

COMPREHENSIVE ORGANIC FUNCTIONAL GROUP TRANSFORMATIONS II

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

Volume

5

Carbon with Two Attached Heteroatoms with at Least
One Carbon-to-Heteroatom Multiple Link

Volume Editor
Ray Jones



ÔUT ÚÜÒPÒÈÙÒÀÚÜÕÖÐÔÁ
 ÔMPÔNÖPÔŠÖÜUWÁ
 VÜÖÈÙÖUÛT ÖNÖPÙÁÖ



9X]hcf g!]b! 7\]YZ`
 5"F ""? Uhf]m_nĩ l b]j Yfg]hmcZ: `cf]XUž`
 ; U]bYgj]`Yž! G5
 F">"? "HUmĩcfž`8YdUfha YbhicZ7\Ya]ghf mž`
 l 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`]Vh]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`]hYfUhi fY`žcf`U`gVYb]ghg`
]bhYfghYX`]b`VX`Ya]W`HfUbgžcfa Uh]cbg`DfYgYbh]b[`hY`j Ughgi V`VW`cZ
 cf[Ub]Wgnb`hYg]g]b`hYfa g`cZ`hY`]bhfcXi V]cb`UbX`]bhYfV`bj 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 YhlcXg`cZYZZVYbhimdYfžcfa]b[`
 U`dUfh]W`Uf`HfUbgžcfa Uh]cb`Cf[Ub]gYX`Vmi`hY`ž bV]cbU`[fci d`
 žcfa YXž`7C: ; H!=k`j`V`b]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 YhlcXg`
 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`5HJWYX`<YhYfcUha`g`

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

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

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

J c`i a Y`.)`7UfVcb`k]h`Hk`c`5HJWYX`<YhYfcUha`g`k]h`Uh`
 @YUghCbY`7UfVcb`!hc!<YhYfcUha`A i`h]d`Y`@]b_`

J c`i a Y`*.`7UfVcb`k]h`H`fYY`cf`ci f`5HJWYX`<YhYfcUha`g`

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

In the decade since 1995, there has been a great deal of activity in the area covered by this volume. The rather cumbersome title of “Carbons with two attached heteroatoms with at least one carbon-to-heteroatom multiple link” encompasses a range of very important functionalities. The most familiar, and one might mistakenly think, fully investigated carboxylate derivatives, such as carboxylic acids, acid halides, esters, and amides, have all seen advances. In the case of amides, this is particularly driven by the peptide synthesis arena, and natural product synthesis also remains a major motivation. Other acyl derivatives, including acyl metals, have seen major developments. Thionoamides and amidines remain important functional groups – the latter, of course, for their potential in heterocycle synthesis amongst others. Metal carbenoids, isocyanates, and carbodiimides are just a few more examples where significant new methodology has appeared. Applications of solid-phase organic synthesis appear in a few chapters.

It is impossible to encapsulate in a short introduction, the many real advances in synthesis of the range of important functional groups covered by this volume – each reader will have favorites, depending on their area of chemical interest. Suffice to say, this volume has something for everyone interested in organic synthesis, since the functions reviewed are core to the synthetic arena.

R. C. F. Jones
Loughborough, UK
August 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 Kyokaishi</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	dimethylaluminum 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	ethylaluminum 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 aluminum 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

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

**Part I: Tricoordinate Carbon Functions with One Doubly
Bonded and One Singly Bonded Heteroatoms, RC=YX**

- 5.01 Acid Halides**, Pages 1-17, F. Aldabbagh
- 5.02 Carboxylic Acids**, Pages 19-125, S. P. Bew
- 5.03 Carboxylic Esters and Lactones**, Pages 127-174, B. R. Buckley
- 5.04 Other Acyloxy Compounds**, Page 175, Not available
- 5.05 Acylsulfur, -selenium, or -tellurium Functions**, Pages 177-199,
A. P. Dobbs and K. M. Windeatt
- 5.06 Amides**, Pages 201-294, P. D. Bailey, T. J. Mills, R. Pettecrew and R. A. Price
- 5.07 N-Heterosubstituted Amides**, Pages 295-356, M. A. Wilson
- 5.08 Acylphosphorus, -arsenic, -antimony, and -bismuth Functions**,
Pages 357-374, K. Afarinkia
- 5.09 Acylsilicon, -germanium, or -boron Functions**, Pages 375-398, P. J. Stevenson
- 5.10 Acyl Metal Functions**, Pages 399-434, G. J. Tanoury
- 5.11 Thio-, Seleno-, and Telluroacyl Halides**, Pages 435-458, M. F. Heaney
- 5.12 Thio-, Seleno-, and Telluroacyloxy Functions**, $R^1C(S)OR^2$, $R^1C(Se)OR^2$,
 $R^1C(Te)OR^2$, etc., Pages 459-491, A. Ishii and J. Nakayama
- 5.13 Functions with Two Chalcogens Other Than Oxygen**, Pages 493-518, T. Murai
- 5.14 Thionoamides and Their Se and Te Analogs**, Pages 519-570, A. J. Moore
- 5.15 N-Substituted Thionoamides and Their Se and Te Analogs**, Pages 571-581,
C. Flynn and L. Haughton
- 5.16 Thioacyl Functions Linked to a Metalloid (Si, Ge, or B) or Metal; and
Their Seleno and Telluro Analogs**, Pages 583-589, C. P. Dell
- 5.17 Iminoacyl Halides and Oxy Functions**, Pages 591-637, R. J. Anderson, P. W.
Groundwater and M. Nyerges
- 5.18 Iminoacyl Functions Linked to Chalcogens Other Than Oxygen**,
Pages 639-654, S. Challenger
- 5.19 Amidines and N-Substituted Amidines**, Pages 655-699, P. J. Dunn
- 5.20 Iminoacyl Functions Linked to Any Heteroatom Other Than Halogen,
Chalcogen, or Nitrogen**, Pages 701-723, M. Casey
- 5.21 N-Heterosubstituted Iminoacyl Functions**, Pages 725-798, B. Dietrich
- 5.22 Diazo Functions with an α -Heteroatom ($RC(X)N_2$)**, Pages 799-812, K. Afarinkia
- 5.23 Phosphoacyl Functions and Their As, Sb, and Bi Analogs**, Pages 813-902, L. Weber
- 5.24 Doubly Bonded Metalloid Functions**, $R^1C(X)=SiR^2_2$, $R^1C(X)=BR^2$
 $R^1C(X)=GeR^2_2$, Pages 903-909, L. Haughton and C. Flynn
- 5.25 Functions Doubly Bonded to a Metal**, Pages 911-947, M. Gómez-Gallego,
M. J. Mancheno and M. A. Sierra

**Part II: Dicoordinate Carbon Functions with Two Doubly
Bonded Heteroatoms, $Y^1=C=Y^2$**

5.26 Functions with at Least One Oxygen, $Y=C=O$, Pages 949-973, P. Molina, A. Tárraga and A. Arques

5.27 Functions with at Least One Chalcogen Other Than Oxygen, Pages 975-990, R. A. Aitken

5.28 Functions with at Least One Nitrogen and No Chalcogens, Pages 991-1009, A. E. Graham

5.29 Functions with Heteroatoms Other Than Chalcogen or Nitrogen ($Y^1=C=Y^2$), Pages 1011-1022, K. Afarinkia

5.01

Acid Halides

F. ALDABBAGH

National University of Ireland, Galway, Republic of Ireland

5.01.1	SINGLY BONDED HALOGEN FUNCTIONS—ACID HALIDES (RCOHal)	1
5.01.1.1	General Methods for Acid Halides	1
5.01.1.1.1	Acid halides from carboxylic acids	2
5.01.1.1.2	Acid halides from acid chlorides	2
5.01.1.1.3	Acid halides from acid fluorides (only from perfluoroacyl fluorides)	3
5.01.1.1.4	Acid halides from carboxylic acid esters	3
5.01.1.2	Acid Fluorides	3
5.01.1.2.1	Acid fluorides from both acid chlorides and carboxylic acids	4
5.01.1.2.2	Acid fluorides from acid chlorides	4
5.01.1.2.3	Acid fluorides from carboxylic acids	6
5.01.1.2.4	Acid fluorides from alcohols and aldehydes	7
5.01.1.3	Acid Chlorides	8
5.01.1.3.1	Acid chlorides from carboxylic acids	8
5.01.1.3.2	Acid chlorides by miscellaneous methods	12
5.01.1.4	Acid Bromides	12
5.01.1.4.1	Acid bromides from acid chlorides	13
5.01.1.4.2	Acid bromides from esters	13
5.01.1.4.3	Acid bromides from carboxylic acids	13
5.01.1.4.4	Acid bromides from aldehydes	14
5.01.1.5	Acid Iodides	14
5.01.1.5.1	Acid iodides from acid chlorides	15
5.01.1.5.2	Acid iodides from acid fluorides (from perfluoroacyl fluorides only)	15
5.01.1.5.3	Acid iodides from carboxylic acid derivatives	15

5.01.1 SINGLY BONDED HALOGEN FUNCTIONS—ACID HALIDES (RCOHal)

5.01.1.1 General Methods for Acid Halides

Acid halides are the most reactive of the standard carboxylic acid derivatives facilitating many synthetic transformations. Methods of preparing acid halides are listed in Houben-Weyl <B-1985HOU(E5/1)587> and Larock <B-1989MI001>. Most notable reviews have been carried out by Ansell <B-1972MI35>, Buehler and Pearson <B-1970MI859, B-1997MI782>, Sustmann <1991COS(6)301>, and Williams <1995COFGT(5)1>. The following sections discuss methods introduced since the review by Williams, although more established procedures still in common use are included.

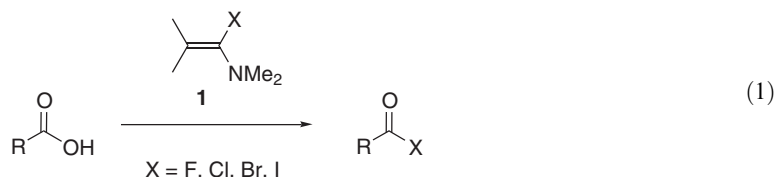
Most acid halides are moisture sensitive and techniques for isolation of acid halides should avoid water/organic extractions. Typically, isolation of acid chlorides, bromides, and iodides is achieved by distillation or recrystallization of the acid halide from the crude reaction residue; however, often yields are generated after conversion to esters or amides. Furthermore, many synthetic transformations do not isolate and characterize the acid halide, simply treating it as a reactive intermediate. In

such cases, caution should be exercised, when assuming the exclusive presence of the acid halide, as a reaction can occur with the carboxylic acid to give the symmetrical anhydride and the reaction is accelerated by the presence of pyridine and other bases. However, acid fluorides are more stable to hydrolysis than the other acid halides because of the greater stability of the C—F bond. In fact, many acid fluorides are isolated after aqueous work-up.

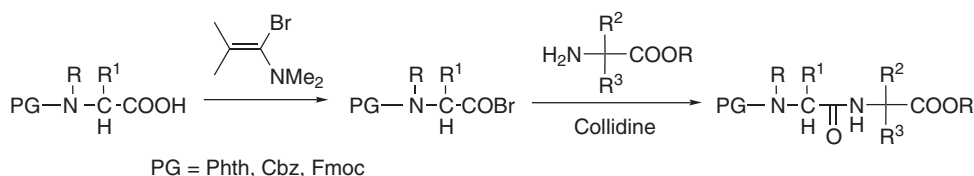
5.01.1.1.1 Acid halides from carboxylic acids

Numerous reagents have been employed to achieve the replacement of the carboxylic acid OH by a halogen, or deoxyhalogenation. Thionyl chloride and oxalyl chloride are the most common reagents for preparing acid chlorides (Section 5.01.1.3.1). Oxalyl bromide (Section 5.01.1.4.3) is typically used for acid bromides. Thionyl bromide is rarely used.

Ghosez and co-workers <1979CC1180> introduced a general approach for preparing acid halides using 1-halo-*N,N*-2-trimethylpropenylamines **1**, as represented by Equation (1). 1-Chloro-*N,N*-2-trimethylpropenylamine is commercially available, and the other α -haloenamines (X = F, Br, I) can be obtained by halogen exchange. An improved synthesis of α -chloro- and bromoenamines has more recently been reported <1998T9207>.



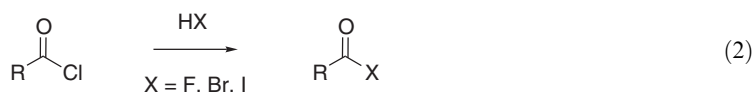
Reactions employing α -chloro- and bromoenamines **1** are very mild with no hydrogen halide evolved. Transformations occur at room temperature or below. 1-Bromo-*N,N*-2-trimethylpropenylamine is used in the preparation of amino acid bromides <2002JOC6372>. For example, various *N*-protected amino acid bromides were obtained by simply stirring the amino acids in CH_2Cl_2 with 1-bromo-*N,N*-2-trimethylpropenylamine at room temperature for 15 min <2001TL3925>. The acid bromides generated *in situ* under neutral conditions were coupled with various α,α -dialkyl amino acids to form the configurationally pure dipeptides in 83–96% yield, as shown in Scheme 1.



Scheme 1

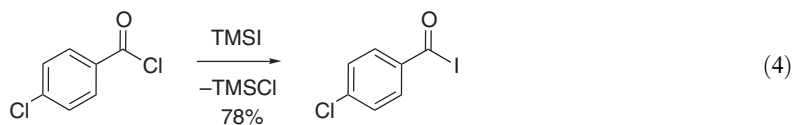
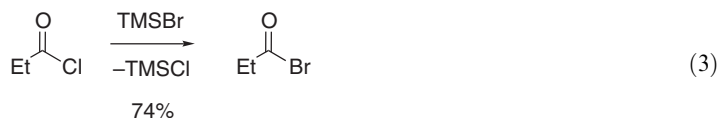
5.01.1.1.2 Acid halides from acid chlorides

Acid fluorides, bromides, and iodides may be obtained from the more readily available acid chlorides by equilibrium exchange reactions. Acid chlorides may be reacted with excess hydrogen fluoride, hydrogen bromide, or hydrogen iodide to give the corresponding acid halide (Equation (2)) <B-1972MI35>.



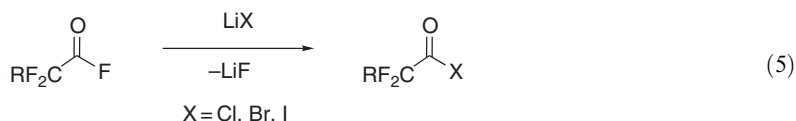
However, it is generally more desirable to perform this transformation under neutral conditions. The exchange has been successfully accomplished using a variety of reagents, including potassium fluoride, tetrabutylammonium fluoride (Section 5.01.1.2.2), sodium iodide (Section 5.01.1.5.1), and diiodosilane (Section 5.01.1.5.3). Trimethylsilyl bromide (TMSBr)

and trimethylsilyl iodide (TMSI) are particularly attractive reagents, because the volatile by-product trimethylsilyl chloride (TMSCl) (b.p. 57 °C) is easily removed by distillation. Representative examples are shown in [Equations \(3\) and \(4\)](#) <1981S216>.

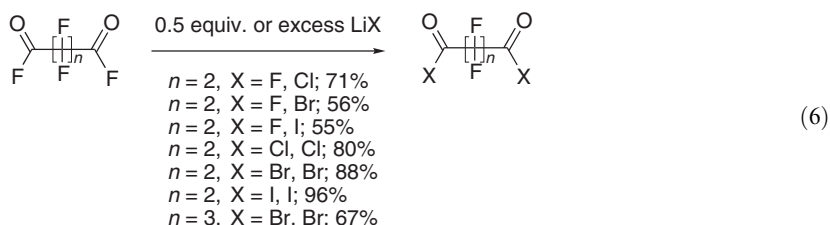


5.01.1.1.3 Acid halides from acid fluorides (only from perfluoroacyl fluorides)

Fukaya and co-workers <1996JCS(P1)915> reported a facile conversion of perfluoroacyl fluorides into other acid halides by simple exchange with an anhydrous lithium halide ([Equation \(5\)](#)). The reaction is facilitated by the strong interaction between lithium and fluoride ions with lithium iodide being the most reactive, and the order of reactivity, as expected, being the opposite to the relative lattice energies of the lithium halides ($\text{LiI} < \text{LiBr} < \text{LiCl}$).

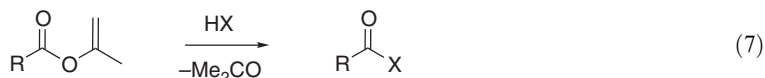


The reaction was found to be highly temperature dependent with respective optimum yields for acid iodide, bromide, and chloride being achieved at 120, 250, and 300 °C. The methodology was extended to diacid fluorides, where using half an equivalent and excess lithium halide, respectively, gave single and double halogen exchange reactions, as shown in [Equation \(6\)](#).



5.01.1.1.4 Acid halides from carboxylic acid esters

Generally, aggressive conditions are required to convert saturated esters into acid halides. There is, however, one general mild route to acid fluorides, chlorides, bromides, and iodides provided by the reaction of labile enol esters, such as isopropenyl esters with the appropriate hydrogen halide ([Equation \(7\)](#)) <1991COS(6)301>.

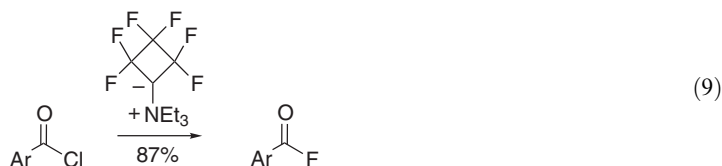
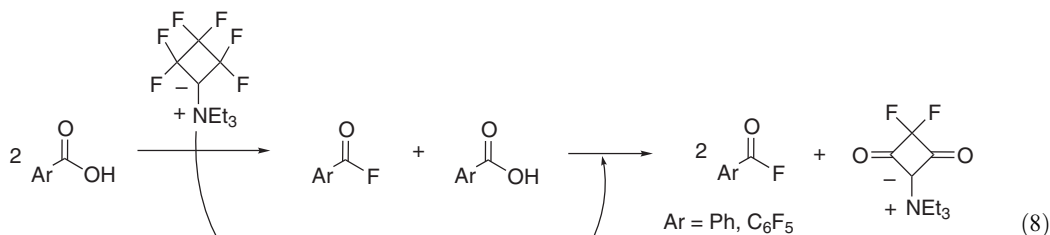


5.01.1.2 Acid Fluorides

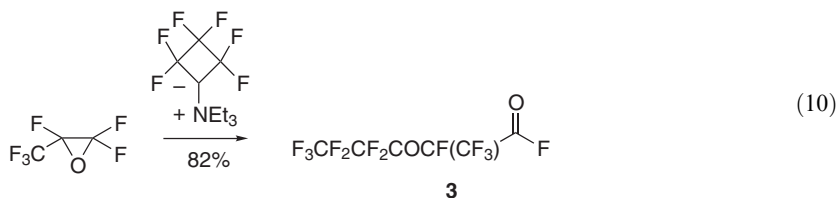
Since the 1990s, a greater number of new methods for preparing acid fluorides have been introduced as compared to other acid halides. This may be due to their greater stability to hydrolysis making them the easiest to handle.

5.01.1.2.1 Acid fluorides from both acid chlorides and carboxylic acids

Pasenok and co-workers have used ammonium perfluorocyclobutane ylide to convert benzoic acid <1996T2977> and benzoyl chloride <1996T9755> into benzoyl fluoride, as shown in Equations (8) and (9). When using carboxylic acids (Equation (8)), it was observed that only half an equivalent of ylide was required, as the intermediate betaine **2** could also fluorinate to yield the acid fluorides in 89–91% yields.



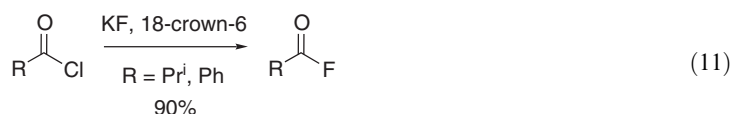
The ammonium ylide was further utilized to catalyze the dimerization of hexafluoropropene oxide in acetonitrile at room temperature by agitation in an autoclave for 2 h to give acid fluoride **3** in 82% yield <1996T9755> (Equation (10)).



DAST and Deoxo-FluorTM are the other alternatives (Section 5.01.1.2.3).

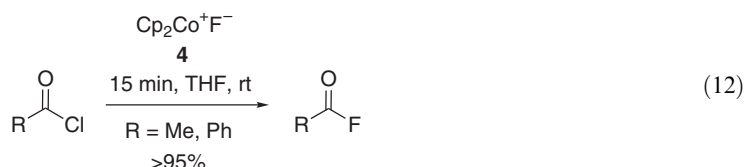
5.01.1.2.2 Acid fluorides from acid chlorides

The conversion of acid chlorides into acid fluorides requires a nucleophilic fluoride or “naked” fluoride ion source. The nucleophilic reactivity of the fluoride ion in potassium fluoride may be enhanced by dispersion onto an inert polymeric support <1989JFC(43)429>. The fluoride ion must be soluble in the organic reaction solvent and the fluoride salt has to be anhydrous in order to maintain the reactivity of the fluoride ion. Traditionally this has been facilitated by using either a variety of metal chelating agents or phase transfer catalysts. Potassium fluoride has been utilized in the presence of 18-crown-6 to convert acid chlorides into acid fluorides at room temperature in excellent yields, as shown in Equation (11) <1979JOC1016>.

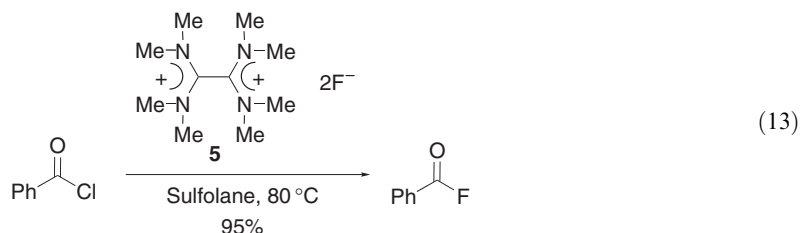


A common phase transfer catalyst used is anhydrous tetrabutylammonium fluoride (TBAF) <1984JOC3216>. A modification of the latter procedure involves using a semimolten mixture of tetrabutylammonium bromide (TBAB) and KF or CsF, for the conversion of benzoyl chloride into the fluoride in 82–84% yield <1995JFC(73)185>.

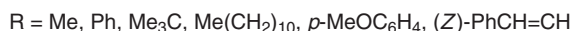
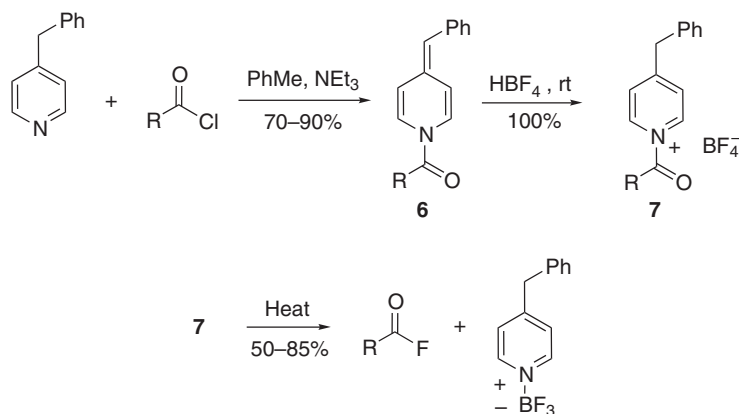
Recent research has focused on the development of new salts that are soluble in common organic solvents. For instance, a variety of organic chlorides have been converted to fluorides using cobaltocenium fluoride **4** isolated from the reaction of perfluorodecalin with cobaltocene <1994JA11165>. It was also used to prepare ethanoyl and benzoyl fluorides in greater than 95% yield, as shown in Equation (12).



Chambers and co-workers have prepared salt **5**, which contains anhydrous fluoride ion that, at 80 °C, in sulfolane converted benzoyl chloride into the fluoride in 95% yield, as shown in Equation (13) <1999JFC(94)213>.



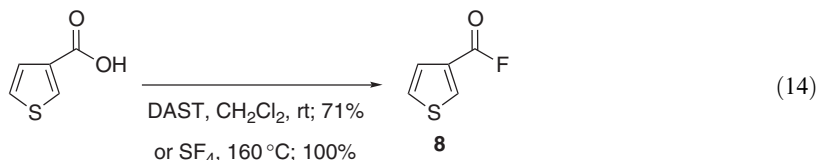
Anders and co-workers have developed a mild synthesis of acid fluorides by exploiting the thermal instability of the BF_4^- anion in 1-acyl-4-benzylpyridinium tetrafluoroborates **7** (Scheme 2) <1999EJO2383>. Salts **7** were prepared from 4-benzylpyridine on treatment with acid chloride and triethylamine to form the moisture-sensitive dihydropyridine **6**, which was converted into the tetrafluoroborate salt **7** in quantitative yield on treatment with tetrafluoroboric acid <1998S883>. The authors proposed that RCOF formation was assisted by the basic pyridine moiety, which upon cleavage of the acyl moiety intercepts the Lewis-acidic BF_3 .



Scheme 2

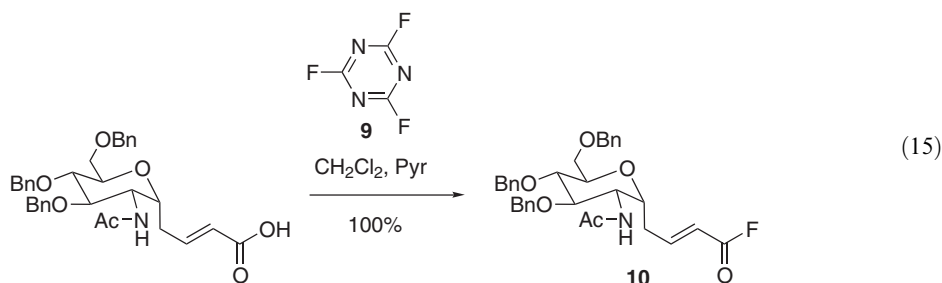
5.01.1.2.3 Acid fluorides from carboxylic acids

Deoxyfluorinations, using nucleophilic fluorinating sources, have routinely been accomplished with dialkylaminosulfur trifluorides, such as DAST ($\text{Et}_2\text{N}-\text{SF}_3$) <1999JOC6252, 2001AJC75>. DAST is easier to use than toxic fluorinating gases such as SF_4 , and recently both have been used to form 3-(fluoroformyl)thiophene **8** in high yields (Equation (14)) <1999JFC(93)73>.



However, DAST can only be used in small-scale reactions, because of its well-known hazardous thermal instability. Bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-FluorTM), $(\text{CH}_3\text{OCH}_2\text{CH}_2)_2\text{N}-\text{SF}_3$, was introduced in 1999 as a thermally less sensitive alternative to DAST, thus making it more amenable to large-scale use <1999CC215>. A solution of Deoxo-FluorTM and benzoic acid or benzoyl chloride in CH_2Cl_2 was stirred for 30 min at 0°C and reportedly formed benzoyl fluoride in 95–96% yield. However, when the reactions were carried out neat at 85°C for 48 h, trifluoromethylbenzene was obtained selectively. Analogous reactions on dodecanoic acid and dodecanoyl chloride allowed the acid fluoride derivative to be formed in 97% yield <1999JOC7048>.

Cyanuric fluoride **9** is probably the mildest fluorinating reagent <1973S487>, allowing the preparation of activated amino acid fluorides as well as acid fluorides containing double bonds, aromatic rings, and hydroxyl groups. For example, the quantitative formation of the carbohydrate acid fluoride **10** was achieved using 8 equiv of reagent **9**, and 1 equiv of pyridine in refluxing CH_2Cl_2 over 16 h, as shown in Equation (15) <2000JOC979>.

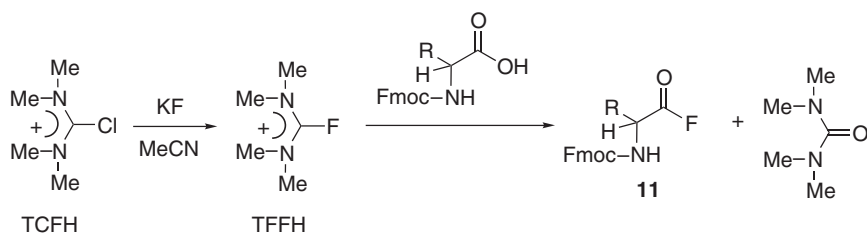


However, commercial cyanuric fluoride **9** is expensive, which makes large-scale reactions a problem. The original preparation by Olah and co-workers <1973S487> used anhydrous HF to convert cyanuric chloride into cyanuric fluoride **9**. An alternative, more cost-effective synthesis of **9** was provided by Nubbemeyer and co-workers, which avoids the use of HF. The latter reaction uses excess sodium fluoride with cyanuric chloride in sulfolane at $150\text{--}200^\circ\text{C}$ providing reagent **9** in 60–78% yield <2000JPR711>.

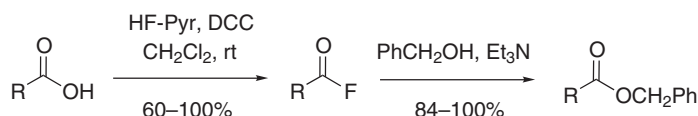
Since the 1990s, there have been several reagents proposed as alternatives to cyanuric fluoride **9**. Carpino and El-Faham introduced tetramethylfluoroformamidinium hexafluorophosphate (TFFH), a nonhygroscopic salt obtained via the reaction of the chloride (TCFH) with excess anhydrous potassium fluoride (Scheme 3) <1995JA5401>. TFFH was used in the synthesis of Fmoc amino acid fluorides **11**, and the reagent was later utilized by Nicolaou and co-workers for the conversion of aryl carboxylic acids to fluorides in 80–97% yield as part of the synthesis of the natural product, everninomicin 13,384–1 <1999AG(E)3334, 1999AG(E)3340>.

Nitrogen salts of hydrogen fluoride provide an easy-to-handle source of anhydrous HF. For instance, hydrogen fluoride–pyridine with DCC in CH_2Cl_2 has been used to generate various acid fluorides *in situ* prior to conversion into the benzyl esters, as shown in Scheme 4. The acid fluorides were also isolated by distillation, and the selective formation of the acid fluoride of (*Z*)-cinnamic acid in 75% yield indicates that the procedure has potential as a cost-effective alternative to reagent **9** <2002JFC(115)75>.

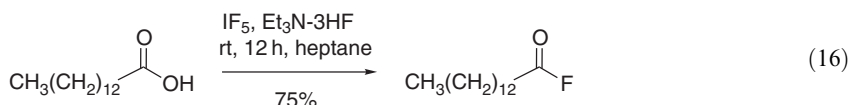
Triethylamine–hydrogen fluoride complex ($\text{Et}_3\text{N}-3\text{HF}$) provides a safe and convenient medium for using the usually hazardous and moisture sensitive chemical, IF_5 <2001CL222>. Equation (16) shows a rare example of an iodine fluoride being used as fluorinating reagent.



Scheme 3



Scheme 4



5.01.1.2.4 Acid fluorides from alcohols and aldehydes

As previously noted by Williams, there are few reliable and general methods for these transformations <1995COFGT(5)1, 1997JOC4916>. Since then, the powerful oxidizing agent bromine trifluoride (BrF_3) has been used to oxidize a series of aliphatic and alicyclic primary alcohols **12** to acid fluorides **13**, as shown in Equation (17) and Table 1 <1996JFC(76)145>. The main by-product was found to be the ester **14**, formed as a result of the reaction of the acid fluoride with the starting alcohol. The main drawbacks of this method are the hazards in using highly reactive BrF_3 and the lack of success for activated benzylic alcohols and compounds that are usually sensitive to carbocation rearrangements such as neopentyl alcohol and myrtanol. An ionic mechanism involving the fluorination of the intermediate aldehyde was proposed.

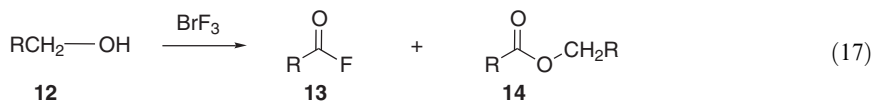
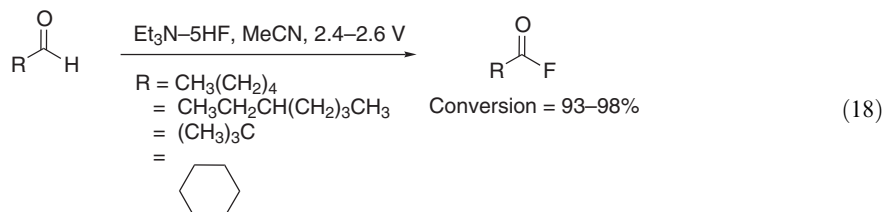


Table 1 Oxidation of primary alcohols **12** to acid fluorides **13** and esters **14** using BrF_3 according to Equation (17)

Alcohol 12 <i>R</i>	13 Yield (%)	14 Yield (%)
<i>n</i> -C ₁₁ H ₂₃	65	20
<i>n</i> -C ₇ H ₁₅	70	15
	70	15
	55	20
Bu-CH Et	85	10

Electrochemical fluorination of aliphatic aldehydes in the presence of Et_3N –5HF gave the respective alkanoyl fluorides in high yields <1994CL849>. Equation (18) shows some of the aldehyde to acid fluoride reactions (Et_3N –3HF and Et_3N –4HF were reported to give lower yields of alkanoyl fluoride). The perceived drawbacks with this method are the specialized equipment required, including a platinum electrode and Teflon cell, and the fact that application to more functionalized aldehydes was not explored.



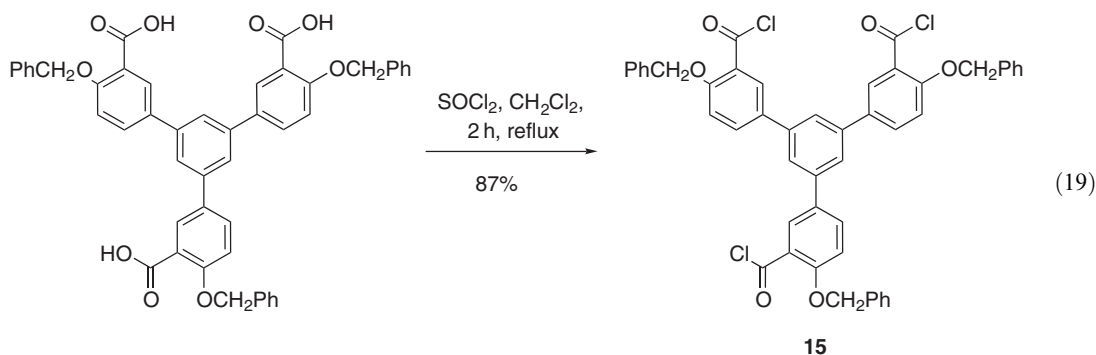
5.01.1.3 Acid Chlorides

Acid chlorides are the most commonly prepared acid halide, and are nearly always made from the carboxylic acid. Thionyl chloride and oxalyl chloride remain the most popular reagents for the following reasons: (i) excess quantities can be used; (ii) reagents are volatile and are often distilled out of the reaction to afford the acid halide; (iii) only gaseous by-products are given off at the end of the reaction; and (iv) both reagents are commercially available and not expensive. The following section gives several recent examples of their use and surveys new methods introduced during the 1990s. Comprehensive reviews of older general methods of preparation have been carried out by Sustmann <1991COS(6)301> and Williams <1995COFGT(5)1>.

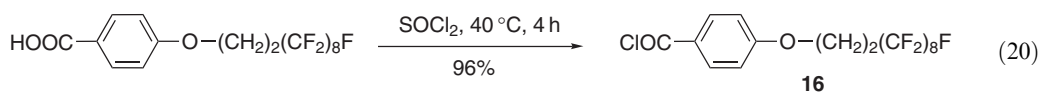
5.01.1.3.1 Acid chlorides from carboxylic acids

(i) Using thionyl chloride

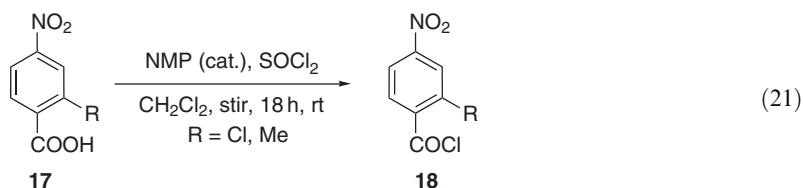
There are numerous examples of thionyl chloride facilitating the conversion of carboxylic acids into acid chlorides. Usually, the reaction is carried out using an excess of thionyl chloride in a refluxing inert solvent for 2–3 h to give high yields of the acid chloride. A recent example is shown in Equation (19) in which three aromatic carboxylic acid groups were simultaneously transformed into the triacid chloride **15** in 87% yield <2002JOC8832>.



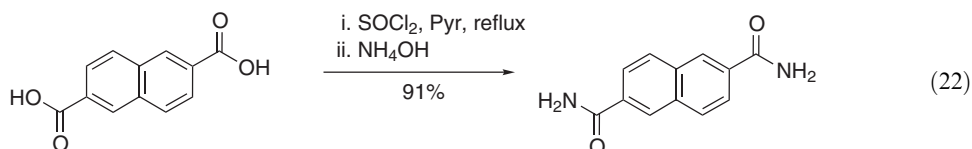
Often, no organic reaction solvent is used, and the carboxylic acid is simply refluxed in neat thionyl chloride, as shown in Equation (20), for the formation of the fluorinated acid chloride **16** <2002JMAC1684>. Acid chlorides are nearly always isolated by simply evaporating the excess thionyl chloride. This helps to avoid aqueous/organic extractions and prevents hydrolysis of the acid chloride. The acid chloride can be purified by distillation or recrystallization, but generally the crude acid chloride does not require purification before use in subsequent transformations. For instance, acid chloride **16** was isolated by evaporating the excess thionyl chloride (b.p. 79 °C), and used for subsequent esterification of polymer side-chains.



Although thionyl chloride will usually react with carboxylic acids in the absence of catalysts, sometimes catalysts such as pyridine, secondary (e.g., dicyclohexylamine) and tertiary amines (e.g., triethylamine), DMF and alkali metal chlorides are required [<1995COFGT\(5\)1>](#). This is especially the case for strong acids and some sterically hindered acids that react only slowly with thionyl chloride. Reviews of these catalysts and discussions of the mechanisms can be found in the previously recommended reviews ([Section 5.01.1.1](#)). The acceleration of the reaction by the catalyst often allows the reaction to be carried out at lower temperatures. For example, aromatic acid chlorides **18** were prepared from the respective 4-nitrobenzoic acids **17** by simple overnight stirring at room temperature with thionyl chloride and a couple of drops of NMP ([Equation \(21\)](#)) [<2000JMC4388>](#). Isolated yields for **18** were not given prior to their use in amide bond formation.



However, such additives are not always added in only catalytic amounts, as for the reaction of 2,6-naphthalene dicarboxylic acid with thionyl chloride (reaction solvent), when an excess of pyridine was added (2.6 molar equiv.), as shown in [Equation \(22\)](#). Evaporation of the volatiles was followed by the addition of ammonium hydroxide yielding 2,6-naphthalene dicarboamide in 91% yield [<1997T8105>](#).



More recently benzotriazole (Bt) has been used as a catalyst; a solution of 1 molar equivalent each of thionyl chloride and Bt in dry CH_2Cl_2 at room temperature was reported to efficiently transform the carboxylic acids to acid chlorides within minutes, as shown in [Equation \(23\)](#). A range of aromatic, saturated, and α,β -unsaturated carboxylic acids were converted to the acid chlorides, as shown in [Table 2](#). At the end of the reaction, Bt separated out as its hydrochloride salt, which was recovered, treated with alkali solution and re-used [<1999SL1763>](#).

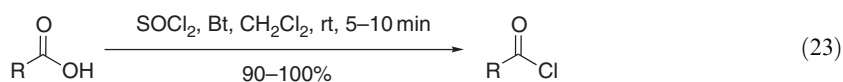
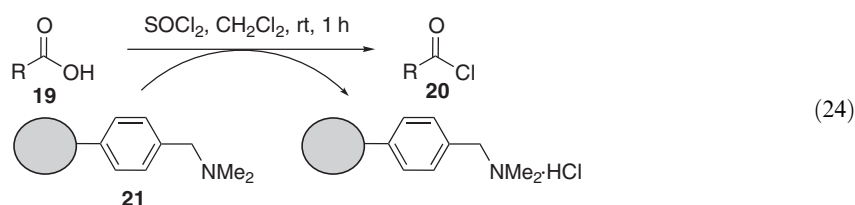


Table 2 Conversion of carboxylic acids into acid chlorides using 1:1 SOCl_2 :Bt according to [Equation \(23\)](#)

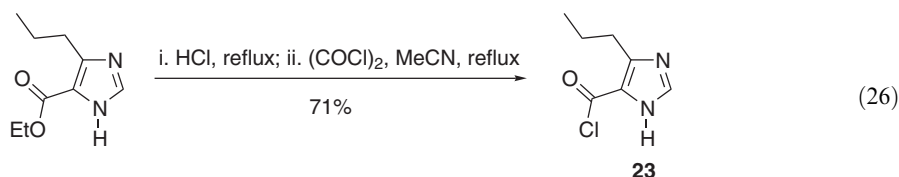
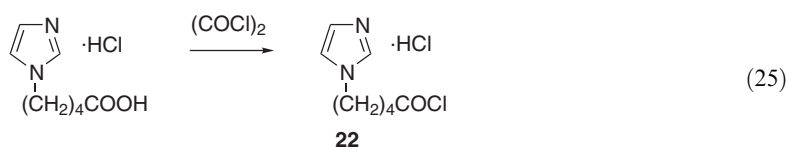
R	Yield (%)
Ph	100
<i>p</i> -NO ₂ Ph	94
<i>p</i> -ClPh	95
<i>o</i> -IPh	92
<i>p</i> -MeOPh	94
<i>p</i> -MePh	92
Ph-CH=CH-	90
Ph-CO-(CH ₂) ₂ -	91
Ph-CO-	90
CH ₃ -(CH ₂) ₆ -	92

One problem with thionyl chloride is that it cannot be used with substrates containing acid-sensitive groups, because of reaction with its by-products, HCl and SO₂. Solutions to this problem have included performing the reaction in the presence of excess base (e.g., pyridine or triethylamine) and careful monitoring of the stoichiometry of the thionyl chloride <1995COFGT(5)1>. The conversion of fatty acids **19** to acid chlorides **20** using thionyl chloride was recently reported under neutral conditions in which the amine-based solid phase resin Amberlyst A-21[®] **21** scavenges the acidic by-products <2000SL1577> (Equation (24)). The reaction mixtures were quenched with either methanol or diethylamine to form methyl esters in 86–90% and diethyl amides in 83–90% yield, respectively. These yields apply only to saturated fatty acids such as lauric, myristic, palmitic and stearic acids; yields for unsaturated fatty acids and simple aromatic acids were lower at 69–79% and 32–46%, respectively. Evaporation of the reaction mixtures revealed that the aliphatic acid chlorides were being formed cleanly, but in the reactions of aromatic and unsaturated carboxylic acid substrates, a considerable amount of anhydride was being formed.

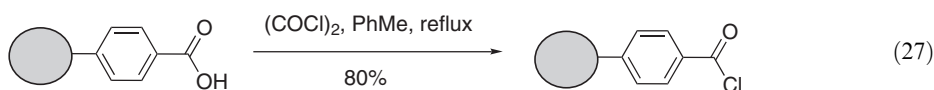


(ii) Using oxalyl chloride

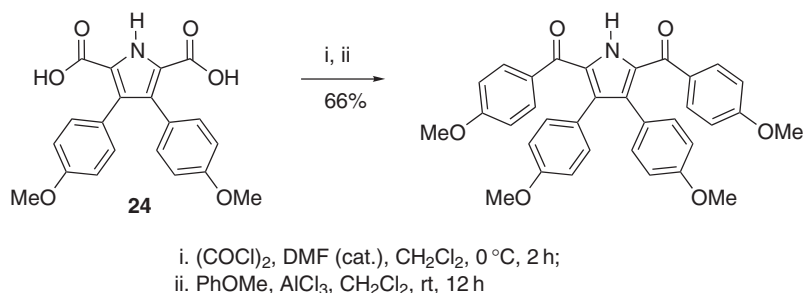
Oxalyl chloride remains the most frequently used alternative to thionyl chloride. Reaction of carboxylic acid with oxalyl chloride produces gaseous carbon dioxide, carbon monoxide, and HCl. As with thionyl chloride, excess amounts of oxalyl chloride (b.p. 63–64 °C) are simply evaporated off at the end of the reaction, so facilitating the easy isolation of the product. Oxalyl chloride is a less aggressive chlorinating reagent than thionyl chloride. For example, the formation of acid chloride **22** was achieved by heating 5-(1-imidazolyl)pentanoic acid hydrochloride with oxalyl chloride in anhydrous acetonitrile solution at 60 °C for 1 h, as shown in Equation (25) <2001BCJ1703>. The use of thionyl chloride under such conditions is avoided, as one would expect it to also chlorinate the imidazole ring <1997TH43>. As with many synthetic pathways involving acid chlorides, compound **22** was not isolated prior to its use in an esterification reaction. However, a number of stable imidazole acid chlorides have been isolated <1998JOC8084, 2002JOC5963>. For example, 4,5-disubstituted imidazole **23** was isolated as a stable solid via the reaction of the hydrochloride salt of the carboxylic acid with oxalyl chloride in refluxing acetonitrile <2002JOC5963>, as shown in Equation (26).



Oxalyl chloride in refluxing toluene was used to convert commercial polystyrene carboxylic acid resin into the acid chloride in 80% yield on the basis of acid chloride content determined by elemental analysis, as shown in Equation (27) <2001OL307>.

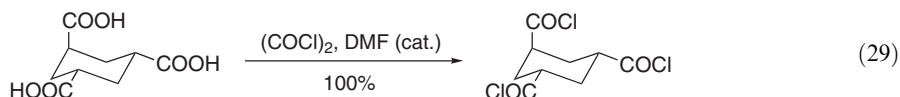
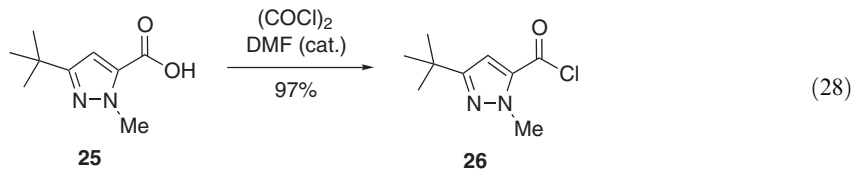


As with thionyl chloride, pyridine or DMF are often added as catalysts to accelerate the reaction and/or to allow the reaction to be carried out at low temperatures. For example, pyrrole dicarboxylic acid **24** was converted into a crude dichloride at 0 °C, which was used in a double Friedel–Crafts reaction as part of the synthesis of marine pyrrole alkaloids, polycitone A and B, as shown in Scheme 5 <2002OL3287>.



