhSiH under carbon monoxide pressure, the silylformylation reaction occurs with total retention of stereochemistry of stereogenic center <2001EJO4321>.

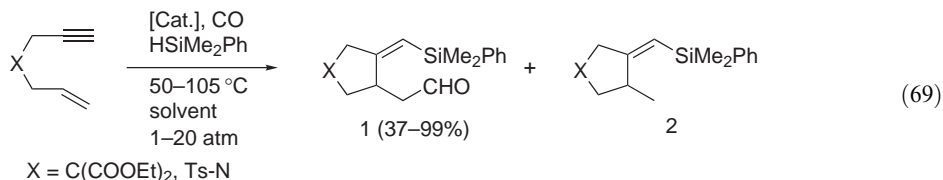
Silylcarbocyclization and silylcyclocarbonylation of alkynes. The silylcarbocyclization of 1,6-diynes has been independently discovered by Ojima <1994JOC7594> and Matsuda <1995TL241>. The reaction of 1,6-diynes with $\text{HSiMe}_2\text{Bu}^t$ and CO in the presence of rhodium complexes gives bicyclo[3.3.0]octanones in good yield. The product distribution is dependent on the structure of the diynes and the solvent used (Equation (68)) <1995TL241, 1996OM5191, 1998JA6690>.



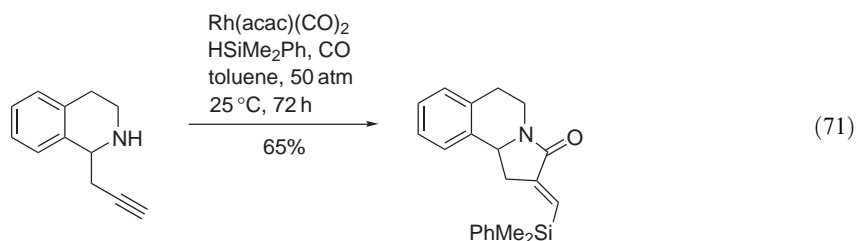
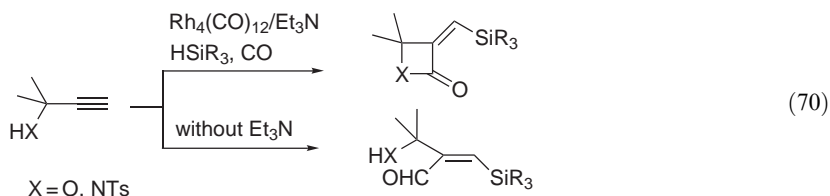
X	Yield (%)		
	1	2	3
CH_2	63	13	0
CH_2	60	0	0
$\text{C}(\text{CO}_2\text{Me})_2$	14	70	0
$\text{C}(\text{CO}_2\text{Me})_2$	0	92	0
NCH_2Ph	8	0	72
NCH_2Ph	11	0	67

(68)

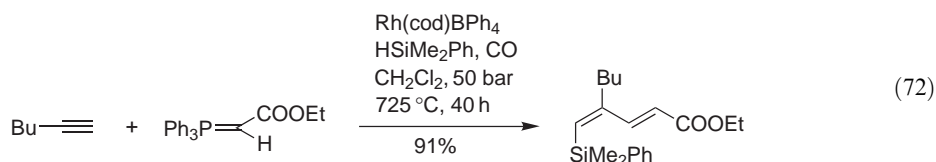
The reaction of 1,6-enyne with hydrosilanes catalyzed by $\text{Rh}(\text{acac})(\text{CO})_2$, $\text{Rh}_4(\text{CO})_{12}$ or $\text{Rh}_2\text{Co}_2(\text{CO})_{12}$ under an ambient CO atmosphere gives 2-methyl-1-silylmethylidene-2-cyclopentane in excellent yield via a silylcarbocyclization process. The same reaction in the presence of a phosphine or phosphite (PPh_3 , $\text{P}(\text{OPh})_3$, $\text{P}(\text{OEt})_3$) and under 20 atm of CO affords the corresponding 2-formylmethyl-1-silylmethylidene-2-cyclopentane with excellent selectivity through a carbonylative silylcarbocyclization process (Equation (69)) <1999TL4703, 2002JA9164>.



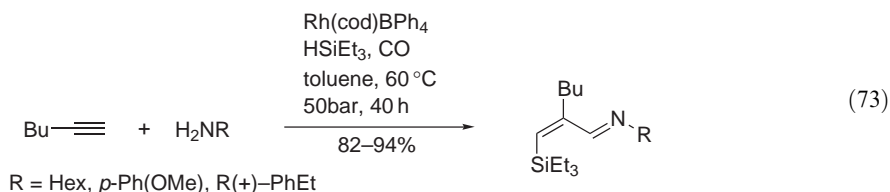
Related reactions of carbonylation. Silylformylation of propargyl alcohols and amines in the presence of $\text{Rh}(\text{CO})_{12}/\text{Et}_3\text{N}$ gives α -silylmethylene- β -lactones and β -lactams (Equation (70)) <1990JA6120, 1991TL7431>. Also, the reaction of 1-propargyltetrahydroisoquinoline gave the expected silylcyclocarbonylation product (Equation (71)) <1996ICA(251)299>.



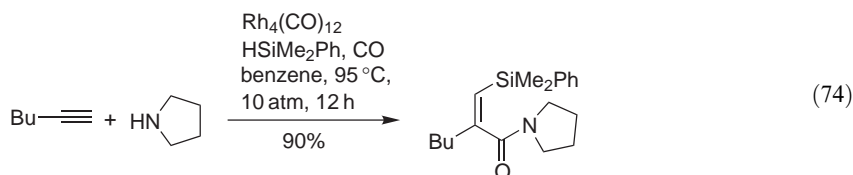
The rhodium(I)-catalyzed silylformylation–Wittig olefination of terminal alkynes with hydrosilanes and carbon monoxide in the presence of stabilized phosphorus ylides leads to substituted 2,4-dienoic esters in a one-pot procedure (Equation (72)) <2000EJO1131>.



Silylformylation of alkynes in the presence of primary amines gives 4-silyl-substituted 1,3-azadienes in a one-pot procedure (Equation (73)) <1998T4493>.



Matsuda reported direct silylcarbamylation of alkynes by the assembly of four components: an alkyne, a hydrosilane, an amine, and CO (Equation (74)) <1999TL2553>.

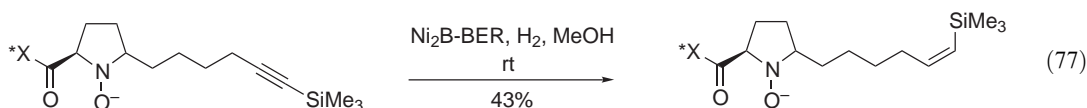
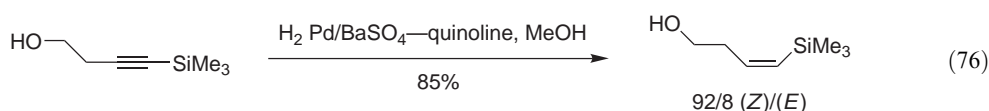
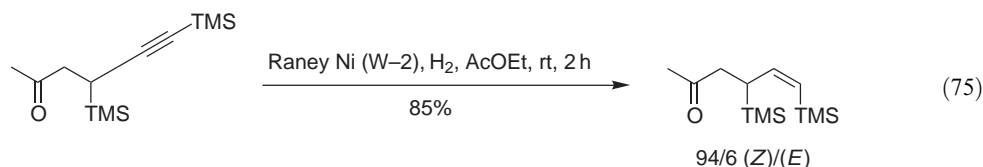


2.18.2.1.2 Vinylsilanes from silylalkynes

Vinylsilanes can be prepared from alkynylsilanes by a number of methods including partial hydrogenation and hydride reduction, hydrometallation, carbometallation, hydrocarbonylation and hydroformylation.

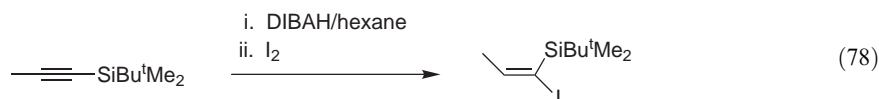
(i) Hydrogenation and hydride reduction

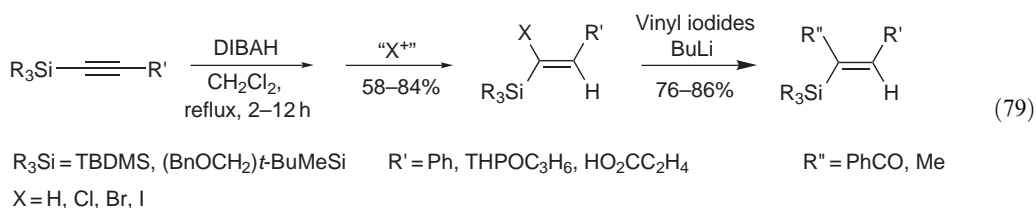
Hydrogenation of alkynylsilanes in the presence of Raney nickel (Equation (75)) <1995COFGT(2)899> as well as P-2Ni partial reduction of the silylalkyne to a vinylsilane was attempted using deactivated palladium catalysts (Pd/BaSO₄—quinoline, MeOH) with moderate success but predominately the (Z)/(E)-ratios were found to depend on the concentration and substituent structure (Equation (76)) <1995COFGT(2)899>. Stereoselective hydrogenation of a silylalkyne catalyzed by nickel boride on a borohydride resin (Ni₂B-BER) <1996TL1057, 2000TA4761> occurs stereoselectively to give the (Z)-product (43%) (Equation (77)).



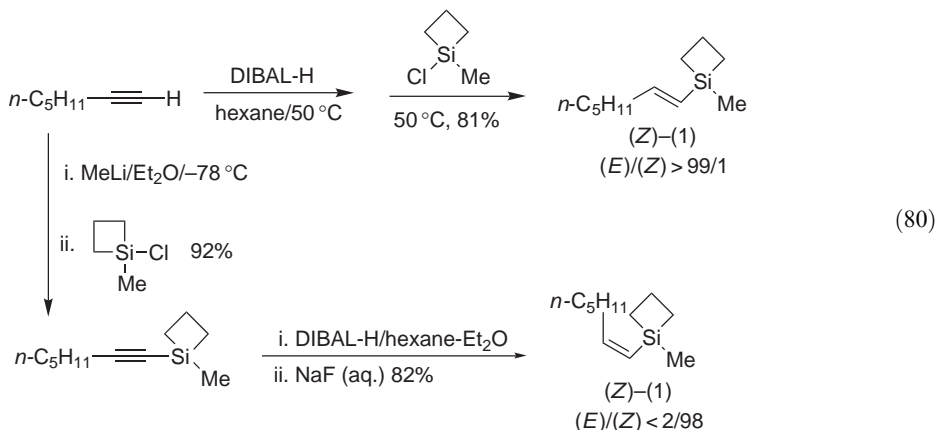
(ii) Hydrometallation of alkynylsilanes

Hydroalumination. Reduction of 3-hydroxypropynylsilanes by LAH leads to (E)-vinylsilanes but an (E)-specific procedure has been described using sodium bis(2-methoxyethoxy) aluminum hydride <1995COFGT(2)899>. *t*-Butyldimethyl(prop-1-ynyl)silane with DIBAL-H provides the (Z)-product (Equation (78)). Reduction of alkynylsilanes by diisopropylaluminum hydride gives rise to the alanes <1996MI769, 1997OM3128>. The stereochemical outcomes of these processes depend strongly on the solvent and the ethynylsilane used (Equation (79)).



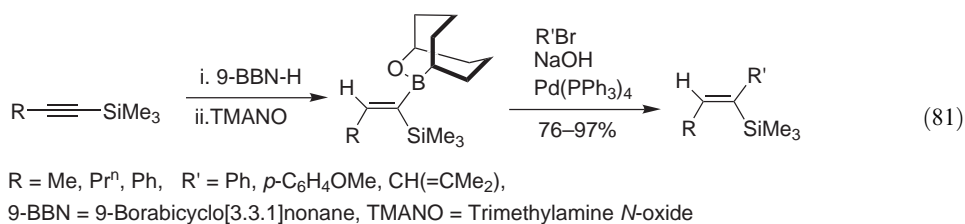


Vinylcyclobutane can be obtained by hydroalumination of 1-heptyne to yield the (*E*)-isomer in >99/1 isomeric purity [<1999JA5821>](#) but the (*Z*)-isomer was obtained by hydroalumination of silylalkyne using a related literature procedure (Equation (80)) [<1995BCJ250, 1999JA5821>](#).

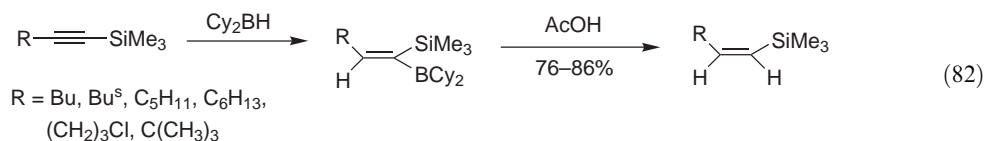


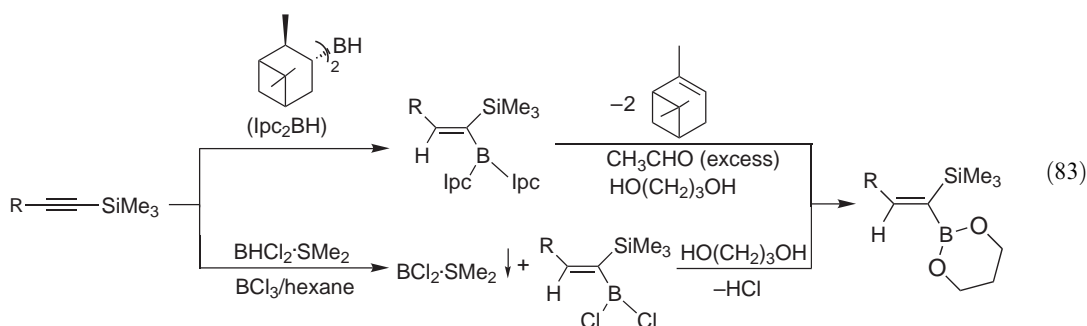
The alanes when treated with aqueous NH_4Cl solution or with I_2 , gave the monosubstituted vinylsilanes and the 1,2-disubstituted iodovinylsilanes. The benzoyl-substituted vinylsilanes were prepared from the corresponding vinyl iodides by a reaction sequence consisting of metal-halogen exchange with BuLi , treatment of the intermediary vinylolithium species with benzaldehyde, and oxidation of the resulting alcohols with CrO_3 or MnO_2 [<1997OM3128>](#).

Hydroboration. Hydroboration of alkynes is a practical route for the synthesis of 1-alkenylboron compounds. (*Z*)-vinylsilanes can be prepared by Suzuki-Miyaura coupling of (*Z*)- α -silylvinyl borinates. The latter compounds are obtained via hydroboration of silylalkynes (Equation (81)) [<1998TL3989, 1999JOM\(584\)98, 2000JOM\(602\)45, 2003JOM\(669\)72>](#).

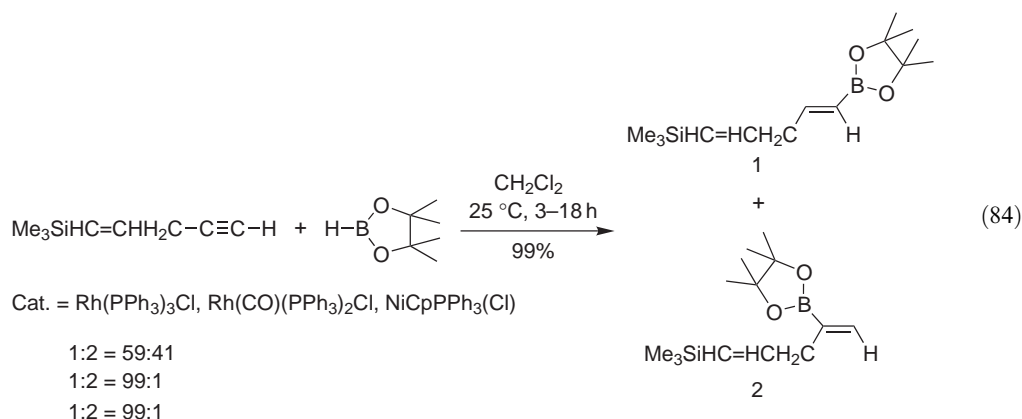


Hydroboration of alkynylsilanes with dicyclohexylborane provides silylboryl alkenes regio- and stereoselectively and subsequent treatment with acids affords the (*Z*)-vinylsilanes in high yield (Equation (82)). Two different procedures have been reported to prepare (*Z*)-2-(1-trimethylsilyl-1-alkenyl)1,3,2,-dioxoborinane (Equation (83)) [<2000TL8027, 2003TL6833>](#).

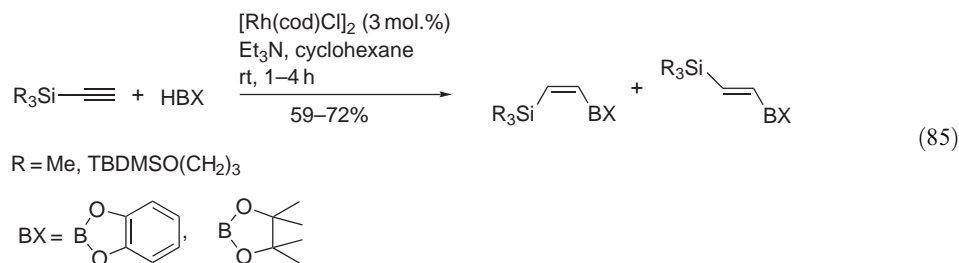




Hydroboration with pinacolboranes catalyzed by $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ gives regioisomers (59:41). Replacement of one phosphine group by a CO ligand profoundly influences the ratio of regioisomers and gives essentially pure *anti*-Markovnikov product. The complex $\text{CpNiPPh}_3(\text{Cl})$ gives the terminal hydroboration product (Equation (84)) <1996TL3283>.

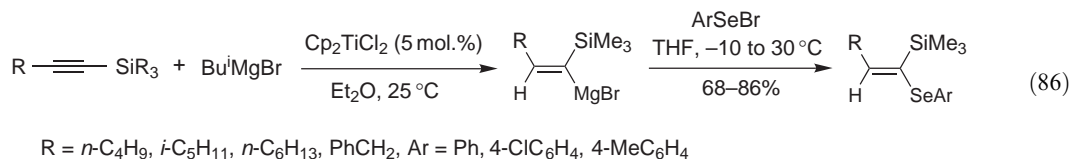


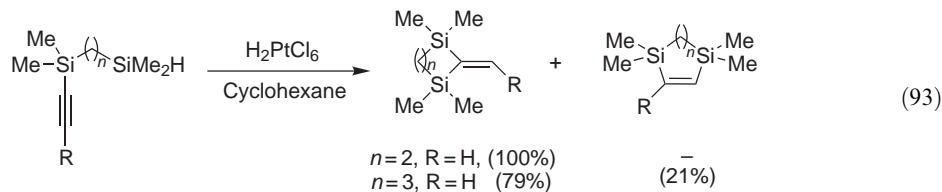
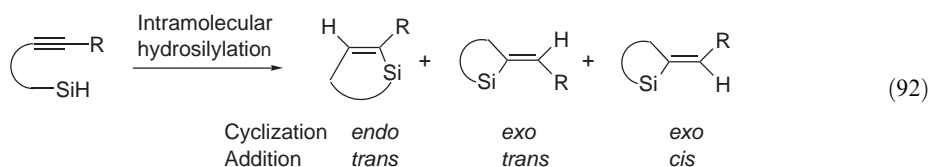
Anti-hydroboration of terminal alkynes with catecholborane or pinacolborane occurs in the presence of a $[\text{Rh}(\text{cod})\text{Cl}]_2$ complex and Et_3N to yield *cis*-1-alkenylboronates (Equation (85)) <2000JA4990>.



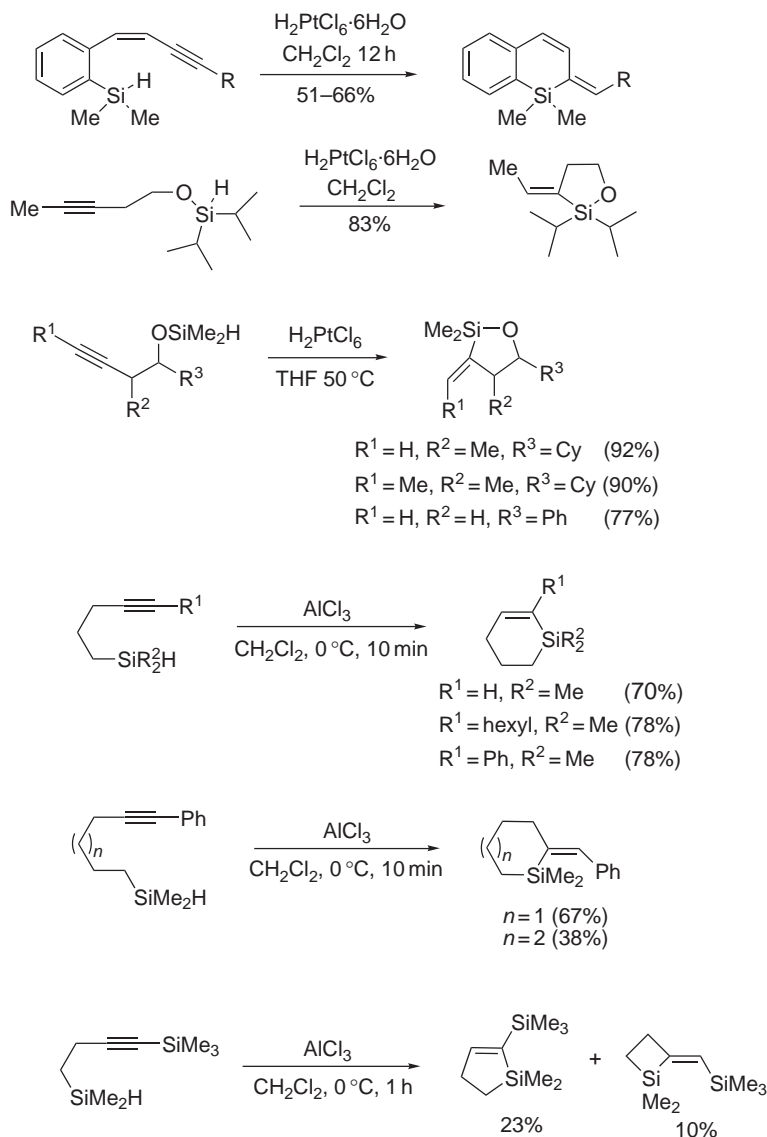
Hydrometallation. Bifunctional-group reagents, which have two different functional groups linked to the alkene carbon atoms, e.g., Si—Zr, Si—Mg, Ti—Si, play an important role in the methods for the stereoselective preparation of substituted vinylsilanes.

Hydromagnesation of alkynylsilanes gives (*Z*)- α -silylvinyl Grignard reagents, which react with selenyl bromides to afford selenylvinyl silanes (Equation (86)) <2002SI347> or alkenyl halides to afford stereoselectively 1,3-dienylsilanes (Equation (87)) <2003JOM(679)14>.



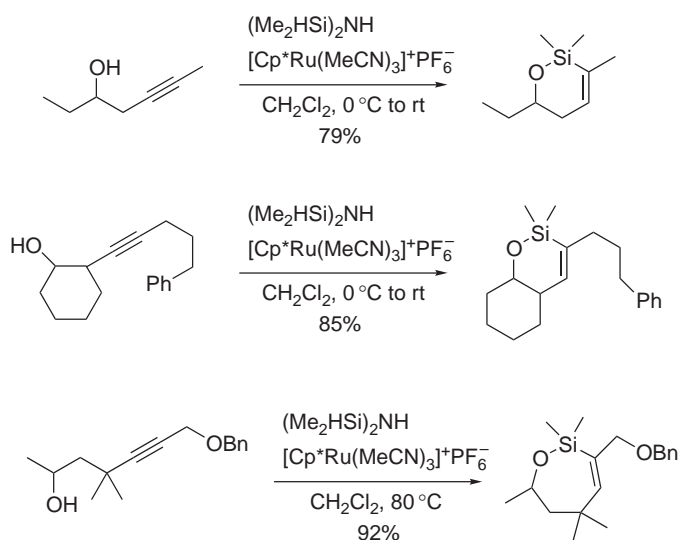


However, whereas the Pt-catalyzed reaction generally proceeds via *syn*-hydrosilylation giving *exocyclic* products <1999S921, 2000OL2173, 2001OL61>, in the presence of a Lewis acid cyclization of alkynylsilanes proceeds in an *endo-trans* or *exo-trans* manner depending on the substrate structure (Scheme 13) <2000JOC8919>.



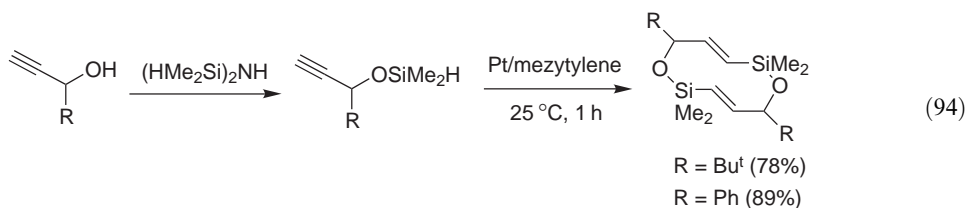
Scheme 13

Ruthenium-catalyzed reactions of homo- and bis-homopropargylic alcohols hydrosilylated *in situ* quantitatively by tetramethyldisilazane produce the *endo-dig* product (Scheme 14) <2003JA30>.



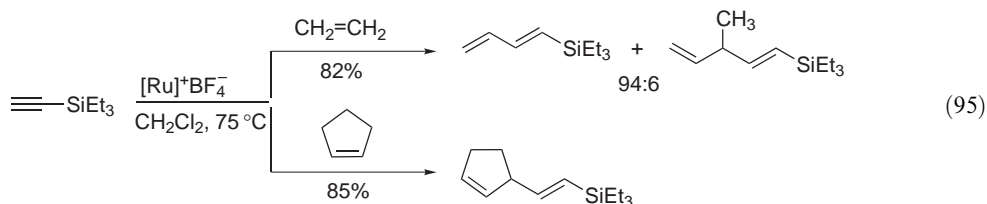
Scheme 14

Reaction of propargylic alcohols, catalyzed by a Pt–mesitylene complex, gives the cyclodimerization product (Equation (94)) <1998JOM(564)57>.

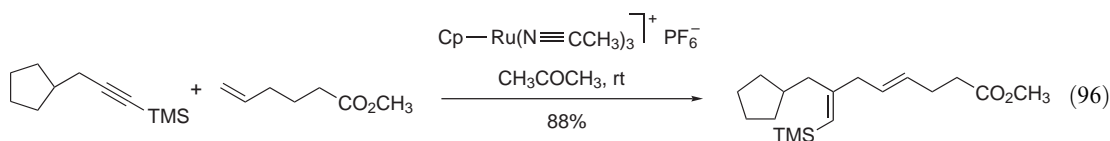


(iv) Other addition reactions

Hydrovinylation. The ruthenium cationic alkylidene complex $[(PCy_3)_2(CO)(Cl)Ru=CHCH=C(CH_3)_2]^+BF_4^-$ catalyzes hydrovinylation of silylalkynes to give the corresponding silyldienes (Equation (95)) <1999OM2043>.

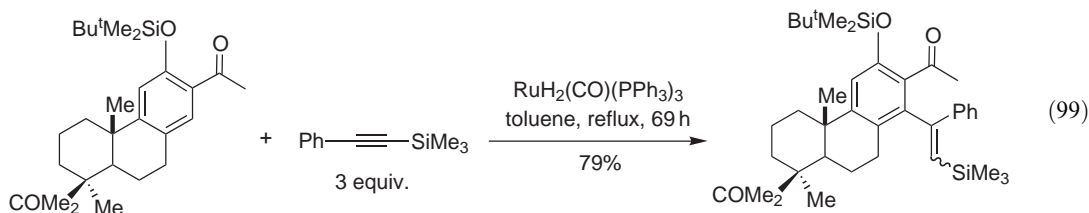
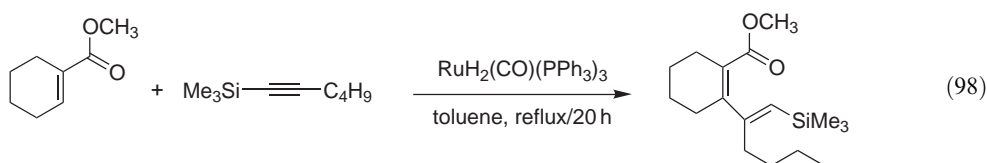
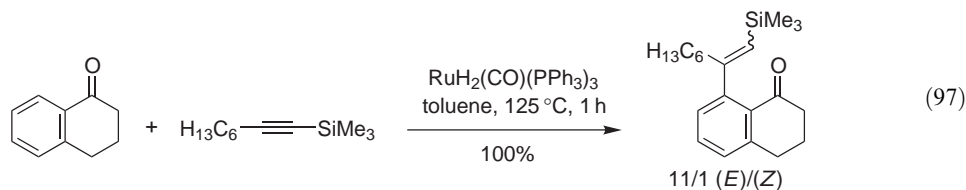


Other ruthenium cationic complexes $[CpRu(N=CCH_3)_3]^+PF_6^-$ catalyze coupling of silylalkynes with alkenes to give geometrically specific vinylsilanes (Equation (96)) <2000OL1761>.

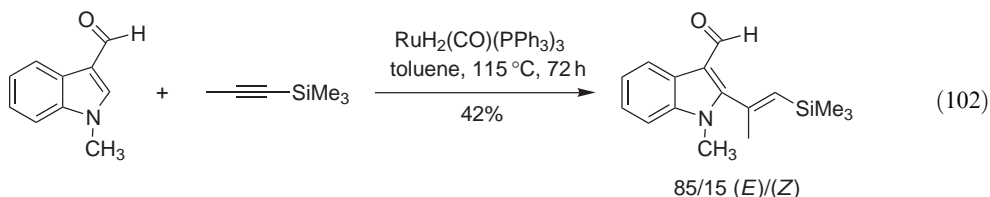
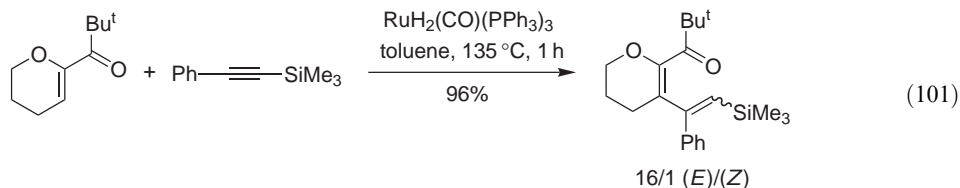
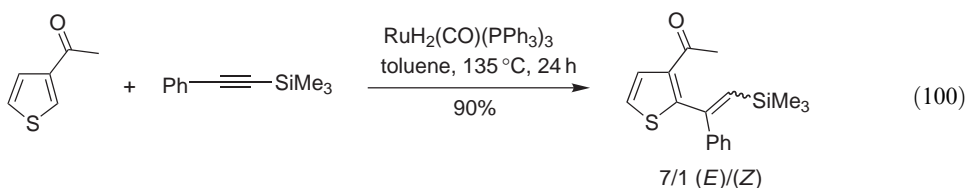


Alkyne	Alkene	Product	Yield (%)
$\text{CH}_3\text{OCH}_2\text{C}\equiv\text{C-SiMePh}_2$			71
$\text{CH}_3\text{OCH}_2\text{C}\equiv\text{C-SiMe}_3$			85
$\text{TsHN-CH}_2\text{CH}_2\text{C}\equiv\text{C-SiMe}_3$			78

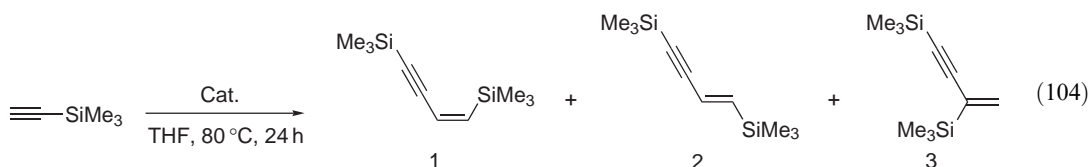
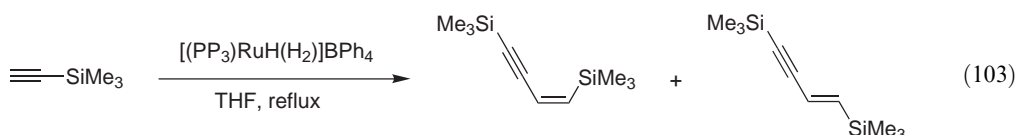
Coupling of substituted aromatic and olefinic reagents with silylalkynes. *Ortho*-vinylation of various aromatic ketones with alkynylsilanes catalyzed by $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ proceeds regioselectively with preference for the (*E*) configuration (Equations (97) and (98)) <1995CL681, 1999JOM(589)168>. Many aromatic ketones have been tested in this reaction, e.g., (Equation (99)) <1995JA5371, 1999JOM(589)168, 2001CL386>.



Heteroaromatic ketones (Equation (100)) <1995CL681> and enones (Equation (101)) <2002JOC(182-183)511> with activated alkene C—H bonds have also been found to undergo coupling with 1-phenyl-2-silylacetylene. $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ is also a catalyst for the reaction of aldehydes with 1-(trimethylsilyl)-1-propyne (Equation (102)) <2001CL386>.

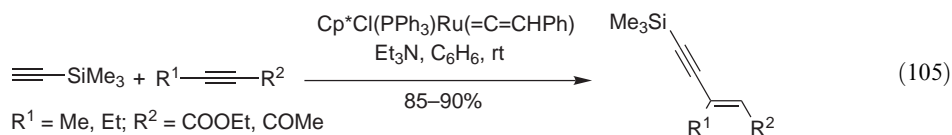


Dimerization of trimethylsilylthyne. Dimerization of terminal acetylenes is a convenient route to an unsaturated C₄ chain. This process has recently been reviewed [<1999ACR311>](#). Dimerization of trimethylsilylacetylene proceeds in the presence of [Ru(PP₃)H(H₂)]BPh₄ or [Ru(PP₃)H(N₂)]BPh₄ [PP₃ = P(CH₂CH₂PPh₂)₃] (Equation (103)) [<1991JA5453>](#). Different stereo- and regioselectivity was observed when Cp^{*}RuH₃L [L = PPh₃, PCy₃, PMe₃] or CpRuCl(PPh₃)₂ were used as catalysts (Equation (104)) [<1996OM3968, 1996OM5275>](#).

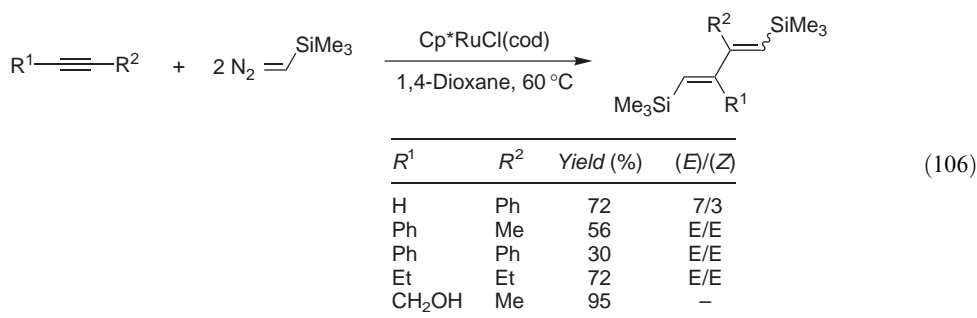


Cat.	Yield 1 + 2 + 3 (%)	
	(conversion)	(1)/(2)/(3)
Cp [*] RuH ₃ (PPh ₃)	100	2/98 (no 3)
Cp [*] RuH ₃ (PCy ₃)	58	1/19 (no 3)
Cp [*] RuH ₃ (PMe ₃)	83	1/3/6
TpRuCl(PPh ₃) ₂	(94)	82/-/15 (no 2)

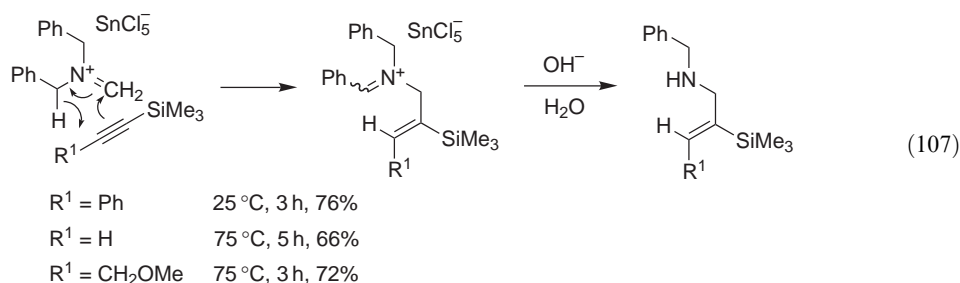
Silylacetylenes have been reported to undergo cross-coupling with internal alkynes (Equation (105)) [<1998JOC3158>](#).



Double addition of trimethylsilyldiazomethane to alkynes. Synthesis of substituted 1,4-bis(trimethylsilyl)buta-1,3-dienes has been achieved via the reaction of terminal or internal alkynes with TMSCH=N₂ (Equation (106)) [<2000JA7400>](#).

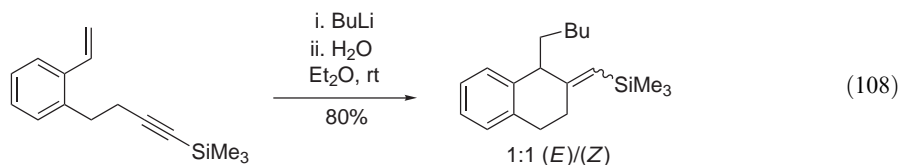


Hydroaminomethylation of silylalkynes. Silylalkynes can be stereoselectively aminomethylated using an iminium salt (Equation (107)) <2003SI1790>.

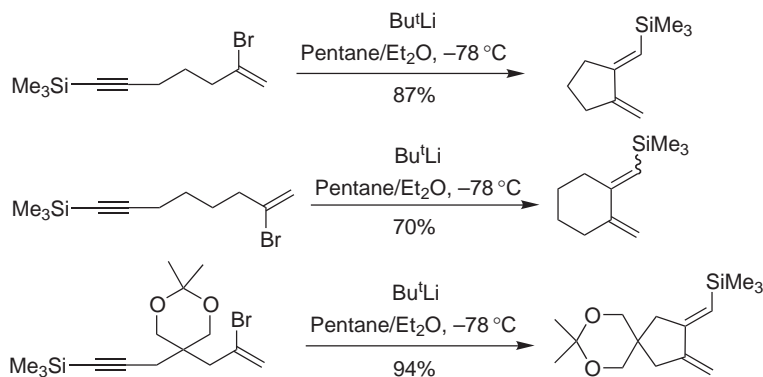


(v) Carbometallation of alkynylsilanes

Carbolithiation. Organolithium addition to a styrene derivative followed by 6-*exo*-cyclization leads to a 1,2-disubstituted product (Equation (108)) <1997TL6467>.

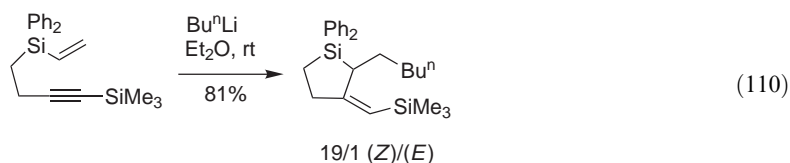
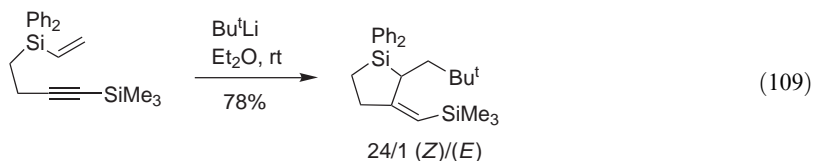


Acetylenic vinylolithiums, can be generated from the corresponding acetylenic vinyl bromide by low-temperature lithium–bromine exchange, cyclize on warming to give isomerically pure conjugated bis-exocyclic 1,3-dienes in good yield (Scheme 15) <1996JOC8216>.

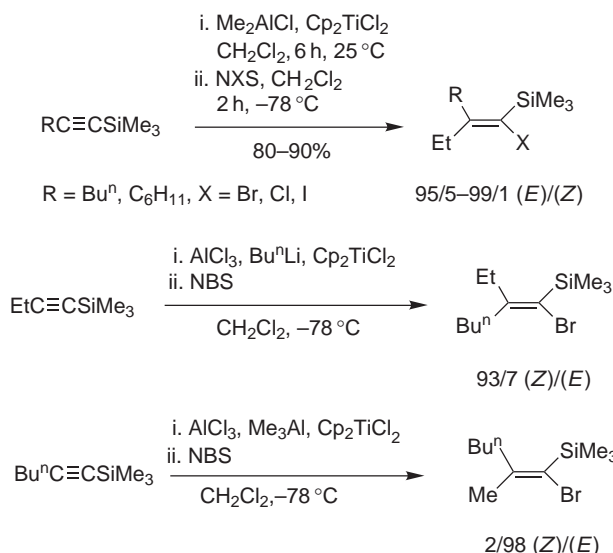


Scheme 15

The same authors report that tandem intermolecular–intramolecular organolithium methodology can also be utilized to convert vinylsilanes into silacyclopentenenes via a 5-*exo*-cyclization process (Equations (109) and (110)) <2003TL7143>.

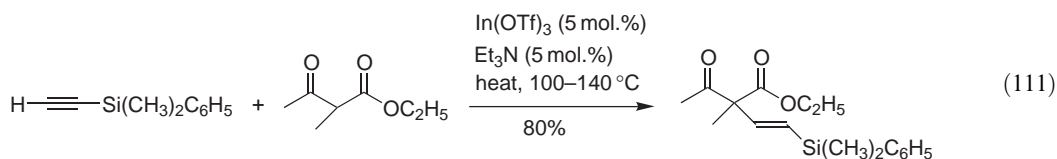


Carboalumination. 1-Halo-1-(trimethylsilyl)-2,2-dialkyl alkenes can be prepared in good yield and with high stereoselectivity by carbometallation of alkenylsilanes using dialkylaluminum chlorides–titanocene dichloride followed by carbon–metal bond cleavage by *N*-halo-succinimides (Scheme 16) <1995COFGT(2)899, 2001MI67>.

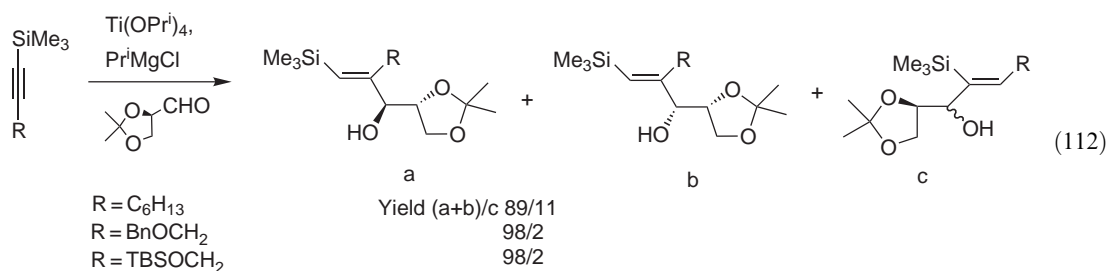


Scheme 16

Carbometallation using indium and titanium compounds. Addition of stoichiometric amounts of β -dicarbonyl reagents to terminal silylalkynes in the presence of catalytic amounts of $\text{In}(\text{OTf})_3$ gives the desired functionalized vinylsilanes with perfect regioselectivity and good yield (Equation (111)) <2003JA13002>.

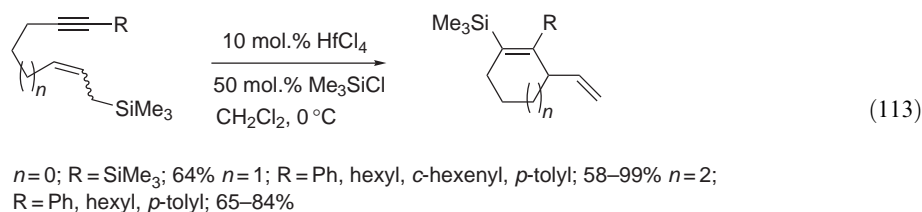


Alkyne–titanium complexes $(\eta^2\text{-alkyne})\text{Ti}(\text{OPr}^i)_2$, readily prepared by the treatment of an alkynylsilane with $\text{Ti}(\text{OPr}^i)_4$ and Pr^iMgCl , react with 2,3-*O*-isopropylidene-glyceraldehyde to afford functionalized vinylsilanes with good diastereoselectivities (Equation (112)) <1997TL4619>.



(vi) *Intramolecular carbosilylation of silylalkynes, silylalkenyne and silyldiynes*

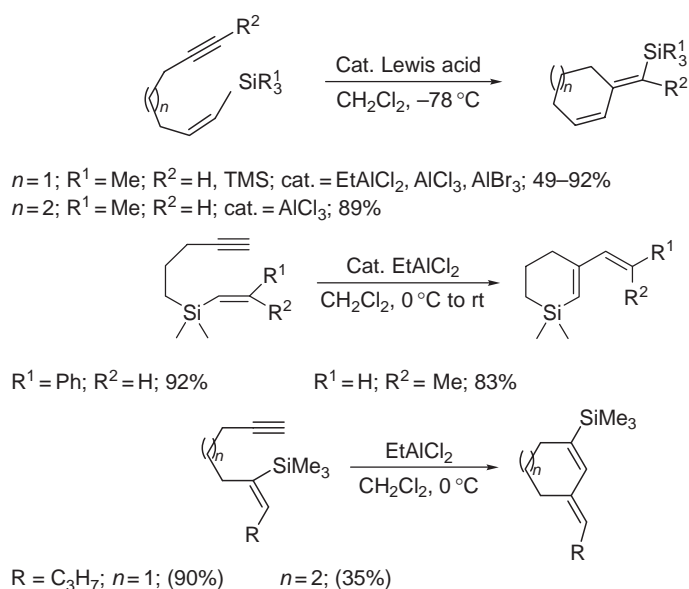
Intramolecular allylsilylation of unactivated alkynes proceeds exclusively in the *endo*-fashion to give five-, six-, and seven-membered carbocycles in moderate-to-high yields (Equation (113)) <1998JA5339>.



(vii) *Intramolecular silylformylation*

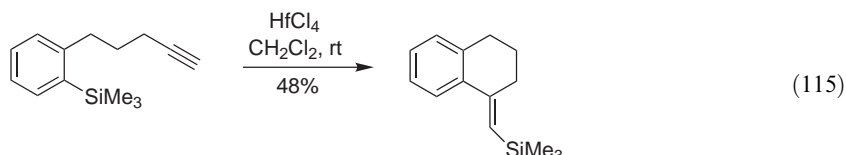
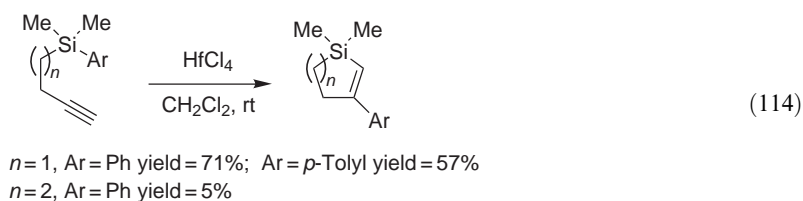
Regioselective intramolecular silylformylation has been reported by Ojima, Matsuda and Salvadori for silyl- and siloxyalkynes <1995JA4419, 1995JA6797, 1999OM5103, 1999JOC9711>.

Intramolecular carbosilylation of silylalkenyne. Intramolecular vinylsilylation reaction using carbon-tethered alkynylvinyl silanes and catalyzed by Lewis acids, such as EtAlCl₂ and AlCl₃, yields six- or seven-membered cyclic (*E*)-dienylsilanes in high yield (Scheme 17) <1999JA3797, 2001JA10899>.

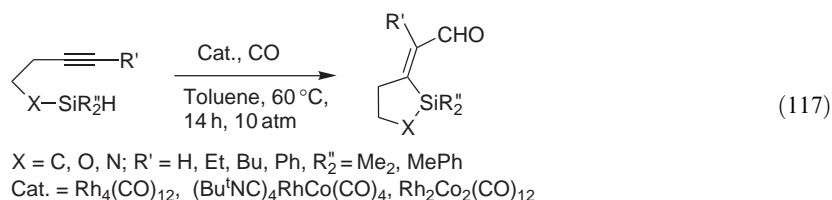
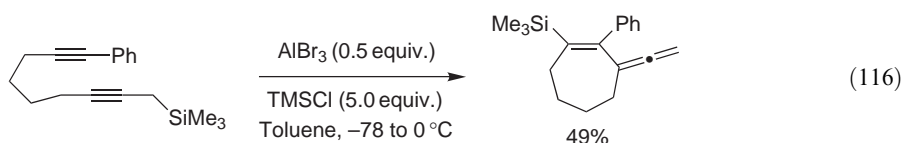


Scheme 17

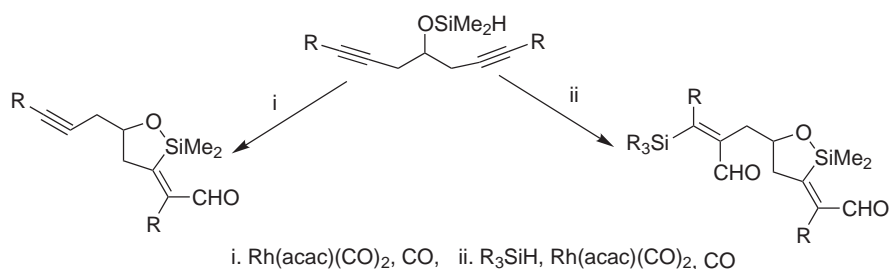
Intramolecular carbosilylation of silylalkynes. Hafnium tetrachloride is an effective catalyst for highly stereoselective *anti*-arylsilylation of C-tethered alkynylaryl silanes giving cyclic (*E*)-vinylsilanes in moderate to good yield (Equations (114) and (115)) <2001JA10899>.



Intramolecular carbosilylation of silyldiynes. The AlBr_3 -catalyzed intramolecular cyclocarbosilylation of silyldiynes gives the silylated cyclic vinylallenes, which can be useful as synthetic building blocks (Equations (116) and (117)) <2000TL4499>.



Ojima has also reported that desymmetrization of dimethylsilyloxyalkadiynes by Rh-catalyzed intramolecular silylformylation affords 5-*exo*-(formylmethylene)-oxasilacyclopentanes in high yield. Novel sequential double silylformylation also provides desymmetrisation, giving 3-(3-silyl-2-formylpro-2-enyl)-5-*oxo*-(formylmethylene)-oxasilacyclopentanes (Scheme 18) <2001OL1303>.



Scheme 18

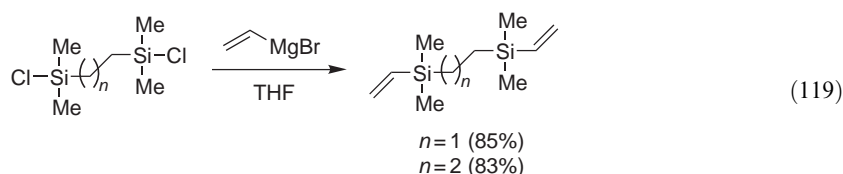
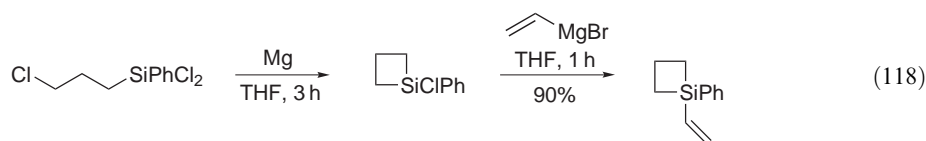
2.18.2.1.3 Vinylsilanes from alkenyl metal and silicon reagents

Silylation of alkenyl metals, mostly with chlorotrisubstituted silanes (e.g., TMS), seems to be the preferred method for synthesis of vinylsilanes. Preliminary alkenyl metal compounds can be prepared *in situ* from either vinyl halides (via halogen–metal exchange) or alkenes (via hydrogen–metal exchange).

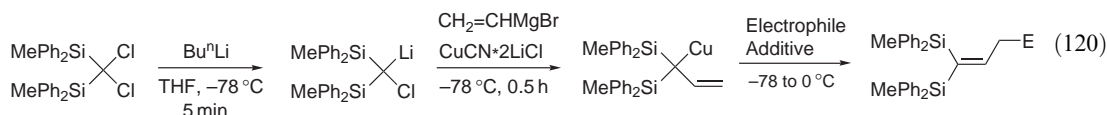
(i) Alkenyl metals via halogen-metal exchange

Vinyl halides are one of the most common starting materials. Metal-halogen exchange followed by silylation using mainly chlorotrisubstituted silanes can provide the vinylsilanes in good-to-high yield <B-2002MI685, B-2002MI713, 2003ACA75>.

Reaction of vinylmagnesium bromide with chlorosilanes readily provides the vinylsilyl product. Although this method of synthesis is straightforward and often efficient it is limited by substrate compatibility with organometallic reagent employed. Recent reports are focused on modification of this method to a one-pot reaction leading to synthesis of complex compounds with vinylsilicon functionality (Equations (118) and (119)) <1995BCJ250, 2003MM5545>.

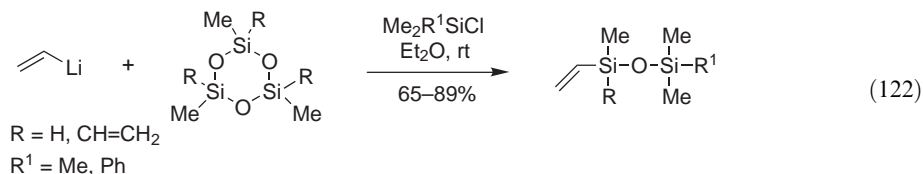
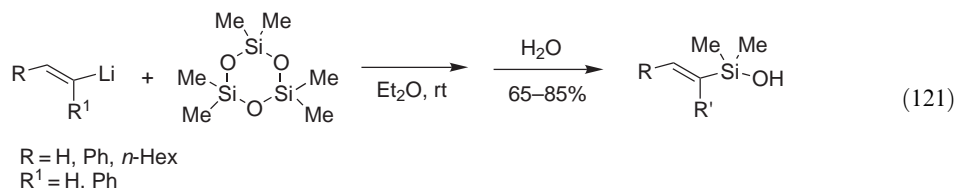


Treatment of vinyl Grignard reagents with chlorobis(silyl)methyl lithium and $\text{CuCN} \cdot 2\text{LiCl}$ affords the bis(silyl)-substituted allylic copper species, which can react with electrophiles to give a variety of 1,1-disilylalkenes (Equation (120)) <2002TL2399>.

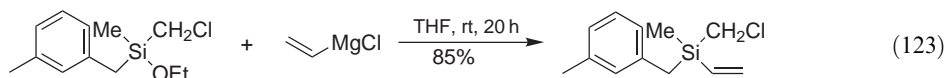


Electrophile	Additive	Product	Yield (%)
Mel			73
			86
PhCHO	TMSCl		69
PhC(O)Me			52

Direct formation of alkenylsilanols and vinylsiloxanes can be accomplished by addition of an organometallic reagent to a number of readily available and inexpensive cyclosiloxanes (Equations (121) and (122)) <1996CL517, 1998BCJ2409>.

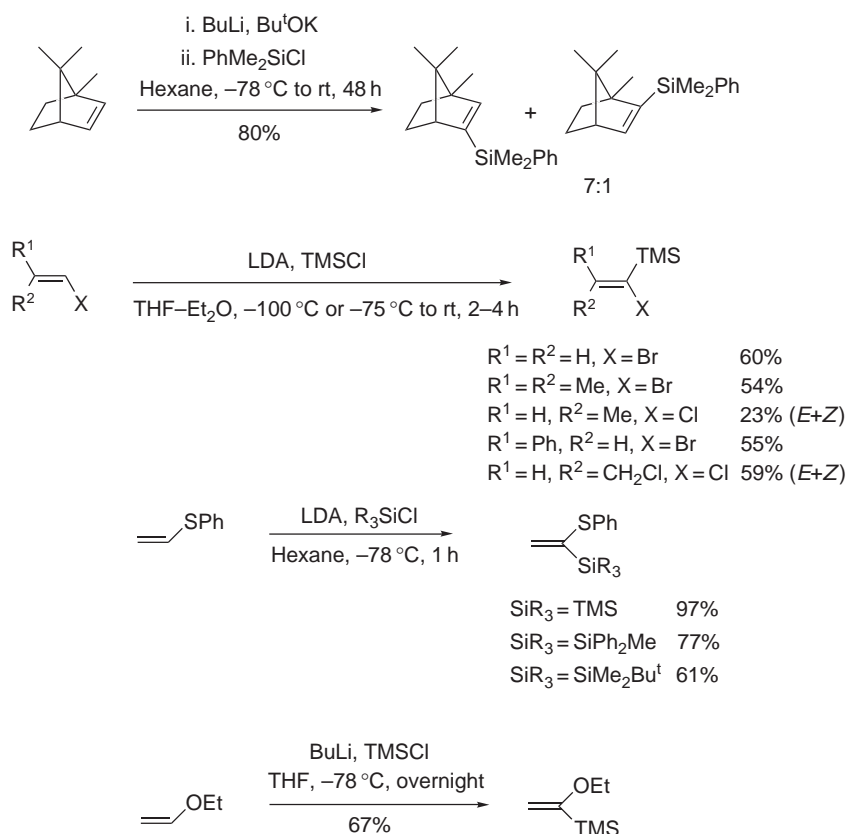


Alkoxysilanes are also good starting materials for the synthesis of vinylsilanes (Equation (123)) <2003OM4343>.



(ii) Alkenyl metals via hydrogen-metal exchange

A large variety of alkenes, cycloalkenes and vinyl heteroatom compounds (e.g., vinyl halides, sulfides, ethers, selenides, and tellurides) can be deprotonated by a strong base under suitable conditions resulting in the formation of alkenyl metals (predominantly lithium), silylation of which gives the desired products. Some representative reactions of preparative value have been reported previously (Scheme 19) <1995COFGT(2)899>.

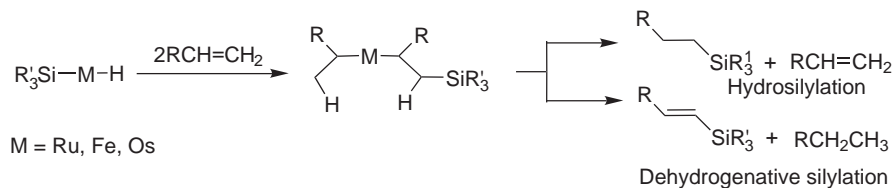


Scheme 19

2.18.2.1.4 Vinylsilanes from transition metal-catalyzed reactions of alkenes and silicon derivatives

(i) Dehydrogenative silylation of alkenes with hydrosilanes

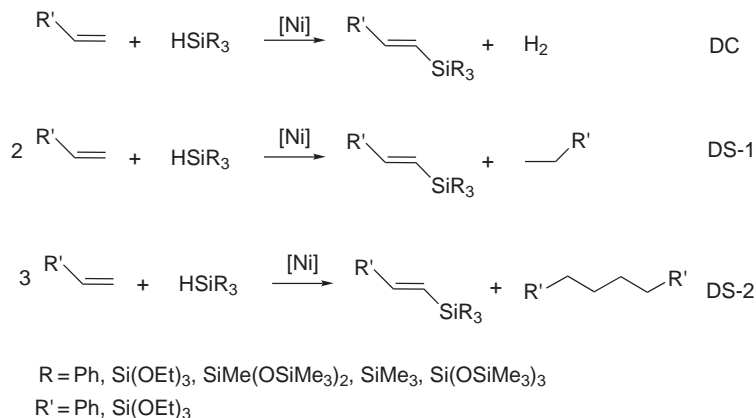
Many alkenes couple with hydrosilanes yielding unsaturated silyl compounds <B-1996MI487, 1997NJC815, B-2002MI491>. In contrast to platinum-catalyzed hydrosilylation, the complexes, particularly cationic of the iron (iron, ruthenium, osmium) and cobalt (cobalt, rhodium, iridium) triads, catalyze dehydrogenative silylation <1997NJC815, 2000MI527> of alkenes forming vinylsilanes, (Scheme 20) usually competitively with the hydrosilylation <1986JA3366, 1988AG(E)289, 1998JOM(128)345>.



Scheme 20

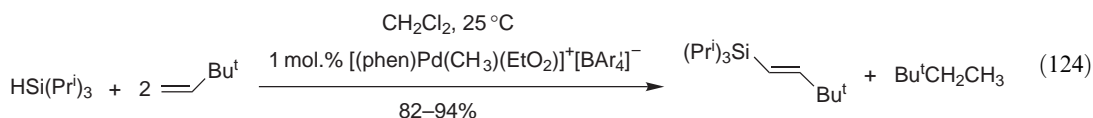
Dehydrogenative silylation has recently become a useful method for synthesis of vinylsilanes although its drawback is the formation of a mixture of products. The formation of vinylsilane is promoted by high alkene to silane ratios <1995OM1082>. $\text{Ru}_3(\text{CO})_{12}$ appears to be a very active catalyst for the dehydrogenative silylation of styrenes <1996JOM(506)339, 1997JOM(530)211, 1999CL1083>, trifluoropropene and pentafluorostyrene <1996CL109> by trialkyl- and phenyldialkylsilanes, and triethoxysilanes. The reactions are facilitated by the presence of electron-withdrawing substituents in the alkenes. Some reactions involving exclusive or highly selective formation of vinylsilanes, particularly in the presence of ruthenium, iron and rhodium complexes such as $\text{RuH}_2(\text{H}_2)_2(\text{PCy}_3)_2$, have also been reported <1995OM1082>.

In the presence of nickel complexes, the dehydrogenative silylation of vinylsilanes, styrene <1998JMO(135)223, 2000JOM(597)175> and other alkenes <1998JMO(135)223> proceeds via three steps, yielding products of direct dehydrogenation (DC), alkene hydrogenation (DS-1), and hydrogenated dimerization (DS-2) according to Scheme 21 <2000JOM(597)175>.



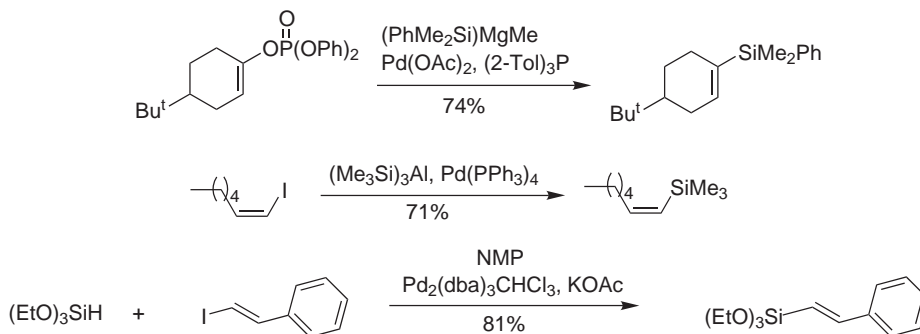
Scheme 21

Interesting variations and extensions of the dehydrogenative silylation have been reported, e.g., rhodium-catalyzed reaction of trisubstituted silanes with divinyl-diorganosilanes <1996BCJ1117>, platinum complex catalyzed dehydrogenative double silylation of dienes with bis(hydrosilane) compounds <1991OM16> and reaction of 1-alkenes with disilanes <1990CC563>. *t*-Butylethene with $\text{HSi}(\text{Pr}^i)_3$ in the presence of a cationic palladium complex yields vinyl-*t*-butyl silane (Equation (124)) <1997JA906>.



(ii) Palladium-catalyzed reactions

The coupling of vinyl halides or enol phosphates with silyl metal and hydrosilane compounds can also be performed in the presence of catalytic amounts of palladium complex (Scheme 22) <1988T4277, 1999TL9255>.

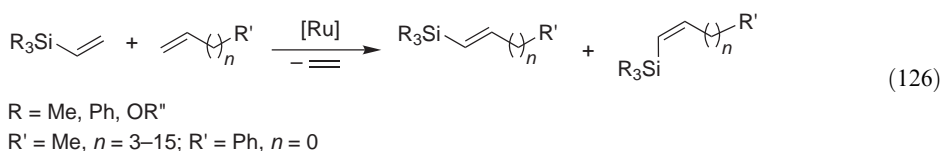
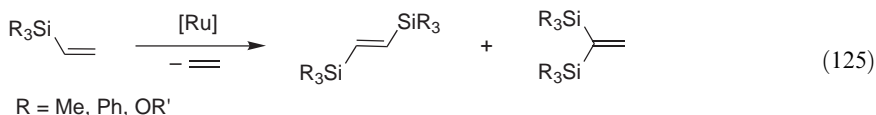


Scheme 22

2.18.2.1.5 Alkenylsilanes from vinylsilanes via catalytic methods

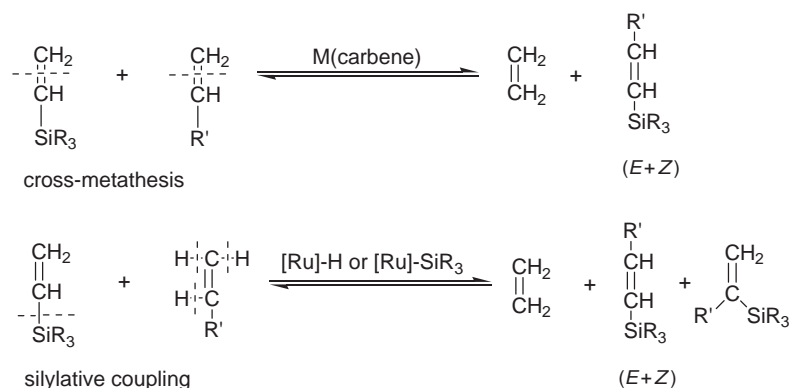
(i) Silylative coupling (trans-silylation) and cross-metathesis of alkenes with vinylsilanes

In 1984, the first effective example of metathesis (disproportionation) of vinyl-substituted silicon compounds catalyzed by Ru complexes was reported <1984JOM(266)C19>. It opened a new route of great synthetic importance and has allowed synthesis of a series of unsaturated silicon compounds with yields much higher than 70%. Numerous reports on vinylsilane disproportionations (Equation (125)) <1997NJC815, 1984JOM(266)C19, 1988JOM(46)329, 1989JOM(362)273, 1991JOM(412)C1, 1994JOM(474)83, 1994JMOC(90)213> and its co-disproportionation with alkenes (Equation (126)) <1988JMOC329, 1989JOM(376)15, 1991JMOC(65)113, 1992JMOC(76)307, 1993JOM(447)163, 1993MI539, 1994JMOC(90)213, 1997MI667> have been published.



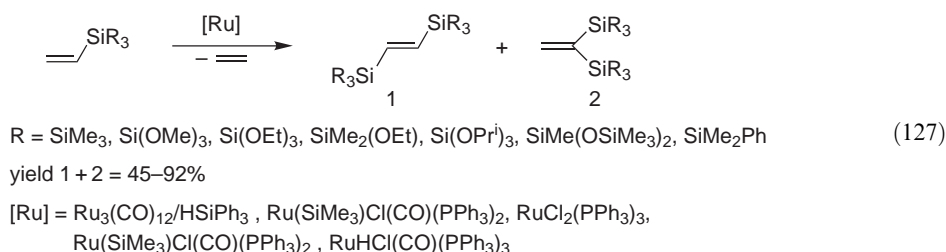
The following ruthenium complexes are active in this reaction: $\text{RuCl}_2(\text{PPh}_3)_3$, $\text{RuHCl}(\text{PPh}_3)_3$, $[\text{RuCl}_2(\text{CO})_3]_2$, $\text{Ru}_3(\text{CO})_{12}$, $[\text{RuCl}_2(\text{p-cymene})]_2$, $\text{RuCl}_3 \times n\text{H}_2\text{O}$ with HSiEt_3 , $\text{HSi}(\text{OEt})_3$, $\text{RhCl}(\text{PPh}_3)_3$, HSiPh_3 as well as LAH used as co-catalysts. However, at that time the results obtained did not permit a distinction between the reaction mechanism involving ruthenium-carbene intermediates, which are classical catalysts of the metathesis, and/or the non-metallacarbene mechanism. Evidence for the migratory insertion of ethylene <1991CC703> and vinylsilane <1995CC2003> into the Ru—Si bond yielding vinylsilane and two bis(silyl)ethene regioisomers

[(*E*)-1,2- and 1,1-bis(silyl)ethene] has now shown that in the reaction referred to as the “metathesis” of vinylsilanes and their “cross-metathesis” with alkenes, instead of C=C bond cleavage, formally characterizing alkene metathesis, a new type of alkene conversion occurs that is a silylative coupling of alkenes with vinylsilanes (Scheme 23) <2003MI691, B-2003MI463, B-2004MI197>.

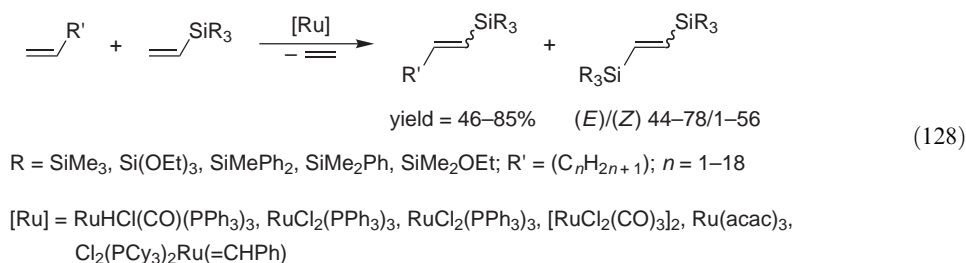


Scheme 23

Since vinyl derivatives of organosilicon compounds are completely inert to productive homo-metathesis, presumably due to steric hindrance of silyl groups, bis-silyl ethenes can only be produced by effective homo-coupling of vinyl trisubstituted silanes. The most synthetically effective results of the homocoupling of vinyl trisubstituted silanes are compiled in Equation (127) <1984JOM(266)C19, 1989JOM(369)117, 1991CC703, 1991JOM(412)C1, 1994JOM(474)83, 1994JMOC(90)213, 1995CC2003, 1997MI667, 1998JMOC(133)41>.



Synthetic and catalytic studies of the heterocoupling of 1-alkenes with vinylsilanes have led to the new methods for regioselective preparation of 1-silyl-1-alkenes. The most synthetically efficient data are compiled in Equation (128). Although well-defined or *in situ* initiated metallacarbenes are inactive in self-metathesis of vinyl-substituted silanes, high catalytic activity of Grubbs' catalyst in cross-metathesis of vinyltrialkoxysilanes and vinyltrisiloxysilanes with 1-alkenes (Equation (128)) <2000OM913> opens a new pathway for synthesis of substituted vinylsilanes <1991JOM(412)C1, 1991CC703, 1992JMOC(76)307, 1993MI539, 1993JOM(447)163, 2001TL1175>.



Finally, the two catalytic reactions occurring between the same parent substances, i.e., silylative coupling (also called *trans*-silylation, silyl group transfer) and cross-metathesis of functionalized (such as *para*-substituted styrenes, vinyl-, and allyl-substituted hetero(*O,N,S,B*)alkenes) with

vinyl-substituted silicon compounds (vinyl trisubstituted silanes, vinylsilsesquioxanes, vinylcyclsiloxanes, vinylcyclsilazanes, tris(dimethylvinylsilyl)benzene) have been used for the synthesis of well-defined molecular compounds with vinylsilicon functionality.

As a consequence, an efficient, stereo- and regioselective synthesis of silylstyrenes was observed when styrenes reacted with vinylsilanes in the presence of both ruthenium (or rhodium [2001OM3423](#)) and iridium ([2002OM3263](#)) complexes containing or generating the M-H bond and Grubbs' type carbene complex. In all cases (*E*-styrylsilanes and siloxanes were exclusively formed ([Equation \(129\)](#))). Cuprous salts (chloride, bromide) have recently been reported to be very successful co-catalyst of ruthenium phosphine complexes markedly increasing the rate and selectivities of all ruthenium phosphine complexes [1994JMOC\(90\)125](#), [1997OM4320](#), [2000NJC671](#), [2000OM1677](#), [2001TL1175](#), [2002JMOC\(190\)79](#), [2002PLP355875](#).


$$\text{SiR}_3 = \text{SiMe}_3, \text{SiMe}_2\text{OEt}, \text{SiMe}_2\text{Ph}, \text{Si}(\text{OMe})_3, \text{Si}(\text{OEt})_3$$

X = H, Cl, Br, Me, OMe yield = 56–100%

[Ru] = RuHCl(CO)(PPh₃)₃, RuHCl(CO)(PPh₃)₃/CuCl, RuHCl(CO)(PCy₃)₂/CuCl,

$$\text{RuCl}(\text{SiMe}_3)(\text{CO})(\text{PPh}_3)_2,$$
$$\text{RuCl}\{\text{Si}(\text{OEt})_3\}(\text{CO})(\text{PPh}_3)_2, \text{RuCl}(\text{SiMe}_2\text{Ph})(\text{CO})(\text{PPh}_3)_2,$$
$$\text{Cl}_2(\text{PCy}_3)_2\text{Ru}(=\text{CHPh}), \text{Cl}_2(\text{PCy}_3)(\text{IMesH}_2)\text{Ru}(=\text{CHPh})$$

A series of 1-silyl-2-*N*(*O*, *S*)-substituted ethenes (with preference to isolated (*E*)-isomers) and 1-silyl-1-*B*-substituted were synthesized in the presence of ruthenium complexes (Equation 130)) <2000OM1677, 2000NJC671, 2002JMOC(190)79, 2004MI1239, 2004TL4065, 2004TL6615, 2004JMOC0000>. The reaction opens a general synthetic route to 1-silyl-2-heteroatom-substituted ethenes. Compounds of this kind, e.g., β -alkoxy-substituted vinylsilanes, are difficult to synthesize by other transition metal-catalyzed reactions (Equation (130)) <1991CC703, 2000OM1677, 2002JMOC(190)79, 2003MI43, 2003MI51>.

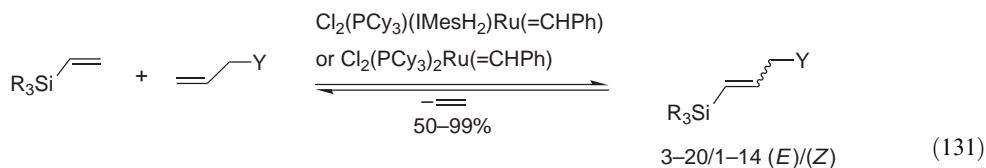


2-4/1-13 (E)/(Z)

$$\text{SiR}_3 = \text{SiMe}_3, \text{SiMe}_2\text{Ph}, \text{Si}(\text{OEt})_3, \text{SiMe}_2(\text{OEt})$$
$$R' = \text{OEt, OPr, OBu, OBu}^t, \text{OC}_6\text{H}_{11}, \text{SiMe}_3, \text{COOMe, NHCOH, Si(OEt)}_3, \zeta\text{-N} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \mid \\ \text{C} \end{array} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \mid \\ \text{C} \end{array}, \zeta\text{-B} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \mid \\ \text{C} \end{array} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \mid \\ \text{C} \end{array}, \zeta\text{-N} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \mid \\ \text{C} \end{array} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \mid \\ \text{C} \end{array}$$

[Ru] = RuHCl(CO)(PPh₃)₃, RuCl(SiMe₃)(CO)(PPh₃)₂, RuHCl(CO)(PCy₃)₂, RuCl₂(PPh₃)₃, Cl₂(PCy₃)₂Ru(=CHPh)

The cross-metathesis of vinylsilanes with alkenes and allyl-substituted heteroorganic compounds in the presence of Grubbs' catalysts gives alkenylsilanes and 1-silyl-3-*N*(*O* or *S*)-substituted propenes, respectively, in moderate to very high yields (Equation (131)) <2001TL1175, 2002OM840, 2002JMOC(190)79, 2003TL7121, 2003MI43, 2003MI51>.

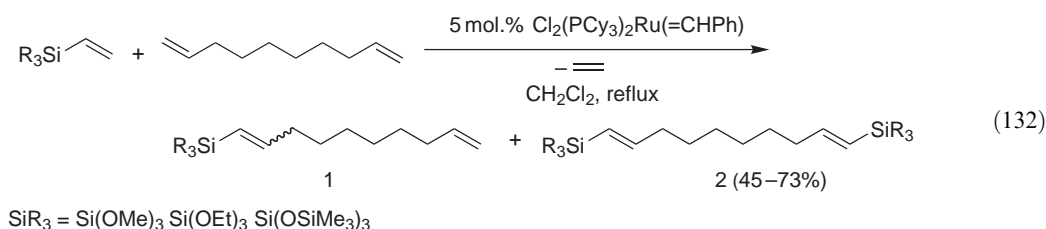


R = OMe, OEt, OSiMe₃, Cl, OCOMe

Y = C₃H₇, SiMe₃, Si(OEt)₃, OEt, OBu, OC₆H₁₁, OPh, OCH₂Ph, OSiMe₃, glycidyloxyl, OCOMe, OCOEt, OCOPr, NMePh, N(COMe)Ph, SCMe₃

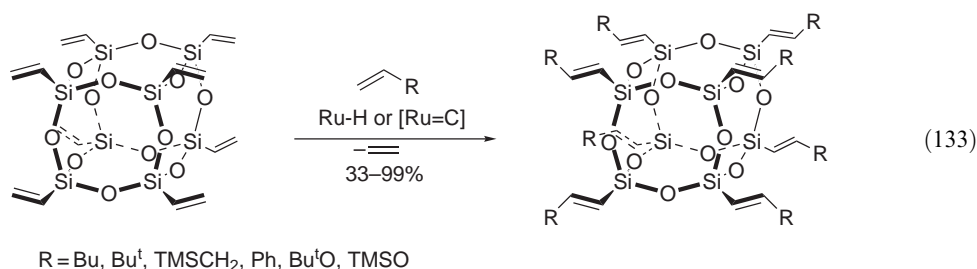
It is a general conclusion that while vinylsilanes undergo productive cross-metathesis (Mo and Ru carbenes) with allyl-substituted functionalized alkenes (exceptionally also vinyl-sulfide), their effective transformation with derivatives containing a functionalized group (with sulfide exception) attached directly to the C—C double bond, can be achieved via silylative coupling catalyzed by metal complexes containing (or generating) M—H and/or M—Si bonds (M = Ru, Rh, Ir).

Cross-metathesis of 1,9-decadiene with trialkoxy- and trisiloxy-substituted vinylsilanes in the presence of Grubbs' catalyst leads to the formation of bis(silyl)dienes with good to high yield (Equation (132)) <2002MI789>.

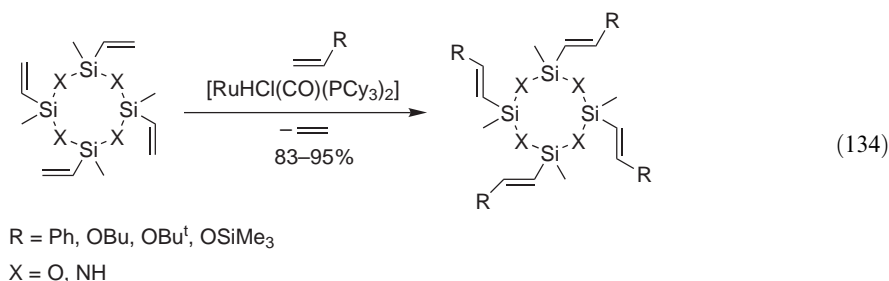


The two reactions discussed can also be used for functionalization of multi-vinylsilicon compounds. While well-defined tungsten alkylidene complexes were found not to convert metathetically vinyltrimethyl silane, the molybdenum complex was revealed to be a very effective catalyst in cross-metathesis of vinyl-substituted silsesquioxanes with a variety of alkenes (100% conversion and high yields of cross-metathesis products) <1997CC1185>.

A recent experiment on the application of Grubbs' catalyst to the cross-metathesis of octavinylsilsesquioxanes has successfully afforded the desired product with high yield and 100% stereoselectivity. Equation (133) shows the successful results of the silylative coupling and cross-metathesis of octavinylsilsesquioxane with alkenes and with vinyl- and allyl-substituted organic and organosilicon compounds <2004MI1239>.



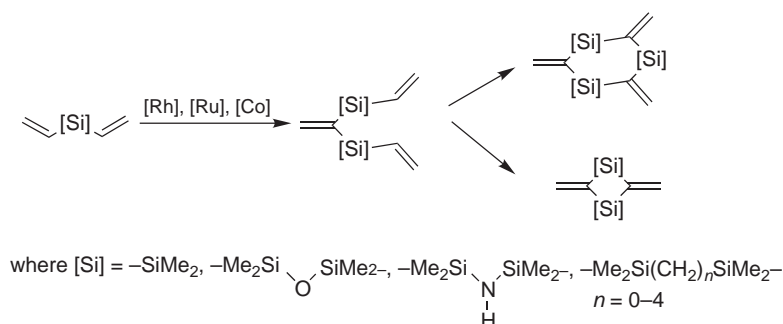
The reactions of vinylcyclosiloxanes and vinylcyclosilazanes with styrene have given the desired products and open a new route to functionalized monomers for ring-opening polymerization of cyclosiloxanes and cyclosilazanes (Equation (134)) <2003OM1835>.



The silylative coupling process can be used for the syntheses of other unsaturated organosilicon compounds. Novel organosilicon dendrimers with silicon-bridged-conjugated structures (with potential optoelectronic properties) have been synthesized by the respective reactions of trivinyl-substituted silane and (1,3,5-tris(dimethylvinylsilyl)benzene with conjugated dienes (1,4-divinylbenzene) <2003OM1835>.

(ii) Ring-closing metathesis (RCM) and ring-closing silylative coupling (RCSC) of silyldienes

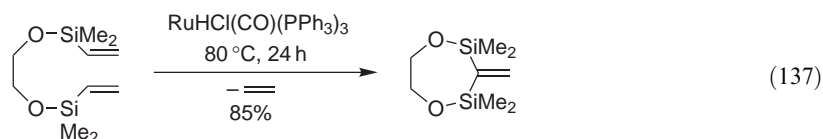
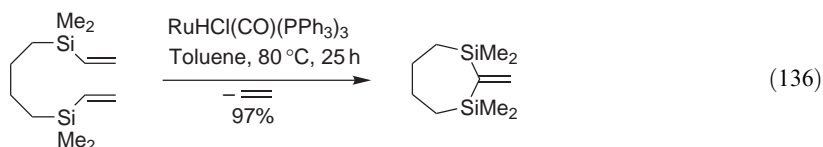
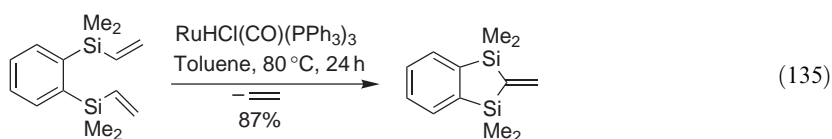
Silicon-containing dienes undergo two types of metathetical transformation [<2003MI691>](#): intramolecular ring-closing metathesis (RCM) leading to cyclic compounds and/or intermolecular acyclic diene metathesis (ADMET) polymerization to yield linear polyenes. Divinyl derivatives of organosilicon compounds are inert to RCM and ADMET polymerization [<1988JA1423>](#). However, divinylsilicon compounds undergo efficient silylative coupling condensation to yield a mixture of linear oligomers (mostly if ruthenium complexes are used as catalysts) and cyclic dimers and trimers (particularly if rhodium or some ruthenium complexes are used), the latter according to [Scheme 24](#).



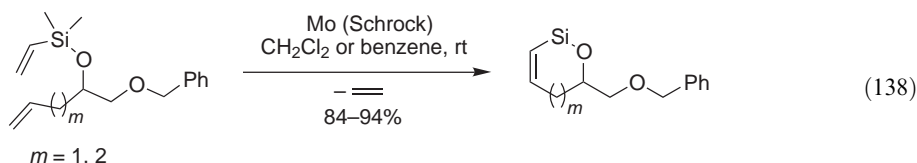
Scheme 24

Gem-dimeric products can be formed when the reaction is catalyzed by $[(\text{cod})\text{RhX}]_2$ ($\text{X} = \text{Cl}$, OSiMe_3) but the final intramolecular ring closure takes place to yield cyclotetrasiloxanes, cyclotetrasilazanes and cyclocarbosilanes in 20–25% yield [<1996JPS\(A\)1443, 1996MI115, 1999MI475, 1999OM3968, 2001MI137, 2003MM5545>](#).

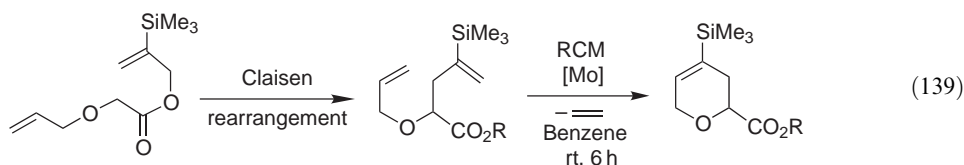
Intramolecular closure has also been reported to furnish cyclocarbosilanes with one *exo*-cyclic methylene group [<1998CC699>](#). It is worth emphasizing that contrary to the ring-closing diene metathesis, which has recently become a very common method of preparation of *endo*-cyclic organic (and heteroorganic) unsaturated compounds (for reviews, see [<B-1997MI006, B-1998MI007, B-2004MI197, 2000AG3140>](#)), the above mentioned ring closure provides a novel route for the preparation of organosilicon compounds containing *exo*-cyclic methylenes ([Equations \(135\)–\(137\)](#)). These compound can be a very useful intermediate for production of other organosilanes, e.g., 1,1-bis(silyl)ethenes, as well as the above mentioned exocyclic siloxane [<2004JOC0000>](#).



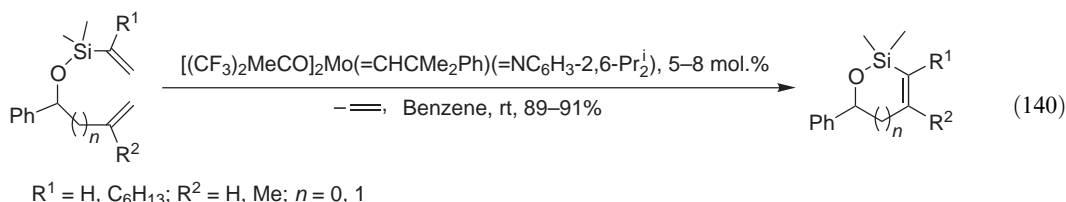
Acyclic vinyl silyl alkenyl ethers, particularly in the presence of molybdenum and ruthenium alkylidene catalysts, undergo cyclization to yield six- and seven-membered rings ([Equation \(138\)](#)).



Piscopio has reported a stereoselective synthesis of functionalized carbocyclic and heterocyclic compounds via tandem ester enolate Claisen rearrangement/ring-closing metathesis (RCM) [<1998JOC3158>](#). A large amount of catalyst (50 mol.%) was reported to be necessary for effective transformation ([Equation \(139\)](#)) [<2003MI691>](#).

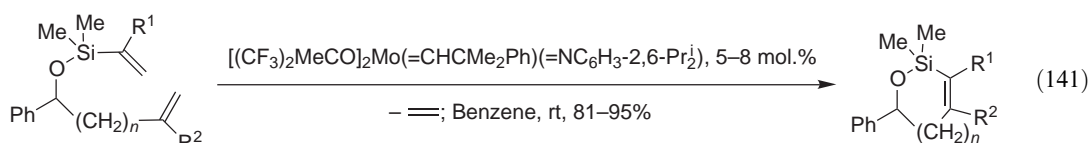


Effective ring-closing metathesis of a series of vinyl silyl alkenyl ethers in the presence of molybdenum carbene complex has been developed by Denmark ([Equation \(140\)](#)) [<2001OL1749>](#).



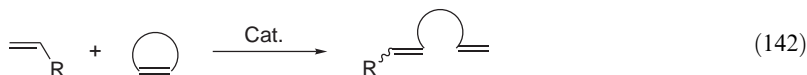
RCM has been applied to the preparation of a series of functionalized trimethylsilyl-substituted carbo- and heterocycles [<2002TL3513>](#).

Alkenyldimethylsilyl ethers of ω -unsaturated alcohols undergo facile ring closure using Schrock's catalyst to afford five-, six-, and seven-membered cycloalkenylsiloxanes bearing substituents on both carbon atoms ([Equation \(141\)](#)) [<1999T3219, 2001OL1749>](#).



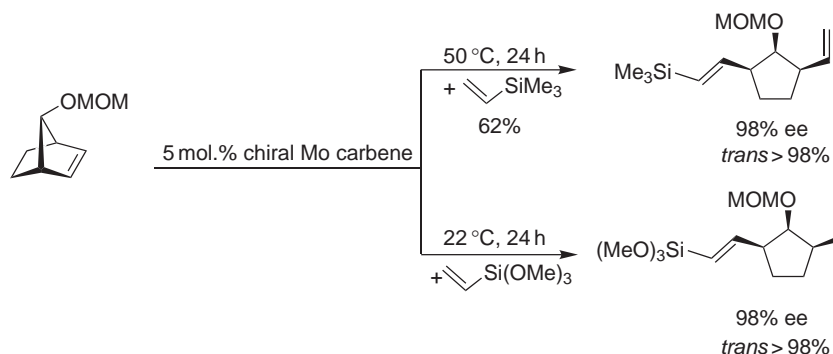
(iii) Tandem ring-opening metathesis/cross-metathesis

The term "ROM/CM" is used for the processes described by [Equation \(142\)](#).

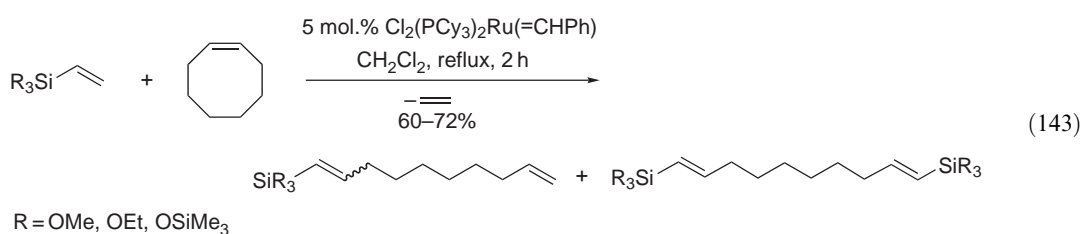


The reaction of a substituted norbornene with $\text{CH}_2=\text{CHSiMe}_3$ and $\text{CH}_2=\text{CHSi(OMe)}_3$ in the presence of a chiral molybdenum complex was reported recently [<1998SL169, 2001JA7767>](#). This reaction is an example of the complex catalytic asymmetric ring-opening metathesis/cross-metathesis performed by the groups of Hoveyda and Schrock. The method in general offers a valuable catalytic approach to optically pure materials that serve as building blocks for enantio-complex molecule synthesis ([Scheme 25](#)).

Cross-metathesis of cyclooctene with both trialkoxy- and trisiloxy-substituted vinylsilanes leads to the formation of mono- and bis(silyl)-substituted dienes [<2002MI789>](#). In the first stage of the process, linear mono(silyl)diene are formed and these subsequently undergo CM with vinylsilanes to form bis(silyl)derivatives ([Equation \(143\)](#)).

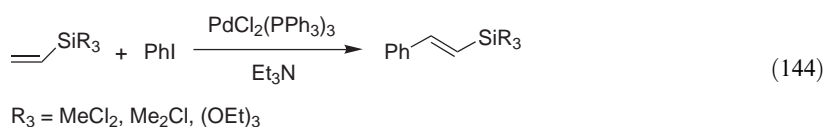


Scheme 25

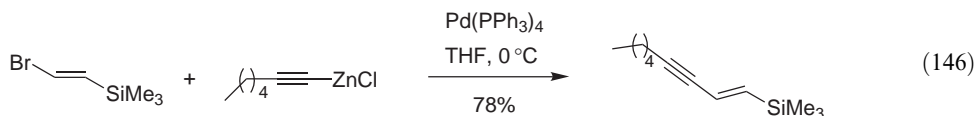
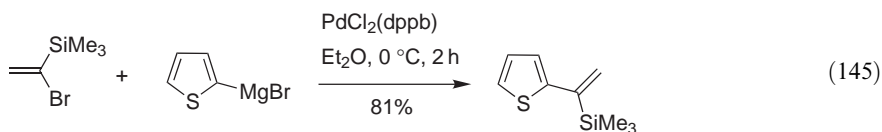


(iv) *Pd-catalyzed cross-coupling of vinylsilanes with organic halides*

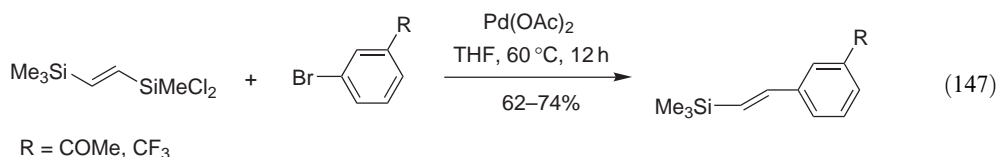
The palladium-catalyzed vinylation (Heck reaction) of trimethylvinyl silane with vinyl halides in the presence of silver salts furnishes 1-trimethylsilyl-1,3-dienes [<1986JOC5286, 1988JOC4909>](#). Treatment of iodobenzene with chloro(methyl)vinyl silanes or triethoxyvinyl silane gives β -substituted vinylsilanes in excellent yield (Equation (144)) [<1990CL2175>](#).



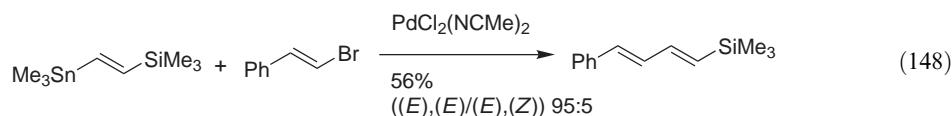
The coupling reactions of α - or β -halovinylsilanes with organic or organometallic species can be effectively applied to the synthesis of a variety of organo-substituted vinylsilanes (Equations (145) and (146)) [<1984TL83, 1989T5621>](#).



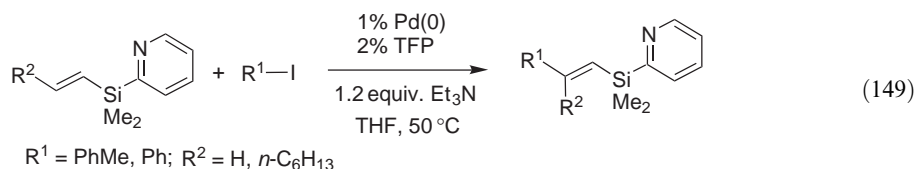
NaOH has been found to be extremely effective in promoting palladium-catalyzed cross-coupling reactions of alkenylchlorosilanes with organic halides under mild conditions giving vinylsilanes (Equation (147)) [<1997TL439>](#).



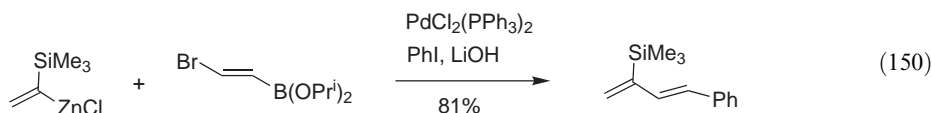
The coupling reactions of vinyl halides or vinyl triflates with organostannanes (Stille reaction) is one of the most effective method for new C—C bond formation. Silylstannylethene is a starting material for the synthesis of organo-substituted vinylsilanes (Equation (148)) <1984JA4630, 1987JA813>.



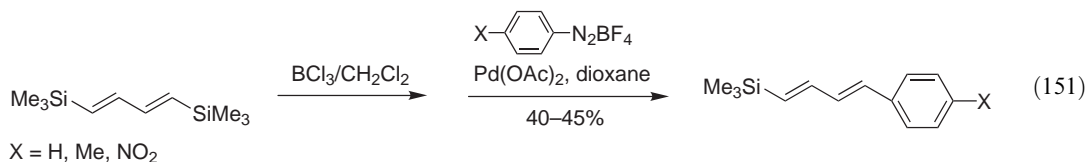
A new strategy for the carbopalladium cross-coupling across vinylsilanes was recently developed by exploiting the directing effect of pyridyl-substituted vinylsilanes, e.g., Equation (149) <2000JA12013>.



Suzuki–Miyaura cross-coupling can also be applied to vinylsilanes. The use of a bromovinylborane reagent together with a silylvinylzinc reagent and iodobenzene in the presence of a palladium catalyst provide a coupled diene in good yield (Equation (150)) <1988CL809>.

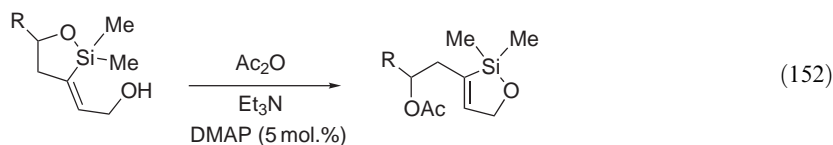


Another example of a Suzuki–Miyaura reaction is provided by the highly regio- and stereo-selective cross-coupling of vinylsilanes with arenediazonium tetrafluoroborates (Equation (151)) <2000JOC1554>.



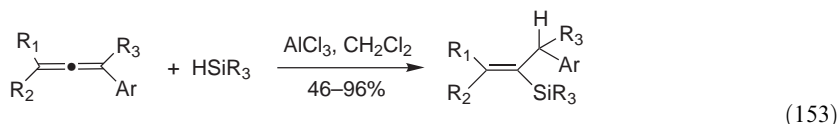
(v) Other reactions of vinylsilanes

Highly functionalized 3-*exo*-hydroxyethylene oxasilacyclopentanes undergo facile DMAP catalyzed skeletal rearrangement to 5-(2-acetoxyalkyl)-2-oxo-1-silacyclopentenes (Equation (152)) <2001OL2333>.



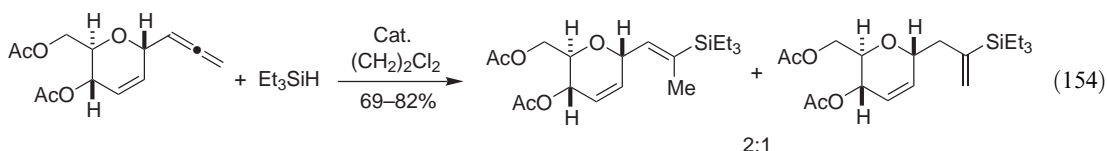
2.18.2.1.6 Vinylsilanes from allenes

Hydrosilylation. AlCl_3 catalyzed hydrosilylation of aromatic allenes produces alkenylsilanes with high regio- and stereoselectivities in moderate to high chemical yield. Not only simple monosubstituted allenes but also disubstituted and trisubstituted allenes undergo hydrosilylation providing a useful route for the synthesis of substituted vinylsilanes that are not available using other methods (Equation (153)) <1999JOC2494>.

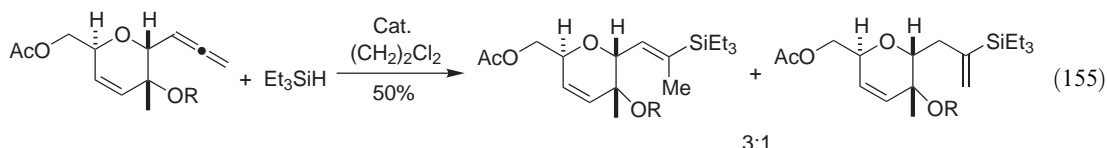


$\text{R}_1, \text{R}_2, \text{R}_3 = \text{H, Me}$
 $\text{Ar} = \text{Ph, } p\text{-Me-C}_6\text{H}_4, p\text{-F-C}_6\text{H}_4$
 $\text{SiR}_3 = \text{SiMe}_2\text{Et, SiMe}_3$

The hydrosilylation of sugar allenes catalyzed by $\text{Co}_2(\text{CO})_8$ and/or alkyne – $\text{Co}_2(\text{CO})_8$ complex provides vinylsilanes having the silyl group at a position away from the neighbouring C chain (Equations (154) and (155)) <2001T10241>.

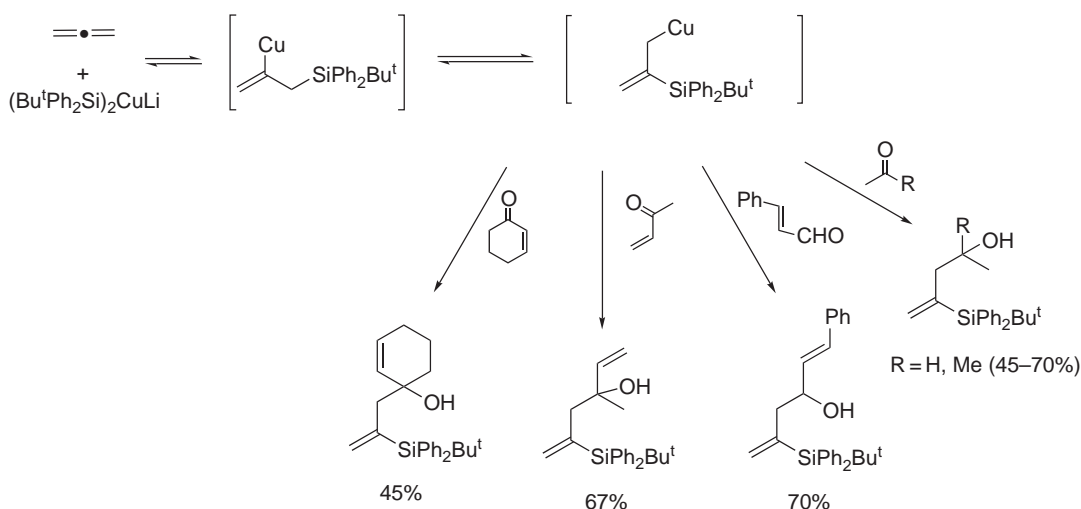


2:1



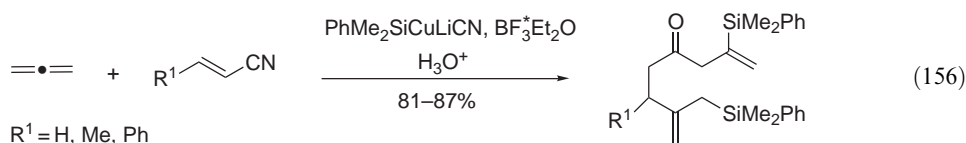
3:1

Silylcupration. Lithium bis-(*t*-butyldiphenylsilyl)cuprate reacts with an allene to give an organocopper intermediate which reacts with enone electrophiles to give functionalized vinylsilanes (Scheme 26) <2003T5855>.

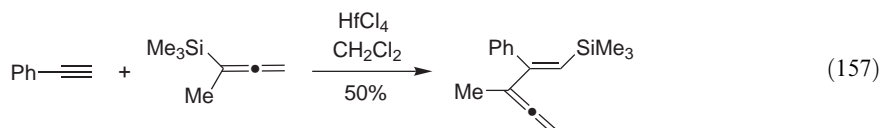


Scheme 26

Silylcupration of allene using phenyldimethylsilylcopper followed by BF_3 -mediated reaction with α,β -unsaturated nitriles affords vinylsilane containing carbonyl groups. The latter are formed by consecutive addition (1,2 and 1,4) of the vinylcopper intermediate formed in the silylcupration of the allene (Equation (156)) <2001CC1606>.

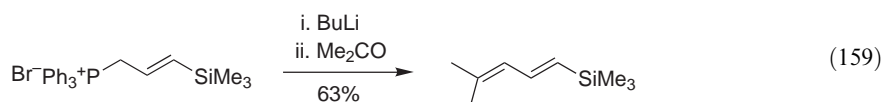
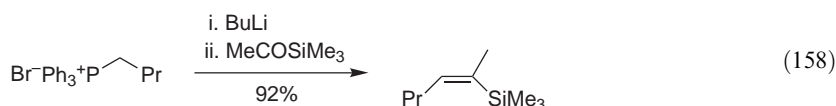


Carbosilylation. The HfCl_4 -catalyzed carbosilylation of phenylacetylene with allenyltrimethylsilane via γ -addition of the allenylsilane to the alkyne gives an allenylvinyl silane in moderate yield (Equation (157)) <2000TL4499>.

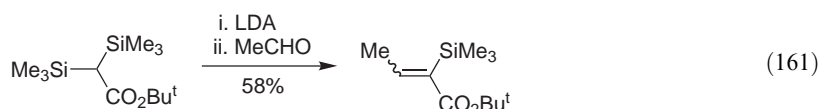
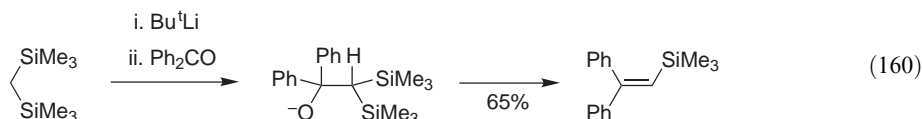


2.18.2.1.7 Vinylsilanes from carbonyl compounds

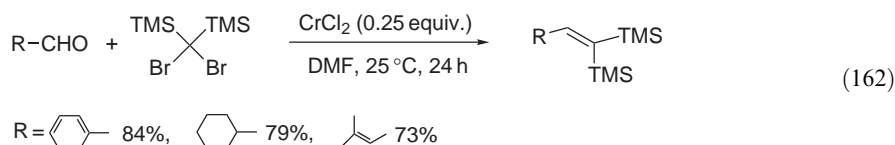
The reaction of nonstabilized ylides with acylsilanes in the presence of lithium salts and at low temperature gives products with moderate-to-good yield and with high (*Z*)-selectivity. The Wittig reactions of $\text{Ph}_3\text{P}=\text{CHCH}=\text{CHSiMe}_3$ with ketones affords the corresponding silylated dienes with good yield (Equations (158) and (159)) <1988TL2425>.



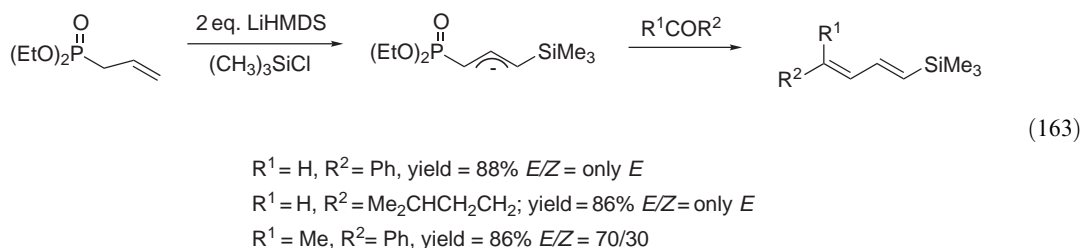
The silyl-Peterson elimination is a key reaction of metal salts of reagents containing at least two silyl groups with aldehydes and ketones. Aldehyde substrates react smoothly to produce vinylsilanes as a mixture of (*Z*)- and (*E*)-isomers. Yields are rather poor in the case of enolizable aldehydes and ketones must be nonenolizable to be of any use (Equations (160) and (161)) <B-2002MI713>.



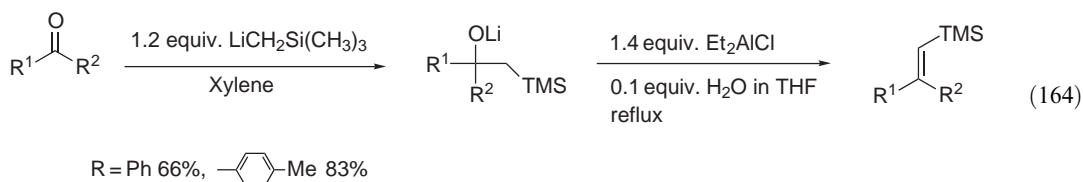
The synthesis of vinylbis(silanes) from aldehydes and dibromomethylenebis(trimethylsilane) occurs with high regio- and stereocontrol under mild conditions (Equation (162)) <1997JCS(P1)2279>.



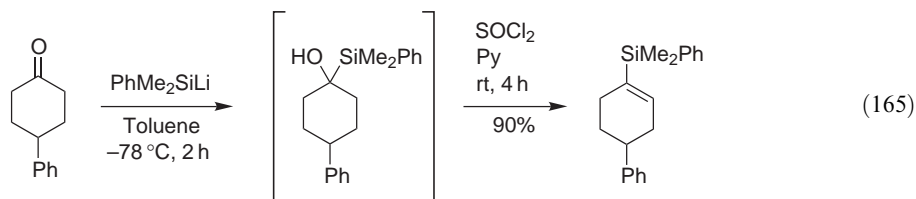
The reaction of allyl anions stabilized by heteroatoms at the α - and γ -positions is a well-known method of introducing various functional groups into the allylic position. Treatment of allylphosphonate with LiHMDS followed by successive addition of chlorotrimethylsilane and a carbonyl reagent affords dienylsilanes in good yield (Equation (163)) <2001TL2345>.



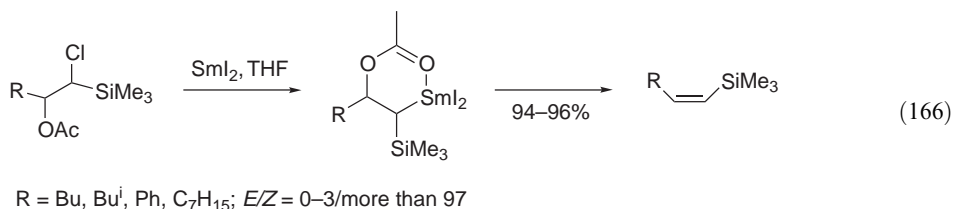
A variety of nonenolizable aromatic ketones can be converted to the corresponding vinylsilanes in a one-pot procedure involving the addition of (trimethylsilylmethyl)lithium to aromatic ketones followed by addition of diethylaluminum chloride and water (0.1 equiv.). Halide and alkoxide substituents are unaffected and this *trans*-stereoselective reaction affords vinylsilanes in good yield (Equation (164)) <2002TL8765, 2001TL1411>.



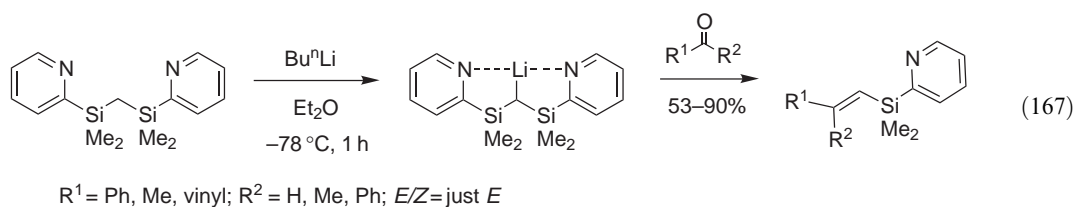
The conversion of ketones into α -silylated alcohols and subsequent dehydration gives vinylsilanes (Equation (165)) <1997TL2381>.



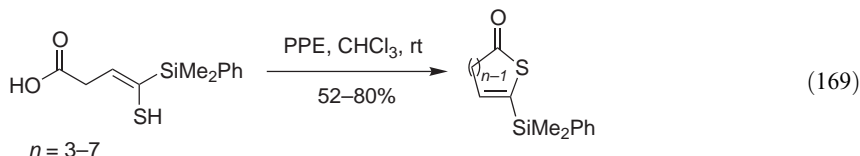
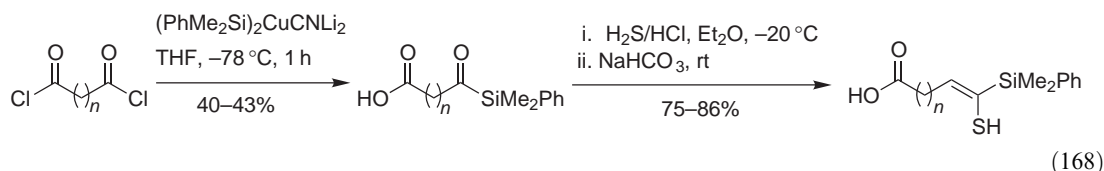
The preparation of (*Z*)-vinylsilanes with high stereoselectivity can be achieved by treatment of readily available *O*-acetyl-1-chloro-1-trimethylsilylalkan-2-ols with SmI_2 (Equation (166)) <2001OL937>.



The reaction of $(2\text{-PyMe}_2\text{SiCH})_2\text{Li}$ with a variety of aldehydes and ketones gives the corresponding vinylsilanes in extremely high yield and with stereoselectivity. The starting material can be easily prepared by the reaction of $2\text{-PyMe}_2\text{SiCH}_2\text{Li}$ with $2\text{-PyMe}_2\text{SiH}$ followed by deprotonation (Equation (167)) <2000OL1299>.



A variety of commercially available acyl chlorides can be converted to the corresponding cyclic thiolactones containing vinylsilyl group in moderate yields via acylsilanes and (*Z*)- ω -carboxy- α -silylenethiols (Equations (168) and (169)) <1999SL486>.



2.18.2.2 Conjugated Dienyl- and Enynylsilanes

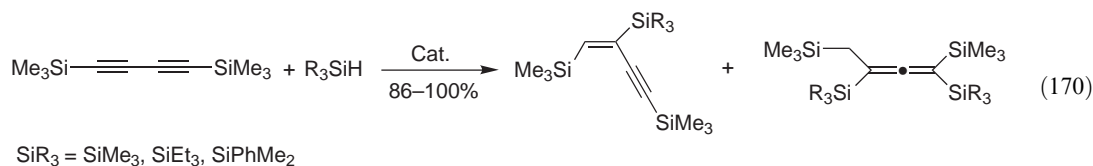
The syntheses of conjugated dienyl- and enynylsilanes have not been separated from those of alkenylsilanes.

2.18.2.3 Cumulenylsilanes

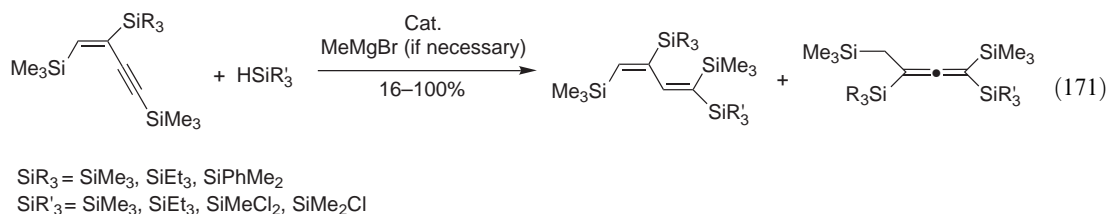
2.18.2.3.1 Allenylsilanes

(i) Hydrosilylation of alkenynes and alkadiynes

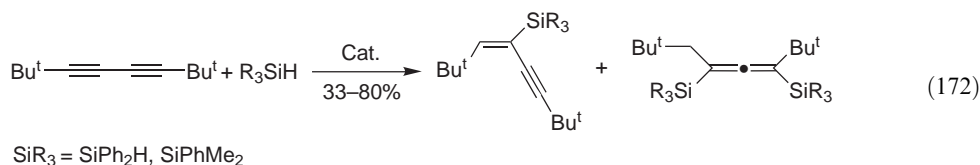
Kusumoto and Hiyama reported the first example of a hydrosilylation of 1,4-bis(silyl)-1,3-butadiyne catalyzed by H_2PtCl_6 , $\text{RhCl}(\text{PPh}_3)_3$ or $\text{Pt}(\text{PPh}_3)_4$ giving an enyne and an allene (Equation (170)) <1992BCJ1280>.

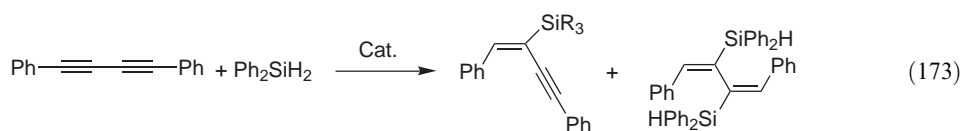


Silyl-substituted butenyne also react with hydrosilanes in the presence of platinum and rhodium catalysts to give silyllallenes (Equation (171)) <1992BCJ1280>.

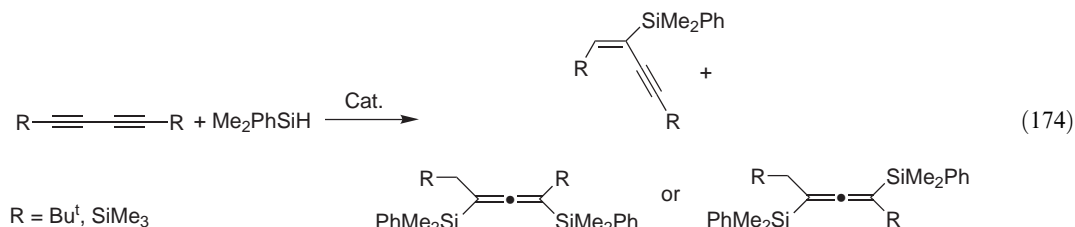


In the presence of achiral $\text{L}_2\text{Ni}(0)$ -butadiyne catalysts [$\text{L} = \text{Ph}_3\text{P}$, (*o*-tol-O) $_3\text{P}$] disubstituted butadiynes undergo stepwise reaction to give initially the 1,2-adducts. Depending on the butadiyne, either a 1,4-addition to the corresponding silyllallenes or a 3,4-addition to the 1,3-butadiene take place subsequently (Equations (172) and (173)) <1997JOM(532)117>.

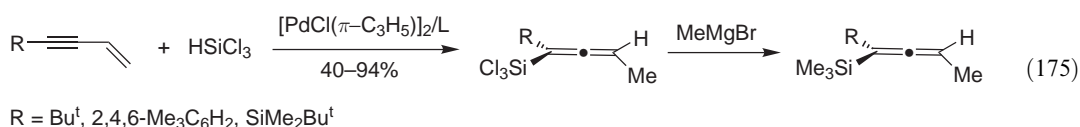




Chiral silyllallenes can be prepared by hydrosilylation of butadiynes catalyzed by Rh and Ni complexes containing chiral phosphine ligands: yields (Rh) 21–39% (ee $\leq 27\%$) and (Ni) up to 49% (ee 11%) (Equation (174)) <1999TL6567, 2000JOM(603)116>.

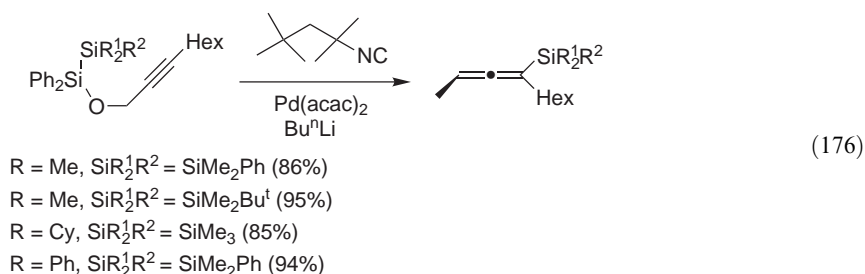


In a manner similar to 1,3-dienes, palladium complexes with chiral ligands catalyze regio- and enantioselective 1,4-addition to 1,3-enynes giving axially chiral allenylsilanes (Equation (175)) <2001JA12915>.

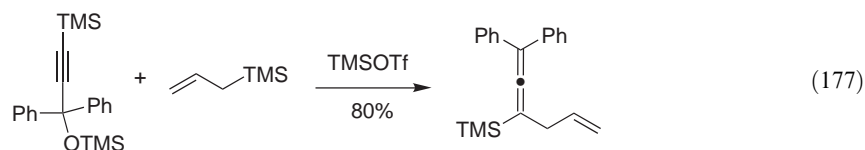


(ii) Miscellaneous methods

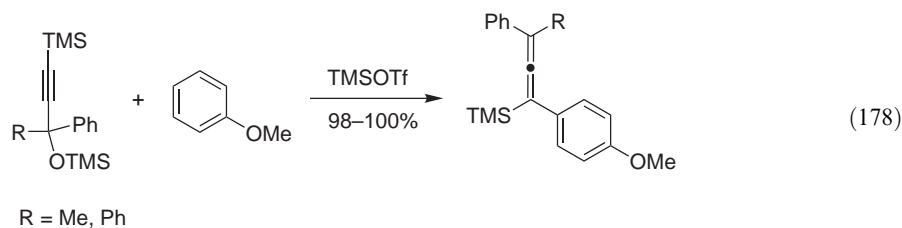
Catalytic reactions. The synthesis of highly enantio-enriched allenylsilanes via intramolecular bis-silylation of silyl-substituted propargylic alcohols in the presence of palladium *t*-alkyl isocyanide complex has been successfully achieved by Ito and coworkers (Equation (176)) <1996JOC4884, 1999JOM(576)300>.



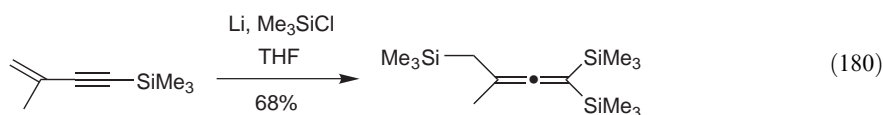
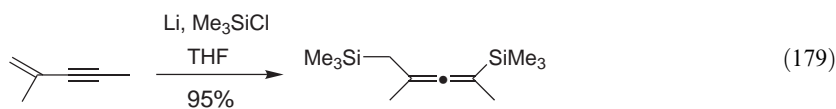
Alkenyl-substituted silyllallenes can be obtained using a coupling reaction of substituted propargyl silyl ethers with alkenyltrimethyl silanes catalyzed by trimethylsilyl trifluoromethanesulfonate (Equation (177)) <2001JOC4635>.



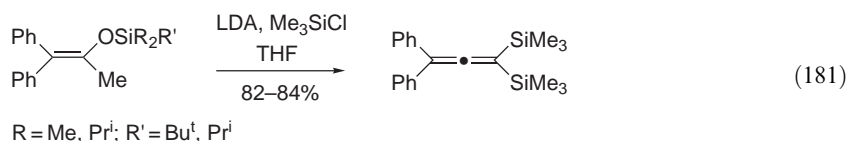
Stoichiometric reactions. Treatment of substituted propargyl silyl ethers, prepared from the corresponding propargylic tertiary alcohols, with trimethylsilyl trifluoromethanesulfonate in anisole leads exclusively to silyllallenylarenes (Equation (178)) <2001JOC4635>.



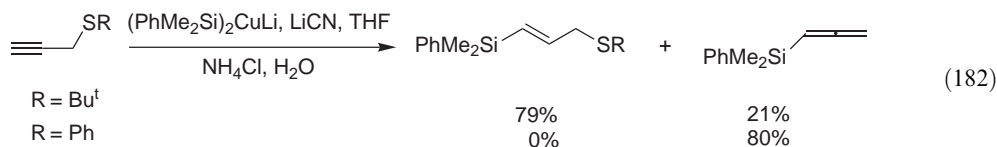
The addition of lithium and chlorosilane to 1,3-enynes affords an efficient route to 1,4-bis(silyl)-2,3-butadienes (Equations (179) and (180)) <1999TL5491>.



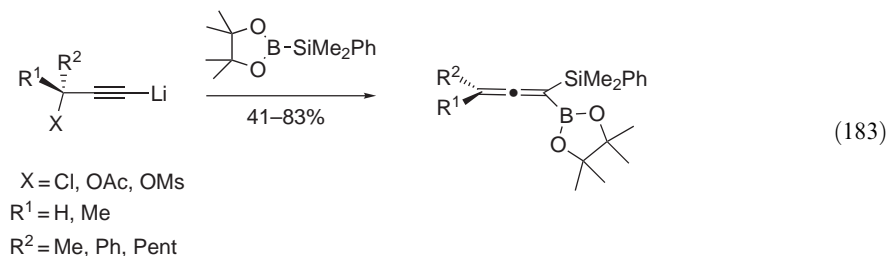
Lithiation of sterically hindered silyl enol ethers results in the formation of bis(silyl)-substituted allenes (Equation (181)) <2001MI573>.



Silylcupration of alkynyl sulfides leads to monosilyllallenes (Equation (182)) <1992SL981>.



1-Boryl-1-silyllallenes can be obtained via *gem*-silylborylation of substituted alkynyllithiums with silylpinacolborane (Equation (183)) <2003OL225>.



2.18.2.3.2 Cumulenylsilanes

Trimethylsilylacetylene can be catalytically dimerized by Ru(cod)(cot)/PR₃ (cod = 1,5-cyclooctadiene, cot = cyclooctatriene) to give either Me₃SiCH=C=C=CHSiMe₃ when PR₃ = PPh₃ or (*Z*)-Me₃SiCH=CH-C≡CSiMe₃ when PR₃ = PBu₃ⁿ, the latter being formed by stereoselective isomerization of initially formed (*Z*)-Me₃SiCH=C=C=CHSiMe₃ <1993BCJ987>.

2.18.2.3.3 Silyl ketenes

No further developments have taken place in this area since the publication of COFGT (1995) <1995COFGT(2)899>.

2.18.2.4 Arylsilanes

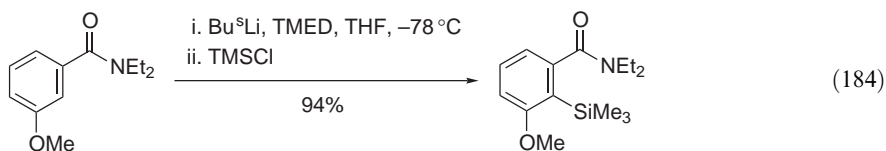
Arylsilanes are important compounds in organic synthesis <2003ACA75, B-1988MI008, B-2002MI685, 2000CRV3163>. Compared to alkenylsilanes, arylsilanes have similar physical and chemical properties and may be prepared by similar methods, i.e., via Wurtz–Fittig coupling of haloaryl compounds with chloro- and alkoxy-silanes, cycloaddition reaction or via TM-catalyzed coupling of aryl derivatives with silicon compounds. These methods of synthesis are both straightforward and efficient and can be performed on a large scale to provide useful quantities of arylsilicon compounds, such as heteroaryl- or arylsilanes containing organic functional groups on the aromatic ring.

2.18.2.4.1 By Wurtz–Fittig-type coupling

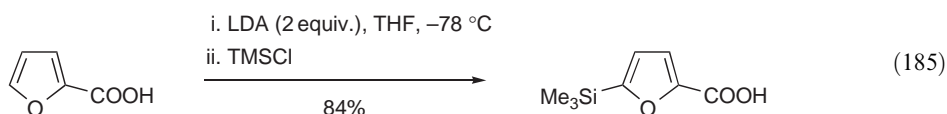
This topic has recently been reviewed <1995COFGT(2)899, B-2002MI685>. The Würtz–Fittig-type coupling <B-2002MI685> between an aryl halide, chlorosilane and metal (Li, Na or Mg) was the first method reported for the preparation of arylsilanes. For example, Ph_4Si was prepared by mixing chlorobenzene, tetrachlorosilane and sodium metal. Both aryl chlorides and bromides have been used extensively in this reaction and the most commonly employed metal is magnesium. However, successful examples using sodium have also appeared. For example magnesium metal was used for synthesis of 2-(trimethylsilyl)pyridine <B-2002MI685>, but the reaction with sodium appeared to be more efficient for synthesis of trimethyl(2-tolyl)silane (86% yield). A useful variant of this method is reaction with magnesium using HMPTA as the solvent <1995COFGT(2)899, B-2002MI685>. This reaction has been studied in detail and is very general. Aryl chlorides, bromides and iodides can be used along with heteroaromatic systems such as pyridines and thiophenes. In addition, hindered systems, which do not form Grignard reagents in high yield, react well under these conditions, e.g., 1-bromo-*t*-butylbenzene gives (2-*t*-butylphenyl)trimethyl silane in 58% yield.

2.18.2.4.2 By silylation of aryl metals

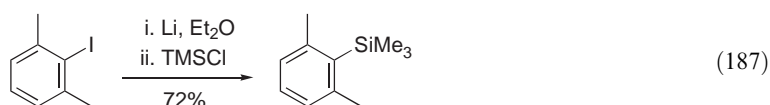
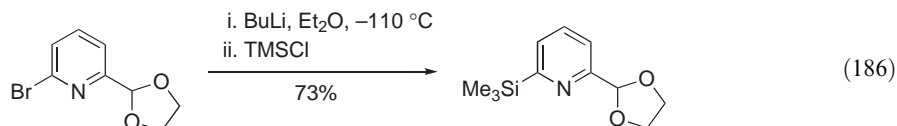
Aromatic rings with appropriate heteroatom-containing substituents can be *ortho*-metalated using organolithium reagents <1995OR1, 1996PAC618, 1996ACR552, B-2002MI685>. The resulting anion(s) can be treated with electrophiles, for example, with trisubstituted chlorosilanes. A vast array of groups can be used to direct *ortho*-metalation (e.g., amides, ethers, sulfides, sulfones, acetals, carbamates, urethanes, some alcohols and acids, and imines) and this method is probably the most versatile for the preparation of silyl-substituted aromatic systems (Equation (184)) <B-2002MI685>.



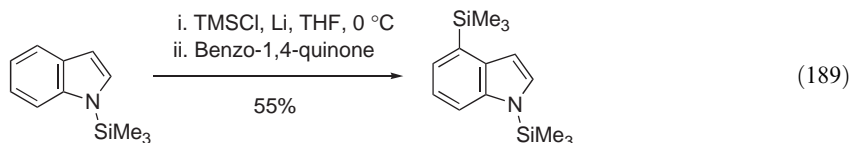
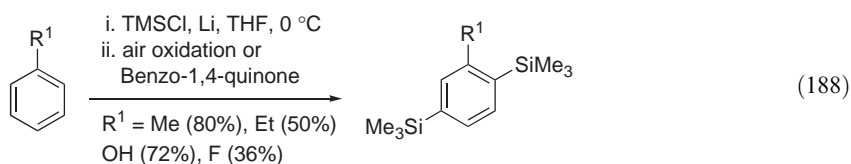
Some heteroaromatic systems, such as furans, thiophenes, pyrroles, indoles and pyrazoles, can be directly lithiated at the α -position without the need of an adjacent directing group. Treatment of these anions with chlorosilanes provides an expedient route to silyl-substituted heteroaromatic systems, e.g., 5-(trimethylsilyl)-2-furoic acid (Equation (185)) <1999CSR209, B-2002MI685>.



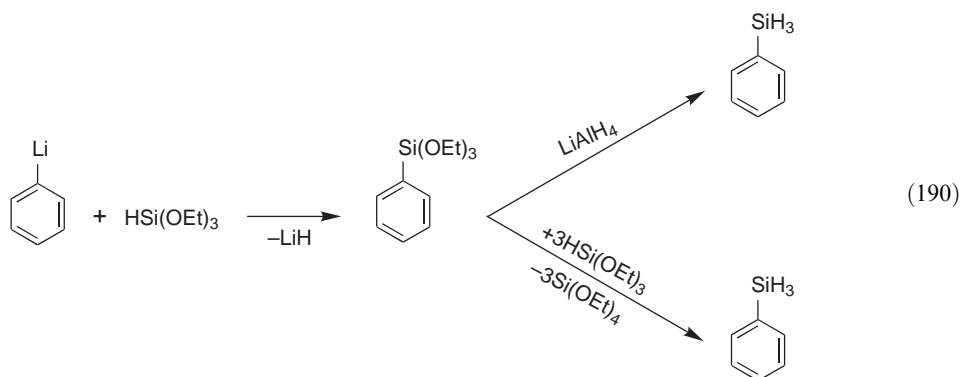
Another method for forming arylsilanes from aryl halides is to treat the aryl halide with either lithium metal or an organolithium reagent <B-2002MI685>. An aryl anion, the final product of halogen-metal exchange, is then treated with chlorosilane to provide the arylsilane. The reactivity of aryl halides toward lithium metal or organolithium reagents follows the order $I > Br > Cl > F$. Thus, most of these reactions start with aryl iodides or bromides. Most chlorides react very slowly (if at all) with lithium and most fluorides are inert. This relative reactivity allows selective exchange with compounds containing polyhalogenated aromatic systems. Examples of halogen-metal exchange in synthesis of arylsilanes are shown in Equations (186) and (187) <1991JCS(P1)501, B-2002MI685>.



A variety of 1,4-bis(trimethylsilyl)-2-substituted phenyl derivatives can be prepared via Birch reduction of a monosubstituted benzene ring followed by either air oxidation or stirring in the presence of *para*-benzoquinone (Equations (188) and (189)) <1962JA2843, 1980JCR(S)236, 1988JOC1815, 1990T8131>.

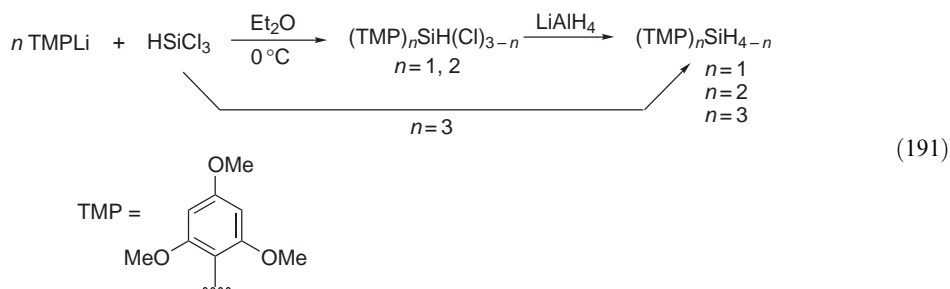


Tetra(alkoxy)silanes Si(OR)_4 [R = Me, Et] are also known to give aryltrialkoxysilanes in almost quantitative yield on treatment with an aryllithium reagent <1992JA6700, 1995CRV1431>. The intermediate Ar-Si(OEt)_3 can be converted into the silane Ar-SiH_3 by reduction with LAH. When tri(alkoxy)silanes HSi(OR)_3 were reacted with aryllithium reagents under similar conditions (4 h at 20°C), a complex mixture of products was observed [Si(OEt)_4 , PhSi(OEt)_3 , $\text{Ph}_2\text{Si(OEt)}_2$, Ph_3SiOEt and Ph_4Si] when equimolar quantities of HSi(OEt)_3 and PhLi were used (Equation (190)) <2002OM680>.

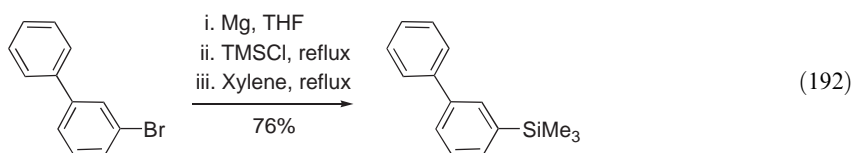


Similar observations were made in the related *in situ* Grignard reactions using bromobenzene, magnesium and HSi(OEt)_3 (in THF at reflux temperature). This reaction is much slower than the PhLi reaction and affords predominantly PhSi(OEt)_3 as the primary product.

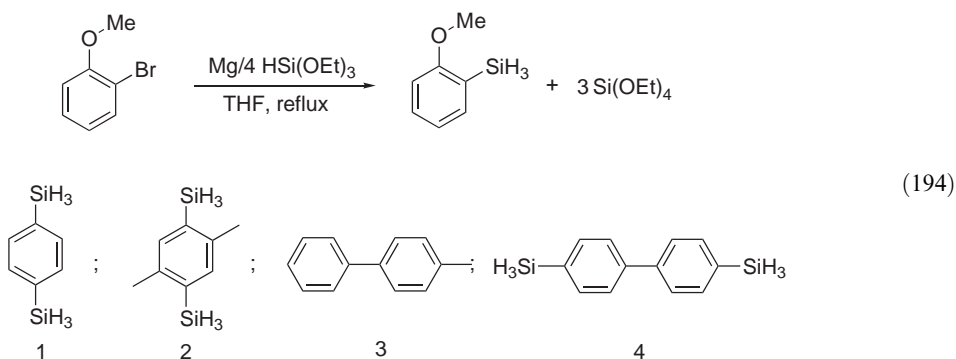
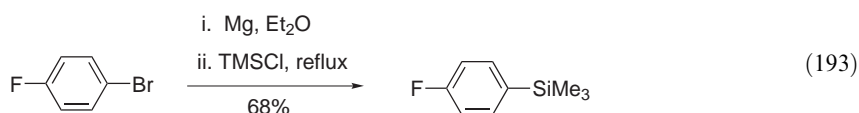
Another way to synthesize hydrogen-rich arylsilanes is direct metallation of 1,3,5-trimethoxybenzene with Bu^nLi (in THF or DME): reaction of the appropriate number of equivalents of TMPLi with HSiCl_3 in Et_2O provides the intermediate chlorosilanes. The mono- and diarylchlorosilanes are reduced by LAH to provide the desired hydrosilane (yield 45%) ([Equation \(191\)](#)) [<1999JOM\(588\)51>](#).



Many arylsilanes have been prepared by the stepwise preparation of a Grignard reagent from an appropriate aryl halide followed by addition of a chlorosilane, e.g., 3-(trimethylsilyl)biphenyl (Equation (192)) <B-2002MI685>.

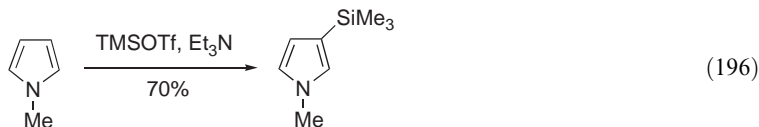
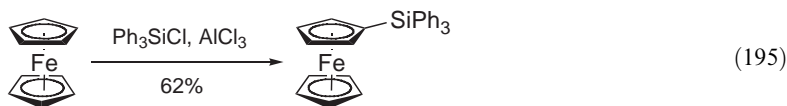


Cyanotrimethylsilane or ethoxytrimethylsilane have also been used instead of chlorosilane. Aryl chlorides, bromides and iodides have been employed using this procedure and the relative reactivity of different halides with magnesium has been used to selectively convert certain halides into trimethylsilyl groups (Equation (193)). The reaction of 2-bromoanisole with $\text{HSi}(\text{OEt})_3$ (4equiv.) and magnesium in THF (3 h) gives 2-silylanisole in 28% isolated yield (Equation (194)) <2002OM680>. The reaction sequence is applicable to other silylaryls but hydrogenation is incomplete. Therefore, LAH is used for additional reduction to give hydrosilane derivatives, e.g., 1–4 <2002OM680>.



2.18.2.4.3 By electrophilic and nucleophilic aromatic substitutions

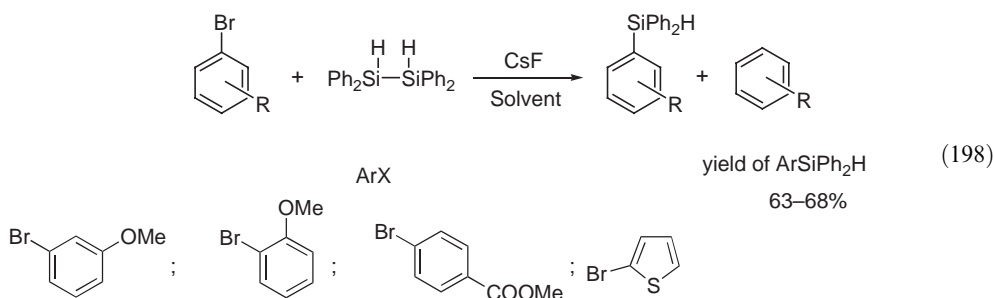
Highly active aromatic systems can be silylated via electrophilic aromatic substitution. For example, ferrocene [<1967JA5054>](#) and 1-methyl-1*H*-pyrrole have been silylated using chloro- and aminosilanes under Friedel-Crafts conditions (AlCl₃) ([Equations \(195\) and \(196\)](#)) [<1986T1299>](#).



The nucleophilic silylation of aryl halides is a known procedure for the preparation of aryl-trimethyl silanes [<1987TL4715, 1986TL2161>](#) and aryltriphenyl silanes [<1957JA1431>](#). The formation of the trimethylsilyl anion from hexamethyldisilane has been achieved *in situ* in the presence of aryl halides and reagents such as MeLi, MeONa, and MeOK ([Equation \(197\)](#)).

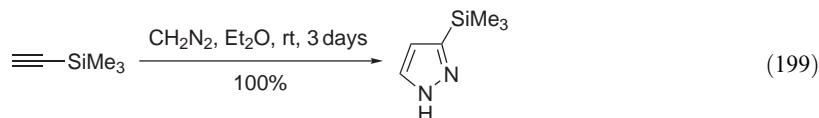


Lachance has found an efficient method for the preparation of aryldiphenyl silanes by cleavage of tetraphenyldisilane with CsF in polar aprotic solvents (HMPA, DMPU) ([Equation \(198\)](#)) [<1998TL171>](#).

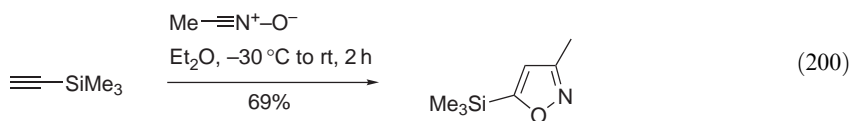


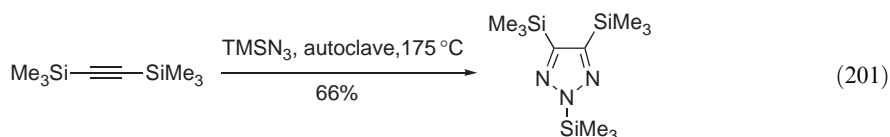
2.18.2.4.4 By cycloaddition reactions

Cycloaddition reactions can also be used as a method for synthesis of arylsilanes, especially heteroarylsilanes. Many silyl-substituted heterocycles have been prepared via [2+3]-dipolar cycloaddition. For example, 3-(trimethylsilyl)-1*H*-pyrazole and a variety of silyl-substituted 1*H*-pyrazoles have been prepared by reaction of diazocompounds with silylacetylenes ([Equation \(199\)](#)) [<1995COFGT\(2\)899, B-2002MI685>](#).

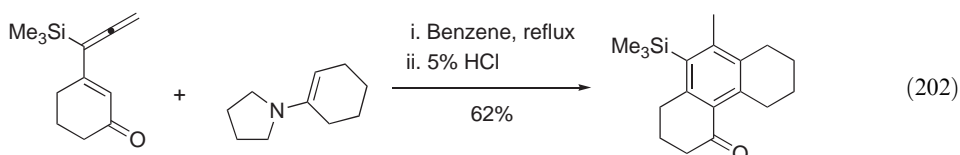


3-Methyl-5-(trimethylsilyl)isoxazole has been prepared by reaction between alkyne and acetonitrile oxide ([Equation \(200\)](#)) [<B-2002MI685>](#) and in a similar manner 3-methyl-4,5-bis(trimethylsilyl)isoxazole was obtained [<B-2002MI685>](#). Tris(trimethylsilyl)triazole has been prepared by cycloaddition between azidotrimethylsilane and an alkyne ([Equation \(201\)](#)) [<B-2002MI685>](#).

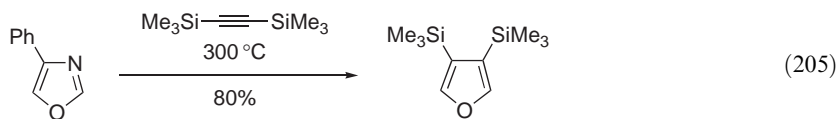
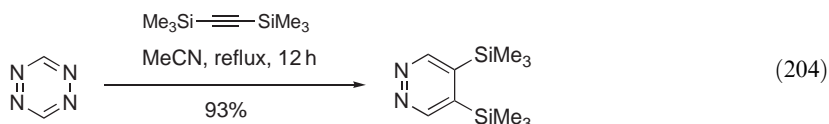
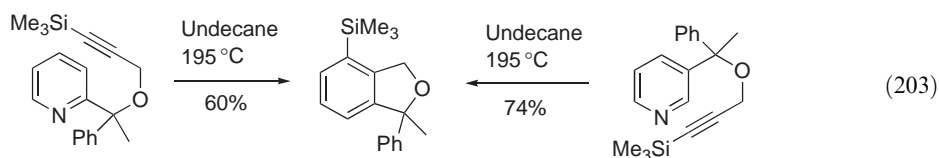




Some aryl- and heteroarylsilanes have been synthesized using a Diels–Alder cycloaddition followed by aromatization of the resulting cyclohexene, or by using a Diels–Alder/retro-Diels–Alder sequence [<1995COFGT\(2\)899, B-2002MI685>](#). When a silyallene was heated with an enamine and the [4 + 2]-cycloadduct treated with 5% HCl an arylsilane was obtained ([Equation \(202\)](#)) [<1989TL1311>](#).

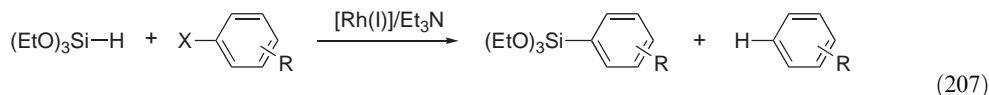
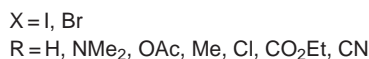
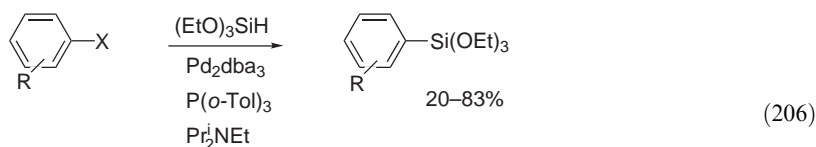


Many examples in the literature show the application of a tandem Diels–Alder/retro-Diels–Alder sequence to synthesis of arylsilanes, e.g., reactions of substituted pyridines at high temperature form arylsilanes in good yield ([Equation \(203\)](#)) [<1990T607>](#). A variety of silyl-substituted pyridazines [<1995COFGT\(2\)899, 1997TL5791, B-2002MI685>](#) and furans [<1994JOC3917, B-2002MI685>](#) have been synthesized using this strategy ([Equations \(204\)](#) and [\(205\)](#)). In the same manner 3,4-bis(trimethylsilyl)thiophene was obtained in 92% yield [<1997JOC1940>](#).

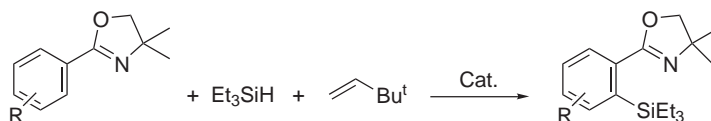


2.18.2.4.5 By transition metal-catalyzed coupling of aryl derivatives with silicon compounds

Transition metal-catalyzed cross-coupling has become a powerful and general method for selective formation of C—Si bonds [<B-2002MI491>](#). Silylation of aryl halides by trisubstituted silanes (mainly triethoxysilane) and disilanes (hexamethyldisilane) catalyzed by palladium, rhodium and ruthenium complexes gives arylsilanes. Palladium-catalyzed silylation of aryl halides with triethoxysilane affords arylsilanes ([Equation \(206\)](#)) [<1997JOC8569, 2002T205>](#). Aryl iodides are significantly more reactive than bromides and the reaction proceeds efficiently with electron-rich and neutral aryl iodides. In the presence of palladium complexes silicon-aryl bonds are also formed in the solid phase. A phenylalanine silane resin has been prepared directly from iodo-substituted phenylalanine with butyldiethyl silane polystyrene in one step [<2002OL4171>](#). The Pd(0)-catalyzed silylation has been extended to aryl bromides [<2001JOC7449>](#). Recently rhodium complexes appeared to be effective catalysts for the silylation of a wide range of aryl halides ([Equation \(207\)](#)) [<2002OL1843>](#).

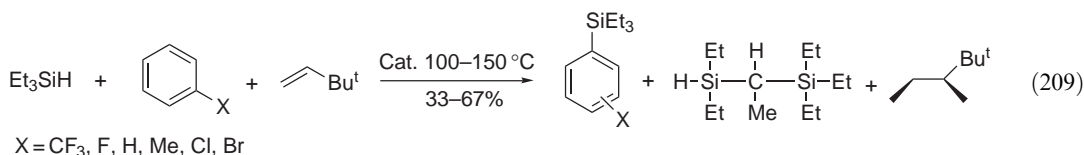


The very attractive reaction of dehydrogenative-silylation of aryloxazolines with trialkylsilanes (mostly triethylsilane) catalyzed by Ru complexes results in formation of *ortho*-silylated aryloxazolines in good to excellent yields. The alkene plays the role of the scavenger of the two hydrogens (Equation (208)) <2001CL422>.

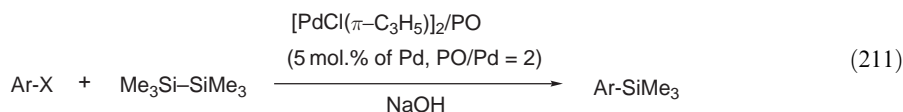
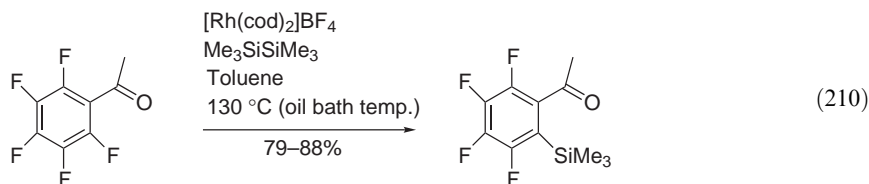


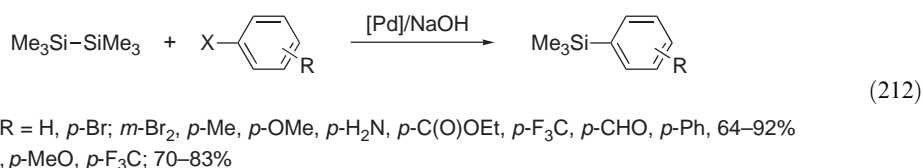
Aryloxazoline R	Yield (%) (time)	
	$\text{Ru}_3(\text{CO})_{12}$	$\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$
2-F	85 (48 h)	0 (72 h)
3-NMe ₂	25 (48 h)	97 (60 h)
3-OMe	33 (20 h)	97 (65 h)
3-Me	39 (20 h)	97 (65 h)
3-F	12 (48 h)	8 (72 h)

A new catalytic route for the formation of arene-silicon bonds based on the dehydrogenative coupling of triethylsilane with arene (Ar-X , where $\text{X} = \text{CF}_3, \text{F}, \text{H}, \text{CH}_3, \text{Cl}, \text{Br}$) using a scavenger has been reported (Equation (209)) <1998OM1455>.

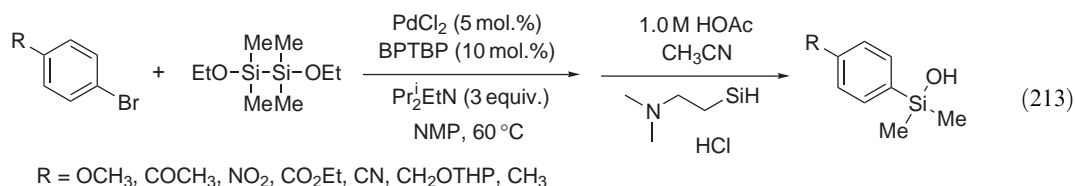


Functionalized fluorobenzenes react with hexamethyldisilane in the presence of a rhodium catalyst to give *ortho*-(trimethylsilyl)fluorobenzenes (Equation (210)) <1998CL157>. Silylation of aryl halides under palladium catalysis can be also achieved using disilanes (Equations (211) and (212)) <2003OL3483, 2000CC1895, 2000SL1801>.





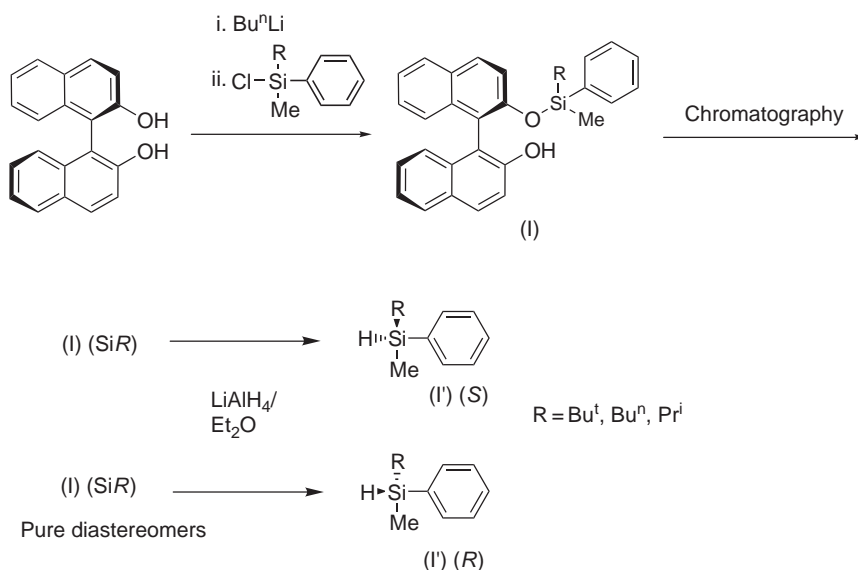
Denmark has developed a general procedure for the formation of aryldimethyl silanes from aryl bromides by a one-pot silylation-hydrolysis procedure (Equation (213)) <2003OL3483>.



2.18.2.4.6 Miscellaneous reactions

Chiral tri(alkyl/aryl)silanes appear to be the most important reagents and synthetic intermediates in this field owing to their facial reactions with C—C multiple bonds and easy transformations into other organosilicon compounds.

Masuda and co-workers have reported the preparation of several optically active tri(alkyl/aryl)silanes by asymmetric synthesis involving chiral auxiliaries <1997BCJ1393>. Schaumann and Wicha <2000CC1029> have reported a procedure in which the treatment of the lithium derivative of (*R*)-BINOL with racemic chloro(*t*-butyl)methylphenylsilane yielded diastereomeric derivatives (I) quantitatively (95%). In order to generate optically active silane and to recover the BINOL, diastereomer (I) (Si*R*) was reduced with LAH in Et₂O (Scheme 27). The hydrosilane (I') (*S*) was obtained in 83% yield (95% ee). Transformation of (I) (Si*R*) into (I') (*S*) indicates that LAH reduction of the BINOL derivative occurred with retention of the configuration around the Si (Scheme 27).



Scheme 27

2.18.3 VINYL- AND ARYLGERMANIUM COMPOUNDS

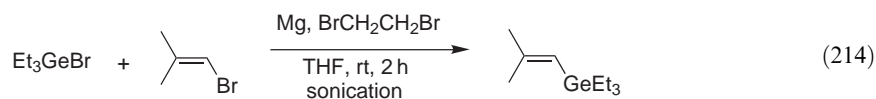
A number of reviews have appeared on different aspects of the synthesis and reactivity of organogermanium derivatives <B-1982COMC(2)399, B-1995MI009, B-1995COMCII137, B-2003MI010, B-2003MI011>. This section does not provide a comprehensive review but summarizes the most efficient methods of the synthesis of alkenyl- and arylgermanium compounds and the new developments since the publication of COFGT (1995) <1995COFGT(2)899>.

2.18.3.1 Alkenylgermanes

A concise review of the most important methods for alkenylgermane synthesis has recently appeared <B-2003MI159>. The most commonly used methods for the synthesis of vinylgermanes involve the use of alkenyl metals, alkynes and alkenylgermanes.

2.18.3.1.1 From alkenyl metals

Treatment of halogermanes with vinylmagnesium or vinyl lithium derivatives is a facile method for introducing vinyl units into organogermanes <1996SL549>. To avoid competitive formation of digermanes, metallic magnesium should be excluded from the reaction mixture before addition of the halogermane, especially when an elevated temperature is used. Alkoxy germanium derivatives have also been employed in reactions with aryl metals <1995JOM(499)143, 2002JA6914>. The Barbier reaction between germanium halides, magnesium turnings and organyl halides in the presence of 1,2-dibromoethane at ambient temperature and under ultrasonic conditions gives organic germanium derivatives in high yield (Equation (214)) <2000TL4905, 2003JOM(671)113>.

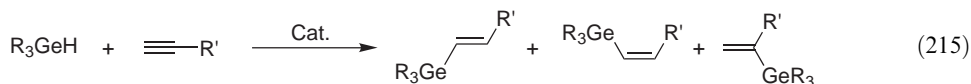


Simple vinylgermanes can be prepared by redistribution of vinylstannanes with germanium(IV) chloride <1998JOM(570)175, 2002OM5911>.

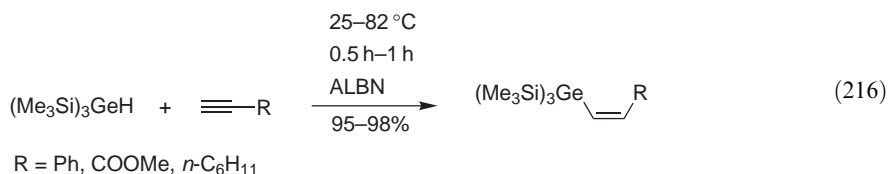
2.18.3.1.2 From alkynes

(i) Hydrogermylation

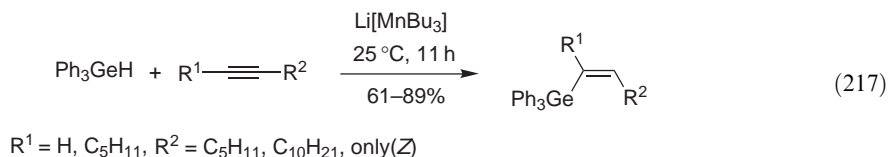
Hydrogermylation of alkynes represents an important route to vinylgermanes. A number of procedures have been proposed providing a range of selectivity patterns. In general, the reaction results in formation of three isomers (Equation (215)) with selectivity determined by both electronic and steric properties of substituents in the reacting partners, type of solvent, character of the catalyst and the ratio of reagents used.



Hydrogermylation can be performed via a radical mechanism. In such processes the $\text{R}_3\text{Ge}^\bullet$ radical can be generated thermally, photochemically or by a suitable radical initiator. The reaction of $(\text{Me}_3\text{Si})_3\text{GeH}$ proceeds stereo- and regioselectively with a variety of alkynes affording 2-alkenylgermanes exclusively and in good yield (Equation (216)) <1997JOC8009>.



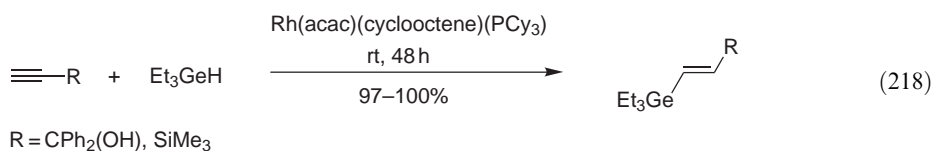
Treatment of selected terminal acetylenes with Ph_3GeH in the presence of tributylmanganate as a radical initiator provides a mixture of stereoisomers in high yield. Hydrogermylation of internal acetylenes under these conditions leads to selective formation of the (*Z*)-isomers in moderate yield (Equation (217)) <2000BCJ2159>.



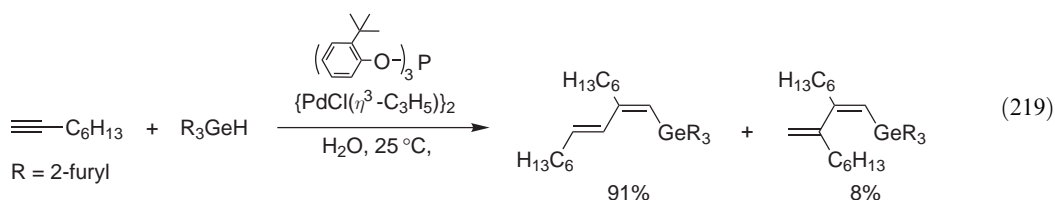
Lewis acid mediated or thermally initiated hydrogermylation of alkynes on a hydride terminated Ge(100) surface results in formation of the alkenyl functionality bonded to the surface through the Ge—C bond <2000L7737>.

Transition metal-catalyzed hydrogermylation of alkynes proceeds in good yield. However, in most cases a mixture of stereo- and regioisomers is formed. Hydrogermylation of $\text{HC}\equiv\text{CR}'$ ($\text{R}' = \text{Ph}, \text{COOEt}$) with R_3GeH ($\text{R} = \text{Et}, \text{Ph}$) performed in the presence of $\text{H}_2\text{PtCl}_6/\text{Pr}^i\text{OH}$ (Speier's catalyst) leads to a mixture of stereo- and regioisomers <1998JOM(558)155>. Similarly, hydrogermylation of a variety of 1-trimethylsilyl-2-organylacetylenes with Me_3GeH in the presence of H_2PtCl_6 produces a mixture. However, subsequent protodesilylation of each isomer with *para*-toluenesulfonic acid monohydrate gives the same product, i.e., $(\text{Me}_3\text{Ge})(\text{R})\text{C}=\text{CH}_2$ <1995JCS(P1)3>.

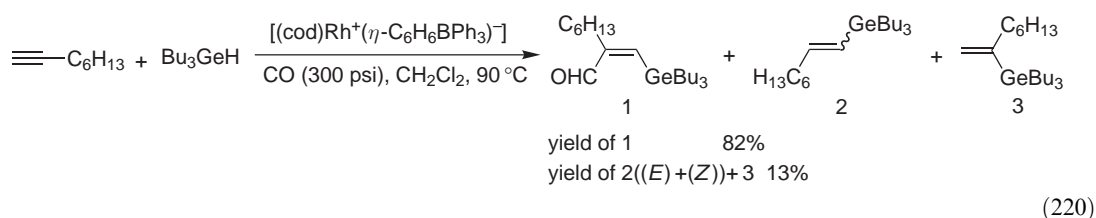
Addition of germanes to alkynols and other selected acetylenes in the presence of a rhodium(I) complex gives alkenylgermanes in high yield and selectivity (Equation (218)) <1999OM2267>.



Palladium-catalyzed hydrogermylation performed on excess alkyne leads to a mixture of alkenyl- and dienylgermanes with the selectivity depending on the germanium substituents, reaction conditions, solvent and catalyst. In hydrogermylation of alkynes with tri(2-furyl)germanes, water is the optimum reaction medium. Without the use of hydrophilic co-solvents or phase transfer catalysts dienylgermanes are formed regio- and stereoselectively in high yield (Equation (219)) <2001OL2521>.

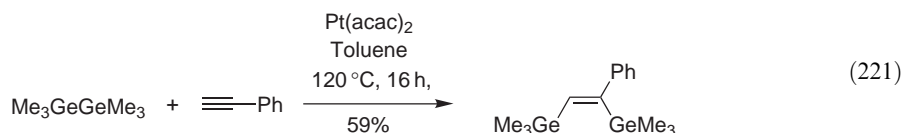


Germa-trane addition to *para*-substituted phenylacetylenes proceeds in the presence of Pd or Rh catalysts in moderate yield and affords a mixture of isomers <2003OM199>. An example of germylformylation of a terminal alkyne has been reported. In the presence of a zwitterionic rhodium complex, (*Z*)-3-germylalk-2-enals were formed in moderate to high yield (Equation (220)) <1995CC1601>. This process is accompanied by competitive hydrogermylation.

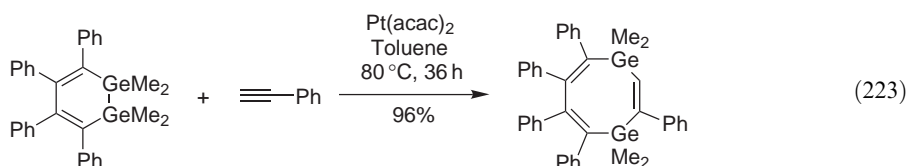
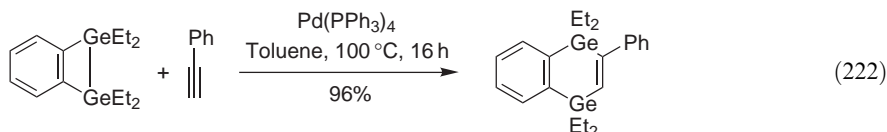


(ii) Other transition metal-catalyzed germylation processes

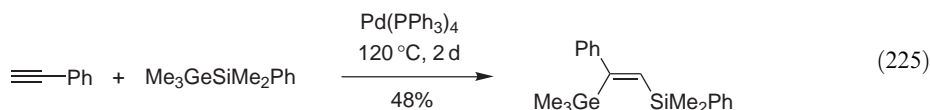
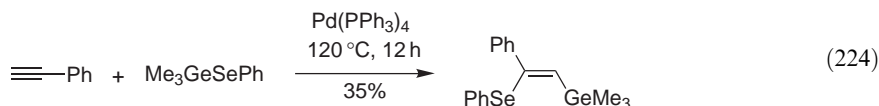
Catalyzed addition of group 14 element-element bonds to alkynes has recently been reviewed [<1999CRV3435>](#). Bis-germylation of selected alkynes has been successfully achieved in the presence of platinum complexes [<2001BCJ123>](#). Hexamethyldigermene reacted with various alkynes in the presence of $[\text{Pt}(\text{acac})_2]$ or $[\text{Pt}(\text{dba})_2]$ to afford (*Z*)-1,2-bis(germyl)ethenes in moderate yield (Equations (221)). In contrast, reaction of alkylchlorodigermenes (e.g., $\text{Me}_2\text{ClGeGeMe}_2\text{Cl}$) with phenylacetylene under the same conditions gives a complex mixture of germylation products.



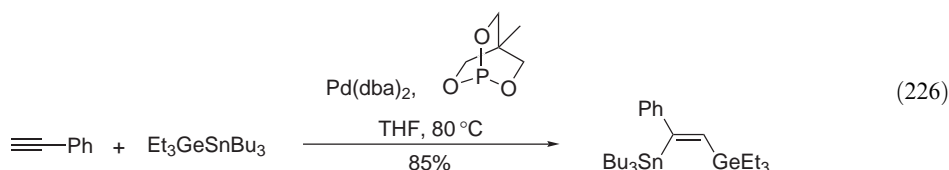
Addition of cyclic derivatives containing Ge—Ge bonds to alkynes leads to the expansion of the ring. 1,2-Bis(dimethylgermyl)carborane in the presence of $\text{Ni}(\text{PEt}_3)_4$ undergoes an effective addition to a number of terminal and internal alkynes with the formation of digermyl six-membered ring compounds [<2002OM3922, 2002CCR\(231\)47>](#). Similarly, palladium-catalyzed addition of octaisopropyltetragermene to 1-hexyne [<2003BCJ1023>](#) or 3,4-benzo-1,2-digermacyclobutene to phenylacetylene (Equation (222)) [<2000JOM\(611\)420>](#) produced new six-membered rings. The latter reaction (Equation (222)) proceeds effectively in the absence of catalyst at 160°C [<1996OM2014>](#). Addition of substituted six-membered rings to alkynes has also been reported (Equation (223)) [<2001BCJ123>](#).



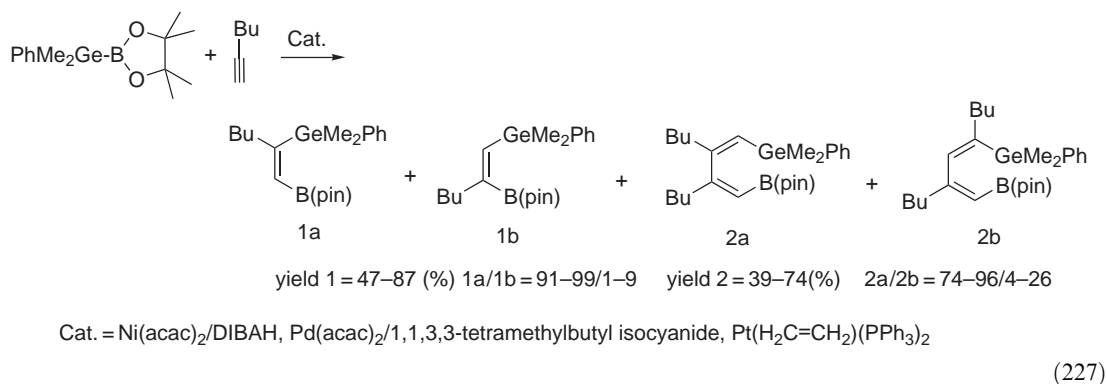
Palladium(0)-catalyzed addition of the germyselane Me_3GeSePh or the silylgermane $\text{Me}_3\text{GeSiMe}_2\text{Ph}$ to phenylacetylene proceeds regio- and stereoselectively (Equations (224) and (225)) [<1998JOM\(564\)1>](#).