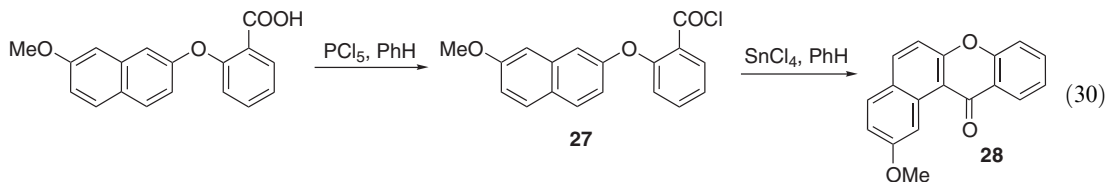
Scheme 5

Pyrazole-5-carboxylic acid **25** was stirred for 16 h at room temperature in the presence of 5 equiv. of oxalyl chloride and one drop of DMF and upon evaporation of the solvent, the acid chloride **26** was isolated in excellent yield (Equation (28)) <1997JOC5908>. Equation (29) shows the chlorination of a cyclohexane tricarboxylic acid using oxalyl chloride and a catalytic quantity of DMF, a reaction that proceeds in quantitative yield <1998T4107>.



(iii) Using phosphorus chlorides

Phosphorus chlorides—PCl₃, PCl₅, and POCl₃—are less frequently used than thionyl or oxalyl chlorides, due to often sluggish reactions, which at higher temperatures give side products such as oxidation products. This has led to their virtual replacement by other reagents. A comprehensive discussion of their use is given by Ansell <B-1972MI35>. Generally excess reagent is required, e.g., excess phosphorus pentachloride in benzene was employed to form acid chloride **27** *in situ*, which upon further treatment with tin tetrachloride catalyst gave the benzo[*a*]xanthone skeleton **28** in a one-pot synthesis (Equation (30)) <2002OL1067>.

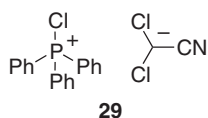


Modified phosphorus halides, including polymer-bound reagents, have been developed, and are now in general use <2000JCS(P1)3815>. Many such reagents allow the synthesis of temperature-sensitive acid halides in good yields. The spent polymer-bound reagents are separated from the acid chloride by filtration. The reader should consult Sustmann <1991COS(6)301> and Williams <1995COFGT(5)1> for detailed discussions.

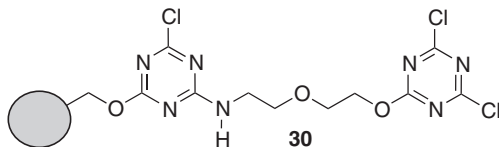
(iv) Miscellaneous reagents which form acid chlorides without hydrogen chloride formation

As already mentioned, thionyl chloride, oxalyl chloride, and the phosphorus halides generate hydrogen halide and other acidic by-products during acid chloride formation, and thus are not compatible with acid-sensitive substrates. A number of methods have been developed to allow acid chloride formation under neutral conditions including $\text{Ph}_3\text{P}/\text{CCl}_4$ <1966JA3440> and the previously discussed 1-chloro-*N,N*,2-trimethylpropenylamine (see Section 5.01.1.1.1).

More recently, hexachloroacetone $\{(\text{Cl}_3\text{C})_2\text{CO}\}$ and Ph_3P in THF or CH_2Cl_2 and in the presence of pyridine or triethylamine were reported to convert highly unsaturated and aromatic carboxylic acids selectively into acid chlorides at temperatures below 0°C <1997TL6489>. The acid chlorides including formyl chloride, which is known to be stable only below -60°C , were formed *in situ* and reacted with amines to form amides. Similarly, various carboxylic acids were converted into acid chlorides at room temperature using a combination of trichloroacetonitrile (Cl_3CCN) and Ph_3P in CH_2Cl_2 <1999TL5323>. In such reactions, chlorotriphenylphosphonium salt **29** reacts with carboxylic acids to produce acid chlorides and triphenylphosphine oxide (Ph_3PO). The $\text{Cl}_3\text{CCN}/\text{Ph}_3\text{P}$ method was found to be most effective with aromatic acids, in particular, those activated by electron-donating groups. The latter acid chlorides were again not isolated, and directly converted into the respective amides in 70–95% yield on reaction with cyclohexylamine.



Solid-supported reagents are sometimes preferred for the synthesis of acid halides because of separation problems associated with Ph_3PO , especially if the products are not volatile and the reaction is carried out on a small scale. One should also note that acid chlorides cannot be purified by column chromatography. To overcome this problem Hodge introduced polymer-supported Ph_3P , which could be used in refluxing CCl_4 . Simple filtration removes the excess and spent phosphine resin leaving the acid chloride product and unchanged starting material <1975CC622>. Solid-supported reagents have been reviewed by Sustmann <1991COS(6)301> and more recently by Ley and co-workers <2000JCS(P1)3815>. Cyanuric chloride solid-phase chlorinating reagent **30** has been recently prepared by modification of Wang resin, and shown to facilitate the conversion of benzoic acid to benzoyl chloride in 70–80% yield in the presence of triethylamine in CH_2Cl_2 or acetone. A variety of other acid chlorides were prepared, but not isolated, since, after removal of the resin by filtration, the acid chlorides were directly converted into the corresponding benzyl amides in high yields <2002TL8909>.

**5.01.1.3.2 Acid chlorides by miscellaneous methods**

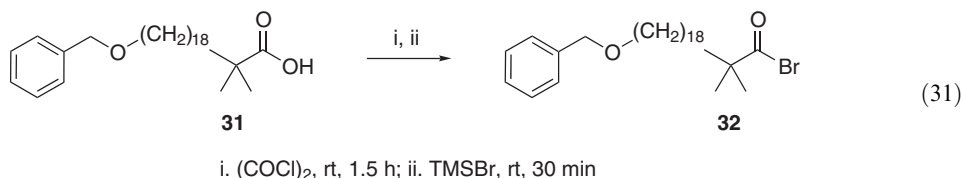
Acid chlorides can be obtained by the oxidation of aldehydes. The functionality may be introduced by Friedel-Crafts acylation or catalytic carbonylation. However, these methods are not commonly used, and the reader should refer to the review by Williams for further details <1995COFGT(5)1>.

5.01.1.4 Acid Bromides

Acid bromides are much less widely used in organic synthesis than acid chloride or fluorides. Acid bromides are rarely isolated.

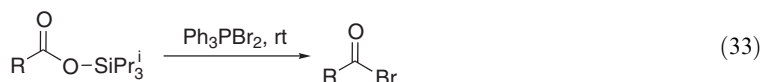
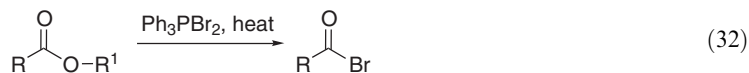
5.01.1.4.1 Acid bromides from acid chlorides

Most often acid bromides are only prepared *in situ*, when a more activated acid halide than acid chloride is required. For example, 20-benzyloxy-2,2-dimethyleicosanoic acid **31** was dissolved in 5 equiv. of oxalyl chloride to give the acid chloride with the excess oxalyl chloride removed by evaporation, followed by direct conversion to the acid bromide **32** upon addition of 5 equiv. of trimethylsilyl bromide (Equation (31)). The solution was again evaporated prior to an esterification reaction with the required alcohol <2001BCJ1703>.

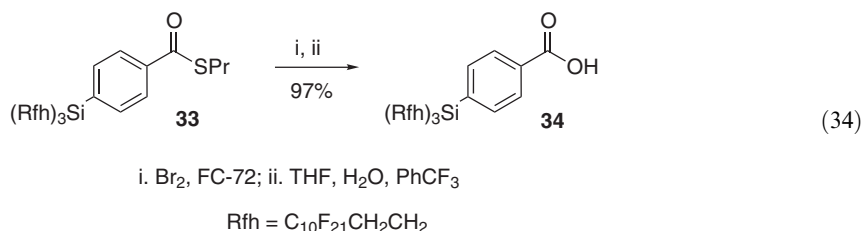


5.01.1.4.2 Acid bromides from esters

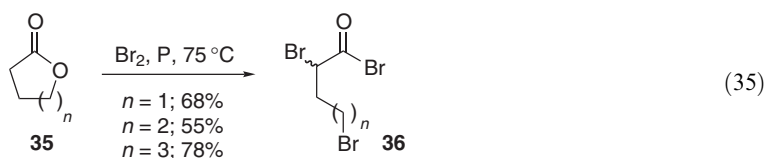
The conversion of esters and trialkylsilyl esters into acid bromides using triphenylphosphine dibromide (Ph₃PBr₂) was reviewed by Williams, and is outlined in Equations (32) and (33) <1981S216, 1995COFGT(5)1>.



More recently, an acid bromide was formed *in situ* via oxidative cleavage of the thioester sulfur-carbon bond **33** with bromine in the commercially available fluorocarbon liquid FC-72, prior to hydrolysis to the required highly fluorinated carboxylic acid **34**, as shown in Equation (34) <1997JOC2917>.



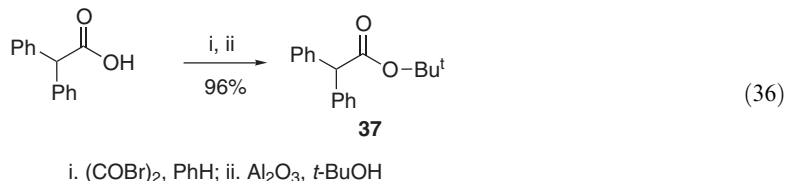
Various lactones **35** were ring-opened upon treatment with red phosphorus and bromine to give the dibrominated acid bromides **36**, as shown in Equation (35) <1996T11177>. A similar ring opening of lactones to give iodinated acid iodides using diiodosilane has been previously reported <1990JOC3922>.



5.01.1.4.3 Acid bromides from carboxylic acids

Oxalyl bromide is the most popular reagents for the synthesis of acid bromides. Procedures for using oxalyl bromide are generally analogous to those used with oxalyl chloride, which are adaptations of the original method by Adams and Ulich <1920JA599>. The procedure involves

stirring and sometimes refluxing the sodium salt of the carboxylic acid in benzene with oxalyl bromide. More recently, oxalyl bromide has been used to prepare a variety of substituted benzoyl bromides for kinetic studies <1993JCS(P2)307>. Hindered acid bromides were prepared *in situ* and used for the synthesis of *t*-butyl esters **37**, as represented by Equation (36) <1994CL209>. There are also several examples of Ph_3PBr_2 <1995COFGT(5)1>, and more recently 1-bromo-*N,N*-2-trimethylpropenylamine being used to accomplish the conversion of carboxylic acids into acid bromides (Section 5.01.1.1).

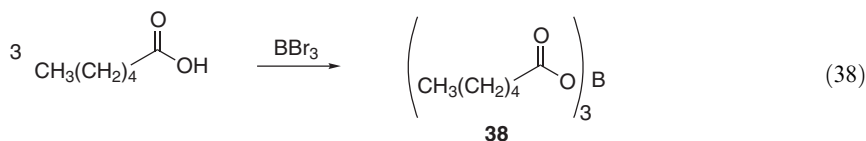


$\text{BBr}_3/\text{Al}_2\text{O}_3$ was reported to convert various carboxylic acids into acid bromides in moderate to high yields, as shown in Equation (37) and Table 3 <1992TL7475>. The boron tribromide was chemisorbed onto activated alumina, and shown to react differently with carboxylic acids than in the absence of the alumina. For example, the reaction of hexanoic acid with neat BBr_3 did not give the acid bromide, but instead the acid was partially converted into hexanoic boric anhydride **38**, as shown in Equation (38). All of the reactions in Table 3 were carried out over 20 h at room temperature, except for the reaction with benzoic acid, which was conducted at 60 °C over the same time period.



Table 3 Synthesis of acid bromides by reaction of carboxylic acids with $\text{BBr}_3/\text{Al}_2\text{O}_3$

Acid	Reaction solvent	Acid bromide, Yield (%)
Hexanoic	None	67
Decanoic	PhH	64
Benzoic	PhH	65
1-Adamantaneacetic	PhH	70
<i>p</i> -Nitrophenylacetic	MeCN	59
3-Bromopropanoic	CH_2Cl_2	84
2-Benzoylbenzoic	CH_2Cl_2	86



5.01.1.4.4 Acid bromides from aldehydes

Aldehydes can be converted into acid bromides via radical bromination facilitated by NBS and AIBN. However, this technique is not in general use because under such conditions NBS can also brominate activated allylic, benzylic and aromatic groups <1995COFGT(5)1>.

5.01.1.5 Acid Iodides

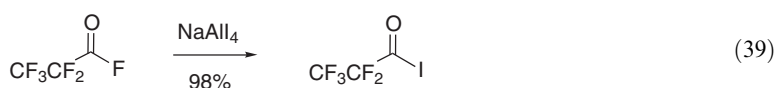
Acid iodides are too reactive to isolate, and are rarely used in organic synthesis. Since the review by Williams <1995COFGT(5)1>, there have been no new methods introduced for specifically making acid iodides. The following is a brief overview of methods currently available.

5.01.1.5.1 Acid iodides from acid chlorides

Acid iodides may be prepared by equilibrium exchange reactions with the more readily available acid chloride (Equation (2)). A mild procedure for the synthesis of alkanoyl, alkenoyl, and aroyl iodides was described by Hoffmann and Haase <1981S715>. The latter method uses 2 equiv. of sodium iodide in thoroughly dried acetonitrile at 0–25 °C. The sodium chloride precipitated out, and the acid iodide was isolated by continuous extraction of the acetonitrile mother liquor with pentane or 2-methylbutane using a reactor-extractor setup. Alternatively, trimethylsilyl iodide can be used as shown in Equation (4) <1981S216>.

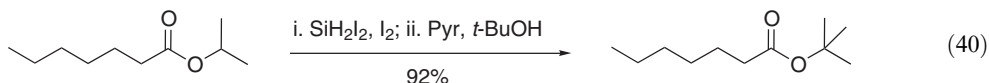
5.01.1.5.2 Acid iodides from acid fluorides (from perfluoroacyl fluorides only)

The replacement of the fluoride by an iodide is usually difficult owing to the greater strength of the C—F bond in comparison to the much weaker C—I bond. However, perfluoroacyl fluorides have been reacted with sodium tetraiodoaluminate to yield the corresponding iodides in almost quantitative yield (Equation (39)) <1991BAU1718>. Fukaya and co-workers described a halogen-exchange requiring higher temperatures (Section 5.01.1.1.3) <1996JCS(P1)915>.



5.01.1.5.3 Acid iodides from carboxylic acid derivatives

Diiodosilane (SiH₂I₂) - iodine can directly convert a variety of carboxylic acid derivatives including carboxylic acids, esters, lactones, anhydrides and acid chlorides into acid iodides in high yields <1990JOC3922>. Equation (40) shows a facile one-pot *trans*-esterification reaction using the weak nucleophilic alcohol, *tert*-butanol, which was successful owing to the high reactivity of the intermediate acid iodide.



REFERENCES

- 1920JA599
1966JA3440
B-1970MI859
B-1972MI35
1973S487
1975CC622
1979CC1180
1979JOC1016
1981S216
1981S715
1984JOC3216
B-1985HOU(E5/1)587
B-1989MI001
1989JFC(43)429
1990JOC3922
1991BAU1718
1991COS(6)301
1992TL7475
1993JCS(P2)307
1994CL209
1994CL849
1994JA11165
R. Adams, L. H. Ulich, *J. Am. Chem. Soc.* **1920**, 42, 599–611.
J. B. Lee, *J. Am. Chem. Soc.* **1966**, 88, 3440–3441.
C. A. Buehler, D. E. Pearson, in *Survey of Organic Synthesis*, Wiley, New York, **1970**, pp. 859–873.
M. F. Ansell, in *The Chemistry of Acyl Halides*, S. Patai, Ed., Interscience, London, **1972**, pp. 35–68.
G. A. Olah, M. Nojima, I. Kerekes, *Synthesis* **1973**, 487–488.
P. Hodge, G. Richardson, *J. Chem. Soc., Chem. Commun.* **1975**, 622–623.
A. Devos, J. Remion, A.-M. Frisque-Hesbain, A. Colens, L. Ghosez, *J. Chem. Soc., Chem. Commun.* **1979**, 1180–1181.
J. Cuomo, R. A. Olofson, *J. Org. Chem.* **1979**, 44, 1016–1017.
A. H. Schmidt, M. Russ, D. Grosse, *Synthesis* **1981**, 216–217.
H. M. R. Hoffmann, K. Haase, *Synthesis* **1981**, 715–719.
D. P. Cox, J. Terpinski, W. Lawrynowicz, *J. Org. Chem.* **1984**, 49, 3216–3219.
B-1985HOU(E5/1)587 *Methoden Org. Chem. (Houben-Weyl)* **1985**, E5/1, pp. 587.
R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, **1989**.
H. Liu, P. Wang, P. Sun, *J. Fluorine Chem.* **1989**, 43, 429–433.
E. Keinan, M. Sahai, *J. Org. Chem.* **1990**, 55, 3922–3926.
I. K. Bil'dinov, L. E. Deev, K. I. Polikevich, P. V. Podsevalov, N. A. Sal'nikova, V. G. Ponomarev, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1991**, 40, 1718.
R. Sustmann, in *Comp. Org. Synth.* **1991**, 6, 301–320.
S. Bains, J. Green, C. L. Tan, R. M. Pagni, G. W. Kabalka, *Tetrahedron Lett.* **1992**, 33, 7475–7476.
D. N. Kevill, D. C. Knauss, *J. Chem. Soc., Perkin Trans. 2* **1993**, 307–312.
K. Nagasawa, K. Ohhashi, A. Yamashita, K. Ito, *Chem. Lett.* **1994**, 209–212.
N. Yoneda, S. Q. Chen, T. Hatakeyama, S. Hara, T. Fukuhara, *Chem. Lett.* **1994**, 849–850.
B. K. Bennett, R. G. Harrison, T. G. Richmond, *J. Am. Chem. Soc.* **1994**, 116, 11165–11166.

- 1995COFGT(5)1 J. M. J. Williams, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 1–21.
- 1995JA5401 L. A. Carpino, A. El-Faham, *J. Am. Chem. Soc.* **1995**, *117*, 5401–5402.
- 1995JFC(73)185 P. S. Bhadury, M. Pandey, D. K. Jaiswal, *J. Fluorine Chem.* **1995**, *73*, 185–187.
- 1996JCS(P1)915 H. Fukaya, T. Matsumoto, E. Hayashi, Y. Hayakawa, T. Abe, *J. Chem. Soc., Perkin Trans. 1* **1996**, 915–920.
- 1996JFC(76)145 S. Rozen, I. Ben-David, *J. Fluorine Chem.* **1996**, *76*, 145–147.
- 1996T2977 S. V. Pasenok, M. E. de Roos, W. K. Appel, *Tetrahedron* **1996**, *52*, 2977–2982.
- 1996T9755 S. V. Pasenok, M. E. de Roos, W. K. Appel, *Tetrahedron* **1996**, *52*, 9755–9758.
- 1996T11177 E. R. Marinelli, T. Arunachalam, G. Diamantidis, J. Emswiler, H. F. R. Neubeck, K. M. R. Pillai, T. R. Wagler, C. K. -Chen, K. Natalie, N. Soundararajan, R. S. Ranganathan, *Tetrahedron* **1996**, *52*, 11177–11214.
- B-1997MI782 C. A. Buehler, D. E. Pearson, in *Survey of Organic Synthesis*, Vol. 2, Wiley, New York, **1997**, pp. 782–793.
- 1997JOC2917 A. Studer, P. Jeger, P. Wipf, D. P. Curran, *J. Org. Chem.* **1997**, *62*, 2917–2924.
- 1997JOC4916 S. Stavber, I. Košir, M. Zupan, *J. Org. Chem.* **1997**, *62*, 4916–4920.
- 1997JOC5908 J. J. Parlow, D. A. Mischke, S. S. Woodward, *J. Org. Chem.* **1997**, *62*, 5908–5919.
- 1997T8105 T. C. Bruice, Y. C. Yip, A. Blaskó, F. C. Lightstone, K. A. Browne, M. E. Petyak, J. Luo, *Tetrahedron* **1997**, *53*, 8105–8120.
- 1997TH43 F. Aldabbagh, Ph.D. Thesis, Loughborough University, U.K., **1997**.
- 1997TL6489 G. B. Villeneuve, T. H. Chan, *Tetrahedron Lett.* **1997**, *38*, 6489–6492.
- 1998JOC8084 J. P. Collman, M. Bröring, L. Fu, M. Rapta, R. Schwenninger, *J. Org. Chem.* **1998**, *63*, 8084–8085.
- 1998S883 R. Wagner, W. Günther, E. Anders, *Synthesis* **1998**, 883–888.
- 1998T4107 K. E. Pryor, G. W. Shipps Jr., D. A. Skyler, J. Rebek Jr., *Tetrahedron* **1998**, *54*, 4107–4124.
- 1998T9207 L. Ghosez, I. George-Koch, L. Patiny, M. Houtekie, P. Bovy, P. Nshimyumukiza, T. Phan, *Tetrahedron* **1998**, *54*, 9207–9222.
- 1999AG(E)3334 K. C. Nicolauo, H. J. Mitchell, H. Suzuki, R. M. Rodríguez, O. Baudoin, K. C. Fylaktakidou, *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3334–3339.
- 1999AG(E)3340 K. C. Nicolauo, R. M. Rodríguez, K. C. Fylaktakidou, H. Suzuki, H. J. Mitchell, *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3340–3343.
- 1999CC215 G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonc, *J. Chem. Soc., Chem. Commun.* **1999**, 215–216.
- 1999EJO2383 R. Wagner, B. Wiedel, W. Günther, H. Görls, E. Anders, *Eur. J. Org. Chem.* **1999**, 2383–2390.
- 1999JFC(93)73 S. K. Ritter, B. K. Hill, M. A. Odian, J. Dai, R. E. Noftle, G. L. Gard, *J. Fluorine Chem.* **1999**, *93*, 73–79.
- 1999JFC(94)213 R. D. Chambers, W. K. Gray, G. Sandford, J. F. S. Vaughan, *J. Fluorine Chem.* **1999**, *94*, 213–215.
- 1999JOC6252 A. C. O'Sullivan, F. Struber, S. V. Ley, *J. Org. Chem.* **1999**, *64*, 6252–6256.
- 1999JOC7048 G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonc, H. Cheng, *J. Org. Chem.* **1999**, *64*, 7048–7054.
- 1999SL1763 S. S. Chaudhari, K. G. Akamanchi, *Synlett* **1999**, 1763–1765.
- 1999TL5323 D. O. Jang, D. J. Park, J. Kim, *Tetrahedron Lett.* **1999**, *40*, 5323–5326.
- 2000JCS(P1)3815 S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, S. J. Taylor, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195.
- 2000JMC4388 K. Kondo, H. Ogawa, T. Shinohara, M. Kurimura, Y. Tanda, K. Kan, H. Yamashita, S. Nakamura, T. Hirano, Y. Yamamura, T. Mori, M. Tominaga, A. Itai, *J. Med. Chem.* **2000**, *43*, 4388–4397.
- 2000JOC979 J. Grugier, J. Xie, I. Duarte, J. M. Valéry, *J. Org. Chem.* **2000**, *65*, 979–984.
- 2000JPR711 S. Groß, S. Laabs, A. Scherrmann, A. Sudau, N. Zhang, U. Nubbemeyer, *J. Prakt. Chem.* **2000**, *342*, 711–713.
- 2000SL1577 C. Girard, I. Trachant, P. A. Nioré, J. Herscovici, *Synlett* **2000**, 1577–1580.
- 2001AJC75 K. A. Jolliffe, *Aust. J. Chem.* **2001**, *54*, 75.
- 2001BCJ1703 T. Komatsu, S. Hayakawa, T. Yanagimoto, M. Kobayakawa, A. Nakagawa, E. Tsuchida, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1703–1707.
- 2001CL222 N. Yoneda, T. Fukuhara, *Chem. Lett.* **2001**, 222–223.
- 2001OL307 K. Parang, E. J. L. Fournier, O. Hindsgaul, *Org. Lett.* **2001**, *3*, 307–309.
- 2001TL3925 A. DalPozzo, R. Bergonzi, M. Ni, *Tetrahedron Lett.* **2001**, *42*, 3925–3927.
- 2002JFC(115)75 C. Chen, C.-T. Chen, C.-H. Su, *J. Fluorine Chem.* **2002**, *115*, 75–77.
- 2002JMAC1684 L. Andruzzi, E. Chiellini, G. Galli, X. Li, S. H. Kang, C. K. Ober, *J. Mater. Chem.* **2002**, *12*, 1684–1692.
- 2002JOC5963 C. P. Causey, W. E. Allen, *J. Org. Chem.* **2002**, *67*, 5963–5968.
- 2002JOC6372 A. DalPozzo, M. Ni, L. Muzi, A. Caporale, R. de Castiglione, B. Kaptein, Q. B. Broxterman, F. Formaggio, *J. Org. Chem.* **2002**, *67*, 6372–6375.
- 2002JOC8832 P. Ballester, M. Capó, A. Costa, P. M. Deyá, R. Gomila, A. Decken, G. Deslongchamps, *J. Org. Chem.* **2002**, *67*, 8832–8841.
- 2002OL1067 M. Querol, H. Stoekli-Evans, P. Belser, *Org. Lett.* **2002**, *4*, 1067–1070.
- 2002OL3287 A. T. Kreipl, C. Reid, W. Steglich, *Org. Lett.* **2002**, *4*, 3287–3288.
- 2002TL8909 G. Luo, L. Xu, G. S. Poindexter, *Tetrahedron Lett.* **2002**, *43*, 8909–8912.

Biographical sketch

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

5.02

Carboxylic Acids

S. P. BEW

University of East Anglia, Norwich, UK

5.02.1	GENERAL METHODS	20
5.02.1.1	By Hydrolysis Reactions	20
5.02.1.1.1	<i>Hydrolysis of esters</i>	20
5.02.1.1.2	<i>Hydrolysis of nitriles</i>	21
5.02.1.1.3	<i>Hydrolysis of amides</i>	22
5.02.1.1.4	<i>Hydrolysis of acyl halides and anhydrides</i>	23
5.02.1.1.5	<i>Hydrolysis of di- and trihalides</i>	23
5.02.1.2	By Carbonation of Organometallic Reagents	23
5.02.1.3	By Oxidation Reactions	24
5.02.1.4	By Miscellaneous Reactions	27
5.02.2	ALKANOIC ACIDS	29
5.02.2.1	Unsubstituted Alkanoic Acids	29
5.02.2.1.1	<i>By hydrolysis reactions</i>	29
5.02.2.1.2	<i>By carbonylation of organometallic reagents</i>	37
5.02.2.1.3	<i>By oxidation reactions</i>	41
5.02.2.2	Haloalkanoic Acids	44
5.02.2.2.1	<i>By hydrolysis reactions</i>	44
5.02.2.2.2	<i>By carbonation of organometallic reactions</i>	49
5.02.2.2.3	<i>By oxidation reactions</i>	49
5.02.2.2.4	<i>By miscellaneous reactions</i>	50
5.02.2.3	Oxygen-substituted Alkanoic Acids	55
5.02.2.3.1	<i>By hydrolysis reactions</i>	55
5.02.2.3.2	<i>By carbonation of organometallic reagents</i>	57
5.02.2.3.3	<i>By oxidation reactions</i>	58
5.02.2.3.4	<i>By miscellaneous reactions</i>	60
5.02.2.4	Sulfur-substituted Alkanoic Acids	62
5.02.2.4.1	<i>By hydrolysis reactions</i>	62
5.02.2.4.2	<i>By carbonation of organometallic reagents</i>	65
5.02.2.4.3	<i>By oxidation reactions</i>	67
5.02.2.4.4	<i>By miscellaneous reactions</i>	67
5.02.2.5	Amino Acids	68
5.02.2.5.1	<i>By hydrolysis reactions</i>	68
5.02.2.5.2	<i>By carbonation of organometallic reactions</i>	75
5.02.2.5.3	<i>By miscellaneous reactions</i>	78
5.02.2.6	Other Nitrogen-substituted Alkanoic Acids	82
5.02.2.6.1	<i>By hydrolysis reactions</i>	82
5.02.2.6.2	<i>By carbonation of organometallic reagents</i>	86
5.02.2.6.3	<i>By oxidation reactions</i>	88
5.02.2.6.4	<i>By miscellaneous reactions</i>	89
5.02.2.7	Other Heteroatom-substituted Alkanoic Acids	90
5.02.2.7.1	<i>By hydrolysis reactions</i>	90
5.02.2.7.2	<i>By carbonation of organometallic reagents</i>	91
5.02.3	α,β -UNSATURATED ACIDS	92
5.02.3.1	By hydrolysis reactions	92
5.02.3.2	By Carbonation of Organometallic Reagents	95
5.02.3.3	By Oxidation Reactions	97
5.02.3.4	By Miscellaneous Reactions	97

5.02.4	HOMO- AND HETEROAROMATIC ACIDS	98
5.02.4.1	By Hydrolysis Reactions	98
5.02.4.2	By Carbonation of Organometallic Reagents	100
5.02.4.3	By Oxidation Reactions	103
5.02.4.4	By Miscellaneous Reactions	105
5.02.5	CARBOXYLIC ACIDS VIA BIOTRANSFORMATIONS	106

5.02.1 GENERAL METHODS

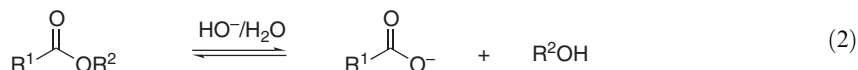
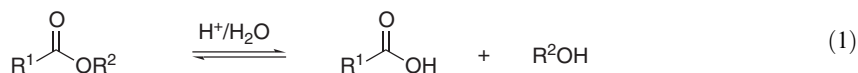
A number of articles, monographs, and books have been published which concern the synthetic methods used to prepare carboxylic acids <B-1968MI502-01, B-1970MI502-01, 1976AR(B)199, B-1977MI502-01, 1978GSM111, B-1978MI502-02, 1979GSM67, B-1979MI502-01, 1980GSM75, 1981GSM87, 1982GSM100, 1982MI502-02, 1983GSM98, 1985GSM96, 1986GSM131, 1987GSM130, 1988GSM75, 1989GSM89, 1990GSM91, B-1991MI502-01, 1992GSM79>. Two reviews on the synthesis of monobasic carboxylic acids have been published <B-1948MI502-01, B-1951MI502-01>. A number of general review articles have been published on the synthesis of dibasic carboxylic acids <B-1947MI502-01, B-1952MI502-01, 1959CRV89, 1966MI502-01, B-1969MI502-02, 1972MI502-01, B-1975MI502-01, 1979MI502-01, 1979MI502-02>; the synthesis of polyacids has been reviewed in four articles <B-1947MI502-02, B-1969MI502-02, 1972MI502-02, 1973RCR939>. Since the publication of COFGT (1995) <1995COFGT(5)23>, a comprehensive search of the literature between 1995 and early 2004 has revealed relatively few new books or monographs dedicated to the synthesis of carboxylic acids. Two reviews on carboxylic acids and esters have been published, which cover the literature from 1996 to 1998 <1998JCS(P1)2451, 1999JCS(P1)3537>. A comprehensive review on the homologation of ketones into carboxylic acids via epoxides, nitriles, vinyl heteroatoms or halides, alcohols, alkenes, acetals and ketals, acrylonitriles, α -hydroxy acids, enamidines, and 1-formylamino-1-arylsulfonyl alkenes has been published <2004T11>.

5.02.1.1 By Hydrolysis Reactions

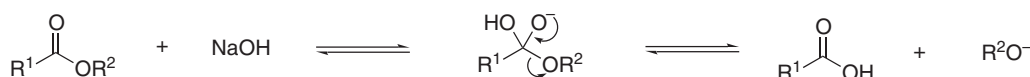
Ester formation results from an equilibrium reaction between alcohols and carboxylic acids. The use of water for the hydrolysis of esters is, in the majority of cases, not trivial. However, a few esters are hydrolyzed when treated with water, for example methyl and ethyl oxalate, ethyl formate, and esters of α -hydroxy acids such as glycolic and lactic acid <1879LA1, 1905JCS747, 1909JCS1004>. The use of supercritical solvents, such as water and carbon dioxide in synthetic chemistry has many advantages over conventional organic solvents. Supercritical solvents are, for example, nontoxic, nonflammable in nature, environmentally friendlier, cheaper, and readily available. Lesutis and co-workers have demonstrated that substituted benzoic esters are hydrolyzed via an autocatalytic acid/base $A_{AC}2$ mechanism in supercritical water. The incorporation of longer aliphatic chains and branched chain alcohols within the ester functionality reduces the rate of hydrolysis <1999CC2063>. Oka and co-workers conducted a study into the effect of using supercritical water on the hydrolysis of racemic methyl 2-phenylpropionate. They concluded that the hydrolysis of this ester in supercritical water takes place via an ionic mechanism, whereby hydroxide ions dissociate from the supercritical water and catalyze the reaction <2002Ag(E)623>.

5.02.1.1.1 Hydrolysis of esters

Since an alcohol is a much poorer leaving group than, for example, a halide, water alone is not capable of hydrolyzing many ester groups. The majority of esters are, however, hydrolyzed using either acidic (hydrolysis) or basic (saponification) conditions. Although the reaction products from a hydrolysis (Equation (1)) and a saponification reaction (Equation (2)) are in principle very similar, they are formed via different mechanisms which require different stoichiometries of reagents. The hydrolysis pathway (Equation (1)) proceeds using catalytic amounts of acid with the basic or saponification reaction (Equation (2)) requiring equimolar quantities of base.



Ingold has classified the acid- and base-catalyzed hydrolysis of esters (as well as the formation of esters, as these reactions are reversible) into eight possible mechanisms, depending on the following criteria: (i) acid- or base-catalyzed, (ii) unimolecular or bimolecular, and (iii) acyl cleavage or alkyl cleavage <B-SMOC1969>. All eight proposed mechanisms proceed via either an $\text{S}_{\text{N}}1$, $\text{S}_{\text{N}}2$, or tetrahedral intermediate. The hydrolysis of an ester using aqueous alkali is, generally, accepted to take place via a two-step mechanism ($\text{B}_{\text{AC}}2$) with the initial formation of a rate-determining tetrahedral intermediate (Scheme 1).



Scheme 1

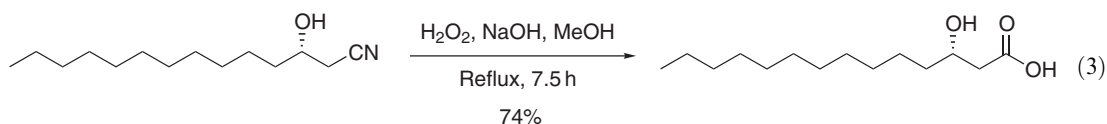
However, Marlier <1993JA5953> and Mata-Segreda <2002JA2259> have challenged this commonly held mechanistic view based on the results they obtained, independently, from heavy-atom kinetic isotope effects. Both authors concluded that the hydrolysis of simple alkyl esters proceeds via a nucleophilic interaction of a water molecule with general-base assistance from a hydroxide ion.

5.02.1.1.2 Hydrolysis of nitriles

The ability to introduce the nitrile group into a wide range of substrates via, for example, the addition of the cyanide anion to carbonyl groups such as aldehydes, ketones, and α,β -unsaturated carbonyl compounds or nucleophilic displacement processes, in conjunction with the relative ease with which the nitrile group is hydrolyzed, make this a particularly useful functional group transformation in synthetic chemistry. Nitrile hydrolysis using acidic or basic reaction conditions yields either amides in the first instance or, since amides can also be further hydrolyzed, carboxylic acids (Scheme 2). If a carboxylic acid is desired, then the reagent of choice for the hydrolysis of a nitrile is methanolic aqueous sodium hydroxide containing hydrogen peroxide (Equation (3)) <1995JOC6148, 1999TA2945>. Due to the harsh reaction conditions routinely employed during this transformation, base-sensitive functional groups can be attacked. The hydrolysis of cyclopropyl nitrile to the corresponding cyclopropyl carboxylic acid has been accomplished using water <55OSC(3)321>.

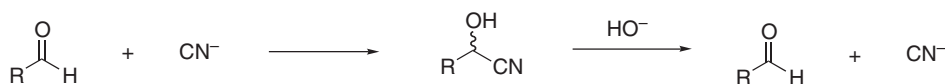


Scheme 2



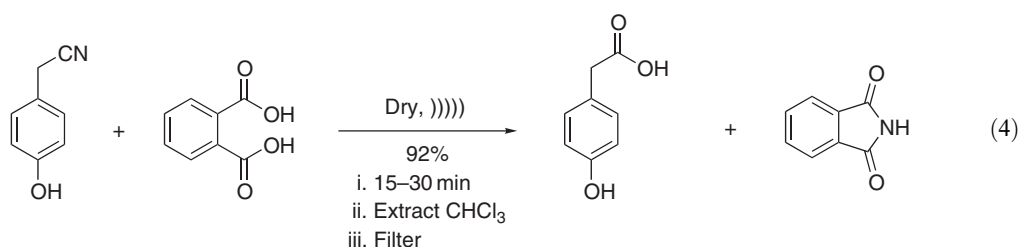
Although a number of procedures are available for the synthesis of amides from nitriles <1980S243, 1998TL3005, 1995TL3469>, this review is concerned with the transformation of nitriles directly into carboxylic acids. A number of general synthetic methods for the acidic hydrolysis of nitriles directly into carboxylic acids have been published <OSC(1)21, OSC(4)496, OSC(4)804, OSC(4)790>.

As recounted, nitriles can be transformed into carboxylic acids using either acidic or basic reaction conditions. However, the hydrolysis of cyanohydrins is ordinarily undertaken in acid; this is a consequence of basic reaction conditions resulting in competitive reversion of the cyanohydrin back to the aldehyde and cyanide anion (Scheme 3).



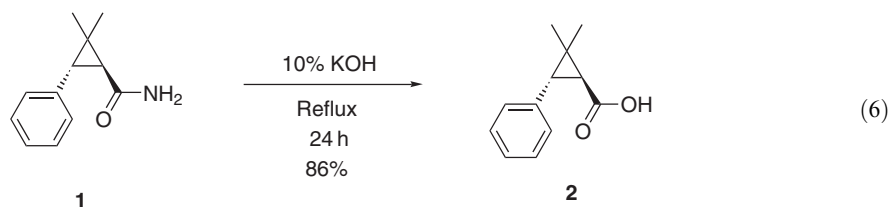
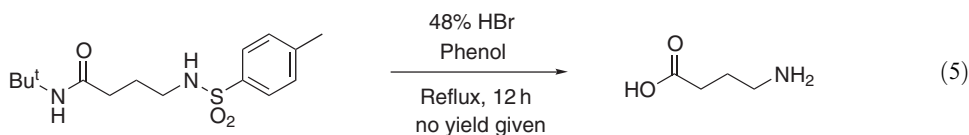
Scheme 3

An alternative protocol for transforming nitriles into carboxylic acids is Matthew's one-pot, "dry" hydrolysis reaction procedure <1898JA648>. Using microwave irradiation, Chemat investigated the potential for rate enhancement in the hydrolysis of nitriles using phthalic acid. The desired carboxylic acids were returned in good-to-excellent yields (53–99%) and significantly shorter reaction times, usually 15–30 min (Equation (4)) <2002TL5555>.



5.02.1.1.3 Hydrolysis of amides

Primary, secondary, and tertiary amides as well as lactams and imides undergo hydrolysis in the presence of alkali hydroxides or mineral acids in much the same manner as esters and nitriles to yield carboxylic acids. Water on its own is not sufficient to hydrolyze the majority of amides; this can be attributed to the N^-H_2 group being a poorer leaving group than water. Similar to the nitrile and ester functional groups, acidic (Equation (5)) <1994JOC1904> and basic reagents <OSC(4)58, 1993JOC898> can be used for transforming amides into carboxylic acids. 2,2-Dimethyl-3-substituted cyclopropanecarboxamides **1** have been saponified, with no evidence of any racemization, to the corresponding carboxylic acids **2** using aqueous 10% potassium hydroxide (Equation (6)) <2003JOC621>.



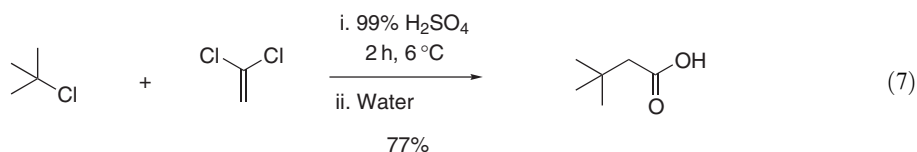
Unsubstituted amides can be hydrolyzed with either acidic or basic reagents, the reaction products being the free acid, the ammonium ion or the salt of the acid and ammonia, respectively. *N*-Substituted and *N,N*-disubstituted amides can be hydrolyzed using similar protocols, resulting in primary or secondary amines, respectively. With recalcitrant amides the use of nitrous acid can often be beneficial, the reaction proceeding via an intermediary diazonium ion. The formation of a diazonium ion significantly increases the rate of the hydrolysis reaction <1990TL3893>. The use of aqueous sodium peroxide <1975JOC1187> or potassium *t*-butoxide and water <1976JA1275> for the hydrolysis of particularly difficult amides has proved useful.

5.02.1.1.4 Hydrolysis of acyl halides and anhydrides

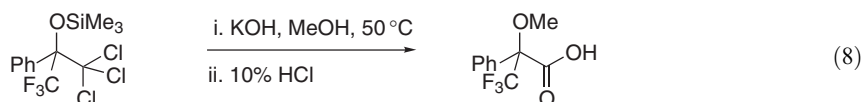
The hydrolysis of acyl halides and anhydrides to the corresponding carboxylic acids can be undertaken using protocols similar to those already outlined for amides (Section 5.02.1.1.3) and esters (Section 5.02.2.1.1). The increased reactivity of acyl chlorides means, however, that the hydrolysis of acid halides is considerably easier and does not, on the whole, require the presence of a base, particularly for aliphatic acid chlorides. Indeed, the hydrolysis of aliphatic acyl chlorides, and more especially acyl bromides, using water should be undertaken with care. Compared to acid chlorides, acid anhydrides are relatively stable to water and, generally, for the efficient hydrolysis of anhydrides the addition of a base is required.

5.02.1.1.5 Hydrolysis of di- and trihalides

The synthesis of 1,1-dihaloalkenes can be readily undertaken via a Corey–Fuchs reaction between an aldehyde, triphenylphosphine, and either carbon tetrachloride or carbon tetrabromide, yielding the corresponding 1,1-dichloro or 1,1-dibromoalkenes, respectively, in generally good yields <1995S1003, 1997BMCL3053, 1999JA6816>. The hydrolysis of 1,1-dihaloalkenes using acidic reaction conditions affords the corresponding carboxylic acids. The use of strong mineral acids, such as sulfuric acid, can pose problems, especially if the 1,1-dihaloalkene has acid-sensitive functional groups. The reaction of carbonium ion precursors, such as secondary and tertiary alcohols, esters of tertiary alcohols or alkenes, with 1,1-dichloroethylene in the presence of concentrated sulfuric acid affords the corresponding carboxylic acid appended with two or more carbon atoms than contained in the intermediate carbonium ion (Equation (7)) <1985S493>.



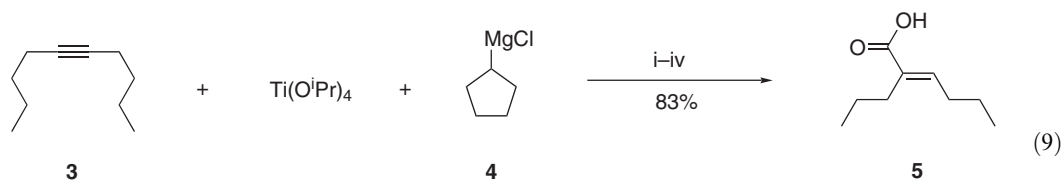
The acid hydrolysis of trihaloalkanes affords carboxylic acids; however, the synthetic utility of this transformation is severely limited by the number of protocols available for the synthesis of the trihaloalkane starting materials. The primary synthetic procedures utilized are: (i) the free-radical addition of a carbon tetrahalide to an alkene and (ii) the free-radical halogenation of methyl groups. Both procedures, being free-radical in nature, impose limitations on the types of functional groups that can be present during the haloalkane synthesis. The hydrolysis of trihaloalkane derivatives usually requires strong acid or base but has been accomplished with water under pressure (Equation (8)), and this therefore precludes the presence of acid- or base-sensitive functional groups in the trihaloalkane starting material <1992JOC3731>.



5.02.1.2 By Carbonation of Organometallic Reagents

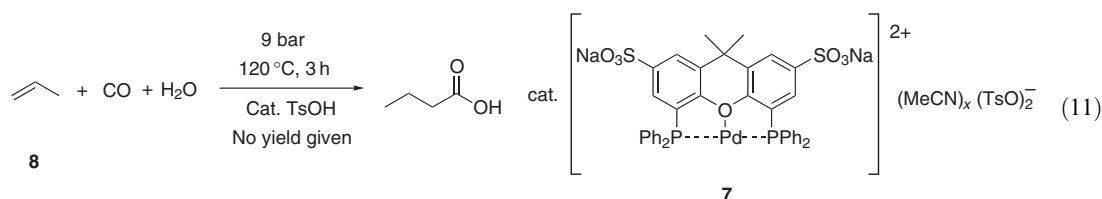
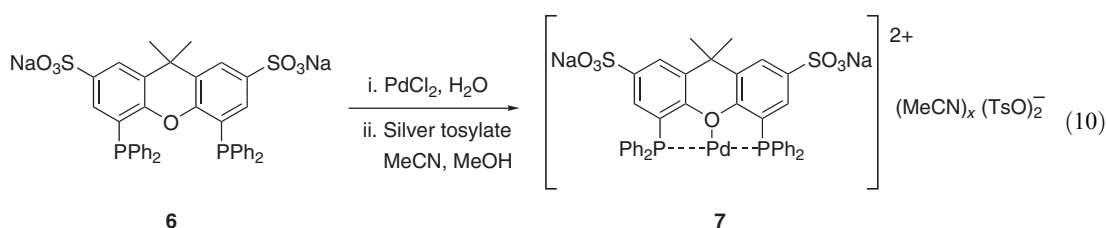
A large number of organometallic reagents have been reacted with both gaseous and solid carbon dioxide affording, in general, the corresponding carboxylic acids in high yields. A general review on the carbonation of organometallic reagents has been published <B-1969MI502-01>, as well as separate reviews which focus on the use of organolithium <1954OR(8)258> and organomagnesium reagents <1970S615>.

The postulated generation of a dialkoxytitanacyclopropane from Grignard reagent **4** and titanium tetra(isopropoxide) or dialkoxytitanacyclopropenes using the same reagents but in the presence of, for example, the nonterminal alkyne **3**, affords when reacted with carbon dioxide and, after hydrolysis, a diversely substituted carboxylic acid **5** (Equation (9)). The choice of solvent (diethyl ether) is critical to success in this reaction, returning carboxylic acids in poor-to-high yields (19–87%) <2002JCS(P1)1159>.