Palladium-catalyzed addition of tributyl(triethylgermyl)stannane to arylacetylenes (Equation (226)) followed by destannylation or Stille coupling provides styrylgermanes in high yield [<2000CL1408>](#).

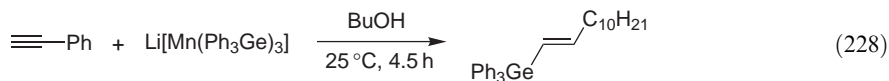


Germaboration of alkynes can be achieved in the presence of Ni, Pd or Pt complexes. Selectivity of this processes strongly depends on the catalyst. The reaction catalyzed by $[\text{Pt}(\text{H}_2\text{C}=\text{CH}_2)(\text{PPh}_3)_2]$ gives selectively products of germaboration, whereas in the presence of Ni and Pd complexes products of germaboration and germaborative dimerization are formed (Equation (227)) <1998OM5233>.



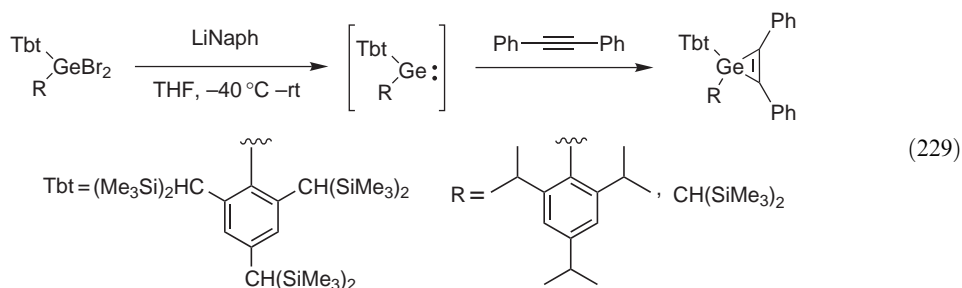
(iii) Non-catalyzed germylmetallation

Treatment of iododecyne with $\text{Li}[\text{Mn}(\text{Ph}_3\text{Ge})_3]$ in THF in the presence of 1-butanol gives (*E*)-1-(triphenylgermyl)-1-dodecene quantitatively (Equation (228)). In contrast, the reaction of 1-dodecyne with $(\text{Ph}_3\text{Ge})_2\text{Cu}(\text{CN})\text{Li}_2$ provides a mixture of regioisomers <2000BCJ2159>. Analogously, in the reaction of $(\text{Me}_3\text{Ge})\text{MeCu}(\text{CN})\text{Li}_2$ with ethyl pent-2-ynoate two geometric isomers are formed <2000OL1407>.



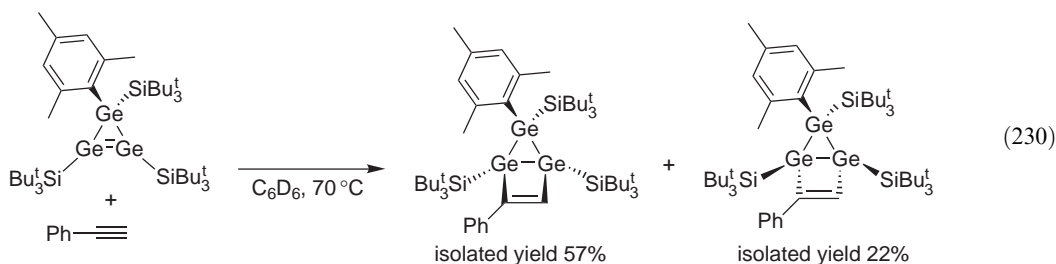
(iv) Addition of germynes to alkynes

Addition of germynes bearing bulky germanium substituents to diphenylacetylene provides 2,3-diphenylgermirenes in good yield (Equation (229)) <1995CL827>. The reverse reaction (germirene thermolysis) is a convenient mild method for generation of germynes.



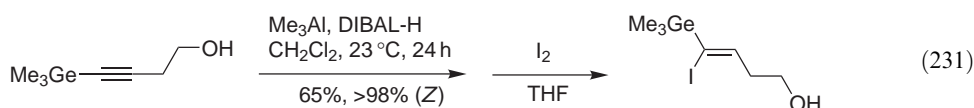
(v) Addition of derivatives containing Ge=Ge or Ge=Si double bond to alkynes

Compounds containing Ge=Ge or Ge=Si double bond or generating such bonds *in situ* <1999OM2206> form cycloaddition products with alkynes (Equation (230)) <2000JA12604, 2000AG4039, 2001JOM(636)41, 2003CRV1429>.



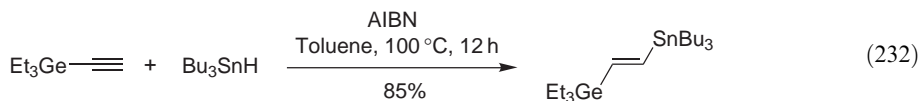
2.18.3.1.3 From alkynylgermanes

Hydroalumination of germyl substituted 3-butyn-1-ol with DIBAL-H in the presence of AlMe_3 gives, (*Z*)-styryl-4-iodo-3-buten-1-ol after iodionolysis, with stereo- and regioselectivity (Equation (231)) <1997TL3829>.

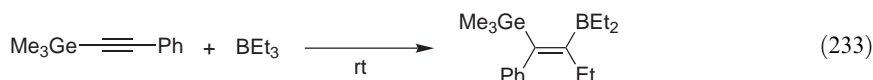


The same product(s) can be obtained by *anti*-carboalumination of substituted propargylalcohols <1997JOC784>. This strategy involves carboalumination followed by effective thermal isomerization of the alkenyl metal.

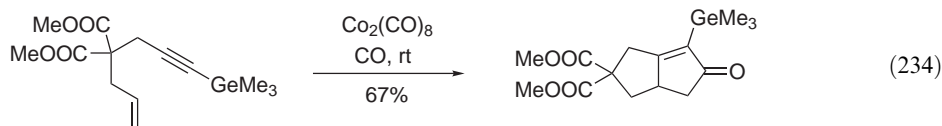
Hydrostannylation of alkynylgermanes proceeds easily in the presence of a radical initiator (Equation (232)). The products can be subsequently converted into a variety of aryl or hetero-arylvinyldermanes by Stille coupling <2000TL9981, 2003S448>.



1,1-Organoboration of phenyl(ethynyl)trimethylgermane using Et_3B (Equation (233)), $(\text{H}_2\text{C}=\text{CHCH}_2)_3\text{B}$ and 1-boraadamantane has been reported <2000ICA(300-302)169, 2001JOM(620)51>.

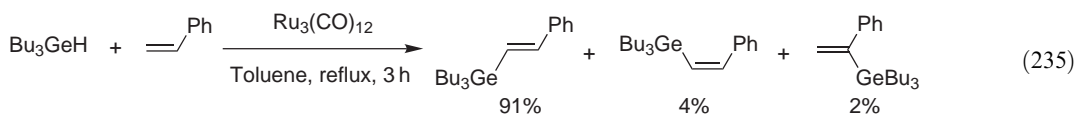


The Pauson-Khand reaction of enynes having a trimethylgermyl group at the alkyne terminus stereoselectively affords the corresponding bicyclo[3.3.0]octenone (Equation (234)) or bicyclo[4.3.0]decenone skeletons <2002TL8575>.



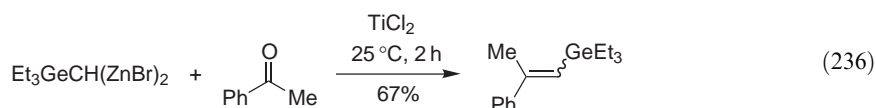
2.18.3.1.4 Miscellaneous reactions

A new method for synthesis of vinylgermanes has been reported: this is dehydrogenative germylation of alkenes with hydrogermane. This reaction, analogous to dehydrogenative silylation, is catalyzed by a number of ruthenium and rhodium complexes of which $\text{Ru}_3(\text{CO})_{12}$ was found to be the most effective (Equation (235)) <1999OM3764>.

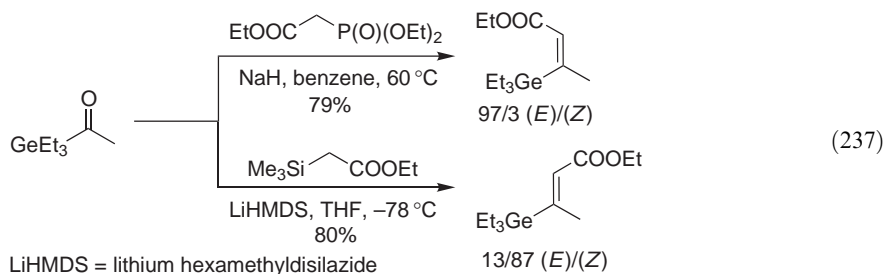


The use of *para*-substituted styrenes or different germanes (e.g., Et_3GeH) also results in the formation of the expected products but in moderate yield (50–60%).

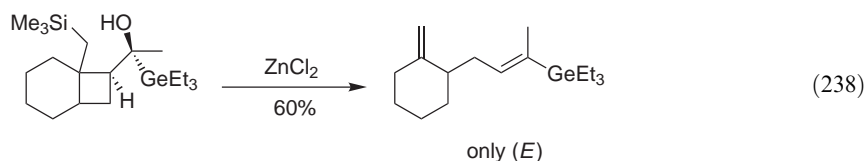
Triethylgermyl-substituted bis(bromozincio)methane (prepared from the corresponding dibromides by Pd catalyzed reaction with zinc) reacts with ketones or aldehydes to give alkenylgermanes (Equation (236)) <2000SL495>. Selectivity of this process is strongly substrate-dependent. Superior results are generally obtained using aldehydes.



Selective synthesis of β -germyl- α,β -unsaturated esters has been achieved using Peterson or Horner–Wadsworth–Emmons olefination protocols (Equation (237)) <1997T8349>.

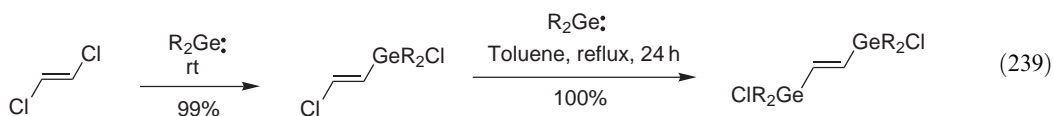


In a related procedure (*E*)-1,5-disubstituted dienyldermanes can be synthesized stereoselectively via zinc halide catalyzed ring-opening of cyclobutane derivatives (Equation (238)) <1997T8349>.



Perfluoroalkenyl iodides ($\text{F}_2\text{C}=\text{CFI}$) react with Et_3GeCl in the presence of a stoichiometric amounts of $\text{P}(\text{NEt}_2)_3$ to yield perfluorovinylgermanes in high yield <1995SC2425>.

Reaction of the stable germylene $[(\text{SiMe}_3)_2\text{CH}]_2\text{Ge}$ with an excess of dichloroethylenes proceeds stereospecifically and gives the vinylgermanes quantitatively (Equation (239)) <1996JOM(521)387>.



In situ generated dichlorogermylene has been reported to undergo insertion into vinyl chloride to form vinyltrichlorogermane. This reaction is performed in the gas phase <1997JGU1725>. Insertion of dibromogermylene into β -bromostyrene results in the formation of β -styryltribromogermane <2000CHE603>.

2.18.3.2 Arylgermanes

Recently, a short review has appeared presenting and discussing the most important methods of synthesis of aryl- and heteroarylgermanes <B-2003MI149>.

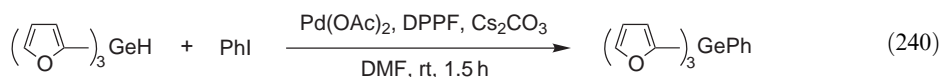
2.18.3.2.1 Synthesis from halogermanes by substitution with aryl metals

Reaction of halogermanes with organometallics provides the most efficient and convenient tool for the synthesis of arylgermanes and remains the standard and most commonly used method <1996OM4488, 1998T9811, 1998JA9844, 1998POL4497, 1998JOM(553)163, 2001CL338, 2001HAC238, 2002JA12174>. This reaction has also been used for solid phase synthesis of aromatics using a germanium based linker <1997JOC2885, 2000JOC5253>. Heteroarylgermanes can be easily prepared by this method <2000ICA(305)46, 1999OM3187>. Alkoxy derivatives of Ge have also been used instead of halides in reactions with aryl metals <1997OM5102, 1999OM4317>. A one-pot reaction of halogenogermanes, aryl halides and magnesium turnings performed at ambient temperature under sonication gives arylgermanes in high yield <2000TL4905, 2003JOM(671)113>. Preparations of oligo- and poly(digermylene-phenylene)s and related compounds have also been reported <1997BCJ713, 1997ICA(260)11, 1998POL3963>.

Reaction of halogermynes with aryllithium derivatives is a convenient method for synthesis of aryl substituted germanium(II) compounds <1994OM167, 1994OM2898, 1996OM741, 1997OM1920, 1997OM2743, 1998CCR(178-180)593, 1998OM2149, 1998OM5602, 2000CCR(210)251, 2001OM1820, 2001OM42, 2001OM418, 2002POL2827>.

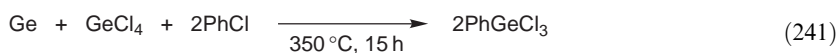
2.18.3.2.2 Palladium-catalyzed coupling of germanes with aryl halides

Pd-catalyzed coupling of various aryl halides with tri(2-furyl)germane provides aryltri(2-furyl)-germanes in good yield (Equation (240)) <2002OL3165>. Products can be used subsequently in palladium-catalyzed cross-coupling with aryl halides.



2.18.3.2.3 Insertion of germynes into aryl halides

An extensive study of the dichlorogermyl insertion into ArCl in a gas-phase synthesis of phenyl-trichlorogermane by the reaction of germanium tetrachloride with chlorobenzene has been made. The effects of hexachlorodisilane and trichlorosilane as initiators has been studied and discussed. A mechanism involving formation of dibromogermylene has been proposed <1995JGU1717>. PhGeCl₃ has been synthesized with high selectivity from elemental germanium, GeCl₄, and chlorobenzene (Equation (241)) <2001OM5583>.



[(SiMe₃)₂CH]₂Ge or [N(SiMe₃)₂]₂Ge undergo insertion into PhX (X = Cl, Br, I) with the formation of the respective phenylgermanes <2003JA8986>. *meta*-Tolyltribromogermane <1999JOM(588)222>, indenyltribromogermane <2000JGU989> and fluorenyltribromogermane <1998ZN(B)1247> have been synthesized by reaction of the dioxane complex of GeBr₂ with the respective bromoaryl derivative.

2.18.3.2.4 Miscellaneous reactions

Phenylchlorogermanes can be synthesized from metallic germanium and chlorobenzene (direct synthesis) in the presence of metal chlorides <2002MI33>.

[4+2]-Cycloaddition of 1,2,4,5-tetrazine with trimethylgermylethyne or bis(trimethylgermyl)-ethyne affords, after nitrogen elimination, mono- or digermyl-substituted pyridazines <1998EJO2885>. Analogous cycloaddition of organic or inorganic azides to conjugated germanium containing acetylenic aldehydes or aldimines produces germyl-substituted triazoles containing a formyl or iminomethyl group <1996JGU1158>.

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Biographical sketch



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He is an author or co-author of 200 publications and 20 book chapters (e.g., *Handbook of Metathesis*, *Encyclopedia of Catalysis*, *Applied Homogeneous Catalysis with Organometallic Compounds* as well as editor and co-author 10 books inter alia “*Comprehensive Handbook on Hydrosilylation*”, “*Progress in Organosilicon Chemistry*”. Professor Bogdan Marciniec was recipient of the Prime Ministry award (2001) and J. Sniadecki Medal of the Polish Chemical Society (2003) for the outstanding achievements in chemistry.



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Professor Marek Zaidlewicz received the M.Sc. (1960), Ph.D. (1965), D.Sc. (1976) degrees from Nicolaus Copernicus University, Toruń, where he became a Professor in 1978, Head of the Chemistry Department (1989–1993), Dean (1993–1999), and Vice-Rector (1999–). He was the British Council Scholar at the Dyson Perrins Laboratory, Oxford University in 1970, post doctoral associate with Professor H. C. Brown in 1974 and 1980, and a Visiting Professor at Purdue University, USA in 1986 and 1993.

His contributions to organoborane chemistry are in the areas of hydroboration of dienes and terpenes, allylboranes, haloboranes, selective reductions with boranes, highly reactive borane-amine adducts, and boronated amino acids for Boron Neutron Capture Therapy. He co-authored several books: *Comprehensive Organometallic Chemistry*, *Inorganic Reactions and Methods*, *Kirk–Othmer Encyclopedia of Chemical Technology*, 4th Ed., *Encyclopedia of Reagents for Organic Synthesis*, *Houben-Weyl Methods of Organic Chemistry—Stereoselective Synthesis*, and *Organic Syntheses Via Boranes*, Vol. 2. Professor Zaidlewicz is also a recipient of the Scientific Achievement Awards, Ministry of Education, Warsaw (1996, 2002).

2.19

Vinyl and Aryl Metals

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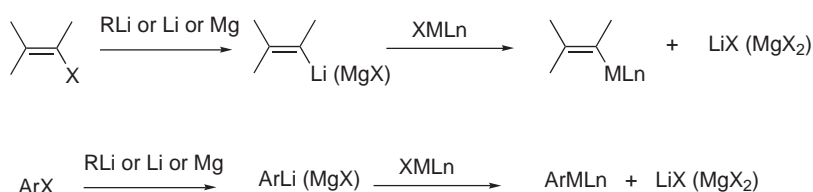
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2.19.1 INTRODUCTION AND GENERAL DISCUSSION

The chemistry of vinyl and aryl metallic compounds has been studied primarily by organometallic chemists, whose interests lie in the structure determination and the stereo- and regiochemistry of metal–carbon bonds. Recent studies on the reactions of organometallics with electrophiles have been carried out with the emphasis on organic synthesis, particularly regioselective C–C bond formations. In COFGT (1995) <1995COFGT(2)951>, vinyl and aryl metals are defined as having σ metal– sp^2 -carbon bonds. The discussions in this edition will follow the definition, classification, preparation, properties, and characterization as described in COFGT (1995). This chapter covers the preparation of thermally stable discrete species that can be characterized and even isolated for full identification or used in a separate step and, also *in situ* generated unstable species or catalytically generated transient species that may or may not be isolated and/or characterized. In most cases, vinyl and aryl metals are conveniently prepared from (i) the organic halides and

related derivatives; (ii) active C—H compounds; (iii) unsaturated compounds such as alkenes, alkynes, allenes, and arenes; and (iv) organometal exchange reactions. A great deal of discussions on the methods of preparation of organometallic compounds was included in COFGT (1995) <1995COFGT(2)951>. Among the most useful methods are oxidative metallation of organic halides and metal–halogen exchange reactions. Once these organometals are obtained, a wide variety of organometals containing other main group metals and transition metals can be prepared via transmetallation.

The majority of the currently known synthetic examples of vinyl and aryl metals may be represented in Scheme 1. In addition, hydrometallation and carbometallation or halo- or oxy-metallation routes are synthetically highly useful reactions due to their regio- and stereoselectivity. The general synthetic procedures were covered extensively in COFGT (1995) <1995COFGT(2)951>. New developments since 1995 are covered in this chapter.



Scheme 1

The importance of metal-catalyzed cross-coupling reactions of vinyl and aryl metals for the construction of C—C bonds between two or more unsaturated centers has been exemplified by their applications to the synthesis of complex natural products and functional materials. An extraordinary diversity of organometallic nucleophiles and organic electrophiles has been disclosed during the 1990s. New synthetic methods for the preparation of novel vinyl and aryl metals are down to a trickle while synthetic applications of existing methods are pouring out. While undoubtedly the quest for identifying milder procedures for vinyl and aryl metals continues, their synthetic applications to the preparation of complex organic molecules attract increasing attention.

2.19.2 OXIDATIVE METALLATION OF VINYL AND ARYL HALIDES

In this section of COFGT (1995) <1995COFGT(2)951>, a detailed overview of oxidative metallation methods was presented. The literature since 1995 has not revealed many new references. A few citations describe the preparation of vinyl and aryl metals via oxidative metallation, but almost all of them use methods reported in COFGT (1995) <1995COFGT(2)951>. Only selected examples, by virtue of their synthetic utility, are described in this chapter.

2.19.3 METAL–HALOGEN EXCHANGE REACTIONS OF VINYL AND ARYL HALIDES

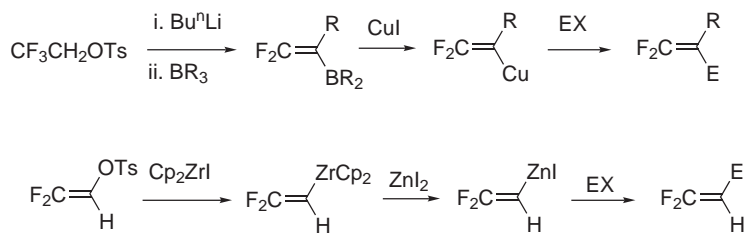
An important and highly useful synthetic reaction for the preparation of vinyl and aryl metals is metal–halogen exchange. Most often, halogens are exchanged with either Li or Mg followed by transmetallation with other metals. Reactivities of halides on *sp*²-carbon depend on the environment of the halogen, including steric and electronic factors. Since vinyl and aryl halides are convenient and easily available synthons, it is hard to find a journal without metal exchange reactions. Some examples which were not mentioned in COFGT (1995), particularly fluorinated alkenes, are given in this section.

The β,β -difluorovinylmetals are generally thermally unstable when they do not contain electron-withdrawing groups (e.g., OPh, SPh, OTs, OC(O)NEt₂, OMEM, *O*-allyl, *O*-phosphazine) on the α -carbon. In the absence of such groups, vinyl fluorides undergo β -elimination of metal fluoride leading to 1-fluoro-alkynes <1997JOC7758>. While lithium and magnesium derivatives of 1-fluoro-2,2-difluoroethene can only be prepared at low temperatures (−110 °C), the corresponding zinc, copper, and cadmium derivatives can be prepared at 60 °C in dimethylformamide

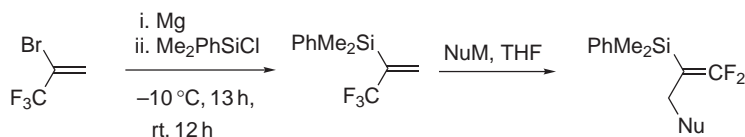
(DMF) via iodide exchange (Equation (1)). These difluorovinylzincs undergo cross-coupling reactions with a variety of aryl iodides. Aryl iodides are preferred over aryl bromides for cross-coupling with 1-fluoro 2,2-difluoroethene <1997JOC7758>.



The nonstabilized 2,2-difluorovinylmetals can be prepared from thermostable 2,2-difluorovinylboron and vinylzirconium species via transmetalation with copper and zinc (Scheme 2) <1997JOC7758, 2003JOC7800, 2003TL707>. Unlike difluorovinylcopper or difluorovinylzinc, 2,2-difluorovinylsilanes are quite thermostable. They can be handled at room temperature and stored in air. Difluorovinylsilanes can be prepared from 1-(trifluoromethyl)-1-vinylsilanes as shown in Scheme 3. Trifluoromethylvinylsilanes can undergo a variety of reactions with nucleophiles—such as hydrides, alkylolithiums, enolates, and sulfur-stabilized anions—to give 1,1-difluoroethylene-2-dimethylphenyl silanes. With the help of tetra-*n*-butylammonium fluoride (TBAF), electrophiles such as aldehydes react at the silicon carbon.



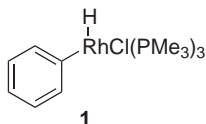
Scheme 2



Scheme 3

2.19.4 OXIDATIVE C—H ACTIVATION

Transition metal complexes are powerful synthetic tools for the activation of unreactive C—H bonds. These reactions have been reviewed <1997CR2879>. Oxidative addition of metals to unactivated aryl C—H bond is made possible. The rhodium complex **1** is prepared from $\text{RhCl}(\text{CO})(\text{PMe}_3)_2$ and benzene by irradiating with 100 W high-pressure mercury lamp at 80 °C with excess CO. The rhodium complex thus obtained is relatively stable <2003JA7762>. Although reactions of this type are possible, their synthetic potential in organic functional group transformation is still limited.



2.19.5 NONREDOX METAL–HYDROGEN EXCHANGE

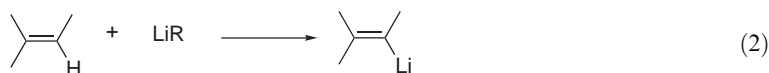
2.19.5.1 Metallation of Arenes via Electrophilic Substitution

While diverse classical electrophilic substitution reactions of aryl and heteroaryl compounds are available for the synthesis of complex organic molecules, they often suffer from harsh conditions and give mixtures of positional isomers. Metallation methods discussed in COFGT (1995) focused on the use of electrophilic metal compounds (B, Al, Sn, Hg, Tl, and Pd). These reactions are now

common and no new information can be added except for reactions which involve direct metallations at the *ortho* position of substituted aromatic compounds (see [Section 2.19.5.2](#), <1995COFGT(2)951>).

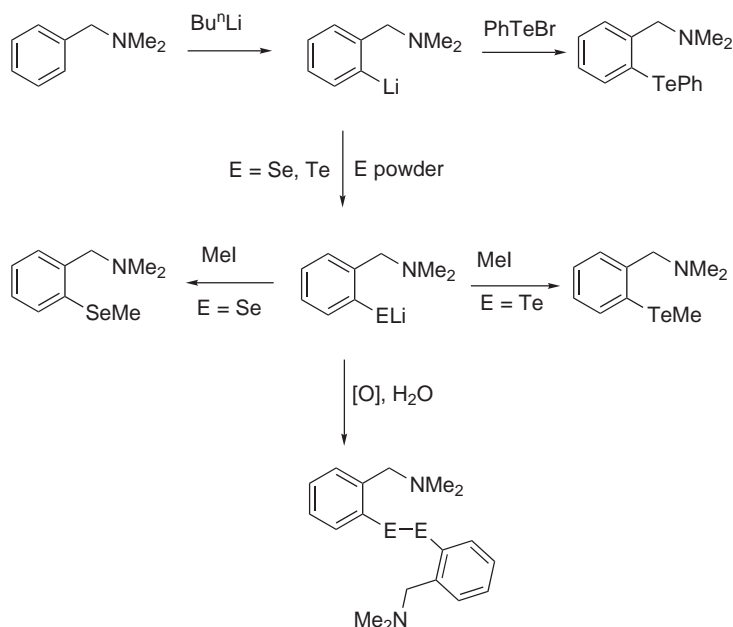
2.19.5.2 Metallation of Alkenes and Arenes via Deprotonation with Bases

Reactions of the type shown in [Equations \(2\) and \(3\)](#) are ubiquitous. Proximal heteroatom-containing groups or carbanion-stabilizing groups on the aromatic ring direct the metallation in a highly regioselective manner <2002JOM150, 1999AN(E)1435>. The majority of reactions focus on the formation of unstable lithium or magnesium derivatives, which are used to form a carbon–aromatic bond. Due to the synthetic importance of such reactions, they have been reviewed on a number of occasions elsewhere <2001EJOC3975, 1997CR2879, 2003AN(E)4302, 2002ACR226>.



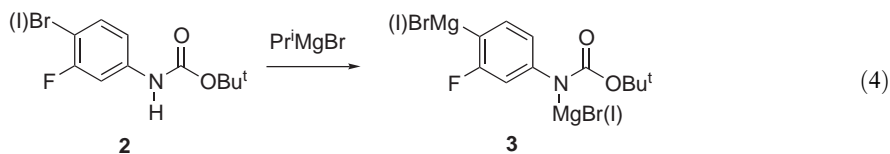
The use of rhodium catalysts such as $\text{RhCl}(\text{PPh}_3)_3$ or $\text{RhCl}(\text{cod})_2$, with $\text{PPr}_2^i(\text{OAr})$ or $\text{P}(\text{NMe}_2)_3$ as co-catalysts, allows the *ortho*-selective intermolecular arylation of phenols <2003JOC8669>. Internally chelated organoselenium, organotellurium, and organopalladium compounds show catalytic activity and therefore function as reagents in organic synthesis, particularly for asymmetric synthesis. *Ortho*-metallation is usually accomplished with the help of sterically bulky substituents and/or chelating groups placed in close proximity to the metal–carbon bond forming position <2002ACR226>. Internal chelating groups are also capable of directing aromatic lithiation with alkyllithium reagents. This process allows the introduction of metals—such as tellurium, selenium, zinc, cadmium, and mercury—by transmetalation at the desired position. Lithiation occurs specifically at the *ortho* position of the aromatic ring irrespective of whether the directing group is electron donating or electron withdrawing. It should be noted that the lithiation of aromatic substrates by lithium–halogen exchange is much more facile and selective than *ortho* deprotonation.

A variety of *ortho*-directing groups—such as $\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{C}(\text{CH}_3)\text{HN}(\text{CH}_3)_2$, and heterocycles (e.g., 2-isoxazole, 2-pyridine, and 1,2-oxazoline)—have been employed. Typical examples for the synthesis of Te and Se compounds are shown in [Scheme 4](#) <2002ACR226, 1996J(D)2719, 2002JOM150>.



Scheme 4

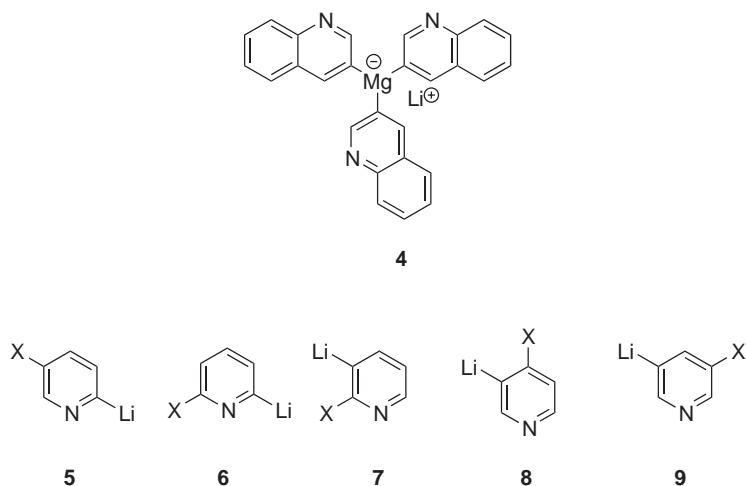
In the presence of carbamates, which are considered to be much better directing groups, halogen exchange occurs exclusively if halogen is present in the aryl ring, even if it is far away from the carbamate group. The carbamate **2** was reacted first with EtMgBr followed by BuⁿLi to obtain arylmagnesium compound **3** in the presence of anhydrous magnesium salt (prepared from EtMgBr and trimethylsilyl chloride (TMSCl)) <2000TL4301>. An alternative procedure uses isopropylmagnesium chloride at –40 °C <2001OPRD80>. No benzyne formation occurs under these conditions (Equation (4)).



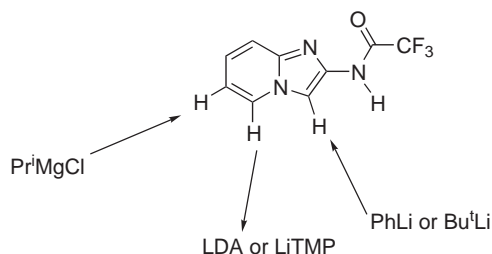
Although halogen–metal exchange reactions were discovered more than 75 years ago, the mechanism of metal-centered anionic substitution at the *sp*²-carbon center in aromatic and vinylic species is still not well understood <2003OL313>. However, their synthetic applications are innumerable. Not all metal-centered anions are supernucleophiles (better than water). Some, such as V(CO)₆[–], are weak nucleophiles and others, such as R₃Sn[–], are strong nucleophiles <2003ARK323>.

Prediction of the site selectivity of generation of aryl metals from arenes is not trivial. It depends on the nature and structure of the base and substitution of the arene. The knowledge of the acidity of a ring proton alone is not sufficient to predict the position of metallation. Site reactivity of disubstituted aryl compounds, such as *o*-fluoroanisole, depends on the base. For this purpose superbases have been developed. They are BuⁿLi–KBu^tO, BuLi activated with *N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDTA), Bu^sLi, and Bu^tLi <2001EJOC3975>.

The formation of heteroaryl metals is complicated due to the fact that they undergo nucleophilic addition very easily due to their low lowest unoccupied molecular orbitals (LUMO) levels. Therefore, lithiation and halogen–lithium exchange reactions require low temperatures and careful conditions. In some cases the superbases or organometallics such as zincates are used for the deprotonation of heteroaryl protons. Like pyridinyl magnesium halides, which can be prepared through halogen–metal exchange using isopropylmagnesium chloride, bromoquinolines cannot be metallated under the same conditions. The Br–Mg exchange of 2-, 3-, and 4-bromoquinolines is possible using a base such as lithium tributylmagnesate (Bu₃MgLi). For example, 3-bromoquinoline has been converted to lithium tri(quinolinyl)-magnesate **4**, which can be trapped with electrophiles <2003T8629, 2003EJOC2115>. 2-Fluoro-, chloro-, and bromopyridines allow either *ortho* metal exchange or *ortho* deprotonation with BuⁿLi at –78 °C (Structures **5–9**). They undergo subsequent reactions with triisopropyl borate <2002T3323, 2003T10043, 2001EJOC3975>.

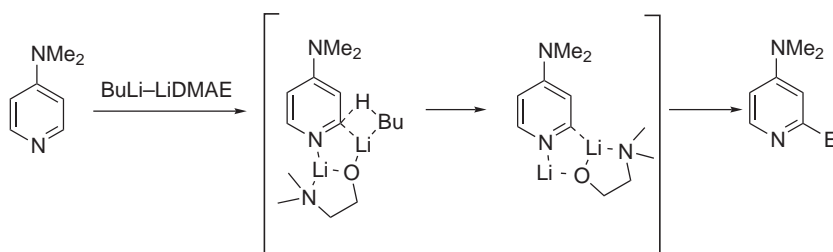


The selective deprotonation of nitrogen heterocycles is not trivial. Acidic amide protons are abstracted before any regioselective ring deprotonation is achieved. The chemoselectivity depends on the base strength and the position of the proton on the ring (Scheme 5) <2002TL9051>.



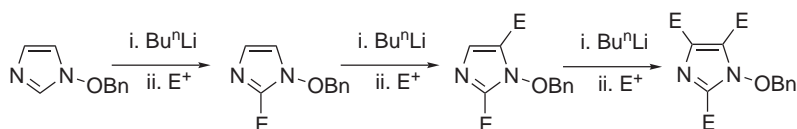
Scheme 5

The α -lithiation of 4-(dimethylamino)pyridine (DMAP) is generally troublesome. However, lithiation with lithium tetramethylmorpholine (LTMP) is possible, if DMAP is complexed first with BF_3 . An even better method appears to be the reaction of DMAP with a mixture of $\text{BuLi}-\text{Me}_2\text{N}(\text{CH}_2)_2\text{OLi}$ in hexane at -78°C . The lithium derivative can then be trapped by a variety of electrophiles (Scheme 6) <2002JOC238>.



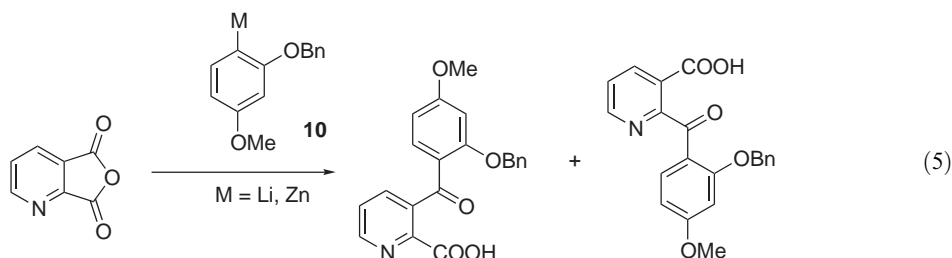
Scheme 6

The lithiation of 1-hydroxy-substituted imidazoles at C-5 is only possible when the 2-position is protected with TMS. The hydrogen atom at the 2-position is acidic and readily exchanges with Bu^nLi . The TMS imidazole is stable enough to form the 5-lithio derivative with Bu^nLi . Various possible ways of preparing substituted 1-hydroxyimidazoles are shown in Scheme 7 <2001JOC8344>.

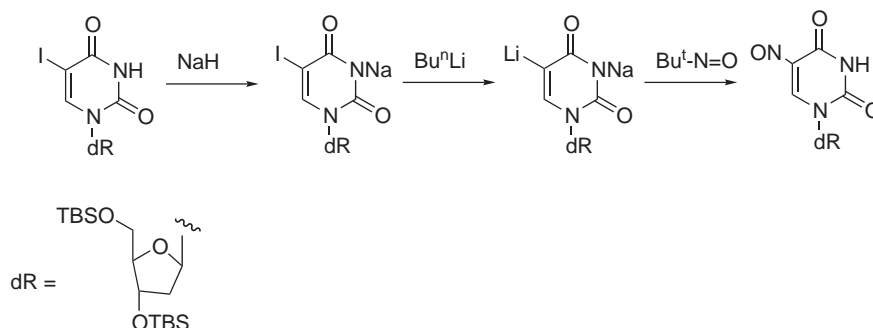


Scheme 7

Although aryllithium reagents are made by halogen–lithium exchange, in order to control the regio- and stereochemistry, the initially formed aryllithium needs to be converted into another aryl metal in some cases. In general, group 1 and 2 metals provide highly nucleophilic and yet basic reagents. The nucleophilicity and basicity is reduced by exchanging the Li with Zn and other metals. For example, nucleophilic addition of aryllithium **10** to the anhydride **11** is not regiospecific with lithium reagents, whereas the corresponding Zn reagent is regiospecific (Equation (5)) <2002BMC3437>.



Halide–metal exchange is generally not difficult, but *in situ* generated vinyl metal may not react with electrophiles under usual conditions. For example, 5-lithiated 2'-deoxyuridine is a useful intermediate for reactions with various electrophiles, such as alkyl halides, carbonyl compounds, and disulfides. However, its formation is less efficient compared to the corresponding ribonucleosides. The major side-product is the dehalogenated uridine [<2002JOM234>](#). Therefore, *t*-butyl dimethylsilyl (TBS)-protected 5-iodouridine is first reacted with sodium hydride at 0 °C in tetrahydrofuran (THF) and then with BuⁿLi at –78 °C to give 5-lithiouridine. This, upon reaction with 2-methyl-2-nitrosopropane gives aminoxyl nucleosides in 72% yield ([Scheme 8](#)) [<2003CC1094>](#).

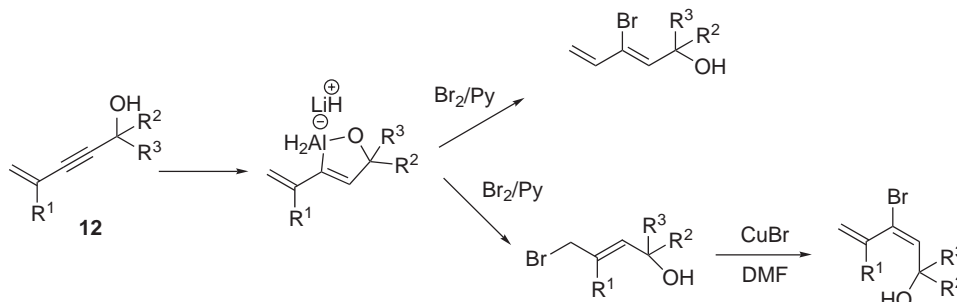


Scheme 8

2.19.6 HYDROMETALLATION

2.19.6.1 Hydroalumination

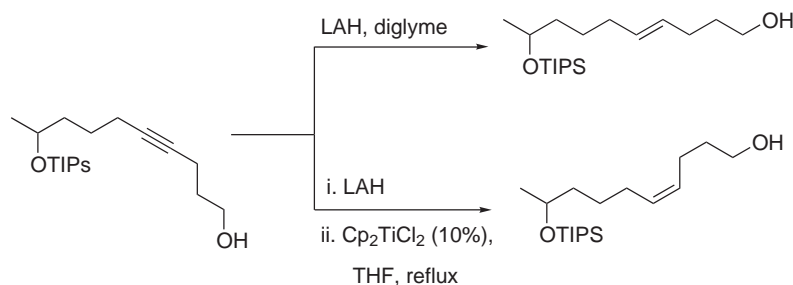
The hydroalumination reactions of alkynes produce *syn*-stereoselective, *anti*-stereoselective, or nonstereoselective compounds. Alkenylaluminum species can be converted regio-, stereo-, and chemoselectively into a variety of useful organic compounds. The common electrophiles, such as I₂, Br₂, cleave *sp*²-C–aluminum bonds with retention of configuration. Hydroalumination is accomplished with a variety of aluminum hydride reagents, but the most common one is diisobutylaluminum hydride (DIBAL-H) in the presence of additives, such as hexamethylphosphoramide (HMPA), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4-5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMPU), DMI, quinuclidine-*N*-oxide (QNO), and *N*-methylmorpholine *N*-oxide (NMO). Vinylalanes react, under a variety of conditions, with a range of electrophiles. The complexing agent HMPA, being a carcinogen, is replaced by NMO for the hydroalumination of propiolic acid esters or its β-substituted esters [<2003JOC9310>](#). The stereochemical outcome for propargyl and homo-propargyl alcohols and their ethers varies and depends on substrate structure and on the structure of the alkylaluminum hydride reagents. Vinylalkynols **12** at the addition step follow the selectivity pattern of propargyl alcohol toward LAH addition. The hydride ion and metal atom are introduced to the triple bond *trans* to each other forming the proposed cyclic intermediate ([Scheme 9](#)). However, the subsequent reaction with electrophiles such as halogen in pyridine gives two possible products in variable ratios, and the ratio depends on the substituents R² and R³ [<2000HCA3291>](#).



Scheme 9

Interestingly, hydroalumination and iodination of 3-butyn-1-ol gives exclusively the (*E*)-isomer (DIBAL-H, 2 equiv. in hexane at -25°C), whereas the corresponding *t*-butyl ether gives a mixture of (*Z*)- and (*E*)-isomers in which (*Z*)-isomer predominates. This is counter intuitive since unfunctionalized alkynes typically undergo *syn*-hydroalumination <1999T14243>. One may infer that the *t*-butyl ether, although sterically hindered, may still coordinate if it is in close proximity to the reaction site.

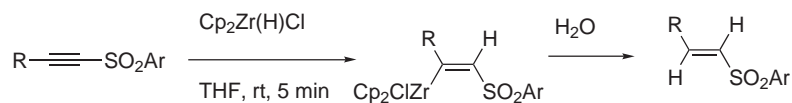
The reduction of internal alkynes with LAH at high temperature (diglyme) is expected to give (*E*)-isomers, but in the presence of a catalytic amount of Cp_2TiCl_2 (10%) in refluxing THF, it gives essentially the (*Z*)-isomer <2002TL1231>. In the latter process, the difference in the (*E*)-to-(*Z*) ratio corresponds to the relative position of the hydroxyl function on the alkyne. The presence of free alcohol is not required for this titanium-catalyzed process and can be used to reduce any internal alkynyl groups to (*Z*)-alkenes. The initial step in this reaction is the reduction of the Ti-complex to Ti-H , which then adds to the alkyne in *syn* fashion followed by metal exchange (Scheme 10) <2002TL1231>.



Scheme 10

2.19.6.2 Hydrozirconation

Bifunctional ethenyl reagents containing both sulfur and zirconium can be prepared via the hydrozirconation of internal acetylenic sulfones. In this case, the product of *anti* addition is observed <1999CC1741>. The hydrozirconation conditions are $\text{Cp}_2\text{Zr(H)Cl}$ (1.2 equiv.) in THF at room temperature (5 min). (*E*)-vinyl sulfone or (*E*)- β -deutero vinyl sulfones are obtained after hydrolysis or deuterolysis (Scheme 11). This approach complements the addition of sulfonyl halides to acetylenes, which produces the (*E*)-isomer and sometimes (*E*) and (*Z*) mixtures. Therefore, the regio- and stereochemistry associated with the addition of $\text{Cp}_2\text{Zr(H)Cl}$ to unsymmetrical acetylenic sulfones may be noted. For example, alkyl substituents on the alkyne give α -alkyl alkenylzirconocenes as the major product, whereas phenyl substituents give the opposite isomer <2000JOM249, 2000T8921> (Scheme 11). The difference in regiochemistry could be ascribed to the dissimilarity of the polarizing ability of the two groups on the triple bond and the long π - π interactions of the phenyl and bicyclopentadienyl groups on the catalyst.

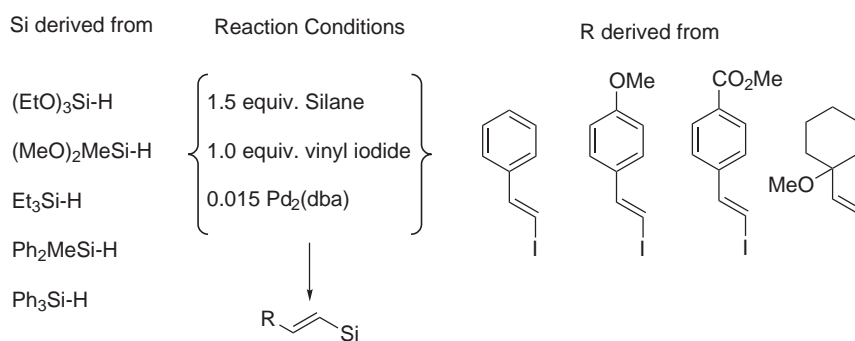


Scheme 11

2.19.6.3 Hydrosilations

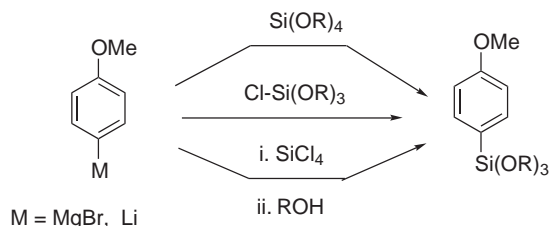
Silicon compounds have advantages over other organometallic reagents such as low molecular weight, higher stability, ease of activation, and conversion to harmless by-products <2003JOC6997>. The addition of organosilanes (H-Si) to unsaturated compounds is one of the most useful reactions for the synthesis of a wide variety of organosilicon compounds

<2002OL3771, 2000OL2491, 2003OL1357, 2003JOC8106>. Their use has been demonstrated in a number of reviews, which deal with Suzuki coupling and other related palladium-catalyzed cross-coupling reactions. Most methods for the synthesis of vinyl silanes utilize alkynes, allenes, or alkenyl halides. Among these methods, the catalytic cross-coupling reactions of organic halides using disilanes as a silicon source are a useful method for stereo- and regiodefined vinyl silanes <2000OL565>. Palladium(0)-catalyzed selective silylation of alkenyl iodides with hydrosilanes give the corresponding alkenyl silanes <1999TL9255> in a regio- and stereoselective fashion. Normally, hydrosilanes such as Et_3SiH form new C—H rather than new C—Si bond. Some examples of vinyl insertion into Si—H bonds are shown in Scheme 12. Ideal conditions for C—Si bond transformations include use of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and KOAc with alkenyl iodides. Use of *N*-methyl-2-pyrrolidone (NMP) and DMF as a solvent combination appears to be essential for this silylation.



Scheme 12

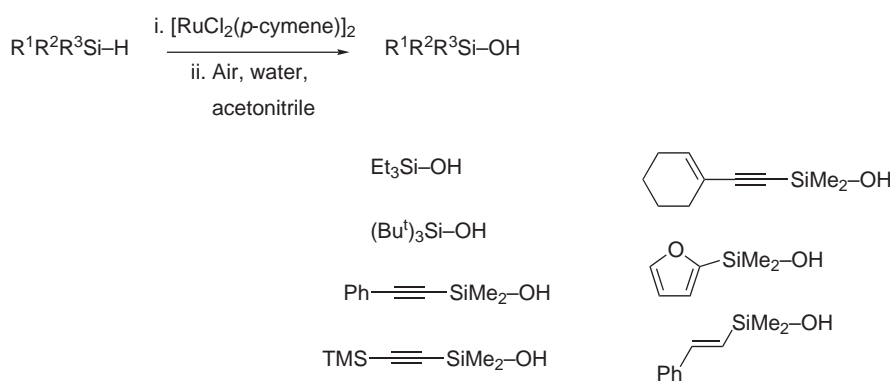
Aryl silanes are both valuable intermediates in organic synthesis <2000OL883> and useful cross-coupling agents. They are generally prepared by the methods shown in Scheme 13.



Scheme 13

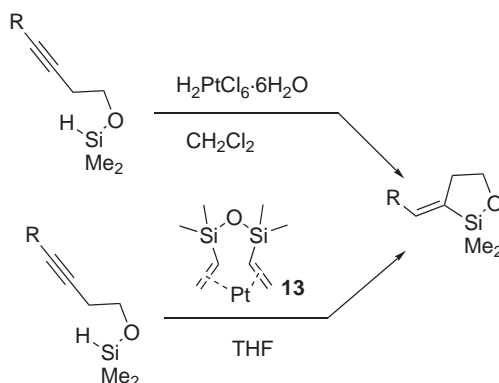
Aryl iodides can be condensed with $(\text{EtO})_3\text{SiH}$ (1.5 equiv.) at room temperature in the presence of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (3 mol.%) with $\text{P}(o\text{-tol})_3$ (2 equiv. with respect to Pd) and Hunig's base (3 equiv.). A palladium complex having bulky phosphines may effectively accelerate the oxidative insertion of Pd into unsaturated species. The nature of halogen substituents affects the rate of silylation—iodides are more reactive than bromides. While aryl halides with electron-withdrawing groups react well, electron-donating functional groups retard the reaction. This results in the reduction of the yields <1997JOC8569>. By changing the ligand from $\text{P}(o\text{-tol})_3$ to $\text{P}(t\text{-Bu})_2(o\text{-biphenyl})$ in the palladium-catalyzed hydrosilylation, aryl bromides <2001JOC7449> can be used as coupling partners. Electronic and steric effects appear to dominate the reaction course. These difficulties are associated with electron-withdrawing groups as well as *ortho*-substituted arenes in the rhodium(I)-catalyzed hydrosilylation of aryl halides with triethoxysilane, but can be circumvented by using rhodium catalysts such as $\text{Rh}(\text{cod})(\text{MeCN})_2\text{BF}_4$. This reaction works best for the hydrosilylation in DMF in the presence of TEA. Under these conditions, aryl compounds with electron-withdrawing groups as well as *ortho*-substituted arenes give good yields of triethoxy silylarenes, but chlorides are still unreactive <2002OL1843>.

Arylsilanols are generally prepared by: (i) hydrolysis of chlorosilanes; (ii) oxidation of organosilanes with a stoichiometric amount of oxidant; or (iii) treatment of siloxanes with alkali metal reagents (Scheme 13) <2000JA12011>. The direct method for the preparation of organosilanols is the oxidation of the corresponding silanes with H_2O_2 and Ti- β zeolite or methyl trioxo rhenium <1999JA2097, 1998CC2609>. This protocol is limited because of the easy formation of silanol dimers. Oxidative hydrolysis of silanes with rhodium complex, $[\text{RhCl}_2(p\text{-cymene})]_2$, is complete in a few minutes at room temperature when a small amount of water (2 equiv.) is present. When the reaction is conducted in the presence of oxygen or air, the ratio of silanol to silanol dimer is improved by as much as 200:1. Acetonitrile is the preferred solvent but other solvents such as DMF, DMSO, or THF are acceptable. A wide variety of organosilanols have been prepared (Scheme 14) <2000JA12011, 2000OL1887>. Functional groups such as conjugated alkenes, alkynes, sulfur, and another silicon group are tolerated. Interestingly, this mild procedure can be used for the oxidation of optically active silanes and causes complete inversion at the silicon center. (+)-Methyl-(α -naphthyl)phenylsilane is converted to (-)-(α -naphthyl)PhMeSiOH in 97% yield <2000JA12011>.



Scheme 14

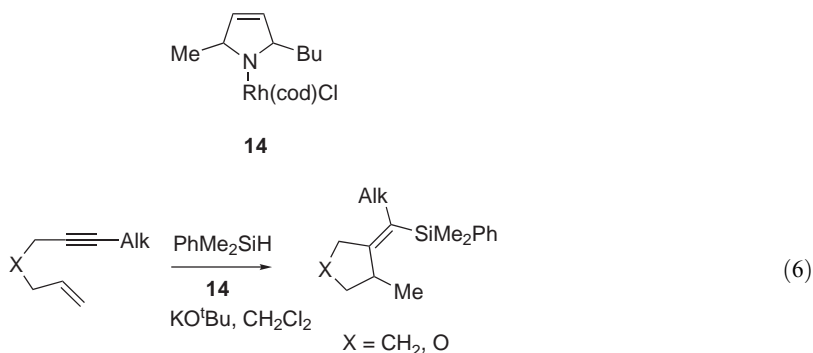
Transition metal-catalyzed hydrosilylation/cyclization has become a useful synthetic procedure. Intramolecular hydrosilylation of alkynes to give vinyl silane is possible using a variety of transition metals. Speier's catalyst ($\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$ in CH_2Cl_2) <2001OL61> and Pt-dimethyldivinylsiloxane **13** have been identified as the preferred catalysts (Scheme 15).



Scheme 15

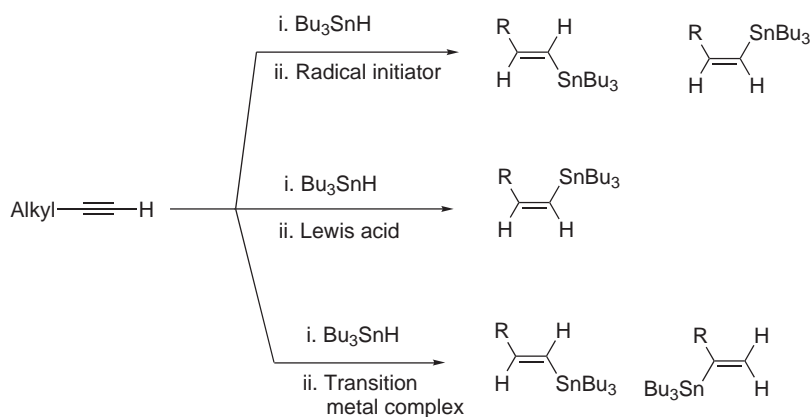
Several examples of hydrosilylation/cyclization using transition metals (Pd, Rh, Pt, Ni, Yt) have been reviewed <2003EJOC4341, 2002ACR905>. Many of these catalysts are used in combination with phosphine ligands. *N*-Heterocyclic carbenes <2002CR3667> are being used as alternatives to

phosphine ligands. Sometimes these *N*-heterocyclic carbenes are referred to as ionic liquids. Cyclosilylation of enyne compounds occurs with silanes and rhodium complex **14**. The complex **14** is prepared from the imidazolium salt 1-*t*-butyl-3-methyl-imidazolium hexafluorophosphate ((MBI)PF₆) and RhCl(cod)₂ in THF and KO^tBu¹ (Equation (6)). A hindered silane, such as Me₂PhSiH, is preferred over Et₃SiH. Terminal alkynes do not undergo cyclization <2003EJOC4341>:



2.19.6.4 Hydrostannations

The addition of hydrostannanes to alkynes provides a straightforward and efficient route to vinylstannanes, which are versatile reagents for C—C bond formation <1998T263, 2004JA474, 2003OL803, 2000T389>. Generally, the hydrostannylation is achieved by: (i) a radical initiator, (ii) a transition metal catalyst, or (iii) a Lewis acid (Scheme 16) <2001JA4101>. Although stannyl radicals induce isomerization of the product, the radical process is still considered to be valuable in many circumstances. Radical hydrostannylation (Bu₃SnH/AIBN), Pd(0)-catalyzed hydrostannylation [Bu₃SnH/Pd(0)], and stannylcupration [Bu₃Sn(R)CuCNLi₂] conditions have been studied with enynols <1997JOC7768>. Except for the radical stannylation reaction, high regio- and stereoselective formation of vinyl- and dienylstannanes is obtained.



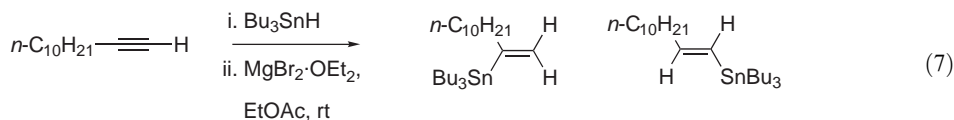
Scheme 16

Transition metal-catalyzed hydrostannylation of alkynes usually occurs via stereospecific *syn* addition of tin hydride. The regio- and stereochemistry is controlled by substrate steric effects. Notable exceptions to this general steric control are the α -regioselectivities obtained with substituted phenyl acetylenes, alkynyl esters, enynes, and phenyl thioalkynes <2000CR3257>. In comparison to metal-catalyzed hydrosilylation, hydroboration, and hydroalumination, hydrostannylation has received much less attention <2000CR3257>.

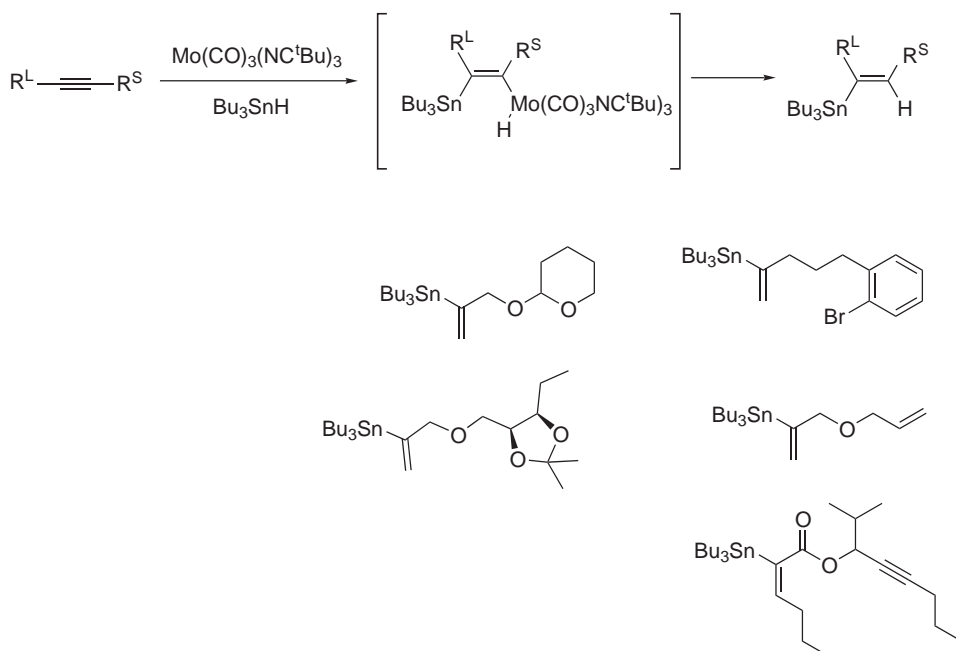
Lewis acid-promoted regioselective intramolecular hydrostannylation is not suitable for alkynes bearing polar groups such as ethers and amines, because the Lewis acid complexing center is blocked. Prop-2-ynylic ethers or amines, which are synthetically much more important than simple alkynes, are not suitable for *trans* addition. Dibutyl chlorostannane exhibits high chemoselectivity toward homolytic hydrostannylation of allyl and homoallyl alcohols. The chemoselectivity is attributed to the coordination

of the polar hydroxyl group to the Lewis acidic tin center in the β -stannyl radical intermediate. This is in clear contrast to the behavior of tributyltin hydride, which gives product mixtures containing predominantly either the (*E*)- or the (*Z*)-isomer. In contrast, under free radical conditions, dibutylchlorosilane with unsubstituted prop-2-ynyl alcohols and ethers gives a clean regiospecific *trans* addition. However, with substituted prop-2-ynyl residues attached to either oxygen or nitrogen, the desired product is produced in variable yields <1998CC1201>. In the absence of a radical initiator, Bu_2SnClH spontaneously adds to alkynes and the isomeric ratio is dependent on the solvent. Radical initiator Et_3B not only accelerates the hydrostannylation but also increases the amount of (*Z*)-isomer <2003JOC8730>. It should be noted that Et_3B -initiated addition of Bu_3SnH to alkynes in toluene is slower than that of Bu_2SnClH and also shows lower (*Z*) selectivity. In general, the stereoselectivity, as a result of the radical initiator Et_3B , is much better than that with 2,2'-azobisisobutyronitrile (AIBN). Stereoselectivity of stannylation of homo- and bishomopropargyl alcohols, however, is low.

The lithium-metalloid exchange reaction is the mildest and most general procedure for the preparation of organolithium reagents. Tin, selenium, aluminum, and tellurium "ate" complexes have also been used in organic synthesis. Characterization of ate complexes is not trivial but they have been found to be of considerable synthetic value. The role of ate complexes in lithium-sulfur, lithium-selenium, and lithium-tellurium exchange reactions has been reviewed <2002HCA3748>. The α -stannylation of simple aliphatic alkynes is difficult due to the lack of metal coordinating groups. The hydrostannylation of simple aliphatic alkynes by the ate complex prepared from $\text{MgBr}_2\cdot\text{OEt}_2$ and $\text{Bu}_2^{\text{n}}\text{SnBrH}$ gives a high degree of α -stannylation product. Optimum yields are obtained with a stoichiometric ratio of the reagents and alkyne: $\text{Bu}_2^{\text{n}}\text{SnIH}:\text{MgBr}_2\cdot\text{OEt}_2$ (0.5:1:2) in ethyl acetate (Equation (7)) <2001JA4101>.



In the presence of transition metal catalysts, alkynes undergo *syn* hydrostannylation giving α,β -(*E*) vinylstannanes as regioisomeric mixtures. This is true with both palladium and molybdenum catalysts. Although the molybdenum catalyst, $\text{MoBr}(\text{allyl})(\text{CO})_2(\text{CH}_3\text{CN})_2$, is suitable for hydrostannylation of propargylic alcohols, it does not show significant regioselectivity with internal alkynes <2000EJOC2761>. Regioselective hydrostannylation can be achieved using the modified molybdenum catalyst $\text{Mo}(\text{CO})_3(\text{Bu}^t\text{NC})_3$. A good level of α -regioselectivity across a range of alkynes is observed (Scheme 17). This protocol tolerates a wide range of functional groups <2000EJOC2761>.

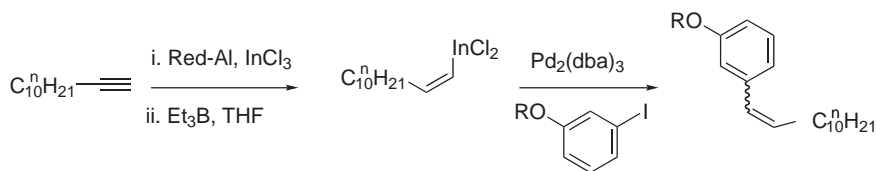


Scheme 17

The steric bulk of isonitrile has a significant effect on the regioselectivity. While phenyl-isonitrile ligand gives moderate regioselectivity, electron-donating alkoxyphenyl isonitrile increases the regioselectivity significantly <2002JOM26, 1999OL1017>. With $[\text{RuCl}_2(p\text{-cymene})]_2$ as catalyst, high regio- and stereoselectivity are observed in the hydrosilation reaction of various terminal alkynes to afford β -(*Z*)-vinyl silanes. A directing effect is also observed with alkynes having a hydroxyl group at the β -position with respect to the triple bond. In these cases, α -vinyl silanes are produced predominantly <2000OL1887>.

2.19.6.5 Hydrogallation and Hydroindation

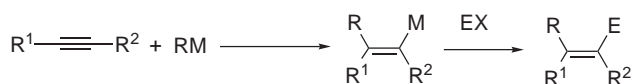
Hydrometallation, e.g., with boranes and aluminum hydrides, usually proceeds in *syn* fashion to give (*E*)-alkyl metals selectively. The preparation of (*Z*)-alkyl metals from alkynes needs several steps and protection of functional groups such as hydroxyl and carboxyl groups. Triethylborane-mediated hydrogallation (HGAlCl_2 is prepared from gallium trichloride and Red-Al in THF) and hydroindation (HInCl_2 is prepared from InCl_3 and DIBAL-H) of alkynes gives hydrogallium and hydroindium compounds, respectively. Indium compounds give high ratio of (*Z*)-isomers at lower temperature and require shorter reaction times than gallium compounds. The regiochemical outcome is dictated by the polar groups in the case of internal triple bond. The addition reactions of GaH proceed via a radical mechanism. Many functional groups—including hydroxyl, carbonyl, and carboxy groups—are tolerated. The hydroindation proceeds much faster at an alkynyl moiety than at an alkenyl group, thus allowing intramolecular cyclization with suitably positioned alkynyl and allenyl groups in the same molecule. The gallium and indium adducts undergo cross-coupling with aryl iodides <2003JOC6627> (Scheme 18).



Scheme 18

2.19.7 CONTROLLED CARBOMETALLATION METHODS

The intermolecular addition of organometallics to alkynes (carbometallation) constitutes an excellent method for the preparation of alkenyl organometallics, which after reaction with electrophilic reagents ($\text{E}-\text{X}$) provide polysubstituted alkenes (Scheme 19). In particular, carbocupration, zirconium-catalyzed carboalumination <1997JOC784>, nickel-catalyzed carbozincation <1998T1299>, allylzirconation <1997TL3031, 1997CC743>, allylgallation and alkylolithiation <2001AN(E)621>, and vinylzirconium and dienylylzirconium <2003JA13258> have high synthetic potential due to wide applicability. Usually they all provide *syn*-carbometallation unless there is a chelating group such as a free hydroxyl group in the β - or γ -position.



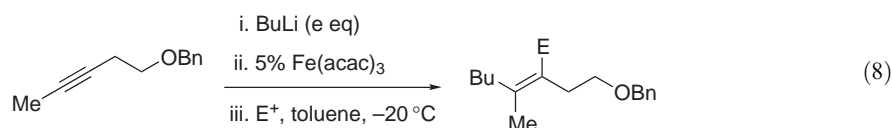
Scheme 19

2.19.7.1 Carbometallation with Organometals Containing Group 1 and 2 Metals

Although organolithium and organomagnesium reactions have been extensively used in organic synthesis, they are rather sluggish and their carbometallation of alkynes has limited synthetic use. Only a particular kind of alkyne (internal alkynes) can be used for synthetic purposes. Vinylolithium intermediates tend to isomerize with ease due to the reagent's basic nature <2003AN(E)4302,

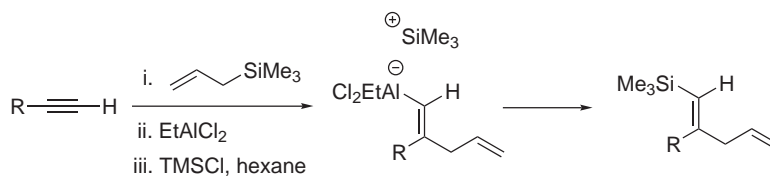
[2000OL419](#)>. In their place more versatile and convenient reagents made up of elements—such as copper, aluminum, zirconium, nickel, gallium, and indium—have been reported ([Section 2.19.7.2](#)).

Stereoselective carbolithiation of alkynes containing functional groups—such as ethers, amines, and aryl rings—with alkylolithium reagents such as butyllithium in the presence of a catalytic amount of FeCl_3 or $\text{Fe}(\text{acac})_3$ is possible ([2001AN\(E\)621](#)>. The reaction solvent is crucial: benzene or toluene is preferred. $\text{Fe}(\text{II})$ salts give poor yields. The Lewis basic metal moiety, in alkyne substrates (e.g., amines, ethers), not only activate the alkyne toward alkylation (butylation) but also control the stereochemistry. The vinylolithium intermediates can further react with electrophiles—such as deuterium chloride (DCl), TMSCl , ketones, and aldehydes—generating tetrasubstituted alkenes stereospecifically ([Equation \(8\)](#)).



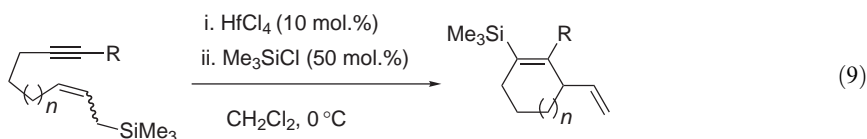
2.19.7.2 Carbosilation, Gallation, and Zincation

Introduction of a C—Si, C—In, C—Zn, or C—Ga unit (instead of an H—Si, H—In, H—Zn, or H—Ga) into unsaturated bonds is referred to as carbosilylation, carboindation, carbozincation, or carbogallation ([1995JA9814](#)>. Allylmethallation reactions of C—C triple bonds are known for organometallic compounds of Mg, B, Al, In, Zn, Ti, Zr, and Ta ([1997CC743](#)>. While some carbon—metal bonds such as C—Al and C—Cu are reactive enough to undergo further carbometallation reactions, most C—Si bonds are inert under the usual reaction conditions. However, allylsilation of simple unactivated acetylenes with allyl silanes are catalyzed by Lewis acids such as EtAlCl_2 . For example, the reaction of phenyl acetylene with allyltrimethylsilane in the presence of TMSCl gives *trans*-allylsilylated alkenes in good yields. Other Lewis acids—such as AlCl_3 , AlBr_3 , and HfCl_4 —are also reasonable but EtAlCl_2 gives the best yields ([Scheme 20](#)) ([1996JOC4874](#)>.

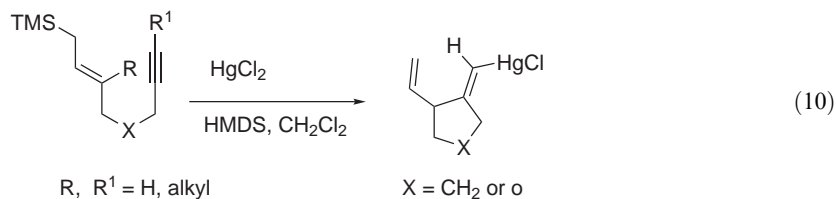


Scheme 20

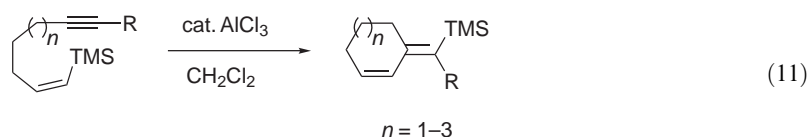
This method is also applicable to other silanes such as crotyltrimethylsilane. In all cases, *trans* product is formed in line with other aluminum-catalyzed carbometallation reactions. Interestingly, in all these reactions excess TMSCl is needed to drive the equilibrium over to the right, in favor of replacing aluminum with silicon. In place of TMSCl — EtAlCl_2 , HfCl_4 catalyzes allylsilation in dichloromethane at 0°C to give similar results. Other Lewis acids—such as ZrCl_4 , TiCl_4 , SnCl_4 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, ZnCl_2 , and $\text{B}(\text{C}_6\text{F}_5)_3$ in dichloromethane—do not catalyze this addition ([1997JA6781](#)>. Metal-catalyzed or metal-mediated intramolecular carbocyclizations of alkynes generally result in the *exo* product. However, HfCl_4 -catalyzed intramolecular allylsilation of unactivated alkynes proceeds exclusively in the *endo* fashion to give five-, six-, and seven-membered carbocycles in moderate to high chemical yields; none of the *exo* cyclization product is observed ([Equation \(9\)](#)) ([1998JA5339](#)>.



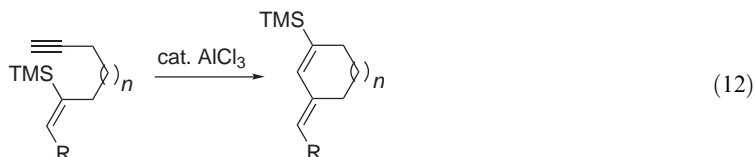
Alkynyl-tethered allylic silanes undergo intramolecular C—C bond formation with mercuric salts <1997JOC8595>. This method can be utilized for the preparation of carbocycles as well as heterocyclic mercurials. In these reactions yields are not very high and undergo five- or six-*endo* ring formation (Equation (10)). In order to suppress the acidity of the reaction, medium hexamethyldisilazene (HMDS) is used.



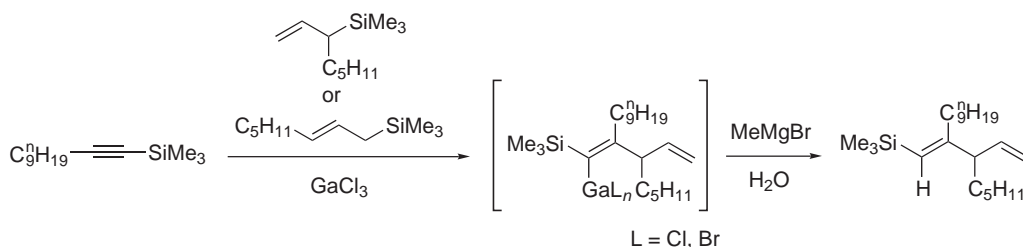
It is known that the reactivity of vinyl silanes toward electrophiles is much lower than that of allyl silanes. In spite of this limitation, intramolecular vinylsilation can be achieved with unactivated alkynes in the presence of a catalytic amount of Lewis acid (EtAlCl₂) to give (*E*)-cyclic dienyl silanes in good yield (Equation (11)) <1999JA3797>. This is a stereo- and regiospecific reaction, and 6- or 7-membered rings can be synthesized. Other Lewis acids such as AlCl₃ and AlBr₃ are ineffective and CH₂Cl₂ or hexane can be used as solvent.



The EtAlCl₂-catalyzed carbosilylation of phenyl acetylene with propargyltrimethylsilane gives the 1,4-enyne in 34% yield <2000TL4499>. Other Lewis acids such as HfCl₄ and ZrCl₄ give lower yields. Nonterminal propargyltrimethylsilanes and allenyltrimethylsilanes give vinylallenes. The allenyltrimethylsilane also gives 1,4-enynes. The vinylallenes, which are useful building blocks, are produced in regio- and stereoselective fashion (Equation (12)).

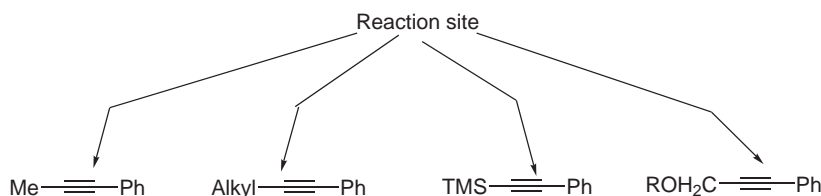


The allylgallation reaction of silylalkane derivatives of alk-1-yne takes place upon reaction with allyl silanes and GaCl₃ <1997CC743> to give allylgallium derivatives which undergo cross-coupling with Grignard reagents (Scheme 21). The gallium-mediated dimerization of alkynes does not occur under these conditions and C—C bond formation occurs regioselectively at the β -carbon atom of the alkyne with an (*E*)-relationship between the silyl and allyl groups. The α - or β -alkylallylsilanes couple at the initial carbon atom having a silicon group. Secondary aliphatic and aromatic alkynes can be reacted under these conditions.



Scheme 21

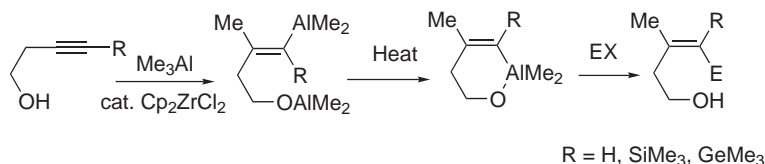
The addition of dialkylzinc or diphenylzinc to substituted phenyl acetylenes occurs in the presence of a catalytic amount of $\text{Ni}(\text{acac})_2$ in THF:NMP solvent mixture. The *syn*-carbozincation occurs with good to excellent regio- and stereochemistry [<1998T1299, 2001MI313>](#). With substituted phenyl acetylenes bearing longer alkyl chains, a lower regioselectivity is observed. Using silylated phenyl acetylenes with substituted propargylic ethers, the opposite regioisomers are obtained selectively. These vinylzinc compounds ([Scheme 22](#)) can be reacted with a variety of electrophiles, such as water, allyl bromide, I_2 , and aromatic or aliphatic ethylene derivatives.



Scheme 22

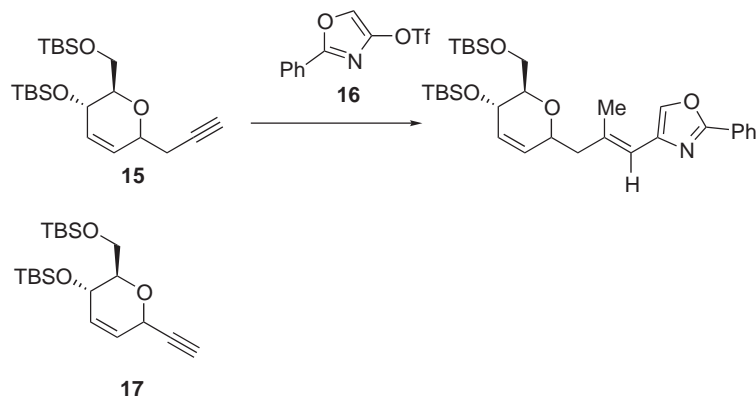
2.19.7.3 Zirconium-catalyzed Carboalumination and Related Reactions

As stated earlier ([Section 2.19.6.1](#)), hydroalumination reactions of hydroxypropynes ($\text{HORC}\equiv\text{CZ}$; $\text{Z} = \text{H, Si, or Ge}$, $\text{R} = (\text{CH}_2)_n$) are stereospecific due to internal chelation by the free hydroxyl group. However, when heated, such carboaluminates undergo isomerization. For example, treatment of 3-butyne-1-ol with Me_3Al (3 equiv.) and Cp_2ZrCl_2 (25 mol.%) in CH_2Cl_2 at room temperature produces, as expected, the *syn*-carboaluminate which upon heating undergoes complete reversal of the stereochemistry to give *anti* product ([Scheme 23](#)) [<1997JOC784>](#).



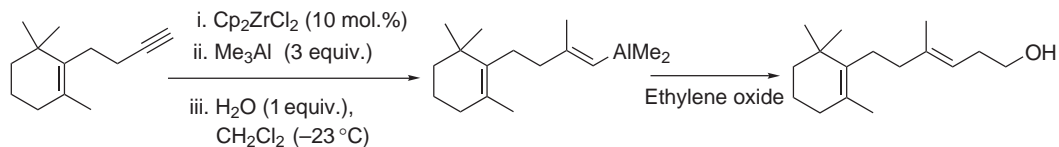
Scheme 23

The zirconium-catalyzed carboalumination of terminal alkynes is a useful reaction for the preparation of trisubstituted alkenes. On a number of occasions this reaction has been used during the synthesis of multifunctional compounds. The carboaluminates undergo C—C coupling with a variety of coupling partners such as alkenyl halides, triflates, mesolates, and nonaflates. In spite of its versatile synthetic applicability, a slight variation in the alkyne structures profoundly influences the viability of the reaction [<2000OL469>](#). For example, optimal cross-coupling reaction conditions (Cp_2ZrCl_2 (10 mol.%), AlMe_3 (1.2 equiv.), $\text{Pd}(\text{PPh}_3)_4$ (10 mol.%), alkyne (1.0 equiv.) and oxazole **16**), developed for the carbometallation of compound **15** ([Equation \(13\)](#)), do not work for alkyne **17**.



(13)

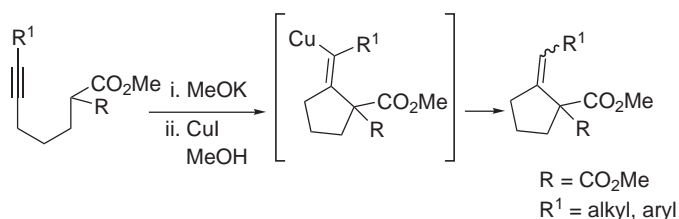
It has been observed that the presence of water (1 equiv.) in zirconium-mediated hydroalumination reactions causes an increase in the reaction rate and requires only a catalytic amount of zirconocene dichloride. Also, the reactivity of alkenylalanes can be substantially increased by converting them into ate complexes using alkylolithium reagents such as Bu^nLi <2003JOC4008>. The combination of these experimental conditions, i.e., ate complex and water addition, allows the preparation of a variety of trisubstituted alkenes (Scheme 24) <2002HCA3478>.



Scheme 24

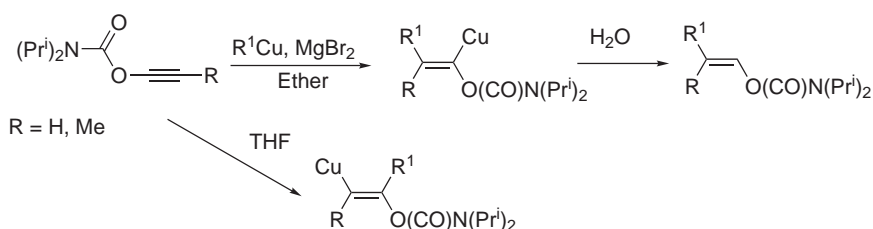
2.19.7.4 Carbocupration of Alkynes

A wide variety of alkane and alkene copper reagents have been added to alkynes in both intra- and intermolecular reactions. These reagents are generally sluggish and are often catalyzed by other reagents such as zirconium and palladium compounds. The intramolecular carbometallation of terminal alkylsilyl reagents using internally generated carbanions gives *exo*-cyclic vinylic copper (Scheme 25). These products are easily protodesilylated in the presence of methanol. Although the addition product generates stereospecifically (*Z*)-vinylcopper, the product isomerizes to the thermodynamically more stable (*E*)-isomer under the reaction conditions <1999TL1297>.



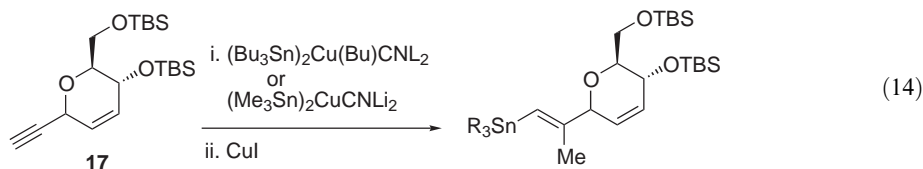
Scheme 25

Organocuprates add to substituted alkynes giving pure stereo- and regioisomers <1997JA4887>. This is not the case when heteroatoms such as oxygen or nitrogen are directly attached to the alkyne carbon atom. Usually, these groups direct the formation of β -substituted (branched) products. Although ethynyl carbamate derivatives are oxo-substituted acetylenes, the electron-withdrawing properties of the carbamyl group and its ability to coordinate organometallic derivatives direct the formation of α -substituted (linear) products. Alkynyl carbamates when reacted with organocopper derivatives (R^1Cu and MgBr_2 in ether at -78°C) give exclusively linear carbometallated products (Scheme 26) <2003OL5087>. The vinylcuprate thus formed can be allylated, protonated, or trapped with aldehydes. Interestingly, in THF the reaction takes a different course, forming mainly β -substituted (branched) products.



Scheme 26

The addition of the (tributylstannyl)butylcuprate reagent (Bu_3Sn)Cu(Bu)CNLi to the pyran **17** followed by trapping of the intermediate alkenylcuprate with MeI gives a vinylstannane in 80% yield (Equation (14)), <2000OL469> while similar zirconium-catalyzed aluminations does not work (see Equation (13)).

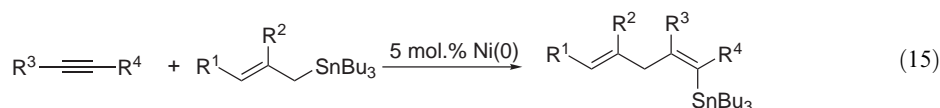


2.19.7.5 Carbometallation with Other Organotransition Metals

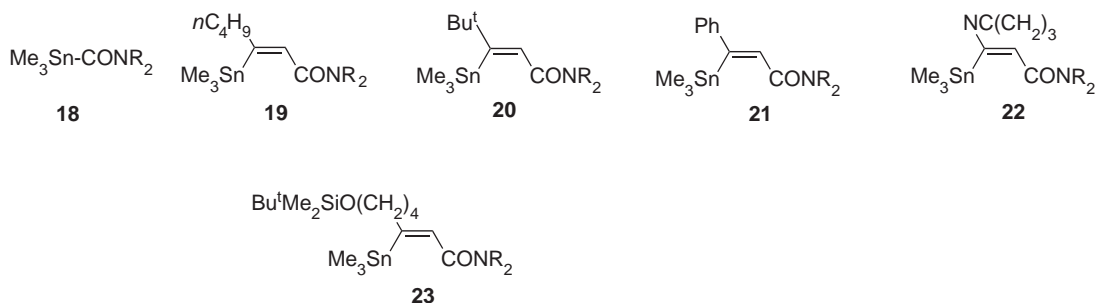
Catalytic carbometallation reactions are ubiquitous and their synthetic importance, particularly for the synthesis of natural products, has been highlighted <1996CR365, 2000T5959, 2003T885>. Alkyne intermediates are capable of undergoing further carbometallation leading to a cascade of carbometallation reactions.

2.19.7.5.1 Stoichiometric carbometallation with organotransition metals

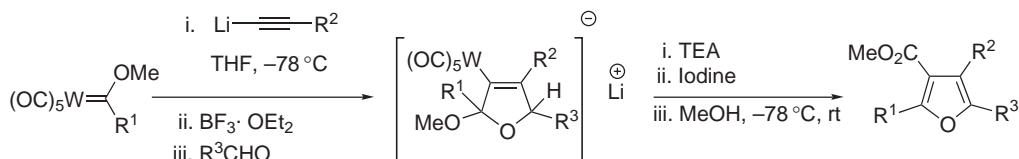
The regiochemistry of carbopalladation of simple alkynes is opposite to that of carboalumination and carbocupration. However, the regiochemistry of intramolecular carbopalladations is normal in the sense that it favors *exo*-mode cyclizations. The intramolecular carbopalladation of the cyano group (alkyne equivalent) is employed for the synthesis of 2-aminonaphthalenes. (2-Iodophenyl)acetonitrile reacts with a variety of internal alkynes to afford 2-aminonaphthalenes <2003JOC339>. Many of the alkenyl metal reagents required for the preparation of allylic alcohols are generated *in situ* using either stoichiometric amounts or excess of one or more transition metal reagents. The preformed alkenylboranes and zirconocenes are transmetallated to promote carbonyl addition. The palladium-catalyzed alkenylstannylation of alkynes proceeds with exclusive *syn*-selectivity and with acceptable regioselectivity <1998JA2975>. The scope of the reaction is limited to alkenylstannanes and alkynes containing relatively electron-deficient groups. Nickel-catalyzed carbostannylation of electron-rich internal alkynes with alkenylstannanes, allylstannanes, or acylstannanes work well <1999JA10221>. Allylstannylation is best achieved with $\text{Ni}(\text{cod})_2$ (no added ligand). $\text{Ni}(0)$ is also a very effective catalyst. The active catalyst is prepared by the reaction of $\text{Ni}(\text{acac})_2$ and DIBAL-H. Its regioselectivity is much better than that with Pd catalysts. Internal alkynes and electron-deficient terminal alkynes are not suitable for the nickel-catalyzed allylsilations. A generalized reaction is shown in Equation (15).



The transition metal-catalyzed addition of homo- and heteroelement–element compounds to triple bonds in one step opens a synthetic route to functionalized alkenes. The replacement of the new carbon–element bond by C–M, C–Hal, or C–C bonds via cross-coupling allows the preparation of tri- and tetrasubstituted alkenes. When two different elements are used, it is possible to introduce the substituents step by step. A special feature of the addition of an element–element compound is the regio- and stereoselectivity. The reaction proceeds in a *syn* fashion, whereas radical addition gives the opposite configuration. The addition reactions of Si–Si, Ge–Ge, Si–Sn, Sn–Sn, and Sn(Si,Ge)–Se(Te) bonds have been reviewed <1999CR3435>. Interestingly, the rhodium complex $\text{Rh}(\text{acac})(\text{CO})_2$ catalyzes the addition of Sn–CONR₂ across the CC triple bond, in which the regioselectivity is reversed relative to nickel-catalyzed reactions <2000OM3269>. The reactions of amide **18** with terminal alkynes result in regio- and stereoselective formation of (*Z*)-β-stannyl-α,β-unsaturated amines via *syn*-addition. The size of the alkyne substituents does not significantly affect the reactivity or the regiochemistry <2000OM3269> **18–23**.

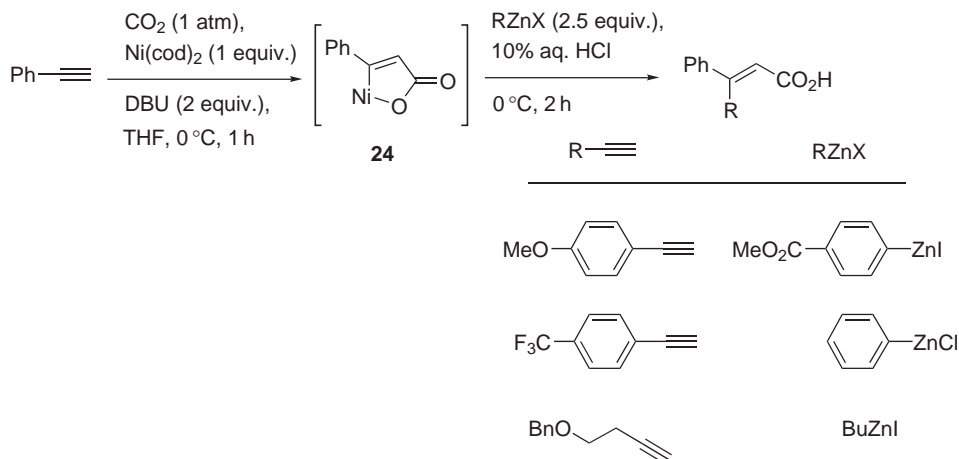


Fischer-type carbene complexes react with alkynyllithiums and the resulting species react with a variety of electrophiles such as aldehydes and imines to give trisubstituted furans and pyrroles, respectively [<1998JOC3164>](#). Use of an isocyanate (a carbonyl equivalent) gives lactams [<1997JOC1918, 2001TL2533>](#). Molybdenum complexes work much better than tungsten complexes (Scheme 27).



Scheme 27

Transition metal-complex-catalyzed reactions of organoheteroatom compounds derived from B—B, Si—Si, Al—Si, Si—P, Si—Sn, and Sn—Sn with aryl halides provide a variety of aryl metal compounds [<1999OL1725>](#). For example, the reaction of phenyltributylstannylselenide with aryl halides in the presence of a catalytic amount of $Pd(PPh_3)_4$ gives diaryl selenides in moderate to good yields. Reactions of this type have been reviewed [<2000CR3163>](#). In the presence of stoichiometric amounts of zero-valent nickel complex, the reaction of alkynes with CO_2 gives a nickelacycle **24** which can be reacted with a variety of organozinc reagents under very mild conditions to provide β, β' -disubstituted acrylic acids in a highly regio- and stereoselective manner (Scheme 28) [<2001OL3345>](#). The intermediate **24** can be hydrolyzed or reduced with diethylzinc to give the *syn* CO_2H addition product. The reaction is not only restricted to simple dialkylzincs but also to functionalized zinc reagents.



Scheme 28

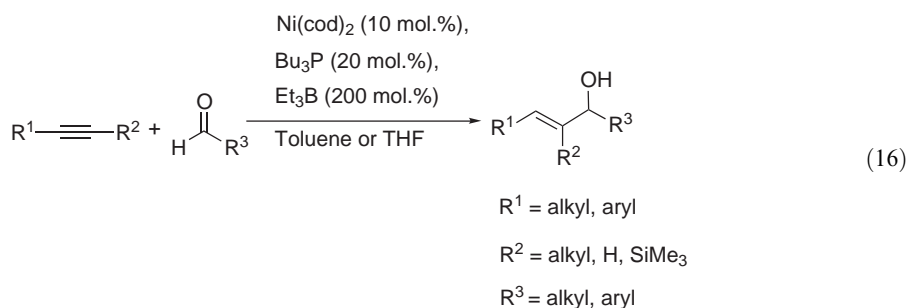
Intramolecular domino reactions have been effectively used for the synthesis of complex natural products. The corresponding intermolecular domino reaction with high selectivity is equally important but less often discussed. For this purpose palladium and nickel catalysts have been used for the tandem coupling of α,β -enones, alkynes, and alkynyltins in a regio- and stereoselective-conjugated enyne synthesis <1996JOC8248>. These reactions have prominence in synthesis and have been reviewed <2000ACR511>.

2.19.7.5.2 Carbometallation with organotransition metals in catalytic reactions

As described in COFGT (1995) <1995COFGT(2)951>, carbopalladation reactions are important C—C bond formation reactions, although palladium and other transition metal complexes have not been isolated. Vinyl- and arylpalladium compounds have been extensively used for the formation of not only C—C bond compounds but also C—N compounds <2003JOC8068, 2001JOC2560, 1998ACR805, 1998AN(E)2046> and C—O compounds <2003JOC6716>.

The treatment of 5-hexynal and an alkenylzinc with a catalytic amount of $\text{Ni}(\text{cod})_2$ (5 mol.%) at 0°C in THF results in stereoselective introduction of the exocyclic trisubstituted alkenes <1997JA9065, 1996JOC1562>. In this reaction organozincs have been synthesized *in situ* from organolithium or organomagnesium reagents and anhydrous zinc chloride. Both sp^2 - and sp^3 -hybridized organozincs, including those that possess β -hydrogens, have been incorporated without competing β -hydride elimination. Pyrrolidines can be prepared by incorporating nitrogen in the tethered chain. The Pt-catalyzed carboselenation of terminal alkynes with selenoesters provides vinylselenium compounds. The organozinc substituent is introduced exclusively *cis* to the alcohol function. When direct addition of organozinc to aldehyde is problematic, catalytic loading is increased to a higher mol.%. In this nickel-catalyzed coupling and cyclization process, vinyl-zirconium reagents can be used instead of alkylzinc compounds to create 1,3-dienes using aldehydes or enone functions as coupling partners <2002OL1743>.

Generally, the reductive coupling of alkynes with aldehyde needs stoichiometric amounts of reducing agent. Consequently, starting materials and products are subjected to further undesired reactions such as reduction, reductive dimerization of the aldehydes, and oligomerization of alkyne. A reductive coupling of alkynes with aldehyde is possible using a catalytic amount of low-valent Ni with phosphine ligands such as Bu_3P and excess Et_3B in either THF or toluene. In all cases, the reaction gives (*E*)-isomer without any regioisomer formation (Equation (16)) <2003OL3871, 2000OL4221>.



2.19.8 OXYMETALLATION, HALOMETALLATION, AND OTHER HETEROMETALLATION REACTIONS

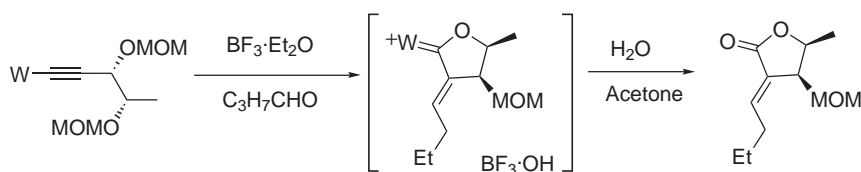
Electronegative heavy atoms, e.g., Hg and Tl, readily undergo oxymetallation and halometallation. A few decades ago oxymercurations were utilized extensively in organic synthesis, but such reactions are now accomplished with less toxic metals. Very little work using oxymercuration, oxythallation, or oxypalladation (Wacker oxidation) reactions have been reported since the publication of COFGT (1995) <1995COFGT(2)951> and none appear to be novel or new.

2.19.9 OXIDATIVE COUPLING AND OXIDATIVE METALLATION OF ALKYNES

2.19.9.1 Oxidative Coupling-ring Expansion Tandem Processes

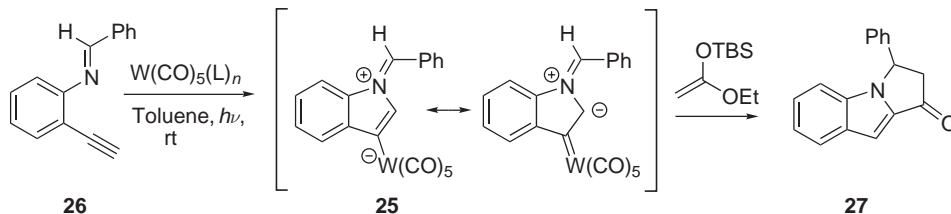
This section deals mainly with the resonance hybrids of metallocyclopropenes and alkyne-metal π -complexes. The organocobalt intermediates (vinyl metals) have not been isolated. The most widely used reaction of this type is the cobalt-mediated synthesis of the five-membered heterocycles, such as pyrroles, imidazoles, furans, and thiophenes. Several reviews have appeared on this type of reaction <1999CEJ3549>. The cyclopentenone is formed by cyclization of an alkyne, alkene, and carbon monoxide in the presence of $\text{Co}_2(\text{CO})_8$ in a formal $[2+2+1]$ -cycloaddition. Alkyne dimerization and insertion of CO is generally referred to as the Pauson–Khand reaction. The Pauson–Khand reaction is tolerant of a wide variety of functionalities such as esters, ethers, thioethers, tertiary amines, amides, sulfonamides, nitriles, and alcohols, which makes this reaction attractive for organic synthesis. For synthetically useful reactions, the substrates (usually 1,6 en-diyne) are reacted with 1 equiv. of $\text{Co}_2(\text{CO})_8$ in methylene chloride and then the resulting complex is decomposed *in situ* by amine *N*-oxides, such as NMO, to give cyclopentenone derivatives <1996JOC7666>.

The reaction of alkynyltungsten complexes with aldehydes and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (-20°C) is presumed to give oxacarbenium salts which are demetallated by acetone/water in air to give lactones (Scheme 29). Other aldehydes such as alkynyl aldehydes can be used.



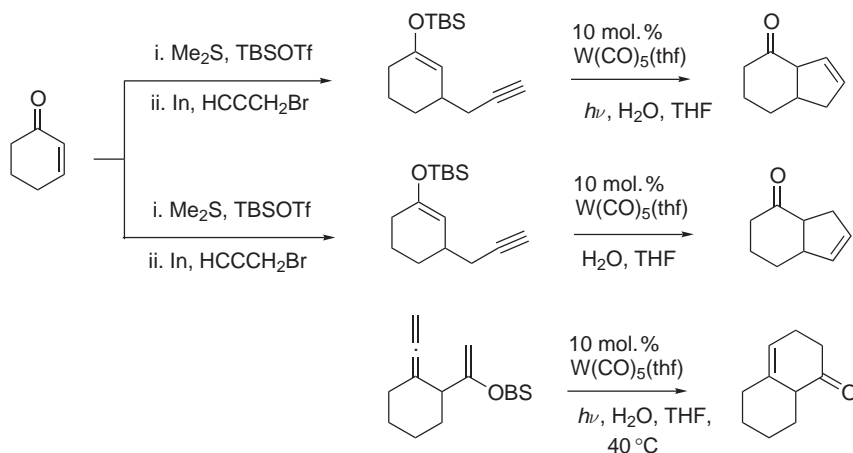
Scheme 29

The tungsten containing azomethine ylide **25**, generated by the nucleophilic *endo* attack of the imine nitrogen of the imine **26** onto the *o*-alkynyl group when activated by $\text{W}(\text{CO})_5$, undergoes $[3+2]$ -cycloaddition with electron-rich alkenes (Scheme 30) <2002JA11592>. Either a stoichiometric amount of $\text{W}(\text{CO})_6$ in toluene at ambient temperature or a catalytic amount of $\text{W}(\text{CO})_6$ (10 mol.%) gives a very high yield of product **27**.



Scheme 30

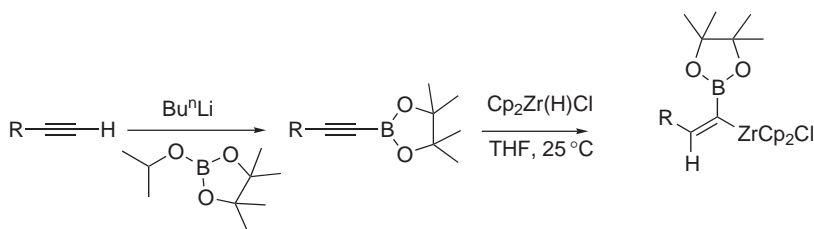
The indium-mediated allenylation of α,β -unsaturated ketones in the presence of *t*-butyldimethylsilyl triflate and dimethyl sulfide gives 6-siloxy-1,2,5-trienes which undergo $\text{W}(\text{CO})_5\text{L}$ -catalyzed 5-*endo* cyclization to give the corresponding cyclopentene derivatives in good yield <2003OL1725>. This type of cyclization of allenyl silyl enol ethers proceeds in a 6-*endo* manner when 5-siloxy-1,2,5-trienes are employed as substrates (Scheme 31).



Scheme 31

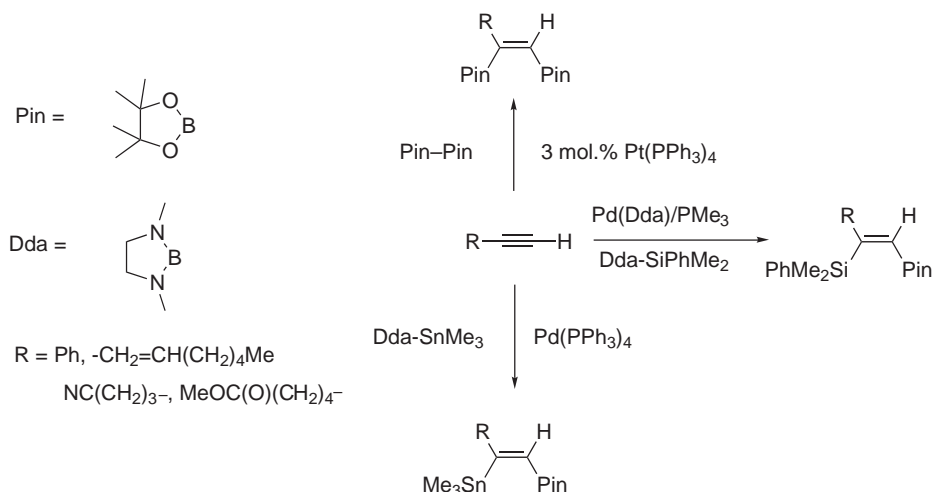
2.19.9.2 Oxidative 1,1-Bimetalloalkenes

Transition metal-catalyzed addition of homo- and heteroelement–element compounds to triple bonds has been reviewed [<1999CR3435>](#) (see [Section 2.19.7.5.1](#)). The chemistry of bimetalloalkenes, e.g., C—Zr and C—B bonds, differs considerably, allowing a sequential substitution on alkenes. In addition, the cleavage of the C_{sp^2} —Zr and C_{sp^2} —B bonds generally occurs with retention of geometry. Thus, the heterobiorganometallic compounds should be synergistic with one another, affording products with unique chemistry not attainable by each reagent by itself. 1,1-Bimetalloalkenes (e.g., Al and Ti, Al and Zr, Al and Hf, Ga and Zr, Zn and B, Zn and Zr, and Sn and Zr) behave as alkylidene-transfer reagents [<1994JA10302>](#). A representative example of a 1,1-bimetalloalkene of B and Zr is shown in [Scheme 32](#). The Bu^t derivative ($R = Bu^t$) is stable and can be isolated. Sequential alkylation occurs first at the zirconium and then on boron [<1994JA10302>](#).



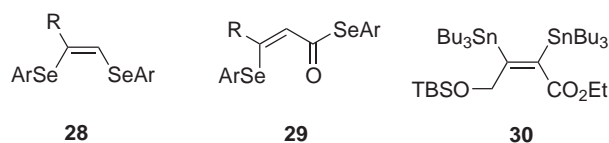
Scheme 32

Interestingly, the addition of bis(pinacolato)diborane to alkynes does not occur with $Pd(PPh_3)_4$. With $Pt(PPh_3)_4$ as catalyst, addition occurs efficiently to terminal or symmetrical diarylalkynes in high yield [<1999CC395>](#). The reaction prefers polar solvents such as DMF or MeCN. Terminal alkynes undergo the reaction at room temperature giving *syn* adducts in high yield and the terminal alkyne carbon ends up with the boryl group selectively. Highly stereo- and regioselective Pd-catalyzed addition of B—Sn and B—Si reagents to alkynes occurs. Boron–silicon reagents are sluggish under these conditions and the active catalyst for this reaction is $Pd_2(dba)_3 \cdot PMe_3$ which requires elevated temperatures. Both the regio- and stereoselectivities are similar to those of B—Sn reagents ([Scheme 33](#)). These bimetallic compounds participate in intramolecular carbocyclizations of ene-yne derivatives [<1999CC395>](#).

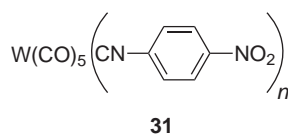


Scheme 33

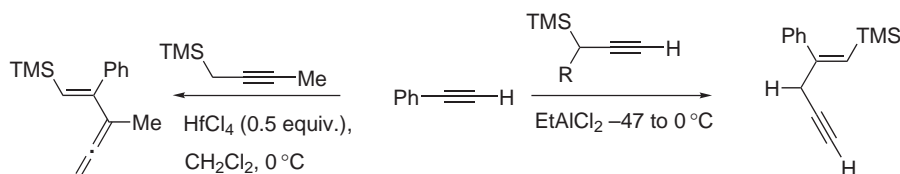
Palladium complexes such as $\text{Pd}(\text{PPh}_3)_4$ catalyze the addition of diaryl diselenides to terminal alkynes, leading to the formation of (Z)-1,2-bis(arylseleno)-1-alkenes **28**. Internal alkynes also react under these conditions, and can be used for carbonylative addition with pressurized CO giving the selenyl esters **29** <1991JA9796>. Functional groups—such as alcohols, amines, esters, and halides—are tolerated. Similarly, tributyltin derivative **30** can be prepared <1999JOC328>.



While the quest for better catalysts that improve the bismetallation of alkyne over Pd /phosphine ligands continues, a catalytic system has been found by replacing the PPh_3 ligand with Bu^tNC . This catalyst $[\text{Pd}(\text{Bu}^t\text{NC})_2\text{Cl}_2]$ enhances the rate of addition of Bu_3SnH (2 equiv.) <2003OL1653> to functionalized terminal alkynes at room temperature. Various functional groups—such as ethers, esters, alcohols, amines, TBDMS ethers, and $\text{N}(\text{boc})$ —are tolerated by this catalyst. Tungsten isonitrile complexes, such as **31**, have been shown to be efficient catalysts for distannation of alkynes in which tributyltin hydride is used as the tin source <2003AN(E)306>.



Quite often propargyl organometallic compounds, particularly substituted ones, undergo isomerization to allenylmetallic compounds with Lewis acids. The EtAlCl_2 -catalyzed carbosilylation of phenyl acetylene (terminal alkynes) with propargyl or allenyl silanes gives 1,4-enyne compounds in moderate yield along with many by-products <2000TL4499> (Scheme 34). Aluminum catalysts also cause the isomerization of alkynyl silanes to allenyl silanes. Complementary to this, HfCl_4 gives allenyl vinyl silanes with nonterminal propargyl trimethylsilanes (Scheme 34).

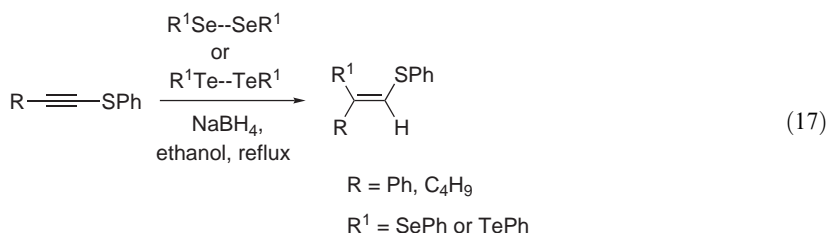


Scheme 34

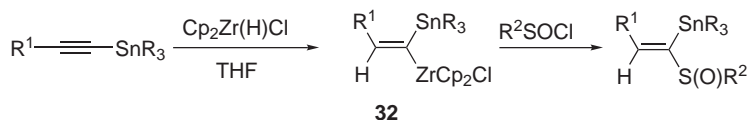
2.19.10 NONREDOX AND REDOX TRANSMETALLATION REACTIONS

Transfer of a carbon group from one metal to another is defined as transmetalation in COFGT (1995) <1995COFGT(2)951>. Transmetalation processes are ubiquitous throughout organometallic chemistry.

The treatment of phenylthioacetylenes with the organic tellurolate or selenolate anions generated *in situ* by the reaction of the appropriate dichalcogenide with NaBH₄ in ethanol gives the corresponding chalcogenes in high yield. The incorporation of the organotellurium (or organoselenium) moiety occurs at the β -position relative to the phenylthio group (Equation (17)) <2001TL1595>. The phenylthio group acts as a directing and activating group for the nucleophilic addition. The reactivity difference between vinylic tellurides (or selenides) and vinylic sulfides toward butyllithium suggests the possibility for selective functional group transformations. Similarly, TMS alkynes in place of phenylthioalkynes allow selective reaction with tellurides/selenides. TMS alkynes are unstable under these conditions and undergo desilylation followed by the expected addition reaction.

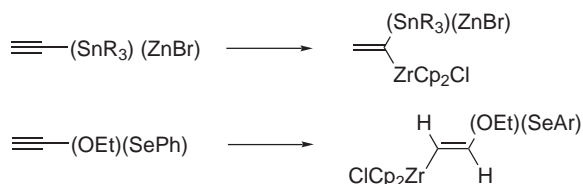


(*Z*)- α -stannyl-substituted α,β -unsaturated sulfoxides can be synthesized by hydrozirconation of alkynylstannanes (Scheme 35) <2000T8921>. The yields are medium to high. The intermediate zirconium complex **32** participates in cross-coupling reactions with a wide range of electrophiles, e.g., with diphenyliodonium chloride in the presence of catalysts such as Pd(PPh₃)₄ and CuI. Although alkylalkynylstannanes exclusively give α -zirconiums, arylalkynylstannanes give a mixture of α,β -zirconated derivatives in almost equal ratio.



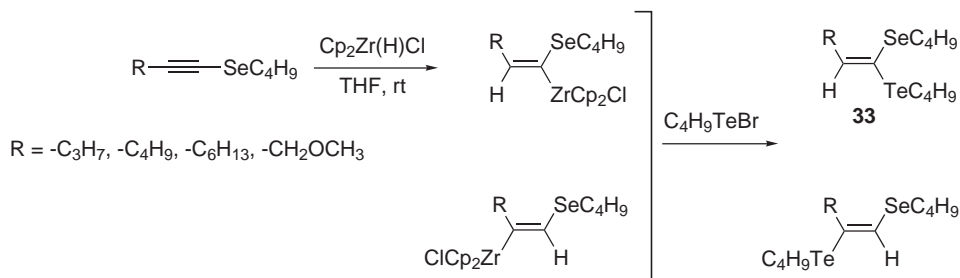
Scheme 35

Hydrozirconation of unsymmetrical disubstituted alkynes generally produces a mixture of two possible regioisomers. However, hydrozirconation of acetylenic chalcogenides occurs in such a way that the zirconium ends up on the carbon bearing the chalcogen. Ethoxyacetylene and arylselenylacetylenes are regioselectively converted into (*E*)-zirconium derivatives using Cp₂Zr(H)Cl (Scheme 36) <2000JOC54>.



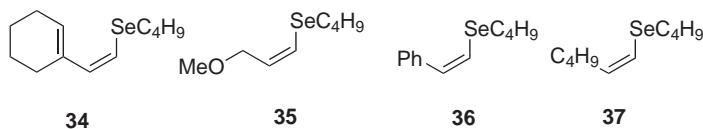
Scheme 36

(Trimethylsilyl)acetylene also gives β -zirconated ethene, whereas (trimethylsilyl)phenylacetylene affords the corresponding α -zirconated silylalkene. Synthesis of ketene butyltelluro(phenylseleno)acetals by Al/Te exchange reaction via DIBAL-H addition to acetylenic selenide is very slow. In addition, Te is added to the α -aluminated vinyl selenide intermediate in *syn* fashion <1996TL831>. On the one hand, hydrozirconation of the butylseleno- or phenylselenoethyne followed by the treatment with butyltellurenyl bromide gives (*E*)-1-butyltelluro-2-butylseleno or 2-phenylseleno ethene in very good yields. In the case of (butylseleno)phenylacetylene, total reversion of regiochemistry is observed. The high regioselectivity is attributed to the electron delocalization of the selenium group into aromatic ring. On the other hand, hydrozirconation of 1-alkylseleno-2-alkylethyne gives a mixture of α - and β -zirconated vinyl selenides and the isomers **33** are major products of the reaction (Scheme 37).

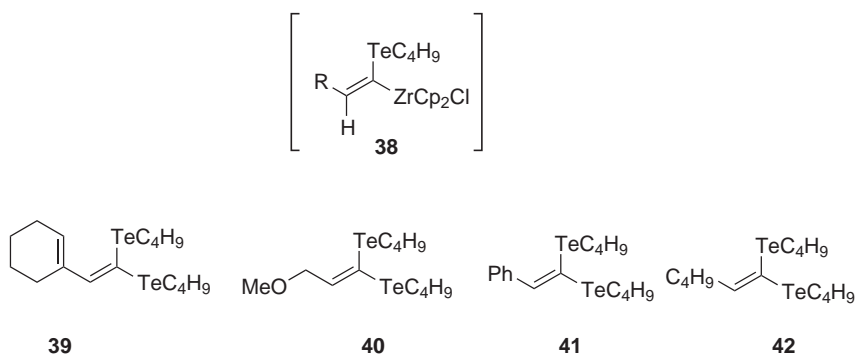


Scheme 37

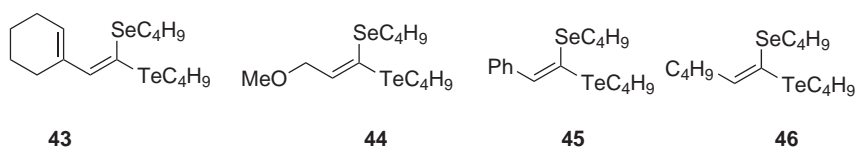
Hydrozirconation of acetylenic selenides using $\text{Cp}_2\text{Zr(H)Cl}$ (2 equiv.) results in 100% stereoselectivity although the regiochemistry is highly dependent on the structure of the starting substrates <1998T2371, 2000JOC54>. Some representative vinyl selenides **34–37** are shown here.



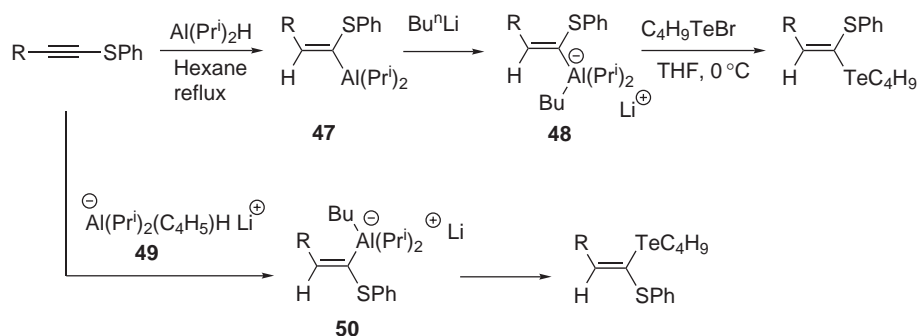
Zr/Te exchange reactions of (*E*)-vinylzirconates with organytellurenyl halides occur with retention of configuration <1995TL1503, 1995TL7623>. The reactions of acetylenic tellurides with Zr—H are faster than the reactions of selenides and occur in a *cis* fashion, placing the zirconium atom at the α -position relative to the butyltellurium moiety. The reaction proceeds via the intermediate **38**. The regiochemistry in this case is the opposite of what has been observed with butyl- or phenylselenoethyne but similar to boron alkynyltributylstannylethyne or zinc alkynyl derivatives <1998T2371>. Some representative ditellurium ethenes **39–42** are shown here.



α -Zirconated vinyltellurides can also react with butylselenyl bromides (prepared *in situ*) to give keten butyltelluro(butylseleno)acetals as a mixture of two stereoisomers of one regioisomer. This is in contrast to the Zr/Te exchange reaction discussed above, which occurs with total retention of configuration. The retention of configuration in the Zr/Se exchange reaction on intermediates of the type **38** is only partial and the compound formed with inversion of configuration is the major product, with the exception of the phenyl derivatives (**38**; R = Ph) <1998T2371>. Although only one regioisomer is formed by quenching, the intermediate with water, other electrophiles such as iodine or NBS give stereoisomeric mixtures **43–46**.



With vinylalkylaluminum reagents, exchange of Al with Te is less efficient but the corresponding aluminum ate complexes are very reactive <2001TL7167>. Reduction of phenylthioacetylenes with DIBAL-H results in *syn*-addition, placing the aluminum on the carbon containing the sulfur moiety. This gives exclusively the α -aluminated phenylthio group and affords exclusively the intermediate **47**. This is then converted into aluminum ate complex **48** by Bu^nLi which is captured by Bu^nTeBr to give the (*E*)-isomer in high yield with 100% regio- and stereoselectivity (Scheme 38) <2001TL7167>. However, the synthesis of (*Z*)-telluro(thio)ketene acetals can be accomplished with high stereoselectivity, with ate complex **49** prepared from DIBAL-H and Bu^nLi . This reagent results in *anti* addition of the hydride and aluminum moiety with the latter group attached to the sp^2 -carbon of the phenylthio group. This intermediate **50** is then trapped by Bu^nTeBr (Scheme 38) <2001TL7167, 2000JOC61>.

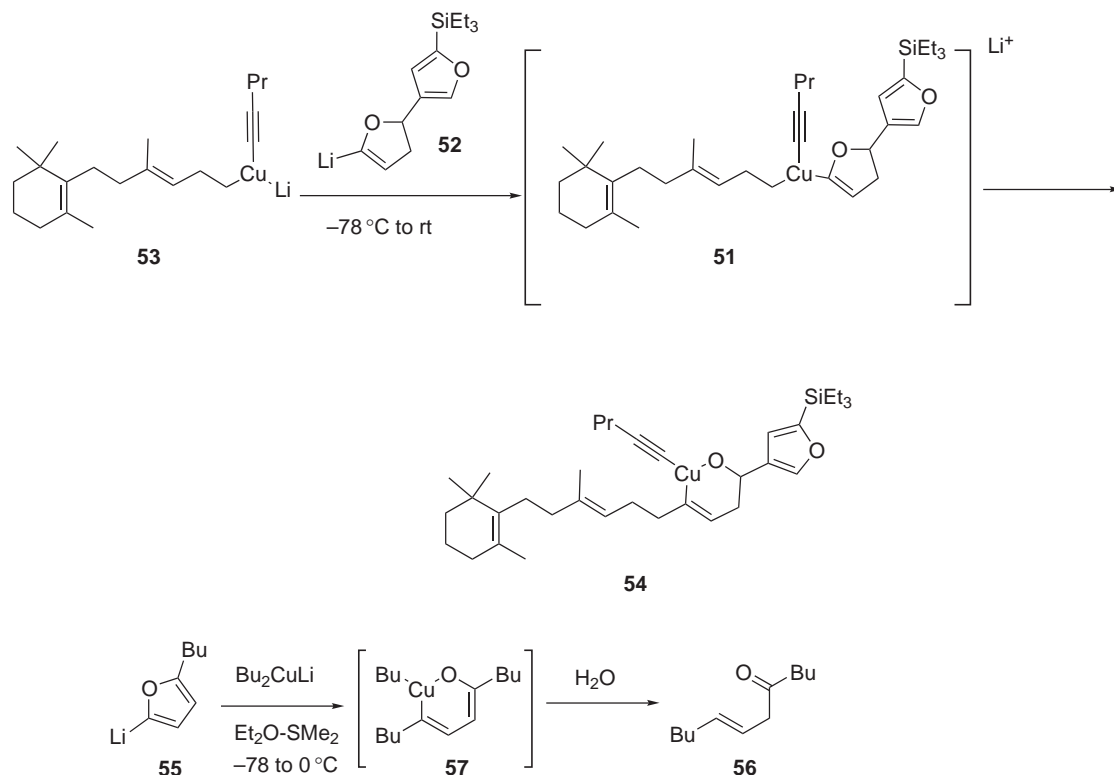


Scheme 38

2.19.11 SUMMARY

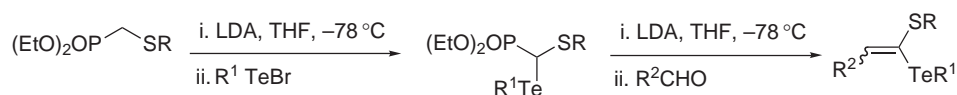
As predicted in COFGT (1995) <1995COFGT(2)951>, several new and modified methods for the preparations of vinyl and aryl metals have been discovered. Because of the opportunity for formation of two or more C—C bonds in one reaction and the excellent atom economy of these reactions, the use of vinyl and aryl metals in synthesis will continue to grow. In this final section, some methods which could not be easily placed in any category defined in COFGT (1995) are presented.

The diorganocuprate **51**, prepared by the reaction of the cuprate **53** and lithiated dihydrofuran **52**, rearranges to vinylcuprate **54** which reacts with iodine to give the vinyl iodide. Similarly, lithium furan **55** is converted into ketone **56** via vinylcuprate **57** (Scheme 39) <2003JOC4008>.



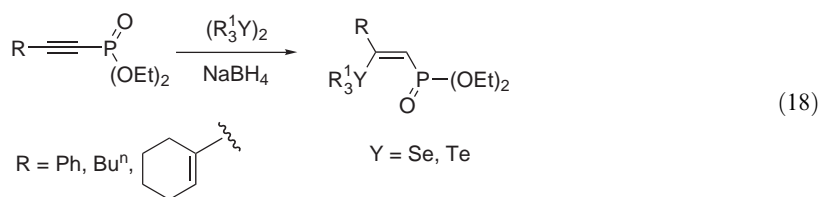
Scheme 39

Ketene (*S*,*Te*)-acetals can be prepared via a Wittig–Horner-type reaction as shown in Scheme 40 <1999T7421>. Thiophosphonates, which can be prepared from triethylphosphonate and chloromethylphenyl- or methyl sulfide, are condensed with aldehydes in good yield. Aromatic aldehydes give good yields of ketene acetals, whereas aliphatic aldehydes provide lower yields (Scheme 40) and ketones do not react at all under these conditions.

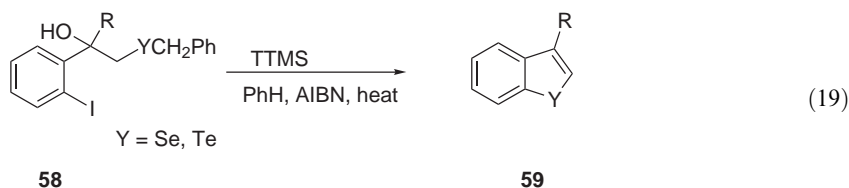


Scheme 40

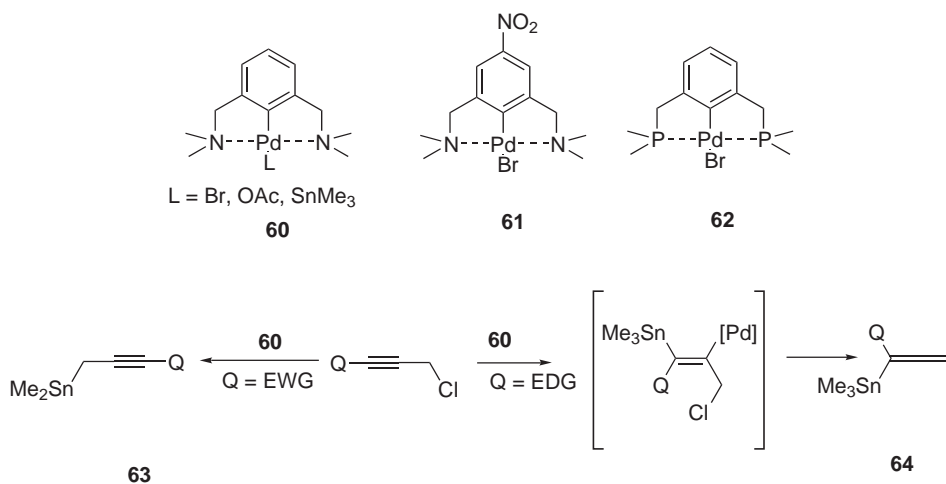
The organyselenolate and organytelluroolate anions, generated from diorganylditellurides and sodium borohydride, react with alkynylphosphonates (Equation (18)). The addition occurs at the β -carbon with (*Z*)-stereochemistry. This is rationalized in terms of Michael-type addition with a carbanion stabilization by the diethoxyphosphinyl group <2000TL161>.



The aryl iodides **58** when treated with tris(trimethylsilyl)silane (TTMS) under standard radical conditions give benzoseleno- or tellurophenes **59** (Equation (19)) <1999JOC6764>.



Palladium and other transition metals catalyze addition of hexaalkylditin to triple bonds. The usual application of this method involves oxidative addition of Pd(0) to the Sn—Sn bond, which subsequently adds to the alkyne substrate. This is generally accomplished in the presence of phosphine ligands. The phosphine complexes **60–62** (generally referred to as “pincer complexes”) <2003T1837, 2003JOC7551, 2002CCC818> catalyze reactions of hexamethylditin with propargylic substrates leading to substitution reactions instead of bisstannane addition and afford either propargylstannanes **63** or allenylstannanes **64** <2004JA474>. This reaction occurs at room temperature in THF and the neutral conditions tolerate a variety of functional groups, such as OH, OAc, COOEt, NR₃, and NR₂Ac. The reactions of propargyl substrates containing electron-donating groups give propargylstannanes **63** while substitution with electron-withdrawing substituents gives allenylstannanes **64** (Scheme 41).

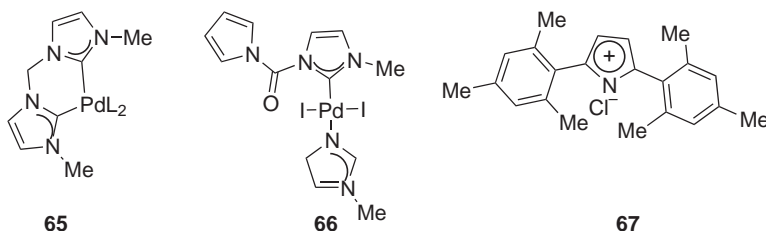


Scheme 41

The electronic character of metal substituents has a dramatic influence on the reactivity of arylmetallic reagents under rhodium-catalyzed conditions. The successful aqueous phenylation of carbonyl compounds and conjugate addition of unsaturated carbonyl compounds have been achieved with trimethyl- and tributylphenylmetal halides and phenyl metal hydroxides under basic conditions. From the viewpoint of atom economy, Ar_mMX_n should be a better choice than ArMR_n¹, where all the R¹ groups are sacrificed. In addition, Ar_mMX_n-based reagents are more readily available and also provide more alternatives for the operational procedure.

However, when the alkyl and aryl substituents (R^1) on the metals are changed to halogens, such as chloro and bromo (e.g., PhSnCl_3), the reaction ceases completely but proceeds again upon the addition of a base <2001JA7451>.

Palladium catalysts with enhanced reactivity for cross-coupling reactions with electron-rich aryl bromides and aryl chlorides continue to be attractive discoveries. Some success in this area has been achieved using bulky electron-rich phosphane ligands such as $\text{P}(\text{Bu})_3$. The *N*-heterocyclic carbene (NHC) ligands as phosphane mimics, have been utilized as alternatives to sterically hindered phosphanes <2003AN(E)1566>. Some examples of NHCs are chelating ligand complex **65**, carboamyl-substituted NHC complex **66**, and imidazolium system **67**.



Ru(II) - or Pt(II) -catalyzed cycloisomerization of *o*-aryl-1-alkynes results in the formation of dihydronaphthalene and dihydrobenzocycloheptene derivatives, depending on the tethered chain length. In a similar manner to the Lewis acid catalysts that activate oxygenated compounds such as aldehydes, ketones, and epoxides by coordination of the oxygen atom, Ru(II) or Pt(II) complexes activate alkynes. The overall result is electrophilic addition to C—C triple bonds from unactivated aromatic rings <2000JOC4913>. *Endo*-cycloisomerization of terminal alkynes tethered to oxygen, nitrogen, carbon, and sulfur nucleophiles is based on the concept of intramolecular nucleophilic addition to metal vinylidene electrophilic intermediates. These transformations have been reviewed <1999CEJ3103>.

The usefulness of vinyl and aryl metals necessitated the discovery of new preparative methods or effective use of existing methods. Here some references are cited where the reader may find the novel structures of vinyl and aryl metals. The utility of organoalkenyl and organoaryl silicon compounds—such as silacyclobutanes <1999JA5821>, vinyl silanes and aryl silanes <1997JOC8569>, and aryltriethoxysilanes <2001JOC7449>—has been demonstrated for the addition reactions with aryl halides, α,β -unsaturated ketones, and nitroalkenes <2003JOC6997>. Fluoride-ion-catalyzed <2001TL4833> and fluoride-ion-free <2001JA6439> Pd -catalyzed <2000JOC5342, 1999JA5821> cross-coupling reactions of alkenyl silanes with aryl halides have been reported. Carbonylative cross-coupling reactions by organoindium compounds <2003OL1103> and cobalt-mediated arylation of heterocycles <2003OL3607> are a few of their applications in organic synthesis. Lewis acid-catalyzed allylation <1999SL519>, cycloisomerization, and cyclization of functionalized dienes <2002ACR905>, tandem, or cascade cyclizations <2003OL3645, 1999AN(E)1435> have found applications in the total synthesis of complex natural products. Heteroaromatic thioethers <2003OL801>, oxygen, and nitrogen heterocycles via transmetallation of alkenylstannanes <1998TL643> have been made possible with alkene- and aryl metals. Cross-coupling <2003OL1895> of aryl- and vinylsilanols <2003JOC9151> has become an easy entry due to convenient ruthenium-catalyzed vinyl silane synthesis. Asymmetric allylic alkylation reactions <2002AN(E)4693>, reactions of organometallic reagents (such as cyclopentadienyl iron, molybdenum, and tungsten complexes <2000CR3127>), and nickel-catalyzed organozinc-promoted intramolecular carbocyclizations of electron-deficient alkenes <1997JA4911> are just a few examples to mention where vinyl and aryl metals are utilized in multistep organic synthesis.

The discovery and development of Pd -catalyzed cross-coupling of vinyl and aryl metals have stimulated interest in C—N, C—S <1998JOC9606>, and C—O bond formation reactions <1998ACR805, 1998AN(E)2046, 1999T11149, 2001MI313, 2002AN(E)1607, 2002CEJ2660, 2003JOC7077, 2000AN(E)4492, 2001JA5108>. The construction of two or three adjacent stereogenic centers in an acyclic system is generally difficult <1996T7235>. However, such transformations can be accomplished by the allylzincation and propargylzincation of various γ -heterosubstituted vinyl metals diastereoselectively. Substituted vinylidene zinc carbenoids rearrange to the corresponding alkynes with complete retention of asymmetric centers present in the starting materials <2000OL419>.

Pearlman's catalyst $[(\text{Pd}(\text{OH}_2)/\text{C})]$ is considered to be the best catalyst for the hydrostannation of unactivated alkenes when compared to palladium catalysts that contain phosphine ligands. Quite often, remarkable differences are observed between ligandless catalysts and phosphine containing palladium catalysts in the hydrostannation of 1,6-diynes <1997JOC8970>.

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2000HCA3291

2000JA12011
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2000JOC61
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2000JOC5342

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2002ACR905
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Biographical sketch



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2.20

Stabilized Substituted Ions and Radicals Bearing One Heteroatom ($R^1R^2C^-X$, $R^1R^2C^+X$, $R^1R^2C\cdot X$)

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2.20.1 STABILIZED CARBANIONS BEARING ONE HETEROATOM ($R^1R^2C^-X$)

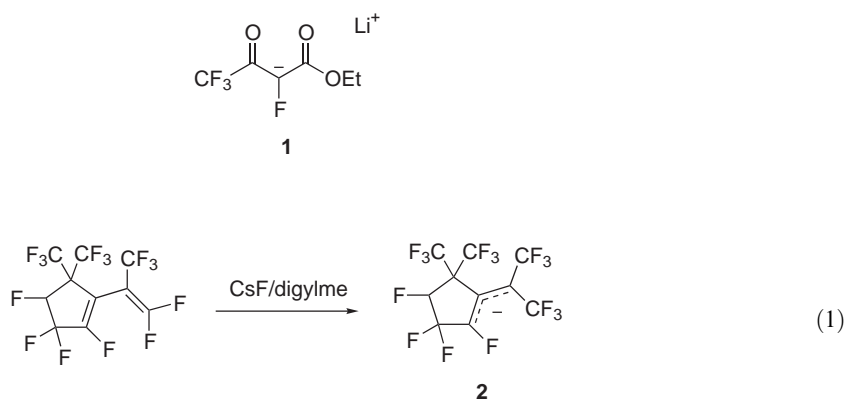
Substituted carbanions bearing one single heteroatom continue to be of great importance in modern synthetic organic chemistry <1997TL7471, 1997TL7625, 1997JA6072, 1998T10449, 1999SL1936, 2000JOC5072, 2001TL4389, 2002OL1551, 2002EJC2970> and chiral organolithium compounds are especially important tools in enantioselective synthesis. Some reviews dealing with this class of compounds have appeared <1997AG2376, 1997AG(E)2282, 1996ACR552, 1994AG185, 1994AG(E)175> since the publication of COFGT (1995) <1995COFGT(2)997>. Attempts have been made to isolate carbanions, which normally are highly reactive intermediates, in order to gain valuable insights into their properties and to better understand their mode of action.

2.20.1.1 Carbanions Adjacent to Halogen

As outlined in COFGT (1995) <1995COFGT(2)997>, carbanions R_2HalC^- , which often form strongly covalent carbon–lithium bonds and thus can be defined as $R_2CHalLi$ species chapter 4.03, <1995COFGT(4)95>, can be prepared by halogen exchange between an alkyl lithium and a dihaloalkane. In general, carbanions bearing both the electropositive metal and the electronegative halogen atoms at the central carbon atom often show low stabilities. A recent example of

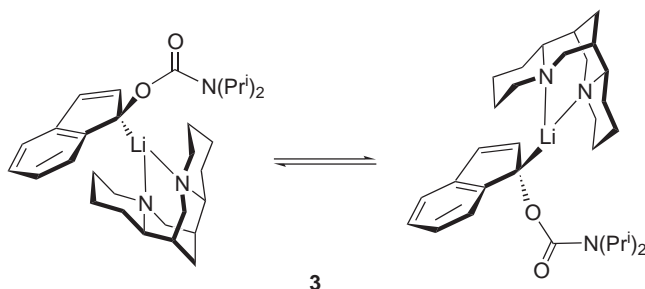
such an α -haloalkyllithium is (9*H*-fluoren-9-ylidene)fluoromethylolithium, which was found to be stable up to -40°C <2001CCC1508>. The stability of alkenylfluorocarbenoids depends mostly on the properties of the β -substituents, the influence of which has been studied using ^{19}F NMR spectroscopy at low temperatures <1995JCS(P1)2681, 2002JFC(113)211> and by means of calculations <2002JFC(116)121>. In addition, fluorine atoms in trifluoromethyl groups *cis* to the lithium atom stabilize, whereas those atoms *trans* to the lithium destabilize these carbenoids <2002JFC(113)211>.

Ethyl 2-chloro-3-oxopropanoate potassium was obtained in 88% yield as an orange solid on treatment of a mixture of ethyl formate and ethyl chloroacetate with potassium *t*-butoxide in diisopropyl ether <2000T7915>. ^{19}F NMR spectroscopy at room temperature was performed on the anion **1** <1997PS1>. The anion **2**, which has its own independent existence, was generated on addition of caesium fluoride to the fluorinated cyclopentene and proved to be stable for several hours (Equation (1)). The ^{19}F NMR resonance frequencies were reported <2000JFC(104)239>. Low temperature ^{19}F NMR spectroscopy was also performed on 1-fluoro-1-lithioethenes <2002JFC(113)211>, and the chemical shifts were calculated by the SOS-DFPT-IGLO method <2002JFC(116)121>. ^{13}C NMR studies were performed with $^{13}\text{C}(1)$ labeled 2,2-diaryl-1-fluoro-1-lithioalkenes <1997TL4877>.



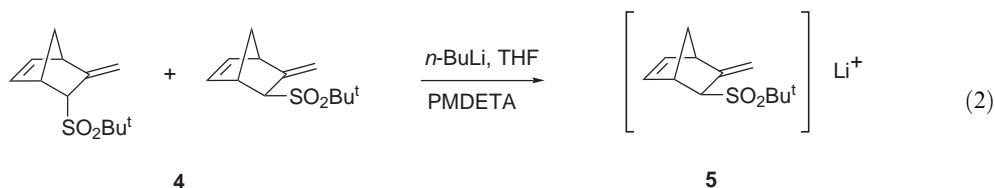
2.20.1.2 Carbanions Adjacent to Chalcogen

Additional anion stabilizing groups such as carbonyl, cyano, or alkene groups enable the formation of α -alkoxylithium anions as described in COFGT (1995) <1995COFGT(2)997>. In continuation of earlier work, 1*H*-inden-3-yl carbamates were deprotonated in toluene using BuⁿLi in the presence of 1 equiv. of (–)-spartein or (–)- α -isospartein to give species **3**: the resulting stabilized anions were subjected to nuclear magnetic resonance (NMR) line shape analysis to study the kinetic behavior with respect to epimerization. It was found that (–)- α -isospartein decreases the configurational stability compared with (–)-sparteine <1999CEJ3464>.



The β -lithiation of oxazolinylloxiranes to give anionic species, which are stable at low temperatures for several hours due to the oxazolinyl and aryl groups, proceeds stereospecifically with complete retention of configuration <2002OL1551, 2002OL173>. The deprotonation of

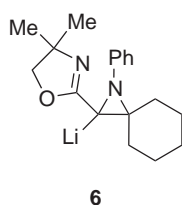
thioethers <1996CL999, 2002T3655>, sulfinyls <2001TL4389, 2003OBC3495>, sulfonyls <2002TL2043>, or selenides <2000TCC113> in the α -position is the key step of numerous organic syntheses. On addition of iron(II) tetrafluoroborate and tripod [$\text{CH}_3\text{C}(\text{CH}_2\text{PPh}_2)_3$] to sodium 2-methanesulfonyl-substituted dicyanomethanide, a crystalline dinuclear complex forms. Three molecules of the dicyanomethanide are the bridging ligands between two iron atoms, which are bonded through Fe—N bonds to the CN groups. Each iron atom has additional three bonds to the phosphorus atoms of tripod. An X-ray structure was presented <2001EJI2625>. Lithium salts of conformationally constrained and restricted allylic α -sulfonylcarbanions have been studied intensively in order to gain knowledge of the mode of coordination between the lithium atom and the allylic α -sulfonyl carbanion in the contact ion pair and thus to understand the high regioselectivity of their reaction with electrophiles <1999EJO1627, 2001EJO4275>. Reaction of both *exo*- and *endo*-**4** with *n*-butyllithium in tetrahydrofuran (THF) in the presence of penta-methylethylenetriamine (PMDETA) gave the carbanion **5** with *exo*-configuration, containing one molecule of PMDETA per formula unit (Equation (2)). An X-ray structure displayed a monomeric species with the lithium cation coordinated to one oxygen atom <2001EJO4275>.

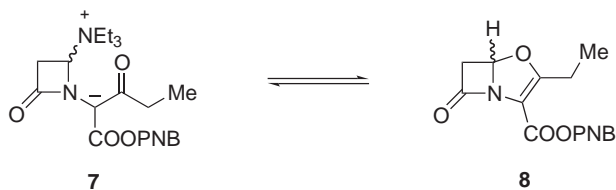


Likewise, an acyclic lithioallylsulfone <1986AG916, 1986AG(E)939> as well as the phenylsulfonyl, norbornenyl, and norbornyl analogs of the salt **5** <1999EJO1627> showed a coordination of lithium only by an oxygen atom and not by the carbon atoms of the allylic partial structure. Typically, the lone pair orbitals at the anionic carbon atom are periplanar to the *S*-Bu^t and *S*-Ph bonds, respectively, which is mainly due to stabilizing $\text{n}_{\text{C}}-\sigma^*_{\text{SR}}$ hyperconjugation <1996JA4622>. Due to this hyperconjugation and Coulomb interactions between the negative charge at the carbon atom and the positively charged sulfur atom, the C—S bond is significantly shortened. The anionic carbon atoms are not planar but have pyramidal angles approximately half-way between sp^2 and sp^3 <1999EJO1627>. In the crystals, *endo* conformations were preferred. ¹H, ¹³C, and ⁶Li NMR experiments to examine the more complicated structures of these anionic species in solution were also carried out. According to cryoscopic experiments, the phenylsulfonyl-substituted anions exist as a 1:1 mixture of monomeric and dimeric species at low temperatures in THF. On the NMR timescale, the *endo/exo* equilibrium is fast, with the *endo* anion being the preferred conformer <1999EJO1627>. A review article about selenium-stabilized carbanions has been published <2000TCC113>.

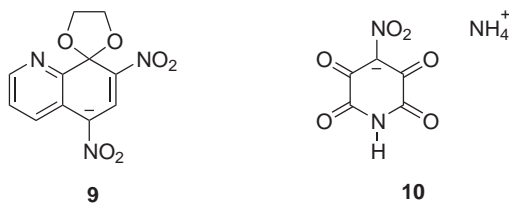
2.20.1.3 Carbanions Adjacent to Nitrogen

The isolation of carbanionic species derived from tertiary amines is successful when other stabilizing features are also present and examples are described in COFGT (1995) <1995COFGT(2)997>. Thus, the aziridinylithium **6** is only stable at low temperatures <1999TL6101, 2000T4415>. Additional informations about aziridinyl anions can be found in a recent review article <1996CRV3303>. The zwitterion **7** is a stable compound on which an X-ray structure analysis was performed. It can be converted into the oxapenem **8** on heating and cleaved again to give the isomer **7** by triethylamine <2001JCS(P1)1281>. Syntheses and X-ray structures of copper(I) and copper(II) complexes of cyanamide squarate dianions, prepared from disodium 3,4-bis(cyanamido)cyclobutane-1,2-dionate dihydrate <1989ZN(B)169>, have been reported <2001JCS(D)1529>.



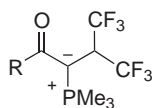


The lithium salt of 2-nitropropane, which is often used for organic synthesis [<1999SL1936, 1997SL1159>](#), was obtained in 95% yield on deprotonation with freshly prepared lithium ethanolate [<1997T5471>](#). A recent additional example of nitro-stabilized carbanionic species is the anion of ethyl 2-nitropropionate, which is a relatively strong acid ($pK_a(\text{H}_2\text{O}) = 6.0$). The anion was generated by tetrabutylammonium hydroxide in water [<1998T4923>](#). The X-ray structures of Meisenheimer complexes of 1,3,5-trinitrobenzene, 1,3-dinitro-5-cyanobenzene [<2001MI1056>](#), and 5,7-dinitroquinoline derivatives such as anion **9**, which adopt sofa-conformations, also belong to this category of stabilized anions. As suggested by the canonical formula **9**, partial double bond character can be attributed to the C—NO₂ bond in the *para* position [<2000JST141>](#). The electron density distributions based on X-ray diffraction data collected at 153 K were determined [<2000MI452>](#). The 2,3,5,6-tetraoxo-4-nitropyridate **10** was obtained as the ammonium salt on treatment of 2-amino-3-hydroxypyridine with HNO₃ in the presence of rare-earth ions such as Ln³⁺ [<1999CHE1484>](#).



2.20.1.4 Carbanions Adjacent to Other Group 15 Elements

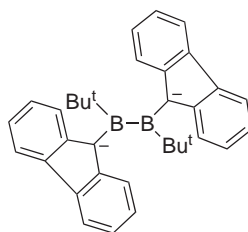
The fluorinated α,β -unsaturated ketones $(\text{F}_3\text{C})_2\text{C}=\text{CH}-\text{C}(\text{O})\text{R}$ ($\text{R} = \text{Ph}, \text{Bu}^t$) reacted with trimethylphosphine to give the ylides **11** as orange compounds [<2002PS1907>](#) after tautomerization. Reaction of Bu^nLi with the silylated iminophosphoranes $\text{Me}_3\text{SiNPMe}_3$ and $\text{Me}_3\text{SiNP}(\text{Pr}^i)_3$ in hexane at 20 °C resulted in the formation of the lithiated species $[\text{LiCH}_2\text{PMe}_2\text{NSiMe}_3]_4$ and $[\text{LiCMe}_2\text{P}(\text{Pr}^i)_2\text{NSiMe}_3]_2$ as air- and moisture-sensitive crystalline solids in quantitative yields, respectively. A band at 512 cm^{-1} was attributed to the $\nu_{\text{Li}-\text{C}}$ vibration. X-ray analyses hint at a relatively polar Li—C bond in the former species. In the latter compound, the Li—C bond displays a considerably different bond length [<1996CB253>](#).



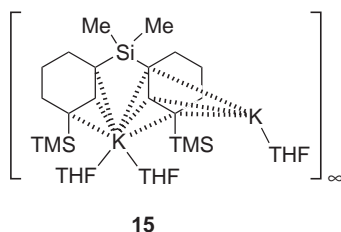
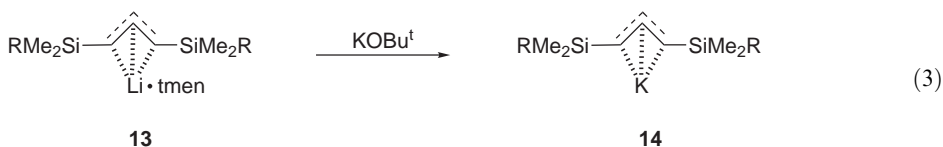
2.20.1.5 Carbanions Adjacent to Metalloids

The π -acceptor boron is able to stabilize carbanions like cyano or formyl groups [<1981JOC1693>](#). Studies on the synthesis and properties of boron-stabilized carbanions have been summarized [<1997JIC433>](#). An *ab initio* computational study on 2-borylallyllithium in

comparison to allyl- and 2-azaallyllithium was reported [<1998JA3357>](#). However, the quantitative deprotonation of alkylboranes is not easily achieved and affords weak nucleophilic bases. On double deprotonation with sodium hexamethyldisilazane, the disodium salt **12** was isolated as a solid orange THF solvate and could be characterized by multinuclear NMR spectroscopy. A single-crystal X-ray analysis was performed on the related structure $[\text{Na}(\text{thf})(\text{OEt}_2)]\text{Na}(\text{OEt}_2)_2$ **12**, which revealed considerable B—C π -bonding. Nevertheless, the B—C distances are longer than they would be in a sterically less strained system. From the almost perpendicular arrangement of the planes, it was concluded that the π -system is not delocalized over the C—B—B—C unit. The corresponding lithium monoborate, possessing the di(*t*-butyl)-substituted boron atom, was obtained on deprotonation of di-*t*-butyl-(1-fluorenyl)borane with $\text{LiNBu}^t(\text{TMS})$, but could not be separated. Deprotonation of the corresponding dimethyl derivative proved to be difficult [<2000EJI1571>](#).

**12**

Silyl-substituted alkenes $\text{RMe}_2\text{SiC}(\text{H})=\text{CHCH}_2\text{SiMe}_2\text{Bu}^t$ ($\text{R} = \text{Bu}^t, \text{Me}$) can be deprotonated with Bu^nLi at reflux temperature to yield silylallyllithium-tmen complex **13** as air-sensitive, colorless crystals which were characterized by ^1H , ^{13}C , ^7Li , and ^{29}Si NMR spectroscopy. The ^1H NMR spectra proved the η^3 coordination mode of each allylic ligand. The complex **13** ($\text{R} = \text{Bu}^t$) showed magnetic inequivalence of the methyl groups attached to the same silicon atom. The X-ray analysis displayed an *exo,exo* orientation of the *t*-butyl groups. They were converted on treatment with an equimolar amount of KOBu^t in hexane at room temperature into the tmen-free complexes **14** (Equation (3)). Crystallization in the presence of pyridine (py) or THF yielded the crystalline complexes $[\text{K}\{\eta^3\text{-CH}(\text{CHSiMe}_2\text{Bu}^t)_2\}\text{L}]$ ($\text{L} = \text{py}$ or THF). The X-ray structure of the dimethylsilyl-ansa-bis(cyclohexenyl)potassium complex **15** was also described [<1999JCS\(D\)1257>](#).

**15**

X-ray structure analyses of an Me_2Si -bridged bis(indenyl) zirconocene complex [<2000JA8093>](#), silylene-bridged ansa-lanthanocenes [<2000OM4134>](#), and an isodicyclopentadienylsilylamido zirconium were also reported [<2000OM4169>](#). Iodonium ylides continue to be attractive reagents in organic synthesis and some reports have appeared [<2002JCS\(P1\)1309>](#).

2.20.1.6 Carbanions Adjacent to Metals

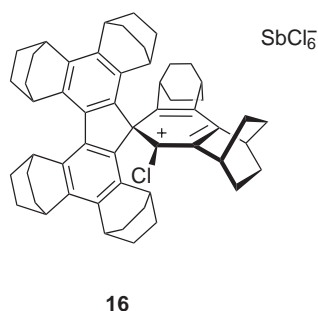
No further advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(2)997>.

2.20.2 STABILIZED CARBOCATIONS BEARING ONE HETEROATOM ($R^1R^2C^+X$)

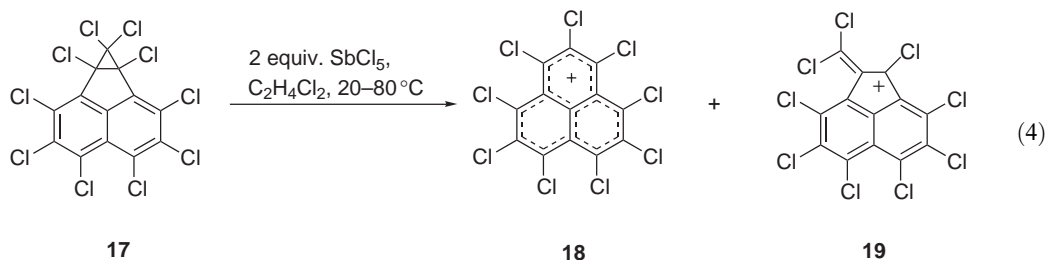
Carbenium ions are key intermediates in numerous organic reactions such as E1 eliminations, S_N1 substitutions, and rearrangements <1995AG(E)1393, B-1995MI>, and continue to be of interest from both synthetic and theoretical points of view. Recent studies deal with hydride affinities of carbenium and iminium ions in solution <1998JOC4671>. Although carbocations have been studied intensively by both calculations and spectroscopic methods <B-1997MI2, B-1997MI3, B-1997MI4>, the number of crystal structure determinations is quite small <1998CRV1277>. Numerous efforts have been devoted to studies of the mechanism and extent to which the cationic carbon atom can be stabilized by electron back-donation from its ligands and by bridging to its neighbors. If the ligand has a free valence electron pair or involves an aromatic carbon atom, $p(\pi)$ back-donation can cause this stabilization. If the ligand is an alkyl group, C—H/C—C hyperconjugative stabilization is invoked. Highly electronegative ligands such as fluorine have very strong inductive electron-withdrawing σ -effects, which counteracts the $p(\pi)$ back-donation, as was demonstrated by natural bond orbital (NBO) analyses.

2.20.2.1 Carbocations Adjacent to Halogen

Experimental results reveal, in agreement with calculations, that chlorine stabilizes carbenium ions more efficiently than fluorine <2000JA481>. Chlorine is the better back-donor than fluorine, which was evidenced by a comparison of the bond lengths. Antimony pentachloride converted a triphenylene derivative by one-electron oxidation in CH_2Cl_2 into a green radical cation, the half-life of which was determined to be ~ 2 h. A slow diffusion of hexane into the CH_2Cl_2 solution resulted in the quantitative formation of a purple arenium ion **16**, obviously formed by chlorine addition and contraction of the central six-membered ring of the starting material. An X-ray analysis was performed <2002OL1435>.

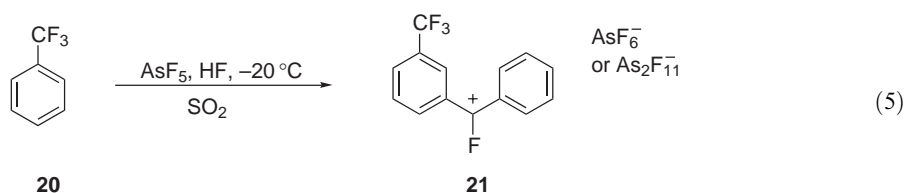


On treatment of compound **17** with $SbCl_5$, a mixture of cationic species **18** and **19** precipitated (Equation (4)). These were isolated under argon and proved to be sensitive toward hydrolysis <2001JA3864>.



The results of a single-crystal X-ray analysis of the carbocation $[(\text{CH}_3)_2\text{CF}^+]\text{AsF}_6^-$, which was first observed by Olah in 1967 using low-temperature ^1H and ^{19}F NMR spectroscopy <1967JA1268, 1969JA2955>, were reported <2000JA481>. The structure of this compound is indeed ionic with a discrete cation and anion. Two connecting fluorine bridges of the carbenium ion were found to neighboring AsF_6^- anions, which help to populate the empty p_z orbital. The C—F bonds are considerably shortened (128.5(11) pm) in comparison to olefinic C—F bonds and indicate a back-donation from fluorine to carbon. Likewise, the C—C bond lengths (143.2 pm) are shorter than the C—C bonds in C=C=C partial structures, thus indicating significant methyl hyperconjugation.

Reaction of excess α,α',α'' -trifluorotoluene **20** with antimony pentafluoride and HF in SO_2 or SO_2ClF solution gave the carbocation **21** as the hexafluoroantimonate, whereas excess AsF_5 yielded the corresponding As_2F_{11} salt (Equation (5)). Both compounds are white solids that are marginally stable at room temperature <2000JA481>. The X-ray structure analyses show that both compounds are ionic. The C_2CF^+ moieties are perfectly planar and again fluorine bridges were determined along the p_z orbitals of the carbenium center. The two aromatic rings, which are twisted, cause a considerable diminishing of the fluorine back-donation, as evidenced by a smaller C—F bond shortening in comparison to $(\text{CH}_3)_2\text{CF}^+$.

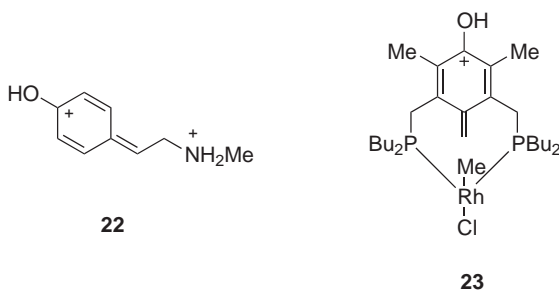


The relative stabilities of perfluorinated 3-alkylidene-1-indanyl and 1-alkylindenyl cations were compared and examined by means of ^{19}F NMR spectroscopy <1998MI80>.

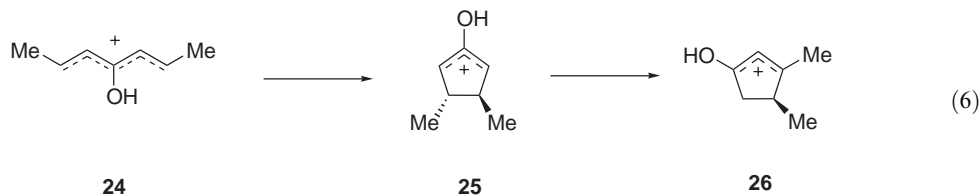
2.20.2.2 Carbocations Adjacent to Chalcogen

Acyl carbocations have been known for a long time and some X-ray analyses have been described in COFGT (1995) <1995COFGT(2)997>. Recently, a ketalization of acylium cations ($\text{R}-\text{C}^+=\text{O}$) in gas-phase ion-molecule reactions with 1,3-propanediol, 3-amino-1-propanol, and 2-methoxyethanol was reported <1996JOC8726>. Starting from 1,3-adamantanedicarbonyl chloride and a 1:1 mixture of SbF_5 and SO_2ClF at -80°C gave the corresponding dicarbonyl dication. ^{13}C NMR reveals that the positive charges reside mostly on the oxygen atoms <1995JOC7351>. Treatment of mono-, di-, and tetracubane-carboxylic acids with FSO_3H in either SO_2ClF or sulfur dioxide gave the corresponding cubylcarboxonium ions, which were characterized by ^{13}C NMR spectroscopy at low temperatures. Some representatives lose CO upon warming <1995JA12107>.

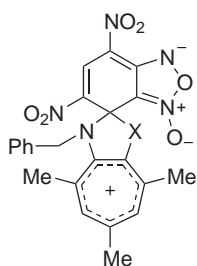
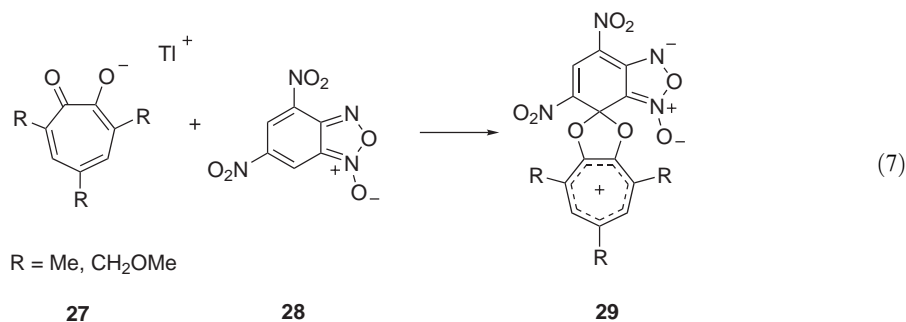
The acylation of aromatics by $\text{MeCO}^+ \text{SbCl}_6^-$ or $\text{PhCO}^+ \text{SbCl}_6^-$ in Friedel–Crafts reactions depends on the acidity of the medium. It was found that the protonated acyl cations are the most active species in strongly acidic media, whereas the acyl cations themselves proved to be relatively weak electrophiles <1995JA3037>. ^{13}C NMR examinations and a comparison to cation **23** <1998JA477> suggest that the synephrine dication, generated by $\text{FSO}_3\text{H}-\text{SbF}_5$, can best be represented by canonical forms with the positive charge delocalized in the benzene ring; **22** is consistent with a shortened carbon—oxygen bond and this is also suggested by calculations <2001OL2781>.



A number of *O*-substituted pentadienyl cations have been studied <1995T7231>. ^1H NMR examination reveals that protonation of (*E*),(*E*)-2,5-heptadien-4-one with HSO_3F in CH_2Cl_2 gives the 3-hydroxy cation **24**, which on warming to 20°C undergoes cyclization ($t_{1/2} = 53$ min at 20°C) to cation **26**, presumably via intermediate **25** by a formal 1,3-hydrogen shift (Equation (6)). Finally, this Nazarov-type reaction yields 3,4-dimethylcyclopent-2-en-1-one.



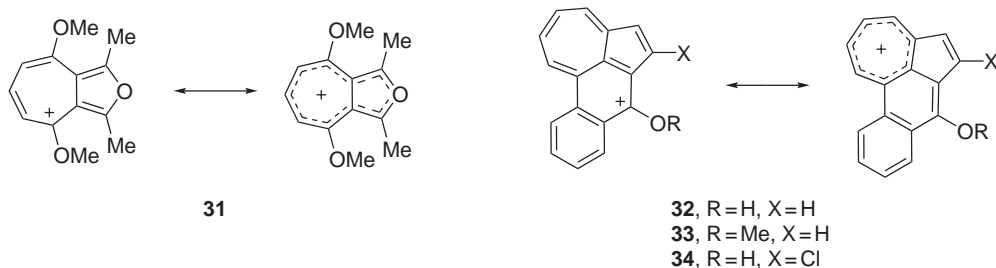
The dipolar spirocyclic σ -complexes **29** were obtained as crystalline solids starting from 4,6-dinitrofuroxan **28** and the thallium salts of the tropolones **27** (Equation (7)). 2-Benzylaminotropone, benzylaminothiotropone, and *N,N'*-dibenzylaminotroponimine yielded the spiro compounds **30**. The enantiotopomerization of the chiral spiro compounds such as **30** ($\text{X} = \text{NCH}_2\text{Ph}$) by dissociation–recombination processes of carbon heteroatomic spiro bonds was investigated by dynamic ^1H NMR spectroscopy <1997MI1445>.



$\text{X} = \text{O}, \text{S}, \text{NCH}_2\text{Ph}$

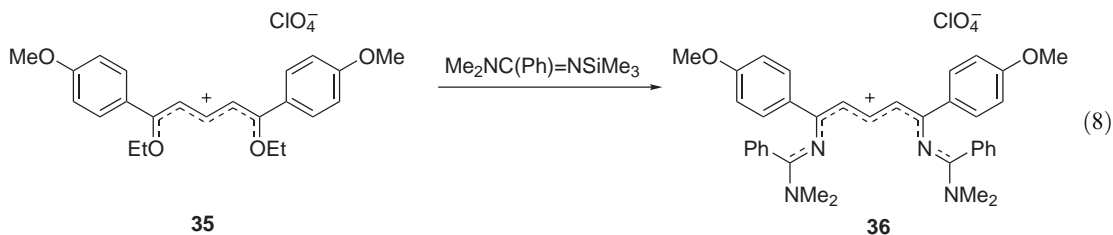
30

The synthesis of furo[*c*]tropylium perchlorate **31**, which possesses a 10-electron heteroaromatic structure of the oxa-azulenium type, and its reactions with nucleophiles have been described <1996ZOB891, 1997MI5235>. 7-Methoxynaphth[3,2,1-*cd*]azulenium perchlorate **33** and 6-chloro-7-hydroxynaphtho[3,2,1-*cd*]azulenium perchlorate **34** were isolated as red-brown and red prisms, respectively. A weak band at 1610 cm^{-1} reveals that the latter species **34** maintains a partial $\text{C}=\text{O}-\text{H}^+$ character, although *ab initio* calculations on the protonated 7*H*-naphth[3,2,1-*cd*]azulen-7-one **32** hint at a considerable contribution of a canonical formula with a cationic seven-membered ring <2001JCS(P1)1353>.

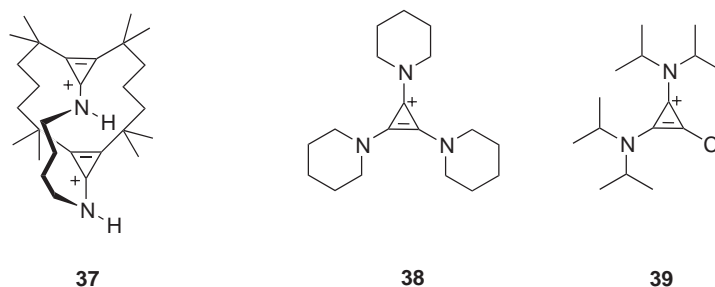


2.20.2.3 Carbocations Adjacent to Nitrogen

The great importance of iminium salts ranges from interesting intermediates in organic synthesis <2003OL3635>, natural products <2003OL3737> to cyanine dyes, from which some new examples have been described <2002OL4261>. According to a recent study, *N,N*-diprotonated hydrogen cyanide ($\text{HC}^+ = \text{N}^+ \text{H}_2$) and the corresponding benzonitrile ($\text{Ph}(\text{H})\text{C}^+ = \text{N}^+ \text{H}_2$) were identified as the active electrophiles in Gattermann and Houben-Hoesch reactions of benzene <1995JA3037>. Considerable interest has been directed to iminium salts as reactive intermediates in, for example, keteniminium ion-initiated cyclization-pinacol rearrangements <2002JOC6421>. An example of a stable species is the dimethyliminium derivative of fluorenone. It was synthesized as an orange solid by methylation of fluorenone methylimine with trimethyloxonium tetrafluoroborate <1998JOC4671>. The carboxonium perchlorates **35** can undergo substitution of one or both of the ethoxy groups on treatment with *N,N*-dimethylbenzamidine or *N,N*-dimethyl-*N'*-trimethylsilylbenzamidine to give cyanine dyes (Equation (8)). According to an X-ray structure analysis, compound **36** is nonplanar. All bonds of the chain show partial double bond character <1998EJO329>.



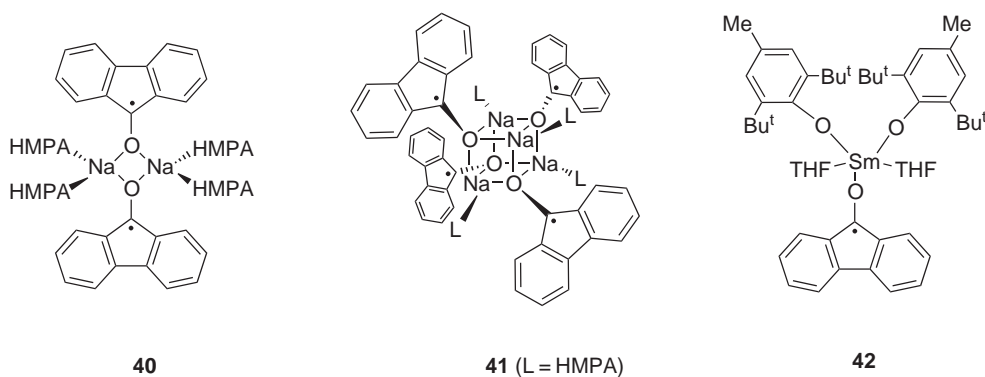
Starting from a bisethoxycyclopropenylum phane, the rings were tethered by reaction with 1,5-diaminopentane to give the bisiminium salt **37** on which an X-ray analysis was performed. Almost equal bond lengths were found in the essentially bicyclic cyclopropenyl rings, whereas the C—N bond lengths correspond to typical C=N double bonds (128 pm) <1999T7769>. The crystal structures of tris-(piperidino)cyclopropenium **38** and bis-1,2-(diisopropylamino)-3-chlorocyclopropenium **39** were determined and their spectroscopic features were examined. Shortened C—C bond lengths and C—N distances averaging 133.3 pm in ion **38** hint at charge delocalization over the C_3N_3 core <1995JCS(F)1523>.



2.20.3 STABILIZED RADICALS BEARING ONE HETEROATOM ($R^1R^2C^{\cdot}X$)

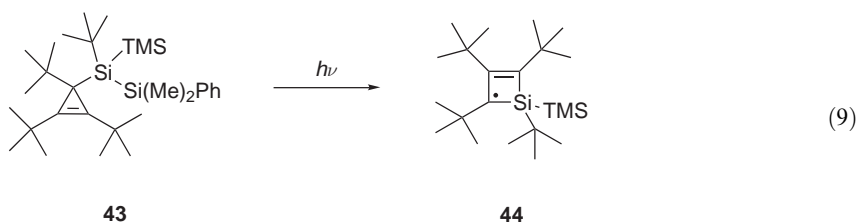
Organic radicals and especially molecules with many nonbonding electrons have attracted much attention as molecular magnets and conducting materials <2002SCI1846>. A review dealing with free radicals has appeared <2001APC1>. The number of isolable free radicals, however, is rather limited. A recent example is a neutral oxophenalenoxyl monoradical, the unpaired electron of which is predominantly delocalized on the two oxygen atoms and the carbon atoms located at short distances between the two oxygen atoms <2003OL3289>. Synthesis and properties of *m*-phenylene-linked aromatic poly-aminium cationic radicals have been described and their half-lives, which were estimated by electron spin resonance (ESR) spectroscopy, was found to be 1 week in solution <2003OL2165>.

Enol ether radical cations were produced during laser flash photolysis by heterolytic cleavage of β -mesylate radicals <2003OL827>. Dimeric and tetrameric sodium fluorenone ketyl complexes **40** and **41** were generated by reaction of fluorenone with sodium metal in THF and subsequent addition of HMPA. An X-ray crystallographic analysis revealed that diradical **40**, formed in 81% yield on addition of 2 equiv. of HMPA to the reaction mixture, is a ketyl-bridged dimeric sodium complex in which each sodium atom is also bonded to two terminal HMPA ligands. The two ketyl moieties are identical and coplanar. Addition of only 1 equiv. of HMPA resulted in the formation of tetradical **41** in 78% isolated yield: this product possesses an Na_4O_4 cubic core according to an X-ray analysis. These ketyl complexes are also available starting from the corresponding pinacol, $NaN(TMS)_2$, and HMPA <1996JA2503>. The samarium ketyl complex **42** was obtained on treatment of fluorenone with the samarium(II) aryloxide in THF $[(ArO)_2Sm(THF)_3]$ and was characterized by X-ray analysis <1995JA4421>. X-ray structures of lithium, potassium, and calcium ketyl complexes have also been reported <2000CEJ2994>.