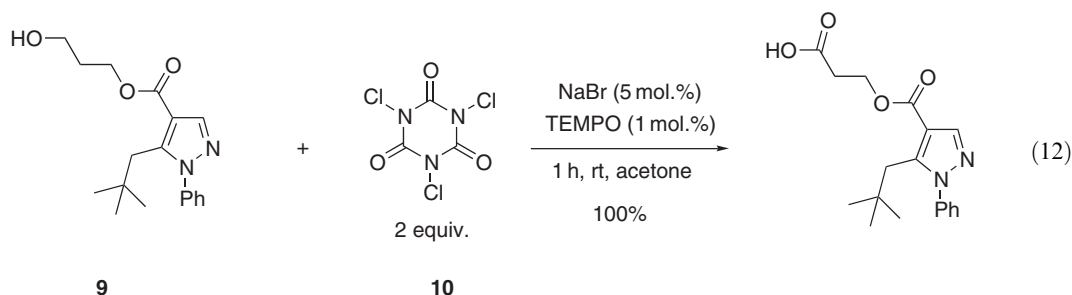
i. Et_2O , -70°C ; ii. -30°C , 15 min; iii. CO_2 , -70°C ; iv. basic/acidic work-up

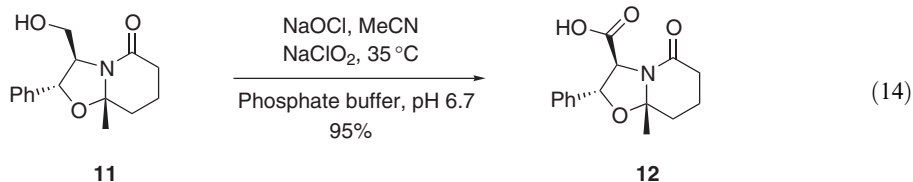
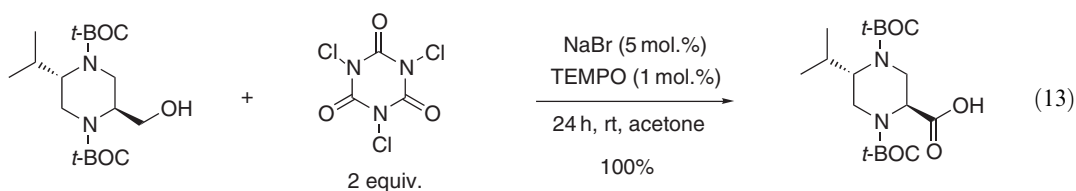
The synthesis of water-soluble ligands for use in catalysis is becoming increasingly important, especially for organic solvent-free synthesis. A water-soluble bidentate catalyst derived from ligand **6** was transformation into species **7** by reacting ligand **6** with palladium chloride and subsequently adding 2 equiv. of silver tosylate (Equation (10)). Utilizing the dicationic catalyst **7**, the hydrocarboxylation of the $\text{C}=\text{C}$ bonds of ethene, propene **8**, and styrene under biphasic reaction conditions has been described (Equation (11)). The hydrocarboxylation reaction was 100% selective for ethene and propene with no evidence of polymer or oligomer formation, and in addition no metallic palladium was observed and turnover numbers remained high <1998CC2431>.



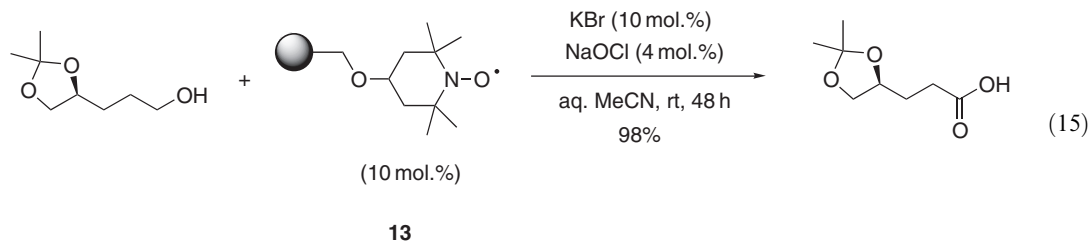
5.02.1.3 By Oxidation Reactions

Several protocols for the conversion of primary alcohols directly into carboxylic acids have been reported. The efficient oxidation of primary alcohols, for example **9**, can be carried out at room temperature using a mixture of trichloroisocyanuric acid **10** in the presence of 1 mol.% 2,2,6,6-tetramethylpiperidiny-1-oxy (TEMPO) and sodium bromide (5 mol.%) <2003JOC4999>. The reaction is usually complete in 1–24 hours, if 2 equiv. of **10** are employed, functional groups (Equation (12)) and chiral nonracemic stereogenic centers (Equation (13)) are tolerated. Oxidation of secondary alcohols yields the corresponding ketones and although α,β -unsaturated alcohols do yield the desired carboxylic acids, the $\text{C}=\text{C}$ bond is chlorinated in the reaction process. An earlier paper reports that a mixture of sodium chlorite and catalytic amounts of sodium hypochlorite in conjunction with catalytic quantities of TEMPO, in an aqueous phosphate buffer (pH 6.7)/acetonitrile mix, readily oxidizes the primary alcohol **11** to the corresponding carboxylic acid **12**. This protocol tolerates functional groups and chiral nonracemic stereogenic centers (Equation (14)) <1999JOC2564>.

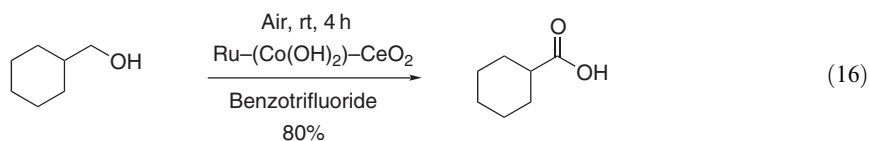




Yasuda and Ley have reported the use of catalytic amounts (10 mol.%) of polymer-supported TEMPO **13** and solid-supported (polystyrene) sodium chlorite, synthesized from Amberlyst IRA 900 by ion exchange with a sodium chlorite solution. Using this heterogeneous reaction mixture the oxidation of a series of primary alcohols to the corresponding carboxylic acids was undertaken (Equation (15)). Importantly, the mild reaction conditions tolerate the presence of ester, epoxide, acetal, and benzyl groups <2001SL1555, 2002JCS(P1)1024>. A review on the use of stable nitroxyl radicals, such as TEMPO in oxidation processes, has been published <1996S1153>.



The oxidation of aliphatic alcohols to the corresponding carboxylic acids using a heterogeneous catalyst composed of microcrystals of cobalt hydroxide and cerium oxide in conjunction with ruthenium under an atmosphere of oxygen has been reported. The specific use of ruthenium, cobalt, and cerium was found to be necessary for the oxidation procedure to return high yields (64–97%) of the acids (Equation (16)). The addition of catalytic amounts of water improved the yields of branched carboxylic acids <2002TL7179>.

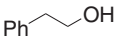
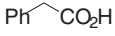
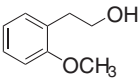
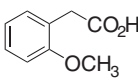
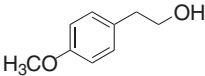
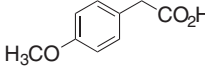
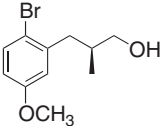
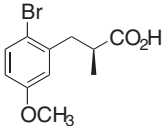


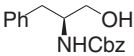
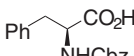
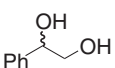
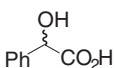
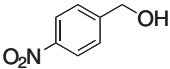
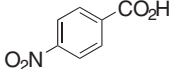


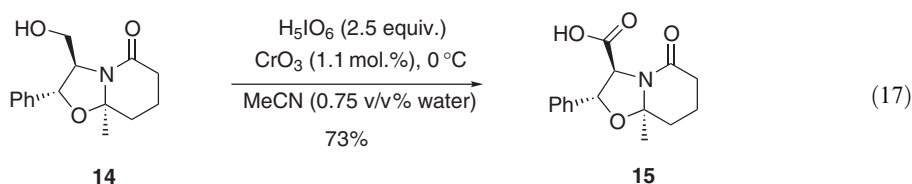
A catalytic procedure that utilizes sodium tungstate and methyltrioctylammonium hydrogen sulfate, as a phase-transfer catalyst, in conjunction with hydrogen peroxide is an efficient, practical protocol for the oxidation of alcohols to carboxylic acids in good to high yields (52–87%). The procedure does not use organic solvents, is organic and inorganic halide-free and is only mildly acidic. A wide variety of alkyl, *t*-butyldimethylsilyl ethers, epoxy, carbonyl, *N*-alkyl carboxamide, and nitrile groups are tolerated <1999BCJ2287, 1997JA12386>.

The oxidation of primary and benzylic alcohols to the corresponding carboxylic acids proceeds in 37–99% yields with catalytic quantities (2.7–3.3 mol.%) of ethyl phosphonate-modified silica in conjunction with sodium bromate as the re-oxidant in refluxing acetonitrile. The catalyst can be recycled, providing consistently good yields of returned carboxylic acid <2003TL769>.

A novel catalytic chromium trioxide (0.6–1.6 mol.%) oxidation of a diverse number of primary alcohols to carboxylic acids (73–100%) has been developed employing periodic acid (1.25–2.5 equiv.) as the stoichiometric re-oxidant, in wet (0.75 vol.%) acetonitrile (Table 1). No significant racemization was observed when, for example **14** with an adjacent chiral nonracemic stereogenic center was oxidized to the corresponding carboxylic acid **15** (Equation (17)). The reaction did not proceed if the chromium trioxide was left out <1998TL5323>.

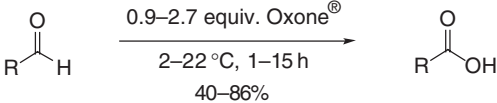
Table 1 Chromium trioxide oxidation of alcohols to carboxylic acids

Substrate	Temp/ H_5IO_6/CrO_3	Product	Yield (%)
	0/2.5/1.1		96
	0/2.5/1.1		98
	0/2.5/1.1		92
	0/2.5/1.1		95
	0/2.5/1.1		90
	0/2.5/1.1		83
	0/3.5/1.6		77
	0/2.5/1.1		100



Oxone[®] (potassium peroxymonosulfate) is a commercially available, cheap, easy-to-handle oxidizing agent. The oxidation of aryl aldehydes to the corresponding aryl carboxylic acids in good-to-excellent yields (71–90%) has been undertaken using Oxone[®] in either aqueous acetone, water, or aqueous acetonitrile buffered with sodium bicarbonate. Oxidizing aliphatic aldehydes using acetone as the solvent resulted in modest increases in the yields. Longer, linear aliphatic alcohols returned higher yields than shorter chained alcohols (Table 2) <1998T401>.

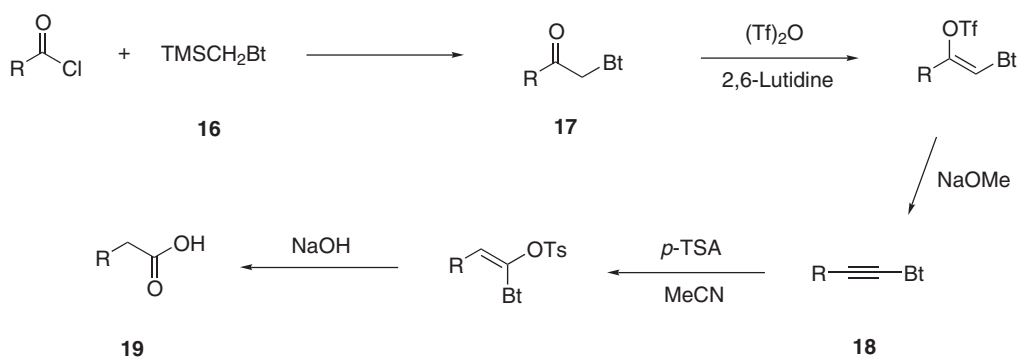
Table 2 Oxidation of aldehydes to carboxylic acids using Oxone[®]



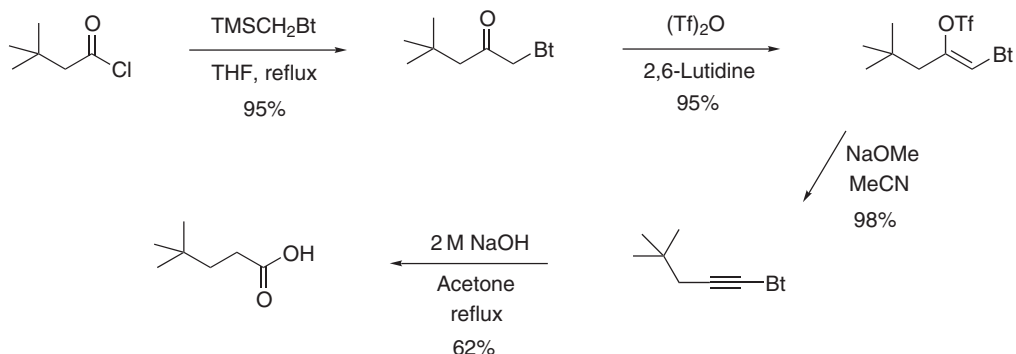
Aldehyde	Product	Oxone (equiv.)	Temp & time	Yield (%)
Phenyl acetaldehyde	Phenylacetic acid	2.7	2 °C, 15 h	63
Butyraldehyde	Butyric acid	0.9	22 °C, 2.5 h	72
Nonyl aldehyde	Nonoic acid	1.8	22 °C, 1.5 h	86
Isovaleraldehyde	Isovaleric acid	1.8	22 °C, 1 h	72
Phenylpropargyl aldehyde	Phenylpropionic acid	0.9	2 °C, 3.5 h	73

5.02.1.4 By Miscellaneous Reactions

A comprehensive review on the homologation of ketones into carboxylic acids has been published. The article covers the synthesis of carboxylic acids using, as starting materials: α -ester epoxides, α -arylsulfinyl epoxides, α -chloro- α -ester epoxides, nitriles, cyanohydrins, vinyl heteroatoms or halides, thioenol ethers, enamines, vinylboronic esters, alcohols, alkenes, acetals, ketals, derivatives of ketene *S,S* and *O,S*-acetals, acrylonitriles, α -aminoacrylonitriles, α -hydroxy acids, and enamidines <2004T13>. The Arndt–Eistert reaction is probably the most important synthetic method for the conversion of a carboxylic acid via a Wolff rearrangement into a one-carbon higher homologated carboxylic acid. The use of ultrasonic irradiation to enhance the rate and, as a consequence reduce the reaction times, of the Wolff rearrangement has been reported <1996TL1781>. The transformation of a series of acyl chlorides into the corresponding one-carbon carboxylic acid homologs has been undertaken using 1-[(trimethylsilyl)methyl]-1*H*-1,2,3-benzotriazole **16**, taking advantage of the anion-stabilizing capabilities and the leaving group properties associated with benzotriazole. Reacting an acyl chloride with 1-[(trimethylsilyl)methyl]-1*H*-1,2,3-benzotriazole **16** afforded *N*-(acylmethyl)benzotriazole **17** and reaction of **17** with triflic anhydride yielded the enol triflate which could be transformed into alkynylbenzotriazole **18** using sodium methoxide. Subsequent saponification with sodium hydroxide afforded the homologated carboxylic acid **19** (Scheme 4) in overall yields of 50–70% <2000OL3789>. This protocol was further elaborated into a convenient, safer alternative to the conventional Arndt–Eistert reaction that is widely applicable to both aliphatic (Scheme 5) and aromatic carboxylic acids <2001JOC5606>.



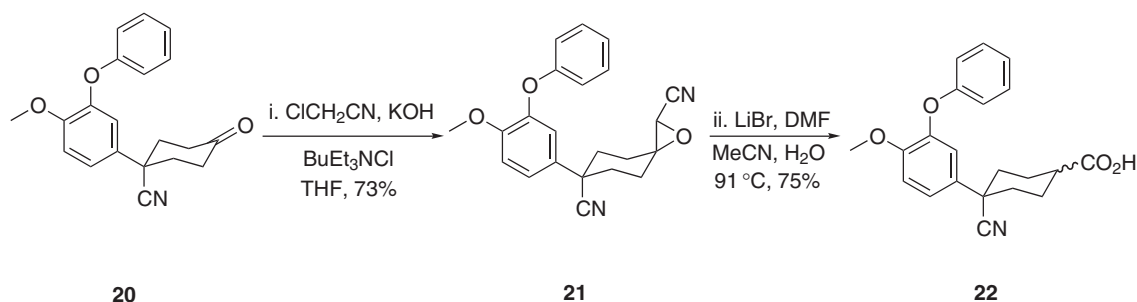
Scheme 4



Scheme 5

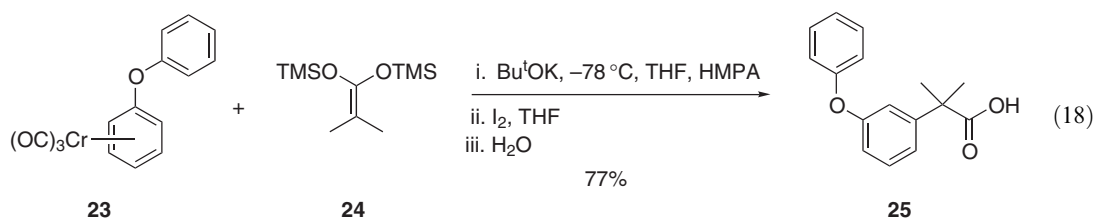
A convenient two-step homologation of aliphatic and aromatic ketones to the corresponding carboxylic acids has been developed. The initial step is the transformation of ketone **20** into epoxynitrile **21** via a Darzens reaction (46–80%). Epoxide ring opening by treatment with Lewis acid and subsequent hydrolysis returns the desired carboxylic acids, for example **22**, in 49–75%

yields (Scheme 6). The methodology does not extend to the use of α,β -unsaturated ketones, i.e., synthesis of α,β -unsaturated carboxylic acids <2002JOC5440>.

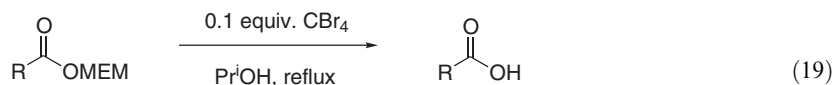


Scheme 6

Arenechromium tricarbonyl species **23** react with bis(trimethylsilyl)ketene acetals, for example **24** affording, via a one-step protocol that includes an oxidative removal of the chromium tricarbonyl species, 3-aryl-2,2-substituted propionic acids **25** in good yields (Equation (18)) <1999CC187>.



The selective cleavage, under mild reaction conditions, of a *p*-methoxybenzyl ester to the corresponding carboxylic acid would be a highly useful synthetic transformation. The deprotection of *p*-methoxybenzyl esters using catalytic quantities of zirconium(IV) chloride (20 mol.%) was rapid (30–90 min), high yielding (67–86%) and tolerant of other substrates, i.e., carbohydrates, terpenes, and amino acids and protecting groups, such as *t*-BOC and trityl groups <2003JOC4574>. A series of MEM-esters have been hydrolyzed, in high yields (91–95%) to the corresponding carboxylic acids (Equation (19)) using catalytic quantities of carbon tetrabromide (10%) in refluxing isopropanol (Table 3). Interestingly, the reaction is not only quicker but also cleaner when conducted in isopropanol instead of methanol. The procedure is widely applicable to many substrate types; for example, primary, secondary, aryl-substituted *sp*²- and *sp*-tethered MEM esters are all rapidly (90 min) cleaved to their corresponding carboxylic acids. The reaction conditions are tolerant of a number of trialkylsiloxyl groups <2001T2121>.



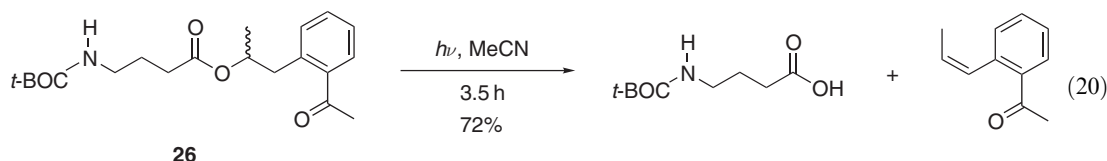
See Table 3

A number of procedures for the photochemical cleavage and release of carboxylic acids have been reported. Carboxylate groups incorporated next to the keto group of an α -keto amide have been photochemically cleaved in aqueous media in good-to-high yields (70–90%) <2003OL71>. The easily synthesized 2,5-dimethylphenacyl group acts as a readily photocleavable protecting group for aliphatic, aromatic, and α -amino carboxylic acid esters. The 2,5-dimethylphenacyl group is readily synthesized by refluxing a mixture of α -chloro-2,5-dimethylacetophenone, the sodium salt of the carboxylic acid to be protected, sodium iodide, and triethylamine. Irradiation of the 2,5-dimethylphenacyl ester using a quartz immersion well reactor affords the free carboxylic acid, after its extraction with sodium carbonate and subsequent release with mineral acid <2000OL1569>.

Table 3 Deprotection of MEM-esters to the corresponding carboxylic acids

Substrate	Product	Yield (%)
		95
		92
		96
		93
		92
		95
		93
		91

A similar photocleavable carboxylic acid protecting group is 1-[2-(2-hydroxyalkyl)phenyl]ethanone or HAPE ester. When subjected to photolysis the HAPE ester **26** undergoes a γ -H abstraction, similar to a Norrish-type II reaction which then, via intersystem crossing, yields an enol which subsequently eliminates a carboxylic acid (Equation (20)) <2003OL4469>.



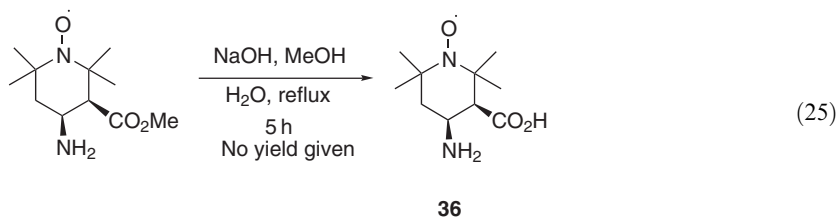
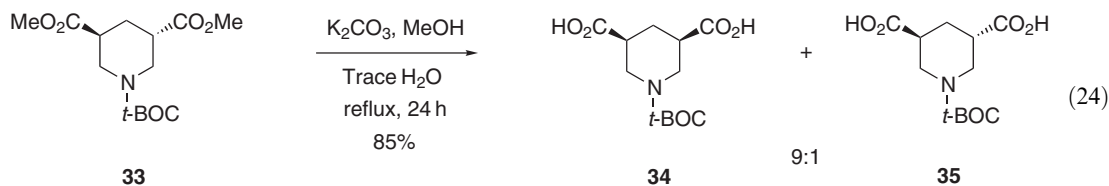
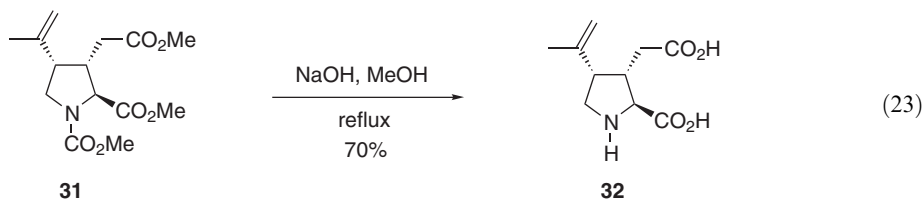
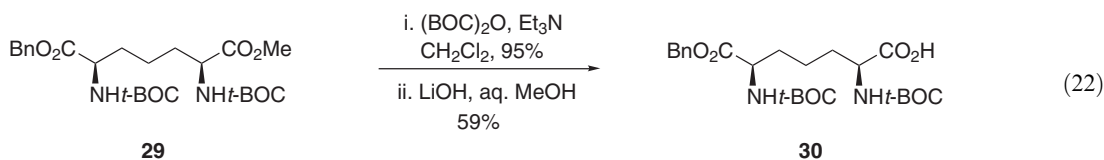
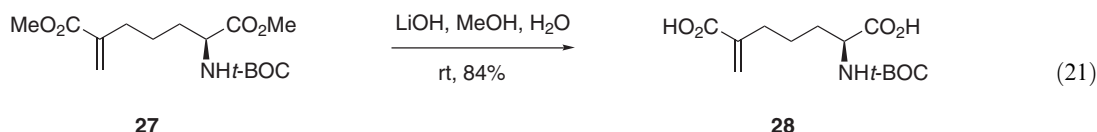
5.02.2 ALKANOIC ACIDS

5.02.2.1 Unsubstituted Alkanoic Acids

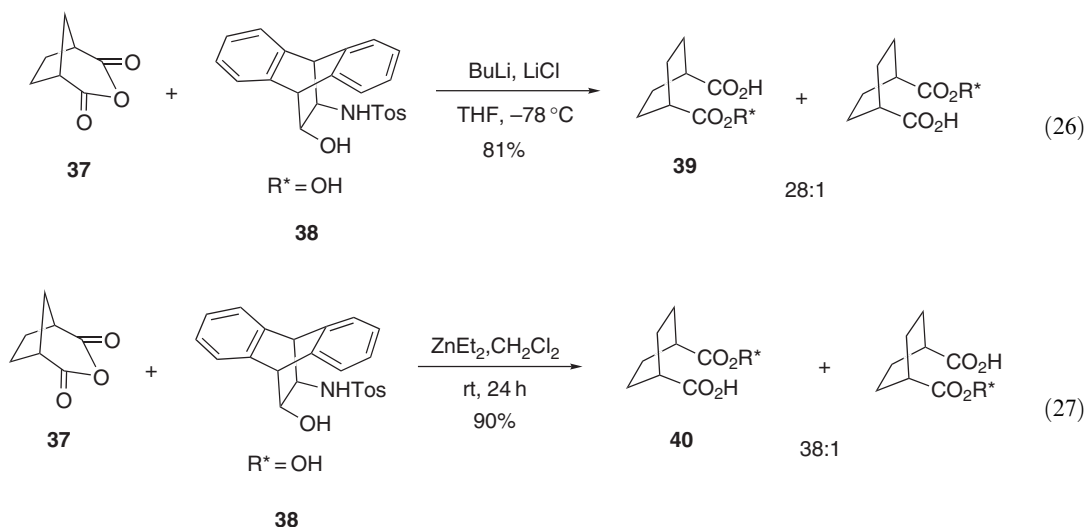
5.02.2.1.1 By hydrolysis reactions

The hydrolysis of an ester, yielding a carboxylic acid and an alcohol, is perhaps one of the oldest and fundamentally most important reaction transformations. It is therefore not surprising that many novel synthetic procedures for the hydrolysis of the ester functional group have been published. The hydrolysis of an ester is routinely undertaken in either acidic or basic reaction conditions, whether acidic or basic conditions are used is often determined by appended functionality present on the starting material. Group 1 hydroxides are convenient and cheap saponification reagents. So long as the carboxylic esters are not sterically hindered, the hydrolysis of methyl and homologous esters using alkali hydroxides is usually rapid and high yielding. Typical hydrolysis reagents, reaction conditions, and yields can be outlined

using the following examples. Treatment of dimethyl ester **27** (Equation (21)) with an aqueous methanolic lithium hydroxide solution at room temperature cleaved both ester groups furnishing the corresponding diacid **28** <1999CC555>. Interestingly, treatment of a mixed methyl/benzyl diester **29** with 1 equiv. of lithium hydroxide afforded selective cleavage of the methyl over the benzyl ester **30** (Equation (22)), demonstrating the orthogonality between the two ester groups <2002CC224>. Substituting lithium hydroxide as a saponification reagent for sodium hydroxide is also viable <2001TL7163>. The last step in Taylor's synthesis of (–)- α -kainic acid utilized a saponification step with sodium hydroxide in refluxing methanol (Equation (23)). Interestingly, not only are the two *trans*-substituted methyl ester groups on **31** hydrolyzed but also the carbamate group, the resulting nitrogen-appended carboxylic acid decarboxylating to afford **32** <1999CC245>. The hydrolysis of dimethyl esters has also been accomplished in high yield using potassium carbonate and trace amounts of water in refluxing methanol (Equation (24)). During this transformation the *trans*-dimethyl ester **33** was isomerized to predominantly the *cis*-dicarboxylic acid **34** (9:1, *cis:trans*) <2003TL1611>. Stable nitroxide free radicals are of interest as spin labels for the study of the conformation and structure within biological systems. The development of chiral nonracemic β -amino acid-derived spin labels for attachment to biological systems is therefore of interest. The final steps in the synthesis of 4-amino-1-oxy-2,2,6,6-tetramethyl-piperidine-4-carboxylic acid **36** (β -TOAC) incorporated a saponification procedure (Equation (25)) <2003TL3381>.



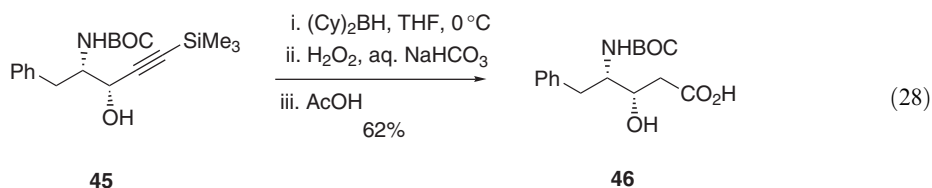
A highly efficient reaction which differentiates between the enantiotopic carbonyl groups of *meso*-1,2-dicarboxylic anhydride **37** has been developed using the chiral nonracemic dilithium salt of an *N*-tosylamino alcohol **38** affording principally the (*S*)-carboxylic acid **39** (Equation (26)). Similarly employing **37**, but incorporating the zinc complex of **38**, afforded the opposite antipode (*R*)-carboxylic acid **40** (Equation (27)) <1996TL9237>.



A new protocol for the transformation of: (i) terminally silylated alkynes, for example **41**, and (ii) terminal thioether alkynes to carboxylic acids of the same chain length, in reasonable yields (30–59%) has been reported (Scheme 7). Conversion of terminal (trimethylsilyl)alkynes **41** to the desired alkyne thioethers **43** was achieved in two steps: benzenesulfonyl chloride addition to the alkyne C—C triple bond, affording **42** was followed by the concomitant β -elimination of the chloride anion and the trimethylsilyl group. Hydrolysis of the alkynyl sulfide on **43** was readily undertaken using an ion exchange Dowex 50X resin impregnated with 20% mercuric sulfate affording carboxylic acid **44** <1996JOC1817>. The transformation of stereochemically enriched propargylic alcohols, an example being **45** into chiral nonracemic 3-hydroxy-4-substituted carboxylic acid **46**, can be readily undertaken via a one-pot hydroboration using dicyclohexylborane. Subsequent oxidative work-up in basic medium affords, in reasonable to good yields (62–99%), the desired carboxylic acids (Equation (28)) <2000T9305>.

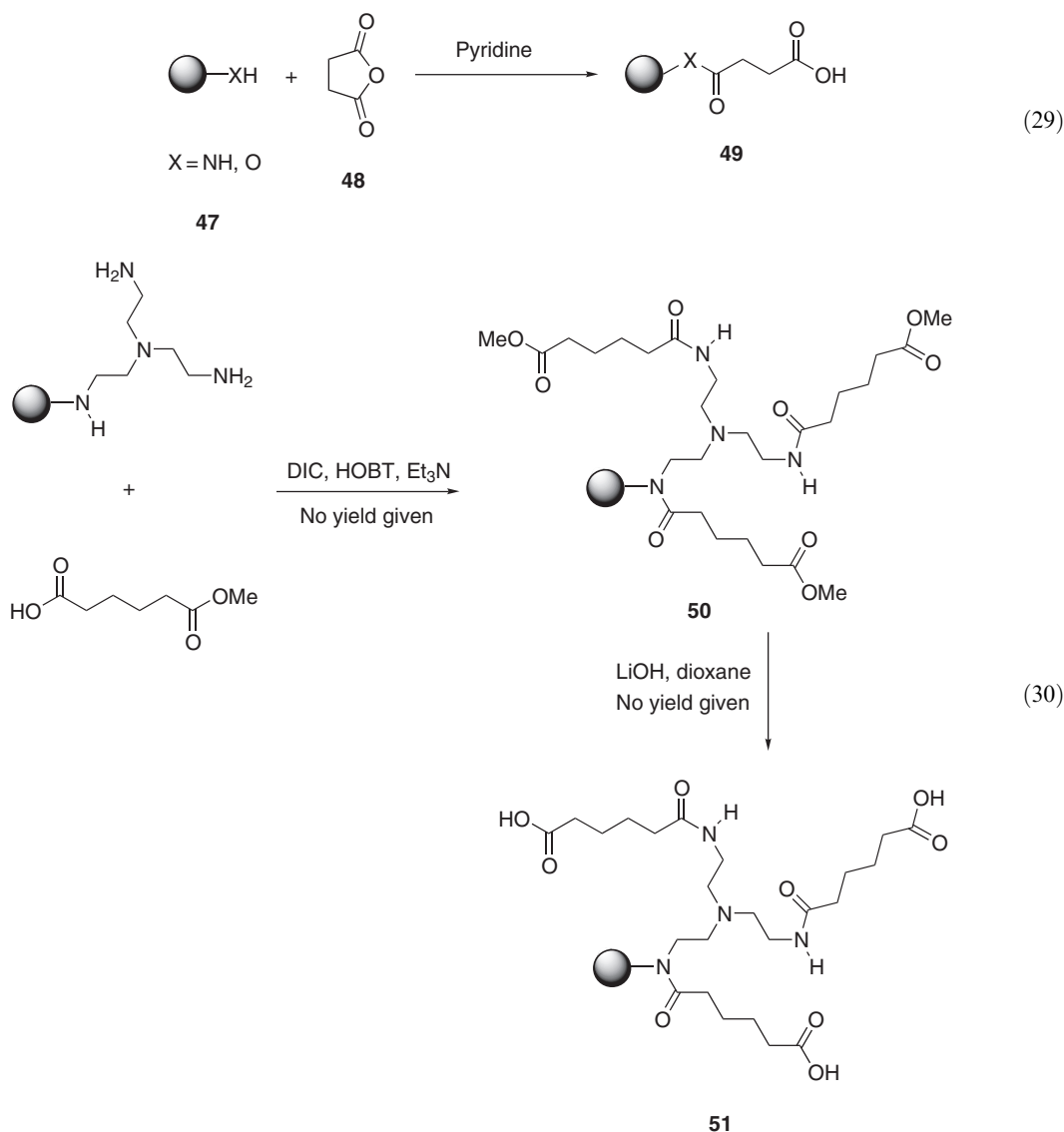


Scheme 7



The use of solid supports in synthetic chemistry has grown substantially in recent years. The synthesis of polymer-bound carboxylic acids, suitable for subsequent manipulation, can be readily undertaken by reacting the desired polymer scaffold **47**, as its alcohol or amine derivative with,

for example, succinic anhydride **48** (Equation (29)) or glutaric anhydride <1996TL1149>. The resulting solid-supported carboxylic acid, for example **49**, can be used for the immobilization of, for example, amines, alcohols, thiols, and phenols. Using polystyrene and TentaGel a number of solid-supported carboxylic acids **51** have been synthesized via the hydrolysis of the corresponding esters **50** (Equation (30) and Scheme 8). In an alternative protocol the synthesis of the ether-linked immobilized carboxylic acid **54** has been undertaken via the oxidation of the primary alcohol on **52** using 1-hydroxy-1,2-benziodoxol-3(*1H*)-one (IBX) affording aldehyde **53**; subsequent oxidation of aldehyde **53** using MCPBA returned the desired carboxylic acid **54** (Scheme 9) <2002CC1748>.



Many of the reagents and catalysts employed in solution-phase deprotection/cleavage protocols can be transformed into the corresponding solid-supported variants. Limura and co-workers have demonstrated the hydrophobic polystyrene-supported sulfonic acid **55** to be a highly effective catalyst for the hydrolysis, in water, of thioesters to the corresponding carboxylic acids (Table 4). Optically active thioester **56** was hydrolyzed with only slight loss of enantiomeric excess, 93–97% ee, to the corresponding carboxylic acid **57** (Equation (31)). The polymer-supported catalyst was superior to other Brønsted acids <2003OL101>.

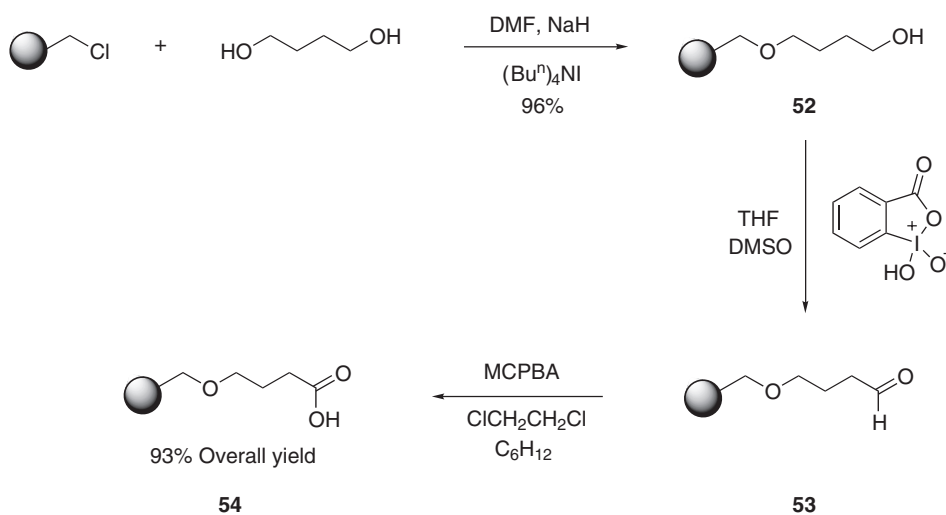
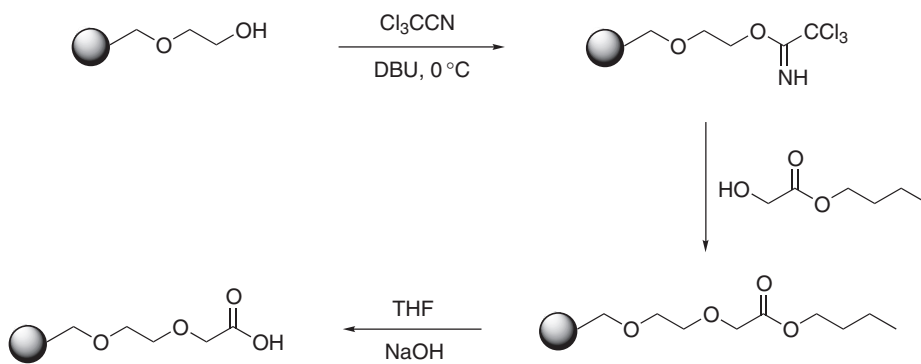
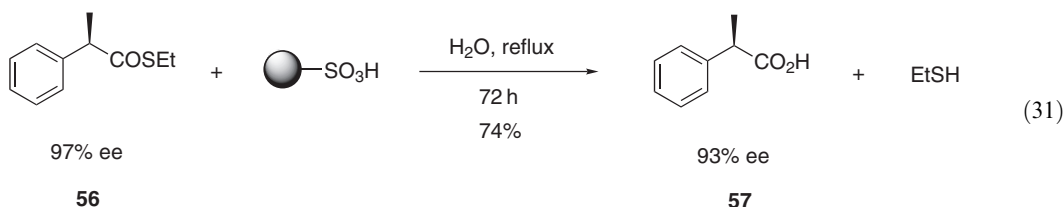
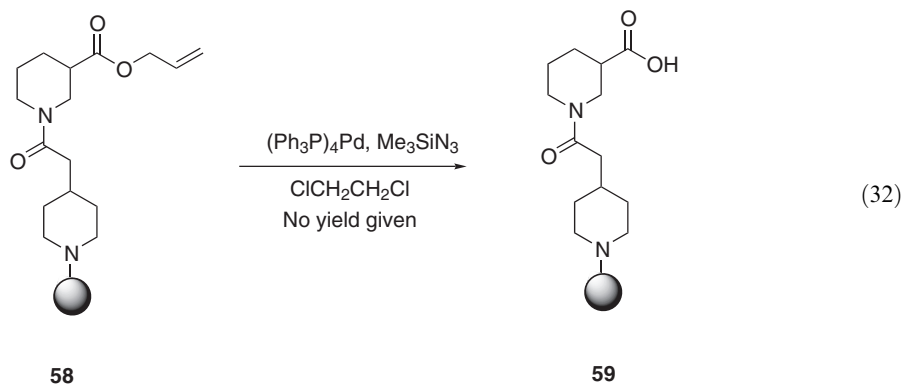


Table 4 Cleavage of thioesters using polymer-supported sulfonic acids

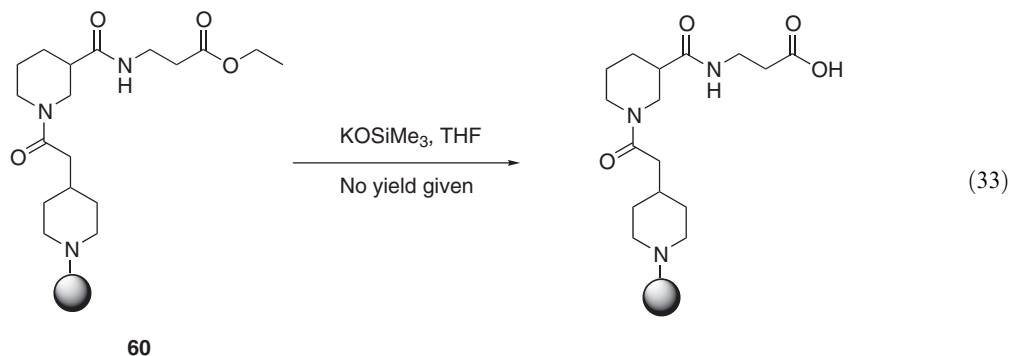
$\text{RCOSR}^1 \xrightarrow[\text{H}_2\text{O, reflux, 24 h}]{\text{PS-SO}_3\text{H (10 mol.\%)}} \text{RCO}_2\text{H} + \text{R}^1\text{SH}$		
$\text{C}_{11}\text{H}_{23}\text{COSEt}$	$\text{C}_{11}\text{H}_{23}\text{CO}_2\text{H}$	93%
$\text{C}_{11}\text{H}_{23}\text{COSBu}^t$	$\text{C}_{11}\text{H}_{23}\text{CO}_2\text{H}$	100%
$\text{C}_{11}\text{H}_{23}\text{COSPh}$	$\text{C}_{11}\text{H}_{23}\text{CO}_2\text{H}$	98%
$\text{Ph}(\text{CH}_2)_2\text{COSEt}$	$\text{Ph}(\text{CH}_2)_2\text{CO}_2\text{H}$	85%
$(E)\text{-PhCHCHCOSEt}$	$(E)\text{-PhCHCHCO}_2\text{H}$	90%
$\text{AcSC}_{12}\text{H}_{25}$	$\text{C}_{12}\text{H}_{25}\text{SH}$	100%
AcSCH_2Ph	PhCH_2SH	80%
$\text{AcS}(\text{CH}_2)_3\text{Ph}$	$\text{Ph}(\text{CH}_2)_3\text{SH}$	100%
$\text{PhCOSC}_{12}\text{H}_{25}$	$\text{C}_{12}\text{H}_{25}\text{SH}$	89%
		99%



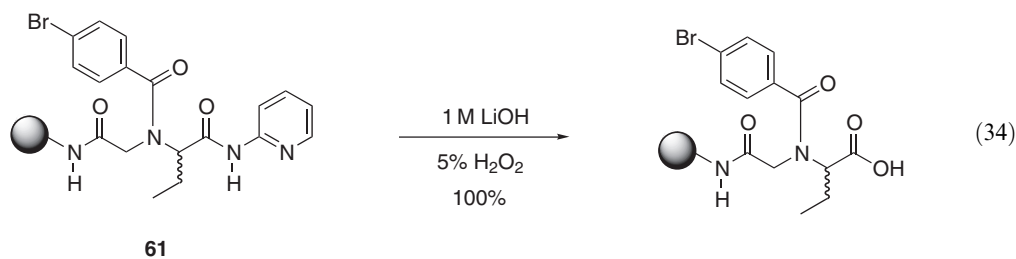
Performing a palladium(0)-mediated cleavage of *O*-allyl ester **58** and incorporating an *in situ* azide trap for the generated π -allyl species, returned the desired carboxylic acid **59** (Equation (32)) <1997TL2629>. Alternative protocols that utilize transition metals for the cleavage of *O*-allyl groups have been reported, i.e., <1998TL4591, 1997TL4861, 1998TL4871, 1996CC141>. Protocols using $\text{Ti}(\text{O-Pr})_4/\text{Bu}^n\text{MgBr}$ <1996TL3663>, DDQ <1996TL6603>, NaBH_4/I_2 <1997TL4721> and $\text{TolSO}_2\text{H}/\text{Pd}(\text{PPh}_3)_4$ <1997JOC8932> have been reported.



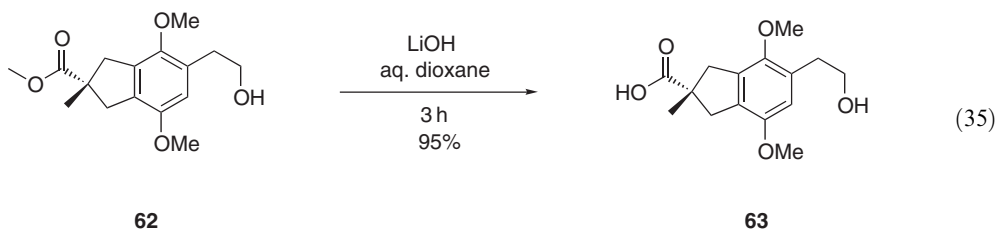
The application of aqueous basic reaction conditions for the saponification of an immobilized ethyl ester failed on a 2-chlorotrityl resin. Negating this problem, the use of potassium trimethylsilanoate in THF resulted in cleavage of the ethyl ester on **60** with no detectable cleavage of the amide bonds (Equation (33)). Interestingly, the use of ether as solvent failed to cleave the polymer-bound ester; presumably, this can be attributed to the poor swelling characteristics of the polymer in this particular solvent <1997TL2629>.



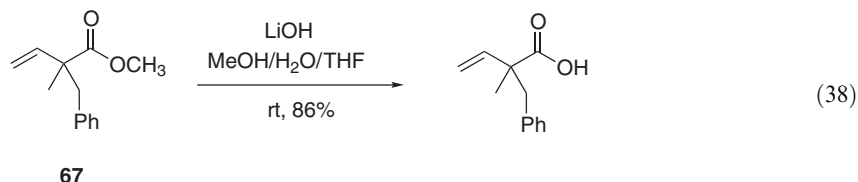
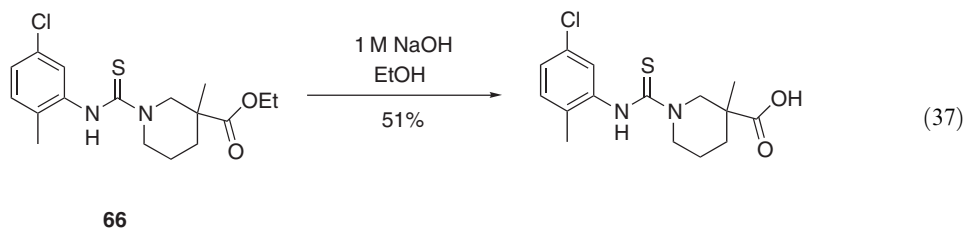
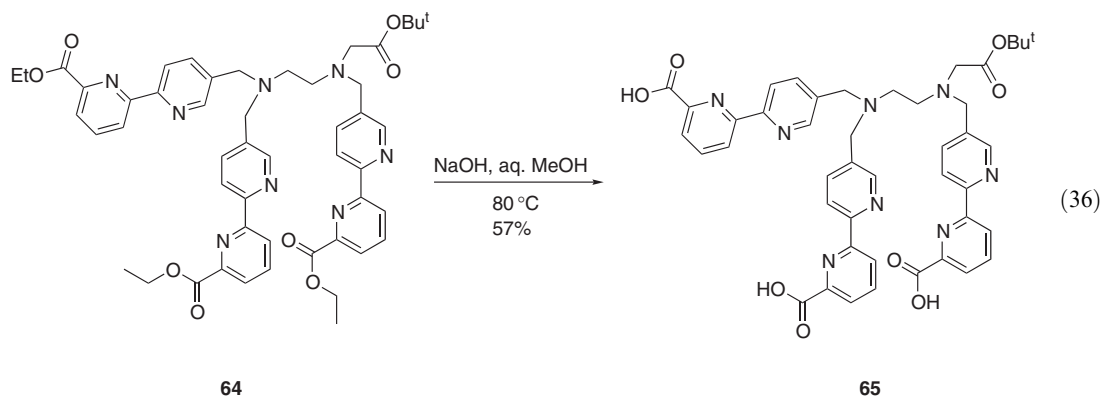
Due to the recalcitrant nature of secondary amides to hydrolysis, distinct secondary amides such as 2-azidophenylamides and 1-cyclohexenylamides <1995JA7842> have been developed that cleave and yield the corresponding carboxylic acids under mild reaction conditions. A hydrolysis protocol utilizing lithium hydroxide and hydrogen peroxide for the cleavage of 2-pyridinyl-*N*-amides, for example **61** supported on Rink resin, has been developed (Equation (34)) <1996TL2943>.



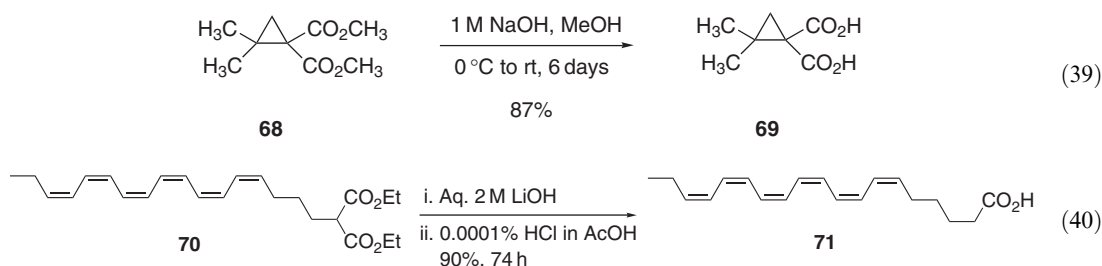
Sterically encumbered methyl esters, for example **62**, can be hydrolyzed using basic reaction conditions. Synthesis of carboxylic acid **63**, precursor to (+)-puraquinonic acid, was undertaken in an excellent yield using an aqueous dioxane (1:1)/lithium hydroxide mixture (Equation (35)) <2002CC2380>.



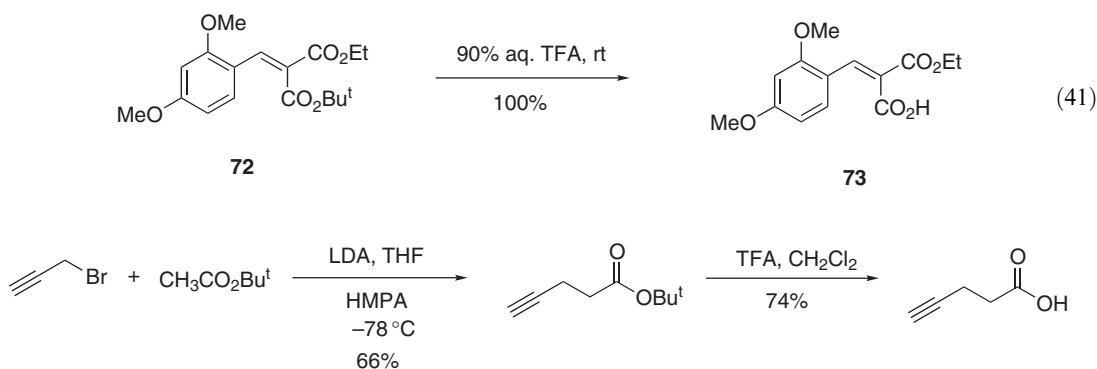
Akin to methyl esters, ethyl ester homologs can be saponified using alkali hydroxides and reaction protocols similar to those employed for the methyl variants; for example, ethyl ester **64** was readily transformed into the corresponding carboxylic acid **65** using aqueous methanolic sodium hydroxide (Equation (36)) <2002JOC3933>. Hydrolysis of tertiary carboxylic acid ethyl ester **66** has been accomplished using sodium hydroxide in ethanol (Equation (37)) <2002BMCL2439>. Hydrolysis of the carboxylic acid methyl ester **67** was undertaken using an aqueous lithium hydroxide/mixed organic solvent-based system (Equation (38)).



Of particular interest is the base-mediated saponification of *gem*-dimethyl esters, for example **68**, to the corresponding malonic acid **69**, without decarboxylation and in high yield (87%), albeit over 6 days, using methanolic sodium hydroxide (Equation (39)) <2001T2781>. Saponification of diethyl malonate derivative **70** to the corresponding dicarboxylic acid **71** was undertaken with aqueous 2 M lithium hydroxide, subsequent decarboxylation of the product using a solution of 0.0001% hydrochloric acid in acetic acid afforded the desired monocarboxylic acid (Equation (40)) <2001JCS(P1)221>.

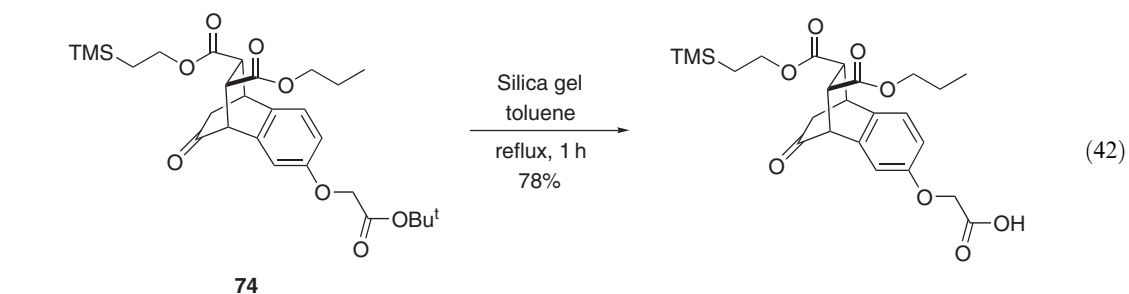


Using aqueous acid, the transformation of esters to the corresponding carboxylic acids is possible; however, the sensitivity of appended groups to extended periods of time in the presence of acid, and quite often at elevated temperatures, should be considered. Chemoselective ester hydrolysis using aqueous acid is sometimes difficult to achieve with certain esters. Subjecting mixed *t*-butyl ethyl diester **72** to 90% aqueous TFA afforded chemoselective hydrolysis of the *t*-butyl ester only, affording in near quantitative yield, carboxylic acid **73** (Equation (41)) <2002T7391>. Further examples of the use of TFA for the cleavage of *t*-butyl esters are outlined (Scheme 10) <1998JA9228>.

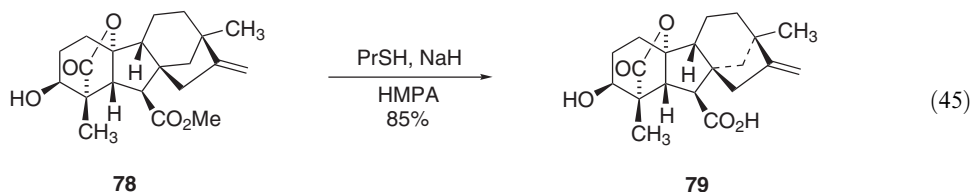
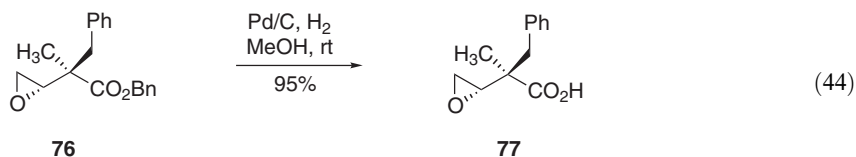
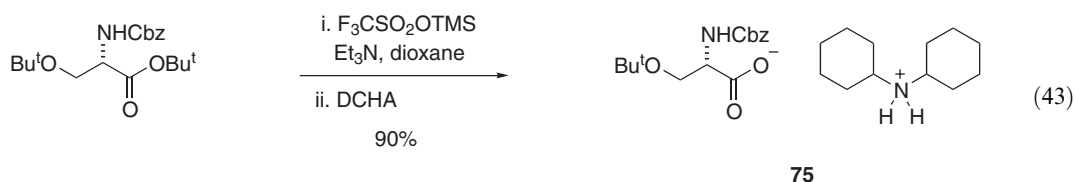


Scheme 10

A protocol for the chemoselective cleavage of a *t*-butyl ester, for example **74**, using silica gel in refluxing toluene has been reported (Equation (42)). The corresponding carboxylic acids are returned in high yields (68–91%). The cleavage reaction is selective for *t*-butyl esters over propyl esters, *t*-butyl ethers, and trimethylsilyl ethyl esters. The procedure benefits from using standard flash grade silica gel, mild reaction conditions, and ease of experimental protocol <2001TL5163>.

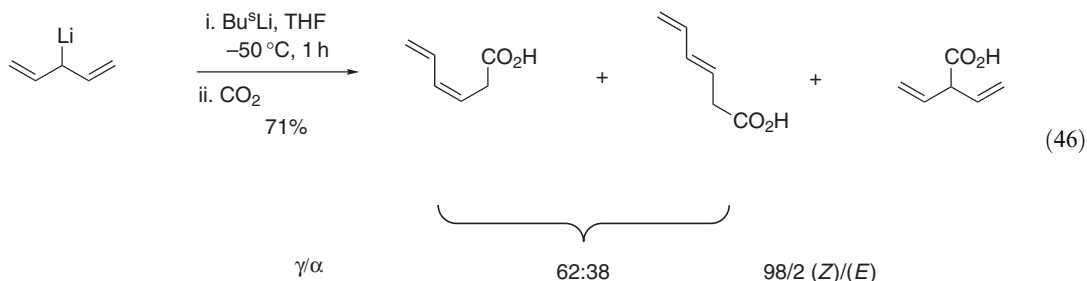


The chemoselective cleavage, using trimethylsilyl triflate, of a *t*-butyl ester in the presence of a *t*-butyl ether during the synthesis of *N*-Cbz-(*O*-*t*-butyl) α -amino acid **75** is noteworthy. The reaction, conducted in the presence of triethylamine, is undertaken in near-neutral reaction conditions and, furthermore, no racemization of the stereogenic center was observed (Equation (43)) <1996S1433>. The hydrogenolysis of the benzyl ester on **76**, affording the corresponding carboxylic acid **77** in an excellent yield, in the presence of an epoxide was undertaken using palladium on carbon under an atmosphere of hydrogen (Equation (44)) <2002BMC913>. The dealkylation of the methyl ester on **78** under nonaqueous conditions has been reported using a combination of sodium *n*-propanethiolate/HMPA, affording carboxylic acid **79** in a 85% yield (Equation (45)) <1997JCS(P1)2989>.

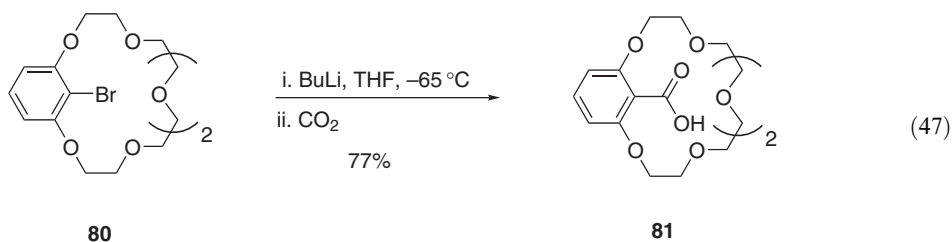


5.02.2.1.2 By carbonylation of organometallic reagents

Perhaps the most direct synthetic route to carboxylic acids is the reaction between an organometallic species and carbon dioxide. Schlosser and co-workers investigated the regio- and stereochemical outcome of quenching a series of substituted 2,4-pentadienyllithium (Equation (46)) and potassium reagents with carbon dioxide affording regioisomeric mixtures of carboxylic acids (49–71%) <2001SI1830>.

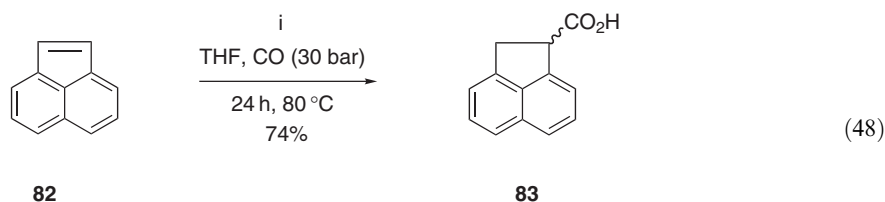


In contrast to its lower homolog 1,3-phenylene-16-crown-5, the direct lithiation of 1,3-phenylene-19-crown-6 using Bu^nLi was found to be slow and incomplete; however, lithiating bromophenylene-19-crown-6 **80** via a bromine–lithium exchange at -65°C and subsequent quenching of the anion with carbon dioxide yielded the corresponding carboxylic acid **81** in a 77% yield (Equation (47)) <1999JOM(572)93>.

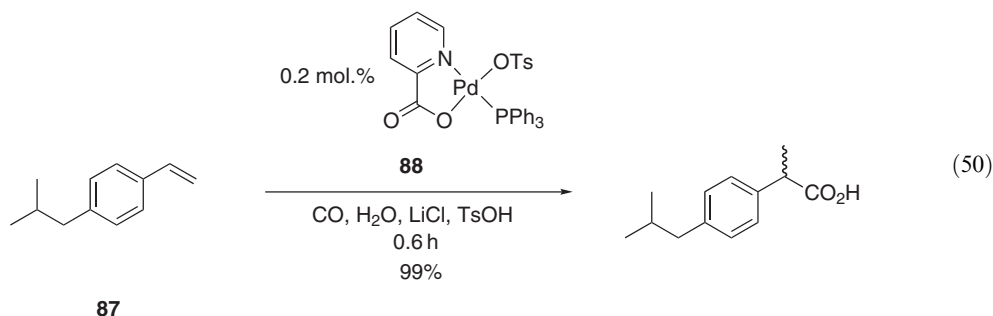
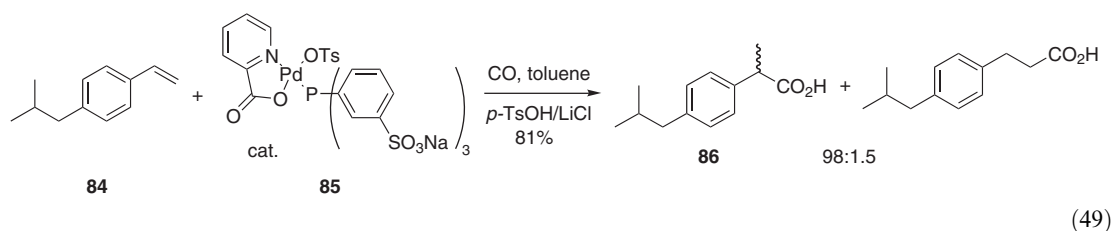


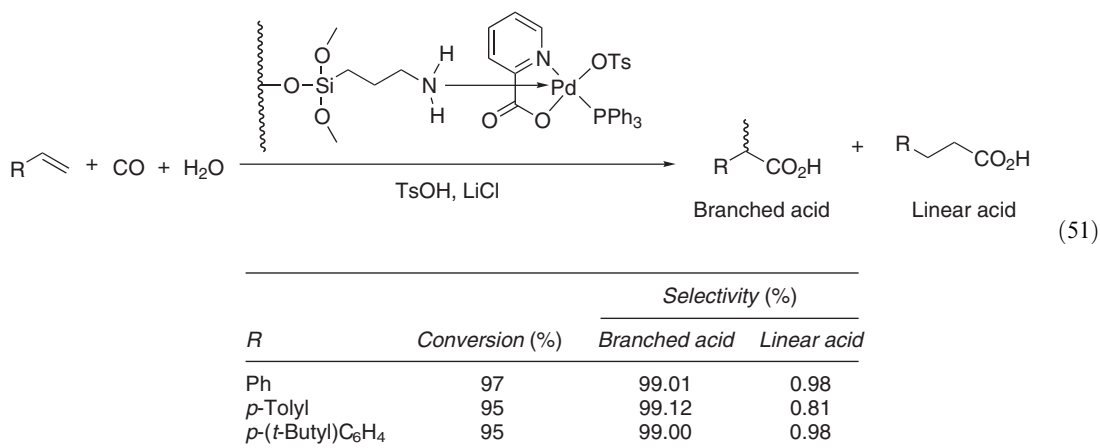
The possibility of undertaking a carbonylation of 1-arylalcohols to yield 2-arylpropanoic acids, many of which, for example Ibuprofen and Naproxen, have biological activity, would be an atom efficient and extremely useful synthetic transformation. Several processes with this goal in mind are known. A highly active catalyst system comprising palladium on carbon, triphenylphosphine, lithium chloride and *p*-toluenesulfonic acid displayed very high TOF (3375 TOF h^{-1}) and selectivities (99.2%) for the synthesis of racemic 2-arylpropanoic acids from 1-arylethanol [<1999CC1067>](#).

The hydrocarboxylation of acenaphthalene **82**, under mild reaction conditions, to give acenaphthalene-1-carboxylic acid **83** in a 74% yield has been reported. A mechanistic investigation using deuteriocarboxylation of the alkene allowed the authors to propose a *cis*-insertion of a palladium-deuteride species into the alkene bond (Equation (48)) [<2000OM4715>](#). Jayasree and co-workers have devised a high-yielding and regioselective synthesis of 2-arylpropanoic acids, for example **86**, via a biphasic, low-pressure, hydrocarboxylation reaction procedure, which utilizes vinylaryl starting materials **84** and a novel, water-soluble pyridine-based palladium complex **85** (Equation (49)) [<2000CC1239>](#). The same authors reported the high-pressure hydrocarboxylation of alcohols and alkenes **87** using the chelated palladium(II) complex **88** containing a chelating anionic pyridine-2-carboxylate (Equation (50)) [<2000OL203>](#). In a further enhancement of the hydrocarboxylation procedure, Jayasree and co-workers immobilized their palladium ligand complex onto two mesoporous supports MCM-41 and MCM-48; the immobilized catalysts were highly effective hydrocarboxylation agents. No leaching of the palladium or erosion of regioselectivity, yield or activity was observed, even when the catalyst was recycled 3 times (Equation (51)) [<2002JA9692>](#).



i. Oxalic acid (1.18 equiv.), $\text{PdCl}_2(\text{CH}_3\text{CN})$ (2.4%), Tris(*p*-fluorophenyl)phosphine (10%)





The enantioselective hydrocarboxylation of vinylarenes, using palladium-derived chiral non-racemic tetrasulfonated 2,4-bis(diphenylphosphino)pentane **90** or 1,2-bis(diphenylphosphino)cyclobutane ligand **91** returned optically active 2-arylpropanoic acids **89** and 3-arylpropionic acids with good conversion (57–100%) and selectivity (38–100%). The ee values of the resulting 2-arylpropanoic acids were poor to moderate, 1–43% (Equation (52)) <1999TA4463>. A number of substituted and nonsubstituted racemic 2-arylpropanoic acids have been synthesized from vinyl aromatics in the presence of carbon monoxide and water, with high regioselectivity and yield, using a palladium complex derived from bis(triphenylphosphine)palladium dichloride, *p*-toluenesulfonic acid, and lithium chloride. Both terminal and internal arylalkenes can be hydrocarboxylated (Equation (53), Table 5). Arylalkenes bearing a halogen substituent in the *para*-position displayed the highest regioselectivities (61–99.8%) for formation of racemic 2-arylpropanoic acids. The hindered alkene, α -methylstyrene although reactive, returned the product 2-methyl-2-phenylpropanoic acid in a lower yield (50%) and regioselectivity (61%) <1999OL459>.

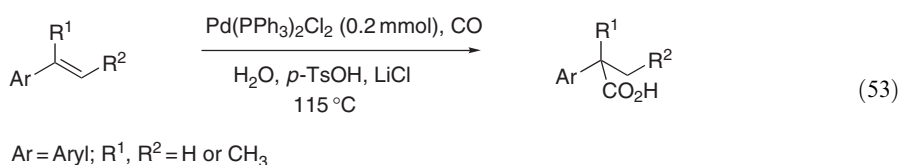
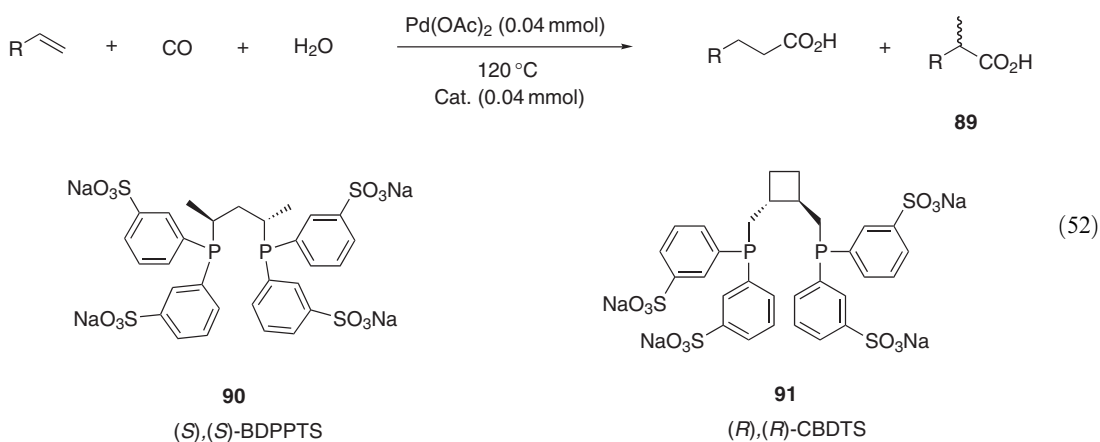

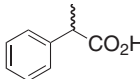
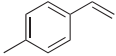
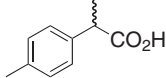
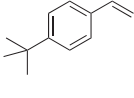
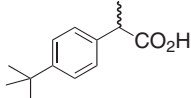
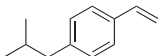
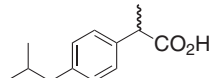
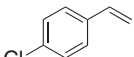
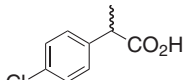
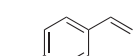
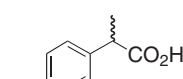
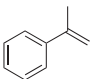
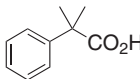
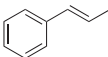
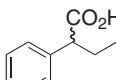
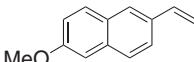
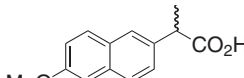
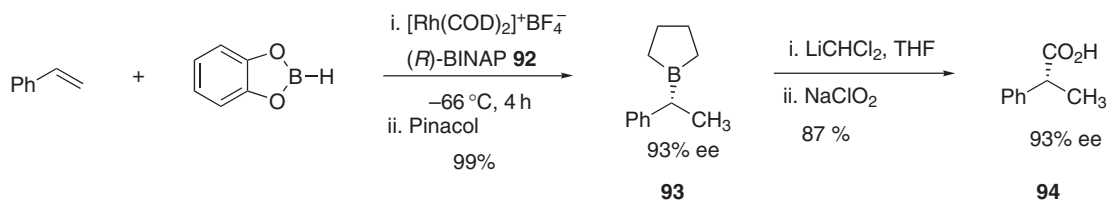


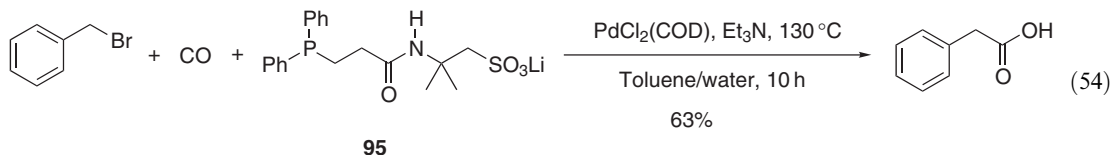
Table 5 Synthesis of racemic 2-arylpropanoic acids from vinyl aromatics

Substrate	Time (h)	Conversion (%)	Product	Selectivity (%)	Yield (%)
	0.22	99		99.3	91
	0.38	98.7		95	98
	0.29	99.2		97.5	92
	0.4	99		97	93
	0.4	99.6		99.8	88
	0.38	98.5		99.7	92
	5.5	85		61	50
	2	90		95.5	85
	1.17	95		97.5	89

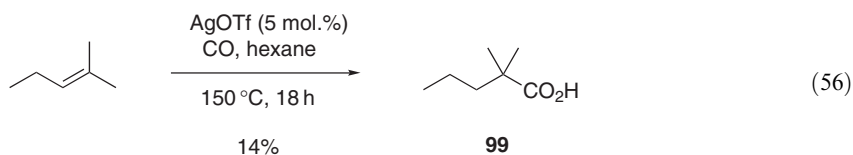
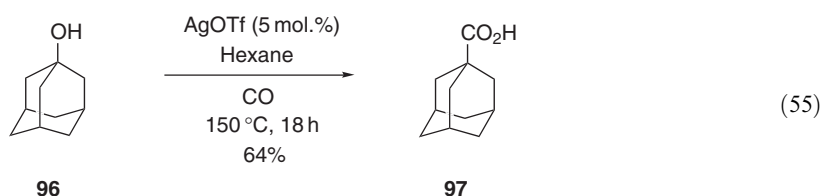
A two-step catalytic asymmetric hydrocarboxylation protocol for transforming vinylarenes into chiral nonracemic 2-arylpropanoic acids, for example **94**, has been developed. Pivotal to the success of this procedure was the separation of the asymmetry-inducing reaction, that is, asymmetric hydroboration, from the C—C bond forming step (Scheme 11). The initial stereochemistry was installed via an enantioselective hydroboration reaction catalyzed by using a chiral nonracemic cationic rhodium BINAP complex **92**, affording **93**. Subsequent homologation and oxidation (NaClO_2) of **93** yielded chiral nonracemic 2-arylpropanoic acid **94** in high ee and good yield [<1999JOC9704>](#). A biphasic catalytic reaction system containing $\text{PdCl}_2(\text{COD})$ and the

**Scheme 11**

water-soluble phosphine ligand **95** mediated the carboxylation of aryl and benzyl bromides to the corresponding aryl- and benzenecetic acids in high yields (63–87%), short reaction times (5 h), and low pressures (5 atm) (Equation (54)) <2000JMOC(A)93>.

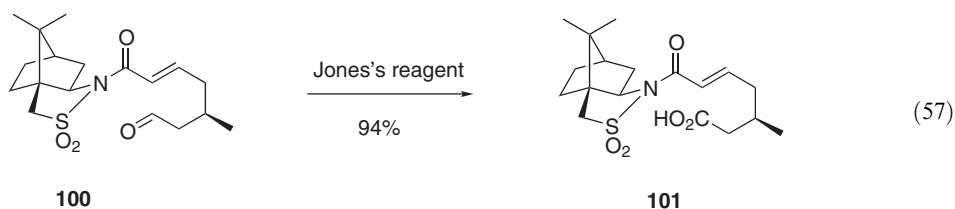


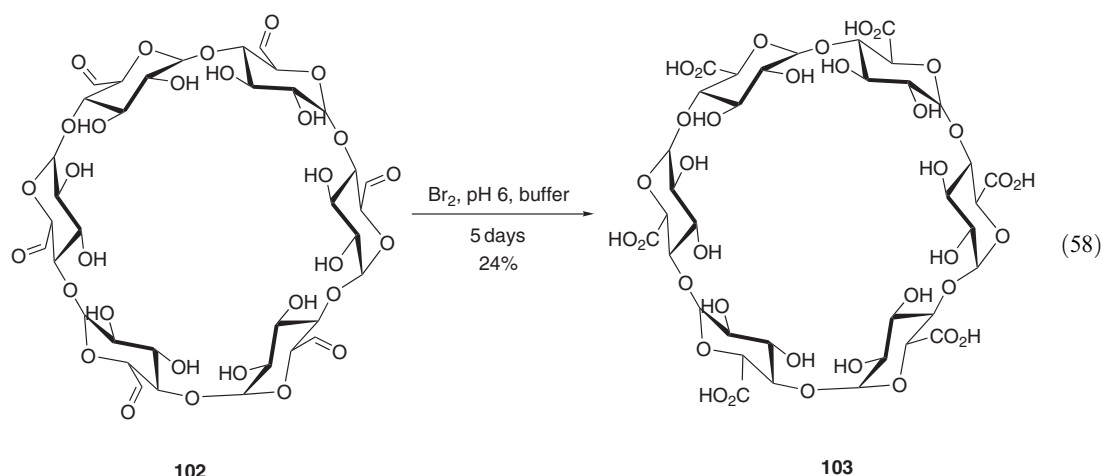
The transformation of tertiary alcohols, for example **96**, into the corresponding tertiary carboxylic acids **97** in moderate-to-good yields (46–69%) under an atmosphere of carbon monoxide has been undertaken via a Koch carbonylation protocol that uses silver trifluoromethanesulfonate as the Lewis acid (Equation (55)). Attempting the synthesis of carboxylic acids using the same Koch carbonylation protocol, but incorporating primary alcohols, disappointingly, returned no detectable amounts of carboxylic acids, the main products being the corresponding ethers (65–72%). Secondary alcohols were unaffected by the reaction conditions used to transform the primary and tertiary alcohols. Substituting alkenes for alcohols in the Koch carbonylation resulted in poor yields (10–14%) of the corresponding tertiary carboxylic acids, for example **99**, (Equation (56)) <2002TL7871, 1997JOC1594>.



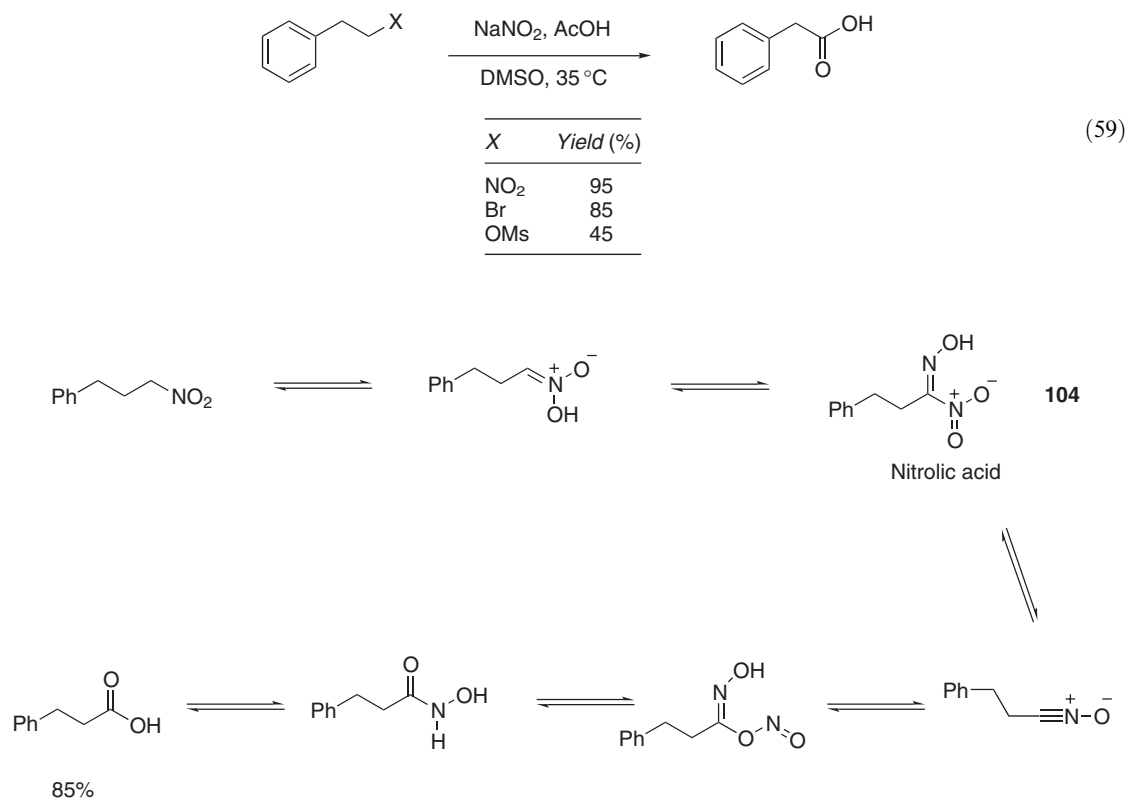
5.02.2.1.3 By oxidation reactions

The oxidation of aldehydes to carboxylic acids is a relatively facile process. A commonly used reagent for this transformation is Jones's reagent. However, the components of Jones's reagent, chromium trioxide, and sulfuric acid result in its high acidity, and the oxidizing agent is, therefore, not always compatible with acid-sensitive functional groups. The use of Jones's reagent for the oxidation of aldehyde **100** has been reported to afford carboxylic acid **101** in high yield (95%) and without loss of stereochemical integrity (Equation (57)) <1996TL8899>. The selective synthesis of mono- and dicarboxylic acid-derived β -cyclodextrinyl aldehyde **103** in low yields (20–24%) via oxidation of polyaldehyde **102** has been accomplished using a buffered (pH 6) aqueous bromine solution. The yields reflect the competitive oxidation of the carbohydrate component of the β -cyclodextrin (Equation (58)) <1995JOC2792>.





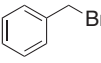
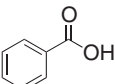
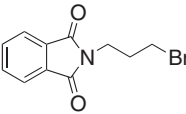
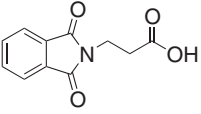
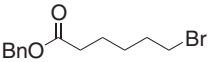
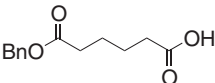
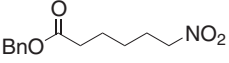
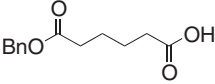
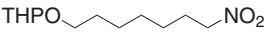
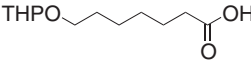
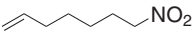
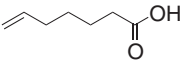
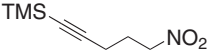
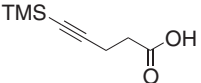
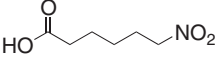
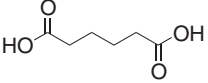

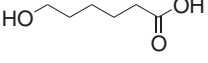
The transformation of primary aliphatic and benzylic bromides, nitrates, and mesylates directly into the corresponding carboxylates, without their isolation, can be undertaken using a combination of sodium nitrite, DMSO, and acetic acid (Equation (59)). The reactions apparently proceed via a nitrolic acid intermediate **104** (Scheme 12). The conditions/reagents used are tolerant of alkene and alkyne double bonds (Table 6) <1997JOC234>.



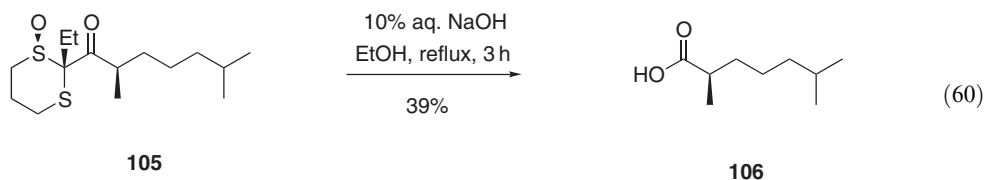
Scheme 12

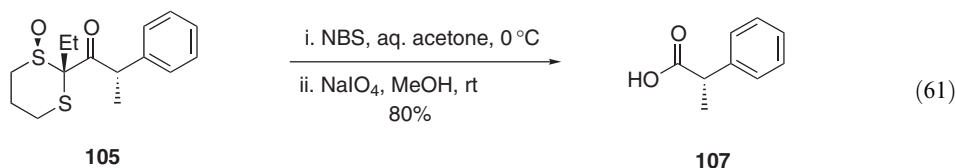
The utilization of optically active 1,3-dithiane-1-oxides as stereocontrolling elements for the synthesis of chiral nonracemic α -methyl aliphatic and aromatic carboxylic acids has been reported. Optically active 2-ethyl-1,3-dithiane-1-oxides **105** are readily deprotonated, allowing the resulting enolate to be quenched with an electrophile in a diastereoselective manner. Subsequent

Table 6 Synthesis of carboxylic acids from alkyl bromides and primary nitroalkanes

Substrate	Product	Yield (%)
		80
		67
		85
		96
		90
		95
		98
		95
		72

dithiane hydrolysis returned the aliphatic α -substituted carboxylic acid **106** (Equation (60)) in reasonable yield (39%) but excellent optical activity (<95% ee). Undertaking a sodium hydroxide mediated hydrolysis procedure for the synthesis of optically active α -arylcarboxylic acids systems was not viable due to racemization of the reaction product. Therefore, a two-step procedure was developed: the first step entailed conversion of the 2-ethyl-1,3-dithiane-1-oxide **105** derivatives into the corresponding α -diketone using NBS in aqueous acetone; it was followed by treatment of the α -diketone with sodium periodate in methanol to yield the α -arylpropanoic acid **107** with no loss of stereochemical integrity (Equation (61)) <1997T13149>.

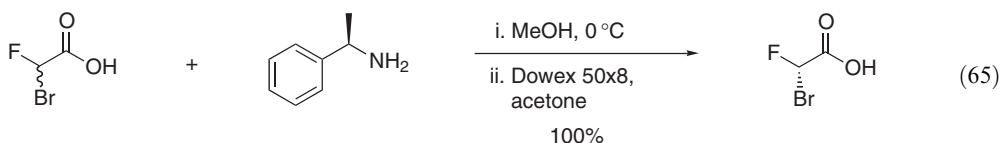
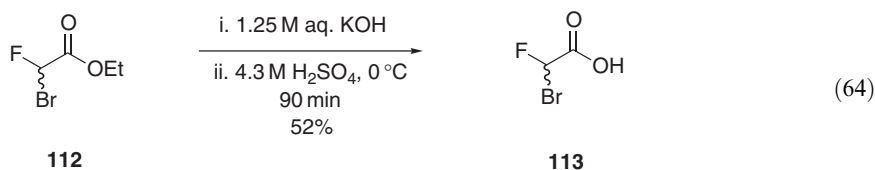
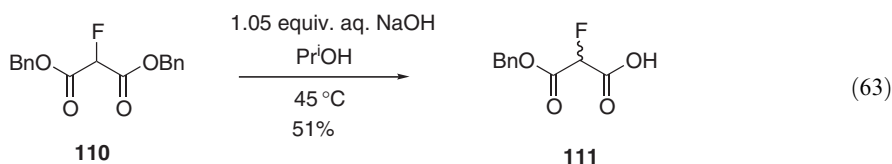
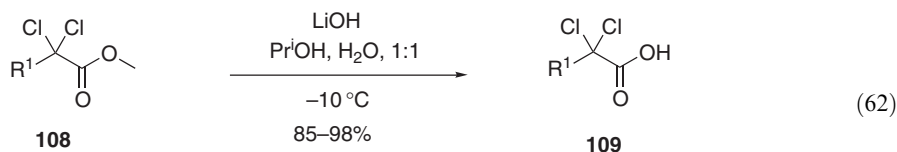


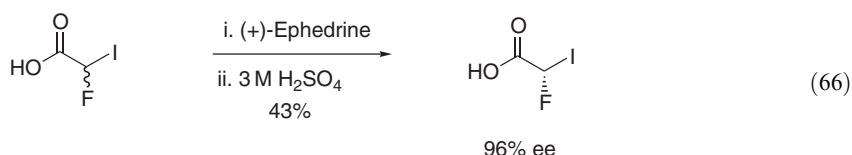


5.02.2.2 Haloalkanoic Acids

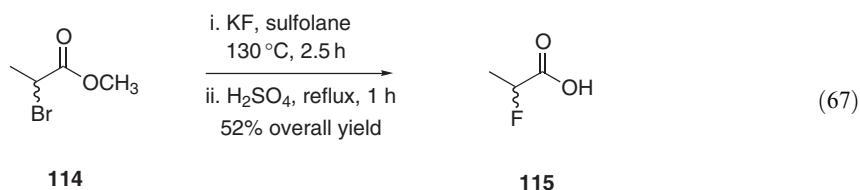
5.02.2.2.1 By hydrolysis reactions

The synthesis of a series of 2,2-dichloro-2-substituted carboxylic acids **109** has been undertaken, in isopropanol via a lithium hydroxide saponification of the corresponding methyl esters (**108**, Equation (62)). Benedetti and co-workers incorporated the resulting carboxylic acids in the synthesis of 2-pyrrolidinones via *N*-protected *N*-allyl-2,2-dihaloamides <1997T14031>. Using sodium hydroxide in aqueous isopropanol the selective hydrolysis of a 2-fluorodibenzyl ester **110** yielded the corresponding racemic 2-fluoromonocarboxylic acid benzyl ester **111** (Equation (63)) in reasonable yield (51%) <1997BMC797>. Racemic bromofluoroacetic acid **113** has been synthesized by saponification of commercially available racemic ethyl bromofluoroacetate **112** using aqueous potassium hydroxide in a 52% yield (Equation (64)). Subsequent resolution of the racemic carboxylic acid was investigated using seven commercially available amines, and of these chiral nonracemic (*R*)- α -methylbenzylamine afforded the best result, yielding (*S*)-bromofluoroacetic acid in a 33% yield and 100% ee (Equation (65)) <2002TA975>. Similarly, racemic fluoroiodoacetic acid was resolved using optically enriched (+)-ephedrine hemihydrate via fractional crystallization in a 43% yield (Equation (66)) <2001JA7207>.

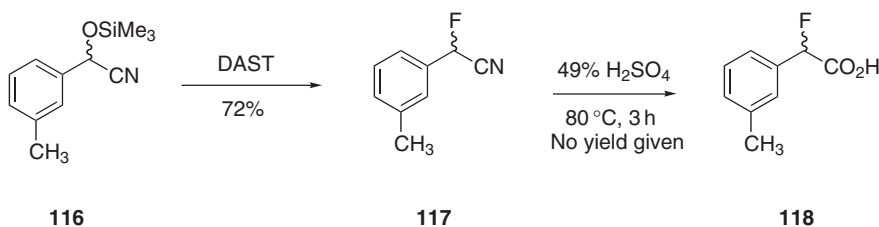




The synthesis of racemic 2-fluoropropanoic acid **115** has been reported via a one-pot, two-step process using, as the starting material methyl 2-bromopropanoate **114**. The 2-bromoester **114** was reacted with spray-dried potassium fluoride in tetramethyl sulfone at 130 °C, and the resulting 2-fluoroester was collected via reduced-pressure distillation and subsequently hydrolyzed to 2-fluoropropanoic acid **115** using 10% sulfuric acid in an overall 52% yield (Equation (67)) <1996T255>.



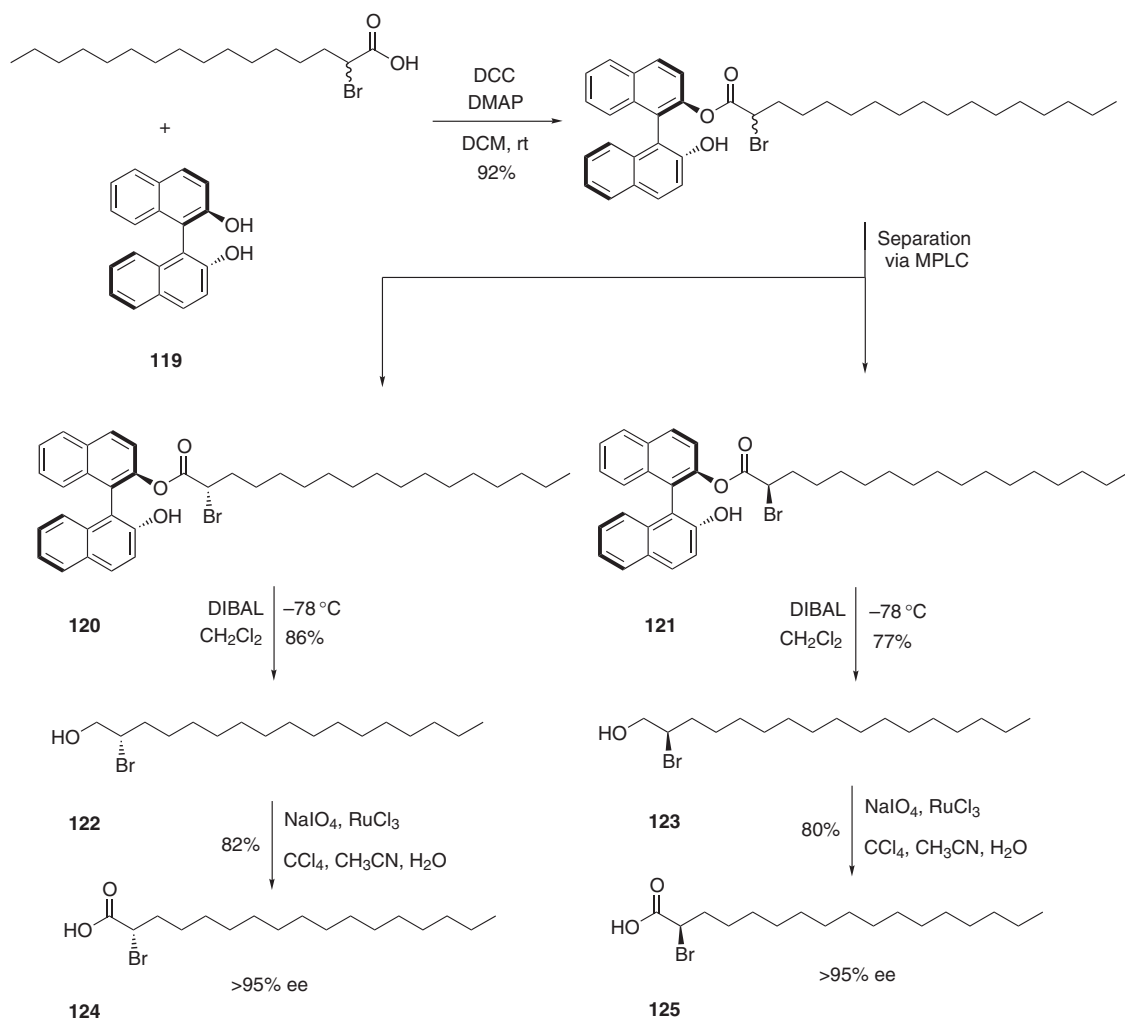
Racemic α -fluoronitriles are readily accessible via the reaction of unprotected or *O*-silylated cyanohydrins with diethylaminosulfur trifluoride (DAST). In a one-pot procedure aryl aldehydes react with trimethylsilyl cyanide to furnish the corresponding silylated cyanohydrins **116**, and these were subsequently transformed using DAST into the α -fluoronitriles **117** (Scheme 13) in reasonable-to-good yields (66–79%). Conversion of the α -fluoronitriles into the corresponding α -fluorocarboxylic acids, for example **118**, was undertaken using 49% aqueous sulfuric acid at 80 °C. Attempting the hydrolysis using hydrochloric acid instead of sulfuric acid resulted in halogen exchange, yielding racemic 2-chloro-2-phenylacetic acid.