Dicationic diradicals and tricationic triradicals of triphenylphosphoranes possessing the $Ar_2C^+-P^+Ph_3$ moiety were found to be stable at $-20^\circ C$. They decompose slowly at room temperature <1997JA5398>.

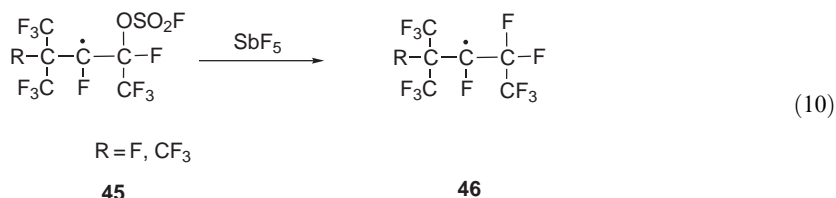
Irradiation of the trisilane **43** in cyclohexane at 254 nm generated a persistent radical **44** by cleavage of one Si—Si bond (Equation (9)). This product **44** is stable for more than 2 years at room temperature in the absence of oxygen. Calculations suggest a C_s symmetric structure with identical C—C bond lengths in a four-membered ring, which are typical for a delocalized π -system. This was confirmed by ESR spectroscopic investigations. The most intense component is a 19-line pattern due to an interaction of the radical with the hydrogen atoms of the *t*-butyl groups at C(2) and C(4) <2000EJO1107>.



ESR and external nuclear double resonance (ENDOR) studies were performed on the radical cations of [2.2](1.4)naphthalenophane, [2.2](1.4)anthracenophane, and pentacene to study intramolecular electron transfers between the 1,4-dimethoxybenzene units <1998EJO1161>.

The reaction of phenyllithium with 1,4-benzoquinone, 2,6-di-*t*-butyl-1,4-benzoquinone, and 1,4-naphthoquinone, respectively, in THF gave phenyl radicals which reacted to form biphenyl and the corresponding lithium semiquinonate $\text{Li}^+(\text{sp}^-)$. The latter can also be obtained by direct reaction between *para*-quinone and lithium. The IR spectrum of $\text{Li}^+(\text{p-C}_6\text{H}_4\text{O}_2^-)$ in either KBr or Nujol showed a single band at 1659 cm^{-1} <1996JA9691, 1998JCS(D)1371>.

Reaction of *N,N,N',N'*-tetrakis(2-pyridylmethyl)benzene-1,4-diamine (tpbd) with one-electron oxidants such as $\text{Fe}(\text{ClO}_4)_3 \cdot 6\text{H}_2\text{O}$, $[\text{Mn}_3\text{O}(\text{MeCO}_2)_6]\text{ClO}_4$, or tetrabutylammonium tribromide in methanol yields the purple colored radical cation $\text{tpbd}^{+\cdot}$, the half-life of which is several minutes depending on the conditions <1997JCS(D)2697>. The fluorosulfonyloxy-perfluoroalkyl radical **45**, generated electrochemically from the corresponding alkene and HSO_3F containing NaSO_3F , was converted into the fluoroalkyl radical **46** on reaction with SbF_5 (Equation (10)). These radicals proved to be unstable in the presence of oxygen and were characterized by means of ESR spectroscopy <1996MI984>.



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2.21

Alkynyl Halides and Chalcogenides

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2.21.1 ALKYNYL HALIDES

The stability, physical, and chemical properties of alkynyl halides vary in a broad range depending on the nature of the halogen. Alkynyl fluorides are the least stable and the chemistry of these compounds is quite different from that of other alkynyl halides. Only a few representatives of alkynyl fluorides have been reported in the literature. In contrast, alkynyl chlorides, bromides, and iodides are relatively stable and have been known since the nineteenth century <1995COFGT(2)1011, B-1969MI651, B-1977HOU(5/2a)110, B-1988MI174, B-1995MI33>. The newest member of the family of alkynyl halides, alkynyliodonium salts $\text{RC}\equiv\text{CI}^+\text{R}'\text{X}^-$, only became readily available in the 1980s <1995COFGT(2)1011>. In the decade 1993–2003, there has been a substantial interest in the synthetic application of alkynyl halides (mainly bromides, iodides, and alkynyliodonium salts), which are valuable precursors in the synthesis of various alkynes by acetylenic nucleophilic substitution or by the transition metal-mediated cross-coupling reactions. The use of alkynyliodonium salts in organic synthesis has been discussed in several comprehensive reviews <2002CRV2523, B-1999MI327, 2003TCC99>.

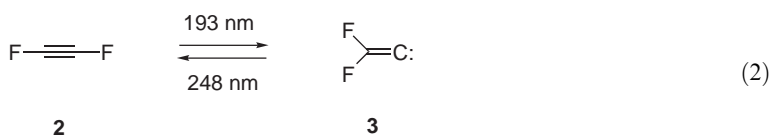
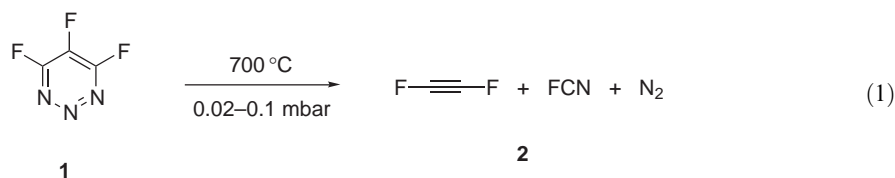
Chapter 2.21, COFGT (1995), provides a comprehensive review on the synthesis of alkynyl halides through 1994 <1995COFGT(2)1011>. In particular, the introductory section gives a detailed general discussion on the most common synthetic approaches to alkynyl halides, which can be classified as: (i) various elimination reactions, (ii) reactions of terminal alkynes, $\text{RC}\equiv\text{CH}$, or alkynylides, $\text{RC}\equiv\text{CM}$, with halogens or electrophilic halogenating reagents, and (iii) alkylation

of haloethynylides, $\text{XC}\equiv\text{CM}$. The present update is organized according to the section in COFGT (1995) <1995COFGT(2)1011> on alkynyl halides and covers the literature for the period 1995–2003.

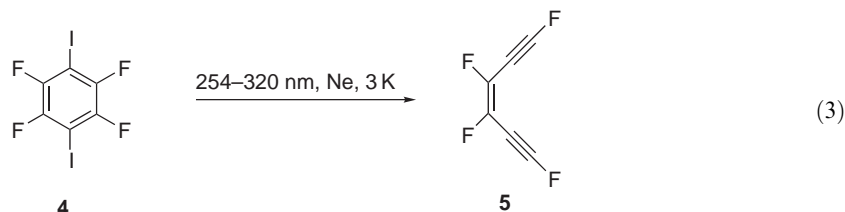
2.21.1.1 Fluorides

The earlier literature on the preparation and properties of alkynyl fluorides has been summarized in the related section of COFGT (1995) <1995COFGT(2)1011>. Only a few examples of alkynyl fluorides are known, namely fluoroethyne, difluoroethyne, fluorochloroethyne, perfluoropropyne, *t*-butyl fluoroethyne, and fluoropropiolyl fluoride. The only known synthetic approach to alkynyl fluorides is based on the elimination reactions. For example, the parent fluoroethyne, $\text{HC}\equiv\text{CF}$, can be prepared by the debromination of 1,2-dibromo-1-fluoroethene with magnesium in tetrahydrofuran (THF) as a colorless gas that condenses below -100°C to a mobile, highly explosive liquid. Alkynyl fluorides in general are highly unstable and explosive even at cryogenic temperatures <1995COFGT(2)1011>. The challenges of synthesizing and handling these compounds have limited any preparative work in this area.

The nonpreparative formation of several alkynyl fluorides has been reported in literature related to spectroscopic studies of fluorinated reactive intermediates <1997JPC(A)6611, 1999JFC(99)99, 2001AG(E)2295>. In particular, the formation of fluoroethyne and difluoroethyne was observed in the photodissociation of difluoroethylene at 193 nm <1997JPC(A)6611>. The extremely unstable pure difluoroethyne **2** can be generated by vacuum pyrolysis of perfluorotriazine **1** at 700°C (Equation (1)) and isolated at -196°C <1991CC456>. The matrix-isolated difluoroethyne has been used as a precursor to the highly reactive difluorovinylidene carbene **3** under ultraviolet (UV) irradiation at temperatures below 40 K (Equation (2)) <1998JA219, 1997AG(E)1983, 1998CEJ1611, 1999CEJ24>. Cryogenic polymerization of difluoroethyne at -196 to -95°C leads to the formation of a new fluorocarbon polymer, polydifluoroacetylene <1999JA3781>.



Perfluoropropyne, $\text{CF}_3\text{CC}\equiv\text{CF}$, was identified as one of the main products of thermal decomposition of squaric acid difluoride instead of the expected difluoroethyne <1999JFC(99)99>. The fluorinated enediyne **5** was obtained by irradiation of diiodotetrafluorobenzene **4** in solid neon at 3 K (Equation (3)) and identified by infrared (IR) spectroscopy <2001AG(E)2295>.

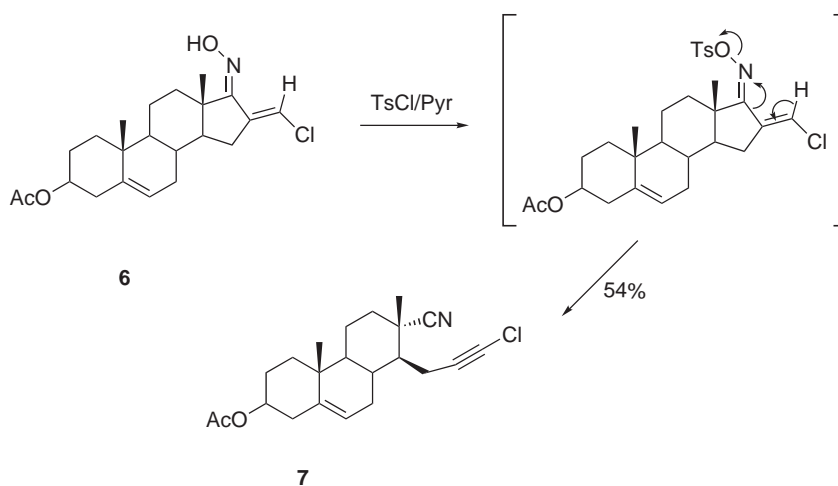


2.21.1.2 Chlorides

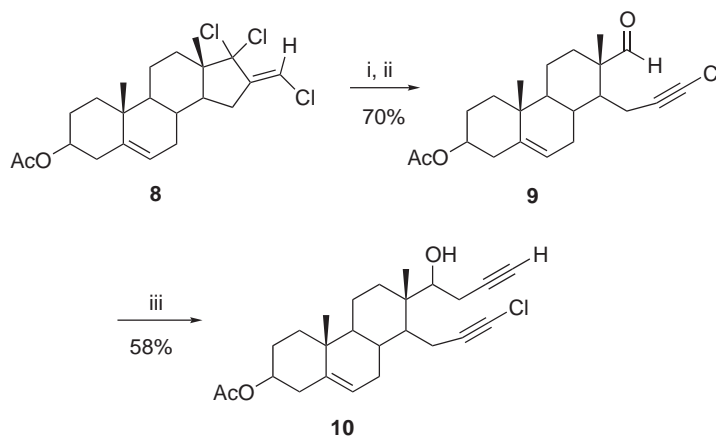
Numerous previously reported alkynyl chlorides have been described in COFGT (1995) <1995COFGT(2)1011>. The parent representative of the class, chloroethyne $\text{HC}\equiv\text{CCl}$, was first prepared in 1880 by the pyrolysis of dichloroacrylic acid. Dichloroethyne, $\text{ClC}\equiv\text{CCl}$, is

obtained by passing a mixture of trichloroethene and ether over heated potassium hydroxide. Pure chloroethyne and dichloroethyne, as well as other simple alkynyl chlorides, are highly explosive, air-sensitive compounds. However, generated *in situ* in solution under inert atmosphere in the dark, they can be stored indefinitely or conveniently used for further transformations without isolation <B-1969MI651>. Interestingly, chloroethyne, dichloroethyne, and some other alkynyl halides have been found in nature as significant components of volcanogenic gases. Their formation is explained by thermolysis of hydrothermal methane and synchronous catalytic halogenation in the presence of highly activated surfaces of cooling magma or juvenile ash <2000MI1122>. Chloroethyne and dichloroethyne can also be present in the groundwater environment as reactive intermediates formed by reductive dechlorination of the common pollutants, perchloroethylene, and trichloroethylene <1998MI3017, 2002IC5844>.

Several convenient synthetic procedures for the preparation of alkynyl chlorides are known <1995COFGT(2)1011>. These procedures are generally based on various elimination reactions or on the reactions of terminal alkynes with electrophilic chlorinating reagents. Examples of the elimination approach include the preparation of steroidal chloroalkynes **7** and **9** by a ring opening reaction of oxime **6** (Scheme 1) <1997TL1845> or a base-promoted conversion of the chloromethyleneandrost-5-ene derivative **8** (Scheme 2) <1997TL6749>, respectively. The steroidal formyl alkyne **9** can be further converted to the diyne **10**, which is a potentially important precursor to the novel artificial enediyne antitumor agents <1997TL6749>.



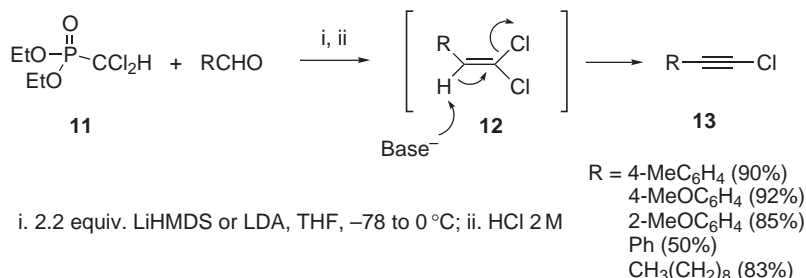
Scheme 1



i. KOH/MeOH-H₂O (4:1); ii. Ac₂O/Pyr; iii. BrCH₂C≡CH/Zn/THF

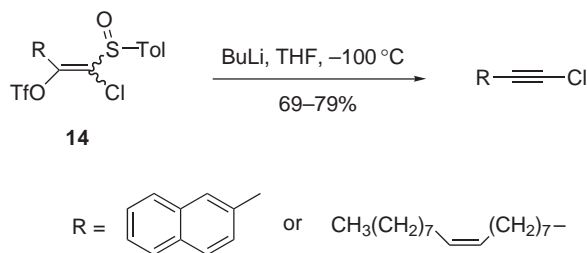
Scheme 2

An interesting general method for the synthesis of chloroalkynes from aldehydes and diethyl dichloromethylphosphonate **11** (Scheme 3) was developed by Savignac and co-workers <1996S1494>. The initial step in this process (Scheme 3) is a classical Horner–Emmons reaction between the phosphonate carbanions and the aldehydes giving dichloroalkene **12**. The second step, which occurs on warming the reaction mixture, is *anti* elimination of HCl affording chloroalkynes **13**.



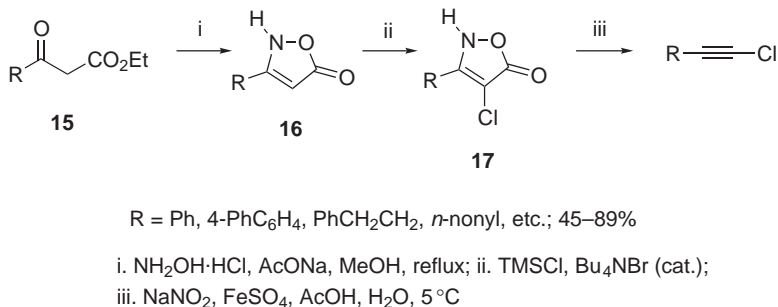
Scheme 3

A multistep procedure for the preparation of alkynyl chlorides and other disubstituted alkynes from carbonyl compounds was developed by Satoh and co-workers <1995T9327>. A key step in this procedure involves the fragmentation of alkenyl sulfoxides **14** upon treatment with butyllithium (Scheme 4).



Scheme 4

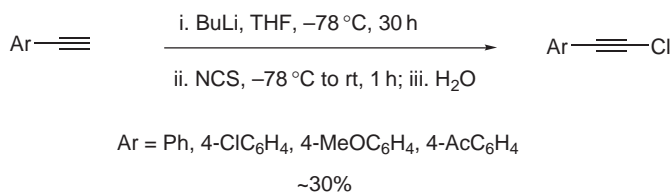
Another general method is based on the fragmentation of isoxazolinones upon treatment with sodium nitrate and ferrous sulfate in aqueous acetic acid <2001CC1894>. The key precursors in this synthesis, chloroisoxazolinones **17**, are prepared by the chlorination of 4-unsubstituted isoxazolinones **16** derived from the corresponding β-ketoesters **15** (Scheme 5).



Scheme 5

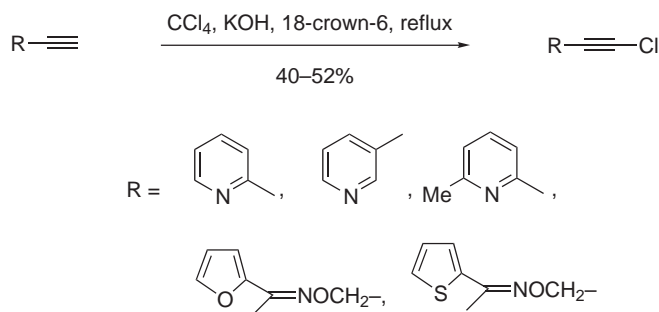
A reaction of terminal alkynes or the corresponding alkynylides with chlorinating reagents such as chlorine, hypochlorites, sulfonyl chloride, and arylsulfonyl chlorides represents another general and widely used approach to alkynyl chlorides <1995COFGT(2)1011>. A convenient modification

of this approach involves the reaction of alkynyllithium derivatives with *N*-chlorosuccinimide (NCS) <2000JOC1780, 2002JOC7451>. In a typical procedure, a terminal alkyne is treated with butyllithium and then NCS in THF at -78°C (Scheme 6), and the resulting chloroalkyne is isolated by column chromatography in a moderate yield <2000JOC1780>.



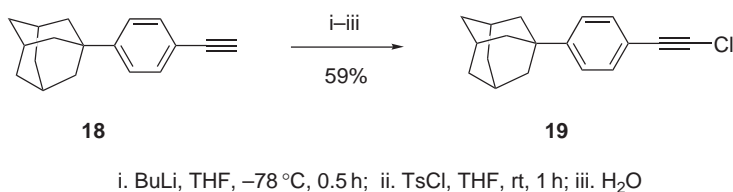
Scheme 6

A convenient method for the preparation of chloroalkynes in moderate yields consists in the chlorination of terminal alkynes with carbon tetrachloride and a base under phase transfer catalysis conditions (Scheme 7) <2001JOC(A)121>.



Scheme 7

An adamantane-substituted chloroalkyne **19** has been prepared by the chlorination of the respective terminal alkyne **18** with tosyl chloride (Scheme 8) <1999JPS(A)4546>. Chloroalkyne **19** was used as a monomer in the preparation of novel polyacetylenes bearing adamantyl groups.



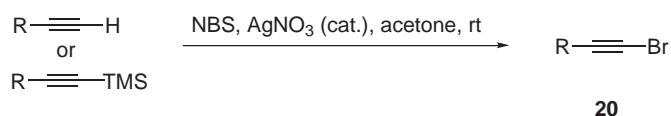
Scheme 8

Since the start of the twenty-first century, alkynyl chlorides have found some synthetic application as reagents in the transition metal-mediated cross-coupling reactions <2000JOC1780, 2002JOC7451>.

2.21.1.3 Bromides

The earlier literature on the preparation and properties of alkynyl bromides has been summarized in the related section of COFGT (1995) <1995COFGT(2)1011>. Alkynyl bromides in general have higher stability than the chlorides and, therefore, have found much broader synthetic applications. During the decade 1993–2003, alkynyl bromides have attracted significant interest as reagents in the transition metal-mediated cross-coupling reactions and several other synthetically useful transformations.

Alkynyl bromides can be prepared by the same general methods as the chlorides. Direct functionalization of terminal alkynes or the corresponding alkynylides with brominating reagents is the most general and widely used approach to alkynyl bromides. A very convenient procedure for the preparation of 1-bromoalkynes **20** in excellent yields consists in the treatment of terminal alkynes or trimethylsilylalkynes with an equivalent of *N*-bromosuccinimide (NBS) in acetone in the presence of silver nitrate as a catalyst (10–35%) (Scheme 9) <1999JCS(P1)675, 2000JA810, 1999JOM(578)229>. This reaction is usually carried out at room temperature and it is compatible with various functional groups. Numerous alkynyl bromides **20** have been prepared by this approach and further used as intermediates in the synthesis of complex organic molecules (Table 1).



Scheme 9

Table 1 Alkynyl bromides **20** prepared from terminal alkynes and NBS (Scheme 9)

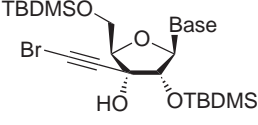
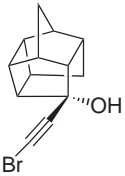
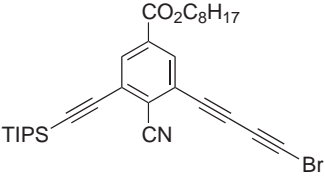
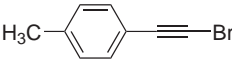
Alkynyl bromide 20	Yield (%)	References
 (Base = uracil or adenine)	100 ^a	<2003OL383>
	85 ^a	<1995T11673>
	98 ^a	<1998AG(E)1285>
Et ₃ Si—C≡C—C≡C—Br	54 ^a	<2000JA810>
Br—C≡C—C≡C—Br	17 ^{ab}	<2000JA810>
	72 ^a	<1999JOM(578)229>
HOCH ₂ CH ₂ —C≡C—Br	95 ^a	<2001JA3194>
HO(CH ₂) ₄ —C≡C—Br	95 ^a	<2001JA3194>
THPO(CH ₂) ₃ —C≡C—Br	97 ^a	<2001JA3194>
TBDPSOCH ₂ —C≡C—Br	85 ^a	<2001OL4173>

Table 1 (continued)

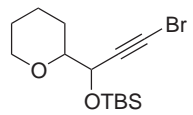
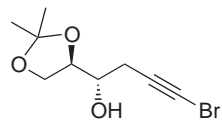
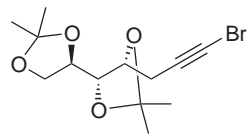
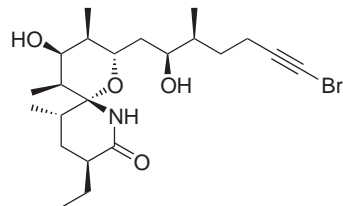
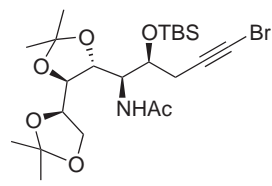
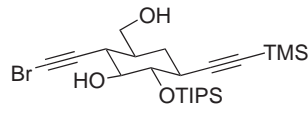
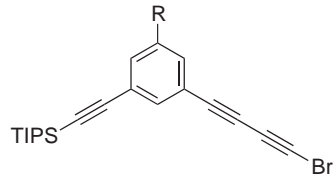
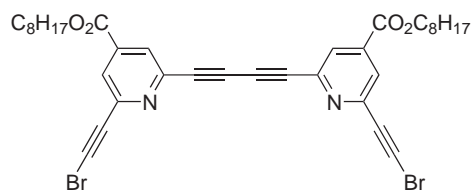
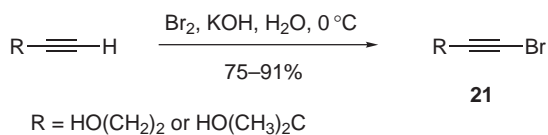
Alkynyl bromide 20	Yield (%)	References
$\text{TBSOCH}_2\text{CH}_2\text{---}\equiv\text{Br}$	84 ^a	<2002TL2427>
	91 ^a	<2001JOC1885>
	81 ^a	<2002TL2427>
	92 ^a	<2002JCS(P1)1890>
	69 ^a	<2000JA3830>
	95 ^a	<2002JOC6758>
	97 ^a	<1999HCA143>
 R = $\text{CO}_2\text{C}_8\text{H}_{17}$, $\text{CO}_2\text{C}_{16}\text{H}_{33}$, $\text{CO}_2(\text{CH}_2\text{CH}_2\text{O})_3\text{CH}_3$	75–97 ^a	<2002JA5350>
	80 ^a	<2000OL3265>
$\text{ArSO}_2\text{---}\equiv\text{Br}$ (Ar = Ph, Tol)	> 95 ^c	<1999JCS(P1)675>

Table 1 (continued)

Alkynyl bromide 20	Yield (%)	References
	87 ^d	<1999T7157>
	77 ^d	<1999CC1625>
	100 ^d	<2000OL85>
	67 ^d	<2001T3629>
	92 ^d	<2002OL2841>
	55 ^d	<2002OL4667>

^a Prepared from terminal alkyne. ^b The product rapidly decomposes at room temperature but can be stored at -30°C . ^c Either terminal alkynes or trimethylsilylalkynes gave the same yields of the products. ^d Prepared from trimethylsilylalkyne.

Terminal alkynes can be conveniently converted to alkynyl bromides by the treatment with bromine and KOH in water at 0°C <1995COFGT(2)1011>. This method has also been applied to the preparation of alkynyl alcohols **21** (Scheme 10) <1998T11741, 2001T4271>. A milder, nonaqueous modification of this procedure consists in a direct bromination of alkynyllithium or alkynylstannane derivatives at low temperature <2000JOC6951, 2000CEJ54>. For example, ethynyladamantane **22** can be selectively converted to alkynyl bromide **23** by the treatment with butyllithium and then with bromine in ether (Scheme 11) <2000CEJ54>. Likewise, direct bromination of alkynylstannane **24** under very mild conditions affords bromide **25** in quantitative yield (Equation (4)) <2001MC99>.

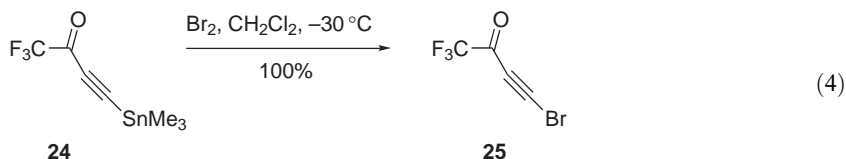


Scheme 10

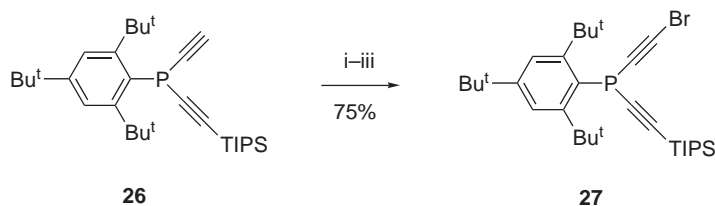


i. BuLi, Et₂O, -75 °C, 1 h; ii. Br₂, ether, -50 °C to rt; iii. H₂O

Scheme 11



Arylsulfonyl bromides can be applied instead of bromine for the bromination of alkali metal alkynylides [<1995COFGT\(2\)1011>](#). Bromoethynylphosphane **27** has been prepared by the reaction of tosyl bromide with the respective lithium alkynylide **26** (Scheme 12) [<2000CEJ3806>](#).



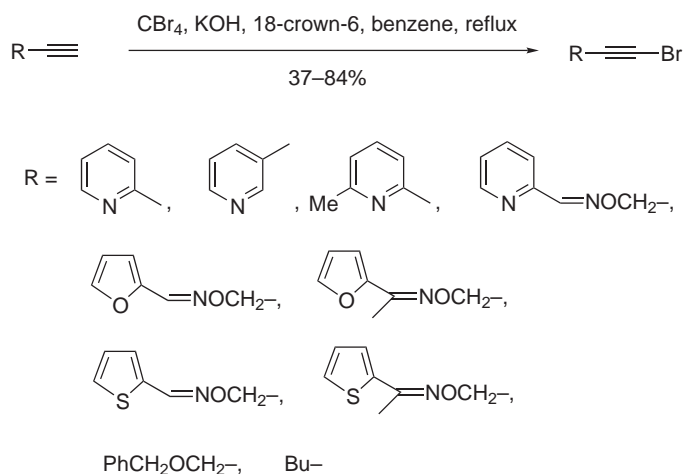
i. BuLi, THF, -78 °C, 20 min; ii. TsBr, THF, -78 °C to rt; iii. H₂O

Scheme 12

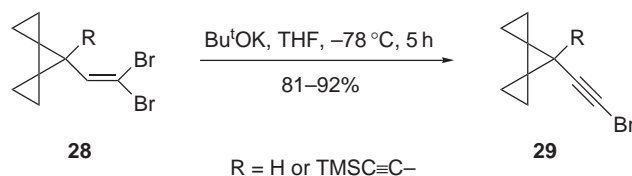
A variety of alkynyl bromides have been prepared in moderate yields by the bromination of terminal alkynes with carbon tetrabromide and a base under phase-transfer catalysis conditions (Scheme 13) [<2001JMOC\(A\)121>](#).

The second major approach to alkynyl bromides is based on various elimination reactions. This approach has been employed in the synthesis of the parent monobromo- and dibromoethyne. Monobromoethyne was first prepared by dehydrohalogenation of *cis*-dibromoethene with sodium hydroxide in ethanol in the form of a relatively stable gas. Dehydrobromination of tribromoethene with sodium hydroxide under similar conditions was used for the preparation of dibromoethyne [<1995COFGT\(2\)1011>](#).

Several convenient procedures for the synthesis of substituted alkynyl bromides by the dehydrobromination of *gem*-dibromoalkenes have been reported in the early 2000s. De Meijere and Kozhushkov have prepared a number of cyclopropanated bromoalkynes **29** by dehydrobromination of dibromides **28** with potassium *t*-butoxide (Scheme 14) [<2002CEJ3195, 2002EJO485>](#). Bromoalkynes **29** were further used as key precursors in the synthesis of spirocyclopropanated macrocyclic oligoacetylenes.



Scheme 13



Scheme 14

Due to the mild reaction conditions, the dehydrobromination methodology has found practical application in the synthesis of complex, multifunctional organic molecules. Examples of the preparation of alkynyl bromides by this approach are shown in [Scheme 15](#) [<2002OL2517, 2002OL1955, 2002OL3847, 2001JOC7231, 2000JA9099, 1999OL319>](#). Several different strong bases have been used in these eliminations ([Scheme 15](#)); the starting *gem*-dibromoalkenes ([30, 32, 34, 36, 38](#)) can be conveniently prepared from the respective aldehydes and CBr₄/Ph₃P.

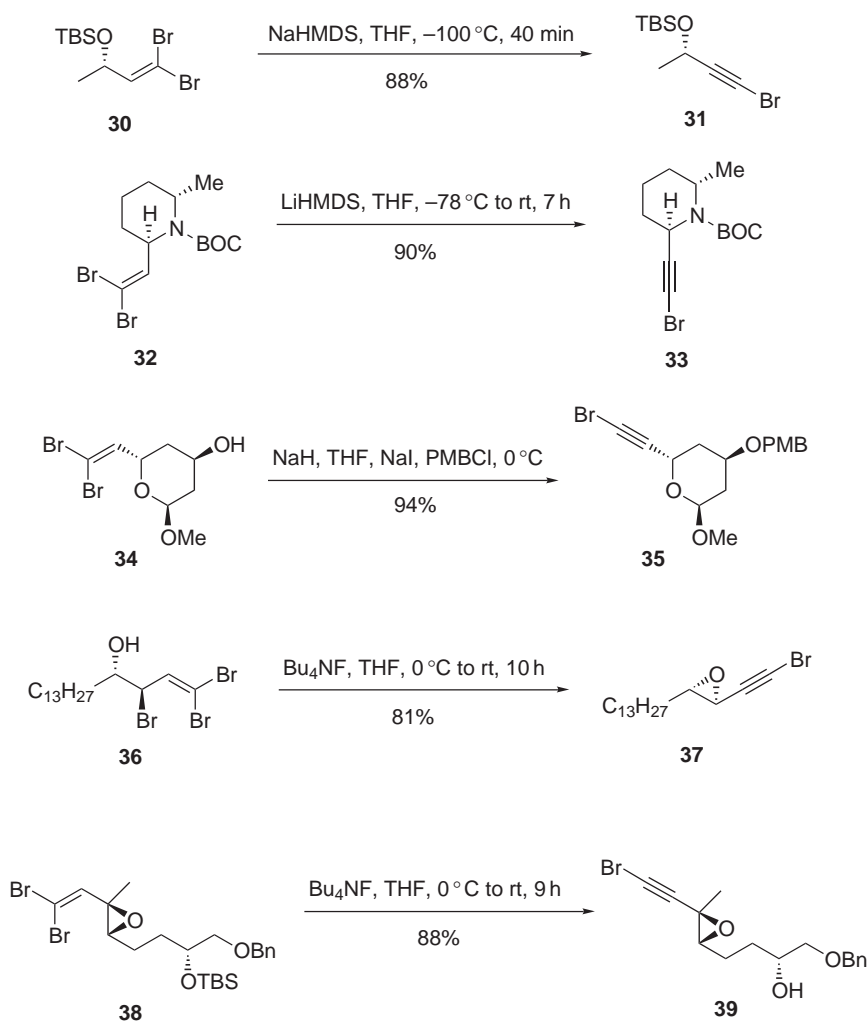
A proposed approach to alkynyl bromides is based on the decarboxylative halogenation of propiolic acids with NBS [<1999JOC6896, 2002JOC7861>](#) or bis(collidine)bromine(I) hexafluorophosphate [<1999TL1495>](#). Specifically, acetylenic acids [40](#) can be effectively converted to bromoalkynes [41](#) by the treatment with NBS at room temperature in the presence of triethylamine as a catalyst ([Scheme 16](#)) [<2002JOC7861>](#). Likewise, the reaction of bis(collidine)bromine(I) hexafluorophosphate with acetylenic acids leads to the corresponding bromoalkynes in high yields under mild conditions ([Scheme 17](#)) [<1999TL1495>](#).

An interesting approach to alkynyl bromides involves the nucleophilic substitution reaction of alkynylselenonium salts [42](#) with tetrabutylammonium bromide ([Scheme 18](#)) [<1999TL931>](#).

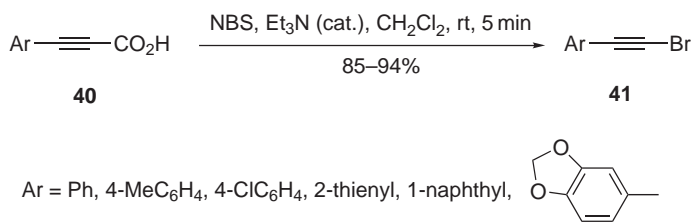
2.21.1.4 Iodides and Alkynyliodonium Salts

2.21.1.4.1 The synthesis of alkynyl iodides

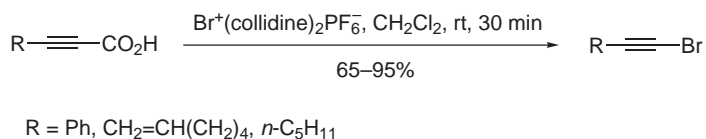
Alkynyl iodides in general have a stability similar to the bromides and are prepared by the same general methods [<1995COFGT\(2\)1011>](#). The parent diiodoethyne is best prepared by passing acetylene through the solution of sodium hypoiodide in water and can be separated as a precipitate [<1995COFGT\(2\)1011>](#). Monoiodoethyne can be conveniently prepared by reacting tributyl(ethynyl)tin with iodine in THF ([Equation \(5\)](#)). The solution of monoiodoethyne in THF can be purified by codistilling with THF at 70 °C. Monoiodoethyne is stable up to 160 °C as indicated by a differential scanning calorimeter studies [<2001OL4185>](#).



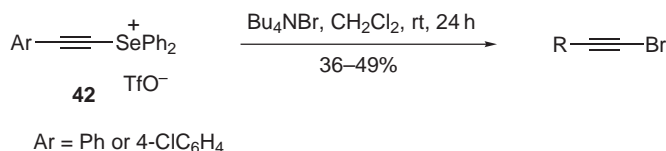
Scheme 15



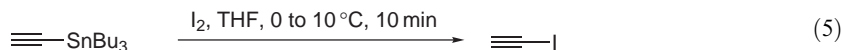
Scheme 16



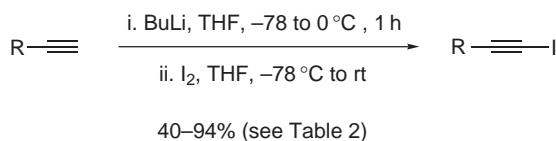
Scheme 17



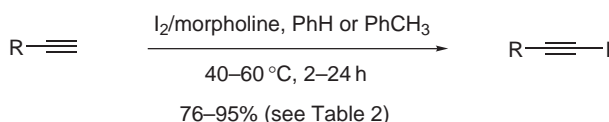
Scheme 18



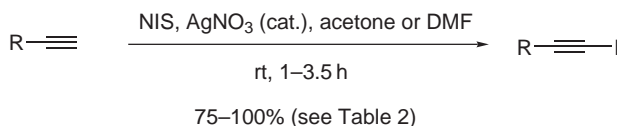
Alkynyl iodides are best prepared by the direct iodination of terminal alkynes or the corresponding alkynylides. The most common modern procedures include the direct iodination of lithium alkynylides (Scheme 19) <2000EJO2557, 2000T9927, 1995JOC4595>, the reaction of terminal alkynes with the iodine–morpholine complex (Scheme 20) <2002JA518, 2000EJO939>, and the treatment of terminal alkynes with *N*-iodosuccinimide in acetone in the presence of silver nitrate (Scheme 21) <2000JCS(P1)737>. Numerous alkynyl iodides (Table 2) have been prepared by these methods and have been further utilized as intermediates in the synthesis of complex organic molecules.



Scheme 19



Scheme 20



Scheme 21

An older procedure for the preparation of alkynyl iodides consists in the treatment of terminal alkynes with iodine and KOH <1995COFGT(2)1011>. This method has also been applied to the preparation of diiodooctatetrayne **43** (Scheme 22) <2002JCS(P1)705>. Product **43** was isolated as a pale yellow solid, which decomposes with explosion at 85–95 °C.

Numerous alkynyl iodides have been prepared by the treatment of terminal alkynes with iodine and sodium methoxide (Scheme 23) <2002JOC9421>.

Several less common iodinating reagents have also been used for the preparation of alkynyl iodides from terminal alkynes. Phenylethynyl iodide was prepared in 94% yield by the iodination of phenylethyne with carbon tetraiodide and a base under phase-transfer catalysis conditions (see Scheme 13 for the analogous bromination) <2001JMOC(A)121>. Trifluoroiodoethane (CF₃CH₂I) has been used for the iodination of 1-heptyne in a moderate yield <1999TL6671>. A polymer-supported electrophilic iodinating reagent **44** can efficiently promote iodination of terminal alkynes under mild conditions (Scheme 24) <1999OL2101>. The polystyrene-bound reagent **44** is very convenient in practical applications. After reaction with an organic substrate, the resin can easily be recovered from the reaction mixture by filtration and converted to the initial reagent **44** by treatment with (diacetoxyiodo)benzene.

Table 2 Alkynyl iodides prepared by iodination of terminal alkynes

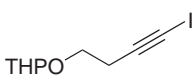
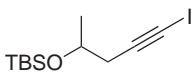
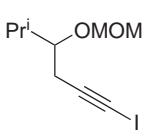
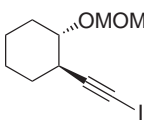
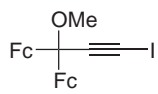
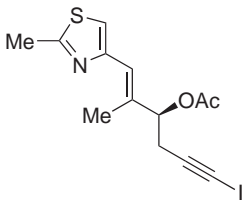
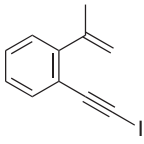
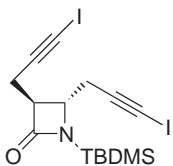
Alkynyl iodide	Reagent ^a	Yield (%)	References
$\text{Ph}-\text{C}\equiv\text{C}-\text{I}$	BuLi/I ₂	80	<2000EJO2557, 2000T9927>
$\text{MOMOCCH}_2-\text{C}\equiv\text{C}-\text{I}$	BuLi/I ₂	65	<2000EJO2557>
	BuLi/I ₂	92	<1995JOC4595, 2001TL3803>
	BuLi/I ₂	86	<2002TL4621>
$\text{CH}_3(\text{CH}_2)_n-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{I}$ $n=3$ or 4	BuLi/I ₂	78–82	<2001OL819, 1995TL3687>
	BuLi/I ₂	62	<2002CEJ3139>
	BuLi/I ₂	73	<2002CEJ3139>
$\text{HO}(\text{CH}_2)_4-\text{C}\equiv\text{C}-\text{I}$	BuLi/I ₂	94	<1999EJO1925>
$\text{TIPS}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{I}$	BuLi/I ₂	55	<2002JCS(P1)705>
$\text{TMS}-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-\text{I}$	BuLi/I ₂	40	<2002JCS(P1)705>
	BuLi/I ₂	62	<1998OM2414>
(Fc = ferrocenyl)			
	BuLi/I ₂	80	<2000TL1863>
	I ₂ /morpholine	89	<2002JA518>
	I ₂ /morpholine	82	<2000EJO939>

Table 2 (continued)

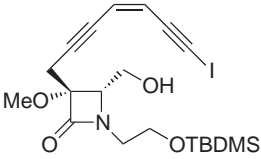
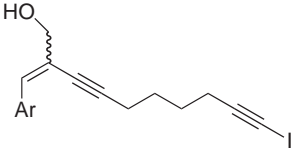
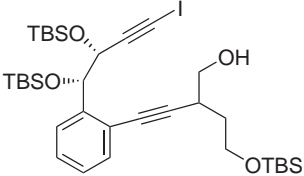
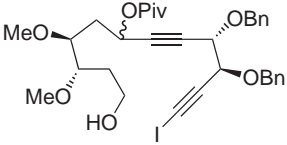
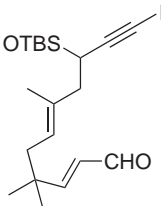
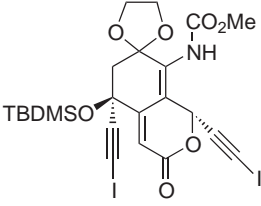
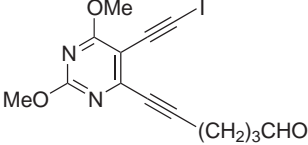
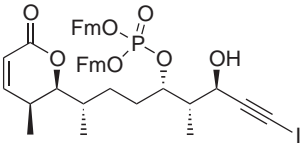
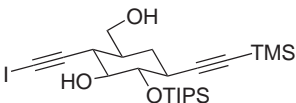
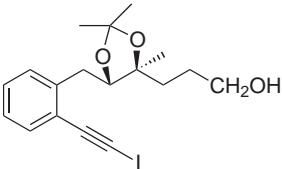
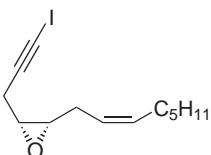
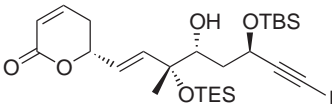
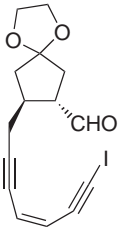
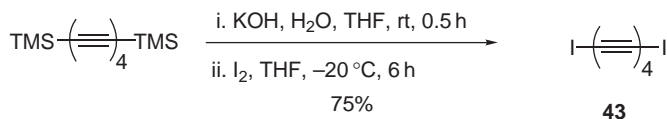
Alkynyl iodide	Reagent ^a	Yield (%)	References
	I ₂ /morpholine	95	<2000TL6523>
	I ₂ /morpholine	76–92	<2001TL4211, 2001TL4215>
Ar = 1-naphthyl, 2-naphthyl, 4-MeOC ₆ H ₄ , 2-TBDMSOC ₆ H ₄			
	I ₂ /morpholine	89	<1997TL5507>
	NIS/AgNO ₃	88	<2000JCS(P1)737>
	NIS/AgNO ₃	96	<2002AG(E)3284>
	NIS/AgNO ₃	89	<1996JA4904, 2000CC1341>
	NIS/AgNO ₃	91	<2000OL3761>
	NIS/AgNO ₃	100	<2002AG(E)1748>
Fm = fluorenylmethyl			

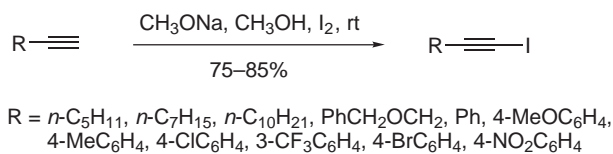
Table 2 (continued)

Alkynyl iodide	Reagent ^a	Yield (%)	References
	NIS/AgNO ₃	94	<1999HCA143>
	NIS/AgNO ₃	75	<2002TL6521>
	NIS/AgNO ₃	86	<2001TL7211>
	NIS/AgNO ₃	83	<2002OL4615>
	NIS/AgNO ₃	98	<2002TL4947>

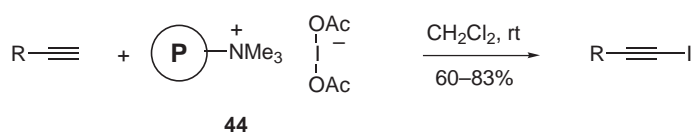
^a For typical reaction conditions see Schemes 19–21.



Scheme 22



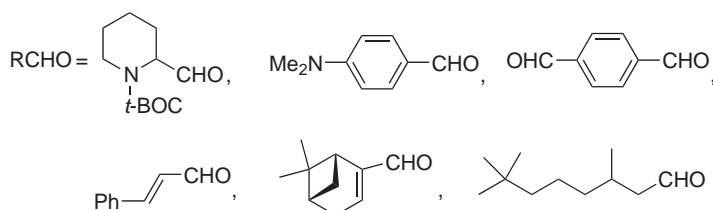
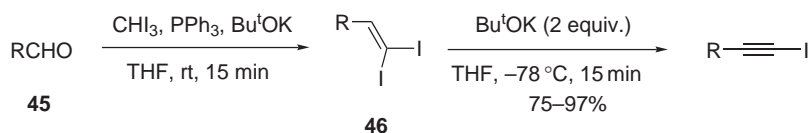
Scheme 23



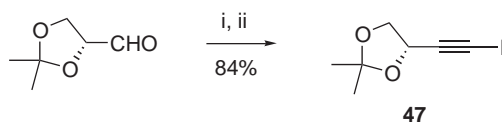
R = MeOCH₂, Ph, HO₂C(CH₂)₃, NC(CH₂)₃, CH₃(CH₂)₄CH(OTBDPS)

Scheme 24

The elimination approach is less commonly used for the preparation of alkynyl iodides compared to the bromides and chlorides. Michel and Rassat have developed a convenient one-pot procedure for conversion of aldehydes to iodoalkynes based on the dehydroiodination of *gem*-diiodoalkenes **46**, which are generated *in situ* from aldehydes **45** and CHI₃/Ph₃P (Scheme 25) <1999TL8579>. This procedure has been employed for the preparation of iodoalkyne **47** (Scheme 26), the key intermediate product in the synthesis of important epoxydienes <2001JOC2146>.



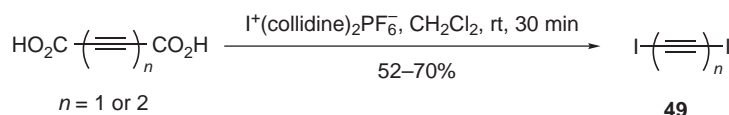
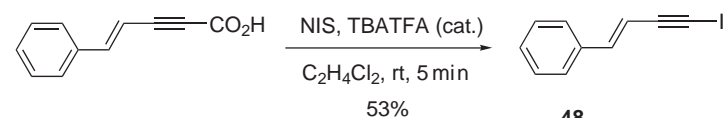
Scheme 25



- i. CHI₃, PPh₃, Bu^tOK (1 equiv.), THF, rt, 15 min
 ii. Bu^tOK (2 equiv.), THF, –78 °C

Scheme 26

Similarly to alkynyl bromides (see Schemes 16 and 17), iodoalkynes can be prepared by the decarboxylative halogenation of propiolic acids with *N*-iodosuccinimide <1999JOC6896, 2002JOC7861> or bis(collidine)iodine(I) hexafluorophosphate <1999TL1495>. In particular, these procedures have been used for the preparation of iodides **48** and **49** (Scheme 27).



Scheme 27

Similarly to alkynyl bromides (see Scheme 18), several arylethynyl iodides were prepared in 74–84% yield by nucleophilic substitution reaction of the respective alkynylselenonium salts **42** with tetrabutylammonium iodide <1999TL931>.

The earlier literature on the preparation and properties of alkynyliodonium salts was exhaustively covered in COFGT (1995) <1995COFGT(2)1011> and in the comprehensive review <1998T10927>. Therefore, this section will only summarize the important subsequent developments in the preparation of these synthetically important compounds. Due to the “hyperleaving group” properties of the phenyliodonanyl group, which has a leaving group ability about 10^6 times greater than the triflate <2000JOM(611)494>, alkynyliodonium salts have found broad synthetic application as reagents for the preparation of various substituted alkynes and in numerous inter- or intramolecular addition/cyclizations via alkylidene carbene intermediates <2003TCC99, 2002CRV2523>.

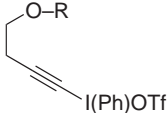
The most general approach to alkynyliodonium salts under very mild conditions involves the ligand exchange reaction of stannylated alkynes **50** with phenyl(cyano)iodonium triflate **51** (Scheme 28) <1995COFGT(2)1011, 1998T10927, 2002CRV2523>. This approach has been utilized by Feldman and co-workers for the preparation of numerous functionalized iodonium salts **52** (Table 3), which were then used as key intermediates in total syntheses of several important natural products <2000OL2603, 2000JOC8659, 1998TL2911, 2002JA9060, 2002JA11600, 2002JOC8528>. Functionalized iodonium salts **52** (Table 3) have low stability and typically decompose above 0 °C; therefore, their preparation and handling should be conducted at low temperatures with final solvent removal at below 0 °C in vacuum <2000JOC8659>.



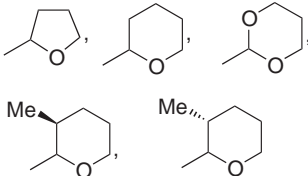
Alkynyliodonium triflate^a

References

<2000OL2603, 2000JOC8659>



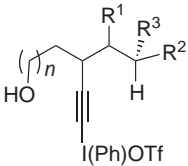
R = TBDMS, CH₂CH=CH₂, Bn,



Me

Me

<1998TL2911>



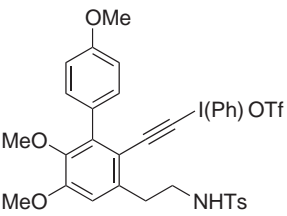
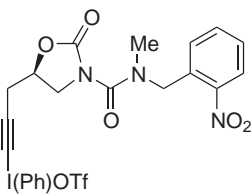
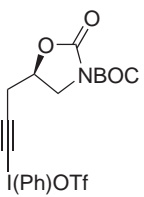
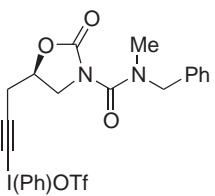
n = 1, R¹ = Me, R² = R³ = H

n = 1, R¹ = R² = (CH₂)₄, R³ = H

n = 1, R¹ = H, R² = R³ = Me

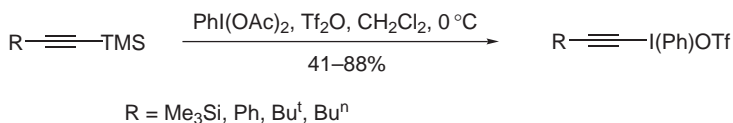
n = 2, R¹ = R² = H, R³ = Ph

Table 3 (continued)

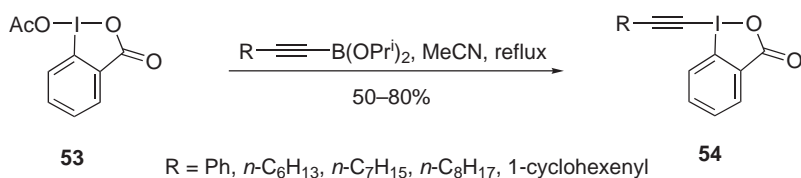
Alkynyliodonium triflate ^a	References
	<2002JA11600, 2002JOC8528>
	<2002JA9060>
	<2002JOC7096>
	<2002JOC7096>

^a Yields were not determined due to the low stability of the products (estimated as quantitative).

Several new approaches to the synthesis of alkynyliodonium salts were developed in the late 1990s and the early 2000s. Kitamura and co-workers have proposed a new procedure based on the reaction of trimethylsilylated alkynes with (diacetoxyiodo)benzene in the presence of trifluoromethanesulfonic acid or trifluoromethanesulfonic anhydride (Scheme 29) <1998SI1416>. Alkynylbenziodoxoles **54** can be obtained from the reaction of acetoxybenziodoxole **53** with alkynylboronates under mild conditions (Scheme 30) <2000SL719>.

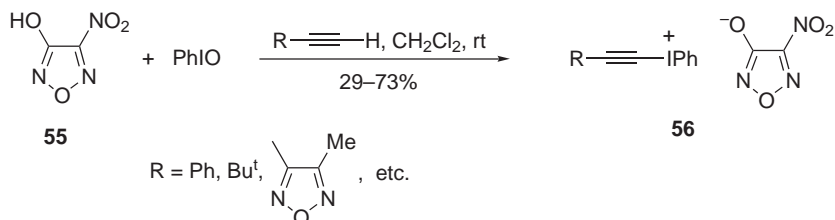


Scheme 29



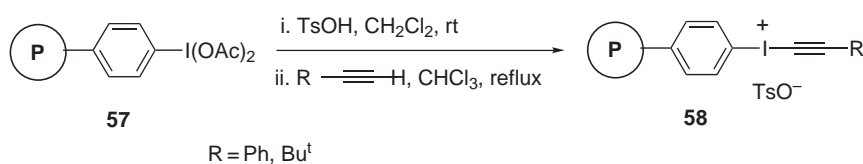
Scheme 30

The novel alkynyl(phenyl)iodonium salts with nitrofurazanylate as a counterion **56** were prepared by the reaction of nitrofurazan **55** with iodosylbenzene and terminal alkynes (Scheme 31) <2001TL5759>.



Scheme 31

Polymer-supported alkynyliodonium tosylates **58** can be prepared by the treatment of diacetate **57** with terminal alkynes in the presence of *p*-toluenesulfonic acid (Scheme 32) <2001TL6373>. Polymers **58** are efficient alkynylating reagents toward sodium sulfinates and benzotriazole.



Scheme 32

2.21.2 ALKYNYL CHALCOGENIDES

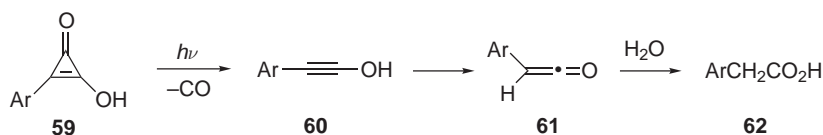
2.21.2.1 The Synthesis of Oxygen-based Functional Groups Attached to *sp*-Carbon

Chapter 2.21 of COFGT (1995) provides a comprehensive review of the earlier literature on the synthesis of alkynyl ethers and esters, which are generally considered as derivatives of the hypothetical ynols, $\text{RC}\equiv\text{COH}$ <1995COFGT(2)1011>. During the decade 1993–2003, considerable interest and research activity has arisen toward the application of ynolate salts and ynol ethers in organic synthesis. The chemistry of ynolate anions has been overviewed by Shindo <1998CSR367>, while the review <B-1994MI1135> summarized the literature on the preparation and reactions of alkynyl ethers and esters.

2.21.2.1.1 Ynols and ynolates

Ynols or hydroxyalkynes are the triple bond analogs of enols. Like enols they are tautomers of the corresponding carbonyl species—ketenes, $\text{RCH}=\text{C}=\text{O}$. According to theoretical calculations, ketenes are about 37 kcal mol^{-1} (155 kJ mol^{-1}) more stable than the corresponding ynols. However, in the gas phase alkynols may exist as relatively stable molecules due to a very high energy barrier for the isomerization. Due to its stability in the form of isolated molecules, hydroxyethyne has been considered as a possible constituent of interstellar clouds, planetary atmospheres, and flames <1995COFGT(2)1011>.

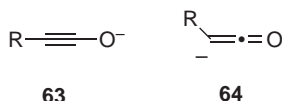
Kresge and co-workers investigated the ynol–ynolate chemistry in liquid solution, using flash photolytic techniques to monitor these short-lived species <1995JA9165, 1996JPO361>. In particular, flash photolysis of a series of arylhydroxycyclopropenones **59** in aqueous solution was found to give arylacetic acids **62** as final products through the intermediate formation of arylnols **60** and then arylketenes **61** (Scheme 33). The kinetic investigation of this process showed that arylnols **60** are remarkably strong acids, with $\text{p}K_{\text{a}}$ less than 3 <1995JA9165>. This indicates that ynols are much more acidic than enols, and more acidic than even carboxylic acids.



Ar = Ph, mesityl, 4-MeOC₆H₄, 2,4,6-(MeO)₃C₆H₂, 1-naphthyl

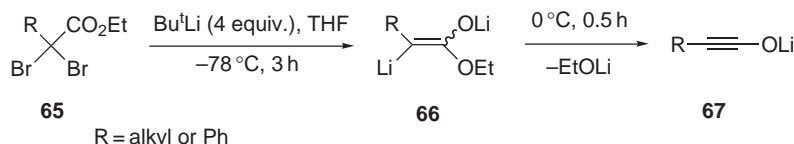
Scheme 33

Ynolate anions **63** are the triple bond analogs of enolate anions and are the ketene anion **64** equivalents (Scheme 34). Similarly to enolates, ynolates have a rich and synthetically important chemistry acting as nucleophilic “ketenylating” reagents <1998CSR367>.



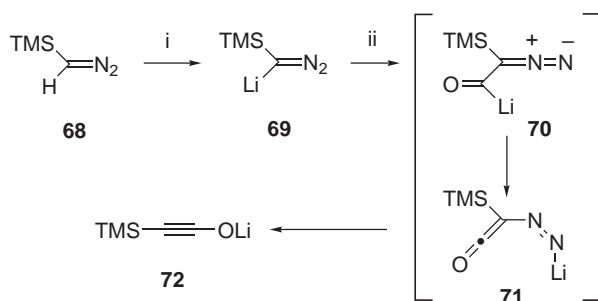
Scheme 34

Several convenient procedures for the *in situ* generation of ynolates have been summarized in COFGT (1995) <1995COFGT(2)1011>. Of these procedures, the most general is the approach based on the fragmentation of α -haloenolate anions that was elaborated by Kowalski and co-workers in the 1980s <1995COFGT(2)1011>. A modified procedure was subsequently developed and utilized in many syntheses by Shindo and co-workers <1997TL4433, 1998T2411, 2001JOC7818, 2001TL8357, 2002TL5039, 2000TL5943, 2000TL5947, 2000JOC5443, 1999JA6507, 2002JA6840, 2002OL3119, 2001OL2029>. This procedure is based on the treatment of α -bromoesters or α,α -dibromoesters **65** with an appropriate strong base to generate ester dianion **66**, fragmentation of which affords the respective ynolate **67** (Scheme 35) <1998T2411, 2001TL8357>.



Scheme 35

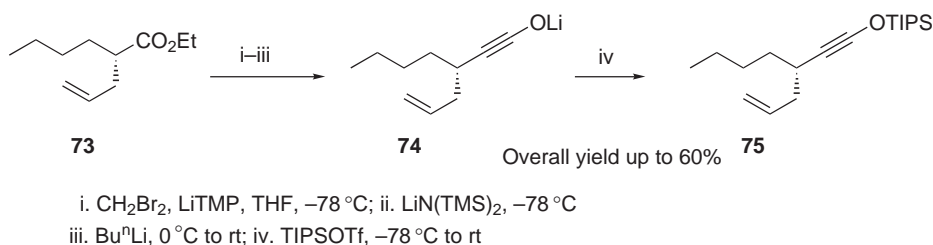
A synthetically attractive trimethylsilylethynolate **72** was originally generated by deprotonation of the appropriate ketene <1995COFGT(2)1011>. Murai and co-workers have developed an alternative approach to compound **72** from the commercially available trimethylsilyldiazomethane **68**, butyllithium, and carbon monoxide (Scheme 36) <1996JA7634, 2001JOC169>. The mechanism of this reaction includes the addition of carbon monoxide to the lithiated trimethylsilyldiazomethane **69** to give a labile acyllithium **70**, which is rapidly converted to a ketene intermediate **71**. Elimination of nitrogen from this intermediate affords the final trimethylsilylethynolate **72** (Scheme 36).



i. BuⁿLi, THF/hexane, -78 °C, 1 h; ii. CO (1 atm), -78 °C, 2 h

Scheme 36

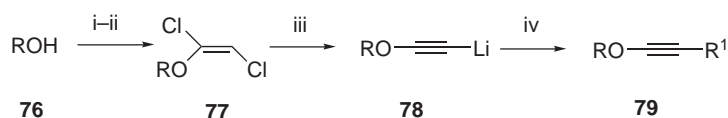
Ynolate anions can be further converted to the synthetically useful silyl ynol ethers by treatment with the appropriate trialkylsilyl triflate. The synthesis of triisopropylsilyloxyalkyne **75** (Scheme 37), the key precursor in the total synthesis of (–)-cylindrocyclophane F, <1999JA7423, 2001JA5925> is an example of this. This reaction involves the generation of ynolate **74** from ester **73** by the procedure of Kowalski <1995COFGT(2)1011> followed by trapping it with triisopropylsilyl triflate (Scheme 37).



Scheme 37

2.21.2.1.2 Alkynyl ethers

Chapter 2.21 of COFGT (1995) provides a detailed evaluation of the known synthetic approaches to alkynyl ethers based on: (i) dehydrohalogenation of haloacetals and haloalkenyl ethers, (ii) functionalization of terminal alkoxyethynes, and (iii) the reaction of alkynyl halides with alkoxide anions <1995COFGT(2)1011>. The most commonly used modern synthetic procedure for the one-pot conversion of alcohols **76** into alkynyl ethers **79** employs the dehydrohalogenation of 1,2-dichlorovinyl ethers **77** generated *in situ* from the respective alkoxides and trichloroethylene (Scheme 38) <1997OS13>. Lithium alkoxyethynylide **78**, formed as the result of this dehydrohalogenation, can be further functionalized *in situ* by the reaction with appropriate electrophiles, such as alkyl bromides, water, or carbonyl compounds. Numerous alkynyl ethers (Table 4) have been prepared by this procedure and have been further utilized as intermediates in the synthesis of complex organic molecules.



Overall yields 66–87% (see Table 4)

i. KH, THF, rt, 40 min; ii. $\text{Cl}_2\text{C}=\text{CHCl}$, THF, $-50\text{ }^\circ\text{C}$, 1 h;
 iii. Bu^nLi , THF, -70 to $-40\text{ }^\circ\text{C}$, 1 h; iv. R^1I , HMPA, $-40\text{ }^\circ\text{C}$ to rt, 3 h

Scheme 38

The parent alkoxyethynes (HCCOR) are the most readily available representatives of alkynyl ethers. Moreover, ethoxyethyne is even commercially available, or can be easily prepared by standard, well-developed procedures. Alkoxyethynes can be further functionalized by standard methods employed for terminal alkynes and alkynylides <1995COFGT(2)1011>. Several examples of the utilization of the commercially available lithium ethoxyethynylide in the syntheses of functionalized alkynyl ethers are shown in Scheme 39 <2001JCS(P1)2657, 1997JA9584, 1998TL4219, 1997OM78, 2000HCA641>.

Nucleophilic substitution of halogen with alkoxide anion at an alkyne carbon represents another general approach to alkynyl ethers. This substitution proceeds via an addition–elimination mechanism and usually affords alkynyl ethers in a relatively low yield <1995COFGT(2)1011>. Nevertheless, the reaction of potassium alkoxide **80** with phenylethynyl

Table 4 Alkynyl ethers **79** prepared from alcohols **76** (Scheme 38)

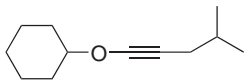
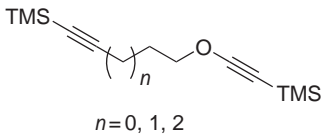
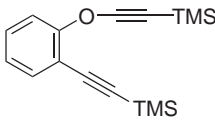
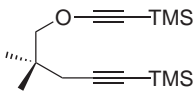
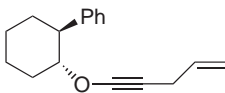
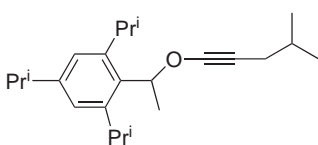
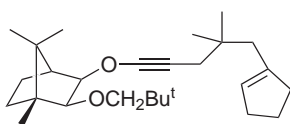
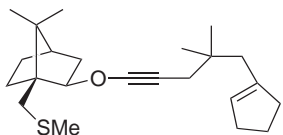
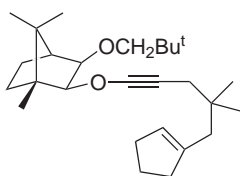
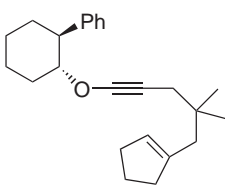
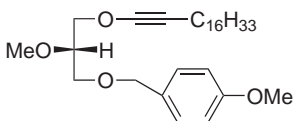
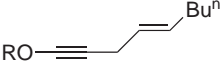
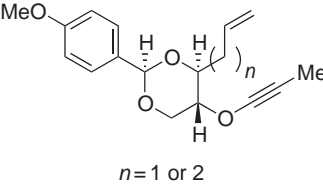
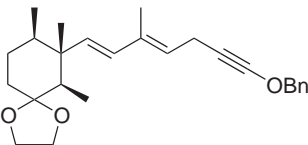
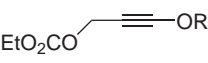
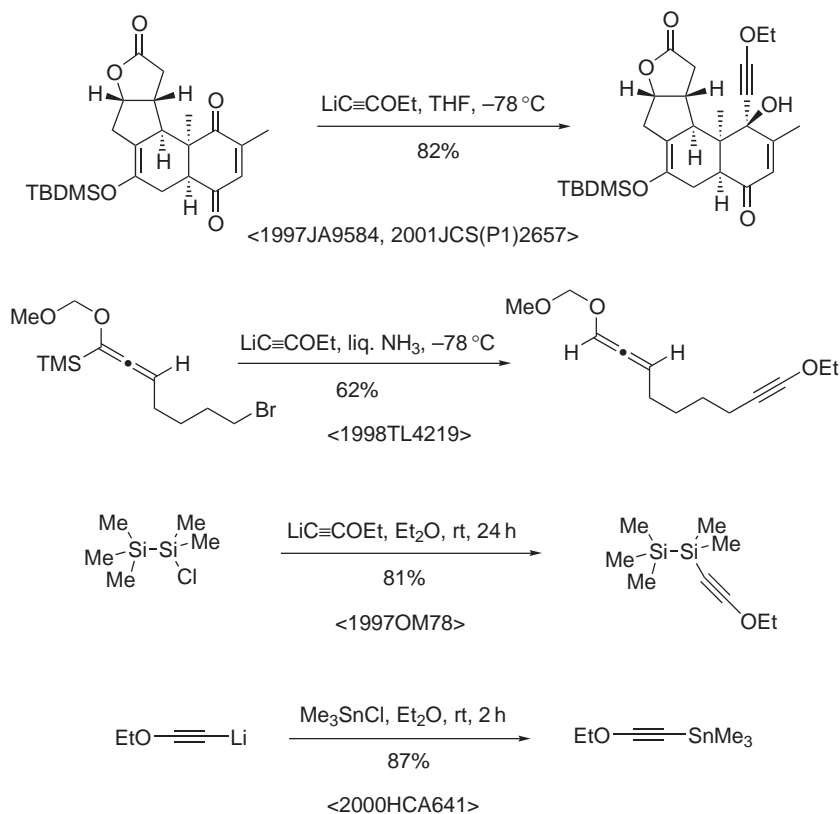
Alkynyl ether 79	Yield (%)	References
	85	<2001JA3369, 2002JA6576>
 $n=0, 1, 2$	NR	<2001TL6987>
	NR	<2001TL6987>
	83	<2001TL6987>
	83	<1997JOC7086, 1998JOC6178>
	75	<1996JOC5210>
	50	<1997JOC4851>
	28	<1997JOC4851>
	56	<1997JOC4851>
	43	<1997JOC4851>
	69	<2001T4277>

Table 4 (continued)

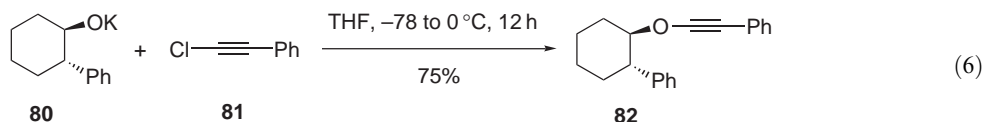
Alkynyl ether 79	Yield (%)	References
 R = menthyl or 2-phenylcyclohexyl	77–94	<1999T11437>
 n = 1 or 2	84–88	<2002T1973>
	77	<2000OL3407>
 R = Bu ⁿ , Bu ^t , cyclohexyl	61–79	<2000OL2369>

NR = Yield not reported.

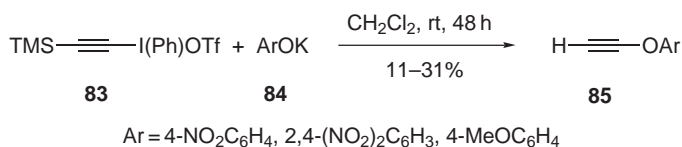


Scheme 39

chloride **81** has successfully been employed for the preparation of alkynyl ether **82** (Equation (6)), an important intermediate in the enantioselective synthesis of 3-substituted and 3,4-disubstituted pyrrolidines <1995JOC3221>.



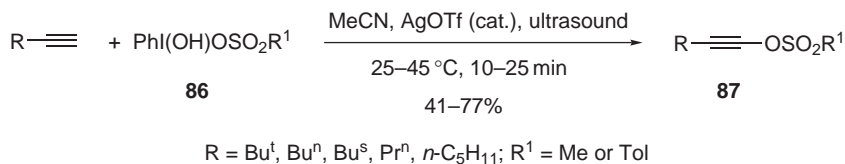
Alkynyliodonium salts, which have a very good leaving group, iodobenzene, react with alkoxide anion under mild conditions affording alkynyl ethers in moderate yield along with the products of carbene cyclization <1995COFGT(2)1011, 1997JCS(P2)1511, 2000MI1182>. (Trimethylsilyl)ethynyl]phenyliodonium triflate **83** has been shown to react with potassium phenolates **84** affording ethynyl phenolate ethers **85** in a low yield (Scheme 40), along with 2-aroxybenzo[b]furans as the C—H insertion products <2000MI1182>.



Scheme 40

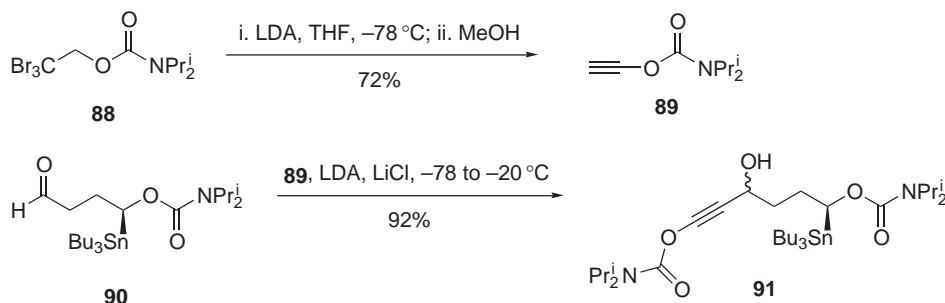
2.21.2.1.3 Alkynyl esters

Because of the low stability and the lack of synthetic approaches, alkynyl esters remained unknown until the mid-1980s. Chapter 2.21 of COFGT (1995) <1995COFGT(2)1011> provides a detailed review of the preparation of alkynyl esters by the reactions of alkynyl(phenyl)iodonium salts with carboxylate, sulfonate, and phosphate anions. Tuncay and co-workers <1999TL599> have reported an improved, one-pot method for the synthesis of alkynyl sulfonate esters from terminal alkynes and [hydroxy(sulfonyloxy)iodo]benzenes **86** under ultrasound-enhanced conditions (Scheme 41). This procedure is based on the *in situ* generation of alkynyl(phenyl)iodonium sulfonates from alkyne and reagent **86** followed by the silver-assisted nucleophilic acetylenic substitution of iodobenzene.



Scheme 41

The reaction of alkynyliodonium salts with the corresponding anionic nucleophiles is the most general and selective approach to alkynyl esters. An alternative approach based on the reaction of lithium alkynolates with the corresponding acid chlorides was discussed in COFGT (1995) <1995COFGT(2)1011>. A later approach to ethynyl carbamate **89**, which is also a member of the family of alkynyl esters, is based on dehydrobromination of 2,2,2-tribromoethylcarbamate **88** with lithium *N,N*-diisopropylamide. The parent ethynyl carbamate **89** can be further functionalized to alkynyl carbamate **91** via the reaction of the respective lithium alkynylide with an aldehyde **90** (Scheme 42) <2002OL2193>.

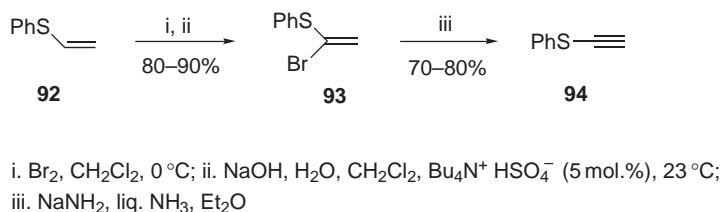


Scheme 42

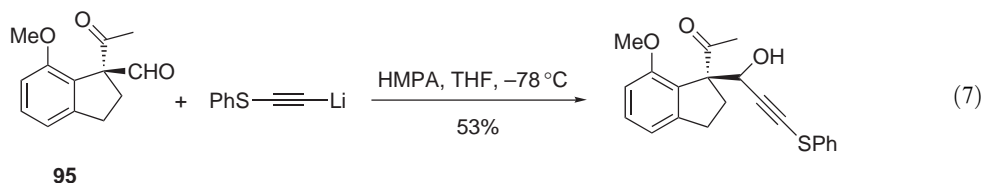
2.21.2.2 The Synthesis of Sulfur-based Functional Groups Attached to *sp*-Carbon

2.21.2.2.1 Alkynyl thioethers

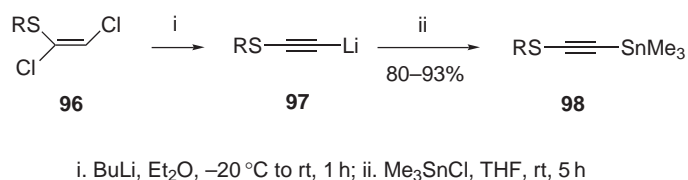
Chapter 2.21 of COFGT (1995) provides a comprehensive review of the earlier literature on the synthesis of alkynyl thioethers via: (i) dehydrohalogenation of halothioethers, (ii) the reactions of alkynylides with the electrophilic thiolyating reagents, and (iii) the reactions of alkynyl halides with thiolates <1995COFGT(2)1011>. Dehydrohalogenation of halothioethers can be achieved by the action of various bases, such as sodium amide, potassium hydroxide, potassium *t*-butoxide, potassium hydride, butyllithium, etc. In particular, dehydrobromination with sodium amide in liquid ammonia is a method of choice for the preparation of the thermally unstable and volatile thioethers <1995COFGT(2)1011>. A detailed, optimized procedure for the preparation of phenylthioethyne **94** from thioalkene **92** via dehydrobromination of bromothioether **93** (Scheme 43) has been given by Magriotis and Brown <1995OS252>. Phenylthioethyne **94** is obtained as a pale yellow liquid, which turns brown-red upon storage in a freezer; it can be stored for several months at -10°C without significant decomposition. The treatment of thioether **94** (as the appropriate alkynylide) with various electrophiles, such as, aldehydes, esters, alkyl or aryl iodides, trialkylsilyl chlorides, is a versatile method for the preparation of a series of (phenylthio)-substituted alkynes in good yields <1995OS252>. A similar phenylthioethynylation of aldehyde **95** (Equation (7)) has been employed in the total synthesis of the antitumor antibiotic fredericamycin A <2000CEJ3897, 2001OL4015>.



Scheme 43

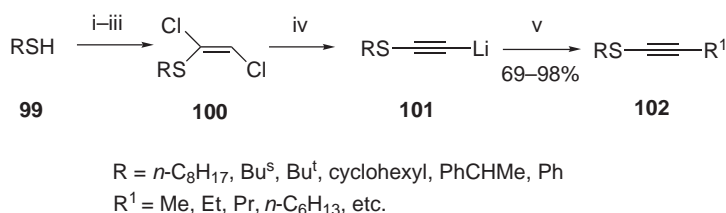


The etherial solutions of lithium alkynylides **97** can be conveniently prepared by dehydrochlorination of vinylic thioethers **96** with butyl lithium and further trapped by the reaction with trimethyltinchloride to afford the respective alkynyl thioethers **98** (Scheme 44) <2000HCA641>.



Scheme 44

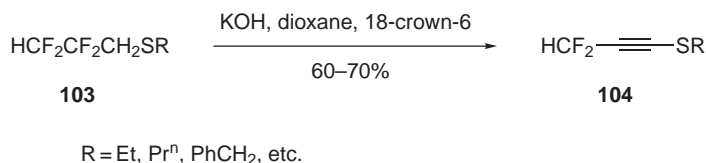
A simple, one-pot procedure for the preparation of alkynyl thioethers **102** from thiols **99** and trichloroethene was developed by Greene and co-workers (Scheme 45) <1995JOC7690>. This method is based on the dehydrochlorination of 1,2-dichlorovinyl thioethers **100** generated *in situ* from the respective thiolates and trichloroethylene (Scheme 45). Lithium thioethynylide **101**, formed as the result of this dehydrohalogenation, can be further functionalized *in situ* by the reaction with the appropriate electrophiles, such as alkyl iodides, trimethylsilyl chloride, or methanol <1995JOC7690>.



i. KH, THF, rt, 2 h; ii. Cl₂C=CHCl, THF, -50 °C, 5 min; iii. MeOH, -50 °C to rt, 1 h;
iv. BuⁿLi, -70 to -40 °C, 1 h; v. R¹I, HMPA, -40 °C to rt, 1 h

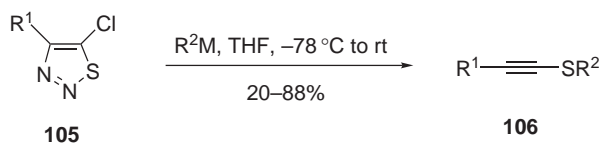
Scheme 45

Fluorine-containing alkynyl thioethers **104** were prepared by dehydrofluorination of 1,1-dihydropolyfluoroalkyl sulfides **103** by the action of potassium hydroxide in dioxane in the presence of 18-crown-6 (Scheme 46) <2001EJO3625, 2000HAC383, 1998HAC151>.



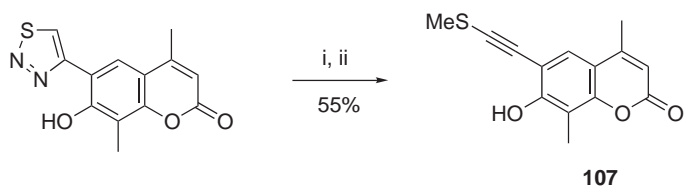
Scheme 46

Not only halothioethers can serve as starting compounds in the elimination procedures. In a procedure developed by Dehaen and co-workers <1999JCS(P2)1473, 2000T3933>, thiadiazoles **105** eliminate nitrogen upon treatment with organolithium or Grignard reagents with the formation of alkynyl sulfides **106** (Scheme 47). A similar procedure has been employed in the synthesis of the Coumarin derivative **107** (Scheme 48) <2000S1529>.



R¹ = Ph, Bu^t; R² = Me, Et, Buⁿ, Bu^t, Ph, PhC≡C; M = Li or MgBr

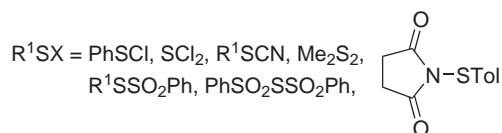
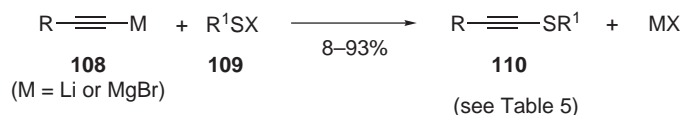
Scheme 47



i. NaH, DMF, 0 °C, 10 min; ii. MeI, rt, 30 min

Scheme 48

The second major approach to alkynyl thioethers employs the reactions of metal alkynylides with the electrophilic thiolating agents, such as sulfenyl halides, disulfides, thiocyanates, thiosulfonates, etc. (Scheme 49). In the period 1993–2003, this approach has been widely used for the preparation of various synthetically useful alkynyl thioethers (Table 5).



Scheme 49

Table 5 Alkynyl thioethers **110** prepared from metal alkynylides **108** and electrophilic thiolating agents **109** (Scheme 49)

Alkynyl thioether	Reagent	Yield (%)	References
$\text{MeOCH}_2\text{—}\equiv\text{SPh}$	PhSCl^{a}	79	<2001TL2729>
	SCl_2^{a}	40	<2000CC75, 2000JCS(D)3675>
	SCl_2^{a}	72	<2000CC75>
	$\text{NCS-CH}_2\text{-OTHP}^{\text{b}}$	72	<2002JOC4218>
		51–58	<1998AG(E)619>
$n = 2 \text{ or } 3$	$n = 2 \text{ or } 3^{\text{b}}$		

Table 5 (continued)

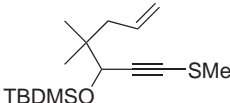
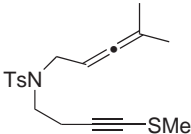

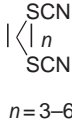
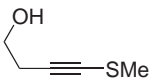
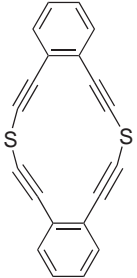
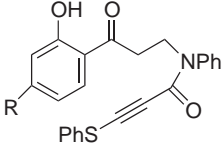
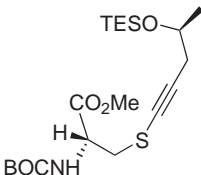
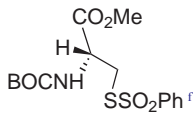
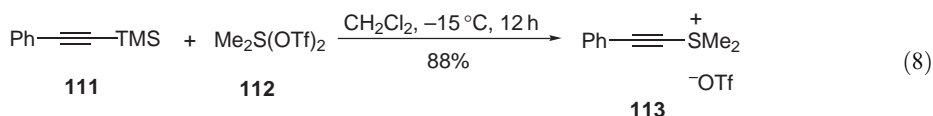
Alkynyl thioether	Reagent	Yield (%)	References
	MeSCN ^c	63	<2000S1009>
	MeSCN ^d	91	<2000S1009>
	 $n = 3-6^e$	8-55	<2000EJO2479>
PhS-C≡C-SMe	Me ₂ S ₂ ^c	53	<2001TL955>
	Me ₂ S ₂ ^c	79	<2001JOC5237>
C ₅ H ₁₁ -C≡C-SMe	Me ₂ S ₂ ^f	41	<2001JOM(627)86>
Ph-C≡C-SMe	Me ₂ S ₂ ^f	78	<2001JOM(627)206>
	PhSO ₂ SSO ₂ Ph ^f	65	<2002TL2079>
 R = H, OMe	PhSSO ₂ Ph ^f	70-78	<1997SL310>
		74	<2002JOC4565>

Table 5 (continued)

Alkynyl thioether	Reagent	Yield (%)	References
		93	<2001OL91>
		73	<2001OL91>
		85	<2001OL91>
		70	<2001OL91>

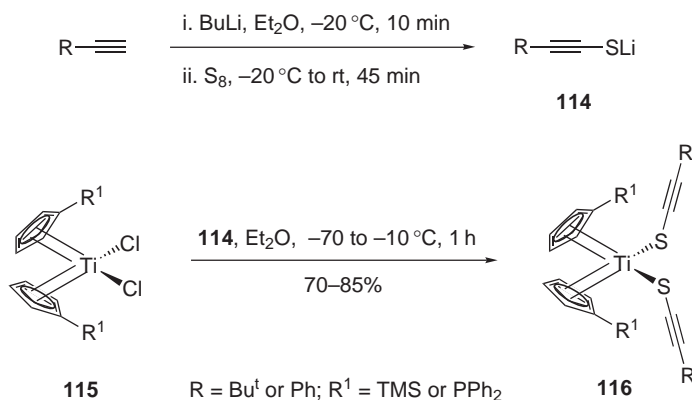
Reaction conditions: ^a RLi, THF, -78 °C; ^b HC≡CMgBr, THF, rt; ^c RLi, THF, -20 °C to rt; ^d RLi, THF, -78 to 0 °C; ^e LiC≡CLi, THF, -40 °C; ^f RLi, THF, -78 °C to rt.