Scheme 13

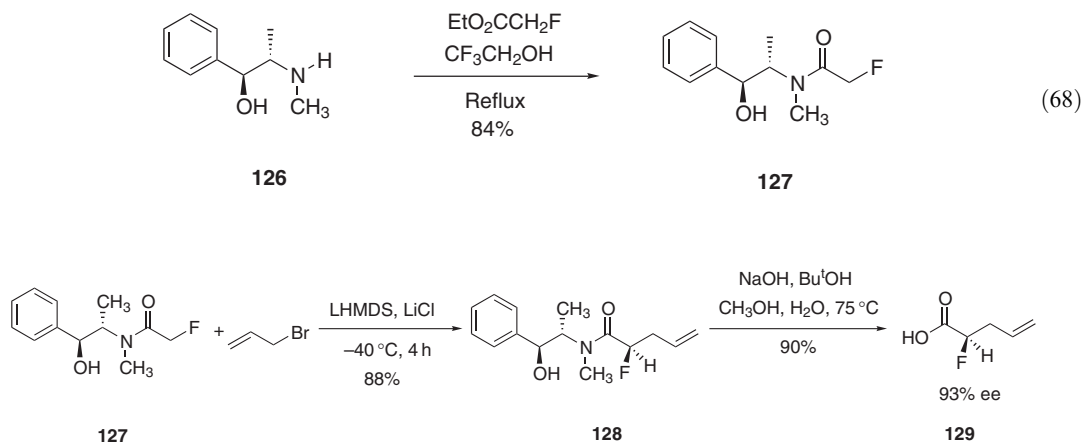
The synthesis of enantiomerically enriched (*R*)- and (*S*)-2-bromohexadecanoic acids with ee values >95% has been undertaken using (*R*)-(+)-1,1-bi-2-naphthol **119** in good overall yields (83%) via a three-step protocol. The first step was a Steglich esterification procedure incorporating **119**, racemic 2-bromohexadecanoic acid, DCC and DMAP (92% yield). Separation of the (*R*)-(+)-1,1-bi-2-naphthyl ester diastereomers **120** and **121** was undertaken using chromatography and subsequent reduction (DIBAL) afforded the corresponding primary alcohols **122** and **123** in good yields. Oxidation of the primary alcohols, without loss of stereochemical integrity, was undertaken using sodium periodate and catalytic quantities of ruthenium trichloride, furnishing the corresponding carboxylic acids **124** and **125** in good yields (Scheme 14). This protocol is particularly useful for the synthesis of enantiomerically enriched 2-substituted long-chain aliphatic acids <2000TA4105>.

(1(*S*),2(*S*))-(+)-Pseudoephedrine α -fluoroacetamide **127** is a nonvolatile, crystalline solid easily synthesized from (1(*S*),2(*S*))-(+)-pseudoephedrine **126** and ethyl fluoroacetate (Equation (68)). Deprotonation of (1(*S*),2(*S*))-(+)-pseudoephedrine α -fluoroacetamide **127** using LHMDs in the presence of excess lithium chloride (6 equiv.) allows the resulting enolate to be quenched with reactive electrophiles; importantly, the enolate must be kept below –40 °C. Subsequent saponification of the



Scheme 14

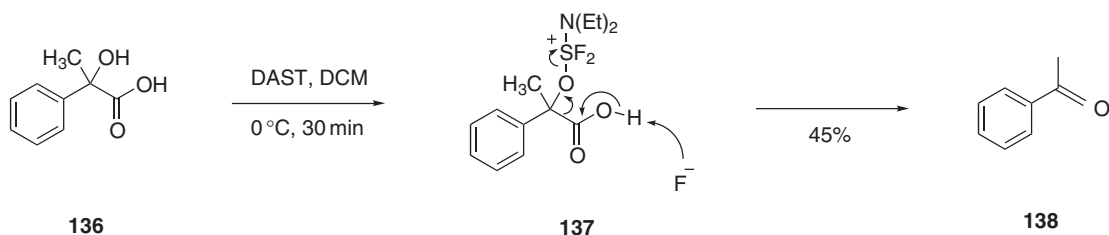
amide bond of **128**, yielding the α -fluoro- α -substituted carboxylic acid **129**, was performed using sodium hydroxide in *t*-butanol; the ease of hydrolysis was attributed to the inductive activation of the carbonyl substituent by the adjacent fluorine atom (Scheme 15) <1998TL1335>.



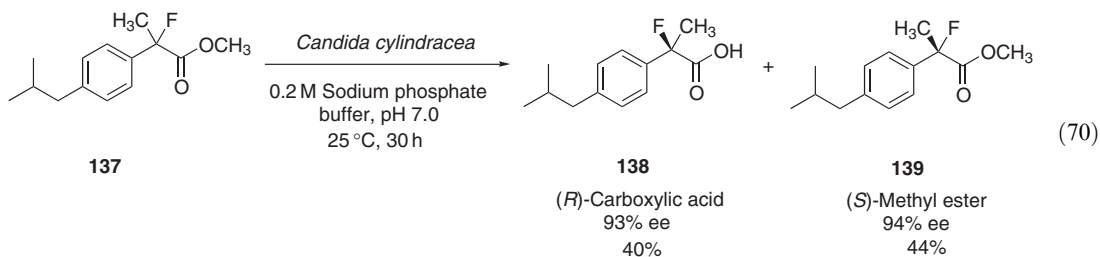
Scheme 15

$$\begin{array}{c}
 \text{R}-\text{C}_6\text{H}_4-\text{CH}(\text{F})-\text{CN} \xrightarrow[\text{pH } 8.5]{\text{Nitrilase, } 20^\circ\text{C}} \text{R}-\text{C}_6\text{H}_4-\text{CH}(\text{F})-\text{CO}_2\text{H} + \text{R}-\text{C}_6\text{H}_4-\text{CH}(\text{F})-\text{CN} + \text{R}-\text{C}_6\text{H}_4-\text{CH}(\text{F})-\text{CONH}_2 \\
 \text{R = H, } o\text{-CH}_3, m\text{-CH}_3, p\text{-CH}_3, p\text{-NO}_2, m\text{-CH}_3\text{O}
 \end{array}
 \quad (69)$$

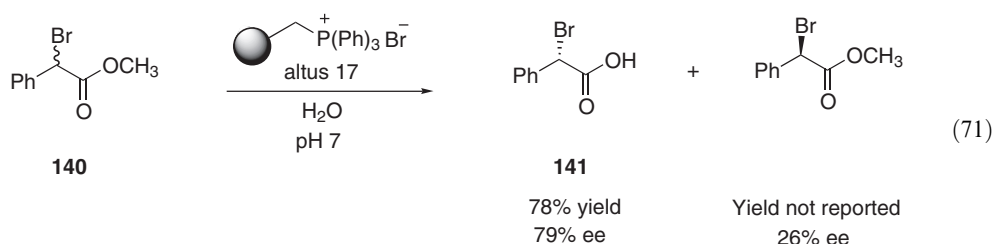
Scheme 16



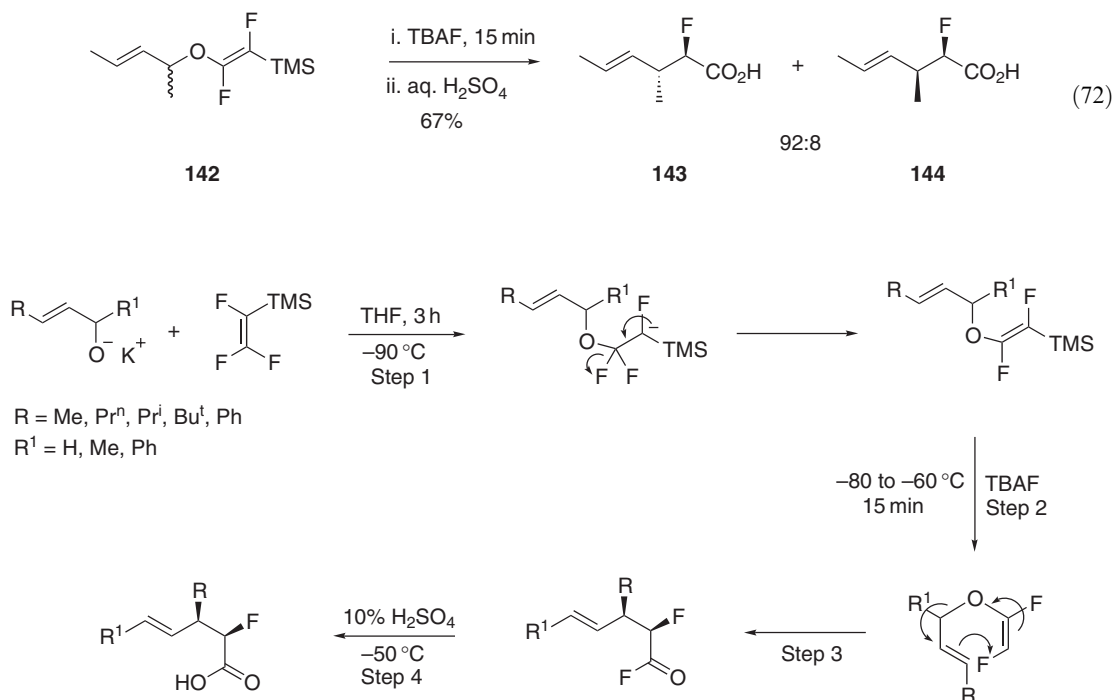
Scheme 17



Novel strategies that incorporate dynamic kinetic resolution protocols for the synthesis of optically enriched carboxylic acids are of interest. Jones and co-workers have demonstrated that a bromide anion derived from a quaternary ammonium bromide or a phosphonium bromide is able to racemize an optically active α -bromo ester faster than an optically enriched α -bromo-carboxylic acid. Combining this chemoselective racemization procedure with enzymatic enantioselective hydrolysis methodology has resulted in a new dynamic kinetic resolution procedure for the synthesis of optically enriched α -bromocarboxylic acids **141** from racemic α -bromocarboxylic acid esters **140**. The lipase employed was the commercially available crosslinked enzyme *Candida rugosa* crystal, Altus 17; this particular enzyme reacted quickly (2.5 h) and with reasonably good enantioselectivities (80% ee) when used in conjunction with a Wang phosphonium bromide polymer (Equation (71)) <1998CC2519>.

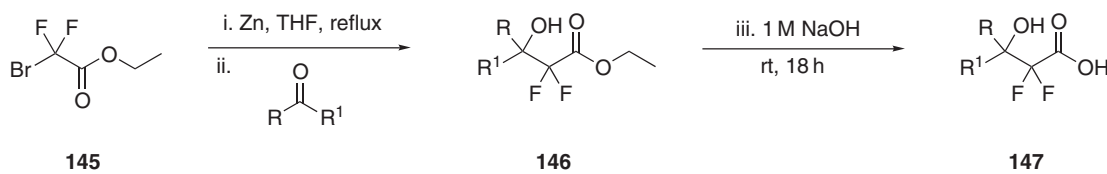


The Claisen rearrangement is a useful synthetic transformation for the stereoselective construction of C—C bonds. Two new asymmetric centers may be created diastereoselectively with the concomitant regio- and stereospecific formation of new C=C bonds. The Claisen rearrangement of allyl fluorovinyl ethers **142** can be performed at low temperatures (-90 to -60°C) affording diastereomeric mixtures of 2-fluoro-4-alkenoic acids **143** and **144** in good yields (Equation (72)). The carboxylic acids are obtained via a one-pot synthesis which proceeds through four steps: the first a reaction between an potassium allyl alkoxide and trifluorovinylsilane, the second a protodesilylation with fluoride, the third a selective Claisen rearrangement, and finally hydrolysis of the acid fluoride to the carboxylic acid (Scheme 18) <1998TL5041>. A one-pot synthesis of α -trifluoromethyl- γ -unsaturated carboxylic acids has been described which proceeds via a [3,3]-sigmatropic rearrangement of allyl fluorovinyl ethers in poor-to-good yields (21–82%) <2001TL2665, 2002JFC(113)167>.



Scheme 18

A series of α,α -difluoro- β -hydroxy carboxylic acids, for example **147**, have been synthesised via a three-step procedure (Scheme 19), which incorporates a Reformatsky reaction between ethyl bromodifluoroacetate **145** and a series of ketones, yielding racemic β -hydroxy- α,α -difluoroesters **146** in good yields (74–95%). Subsequent saponification of the esters using sodium hydroxide afforded the corresponding racemic α,α -difluoro- β -hydroxy carboxylic acids (80–97%), for example **147**. Reacting the β -hydroxy group of the α,α -difluoro- β -hydroxy carboxylic acids with benzene-sulfonyl chloride and subsequent addition of pyridine afforded α,α -difluoro- β -lactones in excellent yields 89–100% <1995JOC5378>.



<i>R</i>	<i>R</i> ¹	Carboxylic acid Yield (%)
Me	Me	80
Et	Et	99
Ph	Bn	93
Bn	Bn	97

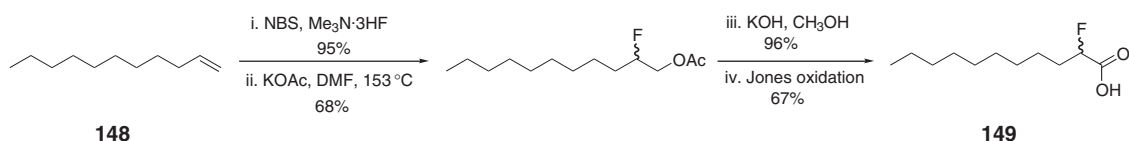
Scheme 19

5.02.2.2.2 By carbonation of organometallic reactions

In COFGT (1995), relatively little was reported on the synthesis of haloalkanoic acids via the carbonylation of organometallic reagents, the notable example being the treatment of perfluoroalkyl iodides with carbon dioxide in the presence of metal couples that comprised zinc and either copper, lead, cadmium, or mercury, yielding the corresponding perfluorocarboxylic acids in fair yields <1976CC885>.

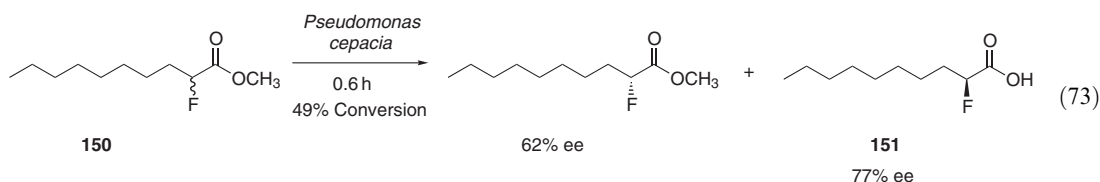
5.02.2.2.3 By oxidation reactions

Racemic 2-fluorodecanoic acid **149** has been synthesized in four steps from the cheap, readily available starting material, 1-decene **148**, in an overall yield of 41%, without the need for chromatography or distillation (Scheme 20). Previous syntheses of racemic α -fluorocarboxylic acid **149** have used either hazardous reagents, for example, liquid hydrogen fluoride, Olah's reagent (hydrogen fluoride in pyridine) or, for the synthesis of enantiopure 2-fluorocaprinic acid, optically enriched and expensive 1-decene oxide.

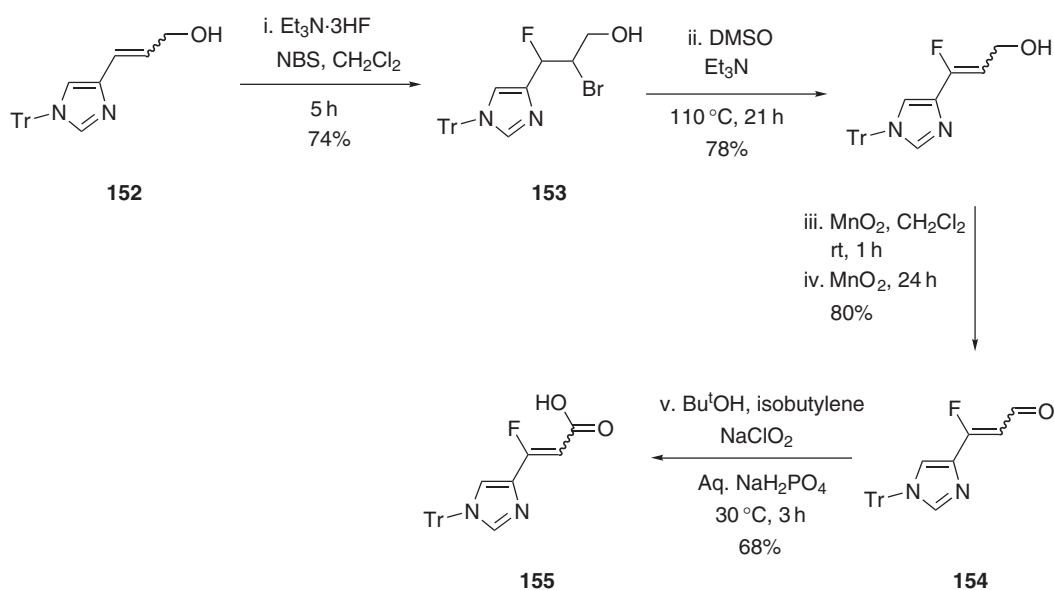


Scheme 20

Racemic methyl and ethyl 2-fluorodecanoates have been partially resolved with moderate success (ee values of 22–77%) using lipases from *Candida antarctica*, *Candida rugosa*, and *Pseudomonas cepacia*. Incorporating methyl ester **150** and the lipase *P. cepacia* afforded optically enriched α -fluorocarboxylic acid **151** in a 77% ee and 49% yield (Equation (73)) <2000TA889>.



The synthesis of β -fluorourocanic acid **155** has been achieved via a five-step protocol (Scheme 21). The addition of FBr, generated from triethylamine trihydrofluoride and NBS, to the allylic alcohol derivative of urocanic acid **152** afforded a diastereomeric mixture of β -fluoro- α -bromo alcohols **153** in reasonable yields (60–78%). Subsequent HBr elimination (52–62%) and preliminary oxidation, transformed the primary alcohol to aldehyde **154** (80%). Oxidation of aldehyde **154** (sodium chlorite) afforded the desired β -fluoro- β -imidazole- α,β -unsaturated carboxylic acid **155** in a 68% yield <2002JOC3468>.

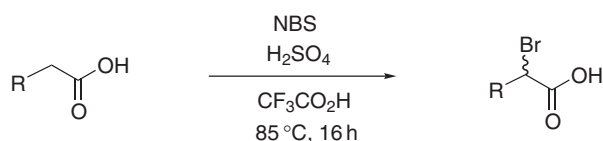


Scheme 21

5.02.2.2.4 By miscellaneous reactions

The deprotonation of aliphatic carboxylic acids, for example **156**, with 2 equiv. of LDA and the subsequent addition of carbon tetrabromide afforded racemic α -bromocarboxylic acid **157** (Equation (74)) <1998TL4757>. The synthesis of α -bromo aliphatic carboxylic acids, for example **158**, on a 0.1 mol. scale, can be readily achieved using the corresponding aliphatic acid and NBS (1.5 equiv.) in a trifluoroacetic acid/sulfuric acid mixture. The racemic α -bromocarboxylic acids are returned in excellent yields (82–89%) with no evidence of any α,α -dibromo adducts (Equation (75)). All attempts at incorporating phenyl-substituted carboxylic acids resulted in aromatic bromination <1998TL9621>.



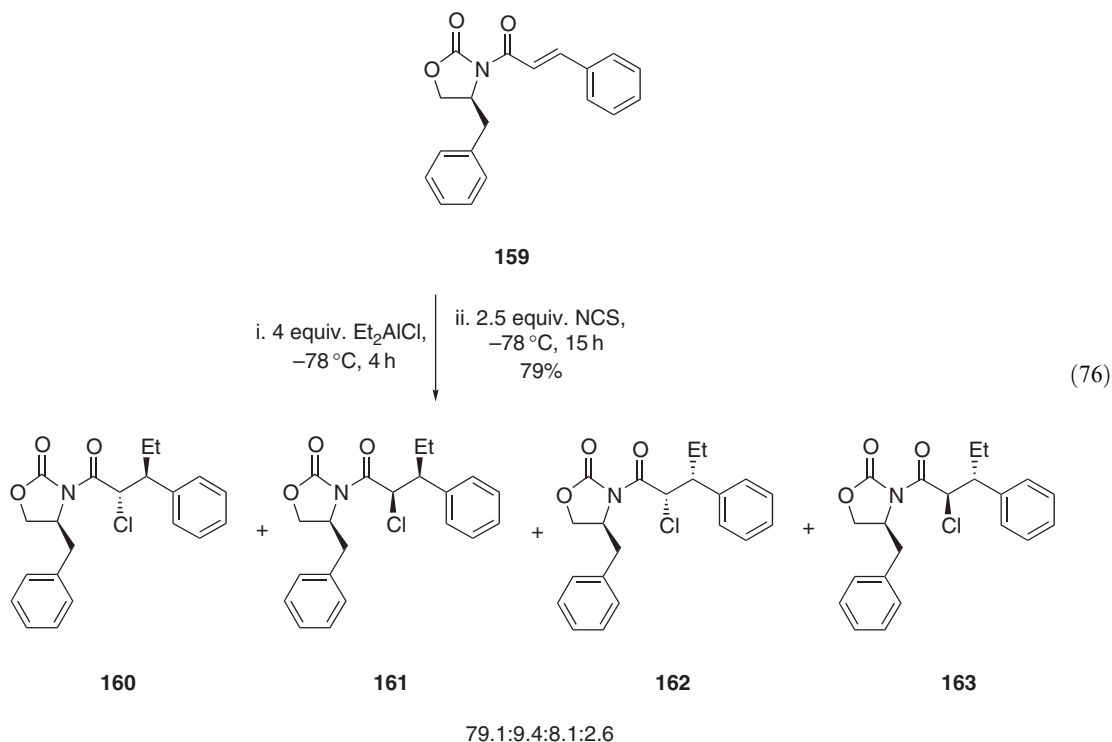


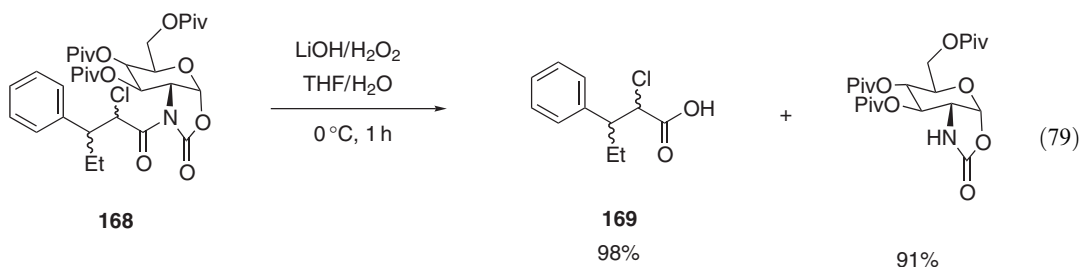
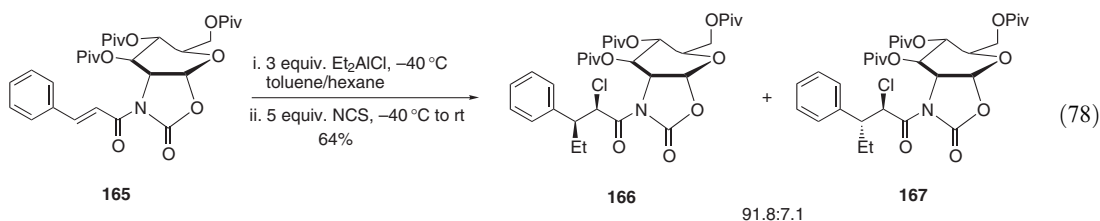
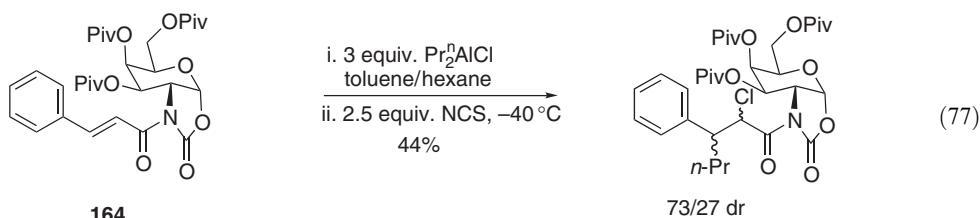
158

(75)

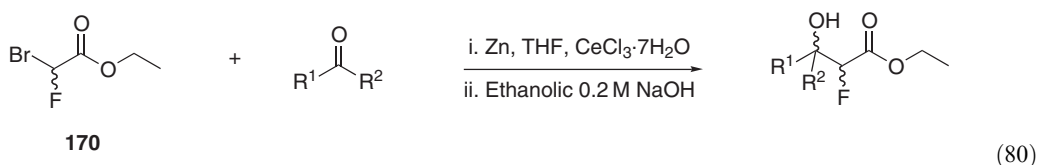
<i>R</i>	Yield (%)	<i>R</i>	Yield (%)
H	88	CH ₃ CH(CH ₃)	86
CH ₃	89	CH ₃ CH ₂ CH ₂	86
CH ₃ CH ₂	87	CH ₃ CH ₂ CH ₂ CH ₂	82

The stereoselective synthesis of β -substituted- α -halocarboxylic acids can be accomplished via a cascade reaction which is initiated by the 1,4-addition of an alkyl group derived from a dialkyl-aluminum chloride to chiral nonracemic α,β -unsaturated *N*-acyloxazolidin-2-one **159**. Subsequent trapping of the resulting aluminum enolate with either *N*-chlorosuccinimide or *N*-bromosuccinimide afforded diastereomeric mixtures of the corresponding β -substituted- α -halo *N*-acyloxazolidin-2-ones (**160–163**) in reasonable yields, 54–87% (Equation (76)). Substituting the (*S*)-phenylalanine derived oxazolidin-2-one chiral auxiliary for *N*-cinnamoyl appended oxazolidin-2-one **164**, synthesized from *O*-pivaloyl(galactosamine), improved the diastereoselectivity of the initial 1,4-conjugate alkylation (96:4). Be that as it may, the diastereoselectivity of the subsequent NCS quenching of the aluminum enolate was poor (Equation (77)). Changing the chiral auxiliary to *O*-pivaloyl(glucosamine) derived oxazolidin-2-one **165** afforded the cascade products **166** and **167** (Equation (78)) in good-to-high diastereoselectivities and reasonable yields (48–77%). Treating β -substituted- α -halo-oxazolidin-2-one **168** with a combination of lithium hydroxide and hydrogen peroxide in aqueous THF afforded β -substituted- α -halocarboxylic acid **169** (Equation (79)) in an excellent 98% yield <1997JOC967>.





Previous protocols for the synthesis of α -fluoro- β -hydroxy esters have been compromised by the use of the highly toxic ethyl fluoroacetate. Furthermore, hydrolysis of α -fluoro- β -hydroxy esters to the corresponding α -fluoro- β -hydroxy carboxylic acids has proved troublesome. Both base- and acid-mediated hydrolysis procedures returned low yields (10–14%, respectively) as a consequence of competing fluoride elimination. Protection of the β -hydroxy group, although solving the problem, does introduce further undesirable reaction steps. A recent report has demonstrated that the presence of catalytic amounts of cerium(III) chloride (4 mol.%) improves the yields (60–95%) and simplifies the synthesis of α -fluoro- β -hydroxy esters (1:1 *erythro*/*threo*) via a synthetic procedure based on a Reformatsky reaction between ethyl bromodifluoroacetate **170** and aldehydes or ketones (Equation (80)). It was proposed that the reaction proceeded via the *in situ* generation of an organocerium reagent. Subsequent hydrolysis of the ethyl ester functionality was undertaken using a cold solution of sodium hydroxide in absolute ethanol, returning the carboxylic acids in excellent yields (>90%) [<2002JOC72>](#). Similarly, the synthesis of racemic β -hydroxy- α,α -difluorocarboxylic acids, for example **171**, has been undertaken in modest to excellent yields (39–93%) via a Reformatsky reaction incorporating ethyl bromodifluoroacetate **170**, zinc and a series of aliphatic aldehydes (Equations (81)–(83)). Subsequent enzymatic resolution of racemic ethyl 2,2-difluoro-3-hydroxyoctanoate **171** via a hydrolysis procedure afforded the corresponding chiral nonracemic carboxylic acid in good yields and ee values (Table 7) [<1996T157>](#).



R^1	R^2	Yield (%)	R^1	R^2	Yield (%)
$n\text{-C}_4\text{H}_9$	H	83	CH_3	CH_3	89
$n\text{-C}_5\text{H}_{11}$	H	90	CH_3CH_2	CH_3CH_2	90
Ph	H	92	Ph	CH_3	90

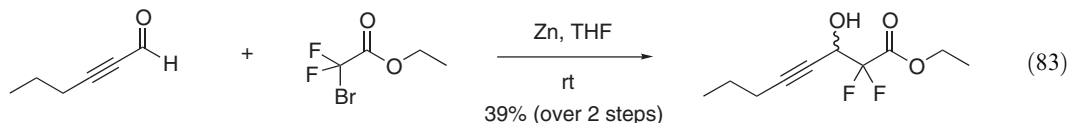
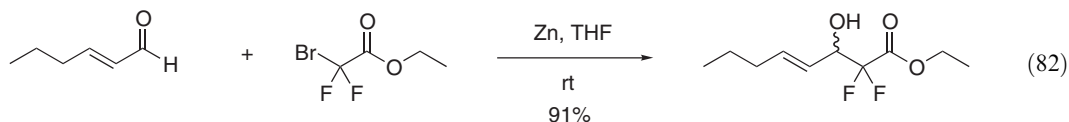
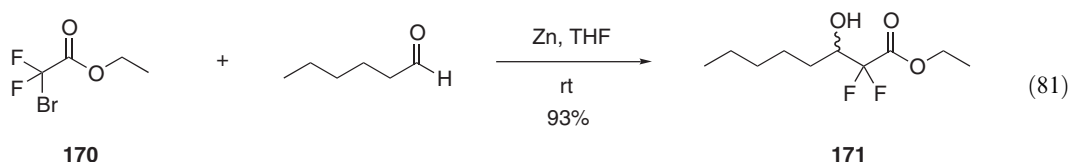
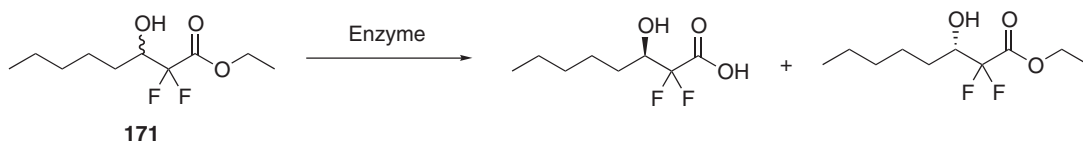
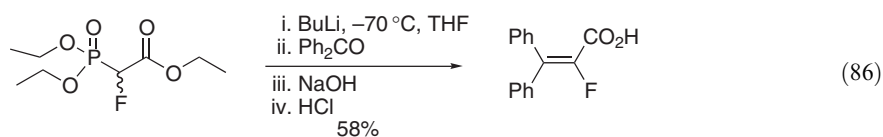
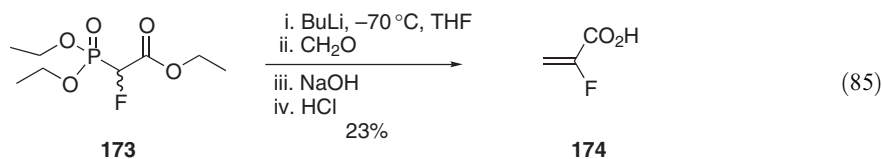
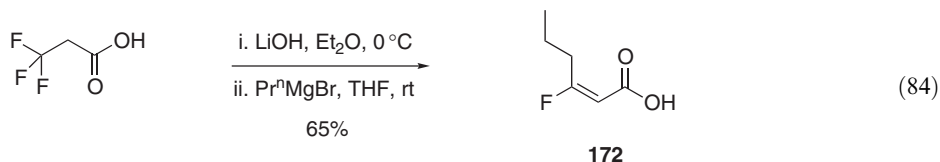


Table 7 Asymmetric enzyme-mediated hydrolysis of ethyl α,α -difluoro- β -hydroxyester

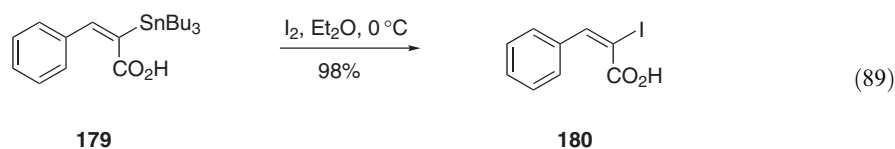
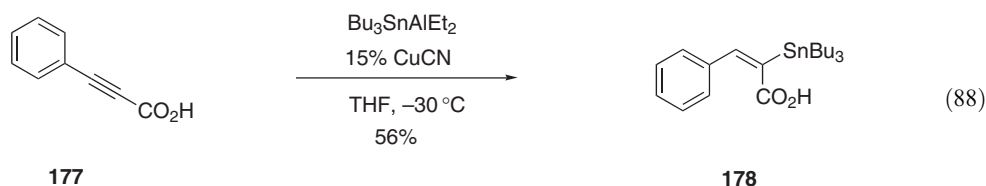
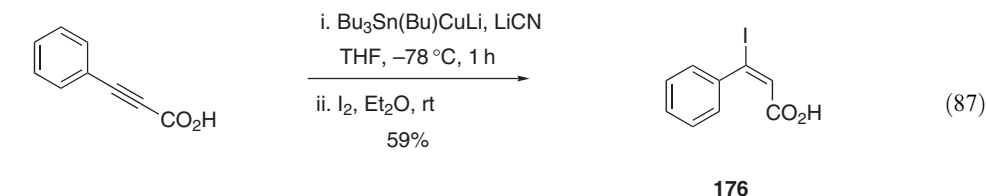


Enzyme source	Time (h)	Carboxylic acid yield (%)	Carboxylic acid ee (%)
<i>Rhizopus japonicus</i>	4	81	79
<i>Pseudomonas fluorescens</i>	1.7	70	73

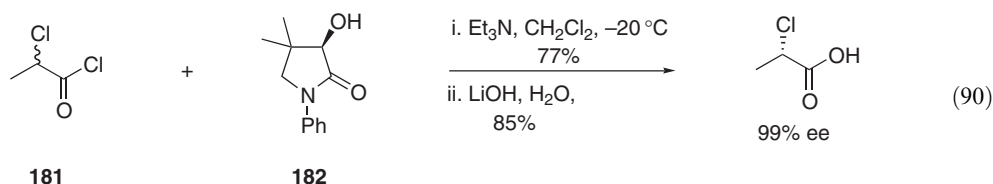
The stereoselective synthesis of (*E*)-3-fluoro-2-alkenoic acids, for example **172**, in good yields (65–70%) has been undertaken by reacting Grignard reagents with lithium 3,3,3-trifluoropropionate (Equation (84)) <1997JFC(86)99>. The synthesis of α -fluoro- α,β -unsaturated carboxylic acids, for example **174**, has been accomplished via a Wittig reaction between ethyl (diethoxyphosphoryl)-fluoroacetate **173** and aldehydes, for example depolymerized formaldehyde (Equation (85)), or ketones, for example benzophenone (Equation (86)). Subsequent saponification using aqueous sodium hydroxide afforded the corresponding carboxylic acids <2002JFC(113)211>.



The synthesis of the β -iodo- α,β -unsaturated carboxylic acid **176**, has been achieved from the corresponding β -stannyl- α,β -unsaturated carboxylic acid. The stereoselective synthesis of the desired vinylstannane starting material was undertaken via a stannylcupration of the corresponding alkyne-appended carboxylic acid (Equation (87)). Numerous (lower-order) anionic tin species were investigated for their potential to undergo conjugate additions to the alkynes, but low conversion rates were observed. Optimum results were obtained using higher-order tin species derived from $\text{Bu}_3\text{Sn}(\text{Bu})\text{CuLi}$ and LiCN ; the (*E*)- α,β -unsaturated carboxylic acids were returned in reasonable yields (51–66%). Incorporating 3-phenylprop-2-ynoic acid **177** afforded the reverse regioselective product, for example, (*E*)- α -stannyl- β -phenyl- α,β -unsaturated carboxylic acid **178** (Equation (88)). Treatment of vinylstannane **179** with a solution of iodine in ether yielded the corresponding α -iodo- α,β -unsaturated carboxylic acid **180** (Equation (89)) <1998TL4277>.

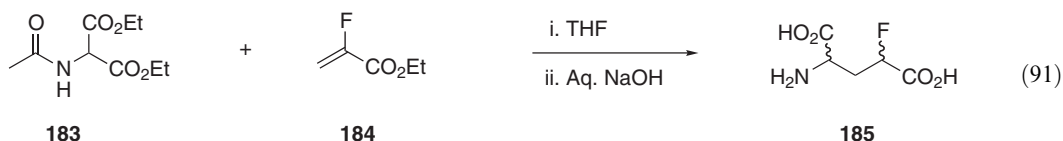


Racemic α -chloropropanoic acids, for example **181**, have been resolved using either (*S*)- or (*R*)-3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinones **182**, returning the corresponding esters in excellent yields (92–99%) and modest-to-good diastereoselectivities (46–96%). Interestingly, the diastereoselectivities of the ester products depended on the amines used, with triethylamine yielding the highest (95% de). Subsequent saponification of the pyrrolidinone esters afforded, optically enriched α -chloropropanoic acids (21–99% ee) in excellent yields (85–99%). The use of acidic conditions, for example, 2 M hydrochloric acid/AcOH, to hydrolyze the esters resulted in epimerisation of the α -chlorocarboxylic acids (Equation (90)) <1998TA2065>.



The synthesis of racemic 4-fluoroglutamic acid **185** has been accomplished in two steps: Michael addition of diethyl acetamidomalonate **183** to ethyl 2-fluoroacrylate **184**, followed by ester hydrolysis affording racemic 4-fluoroglutamic acid **185** (Equation (91)) <1993JFC(60)179>. The key steps used for the transformation of racemic **185** into enantiomerically pure *L-erythro* and *L-threo*-4-fluoroglutamic acids included: (i) synthesis of the *N*-chloroacetyl-4-fluoroglutamic acid methyl ester and subsequent separation of the two diastereomers via recrystallization, and (ii) an enzyme-mediated resolution using an aminoacylase (EC 3.5.1.14) to give the (*R*)- and (*S*)-4-amino-2-fluorobutyric acids in high optical purity <1996TA3545>. The synthesis of

enantiomerically enriched (*R*)- or (*S*)-4-amino-2-fluorobutyric acid has been accomplished from the respective racemic (4(*R*))- or (4(*S*))-4-fluoroglutamic acid using glutamic decarboxylase and pyridoxal 5-phosphate <2000JFC(101)5>.



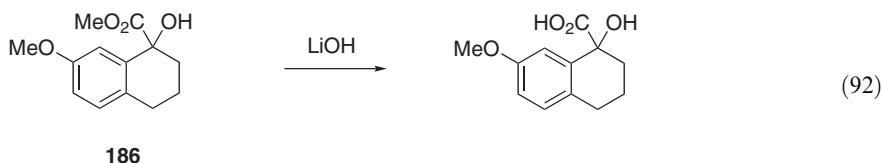
The synthesis of 4-iodoperfluorobutanoic acid from α,ω -diiodoperfluorobutane has been accomplished via electrolysis of an oxygen-saturated DMF solution containing α,ω -diiodoperfluorobutane. The 4-iodoperfluorobutanoic acid was returned in a 53% yield, with 31% of the starting α,ω -diiodoperfluorobutane being recovered <1996JFC(77)21>.

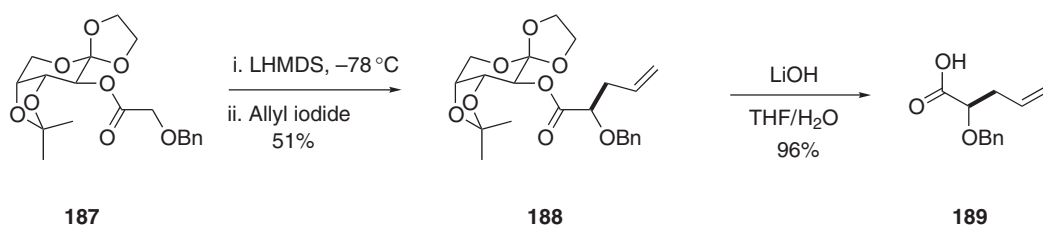
5.02.2.3 Oxygen-substituted Alkanoic Acids

α -Hydroxy carboxylic acids are important building blocks in the synthesis of biologically active molecules. An extensive number of books and reviews on oxygen-substituted alkanolic acids have been published. These include a general report on hydroxy carboxylic acids <B-1945MI502-02> and the synthesis and stereochemistry of β -hydroxy acids via aldol condensations <B-1980MI502-01>. A number of reports have detailed the asymmetric synthesis of α -hydroxy carboxylic acids via, for example, the reduction of chiral hemiacetals <1998JOC4120, 1998T14549>, reduction of α -ketoacids <1995SC1963, 1998JA4345, 1998TL5501>, hydroxy insertions of diazoacetates <1995JOC4449>, condensation of *trans*-1,3-dithiane-1,3-dioxide with aldehydes <1997T16213>, osmium-catalyzed dihydroxylations followed by diol oxidative cleavage <2000TL3209> and the nucleophilic alkylation of oxazin-4-ones <1998TL7153>. A book detailing the synthesis and use of α -hydroxy acids has been published <B-1997MI001>.

5.02.2.3.1 By hydrolysis reactions

The saponification of α -hydroxy esters can be readily undertaken using well-tested procedures that are very similar to those employed for the hydrolysis of conventional ester groups (see Section 5.02.2.1.1 and references therein). The initial stages of an enantioselective synthesis of (*R*)-1-hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid required saponification of the racemic α -hydroxy methyl ester **186**. The hydrolysis was readily undertaken using aqueous lithium hydroxide on a multigram scale (Equation (92)) <2003OPRD198>. *O*-Benzyl protected α -hydroxy- α -substituted carboxylic acids, for example **189**, have been synthesized in moderate to good yields and high diastereoselectivity (83–98% de). The alkylation of a glycolate ester enolate obtained by deprotonation of the D-fructose-derived system **187** (synthesized on a multigram scale) afforded **188**. The chiral auxiliary on **188** was subsequently cleaved using lithium hydroxide in aqueous THF affording the optically active α -benzyloxycarboxylic acids **189** in good yields (84–98%, Scheme 22) <2001TL1835>. A pivotal step in the synthesis of the antitumour agent (+)-geldanamycin was the removal, via hydrolysis, of the norephedrine-based chiral auxiliary used in the asymmetric aldol reaction. A lithium hydroxide mediated saponification of **190** returned the optically-enriched α -methoxy carboxylic acid **191**, which was subsequently esterified in good yield (Equation (93)) <2002OL3549>. The use of other group 1 alkali hydroxides, for example, sodium hydroxide, for the saponification similar esters has been described <2003JOC7555>.

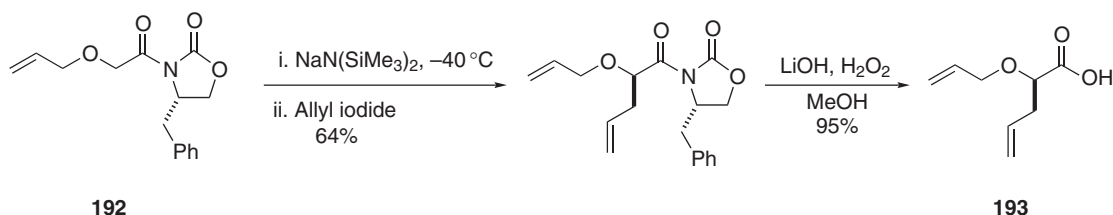




Scheme 22

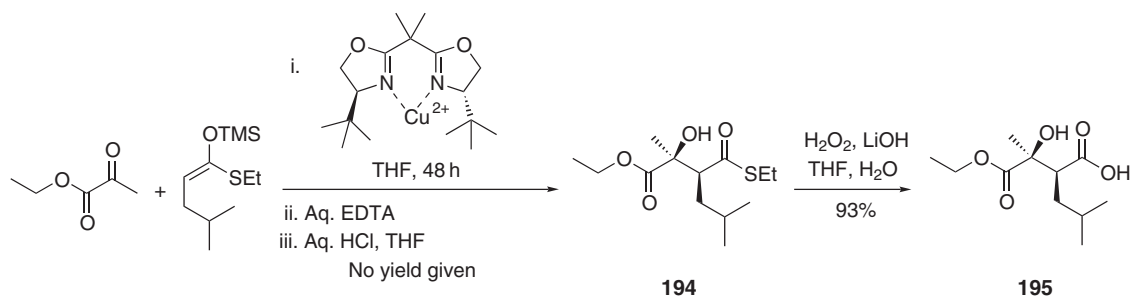


The asymmetric glycolate alkylation of 4-substituted oxazolidin-2-ones, for example **192**, has been used for the enantioselective synthesis of *O*-protected- α -hydroxy carboxylic acids **193** in high yield. Cleavage of the oxazolidin-2-one chiral auxiliary, liberating the *O*-protected- α -hydroxy carboxylic acid **193**, was undertaken using a combination of lithium hydroxide and hydrogen peroxide in methanol (Scheme 23) <2000OL2165>.

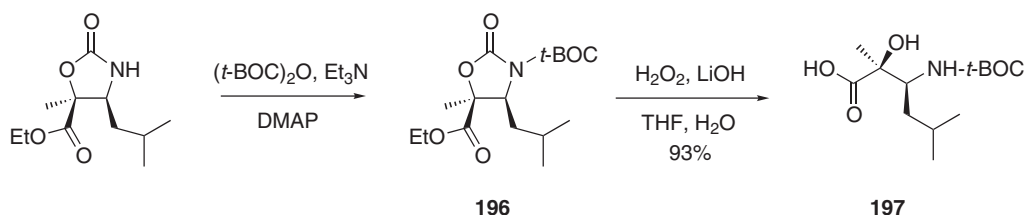


Scheme 23

The synthesis of chiral nonracemic *t*- β -hydroxy carboxylic acids, for example **195**, has been achieved via an asymmetric aldol reaction. The synthetic protocol proceeds via an enantioselective *syn*-aldol addition of enolsilanes to pyruvate esters mediated by a C_2 -symmetric bis(*t*-butyl-oxazoliny)Cu(OTf)₂ complex. Chemoselective hydrolysis of the thioester functionality on **194** using a combination of hydrogen peroxide and lithium hydroxide in aqueous THF afforded the carboxylic acid **195** in an excellent 93% yield (Scheme 24). Using similar cleavage conditions, the hydrolysis of the ethyl ester group and oxazolidin-2-one on **196** was accomplished affording carboxylic acid **197** in an excellent yield (Scheme 25) <2001TL3563>.