A novel phenylethynylsulfonium salt **113** can be prepared by the reaction of the respective trimethylsilyl alkyne **111** with the highly electrophilic dimethyl sulfide ditriflate (DMSD, **112**) (Equation (8)) <1997S351>. Alkynylsulfonium salt **113** was isolated as a relatively stable, white microcrystalline solid.

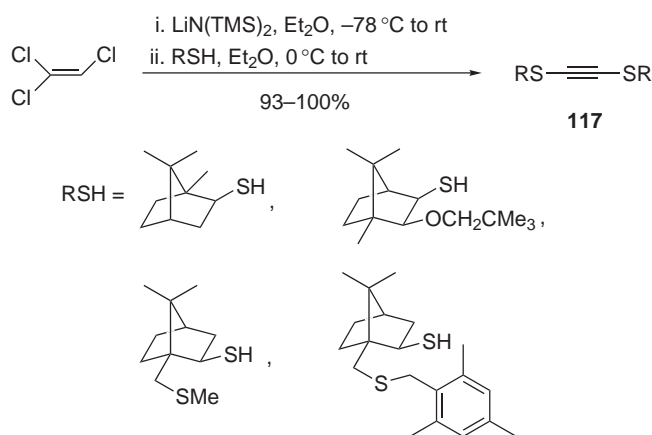


Alkynyl thiolate anions, $\text{RC}\equiv\text{CS}^-$, can be conveniently generated by the reaction of lithium alkynylides with sulfur in ether or a THF-hexane solution and further reacted with the appropriate electrophiles with the formation of various alkynyl thioethers <1995COFGT(2)1011>. The reaction of lithium alkynyl thiolates **114** with titanium(IV) complexes **115** has been used for the preparation of the first thioalkynyl derivatives of titanocene **116** (Scheme 50) <1998JCS(D)3199>. Likewise, the new mononuclear iron carbonyl derivatives $(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2(\text{SC}\equiv\text{CR})$ ($\text{R} = \text{Bu}^t$ or trimethylsilyl (TMS)) were obtained by the reaction of $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2\text{I}]$ and the corresponding lithium alkynyl thiolates. The crystal structure of these complexes was established by X-ray diffraction <2002JOM(649)21>.

Nucleophilic substitution of halogen at the *sp*-carbon of an alkynyl halide represents another general approach to alkynyl thioethers and analogous compounds. In general, alkyl thiolates and aryl thiolates smoothly react with alkynyl chlorides or bromides in aprotic polar solvents to afford alkynyl thioethers in moderate to good yields <1995COFGT(2)1011>. An example of this approach is represented by a one-pot procedure for the synthesis of chiral alkynyl dithioethers **117** in enantiomerically pure form from trichloroethylene and chiral thiols (Scheme 51) <1997TA1575>. This reaction proceeds via the intermediate formation of dichloroethyne and its subsequent reaction with the appropriate alkyl thiolate anion *in situ*.

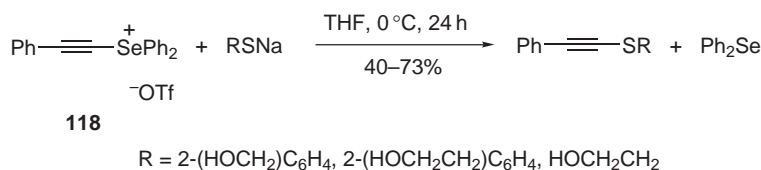


Scheme 50



Scheme 51

Alkynyliodonium salts can also be effectively used as substrates in substitution reactions due to the excellent leaving group ability of iodobenzene [<1995COFGT\(2\)1011>](#). A similar approach employs the reaction of alkynylselenonium salt **118** with thiolate anions ([Scheme 52](#)) [<2000JOC8893, 2000SL49>](#). In this reaction, Ph₂Se serves as a good leaving group in the acetylenic nucleophilic substitution.

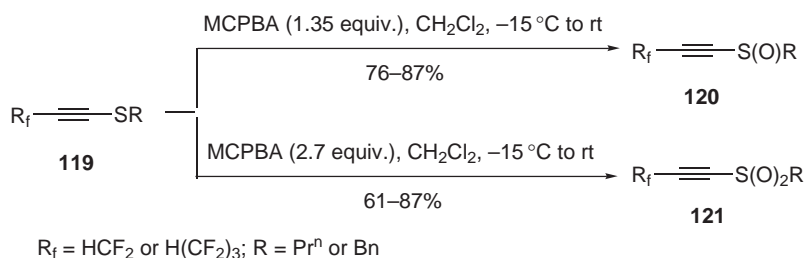


Scheme 52

2.21.2.2.2 Alkynyl sulfoxides and sulfones

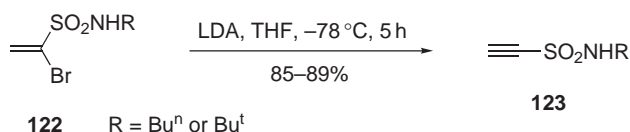
Chapter 2.21 of COFGT (1995) [<1995COFGT\(2\)1011>](#) provides a comprehensive review of the earlier literature on the synthesis of alkynyl sulfoxides and sulfones via: (i) oxidation of alkynyl thioethers, (ii) various elimination reactions, and (iii) by substitution at *sp*-carbon. Alkynyl

thioethers can be oxidized to either sulfoxides or sulfones by 3-chloroperoxybenzoic acid, depending on the stoichiometry of the reactants. Shermolovich and co-workers have utilized this approach for the preparation of fluorinated alkynyl sulfoxides **120** and sulfones **121** from thioethers **119** (Scheme 53) <2001EJO3625, 2000HAC383>. Alkynes **120** and **121** are useful dienophiles in cycloaddition reactions with various dienes <2001EJO3625>.



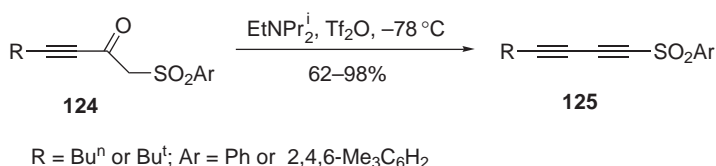
Scheme 53

A variety of elimination procedures have been applied to the synthesis of alkynyl sulfones <1995COFGT(2)1011>. Ethynylsulfonamides **123** have been prepared by dehydrobromination of α -bromoalkenylsulfonamides **122** with lithium diisopropylamide in (THF) (Scheme 54) <1999HAC461>.

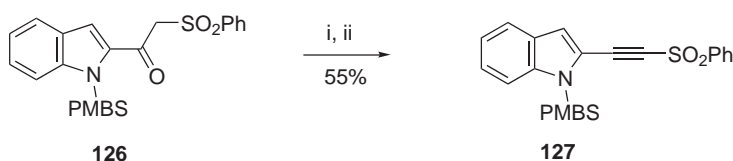


Scheme 54

1-(Arylsulfonyl)alkynes **125** are conveniently prepared from readily available β -ketosulfones **124** by treatment with triflic anhydride and diisopropylethylamine (Scheme 55) <2002JCS(P1)1413>. Vinyl triflates are plausible intermediates in this reaction. In an analogous procedure (Scheme 56), alkynyl sulfones **127** are prepared by elimination from vinyl phosphates, which are generated *in situ* from β -ketosulfones **126** and diethyl chlorophosphate in the presence of sodium hydride <2001JCS(P1)127>.



Scheme 55

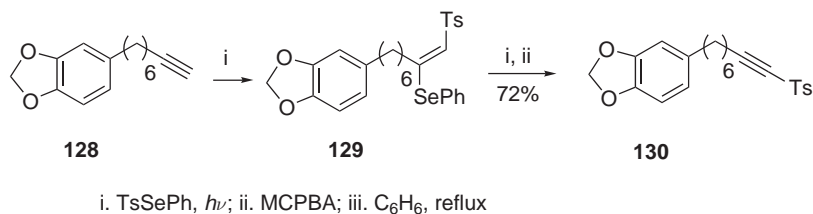


i. NaH, THF, (EtO)₂POCl, rt; ii. Bu^tOK, THF, −78 °C

PMBS = 4-methoxyphenylsulfonyl

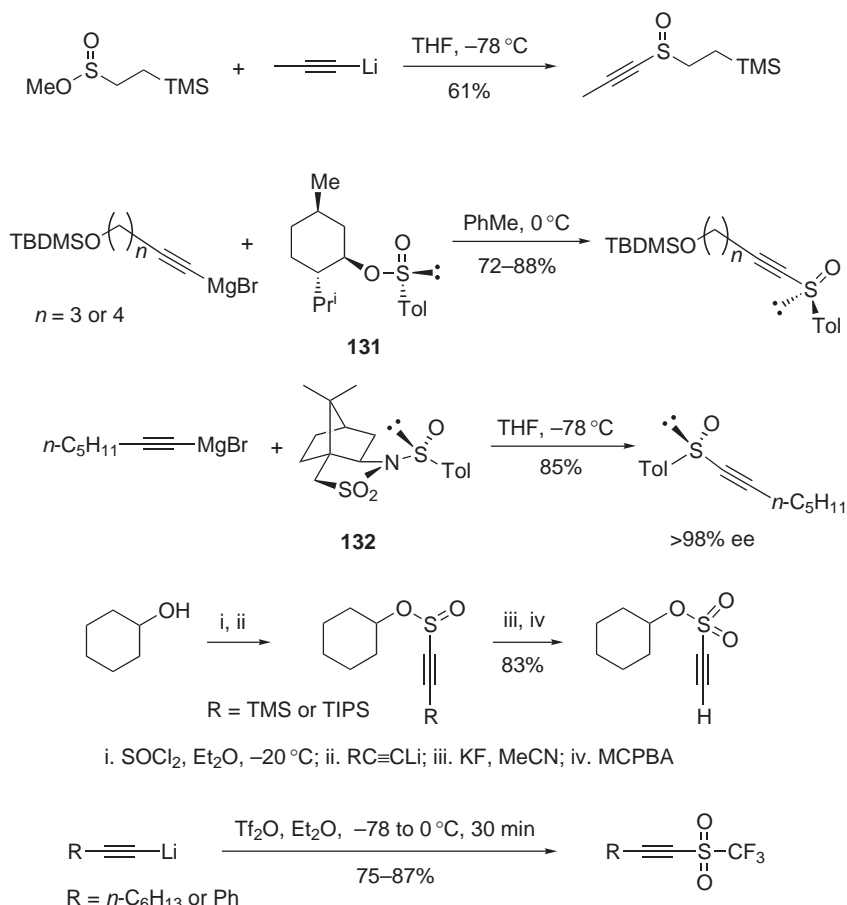
Scheme 56

Similarly, oxidative elimination in selenoalkene **129** affords alkynyl sulfone **130** in good yield (Scheme 57) <2002CC1710>. Selenoalkene **129** can be generated *in situ* by the addition of phenylselenenyl sulfone to terminal alkyne **128**.



Scheme 57

Alkynyl sulfoxides and sulfones can be conveniently prepared by the reaction of a metal alkynylide with an appropriate electrophilic reagent, such as sulfinate ester, alkanesulfinyl chloride, and trifluoromethanesulfonic anhydride. Several specific examples of these reactions are shown in Scheme 58 <2001EJO1643, 1998TL47, 2000T7927, 1997TL2825, 1998JCR(S)326, 1996JA4284>. This approach is particularly useful for the preparation of the enantiomerically pure alkynyl sulfoxides using chiral sulfinate reagents **131** and **132** (Scheme 58) <1998TL47, 2000T7927, 1997TL2825>.



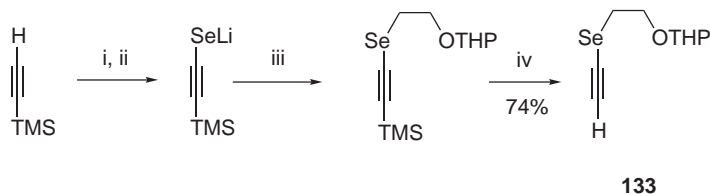
Scheme 58

2.21.2.3 The Synthesis of Selenium- and Tellurium-based Functional Groups Attached to *sp*-Carbon

Chapter 2.21 of COFGT (1995) provides an overview of the earlier literature on the synthesis of alkynyl selenides and tellurides via: (i) the reactions of metal alkynylides with selenium or tellurium, (ii) the reactions of alkynylides with arylselenium bromides, aryltellurium bromides, or diphenyl diselenide, (iii) the reactions of alkynyl halides with metal selenolates and tellurolates, and (iv) various elimination reactions <1995COFGT(2)1011>.

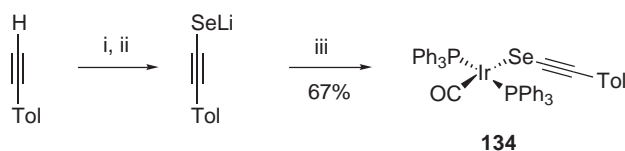
2.21.2.3.1 Alkynyl selenides

The most common approach to alkynyl selenides employs the reaction of a metal alkynylide with elemental selenium or an appropriate electrophilic selenium reagent, such as, arylselenium halides, diphenyl diselenide, or selenocyanates. A well-developed and convenient procedure consists in the treatment of lithium alkynylides with selenium, followed by trapping of the intermediate lithium selenolates with alkyl bromides or other appropriate electrophiles <1997JA8592, 2002JOC4218, 1998OM4117>. In particular, this procedure has been applied toward the synthesis of alkynyl selenide **133** (Scheme 59) <2002JOC4218> and the iridium complex **134** (Scheme 60) <1998OM4117>.



i. BuLi, THF, -70°C , 0.5 h; ii. Se, -70 to 0°C , 2 h;
iii. $\text{I}(\text{CH}_2)_2\text{OTHP}$, -70°C to rt, 2 h; iv. KOH, MeOH, rt

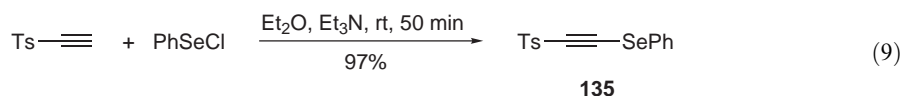
Scheme 59



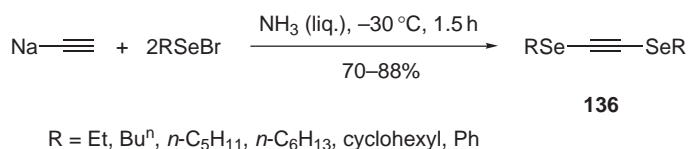
i. BuLi, Et_2O , -20°C , 20 min; ii. Se, rt, 30 min;
iii. $[\text{IrCl}(\text{CO})(\text{PPh}_3)_2]$, THF, rt, 15 min

Scheme 60

Selenium chlorides and bromides can be used as efficient electrophilic arylselenenylating reagents toward metal alkynylides. Phenylseleno(tosyl)ethyne **135** has been prepared in a nearly quantitative yield by the treatment of tosyl ethyne with phenylselenium chloride and triethylamine (Equation (9)) <1998JOC7908>. Product **135** was isolated as a relatively stable white crystalline solid that can be stored in a freezer for several months.

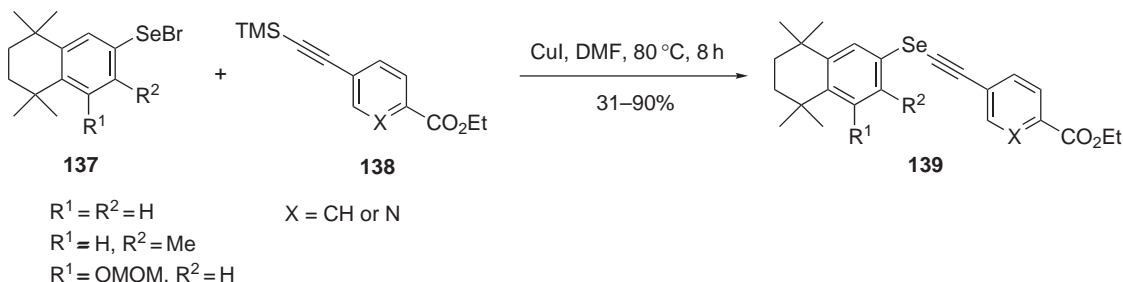


Dialkylselenoethynes **136** have been prepared in good yields by the reaction of alkylselenenyl bromides with sodium ethynylide in liquid ammonia (Scheme 61) <1997SL891>.



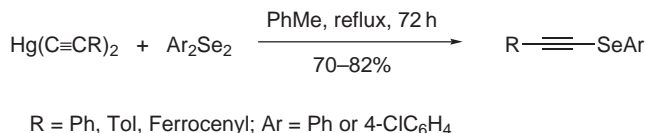
Scheme 61

A series of selenium-containing acetylenic retinoids **139** were synthesized by reacting arylselenium bromides **137** with trimethylsilylalkynes **138** in the presence of copper iodide (Scheme 62) <1998TL9003, 2000TL5193>.



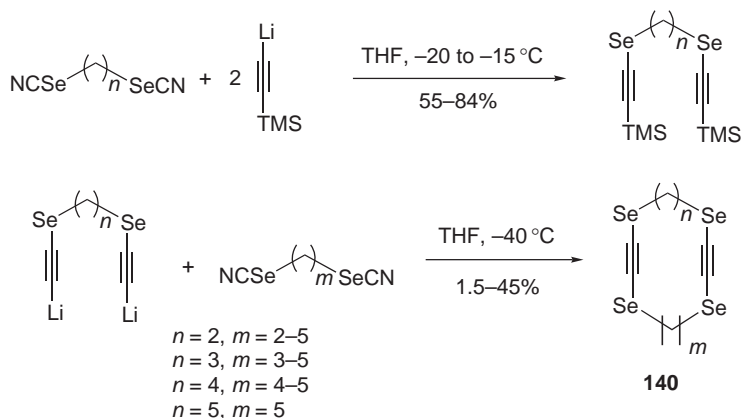
Scheme 62

Several alkynyl selenides have been prepared by the reaction of bis(alkynyl)mercurials with diaryl diselenides in boiling toluene (Scheme 63) <1998JCS(D)1171>.



Scheme 63

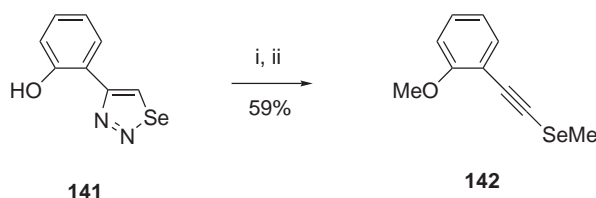
The novel cyclic polyselenadiynes **140** were prepared by a stepwise reaction of the appropriate lithium alkynylides and α,ω -diselenocyanatoalkanes (Scheme 64) <2002JOC4290>. These products, in solid state, assemble in columnar structures due to directional interaction between selenium atoms of neighboring rings <2002JOC4290, 2002JA10638>.



Scheme 64

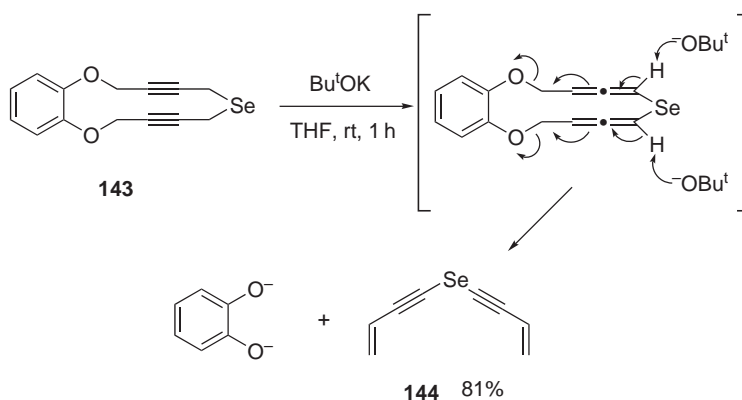
The elimination approach is less common in the synthesis of alkynyl selenides as compared to alkynyl ethers or thioethers <1995COFGT(2)1011>. In a procedure developed by Dehaen and co-workers <2000T3933>, thiadiazole **141** eliminates nitrogen upon treatment with iodomethane affording alkynyl selenolate, which is alkylated *in situ* to give alkynyl selenide **142** (Scheme 65).

The reaction of selenium-bridged cyclic alkyne **143** with a strong base results in a tandem isomerization and elimination of the pyrocatechol dianion to afford bis(3-buten-1-ynyl) selenide **144** in high yield (Scheme 66) <2002EJO3198>.



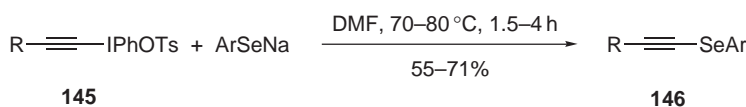
i. K_2CO_3 , MeI, acetone, reflux, 5 h; ii. MeI, 15 min

Scheme 65



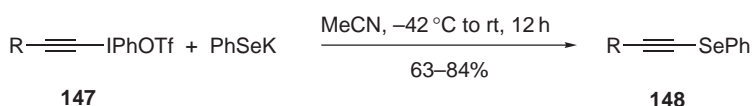
Scheme 66

Nucleophilic substitution of halogen at the *sp*-carbon of an alkynyl halide represents another general approach to alkynyl selenides. Metal selenolates smoothly react with alkynyliodonium tosylates **145** in dimethylformamide (DMF) with the formation of the respective products of acetylenic nucleophilic substitution **146** (Scheme 67) <1997SC3757>. Likewise, the reactions of β -functionalized alkynyliodonium triflates **147** with potassium phenylselenolates afford alkynyl phenylselenides **148** in good yields (Scheme 68) <1997S1378>.



$\text{R} = \text{Bu}^t$ or Ph; $\text{Ar} = \text{Ph}$, 4- ClC_6H_4 , 4- MeC_6H_4 , 2- MeC_6H_4

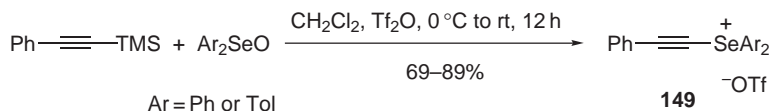
Scheme 67



$\text{R} = \text{TMS}$, CN, CO_2Me , COPh, COBu^t

Scheme 68

In contrast to the alkynyl compounds of sulfur, stable alkynyl selenoxides are unknown. Oxidation of alkynyl selenides with peroxyacids results in the elimination of the selenium moiety and the formation of diynes or terminal alkynes <1995COFGT(2)1011>. The only known stable alkynyl derivatives of polyvalent selenium are represented by phenylethynylselenonium salts **149**, which can be prepared by the reaction of trimethylsilyl alkynes with diaryl selenoxide and trifluoromethanesulfonic anhydride (Scheme 69) <1998JOC6382, 1997TL1809>.

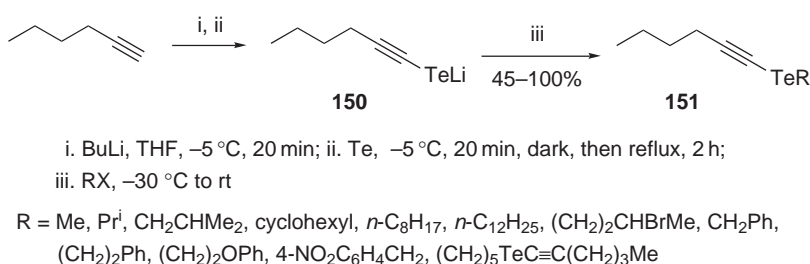


Scheme 69

Similarly to alkynyliodonium salts, alkynylselenonium salts **149** are highly reactive in the reactions of nucleophilic addition and acetylenic nucleophilic substitution <1998JOC6382, 1997TL1809, 1999JCS(P1)2053, 2001JCS(P1)239>.

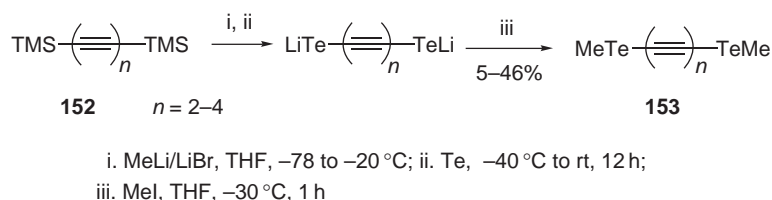
2.21.2.3.2 Alkynyl tellurides

In general, the chemistry of alkynyl tellurides is similar to that of alkynyl selenides. The most common synthetic approach consists in the treatment of lithium alkynylides with elemental tellurium, followed by trapping of the intermediate lithium tellurolates with alkyl halides or other appropriate electrophiles <1995COFGT(2)1011>. Citeau and Giolando have reported the preparation of alkyl(alkynyl)tellurides **151** in good yields by the reaction of lithium hexynyl tellurolate **150** with the appropriate alkyl halides in the absence of light (Scheme 70) <2001JOM(625)23>.



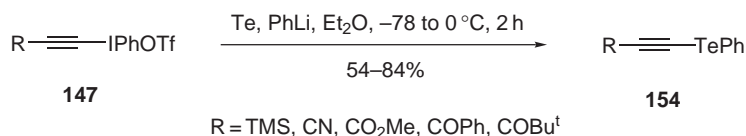
Scheme 70

Gleiter and co-workers used a similar procedure for the synthesis of bis(methyltelluro)alkynes **153** (Scheme 71) <2003OM843>. The transformation of bis(trimethylsilyl)alkynes **152** to the corresponding bis(methyltelluro)alkynes **153** was achieved in a one-pot reaction with methyl lithium followed by insertion of tellurium and then electrophilic capture by methyl iodide. The resulting alkynyl tellurides **153** were isolated as brown-red solids, sensitive to light <2003OM843>.



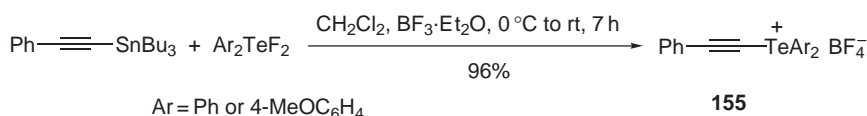
Scheme 71

Similar to alkynyl selenides, the tellurides can be prepared from alkynyliodonium salts via acetylenic nucleophilic substitution. Lithium phenyltellurolate (generated *in situ* from PhLi and black tellurium powder) smoothly reacts with β -functionalized alkynyliodonium triflates **147** in ether with the formation of alkynyl tellurides **154** in good yields (Scheme 72) <1997S1378>. Products **154** were isolated as stable oils or waxy solids and fully characterized by spectroscopy.



Scheme 72

The only known stable alkynyl derivatives of polyvalent tellurium are represented by diaryl(alkynyl)tellurium salts **155**, which can be prepared by the reaction of tributyltin alkynes with diaryltellurium difluorides and BF₃-etherate in dichloromethane at room temperature (Scheme 73) <1996OM3760>.



Scheme 73

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1997TA1575
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1998OM4117

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1999EJO1925
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2.22

AlkynylNitrogen and -phosphorus Compounds

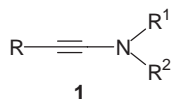
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2.22.1 ALKYNILNITROGEN COMPOUNDS

2.22.1.1 Amines and Their Salts

1-Aminoacetylenes **1**, commonly called ynamines, are very reactive compounds for which highly regioselective transformations can be expected due to the electron-donating ability of the nitrogen atom.

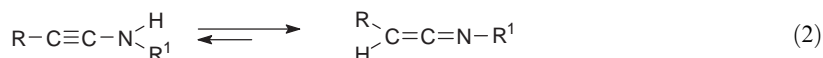
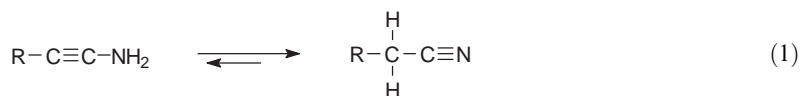


R, R¹, R²=H, alkyl, aryl, vinyl

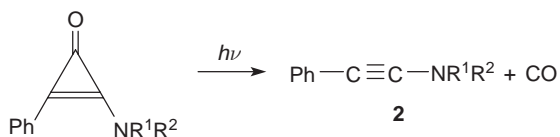
The first report of the attempted preparation of an ynamine appeared as early as 1892 <1892LA268>. The first practical synthesis was described, however, by Viehe only in 1963 <1963AG(E)477>. The development in the chemistry of ynamines has frequently been reviewed since 1967 <1967AG(E)767, 1976T44, 1985TCC98, 2001T7575>. This chapter provides an update on developments in this area since the publication of COFGT (1995) <1995COFGT(2)1039>.

2.22.1.1.1 Primary and secondary ynamines

Primary and secondary ynamines undergo facile tautomerization to nitriles (Equation (1)) or ketenimines (Equation (2)), and these species, therefore, are usually generated and studied at low temperatures in a matrix or in solution <1988JA1337>.



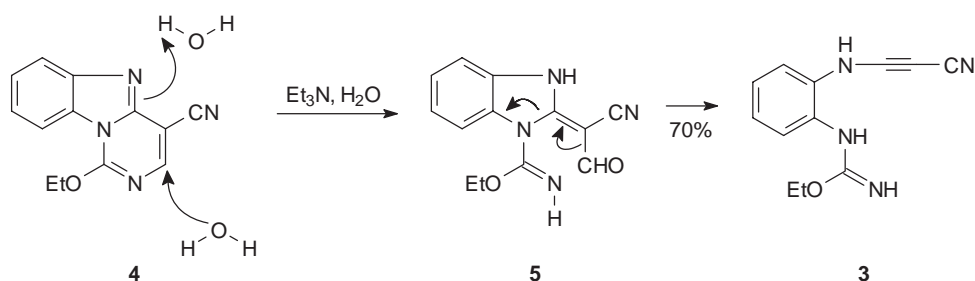
Tertiary ynamines cannot isomerize in this way and a number of such structures have been prepared, isolated, and fully characterized in spite of their high reactivity. As an extension of a preliminary account <1991AG(E)1356>, a full paper describing generation of all three classes of phenylamines **2** by photodecarbonylation of phenylaminocyclopropenones has been published <1996JA4366>. Scheme 1 summarizes the representative series of phenylamines **2a–2i** generated by this procedure.



2	R ¹	R ²
a	H	H
b	H	Pr ⁱ
c	H	<i>o</i> -C ₆ H ₁₁
d	H	Ph
e	H	C ₆ F ₅
f		(CH ₂) ₅
g		(CH ₂ CH ₂) ₂ O
h	CH ₂ CH ₂ CN	CH ₂ CH ₂ CN
i	Me	C ₆ F ₅

Scheme 1

The nitrile-substituted secondary ynamine **3** has been synthesized by Okamoto and co-workers <1995JHC851>. Its preparation involves basic hydrolysis of pyrimido[1,6-*a*]benzimidazole **4** and rearrangement via the intermediate **5** (Scheme 2).



Scheme 2

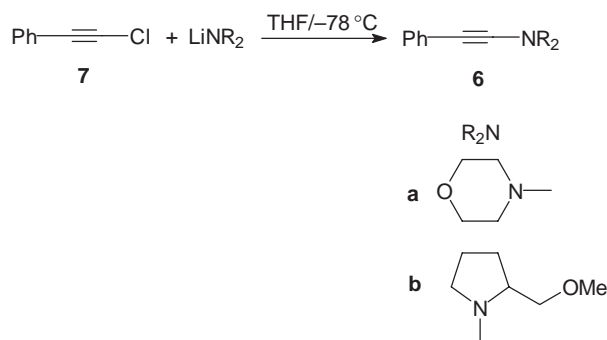
2.22.1.1.2 Tertiary ynamines

Tertiary ynamines constitute the richest group of alkynylnitrogen compounds. They are isolable and thermally stable. However, they can be relatively easily hydrolyzed to form the appropriate amides. Recently, new members of this family of alkynylamines have been prepared by three main preparative approaches based on: (i) substitution reactions; (ii) elimination reactions; and (iii) isomerization reactions.

(i) Substitution reaction

(a) *From acetylide anions and nitrogen electrophiles.* This is one of the oldest approaches to ynamines but has not been used recently for the preparation of new tertiary alkynylamines.

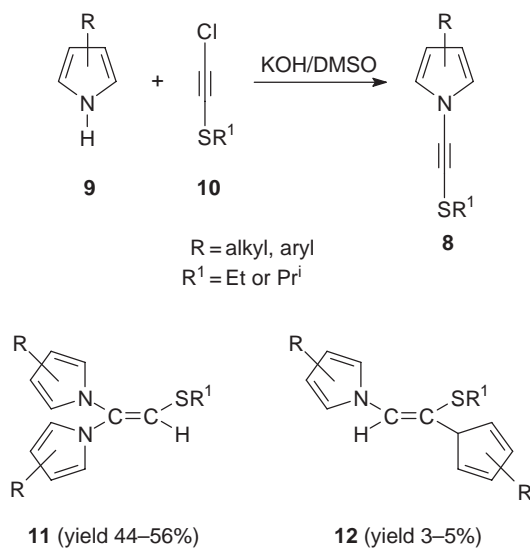
(b) *From alkynyl halides and metal amides.* This general method for the preparation of tertiary ynamines, which is based on nucleophilic displacement of a halogen from an alkynyl halide using secondary metal amides as nucleophile, has recently been extended to the synthesis of 1-dialkylamino-2-phenylacetylenes (**6a** and **6b**) from 1-chloro-2-phenylacetylene **7** (Scheme 3) <2000JOC7291>.



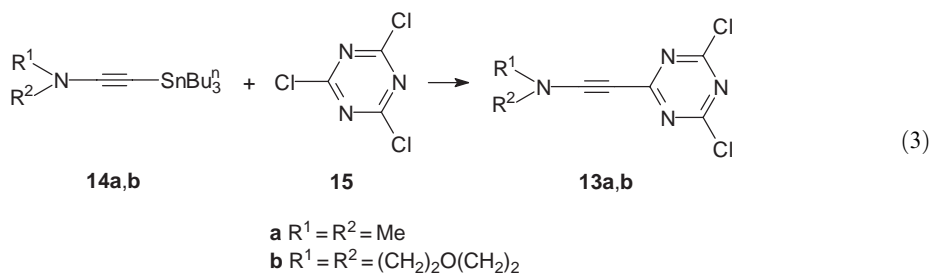
Scheme 3

Thioynamines **8** have been obtained from pyrroles **9** and thioalkylchloroacetylenes **10** most probably via nucleophilic substitution of chlorine in the starting acetylenes **10** using *in situ* generated potassium salts of the pyrroles as nucleophiles. Unfortunately, the bis-pyrrole adducts **11** and **12** are formed simultaneously and the ynamines **8** are only obtained in moderate yields (Scheme 4) <1999JOU916>.

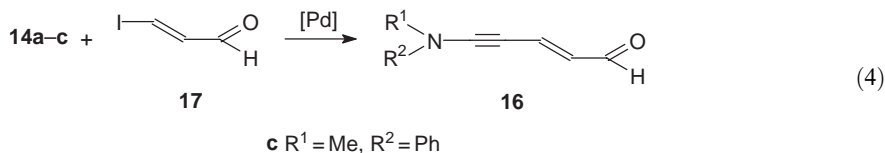
(c) *Functionalization of ynamines at the alkynyl position.* The high reactivity of ynamines substituted at the alkynyl position with a trialkylstannyl or trialkylsilyl group toward a large number of electrophiles allows the preparation of a wide range of diversely functionalized alkynylamines that would be hardly accessible by other methods. Thus, ynamines (**13a** and **13b**) have been reported to be formed by the coupling of a transient stannylnamine (**14a** and **14b**) with cyanuric chloride **15** (Equation (3)) <1999HCA326>.



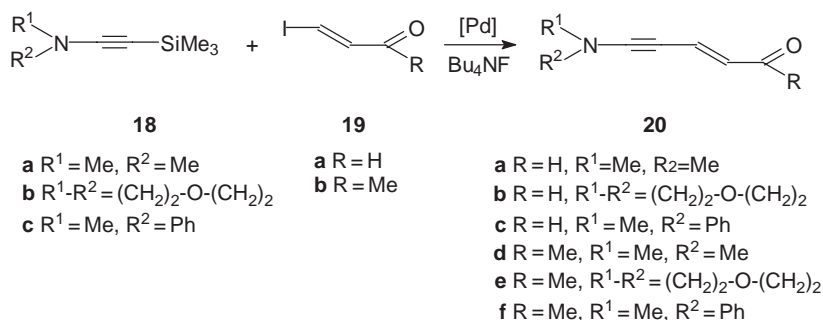
Scheme 4



Several “push–pull” alkenylamines **16** have been prepared by the Pd(0)-catalyzed coupling of the stannylnamines (**14a–14c**) with β -iodoenone **17** (Equation (4)) <1996HCA179>.

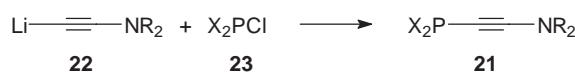


A similar reaction between silylated ynamines **18** and β -iodoenones **19** has been found to afford another rich family of “push–pull” alkynylamines **20** (Scheme 5) <1996HCA179>.



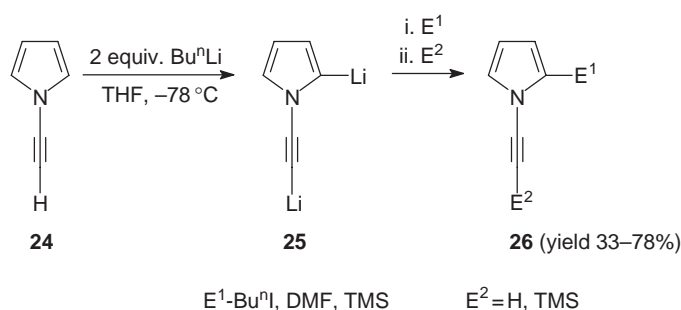
Scheme 5

Functionalizations of ynamines at the alkynyl position can also be achieved by treatment of lithioalkynyl derivatives with a suitable electrophile. In this way phosphorus-containing ynamines **21** have been synthesized by *in situ* trapping of the lithium acetylides **22** by chlorophosphines **23** (Scheme 6) <1993JOU1234>.



Scheme 6

Treatment of ethynylpyrrole **24** with BuⁿLi (2 equiv.) has been found to generate the dianion **25**, which can be selectively trapped to form 2-substituted ethynylpyrroles **26** (Scheme 7) <1995JOM271, 1996JOU1164>.



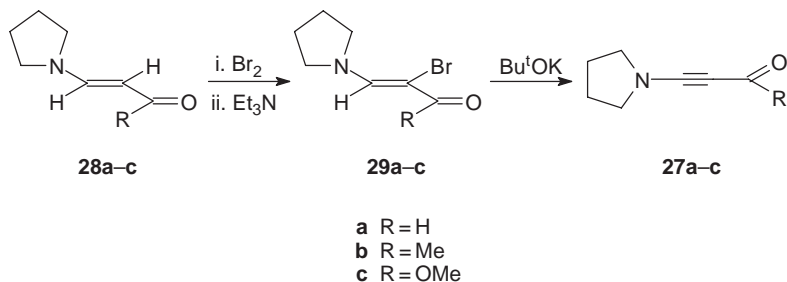
Scheme 7

(ii) Elimination reactions

This section presents the synthesis of ynamines based on procedures in which nitrogen-containing unsaturated substrates, either isolated or generated *in situ*, are converted to the alkynylamines via an elimination reaction.

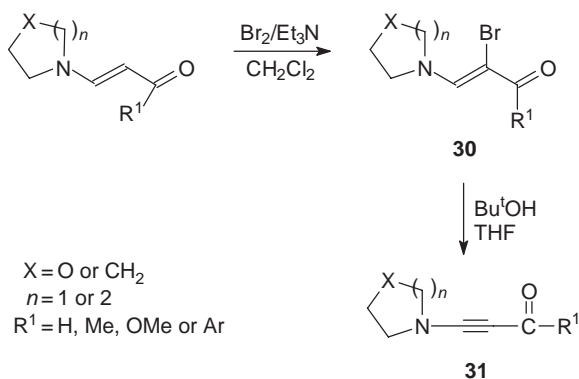
(a) *From α-halogenoenamines.* α-Halogenoenamines, which have previously been widely used as substrates for the preparation of alkynylamines via the elimination approach <1995COFGT(2)1039>, have not received attention since the 1990s.

(b) *From γ-halogenoenamines.* β-Halogenoenamines with an electron-withdrawing group at the β-carbon are easily converted into the corresponding ynamines upon treatment with a base. Most halogenoenamines are not very stable but they are efficiently generated *in situ* from suitable precursors, usually amides or the parent nonhalogenated enamines. It has recently been reported <1999HCA326> that the sequence of the reactions shown in Scheme 8 gave 3-(pyrrolidin-1-yl)prop-2-ynal **27a** starting from 3-(pyrrolidin-1-yl)prop-2-enal **28a** via 2-bromo enamine **29a**. A similar sequence using the enamines (**28b** and **28c**) cleanly afforded the ynamines **27b** and **27c** <1999HCA326>.



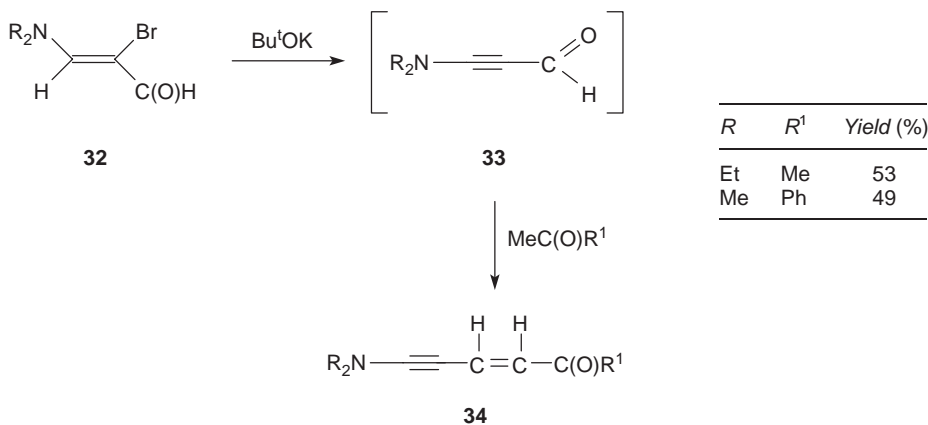
Scheme 8

Previously, it has been reported [<1993JCS\(P1\)3055>](#) that the elimination of hydrogen bromide from (*Z*)- γ -bromo enamines **30** affords the push-pull ynamines **31** (Scheme 9).



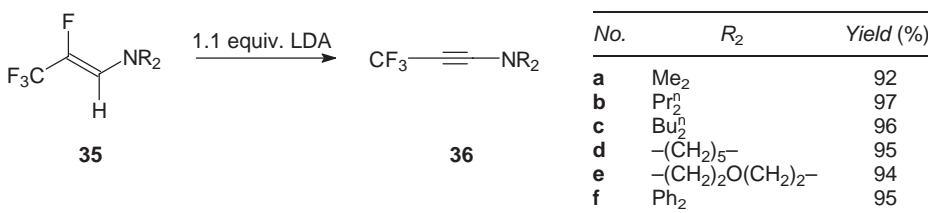
Scheme 9

The analogous *in situ* hydrogen bromide elimination from γ -bromo enamines **32** gives 1-dialkylaminoprop-1-yn-2-als **33**, which have been used as substrates for the preparation of the ynamines **34** (Scheme 10) [<1990JOU2172, 1994JOU49, 1994JOU54>](#).



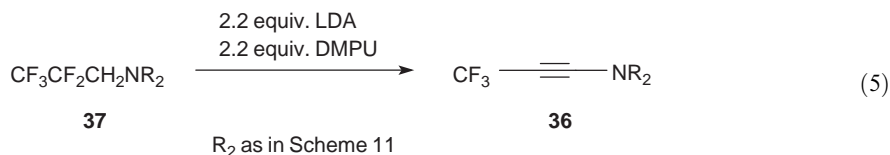
Scheme 10

Similarly, the (*Z*)- γ -fluorotrifluoromethylenamines **35** have also been converted in high yields into the trifluoromethylynamines **36** by elimination using LDA (1.1 equiv.) as base (Scheme 11) [<1998CL615, 2000CL666>](#).

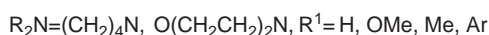
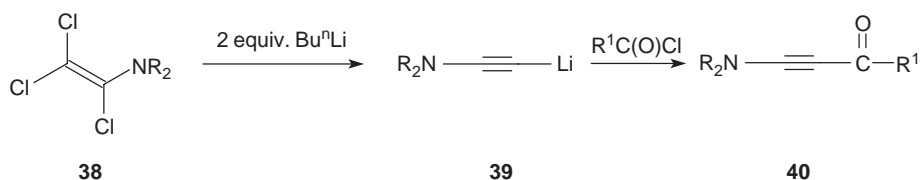


Scheme 11

It is of interest to note that the ynamines **36** are produced by the direct deprotonation of *N,N*-disubstituted (2,2,3,3,3-pentafluoropropyl)amines **37** using LDA (2.2 equiv.) in the presence of *N,N*-dimethylpropyleneurea (DMPU) (Equation (5)) <1998CL615>.

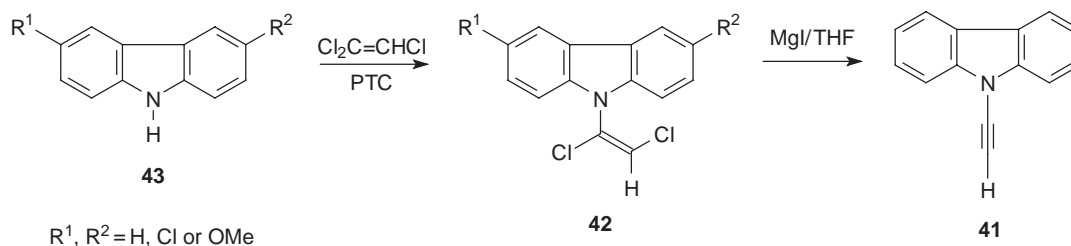


(c) *From trichloroenamines and dichloroenamines.* It has been known for some time that treatment of α,γ -trichloroenamines **38** with Bu^nLi produces the lithiated ynamines **39**, which upon protonation with water give the unsubstituted ynamines <1972CB2963>. Recently, this strategy has been applied to the preparation of the aminoacetylenes **40** functionalized with a carbonyl group (Scheme 12) <1999HCA326, 1996HCA179, 1996HCA192, 1998HCA1792, 1998HCA2282, 1999HCA338, 2000HCA641>.



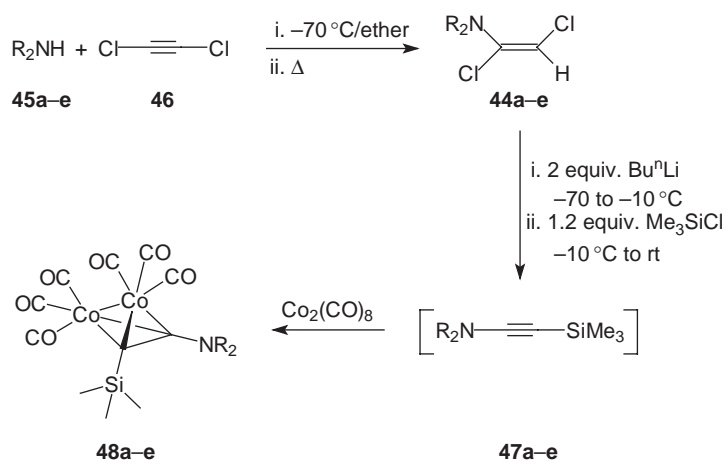
Scheme 12

An elimination protocol has also been applied to α,β -dichloroenamines. 9-Ethynylcarbazoles **41** have been isolated after reductive dehalogenation of enamines **42**, prepared by alkylation of the parent carbazoles **43** under catalytic phase-transfer condition (Scheme 13) <1995BSB117>. A similar sequence of reactions gave ethynylpyrrole **24** <1994JOU335, 1994SC2721, 1995RTC18>.



Scheme 13

α,γ -Dichloroenamines **44**, generated *in situ* by the addition of optically active pyrrolidines **45** to dichloroacetylene **46**, afford the silylynamines **47** following treatment with Bu^nLi and TMSCl . The crude products **47** are obtained in high yield and purity (NMR assay). Upon treatment with octacarbonyldicobalt they produce in high yield the complexes **48**, which are stable for months at room temperature under a CO atmosphere (Scheme 14) <2000JOC7291>.



Entry	Amine 45	Conditions for addition to 44	Crude 47 Yield (%)	Complex 48 Yield (%)
a		90 min, 0 °C	87	94
b		90 min, 33 °C	96	45
c		120 min, 33 °C	85	50
d		90 min, 10 °C	86	80
e		24 h, 33 °C	70	80

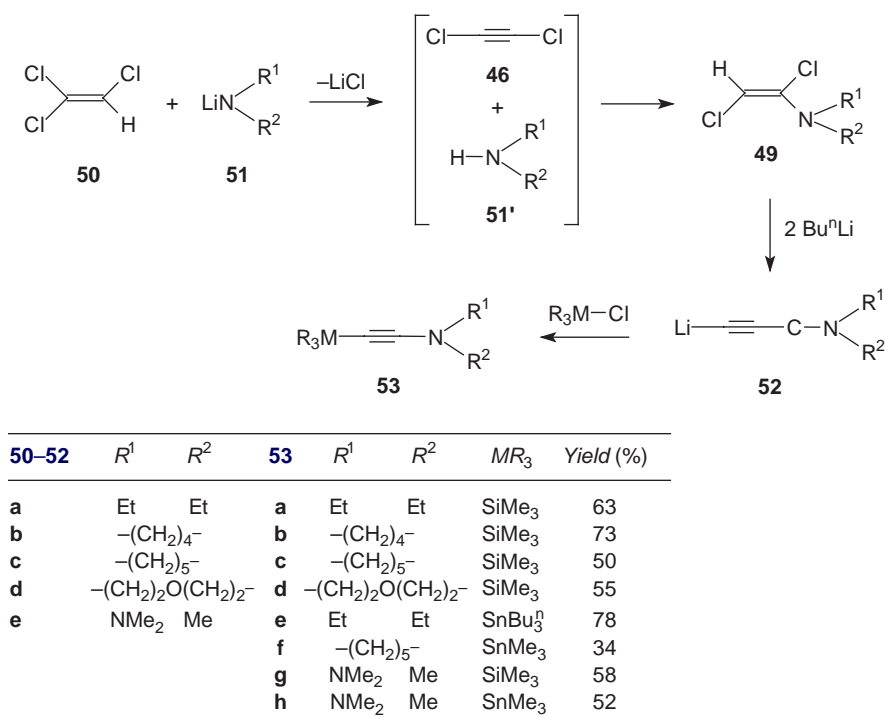
Scheme 14

Another approach to the *in situ* generation of α,β -dichloroenamines **49** based on the reaction sequence shown in Scheme 15 has been reported by Himbert and co-workers <1997S293>.

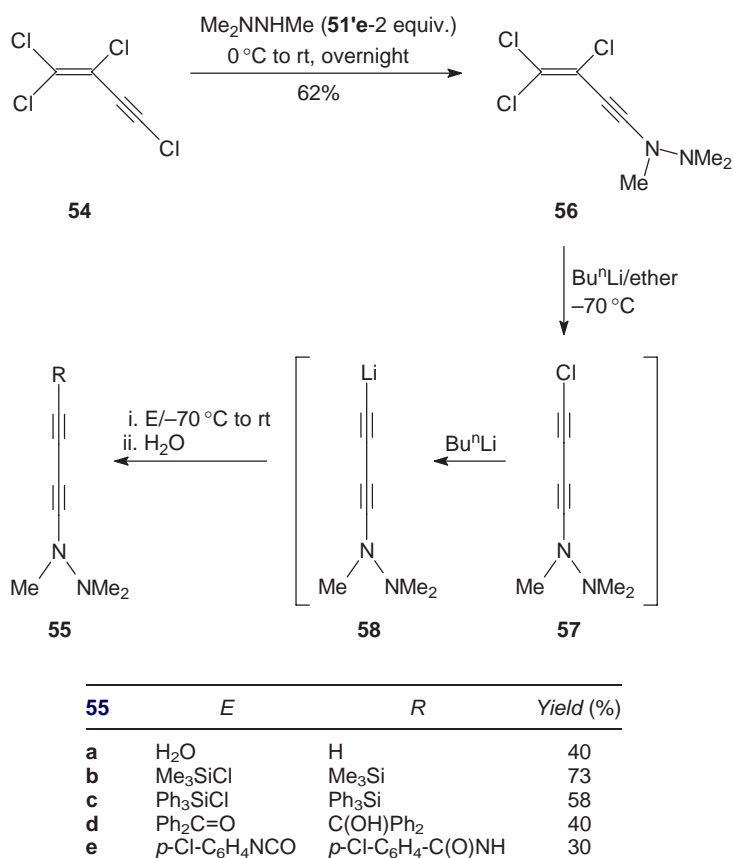
In analogy with published results <B1969MI001>, trichloroethylene **50** upon treatment with the lithium salts **51** affords the enamines **49** via addition of amines to dichloroacetylene **46**. The very unstable dichlorovinyl compounds **49** have not been isolated but were reacted with Bu^nLi (2 equiv.) to form the lithium acetylides **52**. These acetylides give the expected metallated ynaminines (**53a–53f**) and ynhydrazines (**53g** and **53h**) after treatment with TMSCl , chlorotrimethylstannane, or chlorotributylstannane.

(d) *From haloalkenes*. This approach has recently been used for the preparation of a variety of 1,3-butadiynylhydrazines **55** via *N,N',N'*-trimethyl-*N*-(3,4,4-trichloro-1-butyn-1-ynyl)hydrazine **56** starting from perchlorobutenyne **54** and trimethylhydrazine. Treatment of the hydrazine **56** with Bu^nLi followed by various electrophiles affords the derivatives **55** (Scheme 16) <1994S383>.

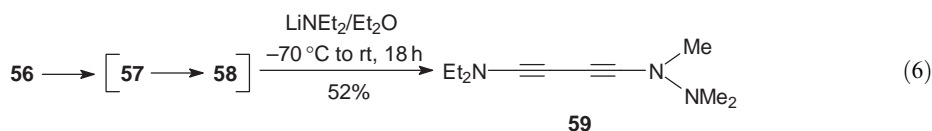
It is of interest to note that the ynhydrazine **56** has been used as a precursor for *N*-(4-diethylamino-1,3-butadiynyl)-*N,N',N'*-trimethylhydrazine **59**. The expected final hydrazine, which could not be purified due to its instability, was formed via the sequence shown in Equation (6) <1994S383>.



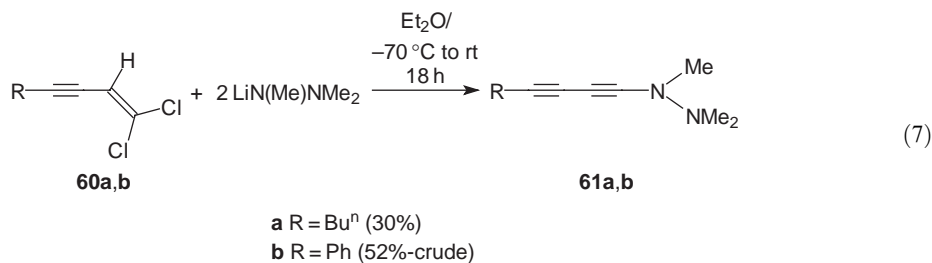
Scheme 15



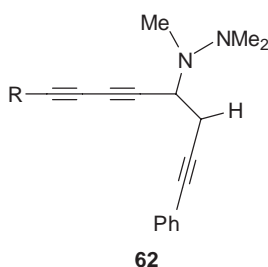
Scheme 16



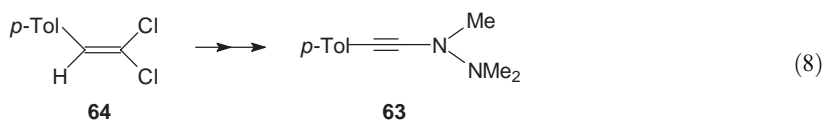
When an elimination/substitution sequence was applied to the 1,1-dichlorobutenynes (**60a** and **60b**) using lithium trimethylhydrazine (2 equiv.), the corresponding 1,3-octadiynylhydrazines (**61a** and **61b**) were isolated in moderate yields (Equation (7)) <1994S383>.



The ynylhydrazine **61** was accompanied by the octenetriyne **62**, formation of which was probably due to the presence of a slight excess of BuⁿLi in the reaction mixture.



A similar sequence has been used to prepare the *p*-tolylethynylhydrazine **63** from 1-(*p*-tolyl)2,2-dichloroethylene **64** (Equation (8)) <2001ZN(B)1196>.

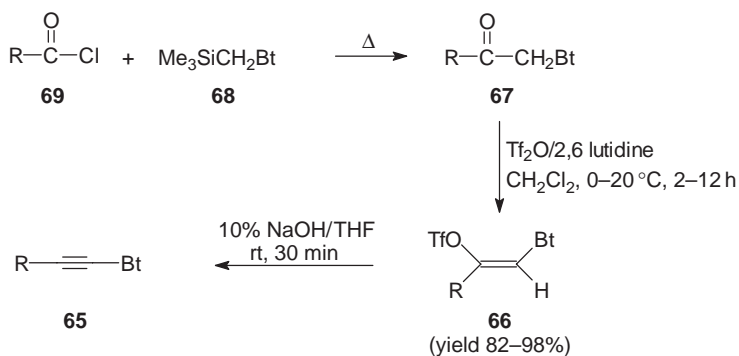


(e) *From enol esters and hydrazones.* Recently, Katritzky and co-workers <2001JOC5606, 2000OL3789> have prepared aromatic and aliphatic alkynylbenzotriazoles **65** by treatment of enoltriflates **66** with sodium hydroxide or sodium methoxide. The starting (*Z*)-enoltriflates **66** are easily obtained stereoselectively from *N*-acylmethylbenzotriazoles **67** (Scheme 17).

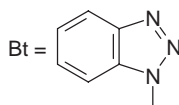
An elimination procedure has been used for the preparation of 1-pyrrolyl-1-octadecyne **70** starting from the (*p*-toluenesulfonyl)hydrazone **71** (Scheme 18) <1997JOC4142>.

(iii) Isomerization reactions

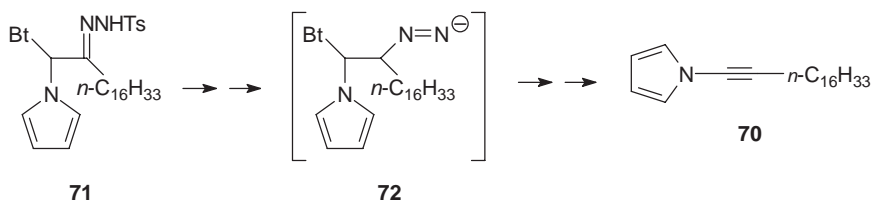
Base-catalyzed isomerization of tertiary propargyl amines has long been used as an economical approach to the preparation of ynamines <1985TCC89>. Recently this methodology has been used for a second synthesis of optically active ynamines <1997JOM321>: the first synthesis was reported in the 1990s <1987TL6397>. The synthetic procedure (Scheme 19) starts with optically active secondary amines **73a** and **73b**, which react with propargyl bromide **74** to give the tertiary propargylamines (**75a** and **75b**). Their isomerization with Bu^tOK affords the ynamines **76a** and **76b** in moderate yields.



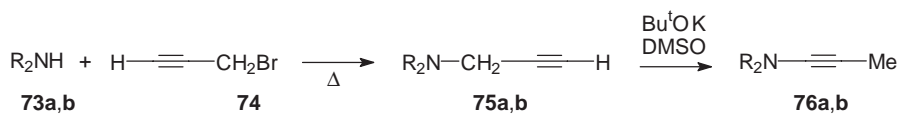
65	<i>R</i>	Yield (%)
a	Ph	98
b	<i>p</i> -ClC ₆ H ₄	97
c	<i>p</i> -MeOC ₆ H ₄	92
d	<i>p</i> -MeC ₆ H ₄	95
e	<i>m</i> -MeC ₆ H ₄	91
f	<i>o</i> -MeC ₆ H ₄	92
g	PhCH ₂ CH ₂	94
h	Me	90
i	Bu ^t CH ₂	98
j	Bu ^t CH ₂ CH(Me)CH ₂	96
k	<i>n</i> -C ₆ H ₁₁	92
l	<i>n</i> -C ₇ H ₁₃	92



Scheme 17



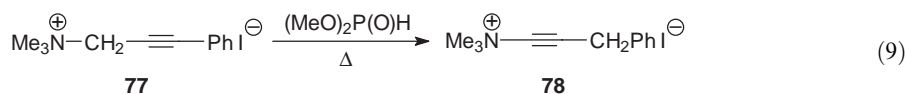
Scheme 18



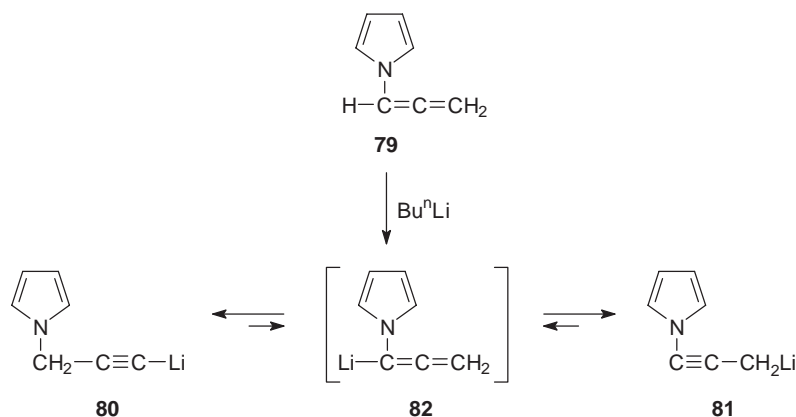
No.	<i>R</i> ₂	Yield (%)
a		23
b		42

Scheme 19

An unexpected and interesting isomerization of trimethyl-(3-phenylprop-2-ynyl)-ammonium iodide **77** into the corresponding ynammonium iodide **78** has been reported to occur upon heating of the substrate **77** with an equimolar amount of dimethyl phosphite (Equation (9)) <1998JGU364>.

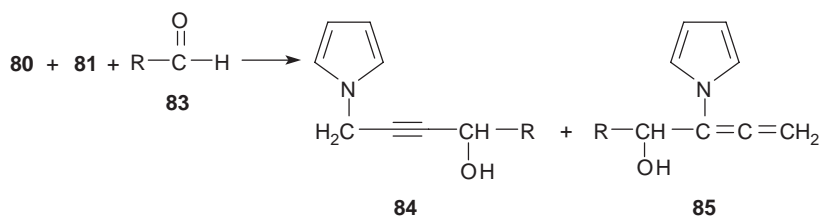


Treatment of *N*-allenepyrrole **79** with BuⁿLi (1 equiv.) has been reported to generate a mixture of the propargylic derivatives **80** and **81** <1996JOU1164>. These are formed via isomerization of the lithioallenepyrrole **82** (Scheme 20).



Scheme 20

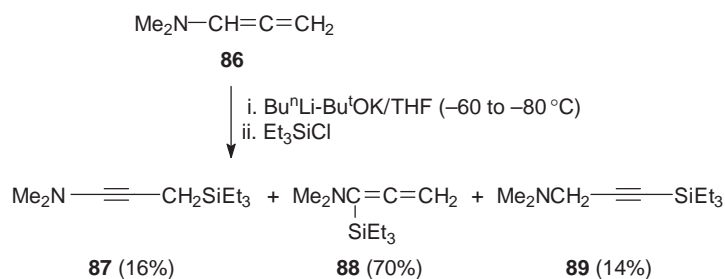
The lithium derivatives **80** and **81** upon reaction with aldehydes **83** afforded a series of ynaminoalcohols **84** and allenic alcohols **85** in the ratios shown in Scheme 21 <1996JOU1164>.



84 or 85	<i>R</i>	<i>Temp.</i> (°C)	<i>Yield</i> (%)		
			84	85	79
a	H	20	42	30	19
b	Me	-20	13	68	9
c	Bu ^t	-80	3	84	13
d	Ph	-30	75	11	8

Scheme 21

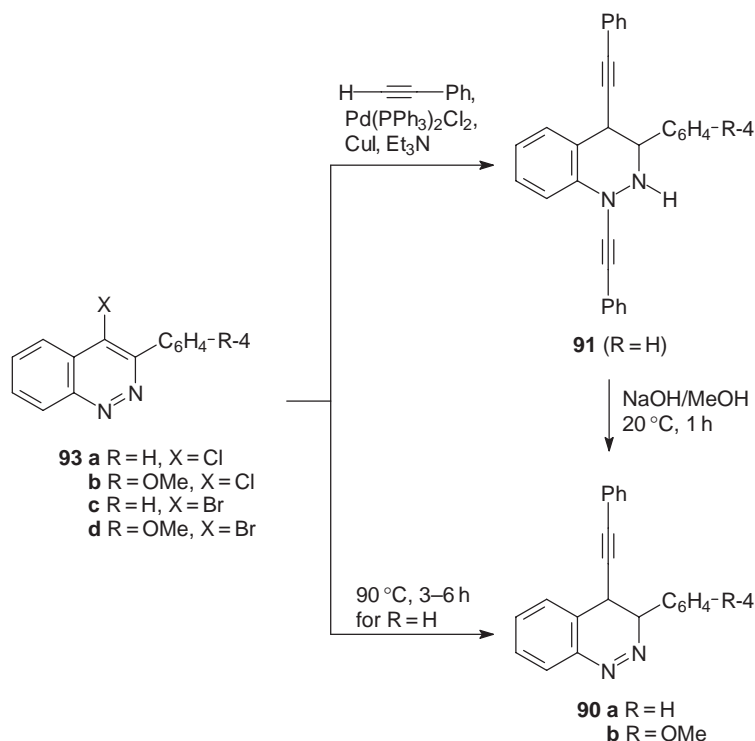
A similar monolithiation of *N,N*-dimethylaminoallene **86** followed by treatment with triethylchlorosilane gives 1-dimethylamino-2-(triethylsilyl)methyl-acetylene **87** accompanied by the silylated allenic and propargylic amines **88** and **89** (Scheme 22) <1996JOU1164>.



Scheme 22

(iv) Miscellaneous methods

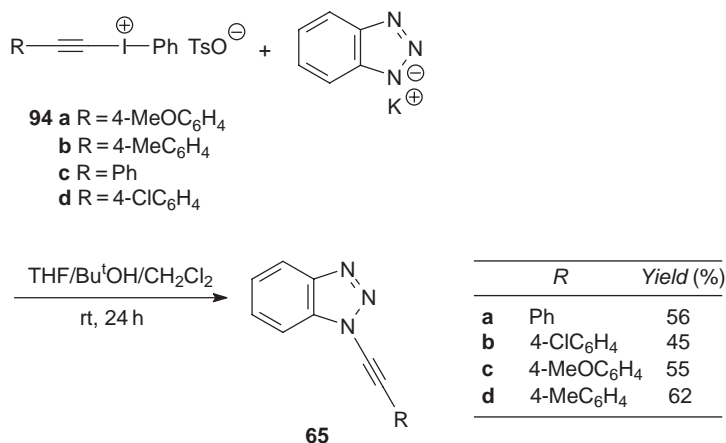
A few ynamines have recently been prepared by procedures that cannot be included in any of the preceding subsections. For example, the mono **90** and bis **91** phenylacetylene-substituted derivatives of 1,2-dihydrocinnoline have been prepared, using the 4-halogeno-3(aryl) cinnolines (**93a–93d**) as substrates, by palladium-catalyzed exchange–addition reactions (Scheme 23) <1998IZV1233>.



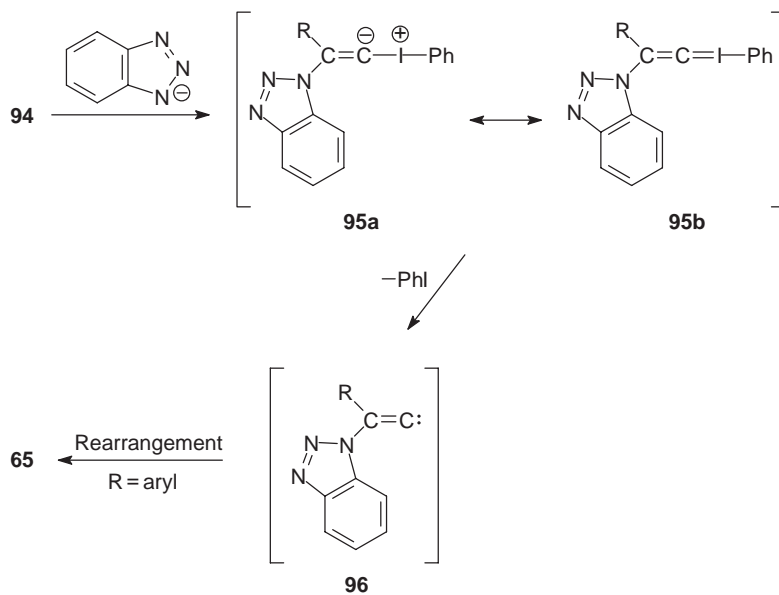
Scheme 23

Alkynyl(phenyl)iodonium salts, which have been recognized as useful synthons of alkynyl cations <1992AG(E)274> and a convenient reagent for the preparation of a variety of push–pull ynamines <1994S1255>, have recently found a new application as substrates for the alkylation of benzotriazole. The reported examples of alkynylbenzotriazoles (**65a–65d**) prepared by the alkylation of the potassium salt of benzotriazole with alkynyl(phenyl)iodonium tosylates **94** are shown in Scheme 24 <1998TL3787>.

It has been suggested that the alkylation of benzotriazole using the salts **94** may proceed via Michael addition of the benzotriazole anion to the β -carbon of the triple bond. This leads to formation of an alkylidenecarbenes **96**, and finally rearrangement gives the alkynes **65** (Scheme 25) <1992AG(E)274, 1998T10927>.

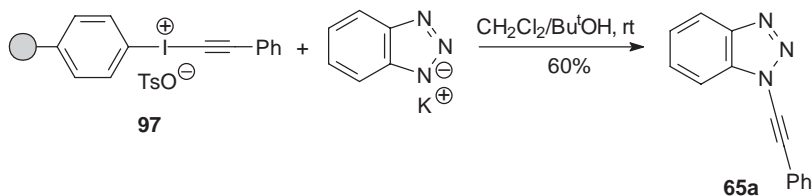


Scheme 24



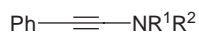
Scheme 25

More recently, resin-bound phenylalkynyliodonium tosylate **97** has been used as an alkynyl transfer reagent in the preparation of phenylethynylbenzotriazole **65a** (Scheme 26) <2001TL6373>.



Scheme 26

Four tertiary ynamines (**1f–1i**) have been generated by photodecarbonylation of phenylamino cyclopropanones according to the procedure presented in Scheme 1 <1996JA4366>.



1f–1i

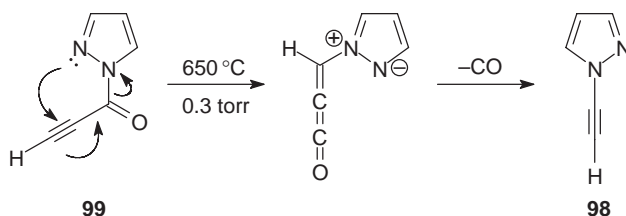
f $\text{R}^1 = \text{R}^2 = (\text{CH}_2)_5$

g $\text{R}^1 = \text{R}^2 = (\text{CH}_2\text{CH}_2)_2\text{O}$

h $\text{R}^1 = \text{R}^2 = \text{CH}_2\text{CH}_2\text{CN}$

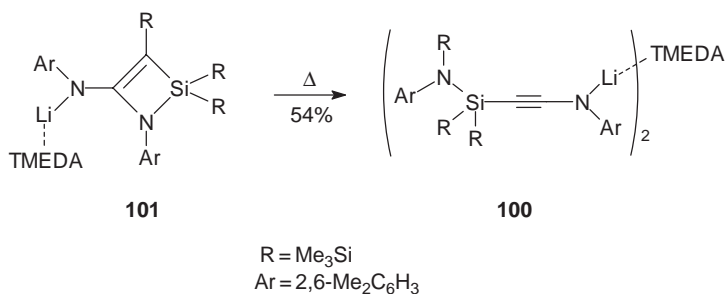
i $\text{R}^1 = \text{Me}, \text{R}^2 = \text{C}_6\text{F}_5$

Detection of the pyrazole derivative **98** as a minor component has been reported during flash vacuum pyrolysis of the amide **99** (Scheme 27) <1994AJC991>.



Scheme 27

Thermolysis of the azasilacyclobutene derivative **101** has been found to afford the dimeric lithioynamine **100**, where TMEDA serves as a linker between two ynamine units (Scheme 28) <1999AG(E)501>.



Scheme 28

2.22.1.2 N=Y Functions

2.22.1.2.1 Nitrosoalkynes

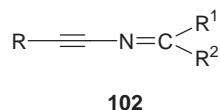
Since the publication of COFGT (1995) <1995COFGT(2)1039>, new papers devoted to the chemistry of this group of alkynylnitrogen compounds have not appeared in the chemical literature.

2.22.1.2.2 Nitroalkynes

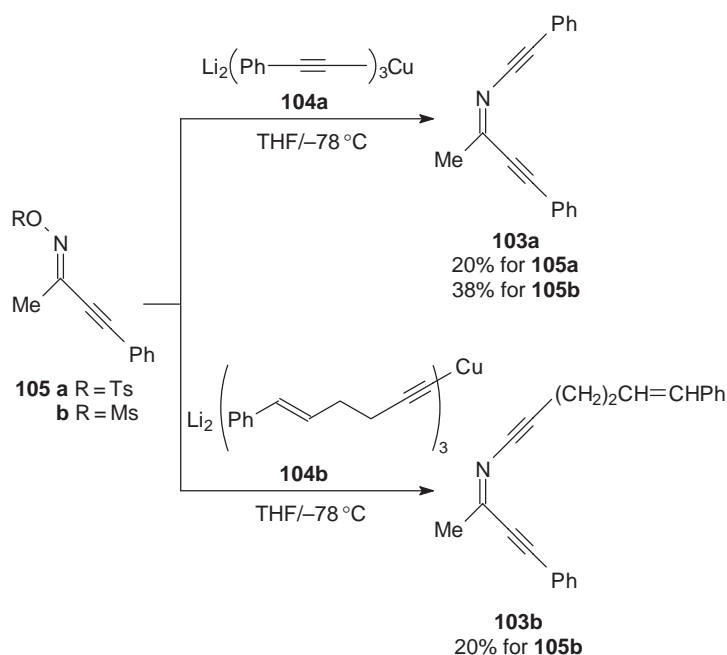
Nitroacetylene was recently prepared by the reaction of NO_2PF_6 with trimethylsilylacetylene. It is stable at room temperature in a dilute solution for about a week <2002S2013>.

2.22.1.2.3 *N*-Methylene ynamines

N-methylene-ynamines have the general structure **102**.



A few new stable members of this family of alkynylamines have recently been prepared by modifications of the original procedure <1987AG(E)918>. This method involves reaction of tosyl esters of ketoximes with the properly constructed acetylenides. Thus, the synthesis of the *C,N*-dialkynylimines (**103a** and **103b**) was achieved by the addition of the cuprates (**104a** and **104b**), derived from phenylacetylene or 6-phenylhex-5-en-1-yne, to either oxime tosylate **105a** or oxime mesylate **105b** (Scheme 29) <1997JA1464, 2003JOC2234>.



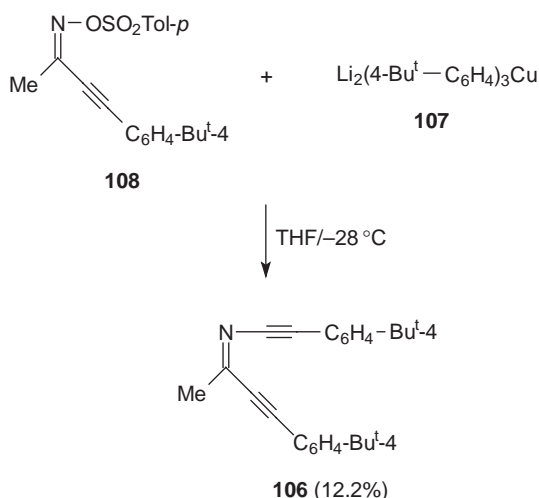
Scheme 29

The *C,N*-dialkynylimine **106** has similarly been prepared by reaction of copper 4-*t*-butylphenylacetylide **107** with the tosylate **108** (Scheme 30) <1998JA376>.

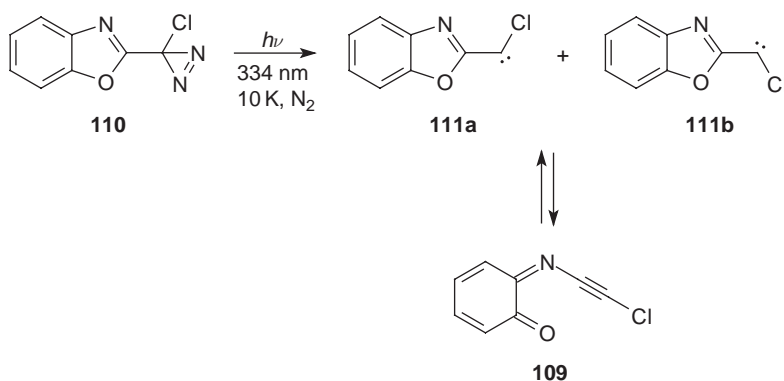
The cyclic *N*-methyleneynamine **109** (a quinoimine) has been observed using UV and IR spectroscopy during photolysis of the matrix-isolated diazirine **110** (ca. 1:800, N₂, 10 K) at 334–350 nm. It was found that, even upon short 334 nm irradiation of the diazirine **110**, the carbene **111** was accompanied by the quinoimine **109**. Continued irradiation at 334 nm, or more effectively at 350 nm, completely converted the initially formed carbene **111** to product **109**. Ring opening of the carbene **111** is reversible: irradiation of the quinoimine **109** at 436 nm (or more slowly at 578 nm) reformed the carbene **111** (Scheme 31) <2002JA7670>.

2.22.1.2.4 Azoalkynes

Since the publication of COFGT (1995) <1995COFGT(2)1039>, new work devoted to the chemistry of this group of alkynylnitrogen compounds has not appeared.



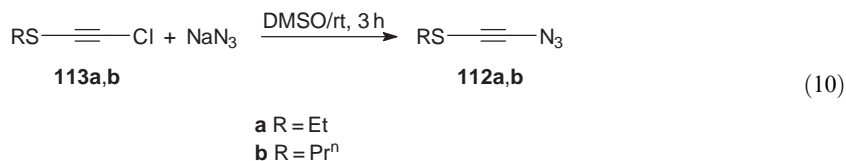
Scheme 30



Scheme 31

2.22.1.2.5 Alkynyl azides

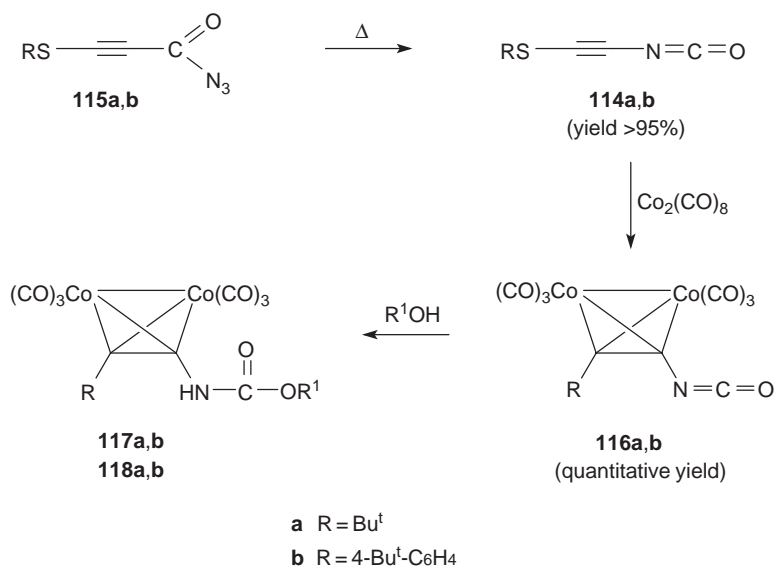
The first isolable members of this group of alkynylnitrogen compounds, namely the azides (**112a** and **112b**), have recently been prepared by the room temperature reaction of the 1-*S*-alkyl-2-chloroacetylenes (**113a** and **113b**) with sodium azide in DMSO (Equation (10)) <2001IZV720>.



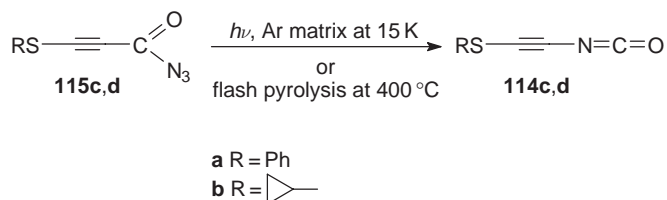
2.22.1.2.6 Alkynyl isocyanates

The first two alkynyl isocyanates (**114a** and **114b**) (with 95% chemical purity) have been prepared by thermolysis of the acyl azides (**115a** and **115b**) in a variety of solvents including CCl_4 , CHCl_3 , CDCl_3 , *n*-heptane, and THF. These isocyanates (**114a** and **114b**) were protected using octacarbonyldicobalt to form the deep-red complexes (**116a** and **116b**) in quantitative yields (Scheme 32) <1998HCA2341>.

Flash pyrolysis at 400°C or matrix photolysis at 15 K of the acyl azides (**115c** and **115d**) has been used to generate the alkynyl isocyanates (**114c** and **114d**) (Equation (11)) <2001CEJ1224>.



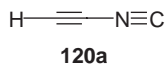
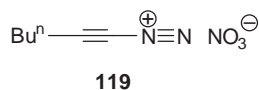
Scheme 32



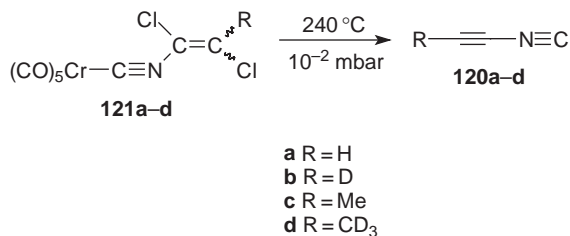
(11)

2.22.1.3 N≡X Functions

A nitrogen representative (X = N) of this class of ynamine derivative, the diazonium nitrate **119**, was generated *in situ* in 1963 and its existence confirmed by a few chemical reactions <1963AG1033>. Ethynyl isocyanide **120a**, the first carbon member of this ynamine family, was reported almost three decades later <1991AG(E)1644>.

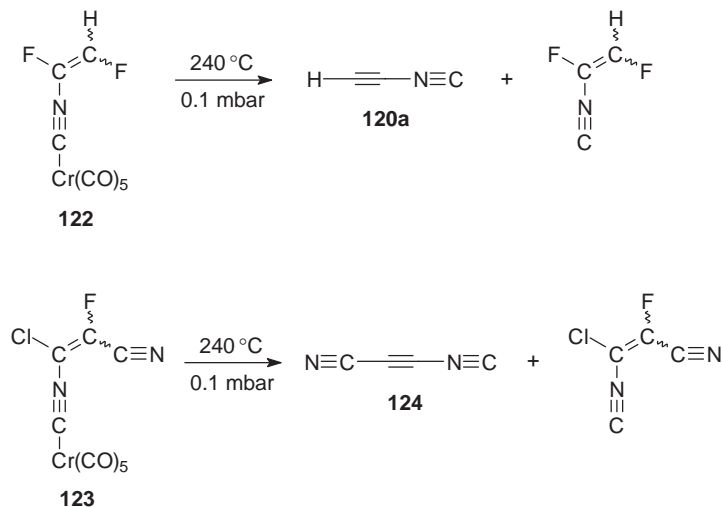


It is of interest to note that compound **120a** was very soon thereafter detected in the interstellar molecular cloud TMC1 <1992AstrophysJL51>. Recently, ethynyl isocyanide and other alkynyl isocyanides (**120a–120d**) have been prepared by flash vacuum pyrolysis of the organometallic precursors (**121a–121d**) (Equation (12)) <2000CEJ3377>.



(12)

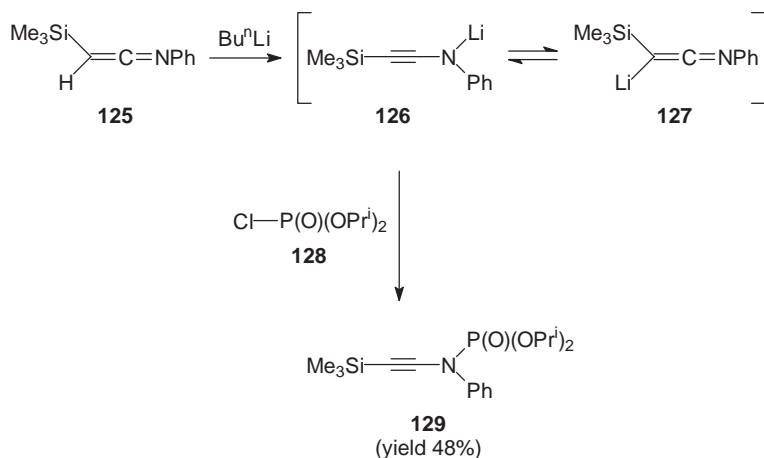
Similarly, flash vacuum pyrolysis of the fluorine-containing organometallic precursors **122** and **123** has been used to generate ethynyl isocyanide **120a** and cyanoisocynoacetylene **124** (Scheme 33) <2001CEJ881>.



Scheme 33

2.2.2.1.4 N—P Functions

Since the publication of COFGT (1995) <1995COFGT(2)1039> a single ynamine containing an N—P bond has been described <1999T5405>. In a study of reactivity of *N*-phenylsilylketenimines **125**, it was found that treatment of the *N*-lithiated ynamine **126** (in equilibrium with the lithiated ketenimine **127**) with diisopropyl chlorophosphate **128** afforded the new silylated and phosphorylated ynamine **129** exclusively (Scheme 34).

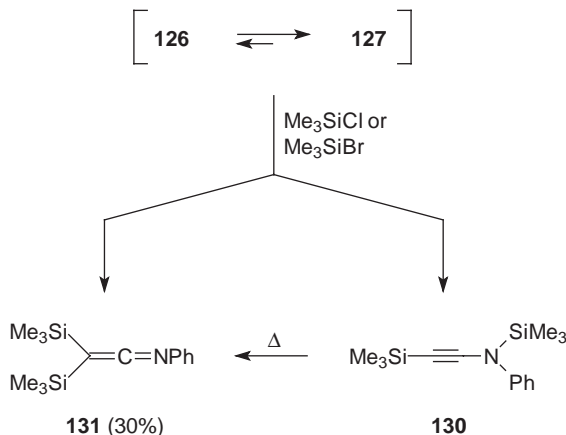


Scheme 34

2.2.2.1.5 N—Si Functions

Since the publication of COFGT (1995) <1995COFGT(2)1039>, only a single ynamine containing an N—Si bond has been described <1999T5405>. This was prepared *in situ* by the reaction sequence shown in Scheme 35. In this approach the TMS group from the halo-trimethylsilane adds both at the terminal carbon of the lithiated ketenimine **127** and at the nitrogen atom of the lithiated ynamine **126**. In the crude reaction mixture both the ynamine **130** and the ketenimine **131**

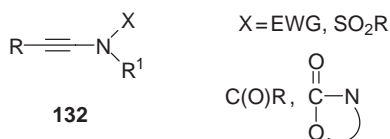
were detected (IR). After distillation only the ynamine **131** was isolated (30% yield). It was suggested that thermal isomerization (**130** \rightarrow **131**) is responsible for the observed interconversion (Scheme 35). Such a process has previously been described [<1996JA4366>](#).



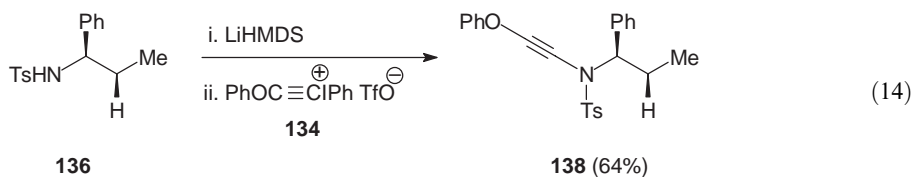
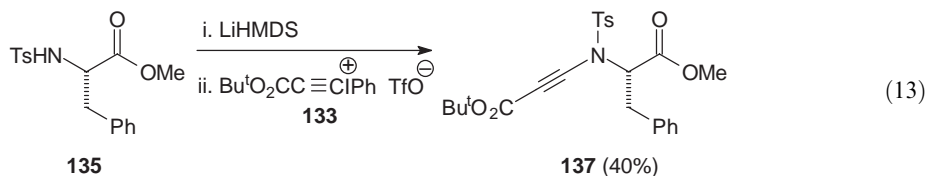
Scheme 35

2.22.1.6 Ynamides

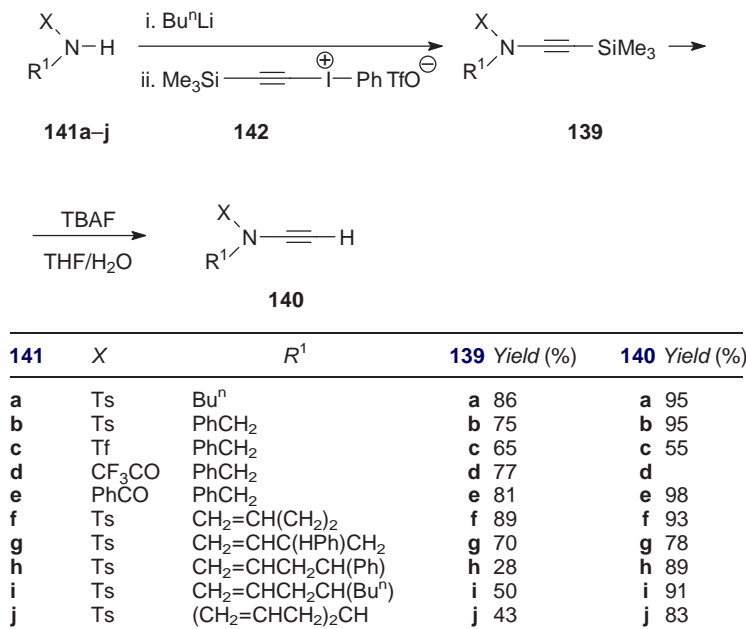
It is interesting to note that compounds functionalized at the nitrogen atom with an electron-withdrawing group (EWG) or an organic acid moiety constitute a stable variant of ynamines and ynamides [<2001T7575>](#). Accepting this formal division of ynamine derivatives, this new section that describes the synthetic approaches reported since 1994 for the preparation of ynamides having the general structure **132** has been added.



Most compounds of this class are *N*-sulfonyl derivatives, which in most cases have been prepared by alkylation reactions of secondary sulfonamides with an alkynyl iodonium salt. The first paper describing this approach appeared in 1996 [<1996JOC5440>](#) and reports the use of alkynyl iodonium salts **133** and **134** as reagents for the alkylation of the optically active α -substituted ethyltosylamides **135** and **136** in moderate yields (Equations (13) and (14)).

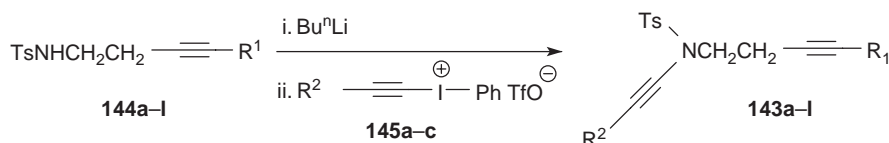


Subsequently, the alkynyl amides **139** and **140** were prepared <1998AG(E)489> by the ethynylation of the amides (**141a–141j**) with the trimethylsilyliodonium triflate **142** followed by desilylation of the purified silaamides **139** (Scheme 36). It should be noted that the alkynyl amides **139** and **140** withstand aqueous work-up and chromatographic purification on silica gel column.



Scheme 36

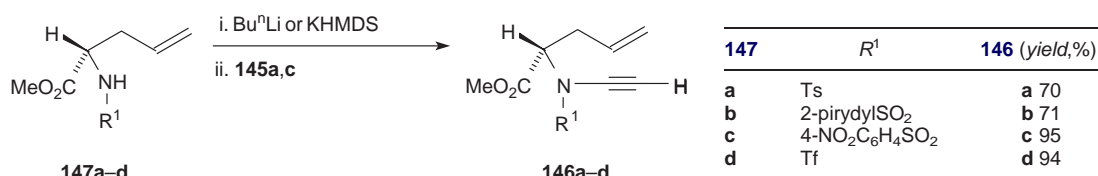
This approach has also been applied to the synthesis of *N*-functionalized 1-alkynyltosyl amides **143a–143l** (Scheme 37) <1999AG(E)2426>. These derivatives were obtained after deprotonation of the secondary tosylamides **144** followed by addition of the alkynyliodonium salts (**145a** and **145c**) in toluene.



144	R ¹	145	R ²	143	Yield (%)
a	SiMe ₃	a	SiMe ₃	a	69
b	(CH ₂) ₂ OTBMS	a	SiMe ₃	b	80
c	(CH ₂) ₂ OBz	a	SiMe ₃	c	66
d	(CH ₂) ₂ OTHP	a	SiMe ₃	d	43
e	(CH ₂) ₂ NHTs	a	SiMe ₃	e	28
f	Ph	a	SiMe ₃	f	72
g	Ph	c	H	g	85
h	CO ₂ Me	c	H	g	35
i	H	b	Ph	i	50
j	H	a	SiMe ₃	j	64
k	(CH ₂) ₂ OBz	b	Ph	k	55
l	CH ₂ OTHP	a	SiMe ₃	l	60

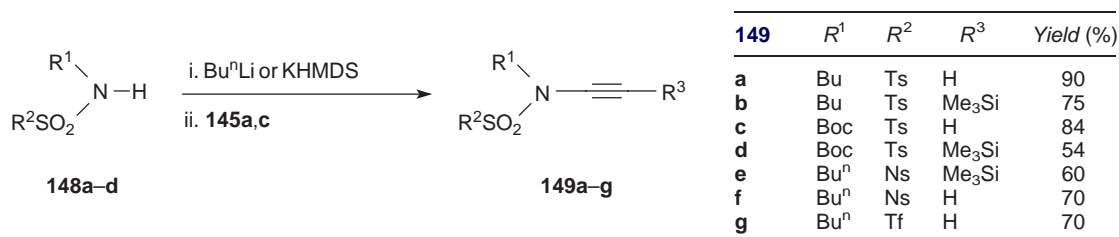
Scheme 37

This methodology has been used for the stereospecific synthesis of chiral *N*-ethynyl-allylglycines (**146a–146d**). Deprotonation of amines (**147a–147d**) (KHMDs in toluene or Cs_2CO_3 in DMF) followed by addition of the iodonium triflates **145a** and **145c** yielded the *N*-ethynylamides (Scheme 38) <1999CC1879>.



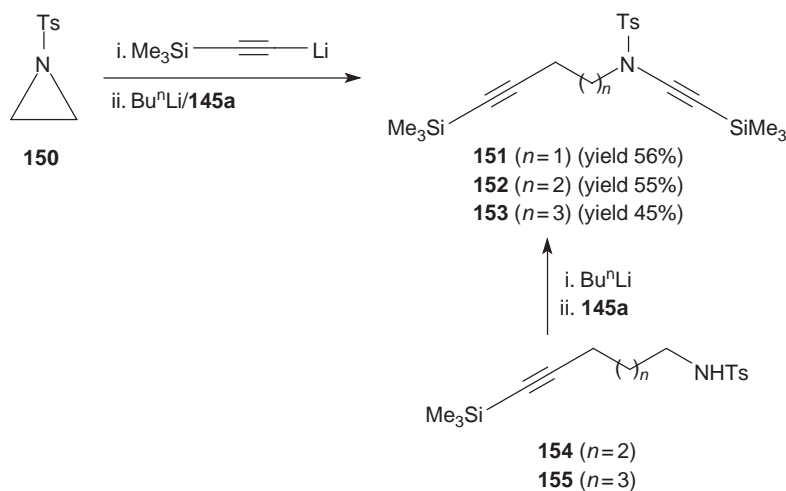
Scheme 38

A similar alkynylation procedure has been applied to several secondary sulfonamides (**148a–148d**) giving the alkynyl amides (**149a–149g**) (Scheme 39) <2000SL1793>.



Scheme 39

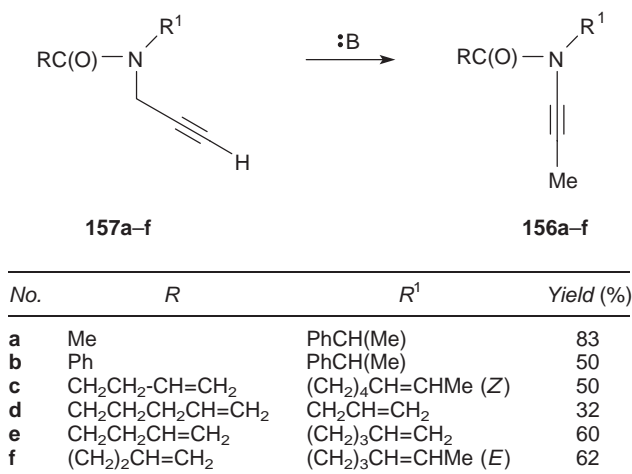
This methodology has been successfully extended to the synthesis of yne-ynamides having 2-, 3-, and 4-carbon tethers between the alkyne and ynamide functions (Scheme 40) <2000JOC7272, 1999OL2037>. Ring opening of *N*-tosylaziridine **150** by lithium trimethylsilyl acetylide followed by alkynylation using the iodoacetylene salt **145a** provided yne-ynamide **151** (58%). Analogous alkynylation of the corresponding alkynyltosyl amides **154** and **155** gave the expected products **152** and **153**.



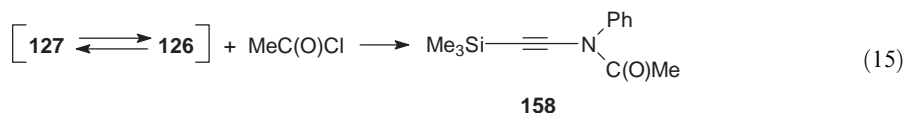
Scheme 40

Six *N*-acylnamines (**156a–156f**) have been prepared by base-promoted isomerization of the corresponding propargylamides (**157a–157f**) (Scheme 41) <2002OL2417>.

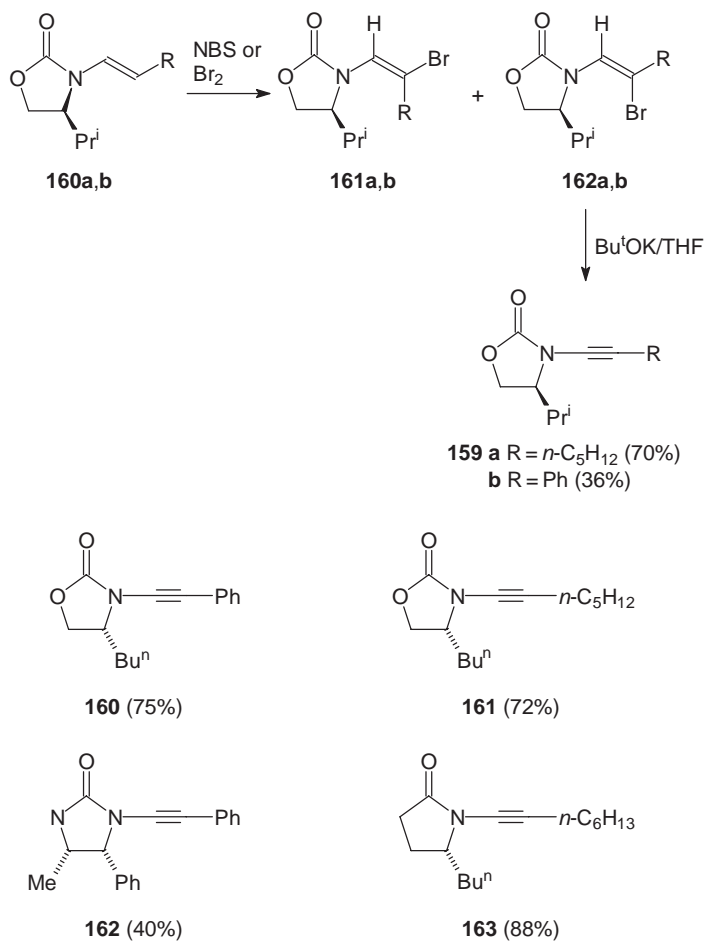
The ynamide **158** (75% yield) was obtained when excess acetyl chloride reacted with lithio-ynamine **126** (in equilibrium with **127**) (Equation (15)) <1999T5405>.



Scheme 41

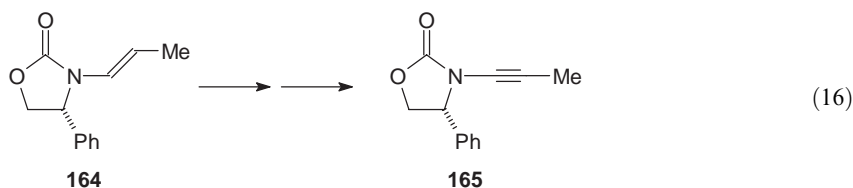


Base-induced elimination of 2-bromoenamides constitutes another approach to ynamides. This protocol has been applied to the preparation of the optically active compounds (**159–163**) functionalized at the nitrogen atom with chiral oxazolidinone residues (Scheme 42) <2001T459>.

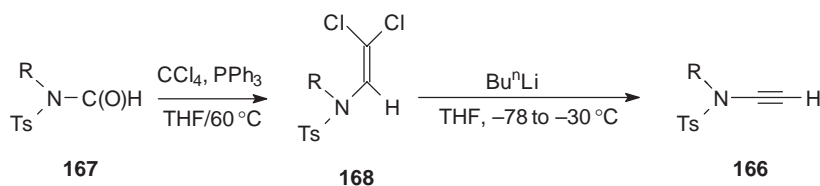


Scheme 42

When enamide **164** was subjected to the reaction sequence presented in Scheme 42, the ynamide **165** was isolated in 50% yield (Equation (16)) <2001T459>.



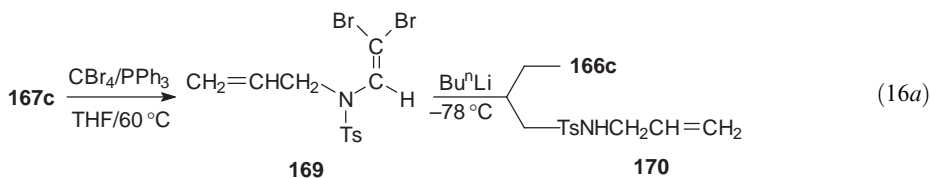
A very efficient, general protocol for the preparation of *N*-tosylynamides **166**, which uses readily available *N*-tosylformamides **167** and involves elimination of HCl from the corresponding dichlorovinylamides **168** as a key step, has been reported (Scheme 43) <2000SL1402>.



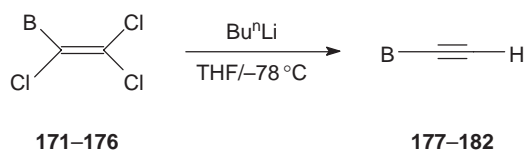
		Yield (%)	
166–168	R	168	166
a	Bn ⁿ	99	86
b	Pr ^l	96	93
c	CH ₂ CH=CH ₂	97	81
d	CH ₂ C(Me)=CH ₂	97	95
e	Bu ⁿ	96	80
f	Ph	81	97

Scheme 43

It is of interest to note that experiments with the dibromovinylamide **169** and BuⁿLi result in a mixture of ynamide **166c** and *N*-allyltosylamide **170** (Equation (16a)) <2000SL1402>.



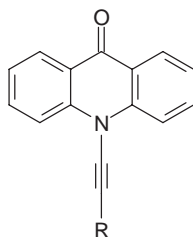
Elimination has been reported to be a useful procedure for converting trichloroenamines derived from nucleic acid bases (**171–176**) into the corresponding ynamides (**177–182**) (Scheme 44) <1994JCS(P1)1089>.



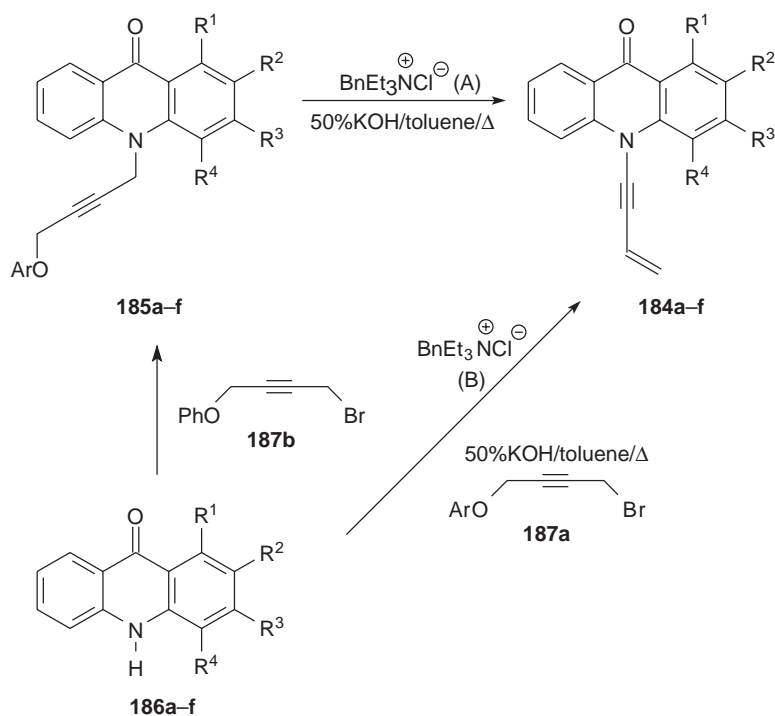
- 171, 177** B = adenin-*N*⁹-yl
172, 178 B = 2,6-diaminopurin-*N*⁹-yl
173, 179 B = 2-amino-6-benzoyloxyadenin-*N*⁹-yl
174, 180 B = *N*⁶-benzyladenin-*N*⁹-yl
175, 181 B = cytosin-*N*¹-yl
176, 182 B = thymine-*N*¹-yl

Scheme 44

10-Alkynylacridones **183** are another electron-deficient example of ynamides and are conveniently considered as a specific group of ynamides.

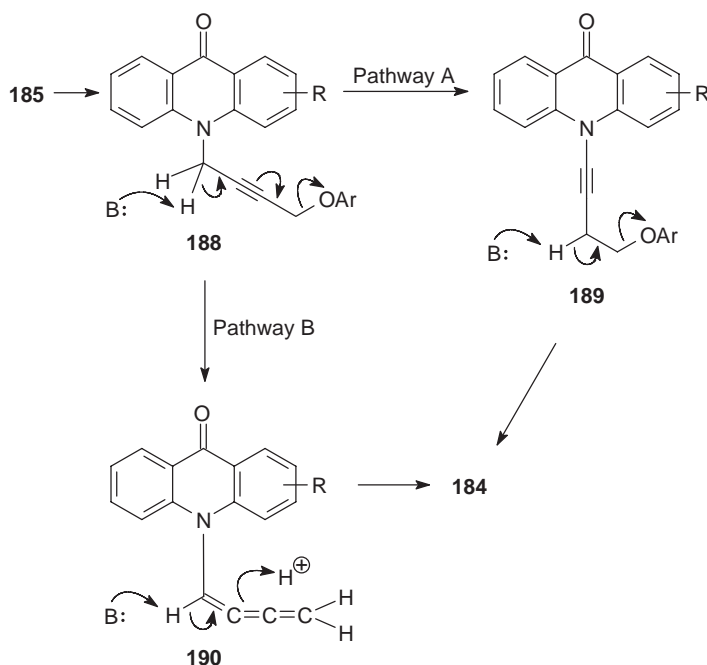
**183**

A number of 10-enynylacridones (**184a–184f**) have been obtained in good yield either by refluxing acridones (**185a–185f**) with benzyltriethylammonium chloride and aqueous potassium hydroxide (50%) in toluene or directly from the acridones (**186a–186f**) and 1-aryloxy-4-chlorobut-2-yne **187a** under the same conditions (Scheme 45) <1994SC217>. It has been proposed that the ynamide (**184**) is formed by the isomerization of the intermediates **188** to **189** (pathway A) (Scheme 46). An alternative mechanism (pathway B) involves base-catalyzed elimination of ArOH from **188** to form an intermediate triene **190** that isomerizes to the enyne **184** (Scheme 46) <1994SC217>.



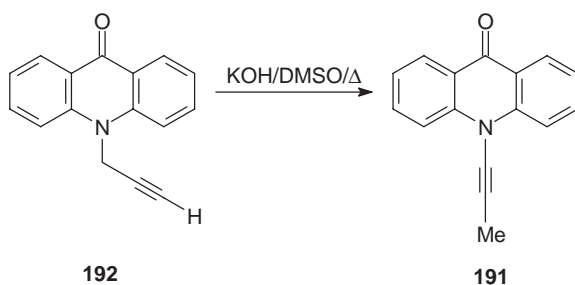
184	<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	<i>R</i> ⁴	<i>Ar</i>	<i>Procedure</i>	<i>Yield (%)</i>
a	H	H	H	H	Ph	A	not given
a	H	H	H	H	Ph	B	68
a	H	H	H	H	4-Cl-C ₆ H ₄	B	72
a	H	H	H	H	4-Cl-C ₆ H ₄	B	65
b	H	Me	H	H	4-MeC ₆ H ₄	B	72
c	H	H	Me	H	4-MeC ₆ H ₄	B	68
d	H	H	H	Me	4-MeC ₆ H ₄	B	70
e	H	Cl	H	H	4-Cl-C ₆ H ₄	B	71
f	H	Br	H	H	4-ClC ₆ H ₄	B	72

Scheme 45



Scheme 46

10-Propynyl-9(10*H*)-acridone **191** has been prepared by base-catalyzed isomerization of the 10-propargyl precursor **192** (Equation (17)) <1999OL1237>.



(17)

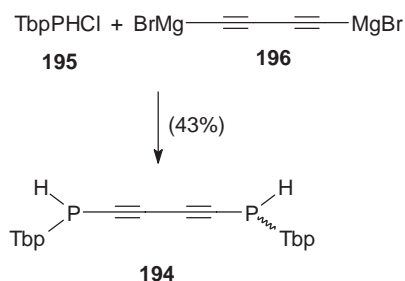
2.22.2 ALKYNYLPHOSPHORUS COMPOUNDS

2.22.2.1 Alkynylphosphines

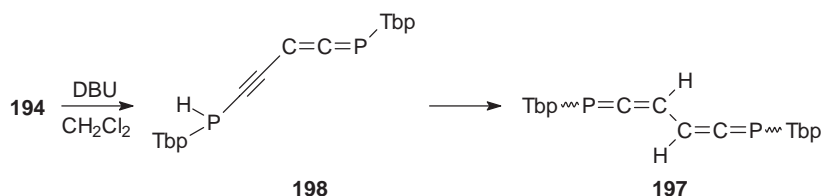
No primary alkynylphosphines have been prepared and isolated as pure chemical species. Only recently have the first examples of secondary alkynylphosphines been reported. In contrast, the tertiary analogs are readily available and they constitute the richest family of alkynylphosphorus compounds.

2.22.2.1.1 Secondary alkynylphosphines

The synthesis of chemically stable secondary alkynylphosphines became possible by utilizing the extremely bulky 2,4,6-tri-*t*-butylphenyl (Tbp) group as a sterically protecting auxiliary. Thus, 1,6-bi-*H*-1,6-diphosphino-2,4-hexadiyne **194** was prepared by the reaction of 2,4,6-*t*-butylphenyl-chlorophosphine **195** with bromomagnesium diacetylide **196** (Scheme 47) <1995TL6429>. The isolated diyne **194** undergoes a base-catalyzed heteropropargylic rearrangement to form 1,6-diphosphahexetraene **197** via the alkynylphosphaallene **198** (Scheme 48) <1995TL6429>.

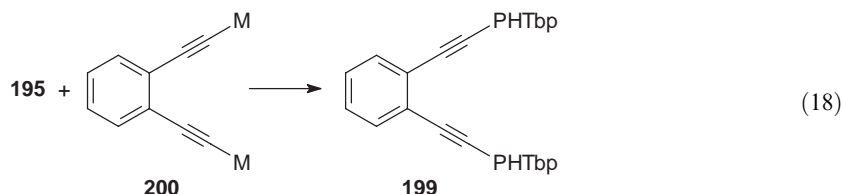


Scheme 47

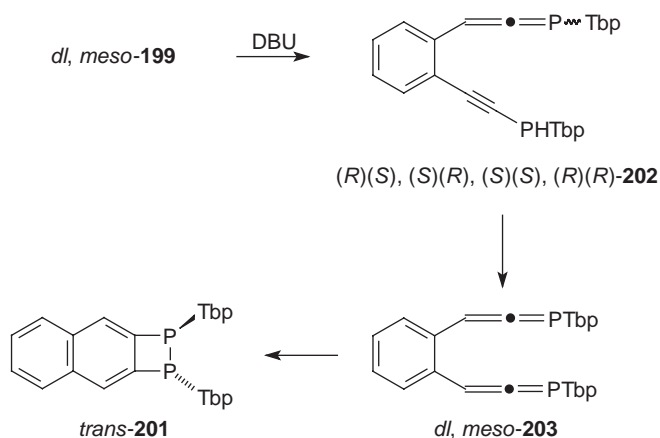


Scheme 48

The same authors prepared bis-alkynylphosphine **199** using the chlorophosphine **195** and a dimetallated 1,2-diethynylbenzene **200** (Equation (18)) <1997LA121>.

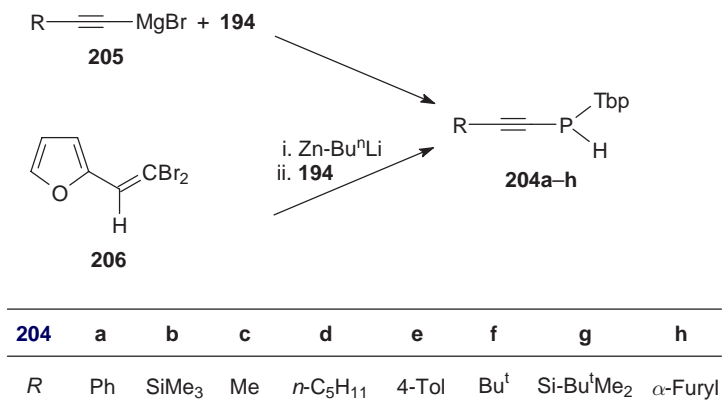


The *dl* and *meso* stereoisomers of phosphine **199** were formed in equal amounts (^{31}P NMR). The addition of a catalytic amount of DBU to the phosphine **199** afforded naphthodihydrodiphosphetane **201** as a single reaction product. Monitoring of this DBU-catalyzed rearrangement by ^{31}P NMR at low temperature revealed the almost quantitative formation of the intermediate mono- and bisallenenes **202** and **203** (Scheme 49) <199LA121>.



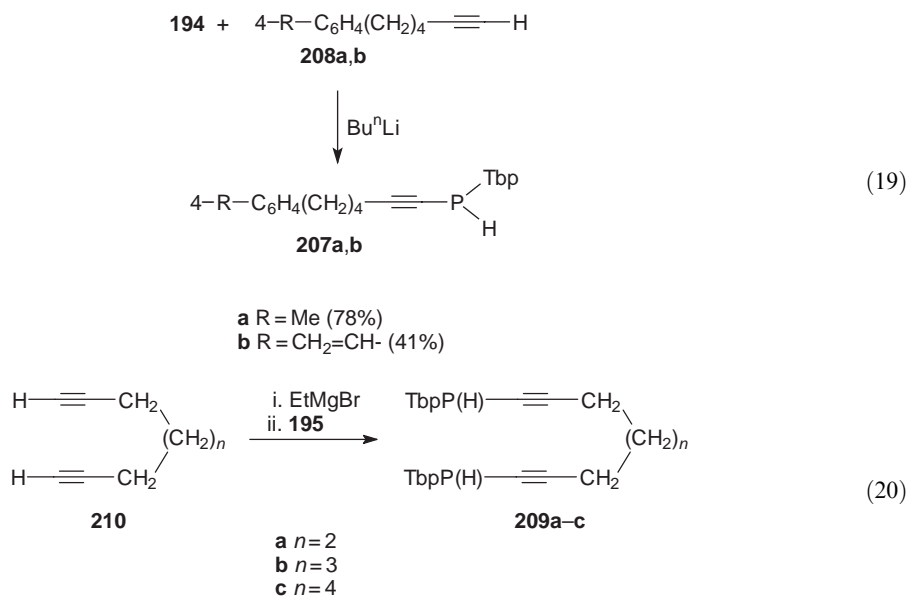
Scheme 49

Earlier, a number of alkynylphosphines (**204a–204h**) were prepared by reaction of the terminal alkynyl Grignard reagents **205** with the chlorophosphine **194** (50–70% yield) (Scheme 50) <1996LA2059>. Alkynylphosphine **204h** was prepared by treatment of 2-(2,2-dibromoethenyl)-furan **206** with BuⁿLi (2 equiv.) and subsequent addition of the lithioderivative to diyne **194** (Scheme 50) <1996LA2059>. Isolation of the alkynylphosphine having a Tbp substituent on the terminal acetylenic carbon has also been reported <2001PS315>.



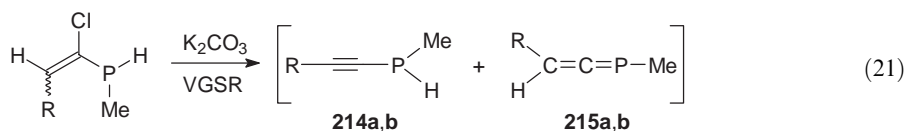
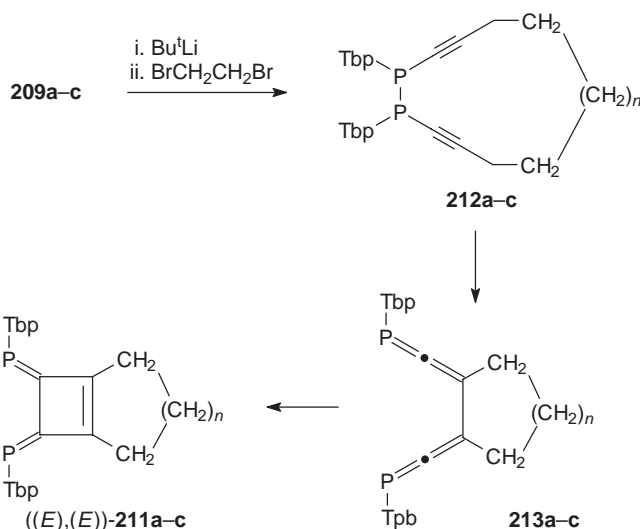
Scheme 50

A similar procedure has been reported by Yoshifuji and co-workers <2001CL248> for the preparation of alkynylphosphines **207** from the alkynes (**208a** and **208b**) and the chlorophosphine **194** (Equation (19)). The same authors used this protocol for the preparation of the bis-alkynylphosphines (**209a–209c**) from bis-acetylenes **210** (Equation (20)) <2002OL569>.

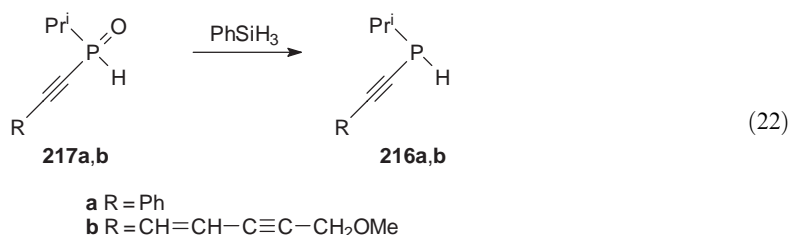


Treatment of the phosphines (**209a–209c**) with Bu^tLi (2 equiv.) and 1,2-dibromoethane (1 equiv.) gave the ring-fused ((*E*),(*E*))-diphosphinidenecyclobutanes (**211a–211c**), formed via the intermediates **212** and **213**, which were detected using ³¹P NMR (Scheme 51). It is of interest that the ((*E*),(*E*))-cyclobutanes (**211a–211c**) are converted to ((*E*),(*Z*))-isomers by addition of a catalytic amount of iodine in benzene <2002OL569>.

Two secondary methylalkynylphosphines (**214a** and **214b**) were formed in a mixture with the corresponding allenes (**215a** and **215b**) in a base-induced dehydrohalogenation of 1-chlorovinyl-methylphosphine when the reaction was performed in the gas phase using K₂CO₃ as a solid base heated to 250 °C (Equation (21)) <1994TL245>.



Two secondary alkynyl-isopropylphosphines (**216a** and **216b**) were isolated upon reduction of the corresponding phosphine oxides (**217a** and **216b**) with PhSiH_3 (Equation (22)) <2002JOM342>. The chemical stability of both phosphines was too low to allow purification by distillation or chromatography but they can be kept in a freezer.

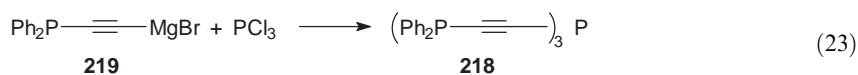


2.22.2.1.2 Tertiary alkynylphosphines

Tertiary alkynylphosphines are still commonly prepared by nucleophilic substitution of tricoordinated phosphorus halides by metal acetylides. Particularly useful are the readily available alkynyl Grignard reagents, which can be generated *in situ* by treatment of the selected acetylene derivatives with an alkyl Grignard reagent, e.g., EtMgBr .

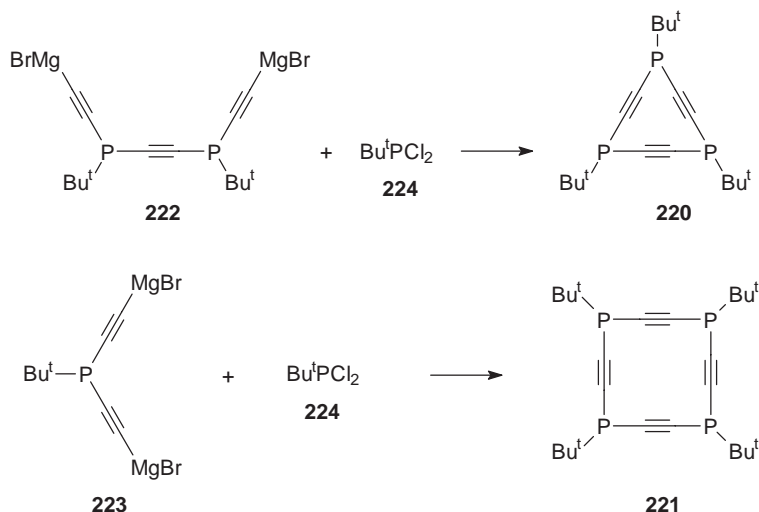
(i) From phosphorus trichloride

Tris-(2-diphenylphosphino)ethynylphosphine **218** has been prepared by the reaction of bromomagnesium acetylide **219** with phosphorus trichloride (Equation (23)) <2000S726>.



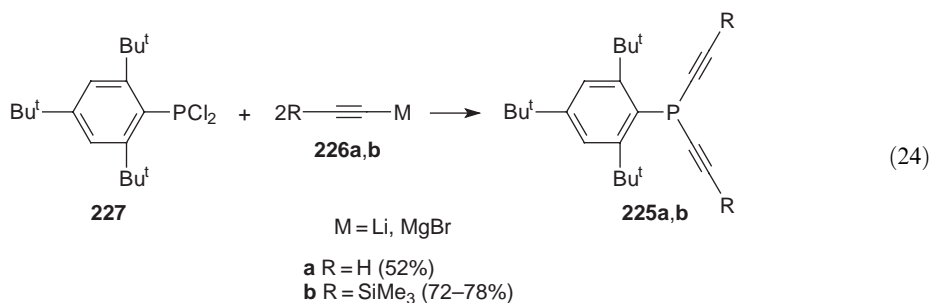
(ii) From phosphinous dichlorides

Two macrocyclic phosphacyclopolyynes **220** and **221** have been prepared by the coupling of bis-Grignard reagents **222** and **223** with *t*-butyldichlorophosphine **224** (Scheme 52) <1990JA7823>.

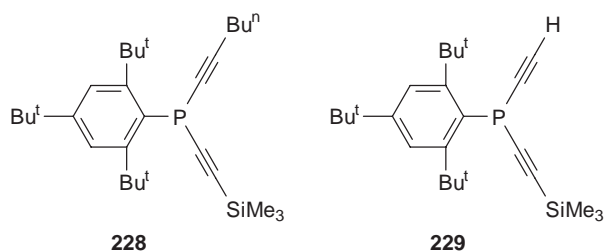


Scheme 52

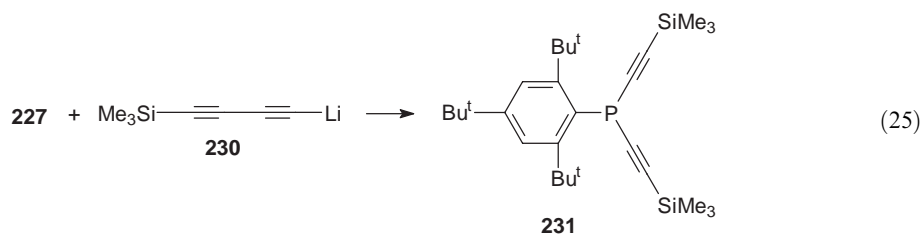
Two 2-substituted diethynyl (2,4,6-tri-*t*-butylphenyl)phosphines (**225a** and **225b**) were obtained by treatment of a solution of metallated acetylenes (**226a** and **226d**) with a solution of 2,4,6-tri-*t*-butylphenyldichlorophosphine **227** at room temperature (Equation (24)) <1995BCJ2633, 2000CEJ3806>.



It is interesting to note that reaction of the dichlorophosphine **227** with lithium acetylide **226b** that was prepared with the use of excess of Bu^nLi also gave the tertiary phosphine **228** and secondary phosphine **229** <1995BCJ2633>.

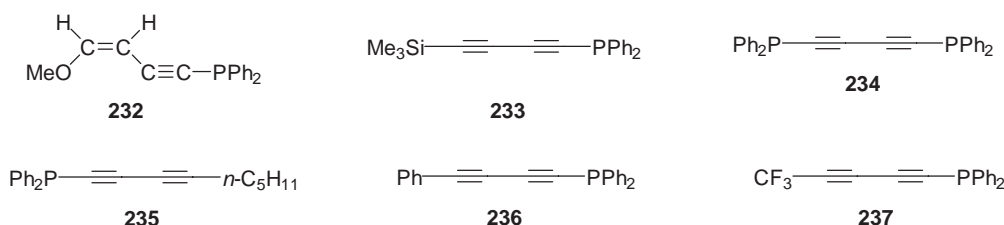
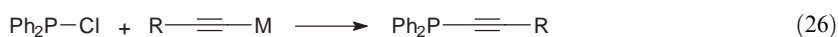


In the reaction of lithium bis-acetylide **230** with dichlorophosphine **227**, the *t*-bis-alkynylphosphine **231** was isolated in 53% yield (Equation (25)) <1995BCJ2633>.

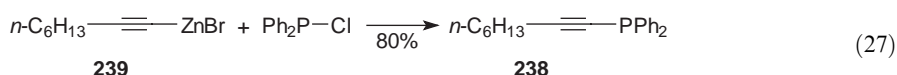


(iii) From chlorophosphines

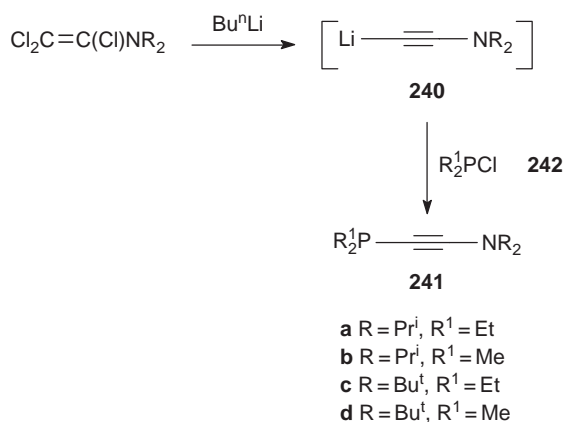
The condensation of diphenylchlorophosphine with metal acetylides (Equation (26)) has often been used as a synthetic procedure leading to the corresponding diphenylalkynylphosphines. Representative examples are compounds **232–237** <1997JOM39, 1995TL3687, 1996CJC2349, 2002CC2420, 2000AG(E)1896>.



Oct-1-ynyldiphenylphosphine **238** has been prepared by coupling of oct-1-ynylzinc bromide **239** with diphenylchlorophosphine (Equation (27)) <1997TA715>.

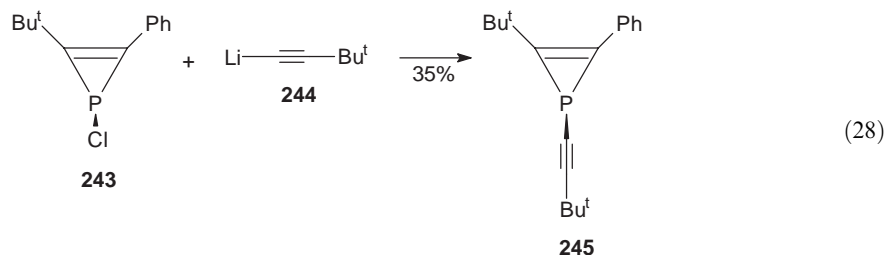


The reaction of the lithioamine acetylides **242** (generated *in situ*) with dialkylchlorophosphines **240** has been shown to afford the terminal aminoalkynylphosphines (**241a–241d**) (Scheme 53) <1993ZOB1767>.

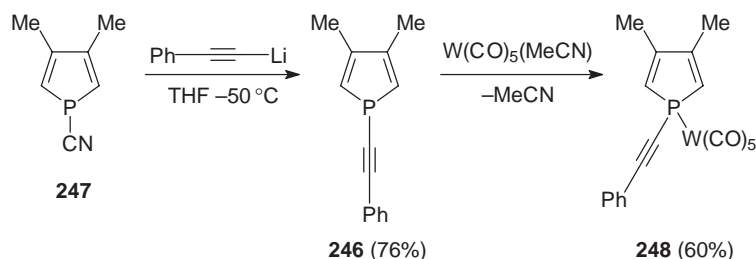


Scheme 53

Substitution of chlorine in 1-chloro-1*H*-phosphirenes **243** using the alkynylorganolithium reagent **244** has been reported to easily occur with formation of the alkynyl-substituted 1*H*-phosphirenes **245** (Equation (28)) <1997CB711>.



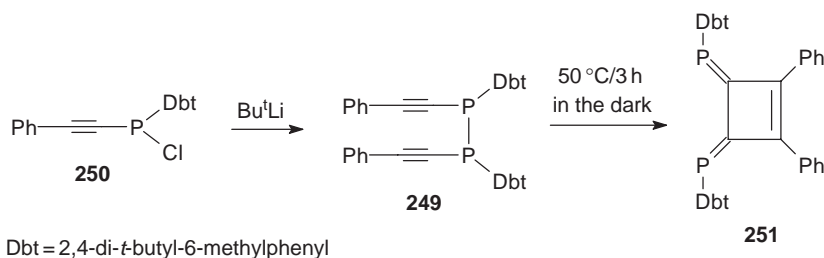
It is interesting to note that 1-alkynyl-3,4-dimethylphosphole **246** has been obtained from the 1-cyanophosphole **247** via nucleophilic substitution using lithium 2-phenylacetylene. Treatment of the isolated alkynylphosphine **246** with $[\text{W}(\text{CO})_5(\text{MeCN})]$ afforded the P- $\text{W}(\text{CO})_5$ complex **248** (Scheme 54) <2001AG(E)1253>.



Scheme 54

(iv) Miscellaneous methods

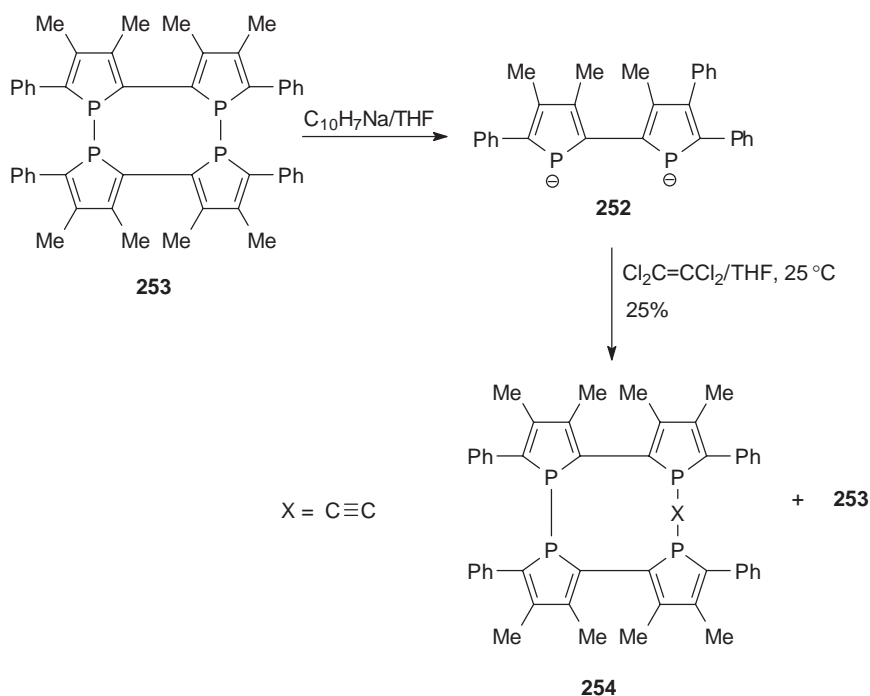
There are some other procedures for the synthesis of tertiary alkynylphosphines. They are, however, few in number and of limited applicability. For example, the synthesis of 1,2-bis(2,4-di-*t*-butyl-6-methyl-phenyl)-1,2-bis(phenyl-ethynyl)diphosphane **249** employs the base-induced coupling of the corresponding phosphinous chloride **250** (Scheme 55) <1997CL87>. Heating the diphosphane **249** in the dark (3 h) gave the diphosphacyclobutene **251** as a mixture of two rotamers (1:2) (Scheme 55) <1997CL87>.



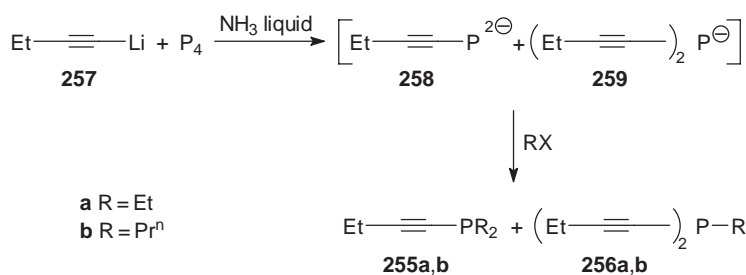
Scheme 55

The reaction of the dianion **252** (generated *in situ* from the phosphole tetramer **253**) with tetrachloroethylene has been found to occur with a formation of the 1,2,5,8-tetraphosphacyclodec-6-yne **254** (Scheme 56) <1994JA3306>.

Mixtures of the alkynylphosphines **255** and **256** have been isolated as products of the reaction of lithium 2-ethylacetylene **257** with elemental phosphorus and subsequent alkylation of the phosphorus anions **258** and **259** with an alkyl halide (Scheme 57) <1997IZV884>.

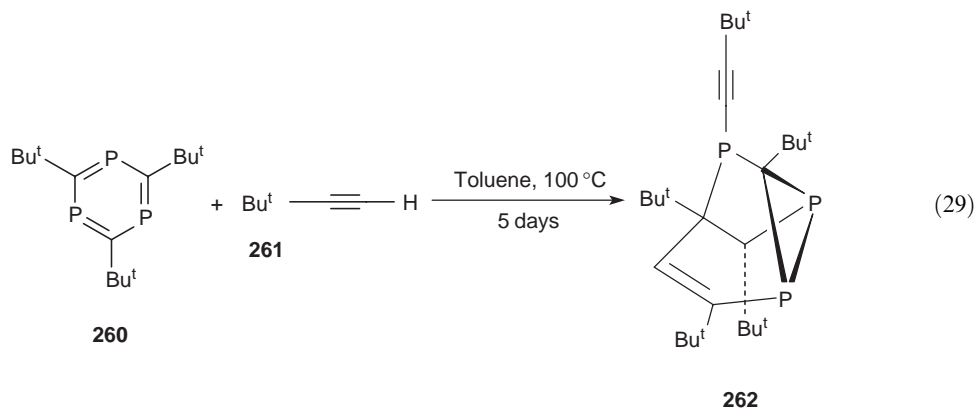


Scheme 56

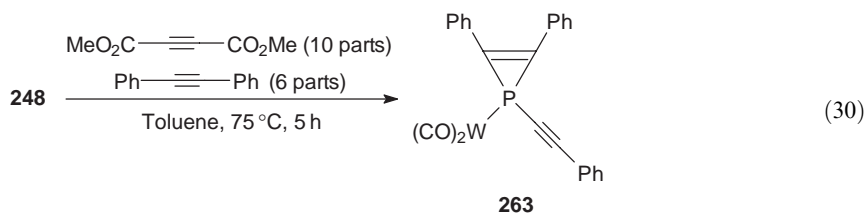


Scheme 57

An interesting cycloaddition has been reported to occur between the triphosphinine **260** and *t*-butylacetylene **261** <2000S529>. It was found that heating both components at a temperature above 100 °C (5 days) gave the tricyclic compound **262** (Equation (29)).



The 1-alkynylphosphirene complex **263** was obtained in a satisfactory yield when the alkynyl-phosphole-tungsten complex **248** was allowed to react with a 10:6 mixture of DMAD and diphenylacetylene (Equation (30)) <2001AG(E)1253>.

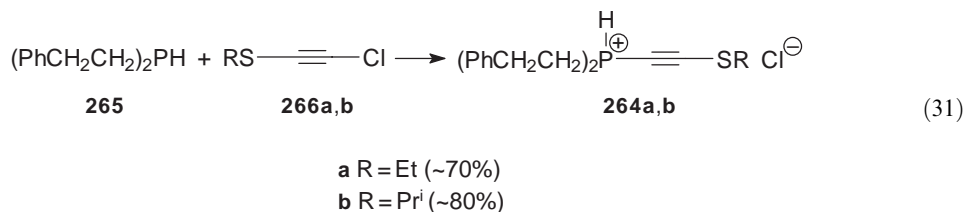


2.22.2.2 Alkynylphosphonium Salts

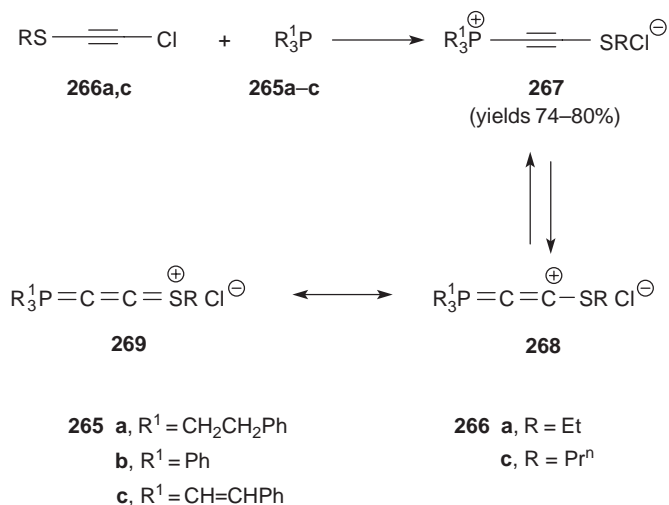
The syntheses of the majority of alkynylphosphonium salts are based on two synthetic procedures: (i) reaction of alkynyl halides with secondary or tertiary phosphines and (ii) quaternization of the isolated alkynylphosphines with an alkyl halide.

2.22.2.2.1 From alkynyl halides

The first examples of dialkylalkynylphosphonium salts to be described have been reported recently <1999ZOB799>. The salts (**264a** and **264b**) were isolated as the only products from the reaction of 2-phenylethylphosphine **265** with 2-S-alkylchloroacetylenes (**266a** and **266b**) (Equation (31)).

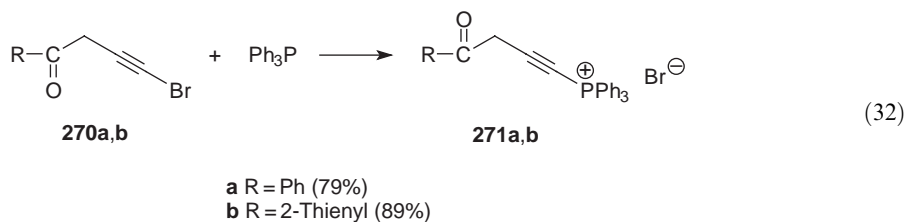


A few phosphonium salts **267** have been prepared <1999ZOB1296> by alkynylation of the tertiary phosphines (**265a–265c**) by chloroacetylenes (**266a** and **266c**). In solution they exist in equilibrium with the cumulenes **268** and **269** (Scheme 58).



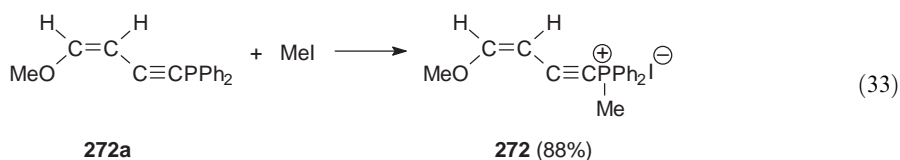
Scheme 58

The reaction of 1-acyl-2-bromoacetylenes (**270a** and **270b**) with triphenylphosphine affords the alkynylphosphonium salts (**271a** and **271b**) (Equation (32)) <1996IZV781>.

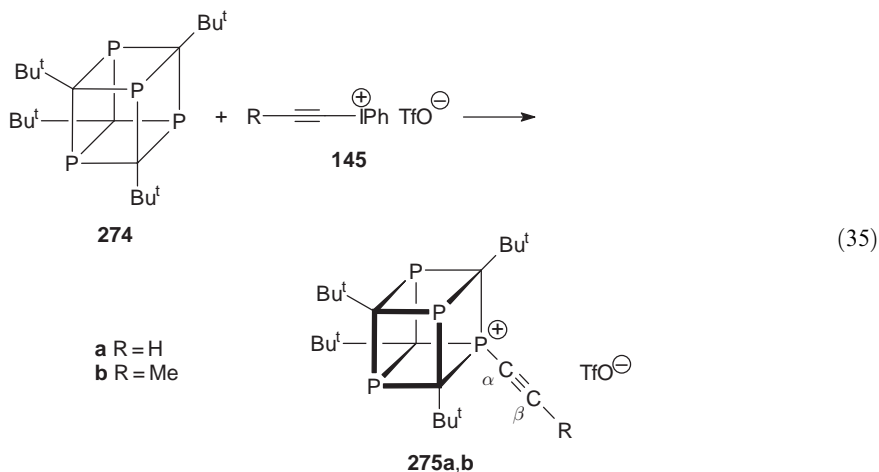
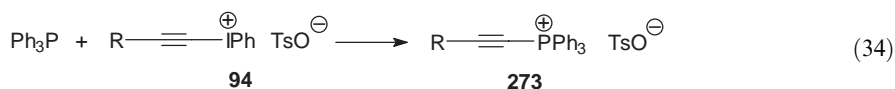


2.22.2.2.2 Quaternization of alkynylphosphines

This reaction has been used occasionally for the preparation of alkynylphosphonium salts. For example, Corriu and co-workers found that treatment of the phosphine **272a** with methyl iodide gives the methylphosphonium iodide **272** (Equation (33)) <1997JOM39>.

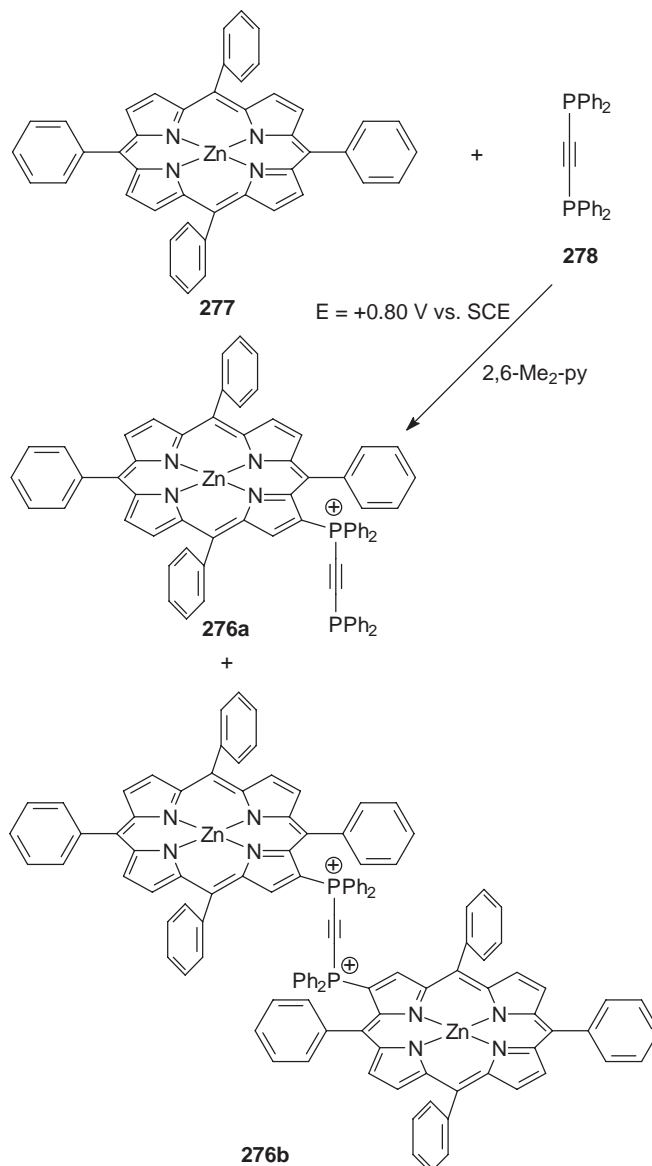


Due to the presence of an activated, polarized C—C triple bond, alkynyl(phenyl)iodonium triflates can serve as alkynylation agents toward a wide variety of nucleophiles <1992AG(E)274>. The reagent **94** was first used to prepare the triphenylalkynylphosphonium salts **273** (Equation (34)) <1992JOC4305>. This procedure has also been used for alkynylation of the tetraphosphacubane **274**, which on treatment with ethynyl and propynyl(phenyl)iodonium triflates **145** at room temperature gives the monophosphonium salts (**275a** and **275b**) (^{31}P NMR) (Equation (35)) <1993JOC4105>.



2.22.2.2.3 Miscellaneous methods

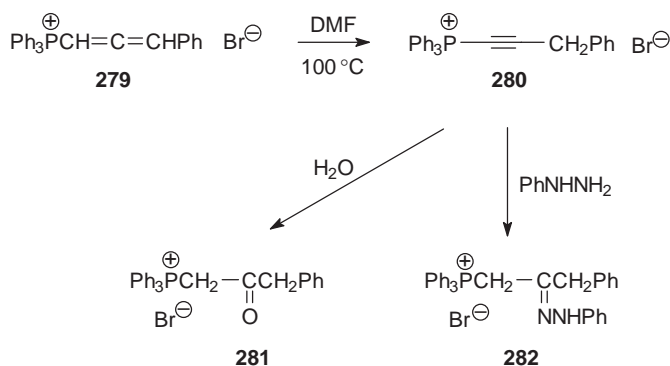
Alkynyl mono- and bis-phosphonium salts (**276a** and **276b**) have been prepared in high yields in a one-pot electrochemical oxidation of the metalloporphyrine ZnTPP **277** and bis-1,2-diphenylphosphinoacetylene **278** in the presence of a base (2,6-lutidine) (Scheme 59) <2001EJIC659, 1996CC2007>.



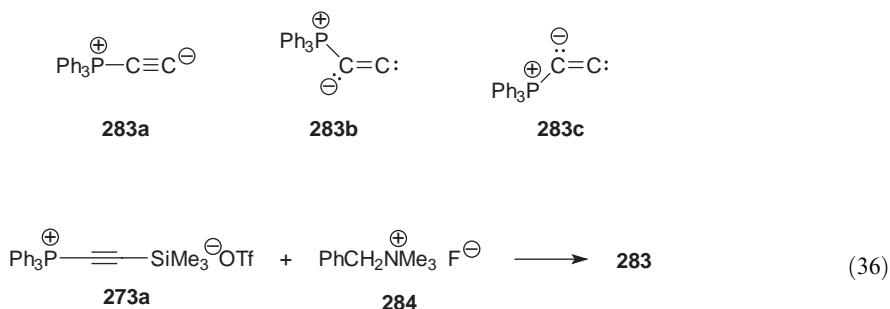
Scheme 59

An interesting isomerization of the phosphoniocumulene **279** to the alkynylphosphonium bromide **280** has been found to occur during heating of the salt **279** at 100 °C in DMF. The isolated phosphonium salt **280** upon treatment with water gave the ketophosphonium salt **281** and with phenylhydrazine gave the hydrazide **282** (Scheme 60) <2002IZV139>.

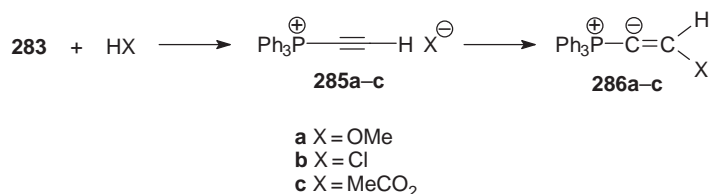
The structure of the triphenylphosphonioacetylide **283a** is of theoretical interest. The structure of this alkynylphosphonium salt can be alternatively viewed as (methylenecarbenylidene)triphenylphosphoranes (**283b** or **283c**) <1998AG(E)338>. The reported synthesis of this alkynylphosphonium salt **283** <1998AG(E)338> is based on desilylation of the phosphonium salt **273a** <1992JOC4305> using benzyltrimethylammonium fluoride **284** at -90 °C (Equation (36)).



Scheme 60



The *in situ* generated acetylide **283** is stable only at low temperature and decomposes upon warming to room temperature. It has been found, however, that at -78°C it reacts with acids (HX) to form phosphonium salts **285**. These salts were characterized (^{31}P NMR) as intermediates existing between -78°C and -30°C , but at about 0°C a further reaction with HX gives the vinylphosphonium salts **286** (Scheme 61) <1998AG(E)338>.



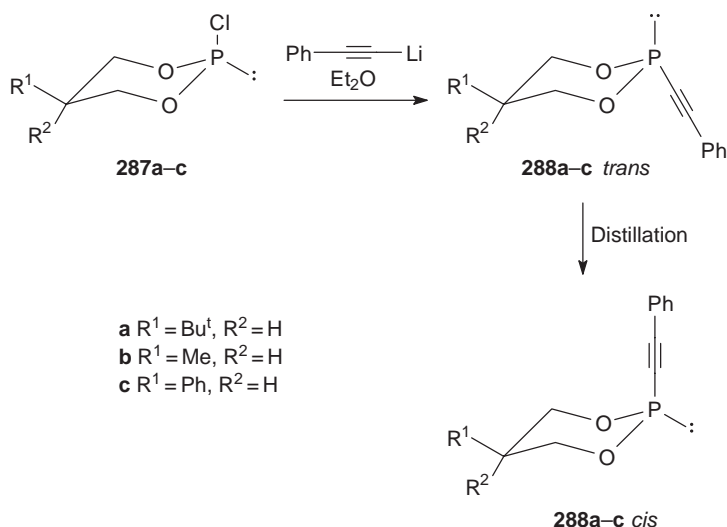
Scheme 61

2.22.2.3 Alkynyl-PX₂ Functions

Since 1994 the results of studies on only two members of this class of alkynylphosphorus compounds have been reported, namely alkynylphosphonites (X=OR) and alkynylaminophosphines (X=NR₂).

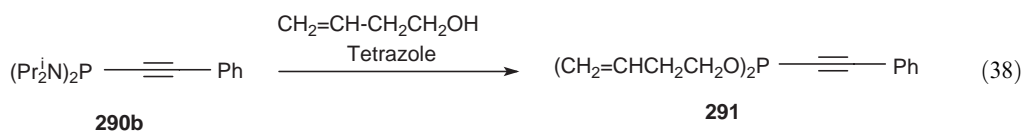
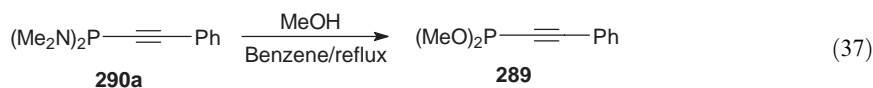
2.22.2.3.1 Alkynyl phosphonites (X=OR)

The reactions of lithium 2-phenylacetylide with the *cis*-2-chloro-1,3,2-dioxaphosphorinanes (**287a–287c**) have been found to occur with inversion at phosphorus giving the alkynylphosphites (**288a–288c**) as the major and highly predominant *trans*-diastereomers. The crude *trans*-products **288a** are converted to the *cis*-isomers **288a** during distillation (*cis* and *trans* refer to the relation of the substituent R¹ to the 2-(2-phenylethynyl) substituent) (Scheme 62) <1995JA12390>.



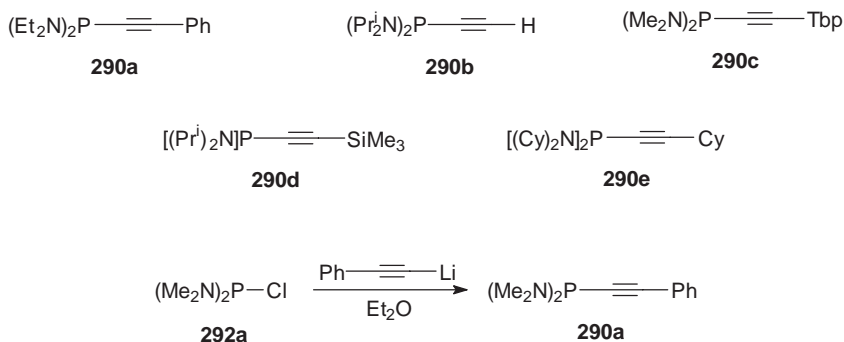
Scheme 62

Another route to alkynylphosphonites is based on alcoholysis of bis-(dialkylamino)alkynylphosphines. This has been used for the preparation of dimethyl 2-phenylethynylphosphonite **289** starting from the corresponding bis(dimethylamino)-2-phenylethynylphosphine **290a** (Equation (37)) <1995PS225> and di(but-30-en 1-yl)-2-phenylethynyl phosphonite **291** starting from bis(diisopropylamino)-2-phenylethynylphosphine **290b** (Equation (38)) <2001TL8231>.

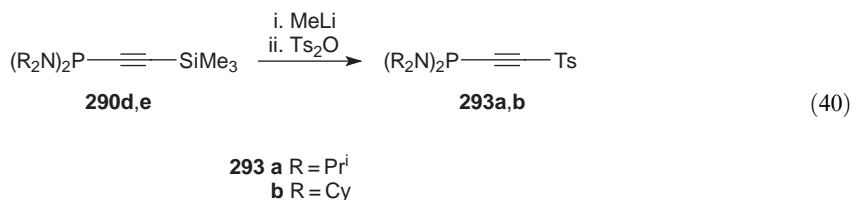


2.22.2.3.2 Alkynylaminophosphines ($X=\text{NR}$)

Bis(dimethylamino)-2-phenylethynylphosphine **290a** has been prepared by treatment of bis(dimethylamino)chlorophosphine **292a** with lithium 2-phenylacetylide (Equation (39)) <1993JA4031>. By the same procedure the alkynylaminophosphines (**290b–290e**) have been obtained from the appropriate bis(dialkylamino)chlorophosphines and metal acetylides <1994PS59, 2001TL8231, 2002PS2011, 1999TL883>.

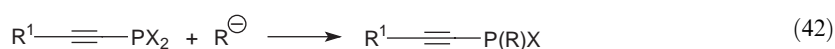
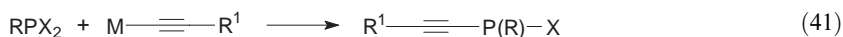


Interestingly, the silylalkynylphosphines (**290d** and **290e**) were converted into the corresponding tosyl derivatives (**293a** and **293b**) by sequential treatment with methyllithium and tosyl anhydride (Equation (40)) <1999TL883>.



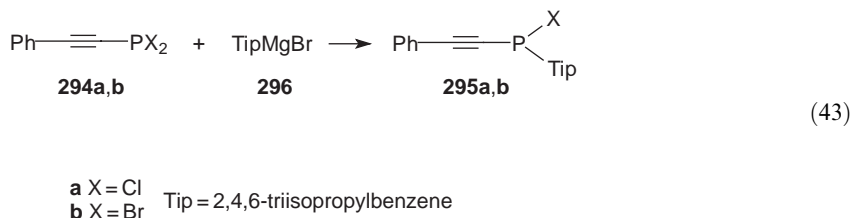
2.22.2.4 Alkynyl (R) P—X Functions

This class of alkynylphosphorus compounds is readily available from the reaction of metal acetylides with alkyldichlorophosphines (Equation (41)) or by the coupling of alkynyldichlorophosphines with an appropriate nucleophile (Equation (42)).

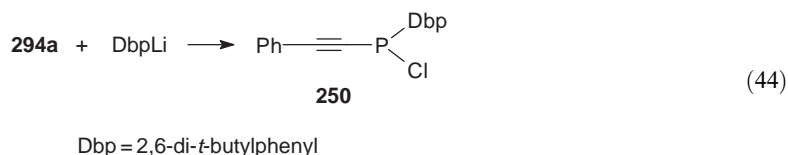


2.22.2.4.1 Secondary alkynylhalogenophosphines

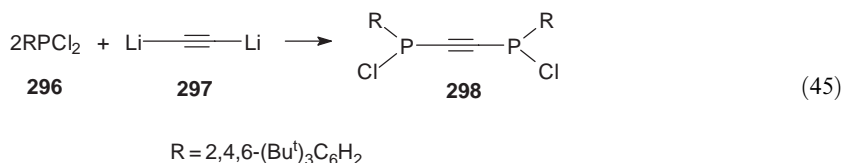
(2-Phenylethynyl)-(2,4,6-triisopropylphenyl)phosphinous halides (**295a** and **295b**) have been prepared by reaction of 2-phenylethynylphosphinous dihalogenides (**294a** and **294b**) with 2,4,6-triisopropylphenylmagnesium bromide **296** (Equation (43)) <1998CC27>.



By a similar protocol the ethynyldichlorophosphine **294a** was converted into the corresponding phosphinous chloride **250** (Equation (44)) <1997CL87>.

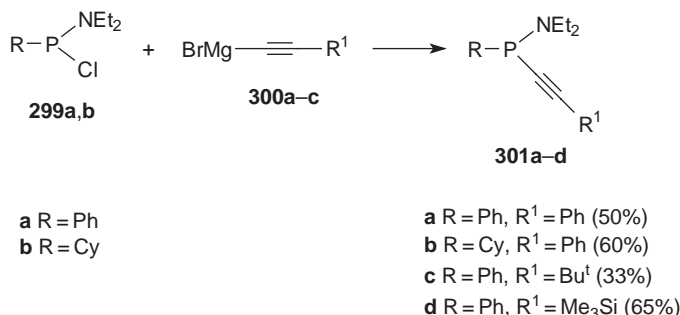


The reaction of the dichlorophosphine **296** with dilithioacetylene **297** affords the corresponding bis-chlorophosphine **298** (Equation (45)) <1995JOM77>.



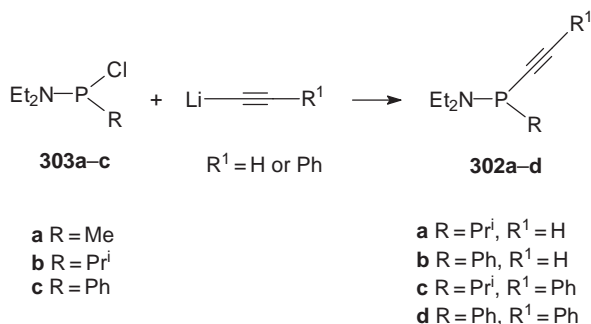
2.22.2.4.2 Secondary alkynylaminophosphines

The reaction of chloroaminophosphines (**299a** and **299b**) with bromomagnesium acetylides (**300a–300c**) has been used for the preparation of alkynylphenyl(cyclohexyl)-*N,N*-diethylaminophosphines **301** (Scheme 63) <1994PS59>.



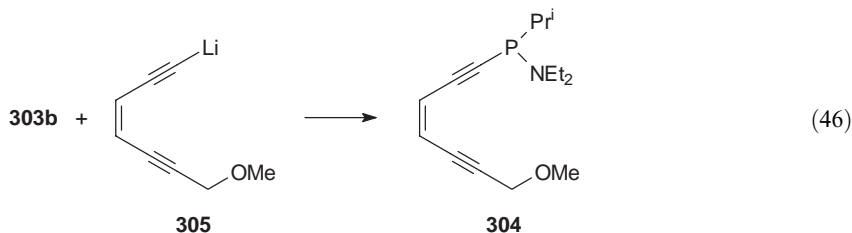
Scheme 63

N,N-Diethylalkyl(phenyl)alkynylaminophosphines (**302a–302d**) have been prepared by condensation of the chloroaminophosphines (**303a–303c**) with lithium acetylides (Scheme 64) <1995TL4421>.



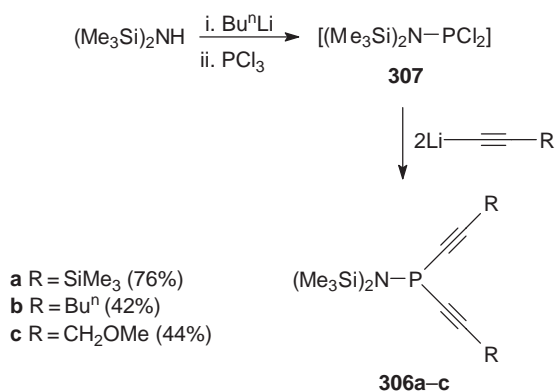
Scheme 64

Similarly, ene-diyne *P*-phosphineamine **304** was obtained by alkynylation of the lithium ene-yne acetylide **305** with **303b** at -78°C (Equation (46)) <2002JOM342>.

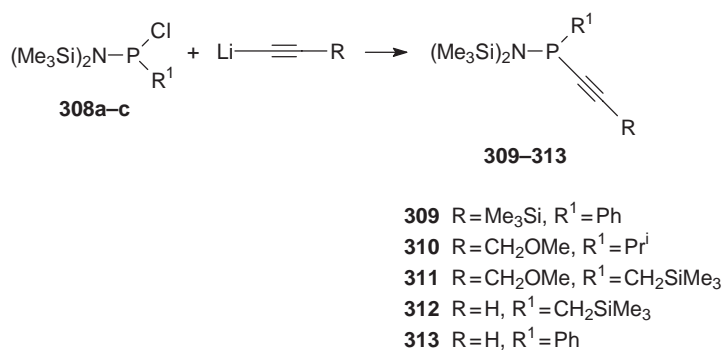


A variety of *P*-acetylenic (silylamino)phosphines has recently been prepared by the reaction of terminal acetylenes with two- or three-coordinate (silylamino)phosphines <2002JOM223>. The symmetrically substituted diacetylenic (silylamino)phosphines (**306a–306c**) have been obtained by reaction of the dichlorophosphine **307** (generated *in situ*) with a *C*-lithio-acetylene (2 equiv.) (Scheme 65) <2002JOM223>.

Similarly, the reactions of the stable mono-chlorophosphines (**308a–308c**) with lithium acetylide or ethynylmagnesium chloride (1 equiv.) gave the monoacetylene derivatives (**309–313**) (Scheme 66) <2002JOM223>.

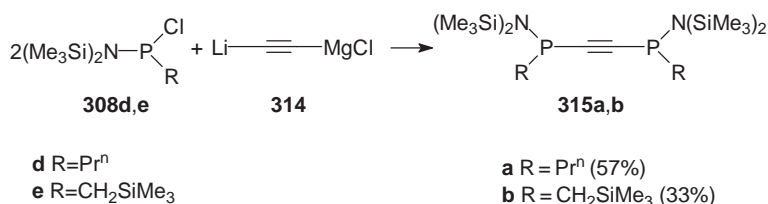


Scheme 65



Scheme 66

Addition of chloroaminophosphines (**308d** and **308e**) (2 equiv.) to the ethynyl Grignard reagent **314** gives the diphosphinoacetylenes (**315a** and **315b**) (Scheme 67) <2002JOM223>. Due to the presence of the two stereogenic phosphorus atoms, the acetylenic bis-phosphines (**315a** and **315b**) are formed as mixtures (ca. 1:1) of diastereomers.



Scheme 67

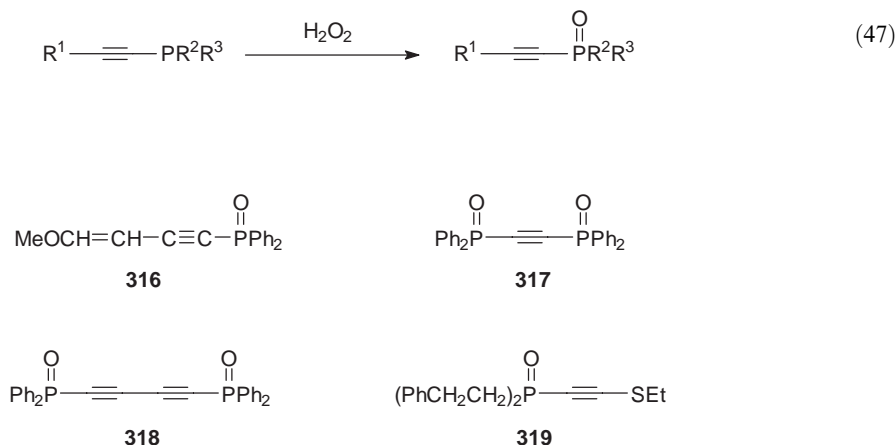
2.22.2.5 Alkynylphosphine Oxides and Imides

2.22.2.5.1 Alkynylphosphine oxides

Alkynylphosphine oxides can be prepared by two main synthetic approaches. The first is based on the oxidation of alkynylphosphines and the second is based on the reaction of a metal acetylide with a halogenophosphine oxides. In a few cases phosphine oxides have been prepared by other specific methods.

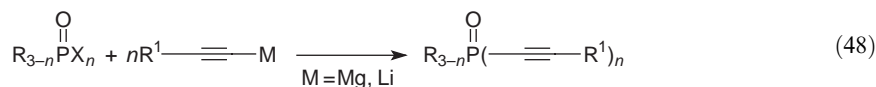
(i) From alkynylphosphines

Oxidation of alkynylphosphines to the corresponding oxides is usually carried out using a 30% hydrogen peroxide solution (Equation (47)). Using this method the alkynylphosphine oxides (**316–319**) have been prepared since 1994 <1997JOM39, 1996JOC8503, 1997JOM39, 1999ZOB799>.

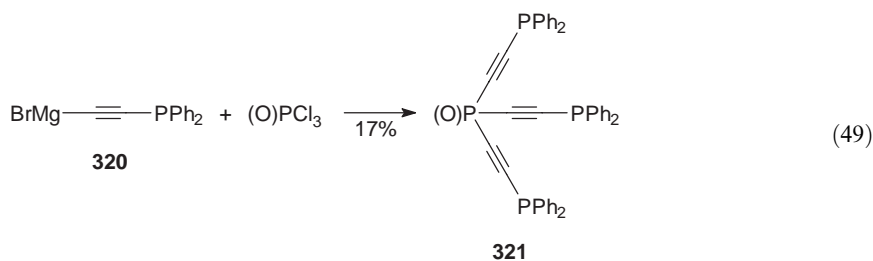


(ii) From chlorophosphine oxides

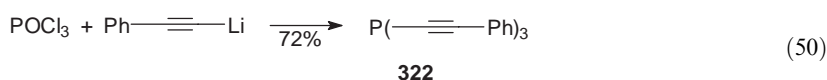
The addition of alkynyl Grignard (or lithium) reagents to a suitable pentavalent chlorophosphorus derivative constitutes a general approach for the synthesis of a variety of mono-, di-, and tri(alkynyl)phosphine oxides (Equation (48)).