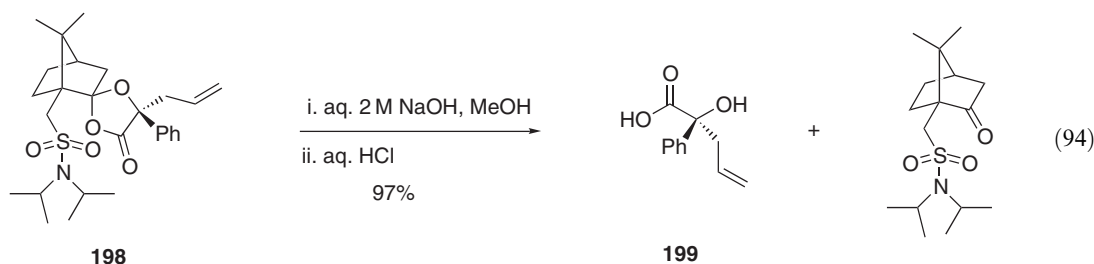


Scheme 24



Scheme 25

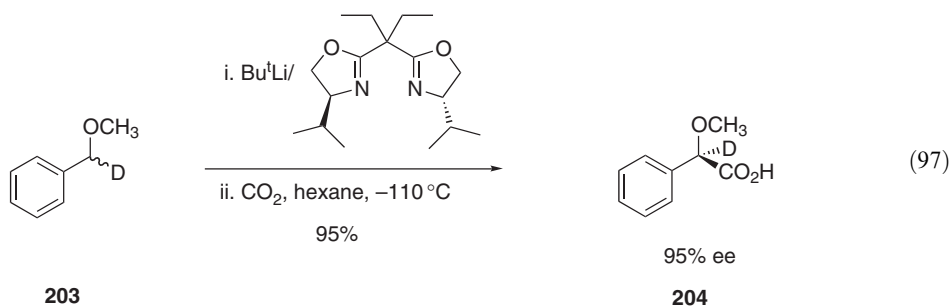
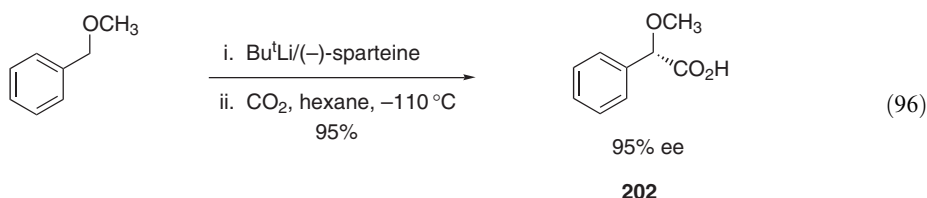
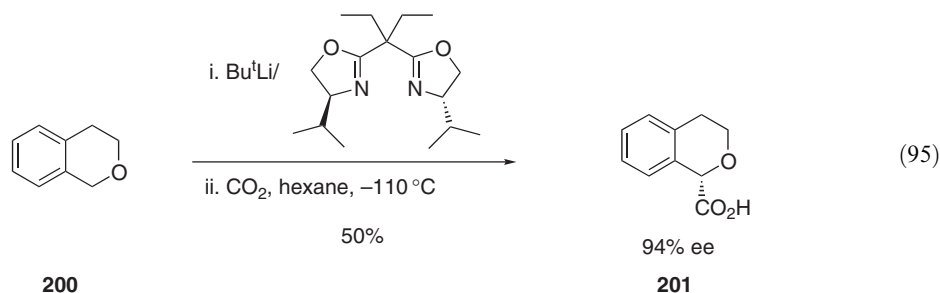
The synthesis of enantiomerically enriched *t*- α -hydroxy- α,α -disubstituted carboxylic acids, for example **199**, via a condensation reaction using either racemic lactic or mandelic acids and (1(*S*))-(+)-*N,N*-diisopropyl-10-camphorsulfonamide as the chiral auxiliary, afforded, after deprotonation and subsequent alkylation, moderate to high yields (67–84%) of the corresponding dialkylated 1,3-dioxolanones **198**. Saponification using aqueous 2 M sodium hydroxide in methanol, followed by acidification returned the *t*- α -hydroxy- α,α -disubstituted carboxylic acid **199** in excellent yields (94–98%) (Equation (94)) <1999OL2061>.



5.02.2.3.2 By carbonation of organometallic reagents

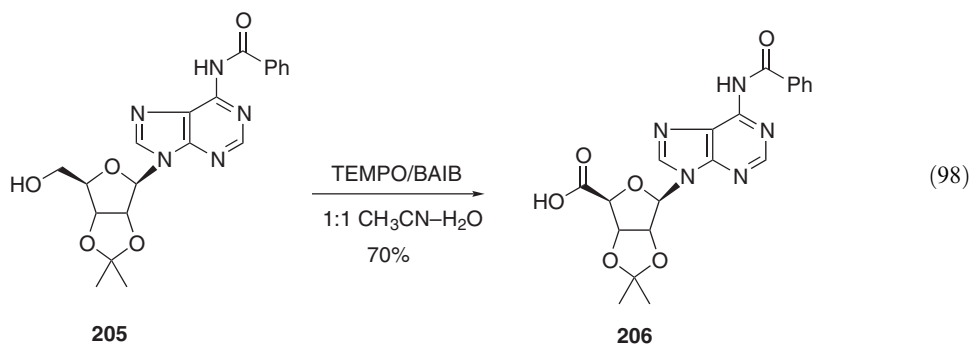
Many substrates, organometallic reagents, and reaction conditions have been utilized for the synthesis of oxygen-substituted alkanolic acids using carbonation procedures <1974S443, 1974JOC600>. A number of reviews detailing the development and use of enantioselective organolithium reactions in, for example, asymmetric carbonylation procedures have been published <1996ACS552, 1997AG(E)2283>.

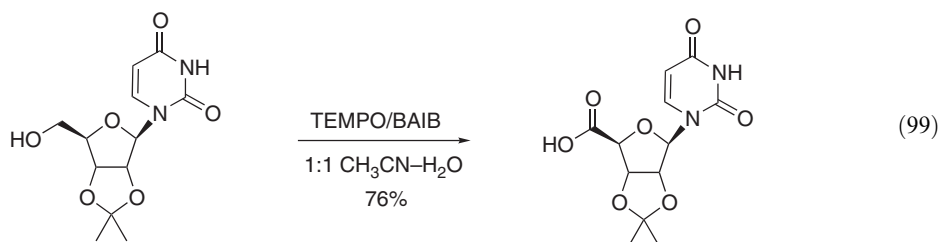
Treatment of isochroman **200** and phthalan with a combination of Bu^tLi and a (*S*)-valine-derived chiral nonracemic bis(oxazoline) derived ligand results in their enantioselective deprotonation. Quenching the optically enriched organolithium species with a variety of electrophiles afforded chiral nonracemic α -substituted products in moderate-to-high enantioselectivities (30–97% ee) depending on the electrophile used. Interestingly, quenching the optically enriched organolithium at -78°C with carbon dioxide afforded the corresponding carboxylic acid **201** in an excellent 89% ee, while lowering the quenching temperature to -110°C afforded an increase in the ee of the product to 94%, albeit at the expense of a lower 50% yield (Equation (95)). Investigating the potential of a $\text{Bu}^t\text{Li}/(-)$ -sparteine complex as the asymmetric deprotonation reagent was disappointing in terms of yield (50%) and ee of the product (5%) <2000TL6121>. In a similar protocol, using a combination of Bu^tLi and (*-*)-sparteine as the asymmetric base complex, the synthesis of chiral nonracemic α -methoxyphenylacetic acid **202** was undertaken in an excellent 95% yield and 95% ee (Equation (96)). The use of Bu^tLi not Bu^sLi and hexane as solvent was critical to maintaining high levels of enantioselectivity in the reaction, using ether and THF afforded high yields (95% and 85%, respectively) but low ee's (1% and 17%, respectively). Interestingly deprotonating racemic (α -deutero benzyl) methyl ether **203** with a combination of *t*- BuLi and chiral nonracemic bis(oxazoline) ligand resulted, after quenching with carbon dioxide in a 74% ee of the corresponding α -deutero- α -methoxyphenylacetic acid **204**. It appears that the reaction is governed by a dynamic thermodynamic resolution, where epimerisation is slower than carboxylation (Equation (97)) <1999TL6809>.



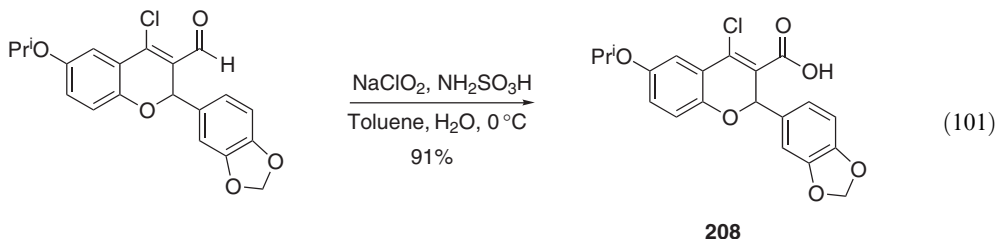
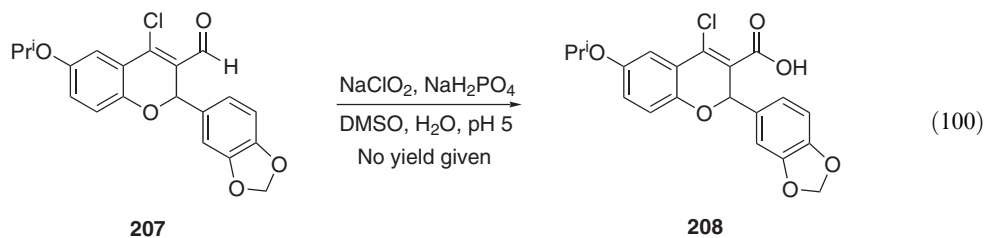
5.02.2.3.3 By oxidation reactions

There are relatively few methods for the synthesis of nucleoside-5'-carboxylic acids [<1886JMC4162>](#). A mild and general procedure for the oxidation of 5'-hydroxymethylene nucleosides **205** to the corresponding 5'-carboxylates **206** has been developed using catalytic quantities of 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO) and stoichiometric amounts of an organic oxidant, [bis(acetoxy)iodo]benzene (BAIB). The combination of TEMPO (20 mol.%) and BAIB (2.2 equiv.) in aqueous acetonitrile afforded the nucleoside carboxylic acids from the corresponding alcohols in good-to-excellent yields (57–90%). Simple trituration of the precipitated solid with acetone followed by ether afforded carboxylic acids of sufficient purity for most purposes. Using this protocol the oxidation of adenosine, *N*-benzoyladenosine ([Equation \(98\)](#)), uridine ([Equation \(99\)](#)), cytidine, and guanosine 2',3'-isopropylidene protected nucleosides was accomplished [<1999JOC293>](#).

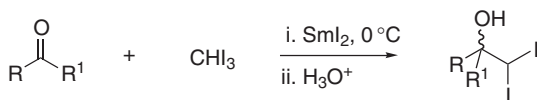




During a several-kilogram synthesis of enantiomerically pure S-1255, a potent ET_A receptor antagonist, the transformation of a chromanone appended aldehyde **207** to the corresponding carboxylic acid **208** was undertaken. Using sodium chlorite as the active oxidant in aqueous DMSO and sodium dihydrogenphosphate afforded the desired carboxylic acid (Equation (100)). The use of sodium chlorite in the presence of sulfamic acid, as an HOCl scavenger, returned carboxylic acid **208** in an excellent 91% yield (Equation (101)) <2002JOC7741>.

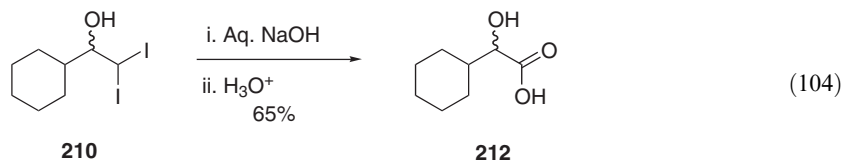
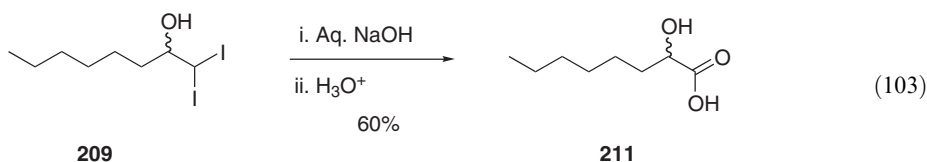


Halomethylation of aldehydes and ketones is difficult to achieve using α -halogenated organo-metallic reagents as a consequence of their thermal instability, but such compounds are useful precursors of α -hydroxy acids. An alternative protocol for the iodomethylation of aldehydes using samarium(II) iodide has been reported <1997AG(E)617>. In a similar protocol, the combination of samarium(II) iodide and iodoform reacted with carbonyl groups to effect a diiodomethylation of the carbonyl substituent affording β,β -diiodoalcohols (Equation (102)) in poor to reasonable yields (23–61%). The diiodomethylation reaction is general for aromatic, α,β -unsaturated, and linear aldehydes. Reacting the β,β -diiodoalcohols **209** and **210** with aqueous sodium hydroxide for 48 h at ambient temperatures returned the racemic α -hydroxy carboxylic acids **211** and **212** respectively in 60–74% yields (Equation (103) and (104)) <1998TL1409>.



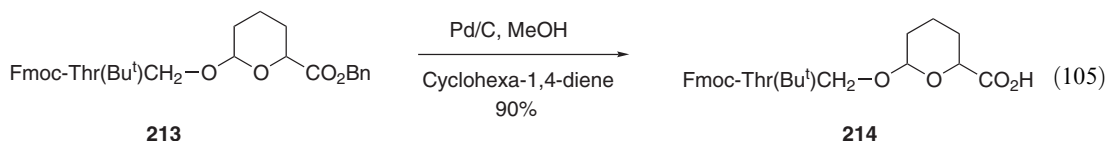
<i>R</i>	<i>R</i> ¹	Temperature (°C)	Yield (%)
Ph	H	0	61
4-Cl-C ₆ H ₅	H	0	60
Furyl	H	0	40
Ph	H	0	58
Cyclohexyl	H	0	62
Ph	H	0	57
-C ₄ H ₉ -		0	40
-C ₅ H ₁₀ -		0	49

(102)

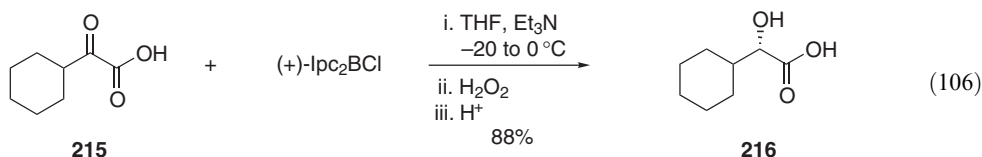


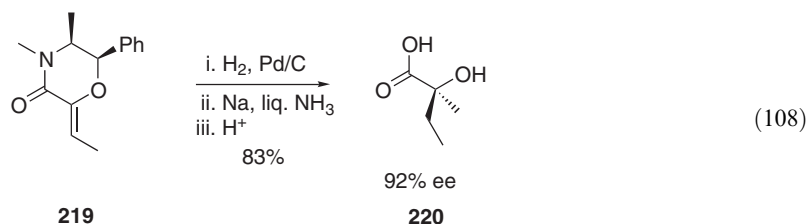
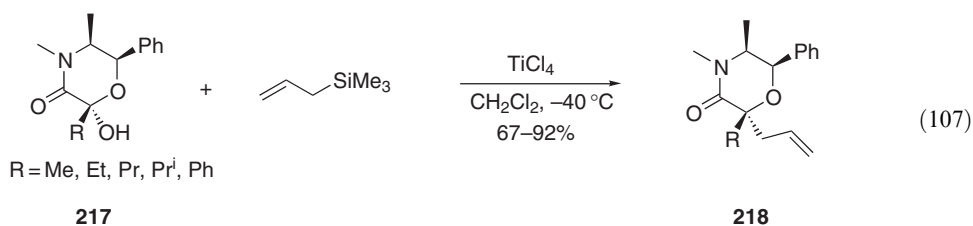
5.02.2.3.4 By miscellaneous reactions

The synthesis of oxygen-substituted acids via the hydrolysis of esters using lithium-appended nucleophiles is known [\[1960HCA113, 1965JCS6655\]](#). The chemoselective cleavage of a benzyl ester appended to a peptide-derived dihydropyran-2-carboxylate ester **213** affording the corresponding free carboxylic acid **214** has been reported. Using transfer hydrogenation techniques, catalytic amounts of palladium on carbon and cyclohexa-1,4-diene resulted in an excellent yield (90%) of the corresponding peptide-derived tetrahydropyran carboxylic acid. Fmoc protecting groups present on the peptides were unaffected by the ester cleavage conditions. The use of alcalases, lipases, and alternative saponification protocols, for example potassium carbonate in aqueous THF, were ineffective for cleavage of the benzyl ester ([Equation \(105\)](#)) [\[1998CC649\]](#).

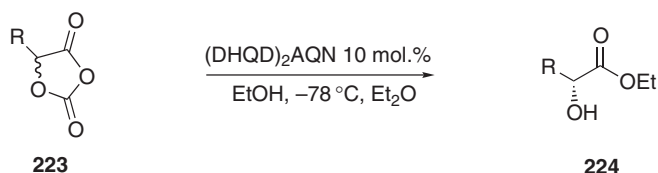
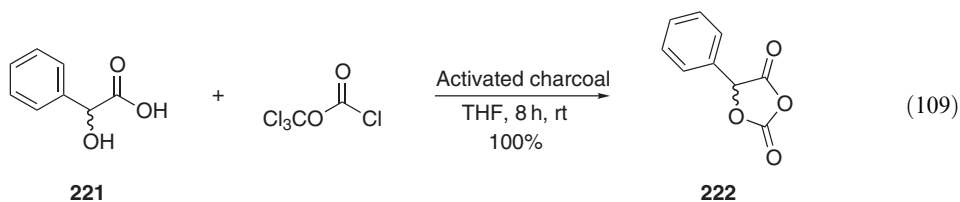


α -Keto acids, for example **215**, have been reduced to chiral nonracemic α -hydroxy carboxylic acids **216** using B-chlorodiisopinocampheylborane in good-to-excellent yields (65–91%) and enantioselectivities (85–98% ee, [Equation \(106\)](#)) [\[1998TL5501\]](#). (1(*R*),2(*S*))-Ephedrine-derived cyclic hemiacetals have been utilized in the synthesis of chiral nonracemic α -hydroxy carboxylic acids. Reacting readily synthesized (1(*R*),2(*S*))-ephedrine hemiacetal **217** with allyltrimethylsilane and a Lewis acid, for example, titanium(IV) chloride, afforded a single diastereomer of the corresponding allyl-appended morpholine derivative **218** ([Equation \(107\)](#)) in reasonable-to-excellent yields (67–92%). Acid-catalyzed dehydration of a hemiacetal substrate equipped with a β -hydrogen, afforded the corresponding α,β -unsaturated morpholine **219**, and subsequent hydrogenation (H_2 , Pd/C) and reductive ring cleavage returned the α -hydroxy acid **220** ([Equation \(108\)](#)) [\[1998JOC4120\]](#).





The condensation of racemic α -hydroxy carboxylic acids, for example **221**, with diphosgene in the presence of activated charcoal afforded the corresponding racemic 5-aryl- and 5-alkyl-1,3-dioxolane-2,4-diones **222** in high yield and purity (Equation (109)). The dynamic kinetic resolution of 5-aryl-1,3-dioxolane **223** was performed using catalytic amounts of (DHQD)₂AQN (10 mol.%) in ether, with ethanol as the nucleophile. The resolution reaction was usually complete within 24 h when conducted between $-20\text{ }^{\circ}\text{C}$ and $-78\text{ }^{\circ}\text{C}$. The resulting chiral nonracemic α -hydroxy esters, for example **224** were isolated in good yields (61–85%) and excellent ee values (60–96%). The efficiency of the dynamic kinetic resolution was impaired (ee values reduced to 60–62%) with 1,3-dioxolane-2,4-diones equipped with *ortho*-substituted benzene rings (Equation (110)).

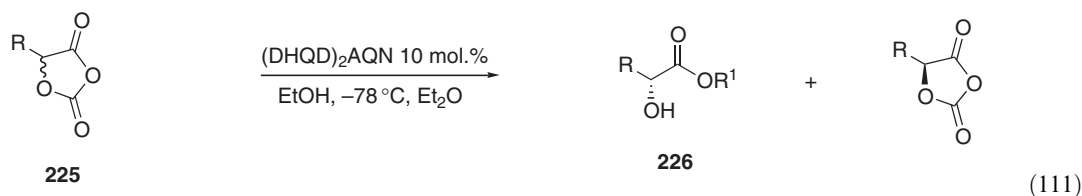


R	Temperature ($^{\circ}\text{C}$)	Time (h)	Yield (%)	ee (%)
C ₆ H ₅	-78	24	71	95
4-ClC ₆ H ₄	-78	24	70	96
4-BrC ₆ H ₄	-78	24	80	96
4-FC ₆ H ₄	-78	24	65	95
4-F ₃ CC ₆ H ₄	-78	24	85	93
4-Pr ⁱ C ₆ H ₅	-20	8	68	91
3,4-C ₆ H ₃	-78	24	65	94
2-ClC ₆ H ₄	-60	10	66	62
2-MeC ₆ H ₄	-20	4	61	60

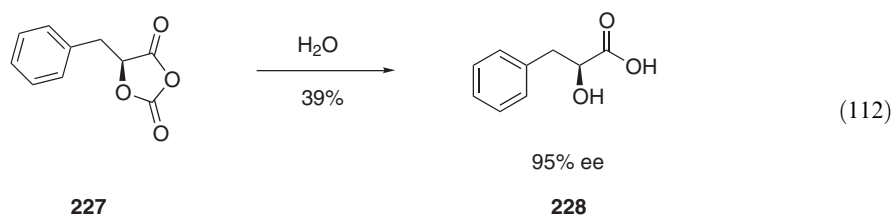
(110)

Performing a kinetic resolution on racemic 5-alkyl-1,3-dioxolane-2,4-dione, for example **225**, using catalytic quantities of (DHQD)₂AQN (10 mol.%) and 1 equiv. of a suitable alcohol (ethanol or allyl alcohol) afforded optically enriched α -hydroxy esters **226** in good yields (46–48%) and excellent 90–96% ee values (Equation (111)). Subsequent hydrolysis of the unreacted chiral

nonracemic 5-alkyl-1,3-dioxolane-2,4-diones **227** returned the corresponding enantiomerically enriched α -hydroxy carboxylic acids **228** in reasonable yields (32–40%) and ee values (85–95%) (Equation (112)) <2002JA2870>.



<i>R</i>	<i>R</i> ¹	Time (h)	α -Hydroxy ester yield (%)	α -Hydroxy ester ee (%)
PhCH ₂	Et	12	47	96
PhCH ₂ CH ₂	Et	24	46	93
CH ₃ (CH ₂) ₃	Et	36	42	92
(CH ₃) ₂ CH	Allyl	6	48	90



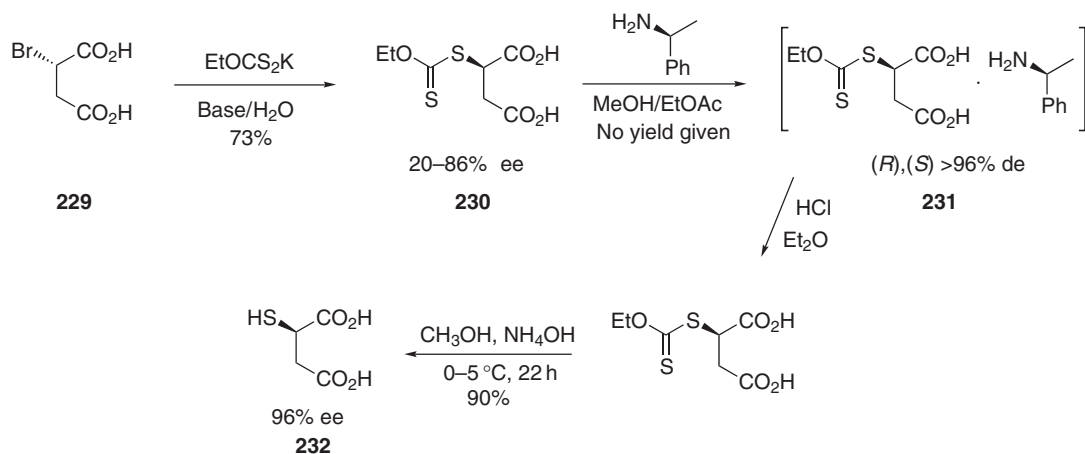
5.02.2.4 Sulfur-substituted Alkanoic Acids

Two reviews on the synthesis of sulfur-substituted alkanic acids have been published <B-1978MI502-03, 1983S605>.

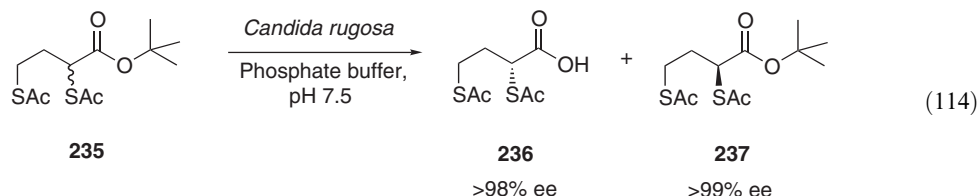
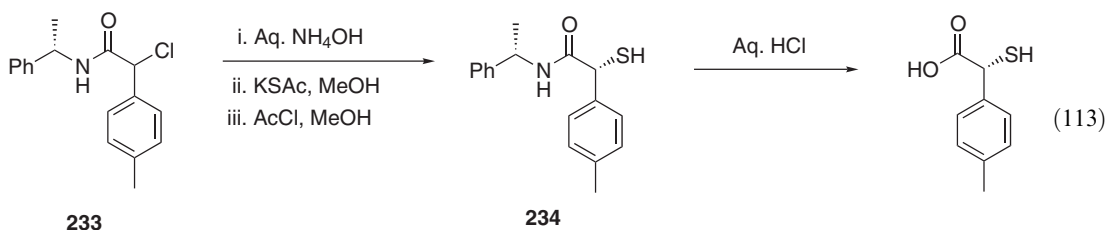
5.02.2.4.1 By hydrolysis reactions

3-Mercaptosuccinic acid **232** is an important chiral multifunctional intermediate employed, for example, in the synthesis of anti-leukemic, anti-microbial, and anti-tubercular agents. A five-step synthesis of enantiomerically enriched (>96% ee) (*R*)- and (*S*)-2-mercaptosuccinic acid has been accomplished in an overall 49–52% yield. The synthesis of (*R*)-2-mercaptosuccinic acid was undertaken via an S_N2 bromide displacement on (*S*)-bromosuccinic acid **229** using a mixture of sodium carbonate (0.5 equiv.) and potassium ethyl xanthate (2.5 equiv.), affording, in quantitative yield, the corresponding (*R*)-ethyl xanthosuccinic acid **230** in an 85% ee. Interestingly, during the displacement reaction no neighboring group participation from the neighboring carboxylic acid was observed. Stereochemical enrichment of the (*R*)-ethyl xanthosuccinic acid using (*S*)- α -methylbenzylamine afforded the carboxylic acid salt **231** optically pure. Release of the free carboxylic acid (hydrochloric acid in ether) and saponification of the thioester with concentrated ammonium hydroxide in methanol afforded (*R*)-2-mercaptosuccinic acid **232** in a 96% ee and 90% yield (Scheme 26) <1998TA1641>.

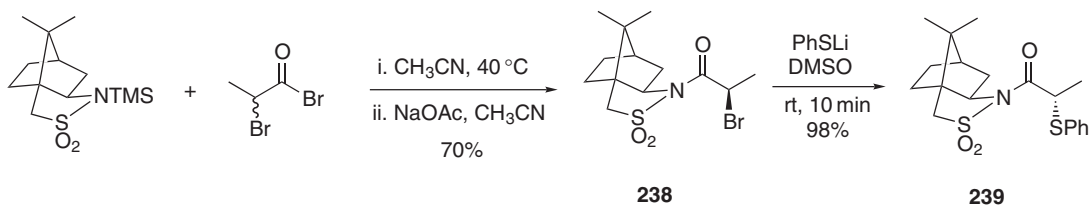
A study by Park and co-workers has reported on the crystallization-induced dynamic resolution of configurationally labile *N*-(*S*)-(1-phenylethyl)- α -chloro- α -arylacetamides (e.g., **233**) using aqueous ammonia. Subsequent reaction of the optically enriched α -chloro derivative with potassium thioacetate affords the corresponding α -mercapto amide (e.g., **234**), after removal of the *S*-acetyl group with acid, in high yield (95%) and good diastereomeric ratio (97:3, Equation (113)). Treatment of the α -mercapto amides **234** with acid affords the corresponding α -mercapto carboxylic acids <2001SL1941>. Lipase derived from *Candida rugosa* enantioselectively and regiospecifically hydrolyzes *t*-butyl 2,4-dithioacetylbutanoate **235**, yielding enantiomerically enriched (*R*)-2,4-dithioacetylbutyric acid **236** (ee >98%) and *t*-butyl (*S*)-2-thio-4-thioacetylbutyrate **237** (ee >99%), respectively (Equation (114)) <1998TA4109>.



Scheme 26



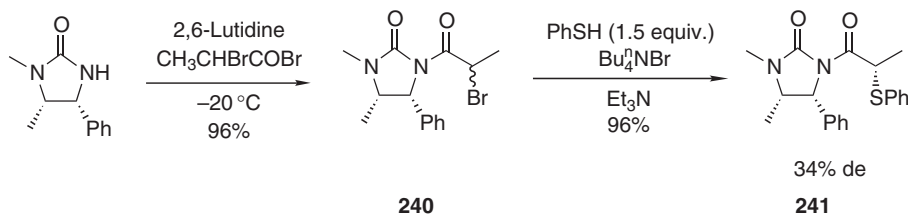
α -Bromoamides derived from Oppolzer's camphorsultam **238** can be prepared diastereoselectively from racemic α -bromocarboxylic acids. Reacting the α -bromoacids with lithium thiophenoxide, returned the corresponding (α -thio-*N*-acyl) camphorsultam, for example **239**, in excellent yields and with complete inversion of the α -center configuration (Scheme 27). Subsequent saponification of the *N*-acyl bond, using aqueous base yields the corresponding α -thiocarboxylic acids <1995TA469>.



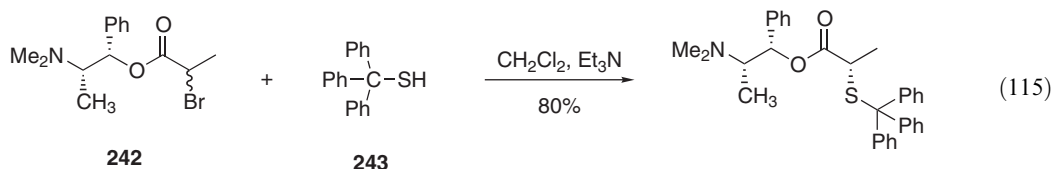
Scheme 27

Attempted dynamic kinetic resolutions (DKR) of α -haloacylimidazolidinones, for example **240**, with a variety of sulfur-based nucleophiles, for example thiophenol (Scheme 28), benzyl mercaptan and methyl thioacetate yielded the corresponding α -thioacylimidazolidinones **241**, in good-to-excellent yields (78–96%). However, rather disappointingly, the reaction displayed low stereoselectivity, with *de* values ranging from 9 to 34%. This was attributed to the high nucleophilicity of the sulfur species toward displacing the bromine relative to epimerization. Conducting the reactions under high dilution had little effect on the observed stereoselectivity. The imidazolidinone chiral auxiliary was

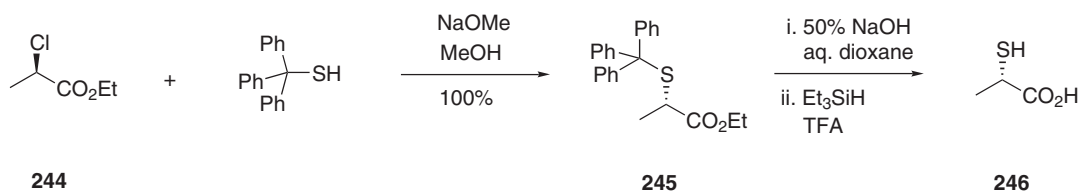
cleaved using either diisopropylethylamine or triethylamine in methanol, affording the corresponding ester in high yields. Similarly, cleavage of the chiral auxiliary with aqueous methanolic solutions of sodium or lithium hydroxide would afford the corresponding α -thiocarboxylic acids after neutralization <2001T6589>. Conversely, the dynamic kinetic resolution of ((*S*),(*S*))-di-*N*-methylpseudoephedrine α -bromoesters **242** using a variety of thiols, for example benzylmercaptan, tritylmercaptan **243** (Equation (115)), and potassium thioacetate, afforded, after chiral auxiliary cleavage, α -thiocarboxylic acid derivatives with excellent stereoselectivities (91:9–97:3 dr) and good yields (57–80%). Cleavage of the pseudoephedrine auxiliary was performed either via reduction or acidic methanolysis without any detectable racemization of the α -thiocarboxylic acid. However, saponification using alkali hydroxides would be expected to cleave the chiral auxiliary from the *N*-acyl substituent, yielding the corresponding *S*-trityl protected α -mercapto carboxylic acids <2002TL8253>.



Scheme 28

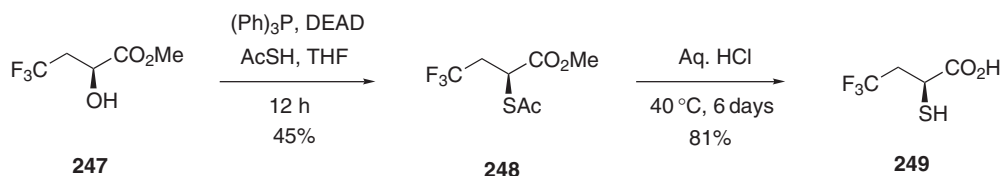


The synthesis of *S*-protected (*S*)-thiolactic acid **245** has been achieved, in quantitative yield, by reacting tritylthiol with ethyl(*R*)-chloropropionate **244**, in the presence of sodium methoxide (Scheme 29). Saponification of the ester on **245** using aqueous sodium hydroxide in dioxane, followed by cleavage of the trityl group using a mixture of TFA and triethylsilane afforded carboxylic acid **246** <2000TL2729>.

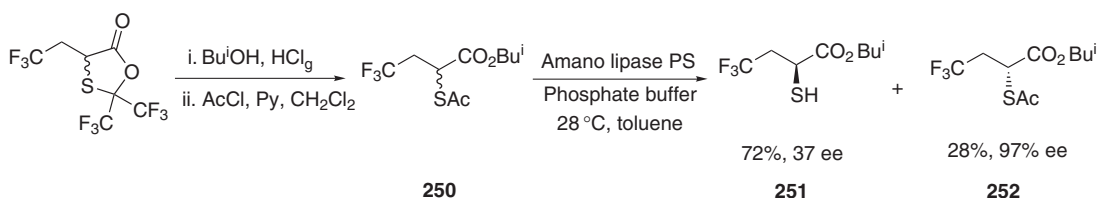


Scheme 29

The synthesis of chiral nonracemic (*R*)-4,4,4-trifluoro-2-mercaptoprobutyric acid **249** has been reported using (*R*)-4,4,4-trifluoro-2-hydroxybutyric acid methyl ester **247** as the starting material. The pivotal reaction during the synthesis was the installation of a thioacetyl group via a Mitsunobu procedure (Scheme 30). Subsequent hydrolysis of the methyl ester and the *S*-acetyl group on **248** was undertaken, with no evidence of any epimerization, using aqueous hydrochloric acid in good yield (81%) albeit slowly (6 days). An alternative method for the synthesis of (*R*)-4,4,4-trifluoro-2-mercaptoprobutyric acid **249** employed an enzymatic hydrolysis procedure using *Pseudomonas cepacia* (Amano Lipase PS) and **250**. This enzyme was stereospecific towards hydrolysis of the acetyl group off the (*S*)-isomer of racemic **250** (72% yield, 37% ee) affording optically enriched **251**. The (*R*)-stereoisomer **252** was returned in an excellent enantiomeric excess (97%) and 28% yield (Scheme 31). Subsequent saponification afforded (*R*)-4,4,4-trifluoro-2-mercaptoprobutyric acid <2000TA2125>.

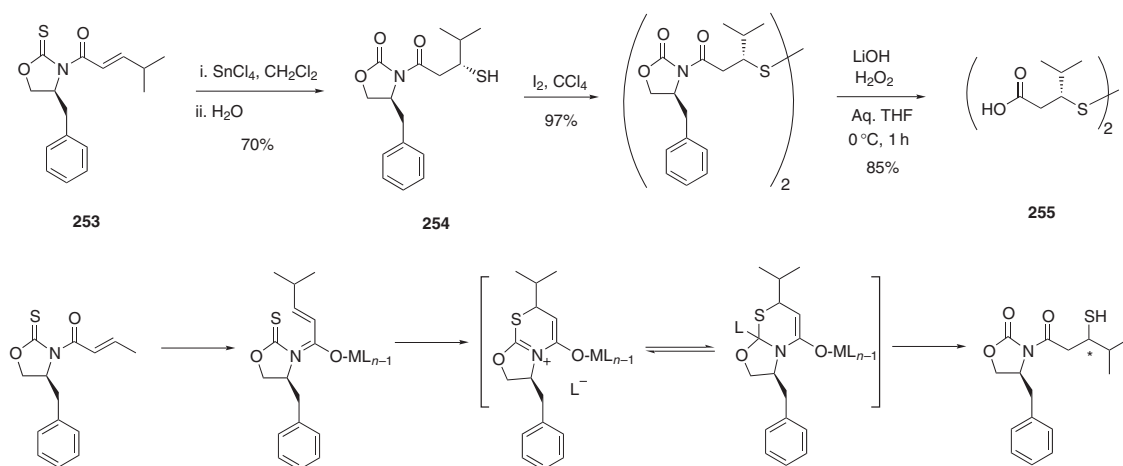


Scheme 30



Scheme 31

An elegant procedure for the synthesis of a wide variety of chiral nonracemic β -mercapto carboxylic acids has been reported by Palomo and co-workers. The methodology is based on an intramolecular cyclization protocol that utilizes chiral nonracemic auxiliaries to control the stereochemical outcome of a sulfur migration process. Employing *N*-enoyloxazolidine-2-thiones, for example **253**, and a Lewis acid to promote the rearrangement, the corresponding β -mercapto carbonyl derivatives (**254**, Scheme 32) are returned in good-to-excellent yields (56–98%) and diastereomeric ratios (65:35 to >98:2). Oxidation of the thiol component of **254** and cleavage of the chiral auxiliary afforded the corresponding carboxylic acid **255** <2001JA5602>.



Scheme 32

5.02.2.4.2 By carbonation of organometallic reagents

The asymmetric deprotonation of prochiral methylene species using complexes generated from chiral nonracemic (–)-sparteine and organolithium reagents is a dynamic area of research. A large number of dipole-stabilized α -alkoxy and α -amino organolithium species have been synthesized and investigated for their potential in asymmetric synthesis. The configurational lability of α -sulfenyl carbanions has; however, precluded their widespread use in asymmetric synthesis. A report by Nakamura and co-workers has detailed the highly stereoselective asymmetric substitution reactions of α -sulfenyl carbanions derived via the transmetalation of α -stannylated benzyl phenyl sulfide **256** and α -stannylated benzyl 2-pyridyl sulfide in the presence of a number of chiral nonracemic ligands (Figure 1). Interestingly, the combination of (–)-sparteine and Bu^tLi as

the asymmetric base in either toluene or cumene as the solvent and benzophenone as the electrophilic quench resulted in products, **257** with low enantioselectivities and yields (Scheme 33). However, transmetallating α -stannylated benzyl phenyl sulfide **258** in cumene at -78°C with Bu^nLi in the presence of a chiral nonracemic bis(oxazoline) ligand afforded, after quenching with carbon dioxide, the α -mercapto carboxylic acid derivative **259** (Equation (116)) in an excellent yield (87%) and 74% ee, determined after reduction of the carboxylic acid to the primary alcohol. Similarly, the α -stannylated benzyl 2-pyridyl sulfide **260** returned the corresponding pyridine-derived α -mercapto carboxylic acid **261** derivative in reasonable yield (60%) and 70% ee (Scheme 34) <2000JA11340>. Nakamura and co-workers have reported the synthesis of optically enriched thiols **263** via highly enantioselective reactions using benzyl 2-quinolyl sulfide **262** as the starting material and a number of electrophiles; the reaction proceeds via a dynamic thermodynamic resolution pathway (Equation (117)) <2002EJO1690>.

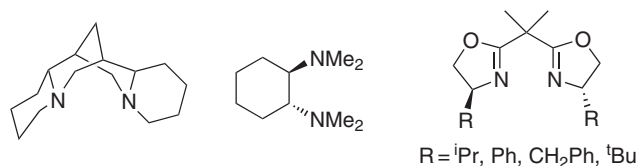
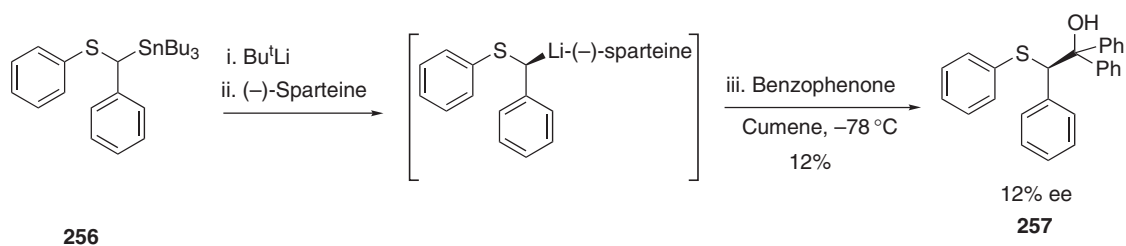
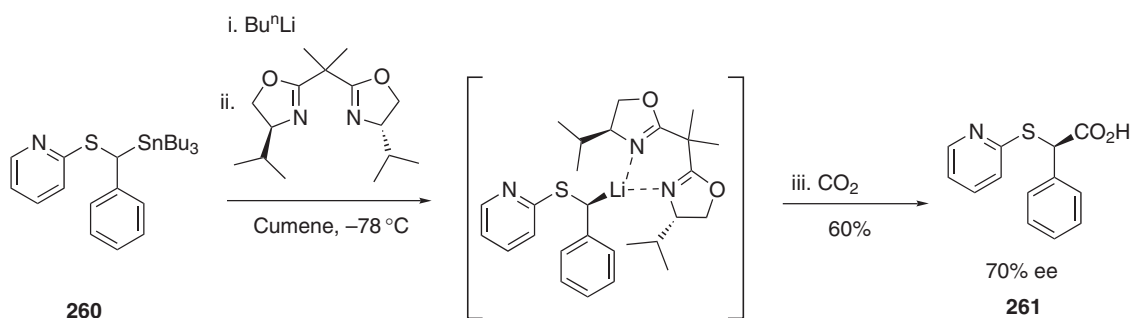
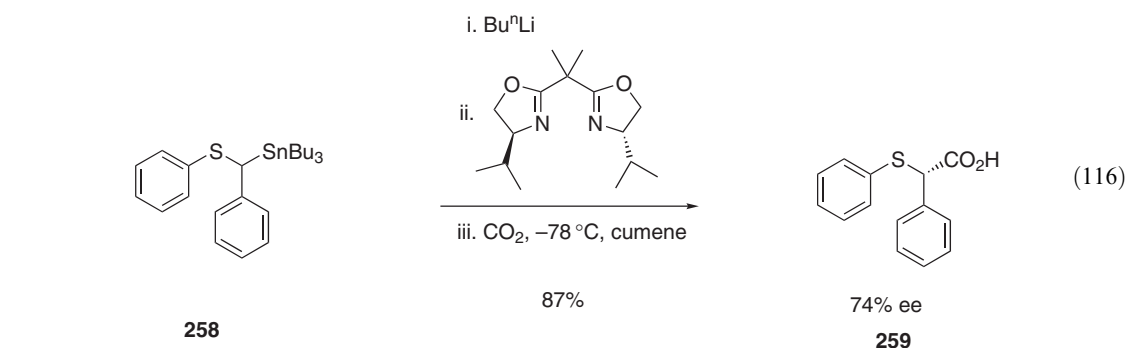


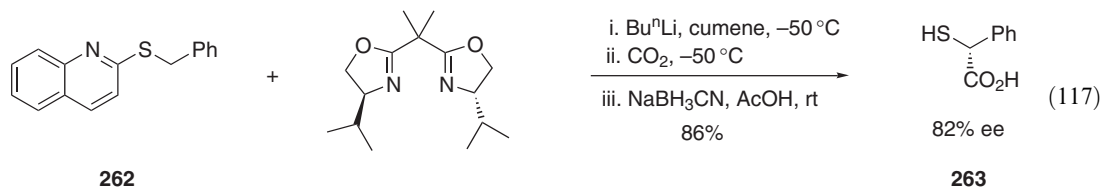
Figure 1



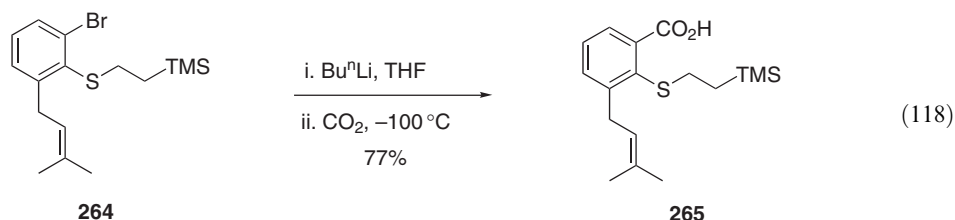
Scheme 33



Scheme 34



Undertaking the synthesis of analogs of the potent antitumour agent leinamycin, Chatterji and co-workers utilized a metal–bromine exchange reaction (Bu^nLi , THF, $-100\text{ }^\circ\text{C}$) performed on thiol-protected thiophenol **264**. Quenching the resulting aryllithium species with carbon dioxide, afforded the desired carboxylic acid **265** in a 77% yield (Equation (118)) <2003JA4996>.

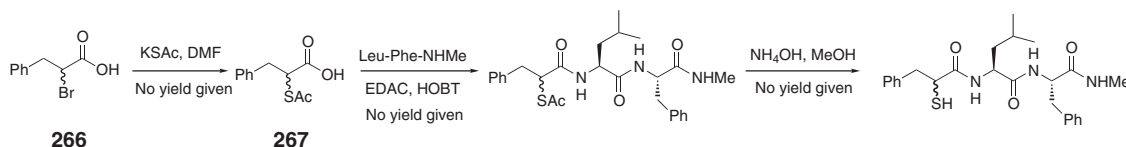


5.02.2.4.3 By oxidation reactions

The haloform oxidation of 2-acetylthiophene using sodium bromite affords a 40% conversion to 2-thienoic acid <1983CC392>, while 3-thienoic acid has been prepared in 95–97% yield by oxidation of 3-thienaldehyde using silver oxide in sodium hydroxide <1963OSC(4)919>.