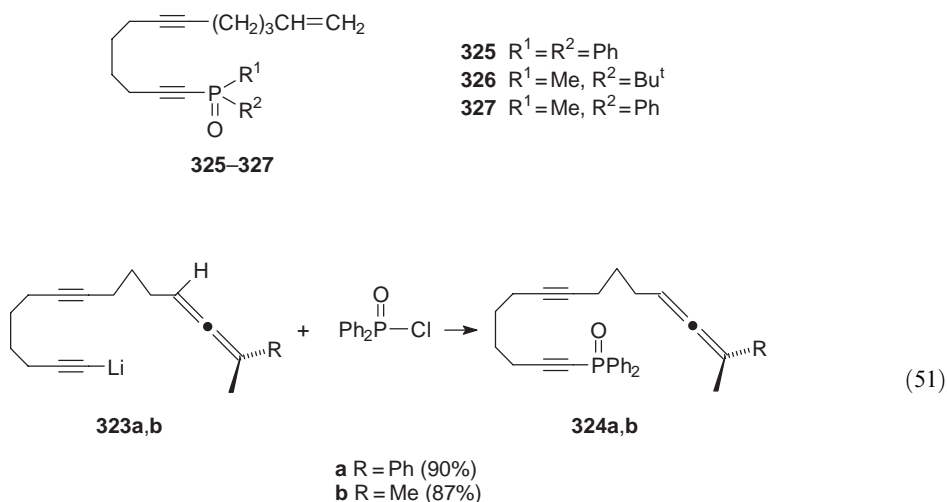
Thus, the reaction of the Grignard reagent **320** with phosphoryl chloride gave the expected trialkynylphosphine oxide **321**, which was present as the major product in the crude reaction mixture, although it was isolated in low yield (Equation (49)) <2000S726>.



Similarly, condensation of phosphoryl chloride with lithium 2-phenylacetylene gave tris-(2-phenyl)ethynylphosphine oxide **322** (Equation (50)) <1999MI222>.

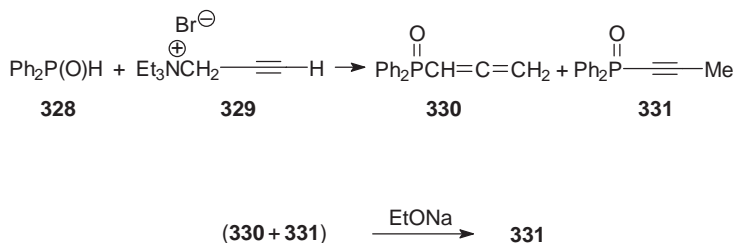


The alkynylation of diphenylphosphinic acid chloride with the lithium acetylides (**323a** and **323b**) afforded the allenediynes (**324a** and **324b**) (Equation (51)) <2000S985>. The alkenediynes (**325–327**) were prepared in a similar way by reaction of the appropriate acetylide with $\text{Ph}_2\text{P}(\text{O})\text{Cl}$, $t\text{-Bu}(\text{Me})\text{P}(\text{O})\text{Cl}$, or $\text{PhMeP}(\text{O})\text{Cl}$, respectively <1999TL707, 1999TL5849>.



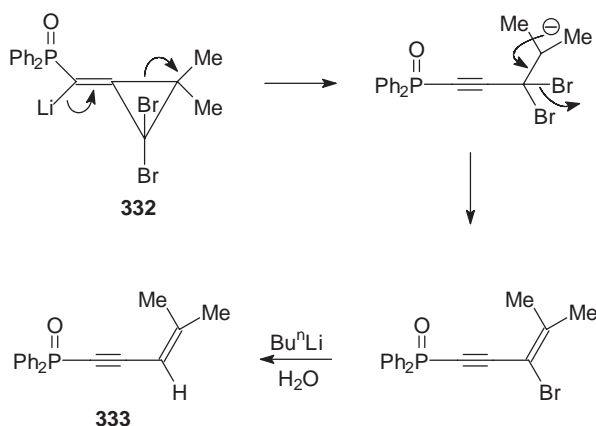
(iii) Other methods

Heating the secondary diphenylphosphine oxide **328** with triethylpropargylammonium bromide **329** was found to afford a mixture of the allene **330** and 2-methylethynyl phosphine oxide **331**. Treatment of this mixture with sodium ethoxide gave exclusively alkynylphosphine oxide **331** (Scheme 68) <1999IZV390>.



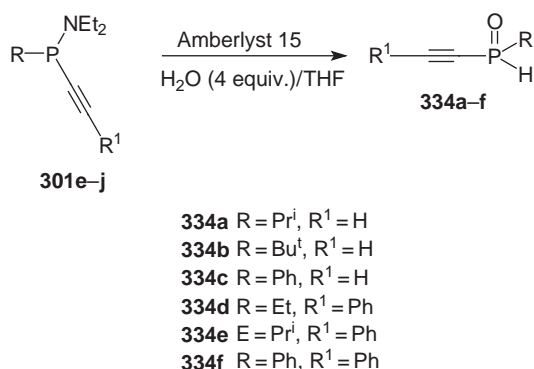
Scheme 68

When the α -lithiated dibromocyclopropane **332** was allowed to warm up from -90 to 0°C , the reaction gave rise to the enyne **333** (35% yield) resulting from the cleavage of the dibromocyclopropane ring and subsequent debromination (Scheme 69) <1997JOC9039>.



Scheme 69

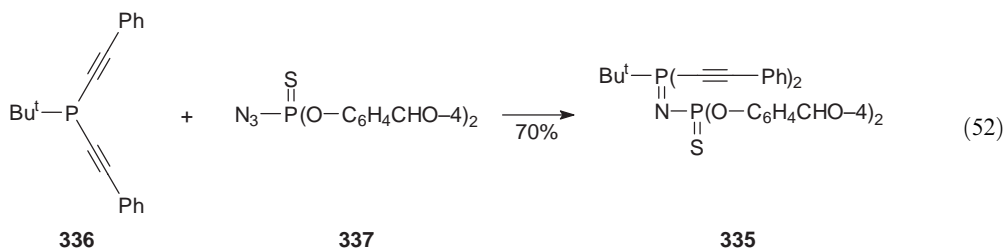
The secondary alkynylphosphine oxides (**334a–334f**) were formed in high yield during the acidic cleavage of alkynylaminophosphines (**301e–301j**) using acidic Amberlyst 15 in THF solution with water (4 equiv.) at room temperature (Scheme 70) <1995TL4421>.



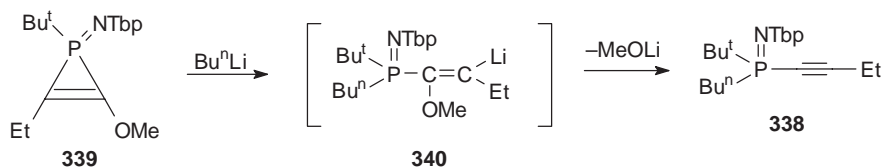
Scheme 70

2.22.2.5.2 Alkynylphosphine imides

Since 1994 only a limited number of new alkynylphosphine imides have been described. Among them is the bisalkynyl imide **335** prepared by the well-known Staudinger reaction (Equation (52)) <1999EJI601>.

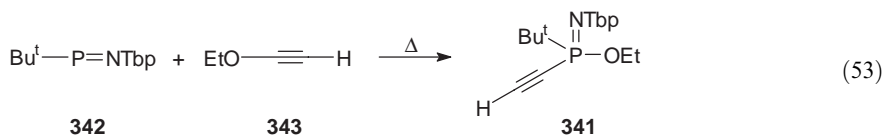


Alkenylphosphine imide **338** has been isolated as the only product when the phosphiren imide **339** was treated with BuⁿLi at room temperature (Scheme 71) <1995JOU363>.

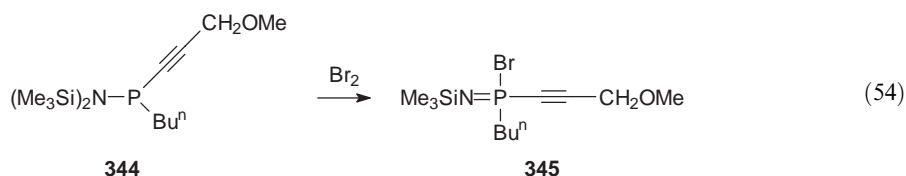


Scheme 71

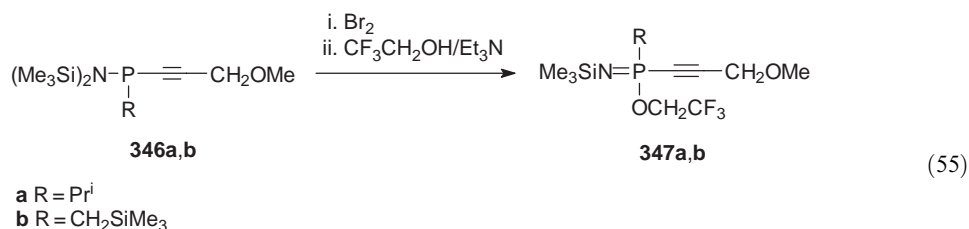
The alkynylphosphinous imide **341** was isolated (70%) when *t*-butyl *N*-[2,4,6-(tri-*t*-butyl)-phenyl]-iminophosphine **342** was heated with ethoxyacetylene **343** in polar solvents (Equation (53)) <1996JOU443>.



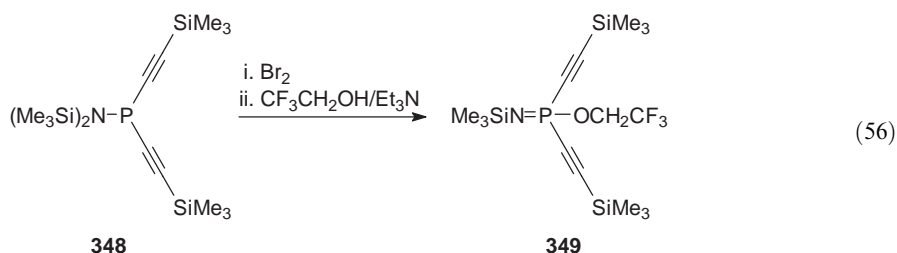
A few alkynyl pentavalent phosphorus imides have been isolated during the oxidative halogenation reactions of alkynyl(silylamino)phosphines. Thus, bromine reacted exclusively at the P(III) center of the silylphosphine **344** giving the *P*-bromophosphorane imine **345** (Equation (54)) <2002JOM223>.



It is also possible to convert the silylaminophosphines (**346a** and **346b**) directly to their *P*-trifluoroethoxy derivatives (**347a** and **347b**) in a one-pot reaction (Equation (55)) <2002JOM223>.



In a similar way, the diacetylenic phosphine **348** gave the *P*-trifluoroethoxy derivatives **349** (Equation (56)) <2002JOM223>.



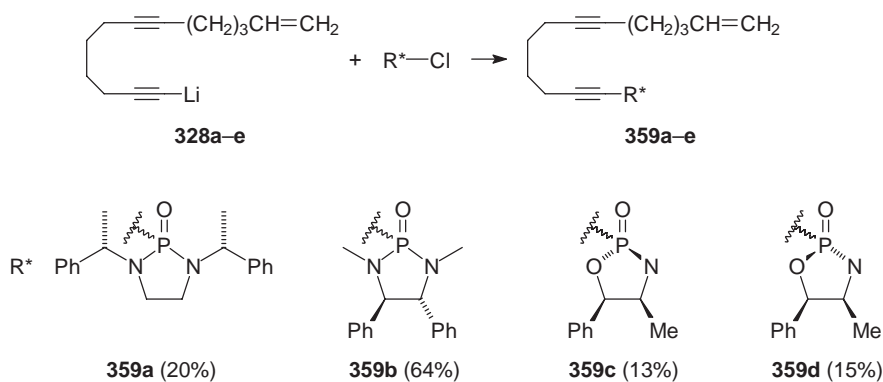
2.22.2.6 Alkynylphosphonates

Since 1994 most alkynylphosphonates have been prepared by three approaches. The first is based on the reaction of alkynylorganometallic reagents with dialkyl chlorophosphates. The second can be considered as a modification of the Michaelis–Becker reaction of an alkynyl halide with a dialkyl phosphite. The third method utilizes an elimination reaction of a substituted alkenylphosphonates.

2.22.2.6.1 From alkynyl organometallic reagents

A series of diethyl 1-alkynylphosphonates **350** was prepared in a one-pot procedure from diethyl chlorophosphate **351a** and an alkynyllithium reagent **356**, generated by reaction of 1-alkynes with BuⁿLi (Scheme 72) <1997SC3171>.

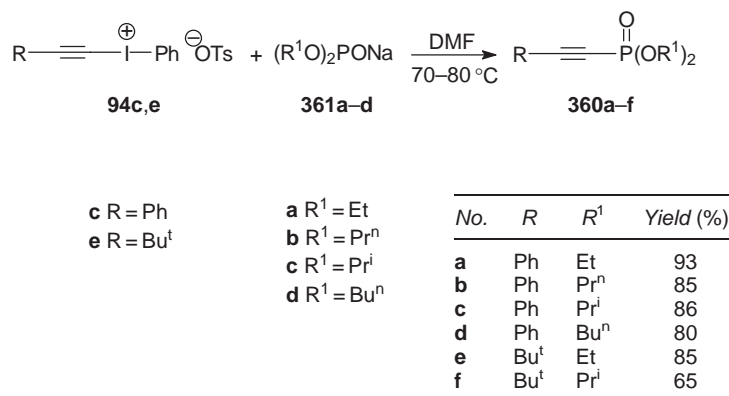
Similarly, the reaction of the alkynyllithium reagents **352** with chlorophosphates (**351a–351c**) gives the terminal carboalkoxyalkynylphosphonates **353** (Scheme 73) <1998JGU539>.



Scheme 76

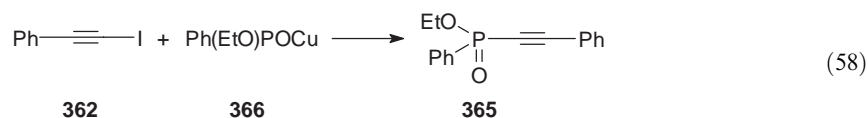
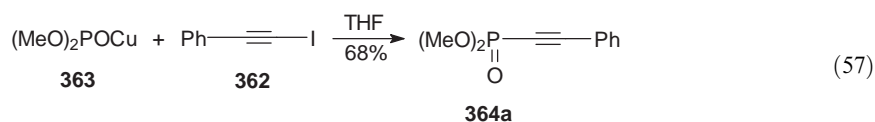
2.22.2.6.2 Alkynylation of dialkyl phosphites

A convenient procedure for the preparation of a variety of dialkyl alkynylphosphonates (**360a–360f**) involves alkynylation of dialkyl sodium phosphites (**361a–c**) with alkynylphenyliodonium tosylates (**94c–94e**) (Scheme 77) <1998SC175>.

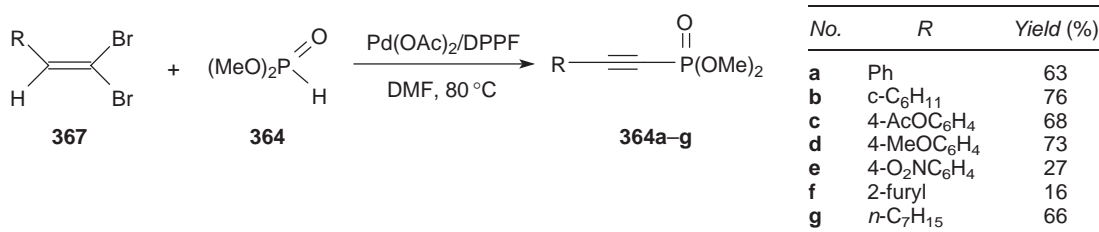


Scheme 77

The reaction of 1-iodoethynylbenzene **362** with copper dimethyl phosphite **363** using ultrasonic irradiation gives dimethyl phenylethynylphosphonate **364a** in an acceptable yield (Equation (57)) <1996TL3717>. *O*-Ethyl phenylethynylphenylphosphinate **365** was obtained in the same way (Equation (58)) <1999BCJ787>.

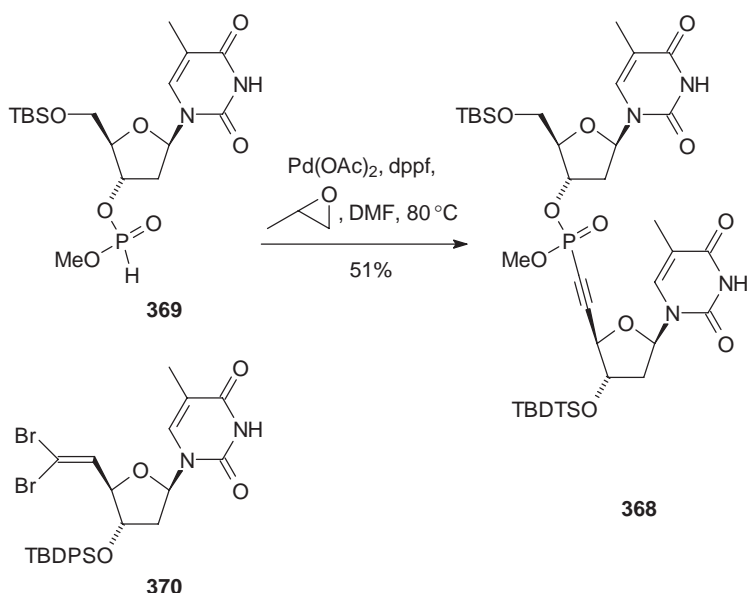


An efficient procedure for the synthesis of alkynylphosphonates (**364a–364g**) is based on the palladium-catalyzed reaction of 1,1-dibromo-1-alkenes **367** with dialkyl phosphites. In general, the best catalytic system for this conversion (Scheme 78) is Pd(OAc)₂ and DPPF <2000OL3873>.



Scheme 78

The utility of this procedure is illustrated by the formation of the alkyne-containing thymidine dimer **368** when compound **369** (1 equiv.) was allowed to react with the bromoalkene **370** under the “DMF/DPPF” coupling conditions (Scheme 79) <2000OL3873>.



Scheme 79

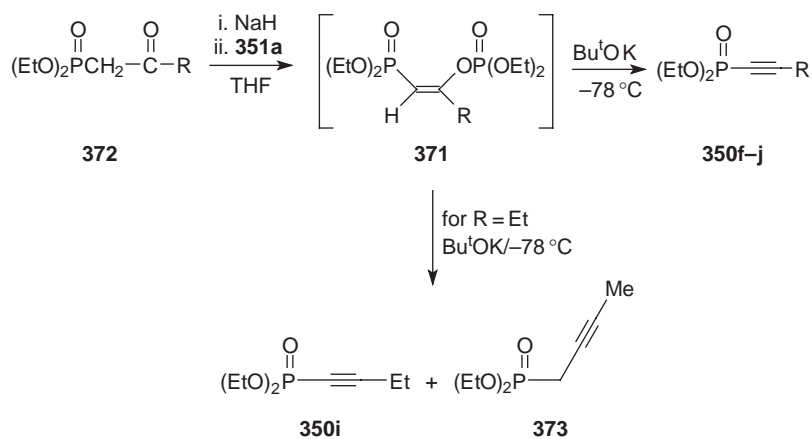
2.22.2.6.3 Elimination of alkenyl phosphonates

A series of 1-alkynylphosphonates (**350d–350j**) has been prepared by the *in situ* β -elimination of the enolphosphates **371**, which were generated by the reaction of sodium enolate of 2-oxoalkylphosphonates **372** with diethyl chlorophosphate **351a** (Scheme 80) <1996SC1563>. In the case of derivative **372e**, the reaction products underwent prototropic tautomerism to give a mixture of **350i** and propargylic phosphonate **373**.

TBAF-catalyzed elimination of an unsaturated fluoro analog of the adenine nucleotide **374** results in elimination of HBr and HF and a formal transposition of one of the 4'-fluoro atoms to the 1' position of alkene system to give fluoroalkene-ynephosphonate **375**. The reaction course is best explained by assuming the formation of a butyldiyne intermediate **376** (Scheme 81).

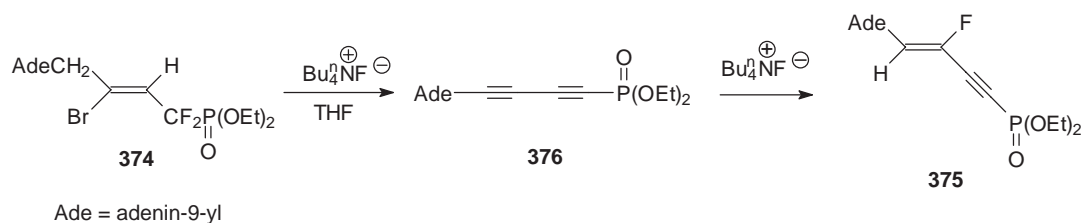
Three alkynylphosphonates (**350a**, **350f** and **350k**) were prepared from the selenoxide **377a** and the (*E*)-isomers of alkenes **377b** and **377c** as a result of the thermal *syn*-elimination of phenylselenenic acid (Scheme 82) <1995TL2871>.

β -Elimination of HCl from α -chlorovinylphosphonate intermediates **378** constitutes a key step in a convenient procedure for the synthesis of alkynylphosphonates **350** using diethyl trichloromethylphosphonate **379** as a precursor. The yield shown in Scheme 83 demonstrates the generality of this protocol <1996TL1783>.

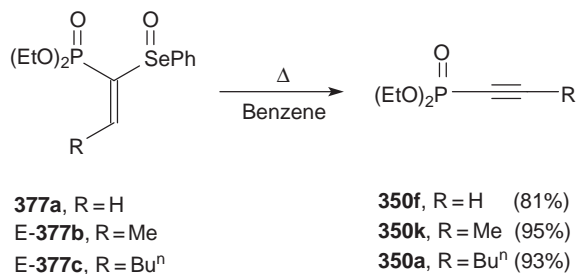


372		350	
No.	R	No.	Yield (%)
a	H	f	90
b	Ph	d	91
c	4-MeOC ₆ H ₄	g	88
d	4-ClC ₆ H ₄	h	95
e	Et	i	43
f	Pr ⁱ	j	72
g	Bu ^t	b	77

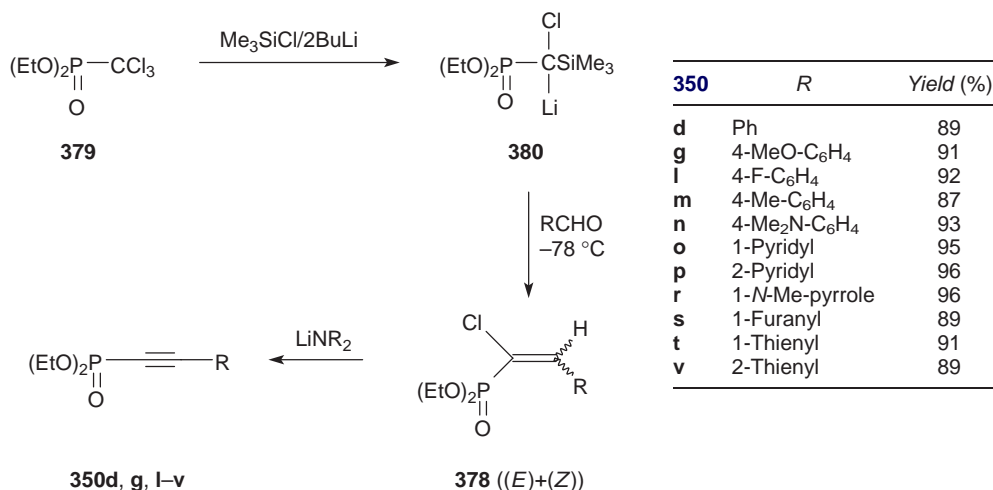
Scheme 80



Scheme 81

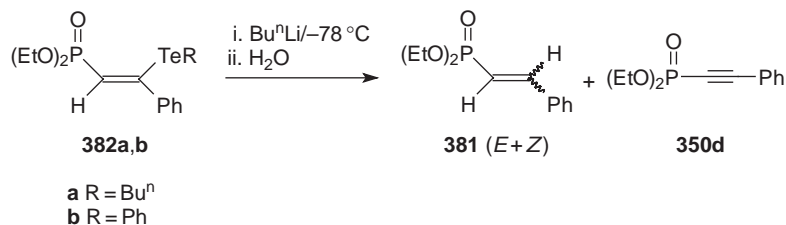


Scheme 82



Scheme 83

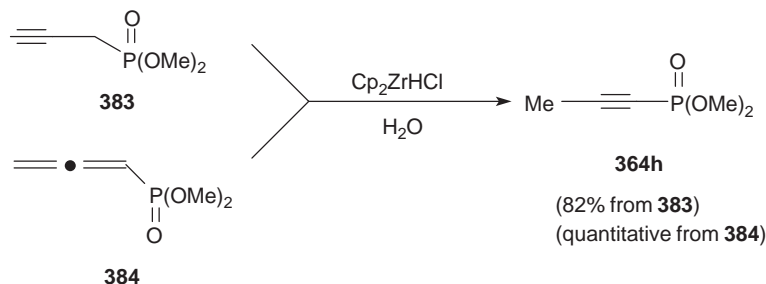
2-Phenylethynylphosphonate **350d** was formed together with (*E*)- and (*Z*)-2-phenylethenylphosphonates **381** when β -phenyltelluro-phenylethenylphosphonates (**382a** and **382b**) were treated with BuⁿLi in THF at -78°C and then with water (Scheme 84) <2000TL5103>.



Scheme 84

2.22.2.6.4 Miscellaneous methods

Dimethyl ethynylphosphonate **364h** was formed as a product of isomerization of propargylphosphonate **383** and allenic phosphonate **384** induced by Schwartz reagent (Scheme 85) <1999JOC3563>.



Scheme 85

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Biographical sketch

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2.23

Alkynylarsenic, -antimony, -bismuth, -boron, -silicon, -germanium, and Metal Compounds

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2.23.1 INTRODUCTION

For general information on the history of the literature covering these compounds up to early 1993 the reader is referred to COFGT (1995) <1995COFGT(2)1075>. This chapter takes up the literature coverage from early 1993 until late 2003 and has the same structure as the corresponding chapter in COFGT (1995), with discussion restricted to the derivatives and methods (Methods 1, 2, etc.) for which there have been significant developments. Some new methods are included and some of the titles of the previous methods have been updated to reflect subsequent progress.

2.23.2 ALKYNYLARSENIC, -ANTIMONY, AND -BISMUTH DERIVATIVES

Organoarsenic, -antimony, and -bismuth chemistry was comprehensively reviewed in <B-1994MI004> and for the period 1982–1994 by Wardell <1995COMCII(2)321>.

2.23.2.1 Toxicity, Stability, and Manipulation

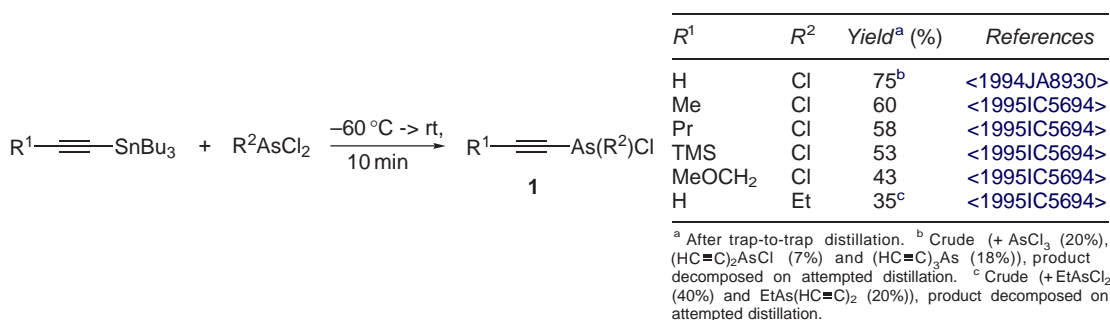
No specific further information on hazards associated with these derivatives has been reported since the publication of COFGT (1995) <1995COFGT(2)1075> but we reiterate here that these derivatives contain a very reactive alkyne group, metalloid center, and ancillary groups and are potentially hazardous and biologically active. Normal laboratory procedures preventing skin contact, inhalation, and ingestion of these derivatives must be adopted. General considerations of the hazards associated with organoarsenic, -antimony, and -bismuth compounds may be found in <B-1994MI005, B-2001MI015>.

2.23.2.2 Alkynylarsenic Compounds

Four general methods for the preparation of alkynyl arsine moieties were identified in COFGT (1995), along with a fifth method of oxidation of the arsenic center after arsenic–alkynyl bond formation <1995COFGT(2)1075>. Progress with, and refinement of, these methods are described below and the development of a sixth method, reduction of the arsenic center after arsenic–alkynyl bond formation, is described.

2.23.2.2.1 Method 1: Reaction of an arsenic halide with a metal acetylide

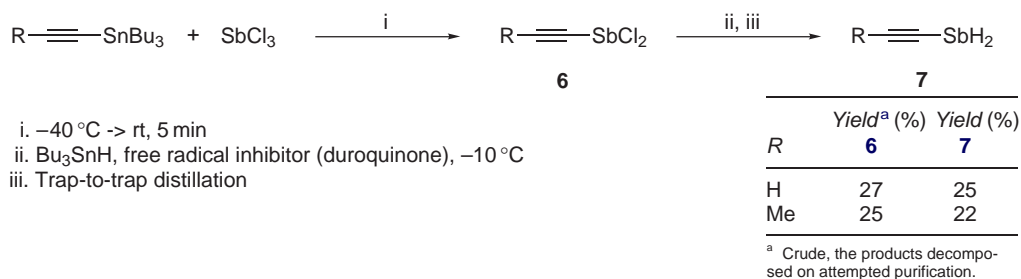
The reaction of a metal acetylide with an arsenic halide is the method used most often for the preparation of alkynylarsenic compounds. Thus a set of novel alkynyl chloroarsines **1** have been prepared by Guillemin and co-workers (Scheme 1) <1994JA8930, 1995IC5694, 2002CEJ4919>.



Scheme 1

2.23.2.2.2 Method 4: Quaternization and related reactions

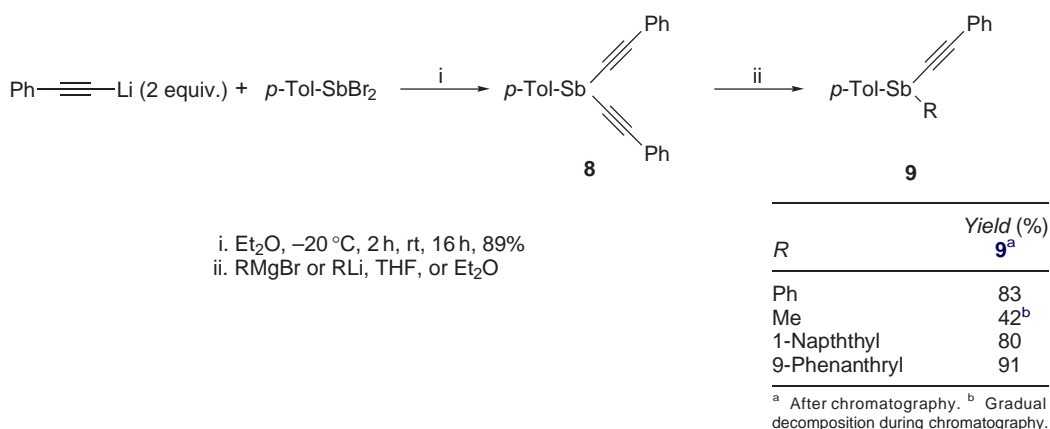
1-Alkynyl(triphenyl)arsonium tetrafluoroborate salts **4** have been synthesized from the corresponding 1-alkynyl(phenyl)iodonium tetrafluoroborates **2** and triphenylarsine, the reaction is thought to proceed via the arsonium salt **3** (Scheme 2) <1995TL261> rather than the



Scheme 5

2.23.2.3.2 Method 3: Modification of preformed alkynyl derivatives

The phenylethynyl substituents of bis-(1-phenylethynyl)-*p*-tolylstibane **8** may be sequentially displaced by Grignard and/or organolithium reagents, and thus alkynylstibanes with three different substituents **9** may be synthesized (Scheme 6). This synthetic method has not been reported with substrates other than compound **8**, which was synthesized by Method 1 <2000SL1503, 2002JOM(656)234>.



Scheme 6

2.23.2.3.3 Method 4: Quaternization and related reactions

In contrast to triphenylarsine, triphenylstibine fails to yield stibonium salts on reaction with 1-alkynyl(phenyl)iodonium tetrafluoroborates: protodeiodination occurs instead <1995TL261>.

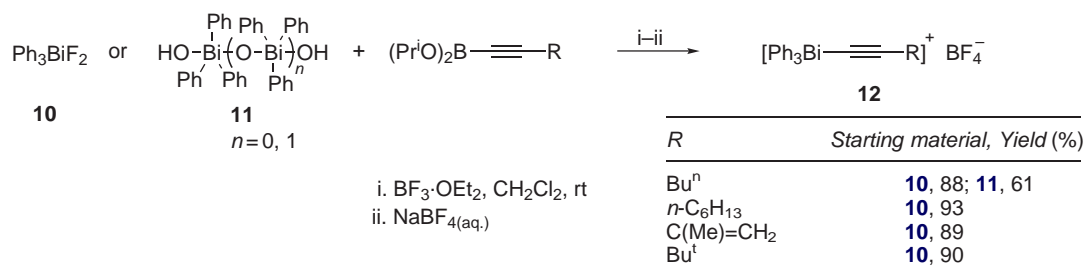
2.23.2.3.4 Method 6: Reduction at antimony

Using the same method as for the alkynylarsines **5**, Guillemin and co-workers have synthesized the alkynylstibines **7** (Scheme 5) <1995IC1466>.

2.23.2.4 Alkynylbismuth Compounds

Suzuki and co-workers have surveyed the applications of bismuth in organic synthesis, but since well-characterized alkynylbismuth compounds remain few in number they received scant mention <1997S249>. Suzuki and Matano have also edited a book entitled *Organobismuth Chemistry* <B-2001MI015>. The structural chemistry of two alkynylbismuth compounds $\{[\text{O}_2\text{S}(\text{C}_6\text{H}_4)_2]_2\text{Bi}(\text{C}\equiv\text{C}-\text{C}_6\text{H}_4-4\text{-Cl})\}$ <1992JCS(P1)1593> and $(4\text{-MeC}_6\text{H}_4)_2(\text{PhC}\equiv\text{C})\text{Bi}[\text{C}_6\text{H}_4-2\text{-}\{\text{C}(\text{CF}_3)_2\text{O}\}]$ <1993OM1857> is discussed and compared with other crystallographically studied organobismuth compounds in Breunig and co-workers' review <1999CRV3277>.

Unlike triphenylarsine and triphenylstibine, triphenylbismuthine fails to react with 1-alkynyl(phenyl)iodonium tetrafluoroborates, presumably due to its lower nucleophilicity <1995TL261>. However, alkynyltriphenylbismuthonium salts **12** may be prepared by the reaction of triphenylbismuth difluoride **10** <2000CC2233> or triphenylbismuth(V)hydroxo compounds **11** <2002S631> with alkynyl-diisopropoxyboranes in the presence of the Lewis acid boron trifluoride etherate (Scheme 7).



Scheme 7

2.23.3 ALKYNILBORON, -SILICON, AND -GERMANIUM DERIVATIVES

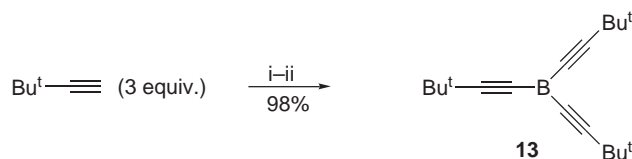
2.23.3.1 Alkynylboron Compounds

Vaultier and Carboni have reviewed the synthesis and synthetic applications of organoboron compounds in general, covering the period 1982–1994 <1995COMCII(11)191>. The Suzuki–Miyaura coupling, the palladium-catalyzed cross-coupling of an organoboron compound and an organic halide or triflate, is a powerful and widely employed method of carbon–carbon bond formation. However, alkynylboranes have been used infrequently in Suzuki–Miyaura couplings because of their high Lewis acidity and ease of hydrolysis (compared to other organoboranes) and the usual necessity of the presence of base in the coupling reaction. For reviews of the Suzuki–Miyaura coupling including discussion of alkynylboron compounds see <B-1998MI012, 1999JOM(576)147, 2002T9633, 2002TCC11, 2002JOM(653)83>. The extension of the utility of the Suzuki–Miyaura coupling has been the incentive behind many alkynylboron compound syntheses in the period 1993–2003. Negishi and Anastasia have reviewed and compared palladium-catalyzed alkynylation reactions and take the view that though results with alkynylboron derivatives are “generally satisfactory” the products of these reactions may just as readily be obtained by the Sonogashira reaction or from alkynylzinc derivatives <2003CRV1979>. The Sonogashira reaction does have some drawbacks and alkynylboron derivatives are less toxic than the organotin reagents used in Stille couplings and many are more stable than other alkynyl metal compounds. Tykwinski has written an overview of palladium-catalyzed couplings of alkynyl with vinyl or aryl species <2003AG(E)1566>.

2.23.3.1.1 Triorganoboranes

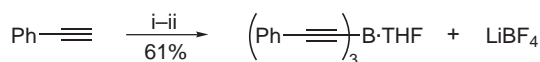
(i) Method 1: Reaction of a boron halide with a metal acetylide

The reaction of a metal acetylide with a boron halide or organoboron halide (usually a chloride) is the method used most frequently for the preparation of triorgano alkynylboron compounds. The first example of a donor-free tris-(alkynyl)borane **13** has been thus prepared (Scheme 8) and its X-ray crystal structure and those of three adducts were determined. Attempts to synthesize other tris-(alkynyl)boranes using the corresponding terminal alkynes failed <2002EJI2069>. All previous examples of tris(alkynyl)boranes are stabilized by donor ligands, e.g., (Equation (1)) <1997CC1797>.



- i. BuLi (3 equiv.), pentane, $-20^\circ\text{C} \rightarrow \text{rt}$, 1 h;
 ii. BCl_3 , $-78^\circ\text{C} \rightarrow \text{rt}$, 12 h

Scheme 8

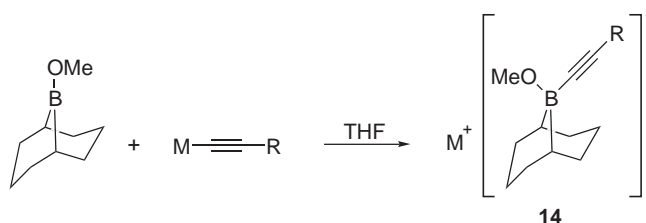


(1)

- i. BuLi, hexanes, THF, toluene, -78°C , 10 min;
 ii. $\text{BF}_3 \cdot \text{OEt}_2$, $-78^\circ\text{C} \rightarrow \text{rt}$

(ii) Method 3: Reaction of an alkoxy-, thio-, or amino-dialkylborane with alkynyl metal reagents

The addition of alkynyllithium reagents to methoxydialkylboranes yields a borate complex that may be converted into an alkynyldialkylborane on treatment with a Lewis acid <1977JOM(131)163, 1995COFGT(2)1075>. Soderquist and co-workers used this method of Brown and Sinclair to synthesize the stable methoxy(alkynyl)borate complexes **14** (Scheme 9), which may be used without isolation as Suzuki–Miyaura coupling partners <1995TL2401>. At about the same time, Fürstner and Seidel also developed this mode of Suzuki–Miyaura coupling and, furthermore, demonstrated that alkynylsodium and -potassium reagents are suitable starting materials (Scheme 9) <1995T11165, 1996LA2107, 2001SL290>. Sodium acetylide does not participate well in this methoxy(alkynyl)borate complex generation—Suzuki–Miyaura coupling sequence; this limitation may be overcome by the replacement of 9-methoxy-9-borabicyclo[3.3.1]nonyl (9-BBN) with trimethyl borate, in which case ligand scrambling occurs in the borate complex <1996LA2107>. Sonogashira coupling of bifunctional compounds suffers from the problem of polymerization of the bisalkynyl component, a problem that may be avoided by Suzuki–Miyaura coupling of a methoxy(alkynyl)borate complex (**14**; $\text{R} = 3\text{-ethynyl-5-heptyloxyphenyl}$) <2003SC3317>.

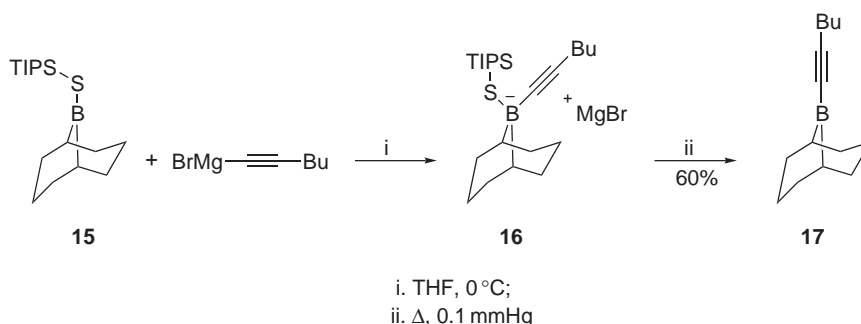


$\text{M} = \text{Li, Na, K}$
 $\text{R} = \text{alkyl, alkenyl, (substituted)phenyl, SiMe}_3$

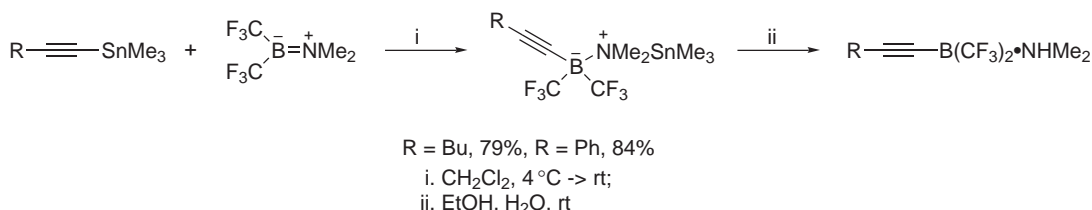
Scheme 9

This method (Scheme 9) of methoxy(alkynyl)borate complex **14** generation fails with simple Grignard reagents, so Soderquist and de Pomar have developed an analogous method using 9-(triisopropylsilyl)thio-9-borabicyclo[3.3.1]nonane **15** which succeeds with various alkylolithium and Grignard reagents including that shown in Scheme 10; the borate complex **16** yields the borane **17** on heating under vacuum <2000TL3537>.

Bürger and co-workers have investigated the novel reactivity of dimethylaminobis-(trifluoromethyl)borane and have discovered that it reacts with alkynyltin reagents to yield the dimethylamine adducts of alkynylbis-(trifluoromethyl)boranes as shown in Scheme 11 <1996JOM(524)225> i.e., an amino variant of Method 3 in which the Lewis base adduct product is not decomplexed.



Scheme 10

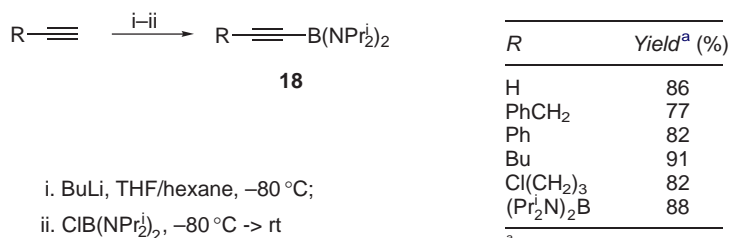


Scheme 11

2.23.3.1.2 Organoboranes with heteroatoms σ -bonded to boron

(i) Method 5: Reaction of an alkynyl metal with chloroaminoborane

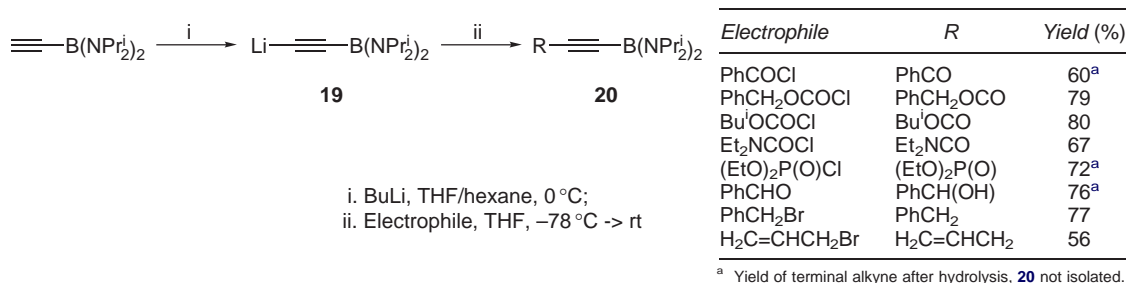
Diaminohaloboranes react with alkynyl metals to yield monoalkynyldiaminoboranes by halide displacement, i.e., the amino substituents are not displaced (cf. alkoxy substituents, Method 6 below) [<1995COFGT\(2\)1075>](#). Thus Vaultier and co-workers synthesized 1-alkynyldis-(diisopropylamine)boranes **18** as shown in [Scheme 12](#) [<1996S45>](#). Ethynylbis-(diisopropylamine)borane (**18**; R = H) may also be prepared in 60% yield from sodium acetylide and chlorobis-(diisopropylamine)borane [<1993CB1593>](#) and it was demonstrated that lithium bis-(diisopropyl)aminoboracetylide **19** may be converted into other alkynylboranes **20** by reaction with electrophiles ([Scheme 13](#)). Lithium bis-(diisopropyl)aminoboracetylide **19** does not over-add to acid chlorides, but does not react at all with alkyl halides. Hydrolysis of the products **20** with dilute hydrochloric acid yields the terminal alkynes, and compound **19** is therefore a lithium acetylide equivalent [<1997TL8863>](#).



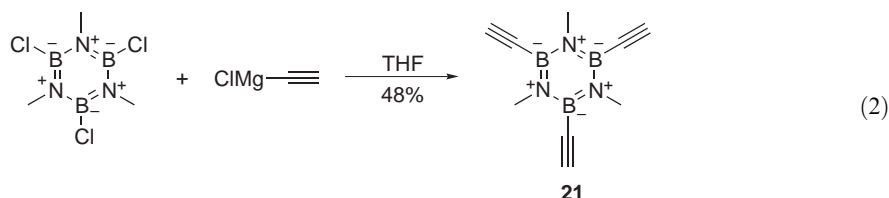
^a After bulb-to-bulb distillation.

Scheme 12

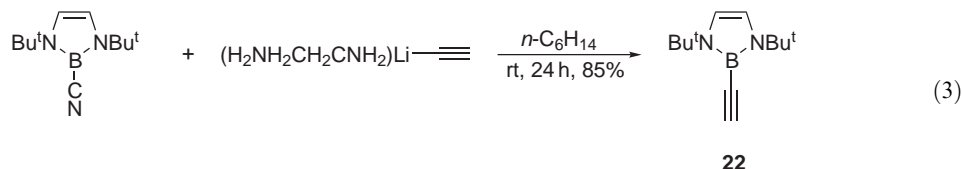
The air-stable trialkynyldiazaborane **21** has been synthesized by this method ([Equation \(2\)](#)) and used in polymer synthesis [<2001PS231>](#).



Scheme 13

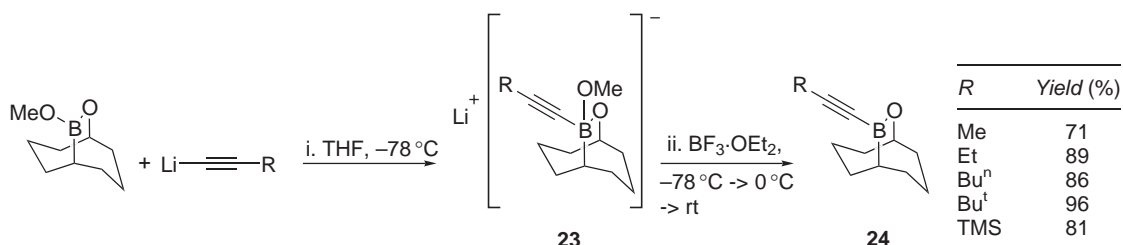


A variant of this method using cyanide as the leaving group was required for the synthesis of 2-ethynyl-1,3,2-diazaborole **22** (Equation (3)) as the analogous reaction with the 2-bromo-1,3,2-diazaborole starting material failed <1999EJI491>.



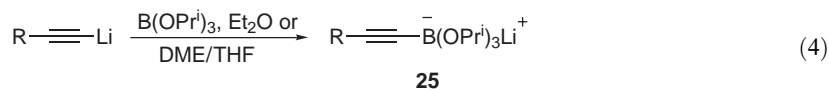
(ii) *Method 6: Reaction of an alkynyl metal with a borate, an alkynyl sodium with a chloroborate, and alkynyldialkoxyboranes from alkynyldiaminoboranes*

Soderquist and co-workers have used a variant of Brown and co-workers' method (described in COFGT (1995) <1995COFGT(2)1075>) in which an alkynyllithium reacts with a boronic ester to yield an alkynyl borinate after dealkoxylation. Thus they synthesized, in a one-pot procedure (Scheme 14), the alkynyl borinates **24**, which are free of coordinated tetrahydrofuran (THF), oxidatively and thermally stable but susceptible to hydrolysis on prolonged (8 h) exposure to an open atmosphere <1995TL6847>. By way of comparison, the preparation of the alkynyl borinate (**24**; R = Me) from the corresponding *B*-1-propynyl-9-BBN-THF complex (prepared according to method 3) by oxidation with trimethylamine *N*-oxide in chloroform (a general procedure for *B*-substituted 9-BBN derivatives <1986JOC1330>) proceeded in 68% yield over the two steps. Soderquist and co-workers consider the synthesis of borinate **24** shown in Scheme 14 to be operationally simpler <1995TL6847>. Alkynyl borinate complexes **23** were used without isolation as Suzuki–Miyaura coupling partners <1995TL6847>.

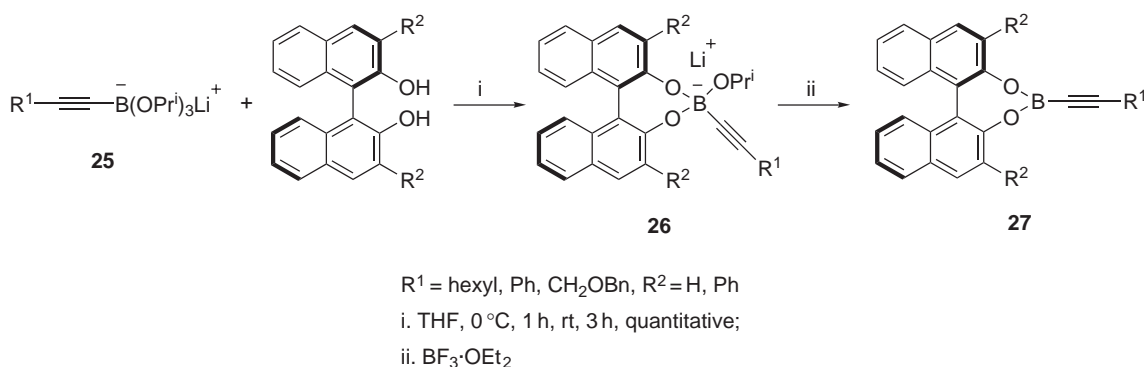


Scheme 14

Alkynyl borate complexes **25** (Equation (4)), synthesized by this method of Brown and co-workers are stable to refrigerator storage and have also been developed as Suzuki–Miyaura coupling partners, and may be so used with or without isolation <2000OL3559, 2000TL8513>.

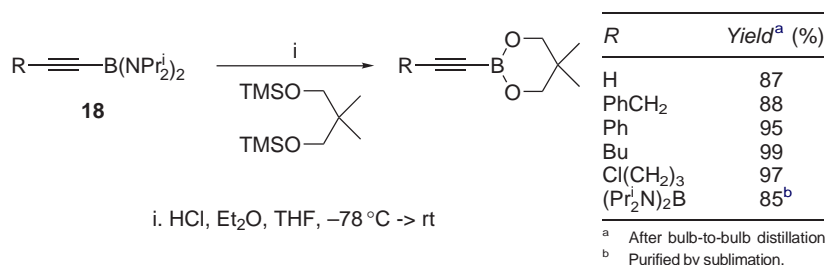


Simple transesterification of alkynyldialkoxyboranes is not a workable process (leading for example to alkynyl–boron bond cleavage to form the free terminal alkyne) <1988TL2631> and modifications of Brown and co-workers' archetypal method have been developed. Chong and co-workers' route to alkynyl (1,1'-binaphthoxy)boronates **27** is shown in Scheme 15 and carries out a transesterification of the alkynyl borate complex **25**. Efforts to synthesize the boronates **27** from the mixed binaphthyl isopropoyl borates failed at the stage of mixed borate preparation. Attempts to isolate and characterize boronates **27** were only partially successful, but nuclear magnetic resonance data is consistent with the structures **27**. These alkynyl boronates **27** may be used *in situ* to transfer alkynyl groups to enones in a 1,4 manner with high enantioselectivity (the precursor borates **26** are unreactive toward enones) <2000JA1822>.



Scheme 15

Monoalkynyldialkoxyboranes may be synthesized in moderate yield by the direct reaction of an alkynyl metal with a dialkoxyhaloborane, but the alkoxy substituents may also be displaced (cf. Method 5) <1995COFGT(2)1075, 2001EJI373>. However, alkynyldiaminoboranes do react at boron with preservation of the alkynylborane moiety under anhydrous acidic conditions (in some cases rigorous exclusion of water is necessary as both starting materials and products are very susceptible to hydrolysis (Scheme 16) <1996S45>), which provides a convenient route to alkynyldialkoxyboranes (Scheme 17) <2001EJI373>.



Scheme 16

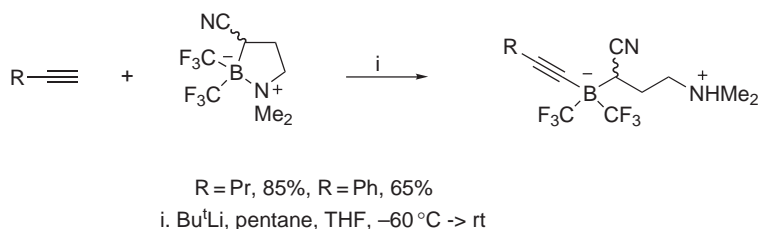


Scheme 17

2.23.3.1.3 Tetraorganoborates

(i) Method 8: Reaction of Lewis-base adducts with alkynyl metal reagents

An unusual example of this method, wherein the Lewis base is internal is shown in Scheme 18. The mechanism of this reaction is thought to proceed via an alkylideneborate anion which is stabilized by the two trifluoromethyl groups bonded to boron <1999JFC(98)143>.



Scheme 18

2.23.3.1.4 Organoborates with heteroatoms σ -bonded to boron

Alkynyl borates (other than tetraorganoborates) may be regarded as adducts of alkynylboranes, and are so classified herein and in COFGT (1995) <1995COFGT(2)1075> for such compounds from which the corresponding boranes have been synthesized (cf. Methods 3 and 6). However, alkynyl borates have also been studied as Suzuki–Miyaura coupling partners <1999JOM(576)147, 2002T9633, 2002JOM(653)83> (cf. Methods 3 and 6) and alkynyl trifluoroborates **28** have been successfully developed primarily for this purpose by Genêt and co-workers <1999EJO1875> and Molander and co-workers <2002JOC8416>.

(i) Method 10: Reaction of alkynyl metals with trimethyl borate followed by fluoride–methoxy exchange

Potassium alkynyl trifluoroborates **28**, which are indefinitely stable in air (unlike most alkynylboranes), may be prepared by boronation of alkynyllithiums followed by *in situ* treatment with aqueous potassium hydrogen difluoride (Scheme 19) <1999EJO1875, 2002JOC8416>. It is noteworthy that silyl-protecting groups endure this process, despite the presence of a fluoride source, and that the reaction fails with alkynes substituted with basic heterocycles, nitriles, or esters. These potassium alkynyl trifluoroborates **28** are isolable and characterizable compounds, in contrast to the corresponding lithium salts, which are (one of several) putative intermediates in the synthetically useful boron trifluoride-mediated additions of alkynyllithiums to various electrophiles (see <2000JA11084, 2003SL937> and references therein). Despite careful studies of the complex mixtures produced from boron trifluoride and alkynyllithiums, in the early 2000s, their precise nature remains unclear <1984TL2411, 2000JA11084>. Wheatley and co-workers have suggested that their crystallized complex (Equation (1)) is the true intermediate in such reactions <1997CC1797>, but this hypothesis remains untested.

		<i>R</i>	Yield (%)	References
$\text{R}-\text{C}\equiv\text{C}-\text{H} \xrightarrow{\text{i-iii}} \text{R}-\text{C}\equiv\text{C}-\text{BF}_3\text{K}^+$ <p style="text-align: center;">28</p> <p>i. BuLi, -78°C, THF, 1 h; ii. B(OMe)₃ (1.5 equiv.), -78°C, 1 h, -20°C, 1 h; iii. KHF₂ (6 equiv.), H₂O, -20°C, 1 h, rt, 1 h</p>		Bu	78	<1999EJO1875> <2002JOC8416>
		Octyl	74	<2002JOC8416>
		Ph	78	<2002JOC8416>
		Ph(CH ₂) ₂	70	<2002JOC8416>
		Cl(CH ₂) ₃	80	<2002JOC8416>
		H ₂ C(Me)C	85	<2002JOC8416>
		TBDMSO(CH ₂) ₂	66	<2002JOC8416>
		TMS	77	<2002JOC8416>
		Et ₃ Si	88	<1999EJO1875>

Scheme 19

2.23.3.2 Alkynylsilicon Compounds

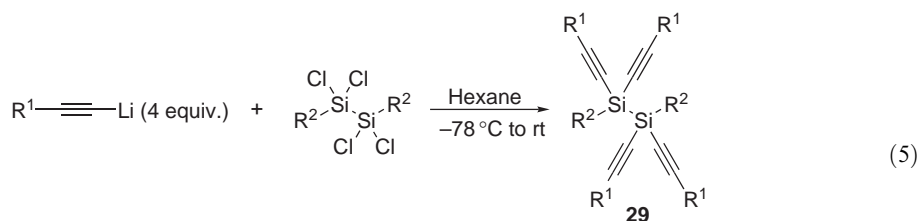
Thousands of alkynylsilicon compounds have been reported, the majority of which are trialkylalkynylsilanes in which the trialkylsilyl group serves as a protecting group for a terminal alkyne (cf. Section 2.23.3.3), and was introduced by Method 1 or 4. This aspect of alkynylsilicon chemistry is reviewed in Greene and Wuts' authoritative book on protecting groups <B-1999MI013> and further discussion of 1-triisopropylalkynes is to be found in Rücker's review of the roles of the triisopropyl group in organic chemistry <1995CRV1009>. Organosilane chemistry in general was reviewed for the period 1982–1994 by Armitage <1995COMCII(2)1> and Colvin <1995COMCII(11)313>.

Four general methods for the preparation of alkynylsilicon compounds were identified in COFGT (1995) <1995COFGT(2)1075>. Examples of the most important methods (1 and 4) are described below, along with the development of three new methods, which, in the early 2000s, are yet to find widespread application.

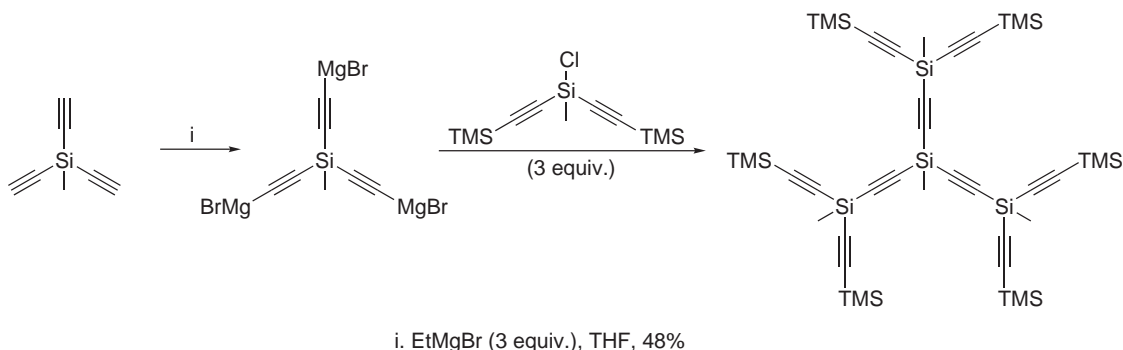
2.23.3.2.1 Method 1: The reaction of an organosilyl halide with an alkynyl metal derivative

As for most of the compounds discussed in this chapter, this is the standard method of synthesis and continues to be extensively employed. Alkynyllithiums are the reagents used most frequently, with alkynylmagnesium reagents also being used regularly. A detailed preparation of ethynyltrimethylsilane from ethynylmagnesium bromide has been published <1999S1727>. Both alkynyllithium and alkynylmagnesium reagents are highly nucleophilic but the less reactive alkynylstannanes have also been used <1995COFGT(2)1075>, as have copper(I) alkynides (in acetonitrile at 100°C with added zinc, tetramethylethylenediamine [1,2-bis(dimethylamino)ethane] or triphenylphosphine), which are sufficiently chemoselective reagents to tolerate the presence of chloro or hydroxyl groups in the alkynide moiety <1996CL379>. However, *in situ* trimethylsilylation of alkynylzinc species has been found to be accompanied by significant levels of alkyne reduction to the corresponding alkenes <2000JOM(601)341>.

Alkynylsilicon compounds are objects of study in their own right. For example, the first tetraalkynyldisilanes **29** were synthesized from alkynyllithiums (Equation (5)) <2003EJI66>, and alkynylmagnesiums have been employed to synthesize silylacetylene dendrimers, part of the synthesis of one of which is shown in Scheme 20 <1999CC1799>.



R¹ = Ph, Bu^t, TMS, Pr, R² = CH(TMS)₃, 62–78%



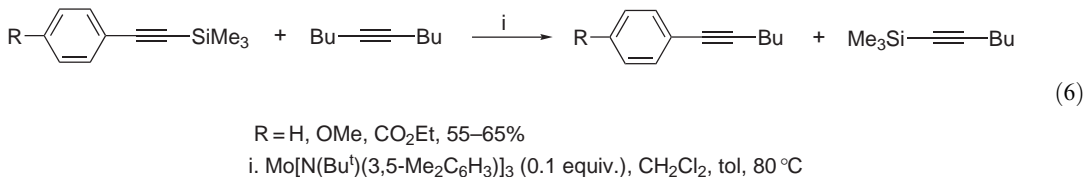
Scheme 20

2.23.3.2.2 Method 4: Modifications of alkynyl silanes

Suitable ethynylsilanes may be converted into metal silylacetylides and reacted with electrophiles to introduce the alkynylsilane moiety, as described in COFGT (1995) <1995COFGT(2)1075>. Applications of lithium (trimethylsilyl)acetylide, which is the commonest of these reagents and is commercially available, have been reviewed <B-1995MI007>. Similarly, 3-lithio-1-triisopropylsilyl-1-propyne is a useful reagent for the introduction of a 1-silyl-1-propynyl moiety <B-1995MI007>.

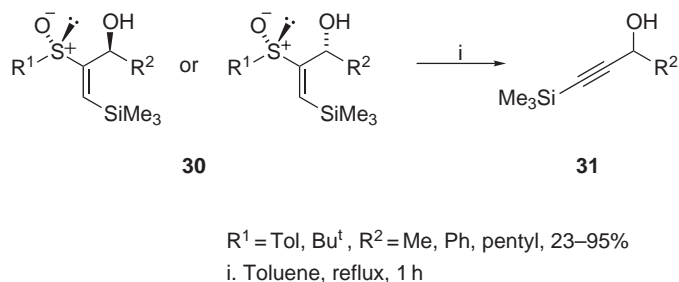
Cross-coupling of suitable ethynyl silanes also provides a convenient means of introducing an alkynyl silane moiety, as discussed by Negishi and Anastasia in a review <2003CRV1979>, and the specific case of trimethylsilylacetylene has been reviewed <B-1995MI007>. Silicon-based cross-couplings (Hiyama couplings) have been an area of intense study in the period 1993–2003. It is noteworthy that cross-couplings of alkynylsilicon compounds (including alkynyl silanes) with loss of the silicon group have also been developed, some of which use activators to generate a hypervalent silicon species *in situ* <B-1998MI010, 2002TCC61, 2003CRV1979>.

Intriguingly, despite the dramatic growth in the applications of alkene and alkyne metathesis over the decade 1993–2003, alkyne cross-metathesis is seemingly yet to be used for the incorporation of alkynylsilicon groups (or the other subjects of this chapter), although initial results in this area have been reported (Equation (6)) <2001OL221>.



2.23.3.2.3 Method 5: Desulfinylation of 2-trialkylsilyl vinyl sulfoxides

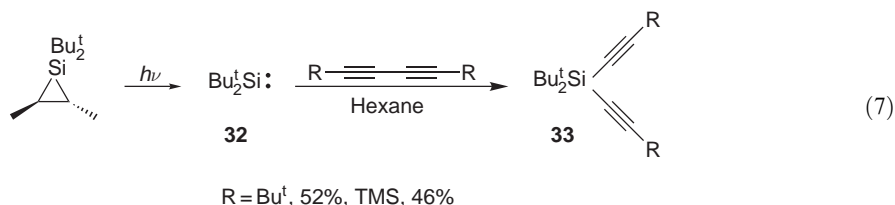
During a study of the preparation of enantiomerically pure propargylic and allylic alcohols, Toru and co-workers discovered that the thermal treatment of 2-trialkylsilyl vinyl sulfoxides (**30**, either diastereomer) caused elimination of sulfenic acid to give the trimethylsilylpropargylic alcohols **31** in high enantiomeric excess (Scheme 21) whereas treatment with base resulted in desilylsulfinylation <2002JOC640>.



Scheme 21

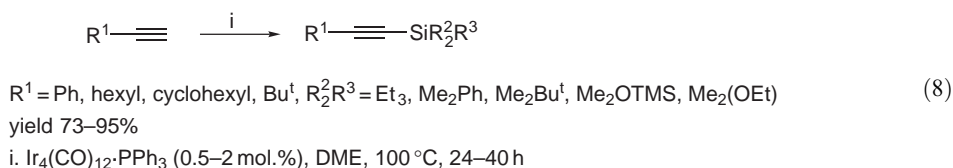
2.23.3.2.4 Method 6: From silylenes

Silylenes (silanediyls) ($R_2Si:$) may be produced by photolysis of appropriate precursors and are highly reactive intermediates that undergo numerous reactions. Silylenes with bulky substituents will undergo smooth reactions to generate cycloaddition, insertion, and rearrangement products with the outcome of their reactions being determined by subtle factors, such as the nature of their precursor and duration of photolysis. Thus, alkynyl silanes **33** have been obtained by the insertion of the silylene **32** into the central C—C bond of diynes (Equation (7)) or by rearrangement of the silacyclopentene products from diynes <1999EJ12301>.



2.23.3.2.5 Method 7: Dehydrogenative silylation of terminal alkynes

Dehydrogenative silylation of terminal alkynes with hydrosilanes proceeds in the presence of an iridium catalyst as shown in (Equation (8)). The reaction (formally) evolves molecular hydrogen which must be scavenged *in situ* for optimum yield of the alkynylsilane product. This may be achieved by use of a second equivalent of alkyne starting material or addition of a sacrificial alkyne or alkene <2000TL907>.

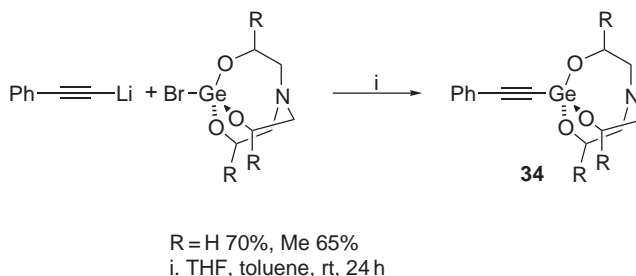


2.23.3.3 Alkynylgermanium Compounds

Organogermanium chemistry was reviewed for the period 1982–1994 by Riviere and co-workers <1995COMCII(2)137> and comprehensively in <B-1996MI008, B-2002MI016>, which include discussions of the compounds' biological activity <B-2002MI017>.

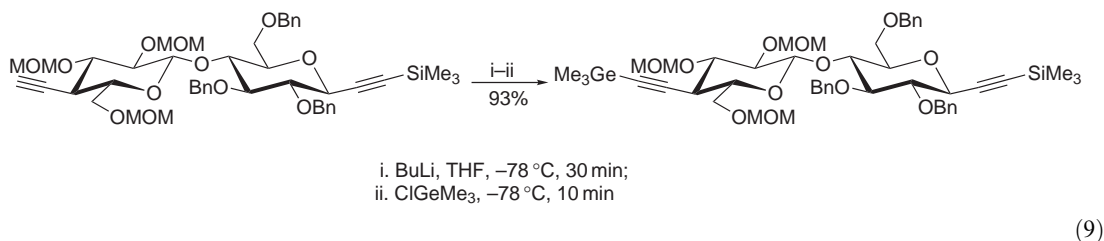
2.23.3.3.1 Method 1: Reaction of an organogermanium halide with a metal acetylide

The alkynylgermatranes **34** (the chemistry of which is discussed below) may be synthesized using this general method as shown in Scheme 22 <2001JOM(627)1>.



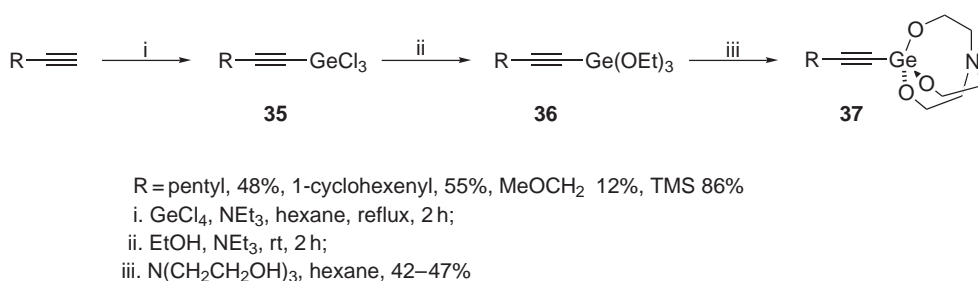
Scheme 22

Vasella and co-workers have developed the trimethylgermyl group as an alkyne-protecting group that is orthogonal to the more commonly employed trimethylsilyl group <1996HCA255, 1996HCA1279, 1996TL7959, 1997HCA1027, 1997HCA2215, 1998HCA2157>. The trimethylgermyl group may be introduced by the most frequently used method of alkynylgermanium compound synthesis, i.e., reaction of a magnesium <1997HCA1027> or lithium acetylide with chlorotrimethylgermane (Equation (9)) <1996HCA1279>. The trimethylgermyl group is best removed without any protodesilylation by treatment with a catalytic quantity of copper(I) bromide in the presence of methanol or water <1996TL7959> and may also be selectively removed by acidolysis <1996HCA1279>. Selective bromo- or iododegermylation is achieved with *N*-bromosuccinimide in the presence of a catalytic amount of copper(I) bromide or iodide in acetone <1996HCA1279, 1997HCA1027>. Conversely, treatment with potassium or cesium fluoride or potassium carbonate accomplishes selective protodesilylation <1996TL7959, 1997HCA1027>.



2.23.3.3.2 Method 2: Condensation of sufficiently acidic terminal alkynes

The synthesis and chemical properties of alkynylgermatranes **37** has been a subject of study in the period 1993–2003. Alkynylgermatranes **37** may be synthesized in a one-pot procedure that avoids isolation of the hydrolytically unstable intermediate trichloro- and triethoxygermanes **35** and **36** (Scheme 23). Treatment of the terminal alkyne with tetrachlorogermane and triethylamine yields the alkynyltrichlorogermanes **35** <1984JGU410>, which is followed by modification of the resultant alkynylgermane <2003EJI3139>. These species also react with organometallic nucleophiles such as Grignard reagents to yield other alkynylgermanes <1998OM1762>. The atrane framework of 1-(phenylethynyl)germatrane (**34**; R = Me) has also been synthesized in 94% yield by reaction of (**35**; R = Ph) with an organotin derivative of a tris-(2-hydroxyalkyl)amine [N(CH₂CHMeOSnEt₃)₃] <2001JOM(627)1>. The internal coordination of nitrogen to germanium in alkynylgermanes increases their reactivity in palladium-catalyzed cross-couplings <2002OM5911, 2003TL451>. Other aspects of their reactivity have been studied <2001JOM(627)1, 2003EJI3139>.



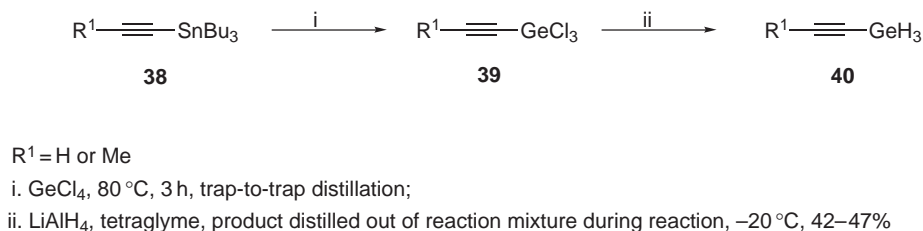
Scheme 23

2.23.3.3.3 Method 3: Modification of preformed alkynylgermanes

Further to the variety of modification methods described in COFGT (1995) <1995COFGT(2)1075>, cross-coupling of ethynyltrimethylgermane with aryl or vinyl halides under Sonogashira conditions (Pd(Ph₃)₄, CuI) provides more complex alkynylgermanes <1996TL7959>.

Guillemin and co-workers have interconverted alkynylgermanes (isolated by cold trap techniques) in order to access primary alkynylgermanes **40** (Scheme 24). The starting

alkynyltrichlorogermanes **39** were obtained by Method 1 from the alkynyltrialkylstannanes **38**. Chemoselective reduction gave the primary alkynylgermanes **40**, which were characterized at low temperature ($<-50^{\circ}\text{C}$) [<1995CC699, 1998JOM\(570\)175>](#).



Scheme 24

2.23.4 ALKYNYL METAL DERIVATIVES

As can be seen throughout this and the corresponding chapter in COFGT (1995) [<1995COFGT\(2\)1075>](#), alkynyl metal derivatives, especially alkynyllithiums and alkynylmagnesiums, are exploited extensively in the synthesis of other alkynyl compounds. The standard method of preparation of alkynyllithium compounds is by treatment of a terminal alkyne with *n*-butyllithium. Alkynylmagnesium compounds are best prepared by treatment of a terminal alkyne with an *n*-alkyl Grignard reagent. The definitive texts on organolithium and organomagnesium reagents remain those by Wakefield [<B-1988MI001, B-1995MI006>](#). Plenty of examples of the generation and applications of these species may be found throughout these chapters, and alkynylmagnesiums may also be employed in cross-couplings for the incorporation of the alkynyl group in “less demanding cases” [<2003CRV1979>](#). The reagents lithium acetylide, propynyllithium, lithium (trimethylsilyl)acetylide, 1-lithio-3-trimethylsilyl-1-propyne, lithium chloroacetylide, dilithium acetylide, 1,3-dilithiopropyne, ethynylmagnesium bromide (a detailed description of the preparation of which has been described [<1999S1727>](#)), and propynylmagnesium bromide have been reviewed [<B-1995MI007>](#).

The methods of preparation of alkynyl metal derivatives described in COFGT (1995) are, in general, most satisfactory [<1995COFGT\(2\)1075>](#) and there has been little incentive for the development of new methods. Hence there are few new methods to be described herein. The new methods that have been developed in the period 1993–2003, either generate and use the alkynyl metal species *in situ* without isolation or characterization (other than structural studies, which are adequately described in the reviews cited) or, better still, are catalytic in metal.

Long and Williams have reviewed the synthesis and applications of transition metal alkynyl σ complexes; of the metals covered in this chapter, only copper and mercury are discussed therein [<2003AG\(E\)2586>](#).

2.23.4.1 Alkynylcopper Compounds

Organocopper reagents in organic synthesis is the subject of a book edited by Taylor [<B-1994MI002>](#), and organocopper chemistry in general was reviewed for the period 1982–1994 by van Koten and co-workers [<1995COMCII\(3\)57>](#). Long and Williams’ review discusses briefly the chemistry of alkynylcopper compounds [<2003AG\(E\)2586>](#).

Hosomi and co-workers and Mori and co-workers have discovered that 1-trimethylsilylalkynes transfer their alkynyl group to copper (i.e., direct conversion of alkynylsilane to alkynylcopper(I) species) by treatment with copper(I) chloride in anhydrous dimethylformamide (DMF) or *N,N'*-dimethylimidazolidinone (DMI) at 80°C . The reaction is thought to proceed via a copper–alkyne π -complex and to yield the species $[\text{Cu}_2\text{Cl}(\text{C}\equiv\text{CPh})]_n$ from 1-phenyl-2-trimethylsilyl-1-ethyne [<1997TL3977, 2001JOM\(620\)282>](#). Such species thus prepared undergo a range of reactions: (i) with acyl halides they yield alkynyl ketones, and a version of this sequence catalytic in copper(I) chloride was developed and demonstrated for a range of 1-trimethylsilylalkyne substrates [<1997TL3977>](#); (ii) under aerobic conditions they undergo oxidative (Glaser) coupling to yield diynes [<2000JOC1780, 2001JOM\(620\)282>](#); and (iii) when formed in the presence of a palladium

catalyst they are successful cross-coupling partners in what is a modified Sonogashira coupling (a “sila-Sonogashira” coupling), also catalytic in copper(I) chloride <1997CL1233, 2000JOC1780>.

The Sonogashira coupling, which is catalytic in copper(I), is the most widely used palladium-catalyzed alkynylation reaction. In it an alkynylcopper(I) species is generated *in situ* from a terminal alkyne and a copper(I) salt (usually the iodide). Modifications of this classical method have been made, e.g., as discussed above <2003AG(E)1566>. Reviews of the Sonogashira reaction have been published <B-1994MI003, B-1998MI011, 2002JOM(653)46, 2003CRV1979>. Siemsen and co-workers have reviewed alkyne couplings (i.e., Glaser coupling and related methods), many of which involve *in situ* alkynylcopper(I) species <2000AG(E)2632>.

2.23.4.2 Alkynylzinc Compounds

Organozinc chemistry in general was reviewed for the period 1982–1994 by Knochel <1995COMCII(11)159>, who also co-edited a book devoted to the subject <B-1999MI014> and co-wrote an earlier review <1993CRV2117>.

Negishi is the principal exponent of the use of alkynylzinc salts in cross-couplings for the introduction of alkynyl groups. He regards this method (Negishi coupling) as superior to the other available options in most contexts, and has conducted a set of comparison experiments <1997JOC8957, 2000OL3687, 2003OL1597> (for a detailed comparison of the cross-coupling alkynylation methods in all contexts see <2003CRV1979>). The alkynyl zinc salts used are usually halides (bromides) generated *in situ* by the traditional method (from alkynyllithium or -magnesium reagents).

Alkynylzinc triflates are generated from the combination of zinc(II) triflate, a terminal alkyne, and a tertiary amine. Carreira and co-workers have collected spectroscopic evidence for the (reversible) generation of these alkynylzinc salts, which have been exploited in asymmetric synthesis (in the presence of a chiral ligand and electrophilic substrate such as an aldehyde) in protocols that are usually catalytic in zinc <2000ACR373>.

2.23.4.3 Alkynylmercury Compounds

WARNING: As noted in COFGT (1995) <1995COFGT(2)1075>, all organomercury compounds should be treated as being extremely toxic and handled and destroyed appropriately.

Organomercury chemistry in general was reviewed for the period 1982–1994 by Larock <1995COMCII(11)389> and alkynylmercury compounds are discussed briefly in Long and Williams' review <2003AG(E)2586> and a review by Mingos and co-workers on alkynyl complexes of group 11 and 12 metals <2002JOM(641)126>.

No significant advances in the synthesis of alkynylmercury compounds have been made in the decade since the writing of COFGT (1995) <1995COFGT(2)1075>.

2.23.4.4 Alkynylaluminum Compounds

Organoaluminum chemistry in general was reviewed for the period 1982–1994 by Eisch <1995COMCII(11)277> and Zheng and Roesky have reviewed alkynylaluminum compounds specifically concentrating on their bonding and structures but including some synthesis <2002JCS(D)2787>. The methods of synthesis described in COFGT (1995) <1995COFGT(2)1075> continue to be those used in the early 2000s.

Sodium tetraalkynylaluminates have been reinvestigated by Blum and co-workers for use as cross-coupling partners. They prepared these reagents using the proven method of reaction of terminal alkynes with sodium aluminum hydride <1995COFGT(2)1075> and used them either as isolated compounds or *in situ* in palladium-catalyzed cross-couplings with aryl bromides. All four alkynyl moieties of the tetraalkynylaluminate will couple <2002JOC6287, 2003AG(E)1566>.

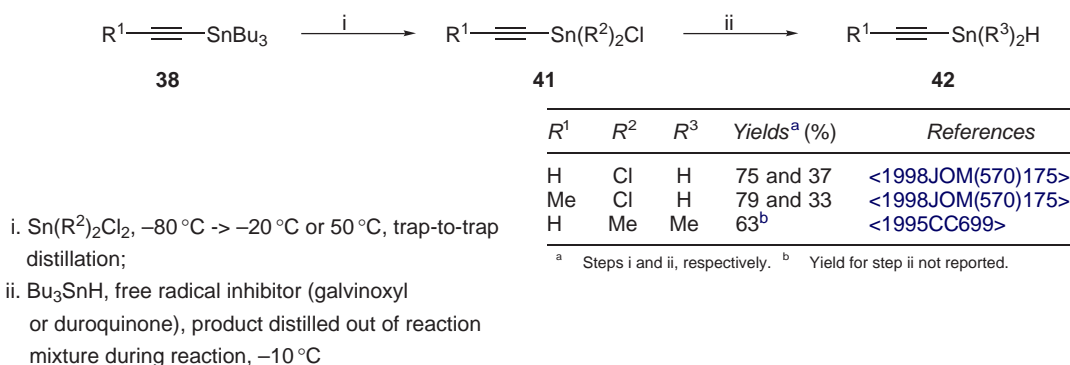
2.23.4.5 Alkynyltin Compounds

WARNING: Organotin compounds are toxic. For a discussion of their toxicology see <B-1996MI009>. Organotin chemistry has been comprehensively reviewed in <B-1996MI008, B-2002MI016>, which

included discussion of these compounds' biological activities <B-2002MI018>. The chemistry of tributylstannyethyne has been reviewed, including its use in Stille couplings <B-1995MI007>. The Stille coupling in general has been reviewed <1997OR1>, while Negishi and Anastasia have compared the Stille protocol to other palladium-catalyzed alkynylations <2003CRV1979>.

Brandsma and Verkruijsse have published a detailed description of the preparation of ethynyltrimethylstannane and ethynyltributylstannane from ethynylmagnesium bromide and the corresponding trialkylchlorostannane, i.e., using the general method <1999S1727>.

Guillemin and co-workers have interconverted alkynylstannanes (isolated by cold trap techniques) as shown Scheme 25, in order to access primary and tertiary alkynylstannanes **42**. The starting alkynyltrialkylstannanes **38** were obtained by the standard approach (i.e., reaction of ethynyllithium <1981JOC5221> or lithiated allene <1983JOC5302> with tributyltin chloride) and redistributed with tin tetrachloride or dimethyltin dichloride to give the alkynylchlorostannanes **41**. The stannane **41** underwent chemoselective reduction under optimized conditions to yield the alkynylstannanes **42**, which as pure compounds are unstable above -100°C but may be stored in solution at -40°C <1995CC699, 1998JOM(570)175>.



Scheme 25

2.23.4.6 Alkynyllead Compounds

Organolead chemistry, including biological activity <B-2002MI018>, has been comprehensively reviewed <B-1996MI008, B-2002MI016>.

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Biographical sketch

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