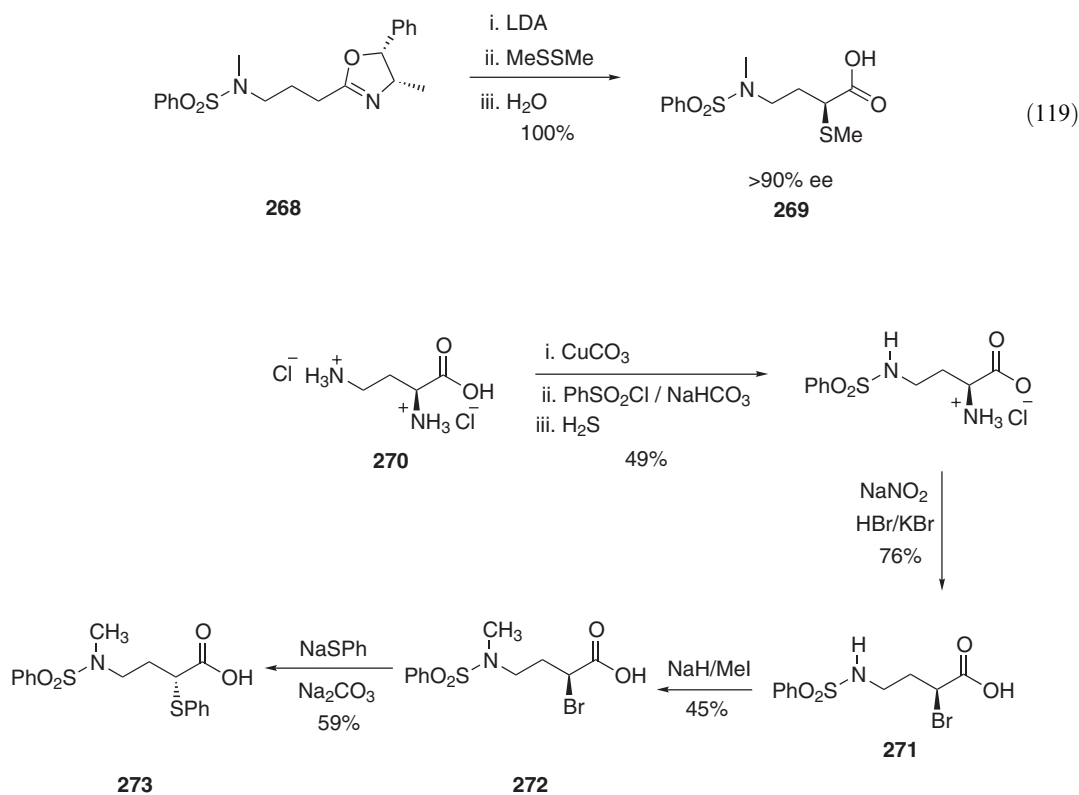
5.02.2.4.4 By miscellaneous reactions

Transforming α -bromo- α -substituted carboxylic acid **266** into an α -thio- α -substituted carboxylic acid **267** can be accomplished using a solution of potassium thioacetate in DMF; saponification of the acetyl group and release of the free α -thiocarboxylic acid was performed using ammonium hydroxide in methanol (Scheme 35) <1997BMCL2765>.



Scheme 35

Chiral nonracemic ω -benzenesulfonylamino- α -methylthio- and ω -benzenesulfonylamino- α -phenylthiocarboxylic acids have been synthesized via a stereoselective α -sulfenylation of chiral nonracemic 2-(ω -benzenesulfonylaminoalkyl)-1,3-oxazolines **268** using a variety of disulfides in the presence of excess LDA. Following hydrolysis of the 1,3-oxazoline species, the α -mercapto carboxylic acids **269** were returned in good yields (77–100%) and ee values (80% to >90%, Equation (119)). The synthesis of α -sulfenylated- ω -benzenesulfonylamino carboxylic acids has also been accomplished using chiral nonracemic (*S*)-(+)-2,4-diaminobutanoic acid **270** as the starting material. Transformation into the γ -benzenesulfonylamino acid derivative allowed the α -amino group to be diazotized and transformed into the α -bromo carboxylic acid **271**. After *N*-methylation affording **272**, subsequent displacement of the bromine using either sodium methylthiolate or phenylthiolate afforded the chiral nonracemic α -mercapto carboxylic acid **273** (Scheme 36) <1997TA2433>.



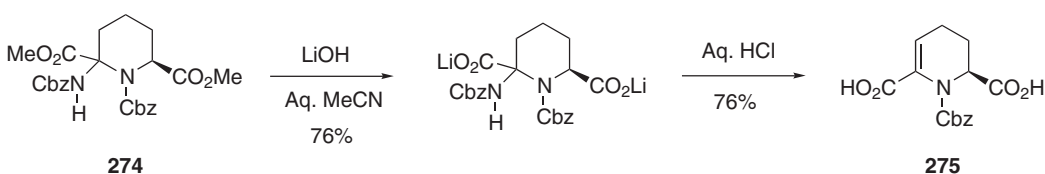
Scheme 36

5.02.2.5 Amino Acids

Extensive literature exists on this class of carboxylic acid. General reviews on the chemistry of amino acids and proteins are available, for example: <B-1960MI502-02, B-1961MI502-01, B-1961MI502-02>; natural amino acids <B-1943MI502-02>; the isolation and synthesis of naturally occurring α -amino acids <1946CRV501>; synthesis of optically active α -amino acids <B-1989MI502-01>; and the enantioselective synthesis of β -amino acids <B-1997MI502-01>.

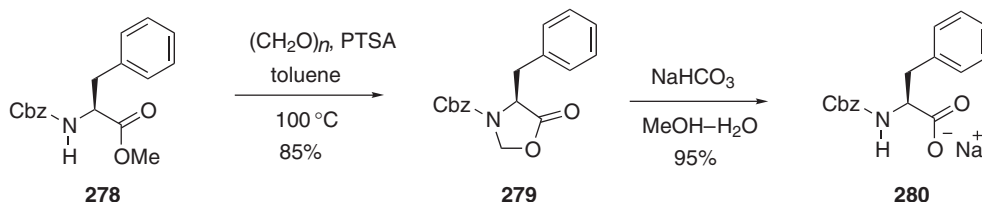
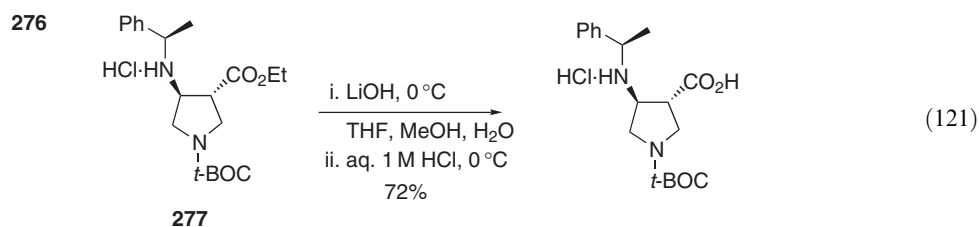
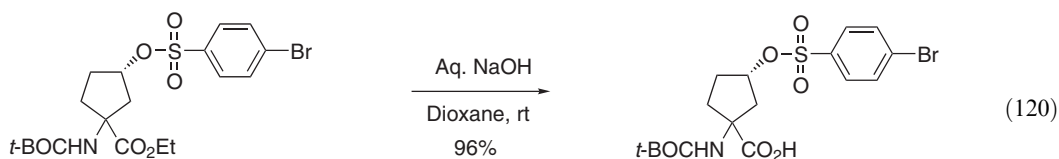
5.02.2.5.1 By hydrolysis reactions

Akin to the saponification of esters to the corresponding carboxylic acids, α -amino acid esters are readily hydrolyzed by the action of group 1 alkali hydroxides to α -amino acids. As an example, lithium hydroxide (3 equiv.) in aqueous acetonitrile was used for the saponification of the methyl ester **274** appended to a tetrahydropyridine ring. Subsequent acidification afforded the 1,2,3,4-tetrahydropyridine-2,6-dicarboxylic acid **275** in a 76% yield (Scheme 37) <2001JCS(P1)2217>. Similarly, the use of sodium or lithium hydroxide for the saponification of ethyl ester-derived amino acids **276** and **277** in 96% and 72% yields, respectively, has been reported (Equation (120))



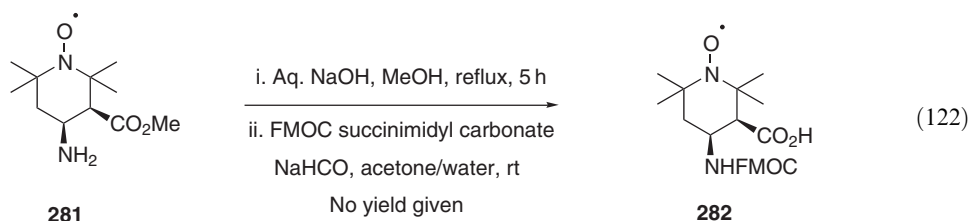
Scheme 37

<2003TL695> and (Equation (121)) <2001JOC3597, 2002JOC2509>. The use of sodium hydroxide for the saponification of methyl esters works equally well <2002JOC2511>. A key issue in peptide chemistry is the development of suitable protecting groups for the amine and carboxylic acid groups which can, when desired, be cleaved without compromising the stereochemical integrity of the amino acid. A simple, racemization-free procedure for the synthesis and subsequent cleavage of 5-oxazolidinones, for example **279**, to the corresponding carboxylic acid salt **280** has been developed using *N*-protected α -amino acid methyl ester **278**. The procedure is efficient, high yielding (75–95%), and can be used for the majority of *N*-Fmoc, *N*-Cbz-protected, but not *N*-*t*-BOC-protected amino acids (Scheme 38) <2003TL7663>.

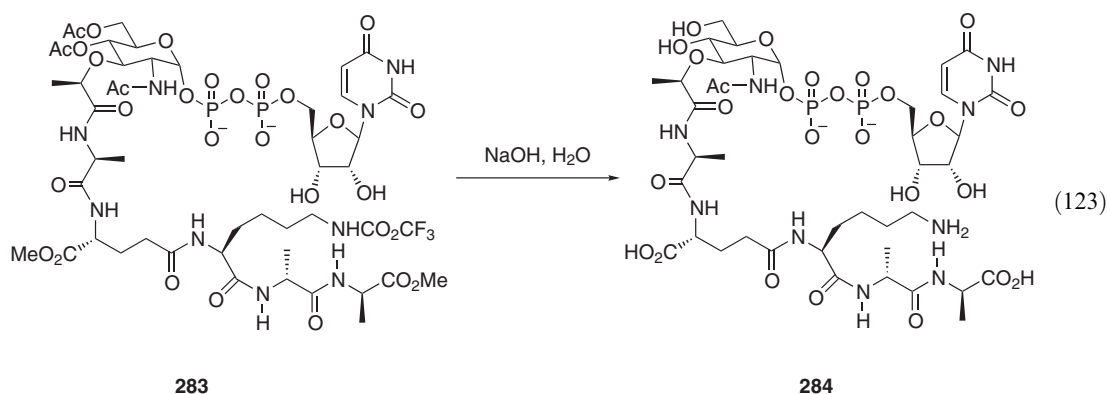


Scheme 38

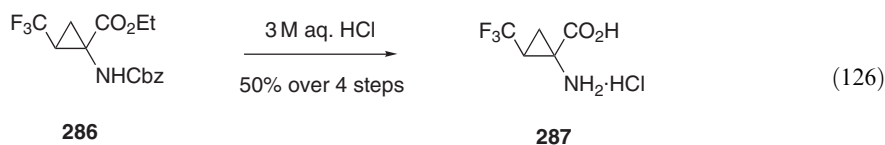
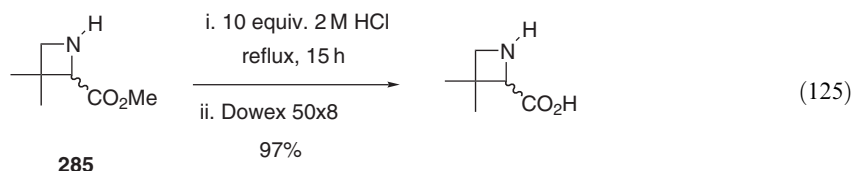
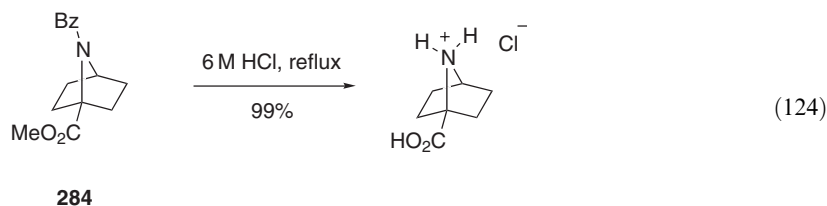
Stable nitroxide free radicals are of interest as spin labels in studying the conformation and structure of biological systems. The development of a chiral nonracemic β -amino acid which possesses a stable nitroxide free radical entity suitable for attachment to biological systems is of interest. The final steps in the synthesis of 4-amino-1-oxy-2,2,6,6-tetramethylpiperidine-4-carboxylic acid **282** (β -TOAC), a nitroxide-appended amino acid, incorporated a high-yielding methyl ester saponification of **281** (Equation (122)) <2003TL3381>.



During the synthesis of the bacterial cell-wall precursor UDP-*N*-acetylmuramylpentapeptide **284**, a global deprotection strategy was undertaken that aimed to selectively saponify a number of glycosyl acetates and α -amino acid methyl esters on **283** without cleavage of the important diphosphate linkage (Equation (123)) <1998JA1916>.



The hydrolysis of α -amino acid *t*-butyl esters to the corresponding α -aminocarboxylic acids can be accomplished using 1.7 M hydrochloric acid in methanol <1999JOC282>. The action of aqueous 6 M hydrochloric acid at reflux simultaneously cleaved both a methyl ester and a benzoylamide attached to the 7-azabicyclo[2.2.1]heptane ring system of **284** in an excellent 99% yield (Equation (124)) <2001T545>. Using refluxing hydrochloric acid, the hydrolysis of racemic 3,3-dimethylazetidine-2-carboxylic methyl ester **285** was accomplished in an excellent 97% yield (Equation (125)) <1998T2619>. Similarly, in the final stages of a total synthesis of (\pm)-*trans*-trifluoronorcoronamic acid, the action of 3 M hydrochloric acid at reflux hydrolyzed both the ester and the *N*-Cbz group of **286** affording the racemic α -amino acid hydrochloride salt **287** (Equation (126)) <2003CC536>. The simultaneous hydrolysis of the methyl ester and the *N*-acetyl group off the enantiomerically enriched piperidine α -amino acid **288** has been accomplished by Teoh and co-workers using 6 M hydrochloric acid at reflux, affording the corresponding chiral nonracemic α -amino acid hydrochloride salt **289** (Equation (127)). Using TFA, the simultaneous cleavage of sixteen amino acid *t*-butyl esters off a tetraphenylporphyrin ring system, for example **290** (Equation (128)), was undertaken in reasonable-to-excellent yields (44–100%) <2003BMCL2651>. During the synthesis of the glycopeptide *N*-acetylmuramyl-L-alanyl-D-isoglutamine **292** the simultaneous hydrolysis of a *t*-butyl ester and a 4,6-benzylidene acetal from **291** was performed with 90% TFA (Equation (129)) <2003JMC978>. The selective hydrolysis of the ethyl ester on **293** in the presence of a *t*-butyl ester and an *N*-*t*-BOC-protected amino acid has been reported (Equation (130)) <2003BMCL2659>. The simultaneous deprotection of both an *N*-*t*-BOC and a *t*-butyl ester group has been undertaken in an excellent yield (92%) using TFA <2003T5241>. Similarly, cleavage of a *t*-butyl ester and a monomethoxytrityl thioether off **294** using a combination of TFA and triisopropylsilane yielded the desired mercaptocarboxylic acid **295** (Equation (131)) in good yield (90%) <2002TL4439>.



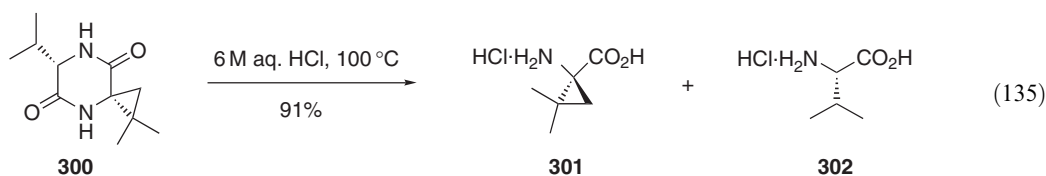
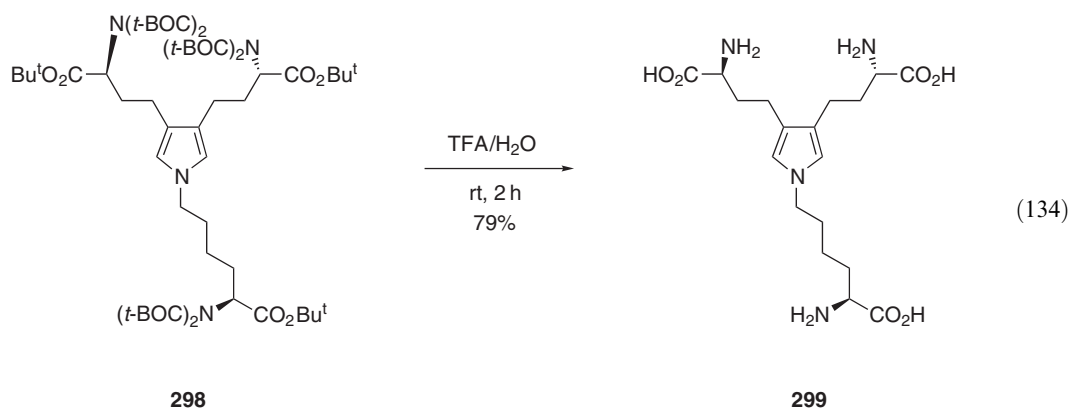
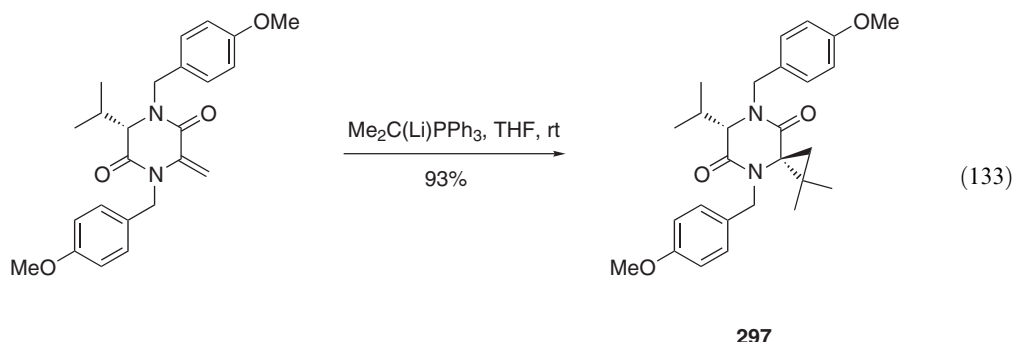


295



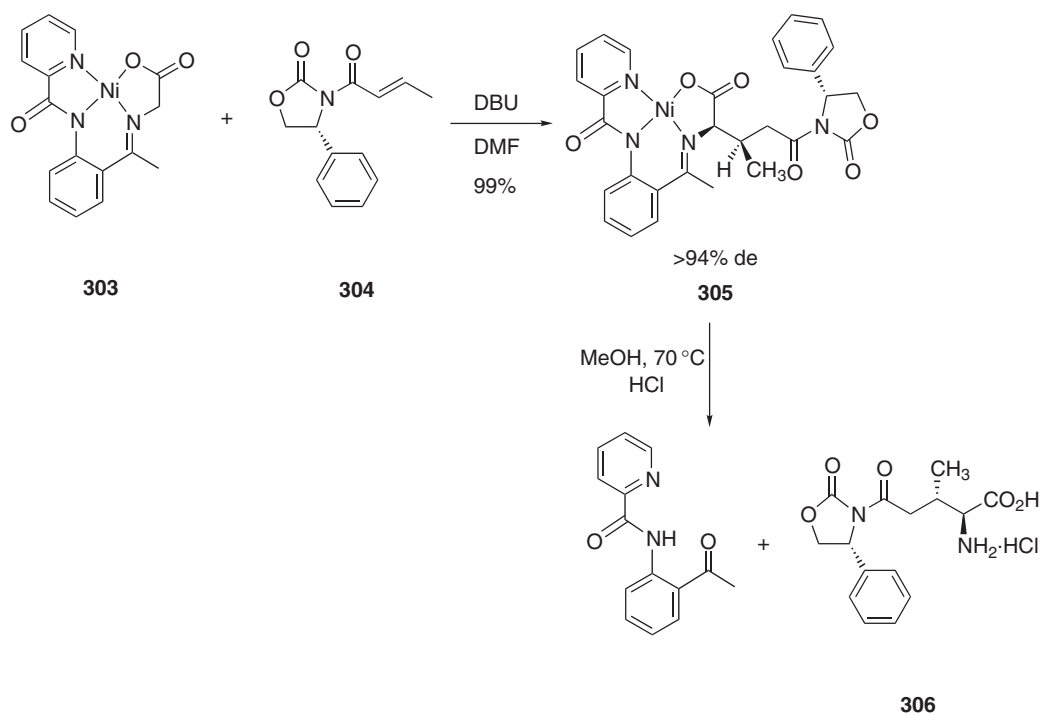
The construction of peptides incorporating nonproteinogenic α -amino acids, which restrict the conformational flexibility of the peptide system, is an area of active research. Of particular interest in this respect are chiral nonracemic 1-aminocyclopropane-1-carboxylic acids. The diastereoselective synthesis of diketopiperazine spirocyclopropanes, for example **297**, which are, after hydrolysis, precursors of stereochemically enriched 1-aminocyclopropane-1-carboxylic acids has been reported

(Equation (133)). The simultaneous hydrolysis of a *t*-butyl ester and a *N,N*-di-*t*-BOC protected α -amino acid from **298** to yield the corresponding optically active α -amino acid **299** has been accomplished using TFA in an 79% yield (Equation (134)) <2001JOC11>. Refluxing *N,N*-bis(*p*-methoxybenzyl)diketopiperazines, for example **300**, with TFA cleaved the *p*-methoxybenzyl groups. The resulting diketopiperazines were subsequently hydrolyzed using aqueous acid (6 M hydrochloric acid, 100 °C) affording the corresponding α -amino acid hydrochloride salts **301** and **302** (Equation (135)). Although the efficiency of chiral nonracemic diketopiperazines as asymmetric reagents is without question, the conditions required for their subsequent hydrolysis are rather harsh <2003OBC2531>.

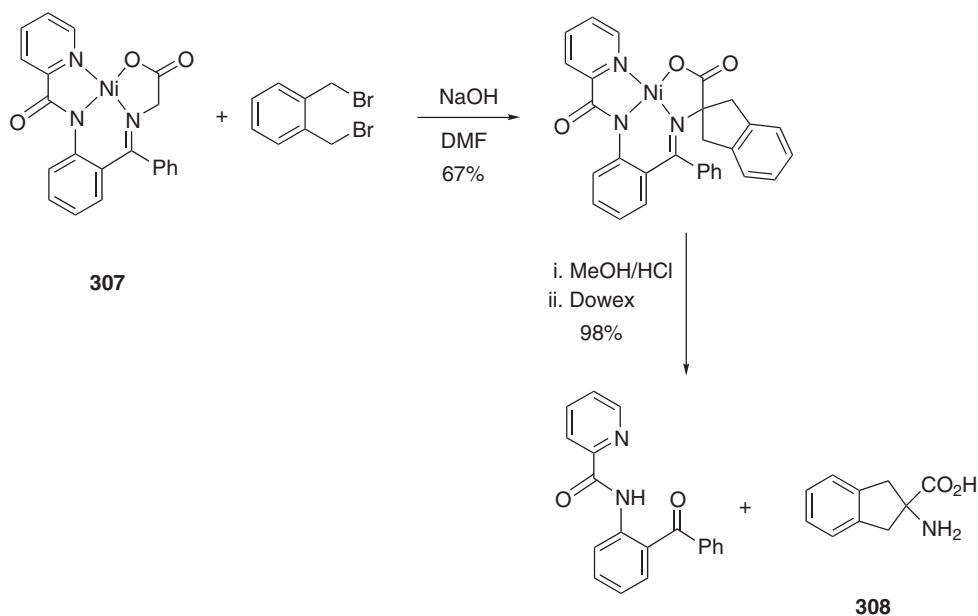


The asymmetric Michael reaction is a powerful synthetic process. The Michael addition reaction between glycine and α,β -unsaturated carboxylic acids is of particular interest as the protocol can be used to construct chiral nonracemic β -substituted glutamic, pyroglutamic acid, glutamine and proline amino acids. Work by Soloshonok and co-workers has demonstrated that enantio-merically enriched (*S*)- or (*R*)-3-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **304** are capable of acting as Michael acceptors in addition reactions with achiral Ni(II) complexes of glycine Schiff bases **303**, affording complexes similar to **305**. Subsequent acid hydrolysis of **305** yielded stereo-chemically enriched α -amino acid-appended oxazolidin-2-ones **306** (Scheme 39). The excellent chemical yields (96–99%) and diastereoselectivities (94–99%) of these reaction products, combined with the simplicity of the protocol render this an extremely powerful piece of synthetic methodology <2000OL747>. Similarly, using the Ni(II)-complexed glycine Schiff base **307**, the synthesis of racemic 2-aminoindane-2-carboxylic acid **308** has been reported (Scheme 40). This protocol benefits from being efficient, high yielding, easy to scale up, and requires no purification of the intermediates <2003JOC4973>.

The synthesis of α -amino acids with novel β -side chains is of interest, given the potential for this class of compound to possess biological activity. Blaskovich and co-workers have demon-strated that base-stable 2,6,7-trioxabicyclo[2.2.2]octane (OBO) esters are suitable α -amino acid

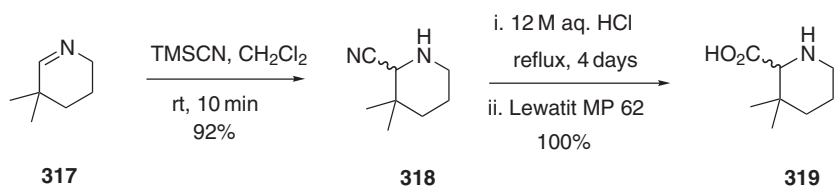


Scheme 39

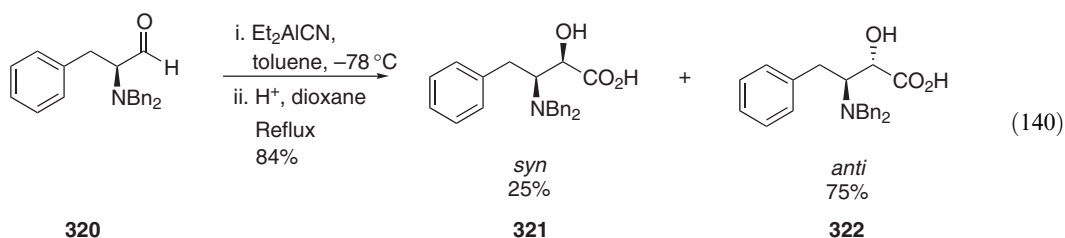


Scheme 40

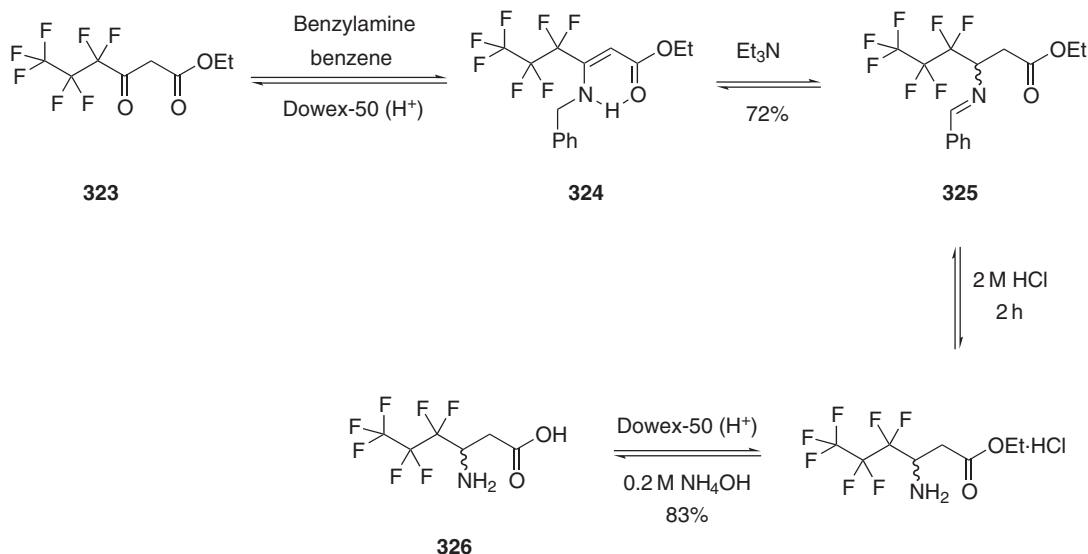
carbonyl protecting groups that are resistant to attack by organometallic reagents [\[1998JOC3631\]](#). Turner and co-workers have developed a protocol for the synthesis of β -substituted α -amino acids that incorporate; (i) an OBO-protected amino acid and (ii) an aziridine ring that is amenable to regioselective ring-opening with lithium acetylides. Cleavage of the OBO ester on **309** by exposure to TFA for short periods of time returned the optically active α -amino acid **310** in high yield (89% over three steps) and minimal racemization ([Equation \(136\)](#)) [\[2001TL8713\]](#).



Scheme 41



The synthesis of fluorinated β -amino acids in good yields (70–83%) can be achieved from fluorinated β -keto esters, for example **323**, via a base-catalyzed [1,3]-proton shift on enamine **324**, affording imine **325**. Subsequent imine and ester hydrolysis **325** afforded the corresponding fluorinated racemic β -aminocarboxylic acids, for example **326** (Scheme 42) <1996T6953>.

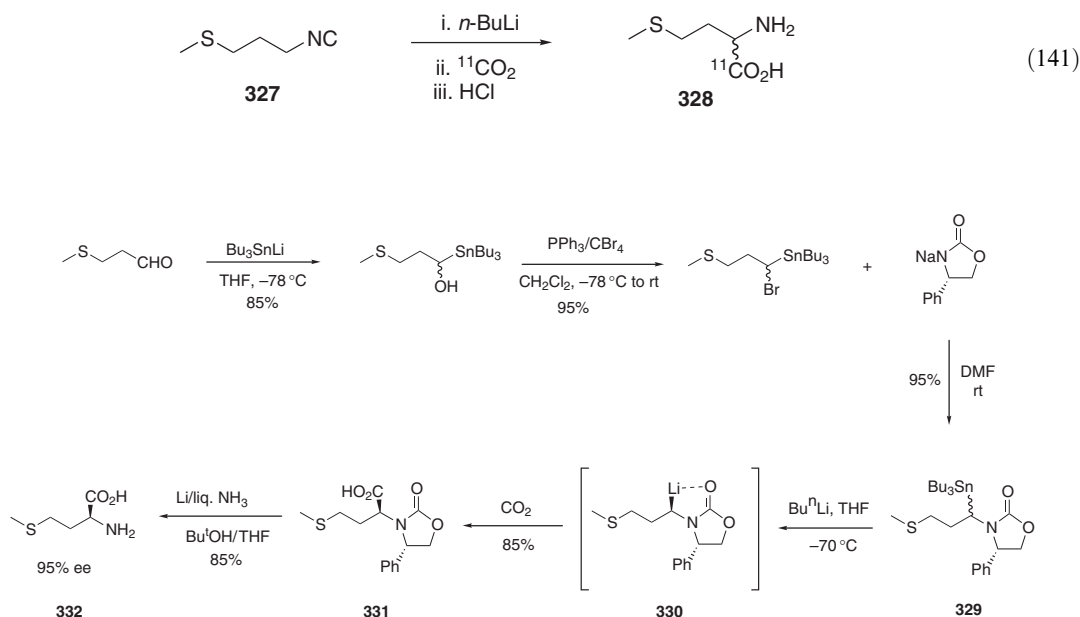


Scheme 42

5.02.2.5.2 By carbonation of organometallic reactions

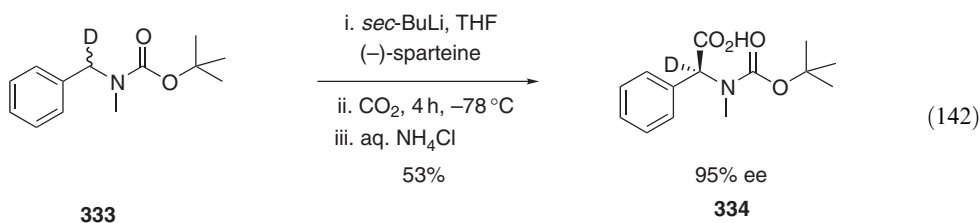
A review concerned with the synthesis, application and uses of α -lithiated carbons adjacent to heteroatoms has been published <1996ACR552>. The racemic synthesis of radiolabeled [^{11}C]-methionine **328** has been undertaken. Pivotal to the synthesis was the deprotonation of one of the protons on the methylene group next to the isonitrile on **327**, which was accomplished using Bu^nLi , allowing the resulting nucleophile to be quenched with $^{11}\text{CO}_2$ (Equation (141)). Subsequent attempts at performing an enantioselective synthesis using a combination of Bu^nLi

and (–)-sparteine were unsuccessful, as was the use of enantioenriched α -aminostannanes, synthesized via the procedure reported by Chong and co-workers <1992JOC2220, 1993TL51>. Using Evan's α -tributylstannyloxazolidin-2-one **329** was investigated; subsequent transmetalation **330** followed by carboxylation using $^{11}\text{CO}_2$ afforded the desired ^{11}C -carboxylic acid appended oxazolidin-2-ones **331**. Cleavage of the chiral auxiliary to reveal amine **332** was performed using a dissolved metal reduction protocol (Scheme 43). Using this procedure L-[^{11}C]-methionine **332** was obtained in an excellent 85% yield and >95% ee <1997TL7547>.



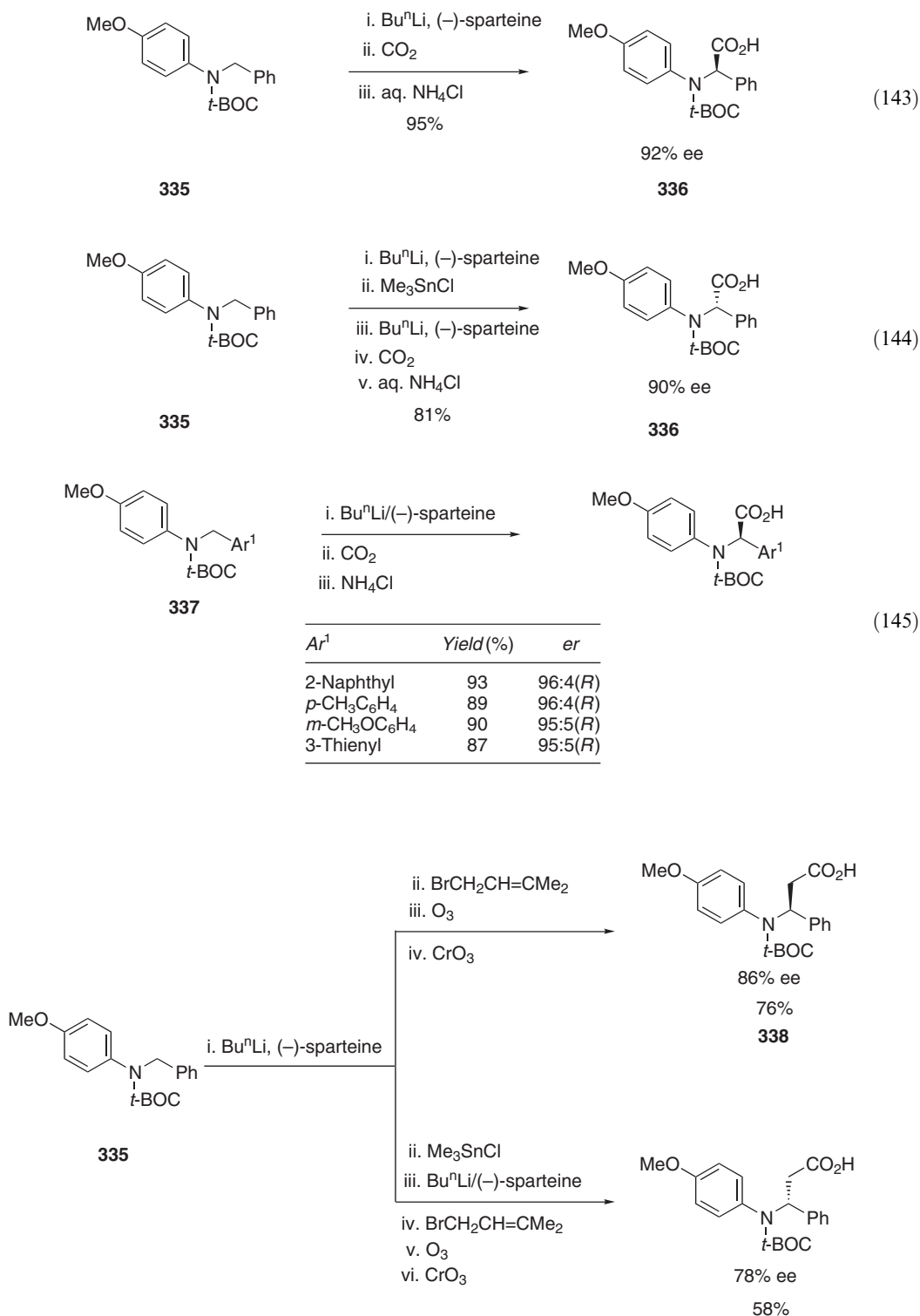
Scheme 43

Schlosser and co-workers have demonstrated that a combination of Bu^sLi and (–)-sparteine can, under optimum experimental conditions, perform kinetic resolutions on racemic α -D-*N*-*t*-BOC-*N*-methylbenzylamines **333**. Subsequent quenching of the anion using carbon dioxide as the electrophile afforded chiral nonracemic carboxylic acids **334** in 95% ee (Equation (142)). The correct choice of solvent is critical for the formation of carboxylic acids with high enantioselectivities. Interestingly, a reversal of product stereochemistry from (*S*)- to (*R*)-1-(*N*-*t*-butoxycarbonyl-*N*-methylamino)-1-phenylacetic acid was observed when the solvent was changed from THF to hexane <1995JA12342>.

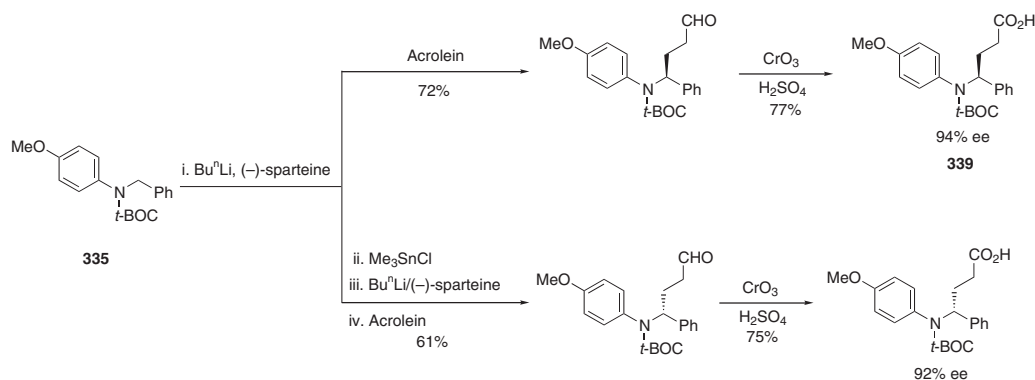


Similarly, Park and co-workers have demonstrated that a combination of $n\text{-BuLi}$ and (–)-sparteine is able to asymmetrically deprotonate a benzylic proton on *N*-*t*-BOC-*N*-(*p*-methoxyphenyl)benzylamine **335**; subsequent addition of carbon dioxide quenches the chiral nonracemic (*R*)-phenylglycine anion resulting in high yields (85–93%) of carboxylic acid **336** (Equation (143)). Using **335**, but substituting carbon dioxide for trimethyltin chloride and subsequently undertaking a transmetalation of the organostannane using Bu^nLi , followed by quenching with carbon dioxide afforded the opposite enantiomer **336** in high ee and yield 90% and 81%, respectively (Equation (144)). A variety of *N*-*t*-BOC-*N*-(*p*-methoxyphenyl)arylmethylamines **337** have been lithiated and quenched with carbon dioxide (Equation (145)). Incorporating **335** and similar asymmetric deprotonation methodology to that recounted, highly enantioenriched β -amino acids were synthesized. Quenching asymmetrically

deprotonated *N*-*t*-BOC-*N*-(*p*-methoxyphenyl)arylmethylamine with 4-bromo-2-methyl-2-butene allowed the allylic double bond to be oxidized (ozone) affording the corresponding aldehyde. Oxidation of the aldehyde using Jones's reagent returned the β -amino acid **338** in a 76% yield and 86% ee (Scheme 44). Highly enantioenriched α -aryl- γ -amino acids **339** are also accessible, in good yield (75–77%) and ee (92–94%) using this methodology (Scheme 45) <1997JOC1574>.

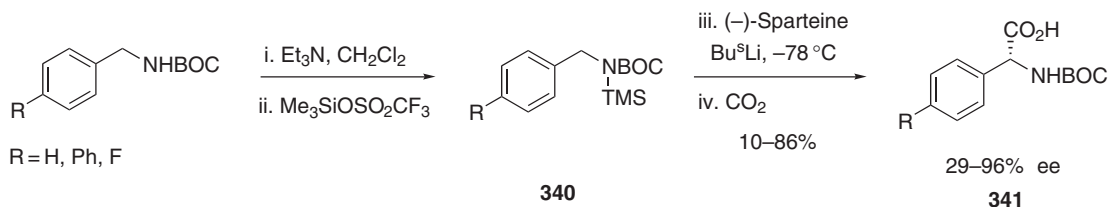


Scheme 44



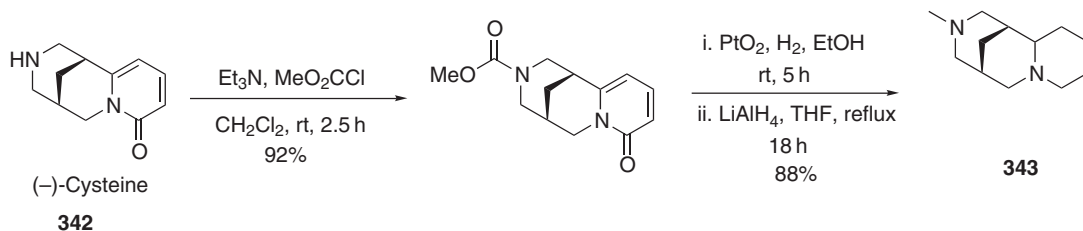
Scheme 45

Treating an *N*-TMS-*N*-*t*-BOC-protected benzylamine **340** with a chiral base complex derived from (–)-sparteine and Bu^sLi, followed by quenching of the lithiated species with carbon dioxide, returned chiral nonracemic *N*-*t*-BOC-protected phenylglycines **341** in poor-to-good yields (10–86%) and ee values in the 29–96% range (Scheme 46). Interestingly, the enantioselectivities are generally higher when a pre-formed complex of (–)-sparteine and Bu^sLi was employed. <1997TL6505, 2001T2965>.



Scheme 46

Of interest within the context of using (–)-sparteine in asymmetric deprotonation strategies is the recent synthesis of a (+)-sparteine surrogate. The starting material was the readily available (+)-cystine alkaloid **342**, which can be transformed in three steps, on a multigram scale, into the (+)-sparteine mimic **343** in high yield (Scheme 47). Subsequent studies using the (+)-sparteine mimic **343** confirm its ability to act as an enantioselective base in conjunction with Bu^sLi and a variety of substrates and electrophiles <2002JA11870>.

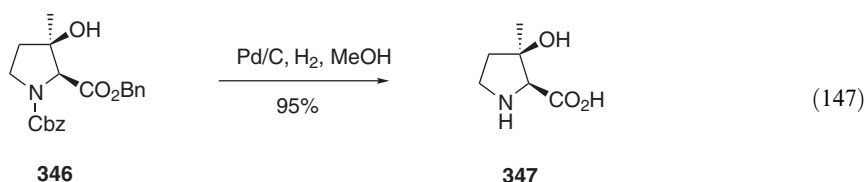
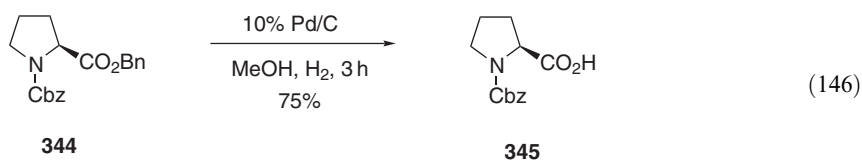


Scheme 47

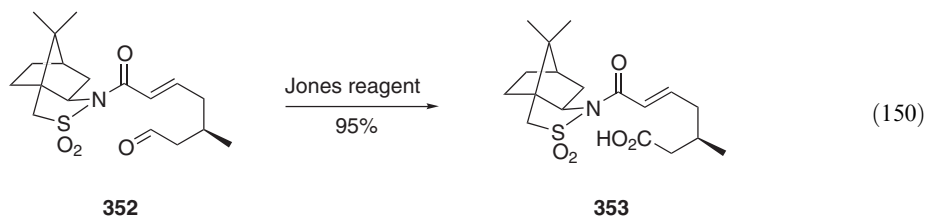
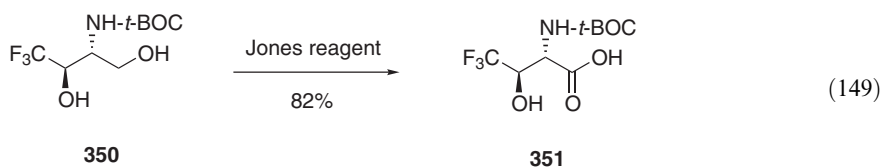
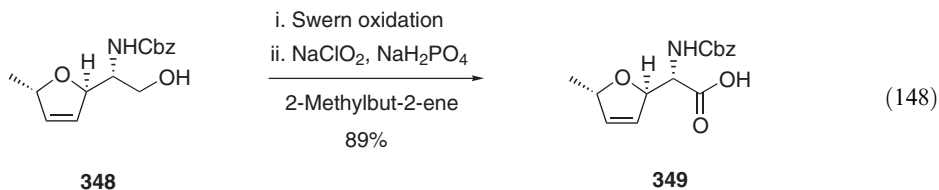
5.02.2.5.3 By miscellaneous reactions

Hydrogenolysis under mild reaction conditions (1 atm H₂, Pd/C, CH₃CO₂H) of α-aminocarboxylic acid *O*-benzyl esters yields the corresponding α-aminocarboxylic acids <2003TL7011>. Chemoselective cleavage of the *O*-benzyl ester group contained within *N*-Cbz-(*S*)-proline **344** via

treatment with an ethylenediamine-poisoned Pd/C catalyst in the presence of hydrogen yielded **345** in a 75% yield (Equation (146)) <1998JOC7990>. Interestingly, when the similar *N*-Cbz-(*S*)-proline-*O*-benzyl ester **346** was reacted with a Pd/C catalyst (that was not poisoned) in the presence of hydrogen, cleavage of both the *N*-Cbz and the *O*-benzyl groups resulted in **347** (Equation (147)) <2003JOC7479>.



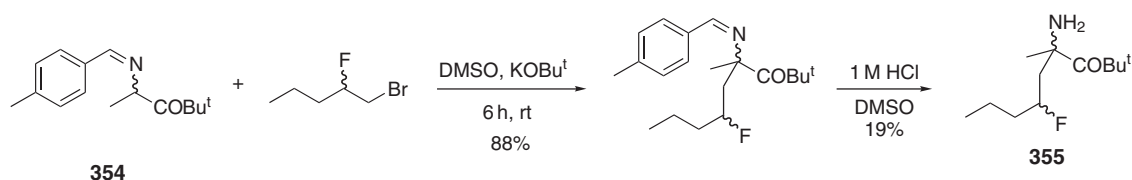
Several procedures for the oxidation of β -amino alcohols to the corresponding α -amino acids are available. A particularly mild, albeit two-step protocol, involves oxidizing β -amino alcohol **348** to the α -amino aldehyde (Swern oxidation) and then subsequently oxidizing the aldehyde to the α -aminocarboxylic acid **349** using a sodium chlorite solution buffered with sodium dihydrogen orthophosphate in aqueous *t*-butanol (Equation (148)) <1998CC761>. Jones's reagent has been used in a one-pot *N*-*t*-BOC-protected β -amino alcohol **350** to *N*-*t*-BOC α -amino acid **351** oxidation protocol (Equation (149)). Interestingly, the normally acid-labile *N*-*t*-BOC group was unaffected by the (acidic) Jones's reagent, and high yields (80–82%) of the desired chiral nonracemic *N*-*t*-BOC α -amino acids were returned <2003JOC7544>. Jones reagent has been used to transform the aldehyde **352** into the corresponding carboxylic acid **353** in a 95% yield (Equation (150)), with no erosion of diastereomeric excess (94% de) <1996TL8899>.



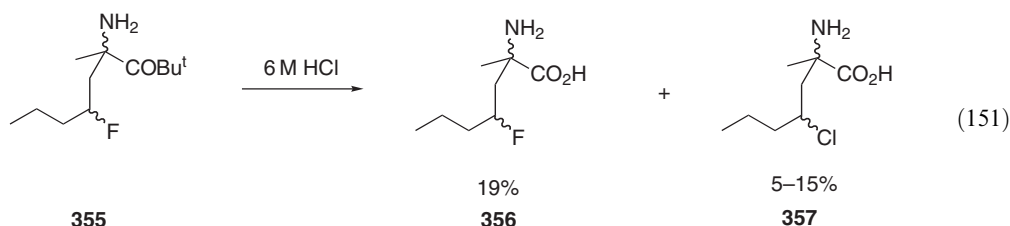
Chemoselective deprotection of 2-(hydroxymethyl)-1,3-dithiane (Dim) esters of *N*-*t*-BOC α -amino acids can be undertaken electrochemically returning the corresponding carboxylic acids in good yields (65–74%) <2000OL799>.

Deprotonation of the alanine ester imine **354** Schiff bases with potassium *t*-butoxide in DMSO or DMF allowed the resulting enolates to be alkylated with 2-fluoroalkyl halides, subsequent acidic hydrolysis of the Schiff base (1 M hydrochloric acid), affording the corresponding γ -fluoro- α -methyl- α -amino *t*-butyl ester **355** in poor-to-good yields (19–88%). The diastereoselectivity observed did not depend on the solvent or temperature employed, however, it did depend, to a

certain extent on the leaving group, for example, Br versus I, gave 26 and 36% de, respectively (Scheme 48). Hydrolysis of the *t*-butyl ester **355** was accomplished using 6 M hydrochloric acid (Equation (151)); the desired reaction product, **356**, was contaminated with small amounts (5–15%) of the corresponding γ -chloroamino acid **357** <1998T5929>.

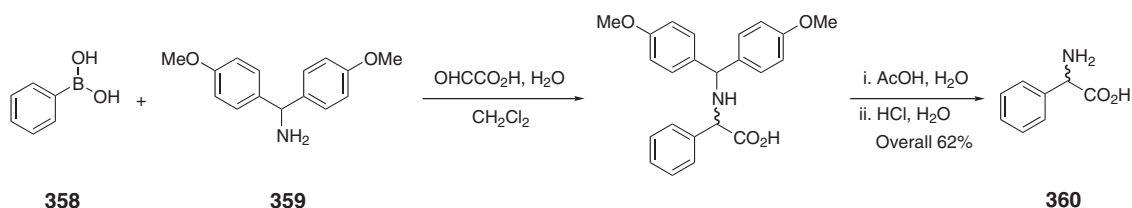


Scheme 48

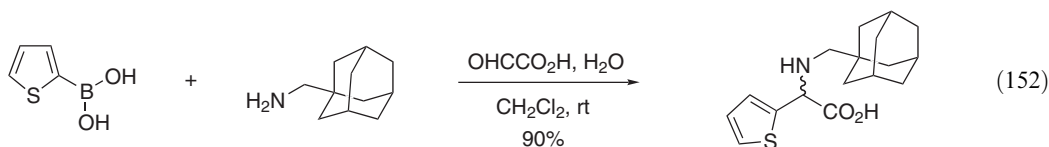


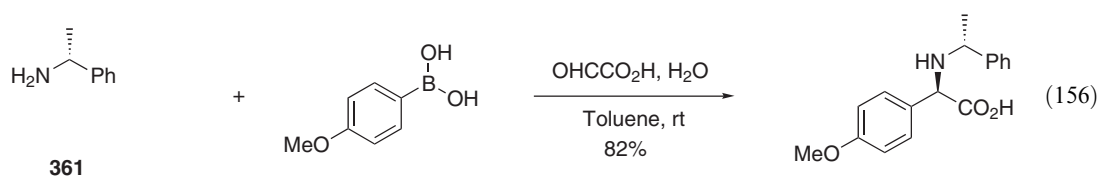
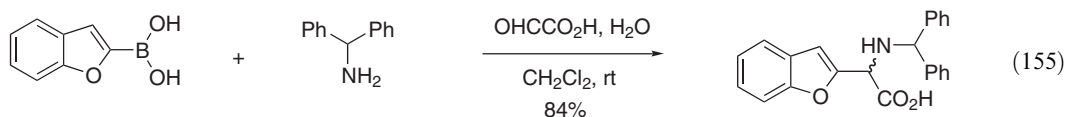
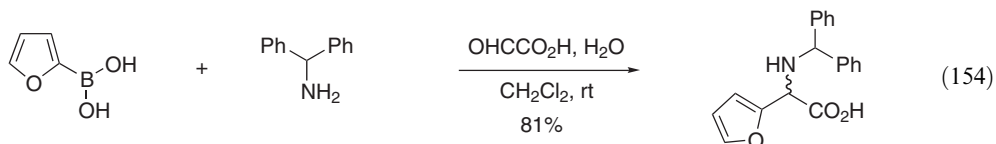
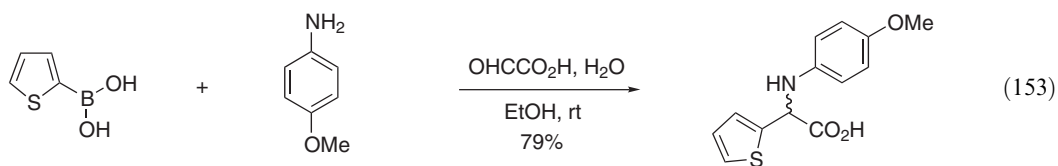
The synthesis of racemic and optically active γ - and δ -fluoro- α -amino acids has been reported <1997LA1201>.

A three-component coupling Mannich reaction between heteroaryl and arylboronic acids, for example **358**, the amine **359** and glyoxylic acid has been developed for the synthesis of racemic or optically active α -heteroaryl and α -arylglycine amino acids **360** (Scheme 49). A diverse collection of novel α -amino acid derivatives have been synthesised using this methodology (Equations (152)–(155)). The incorporation of the chiral nonracemic (*R*)- α -methylbenzylamine **361** resulted in modest amounts of diastereoselectivity (de 28–35%, Equation (156)). The reaction benefits from: (i) the availability of arylboronic acids, (ii) high convergence and high yields, and (iii) experimental simplicity <1997T16463>. Extending this Mannich three-component protocol, the synthesis of racemic β - γ -unsaturated α -amino acids **362–365** has been accomplished from alkenylboronic acids, returning a variety of amines and α -keto acids (Table 8) in 50–96% yields. The incorporation of either chiral nonracemic (*S*)- α -methylbenzylamine **366** (Equation (157)) or (*S*)-2-phenylglycidol **368** (Equation (158)) affords the corresponding chiral nonracemic β - γ -unsaturated α -amino acids **367** and **369** in 66% and 99% diastereoselectivity, respectively. Subsequent hydrogenation of **369** returned chiral nonracemic α -amino acid **370** in a 76% yield (Equation (159)) <1997JA445>.

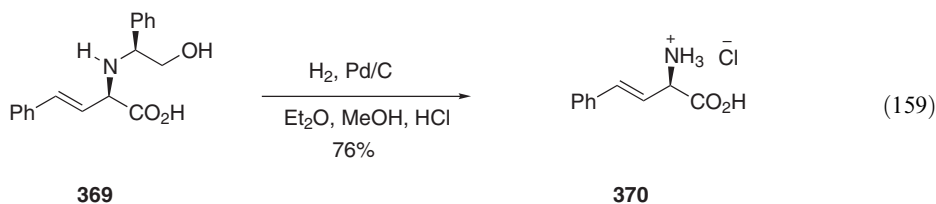
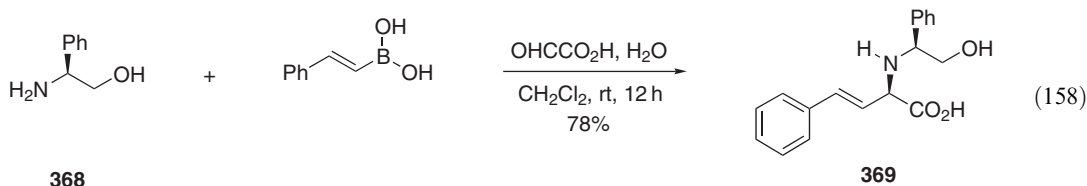
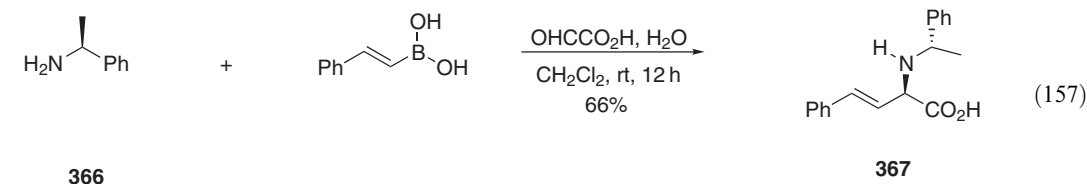


Scheme 49



**Table 8** Synthesis of α -amino acids from alkenylboronic acids

Boronic acid	Amine	Solvent	Temperature (°C)	Product	Yield (%)
		EtOH	25	 362	94
		CH ₂ Cl ₂	25	 363	96
		CH ₂ Cl ₂	25	 364	87
		EtOH	50	 365	78

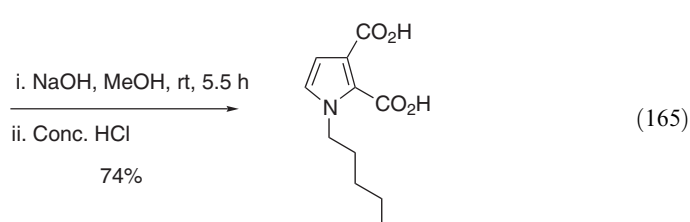
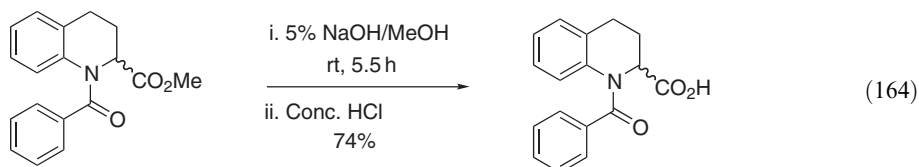
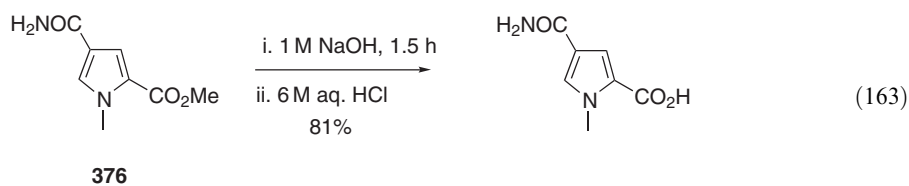
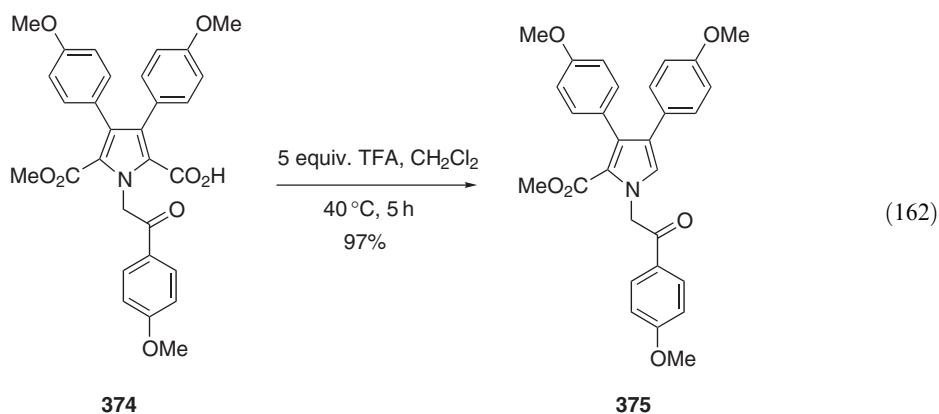
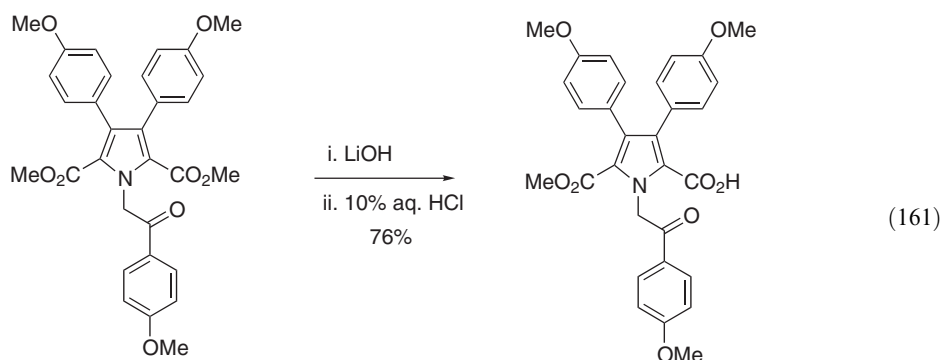
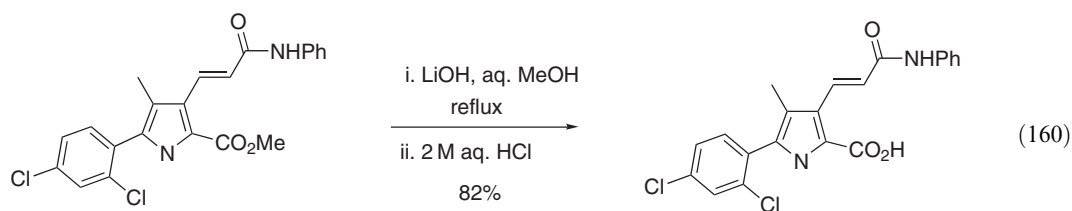


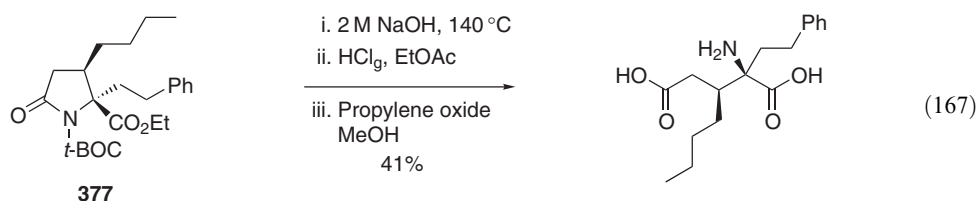
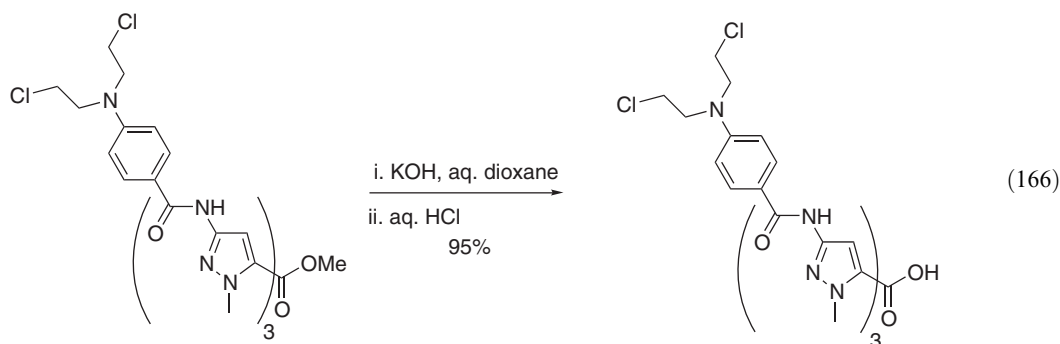
5.02.2.6 Other Nitrogen-substituted Alkanoic Acids

A number of general reviews concerned with nitrogen-substituted carboxylic acids [<1979COC841>](#), the synthesis of carpyrinic acid and related pyridine heterocycles [<1972S464>](#) and folic acid [<1961AG449>](#) have been published.

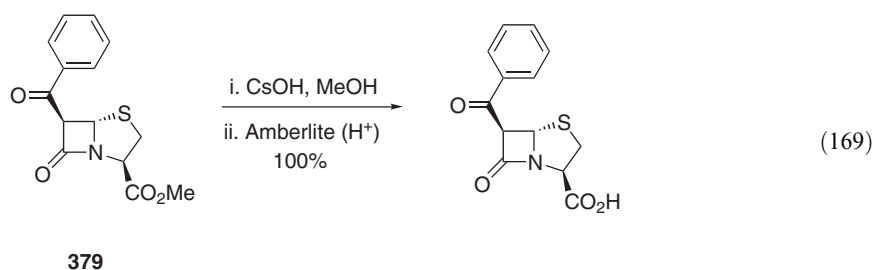
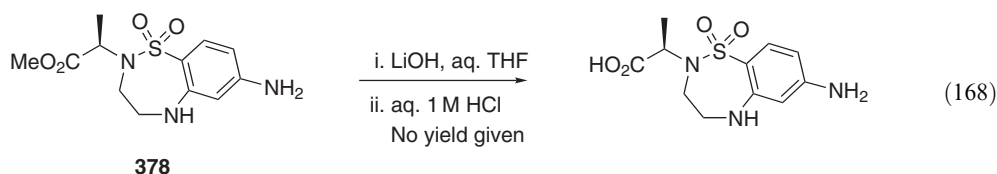
5.02.2.6.1 By hydrolysis reactions

The saponification of pyrrole carboxylic ester **371**, affording **372** has been undertaken using lithium hydroxide in aqueous methanol at reflux (Equation (160)) [<1998JMC808>](#). Selective monohydrolysis of pyrrole 2,5-diester **373** (Equation (161)) has been undertaken using lithium hydroxide yielding **374** in a 76% yield. The efficiency of the monohydrolysis was attributed to phenacyl enolate generation, which under the reaction conditions employed was followed by enol lactone closure onto either of the dimethyl esters with subsequent preferential hydrolytic cleavage of the enol lactone using the lithium hydroxide. When monocarboxylic acid **374** was treated with TFA at 40 °C it underwent a decarboxylation reaction returning pyrrole monoester **375** in an excellent 97% yield (Equation (162)) [<1999JA54>](#). The saponification of pyrrole carboxylic ester **376** has been accomplished using sodium hydroxide in water returning the corresponding carboxylic acid (Equation (163)) in a good yield (81%) [<1995JMC1140>](#). A number of protocols for the saponification of a variety of heterocyclic esters using sodium hydroxide as the base have been reported [<2001TL5525, 1996TL7801, 1999JOC346>](#), (Equation (164)) [<2002JOC2192>](#), (Equation (165)); the use of potassium hydroxide for the saponification of esters has also been reported (Equation (166)) [<1999BMC251, 1997JCS\(P1\)2997>](#). Saponification of *N*-*t*-BOC protected pyroglutamate **377** to the corresponding glutamic acid has been undertaken at 140 °C in a sealed tube. Subsequent acidification with hydrochloric acid in ethyl acetate and propylene oxide, returned the desired dicarboxylic acid in a 41% (Equation (167)) [<1998T9447>](#).

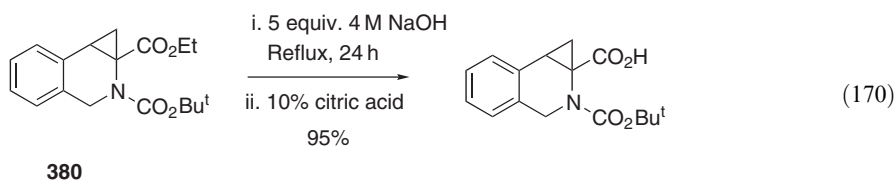




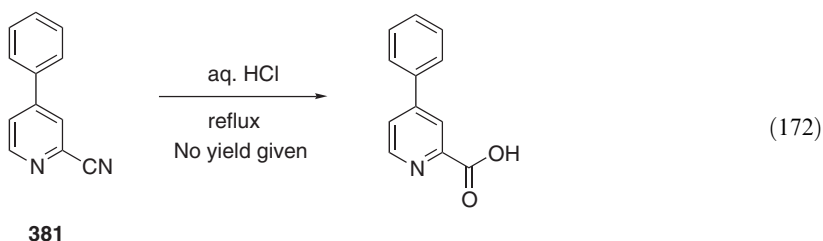
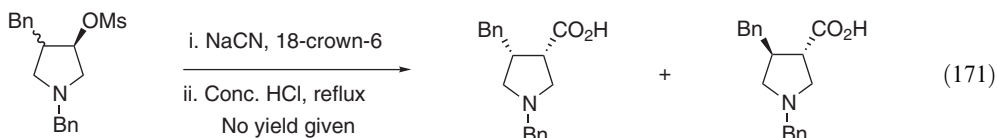
A series of D-alanine-appended benzothiadiazepines, for example **378**, have been synthesized and the methyl ester subsequently saponified to the corresponding carboxylic acids using lithium hydroxide in aqueous THF (Equation (168)) <2003JMC1811>. During the synthesis of a series of optically active bicyclic β -lactams it was necessary to saponify a methyl ester to the corresponding carboxylic acid without causing racemization. A number of protocols were investigated, which included the use of enzymes, and propargyl esters, which are readily hydrolyzed when treated with dicobalt octacarbonyl and TFA, but none of the procedures worked. Saponification of the esters on **379** was, however, successful when caesium hydroxide was used, and purification of the acid was undertaken simply by triturating the crude solid with acetone, returning the carboxylic acid in an excellent yield and with no evidence of any racemization (Equation (169)) <2003OBC1308>.



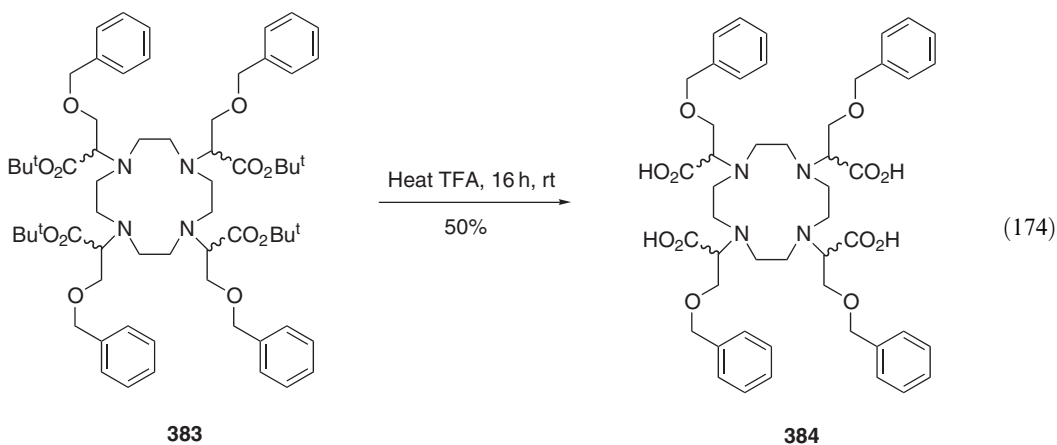
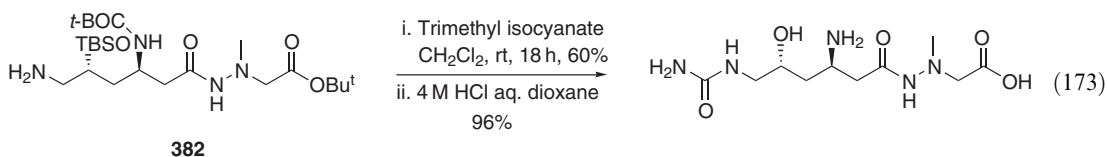
The use of acidic reaction conditions for the hydrolysis of a variety of esters and nitriles to the corresponding carboxylic acids has been reported. One important difference between the use of acidic and basic conditions and the susceptibility of esters to hydrolysis can be found when methyl or ethyl esters are present in a molecule with a *t*-butyl ester **380**. Employing relatively acidic reaction conditions will, more than likely, result in the hydrolysis of all ester types, but switching to basic reaction conditions does have the advantage that of these three ester types the methyl and ethyl esters are rapidly saponified allowing the more robust *t*-butyl group to remain intact (Equation (170)) <2000JOC5469>.



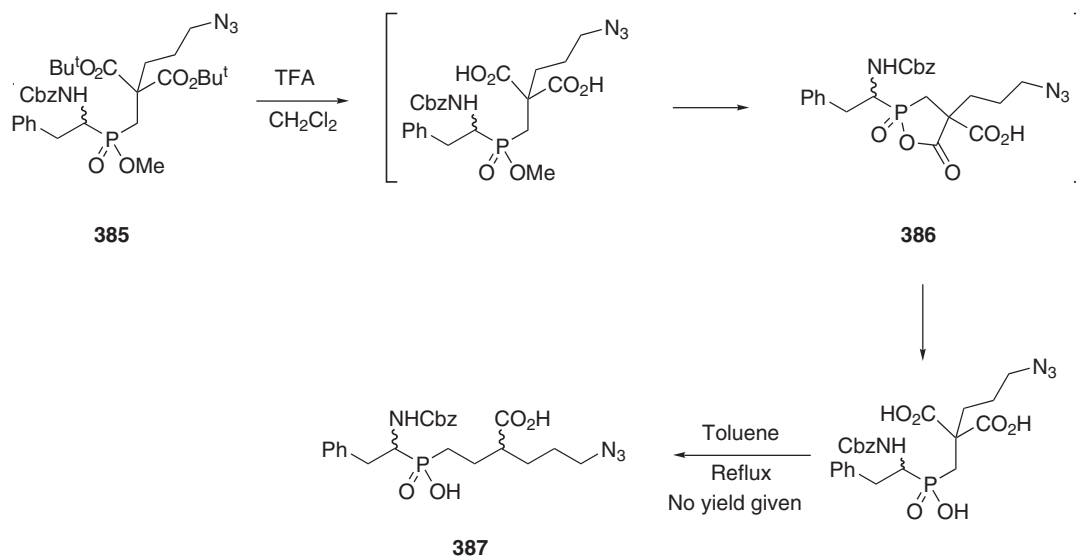
The ease of introducing a nitrile group via, for example, a nucleophilic displacement allows the nitrile functionality to act as a latent carboxylic acid (Equation (171)) <2001T6579>. Transformation of the nitrile group of **381** into the corresponding carboxylic acid is routinely undertaken using relatively harsh, acidic reaction conditions often at elevated temperatures (Equation (172)) <1999TA4331>.



The hydrolysis of the *t*-butyl ester appended to the negamycin analog **382** has been undertaken using 4 M hydrochloric acid, returning the carboxylic acid in an excellent 96% yield (Equation (173)) <2003BMCL2413>. Paramagnetic compounds are frequently used in magnetic resonance imaging (MRI) as imaging agents. They act by enhancing the contrast of the image indirectly by lowering the magnetic relaxation times of the protons in the surrounding tissue. A novel contrasting agent, benzyloxymethyl Gd(III) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetra acetate has been synthesized in three steps. One of the key steps prior to metal chelation was the hydrolysis of the *t*-butyl esters on **383** using neat TFA, returning racemic tetracarboxylic acid **384** in a reasonable 50% yield (Equation (174)) <2003OBC1707>.

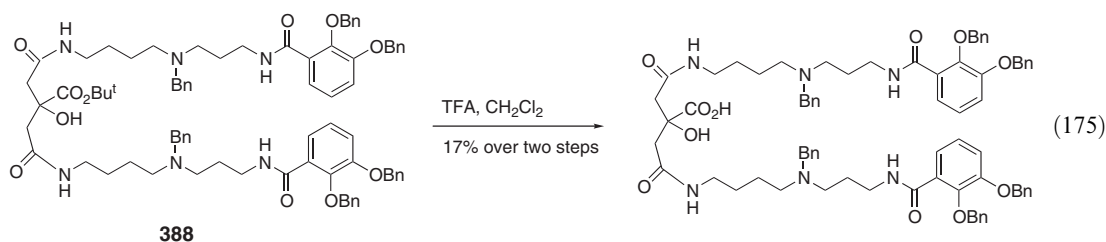


Peptidomimetics have found widespread use in biological and medicinal chemistry. Phosphinic acid dipeptides have been synthesized via a conjugate addition reaction between a mono-substituted phosphinate and an α -substituted di-*t*-butyl acrylate ester. Subsequent hydrolysis of the *t*-butyl groups on **385** using TFA afforded, after decarboxylation the corresponding carboxylic acid **387**, presumably via the five-membered ring system **386** (Scheme 50) <2002TL4973>.



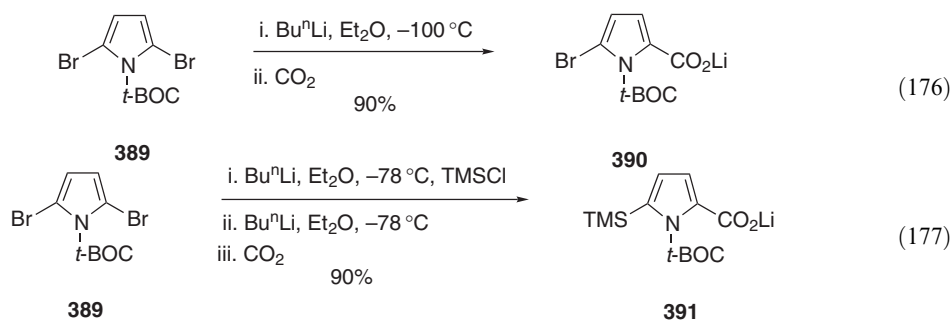
Scheme 50

During the total synthesis of petrobactin, a siderophore isolated from the marine bacterium *Marinobacter hydrocarbonoclasticus*, the hydrolysis of the *t*-butyl ester of **388** was undertaken using TFA (Equation (175)). Interestingly, protonation and subsequent elimination of water resulting in the formation of the corresponding α,β -unsaturated carboxylic acid was not reported by the authors <2003T2007>.

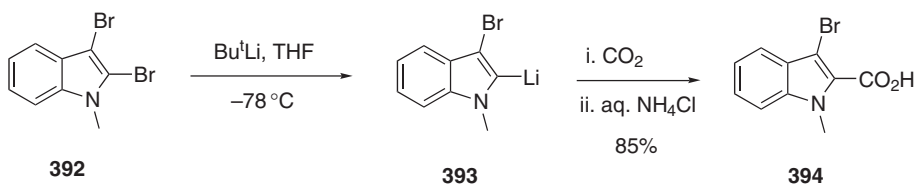


5.02.2.6.2 By carbonation of organometallic reagents

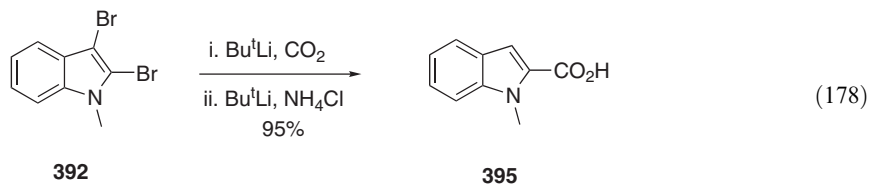
Unfortunately 5-bromopyrrole-2-carboxylic acid is difficult to synthesize via the direct bromination of pyrrole-2-carboxylic acid. Readily available 2,5-dibromopyrrole **389** can, however, be monometalated using Bu^nLi at -100°C , and subsequent quenching of the anion using carbon dioxide affords clean conversion into the corresponding monocarboxylate **390** (Equation (176)) in an excellent yield (90%). Similarly, exchanging the electrophile for trimethylsilyl chloride after the first monometalation afforded the corresponding 5-trimethylsilyl-2-bromopyrrole; a second halogen-metal exchange, again with Bu^nLi , allows the resulting anion to be quenched with carbon dioxide affording **391** in a 90% (Equation (177)) <1999JA9574>.



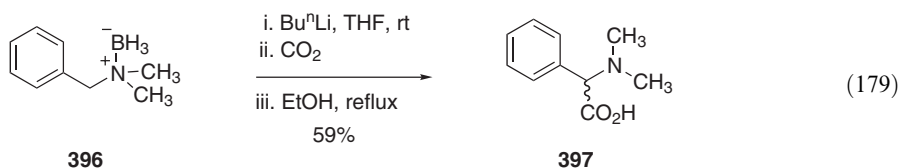
2,3-Dibromo-1-methylindole **392** undergoes a single metal-halogen exchange with Bu^tLi , and quenching of the resulting organolithium species **393** with an electrophile, for example, carbon dioxide, returned 3-bromo-2-carboxy-1-methylindole **394** in an 85% yield (Scheme 51). In a one-pot operation, it is possible to sequentially replace both bromine atoms on 2,3-dibromo-1-methylindole **392** with different electrophiles, affording for example when carbon dioxide and a proton source are used, 2-carboxy-1-methylindole **395** in a 95% yield (Equation (178)) <2002TL7135>.



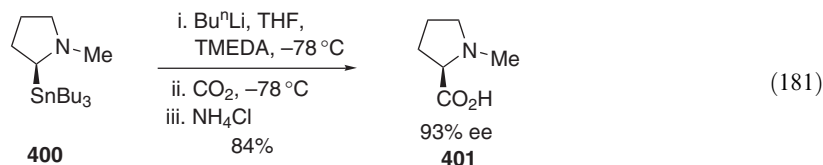
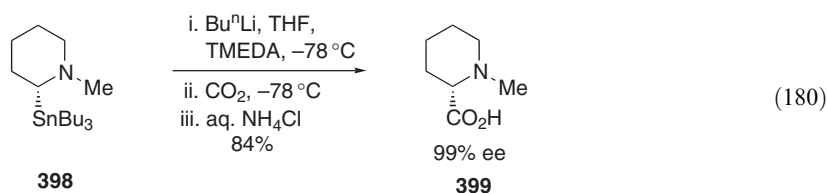
Scheme 51



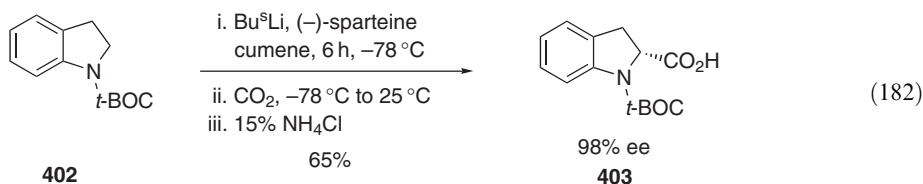
Simpkins and co-workers have utilized the formation of borane-amine adducts, for example **396**, to regioselectively direct the metallation of benzylamines alpha to the nitrogen atom. The borane adduct effectively enhances the acidity of the benzylic protons, removing the donor ability of the nitrogen lone pair. Using this protocol, a variety of racemic α -carboxyl-*N,N*-dimethylbenzylamines **397** have been synthesized (Equation (179)) <1995TL8697>.



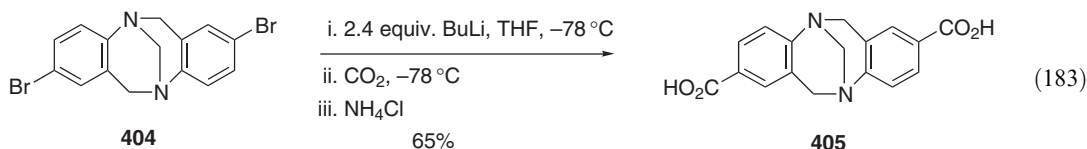
The synthesis of 2-lithiopiperidine and 2-lithiopyrrolidine is conveniently undertaken via transmetallation of the corresponding 2-tributylstannyl derivative, synthesized according to the method of Beak and co-workers <1993JOC1109, 1989TL1197>. Transmetallation of the 2-stannylpiperidine **398** and pyrrolidine **400** was performed with Bu^nLi at -78°C , the reaction being complete within 5 min. Quenching the anion with carbon dioxide afforded the corresponding carboxylic acids **399** and **401** (75–85%). Lithiated piperidines and pyrrolidines are remarkable in that their configurational stability exceeds their chemical stability. Employing enantiopure 2-lithiopiperidines and pyrrolidines afforded chiral nonracemic carboxylic acids (Equations (180) and (181), respectively) <1995JOC5763>.



The asymmetric lithiation of *N*-*t*-BOC-indoline **402** with a combination of $\text{Bu}^s\text{Li}/(-)$ -sparteine and subsequent quenching of the resulting anion afforded chiral nonracemic 2-carboxyl *N*-*t*-BOC indolines **403** (Equation (182)) in an excellent enantiomeric ratio (99:1) and reasonable yield (65%) <1997JOC7679>.

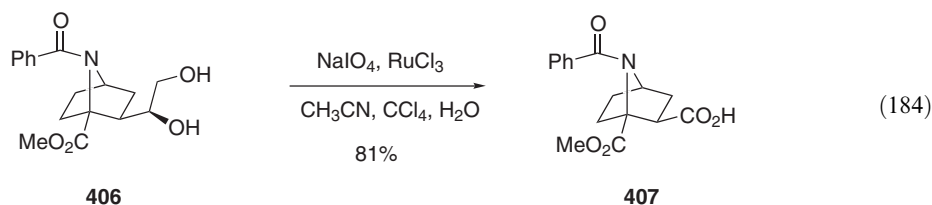


Tröger's base is a chiral but racemic rigid molecule with a concave shape. A novel protocol for the synthesis of 2,8-dihalo-substituted analogs of Tröger's base has been published <2001S1873>. A general method for the preparation of C_2 -symmetric 2,8-difunctionalized analogs of Tröger's base via an efficient double metal–halogen exchange incorporating **404** and its subsequent reaction with electrophiles has been reported. Similarly single metal–bromine exchanges have been undertaken affording asymmetric functionalised analogs of Tröger's base. Using carbon dioxide as the electrophile the corresponding mono and dicarboxylic acids **405** (Equation (183)) were returned in 61% and 65% yields, respectively <2002JOC6008>.

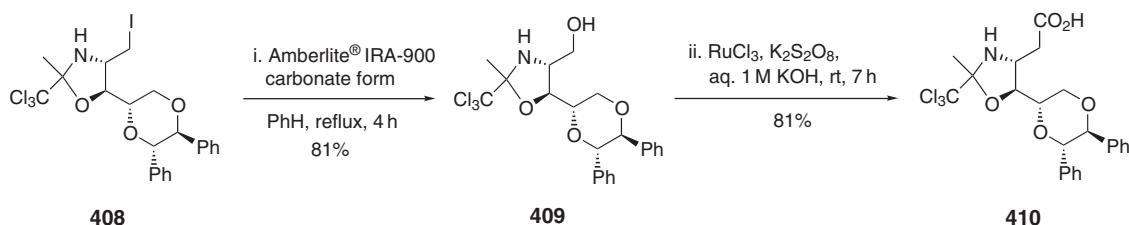


5.02.2.6.3 By oxidation reactions

The synthesis of a number of enantiomerically pure 2-substituted 7-azabicyclo[2.2.1]heptane-1-carboxylic acids has been described. The key step in the synthesis of the precursors was an intramolecular Diels–Alder reaction between Danishefsky's diene and a chiral nonracemic oxazolone derived from (*R*)-glyceraldehyde. Subsequent functional group transformations included the oxidative cleavage of the appended diol on **406** into the corresponding carboxylic acid **407** in an excellent 81% yield (Equation (184)) <2001T6417>.



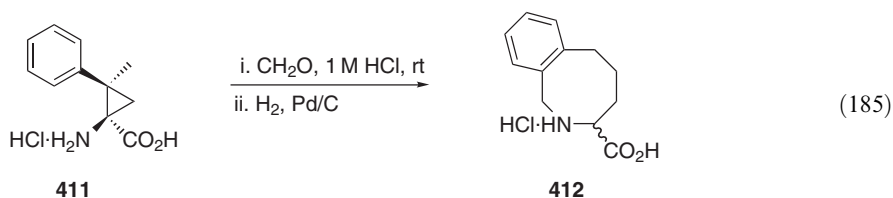
During the synthesis of (+)-polyoxamic acid, transformation of the primary iodide on **408** into the corresponding primary alcohol **409** was undertaken via displacement of the iodide using Amberlite® IRA-900 in refluxing benzene. Subsequent oxidation of the alcohol on **409** was performed using stoichiometric quantities of Oxone® as the oxidant and catalytic amounts of ruthenium trichloride, and the desired carboxylic acid **410** was returned in an 81% yield (Scheme 52) <2002CC1116>.



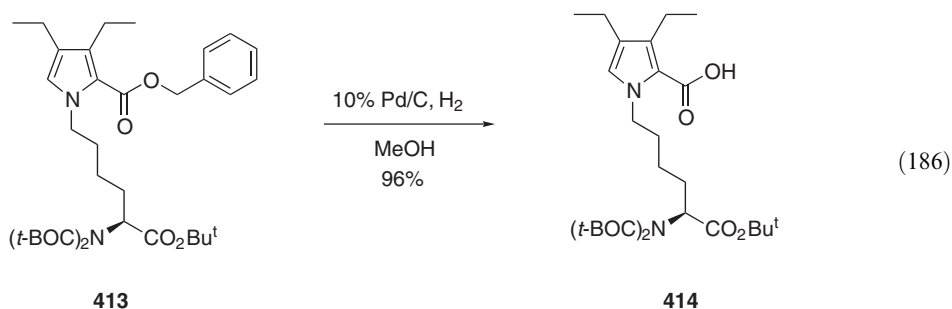
Scheme 52

5.02.2.6.4 By miscellaneous reactions

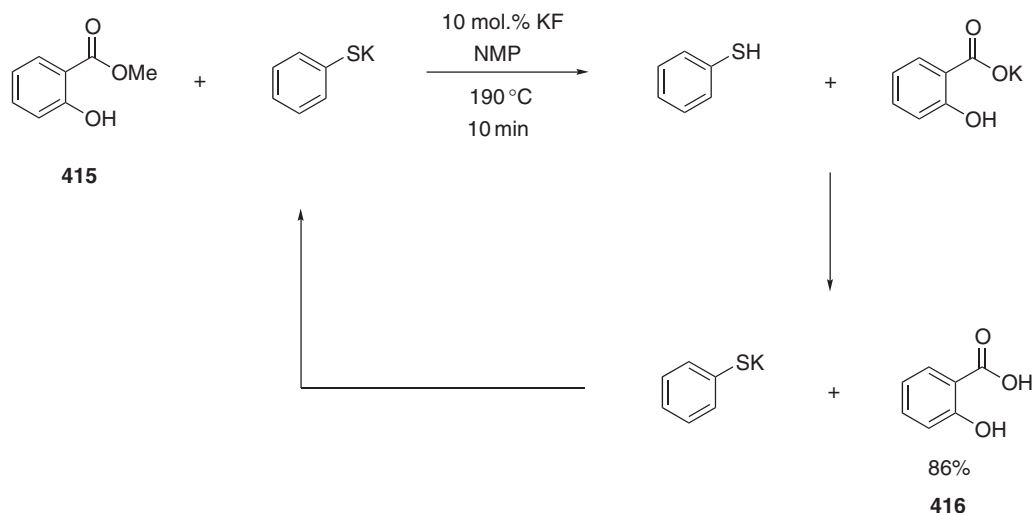
The reaction of *cis*-2,3-methanophenylalanine hydrochloride **411** with 1 M hydrochloric acid at ambient temperature afforded in an excellent yield (100%) racemic 2,3-dihydro-1*H*-2-benzazepine-3-carboxylic acid **412** (Equation (185)). The mechanism is thought to proceed via a novel [3,3]-sigmatropic rearrangement, followed by a [1,5]-hydrogen shift <2001JOC2884>.



The hydrogenolysis of the pyrrole-appended benzyl ester on **413** to give the corresponding pyrrole carboxylic acid **414** was undertaken using palladium on carbon as the catalyst in conjunction with hydrogen. A *N,N*-di-*t*-BOC-protected *t*-butyl ester remained intact during the cleavage procedure (Equation (186)) <2001JOC11>



The combination of thiophenol and a catalytic amount of potassium fluoride converts benzyl and methyl esters **415** into the corresponding carboxylic acids **416** under nonhydrolytic reaction conditions (Scheme 53), whereas ethyl esters returned lower yields. However, the high temperatures required for the procedure may be incompatible with thermally sensitive compounds <1998CL297>.



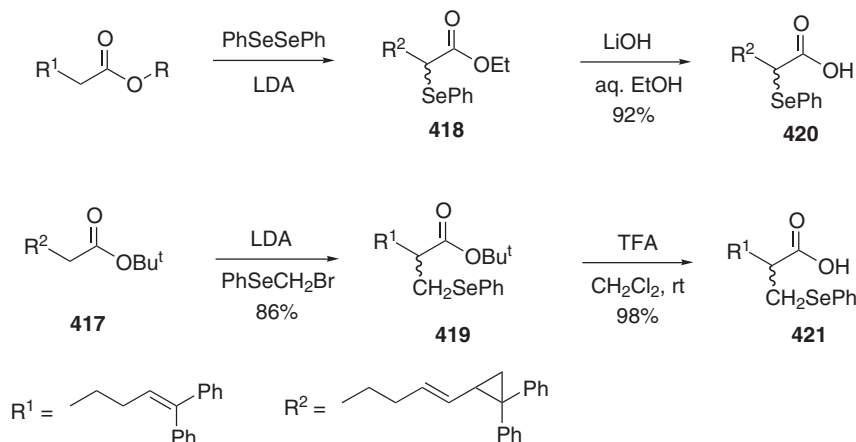
Scheme 53

5.02.2.7 Other Heteroatom-substituted Alkanoic Acids

The synthesis of phosphorus-containing carboxylic acids has been reviewed [<B-1983MI502-01>](#).

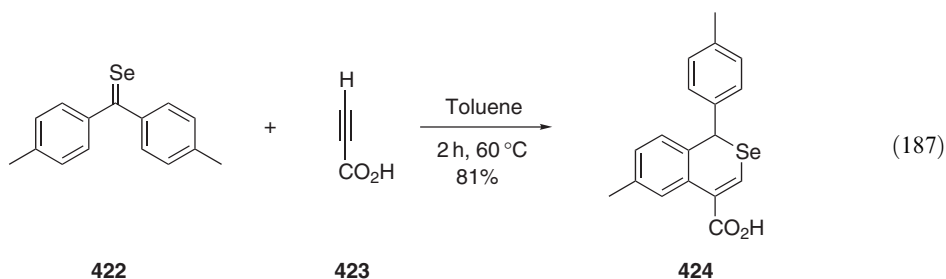
5.02.2.7.1 By hydrolysis reactions

Model studies undertaken by Miranda and co-workers on the mode of action of coenzyme B₁₂-dependant enzymes required the synthesis of racemic phenylselenium-substituted carboxylic acids. The synthesis of the ethyl or *t*-butyl ester precursors was undertaken via a deprotonation-electrophile quench series of reactions. Thus, using LDA as the base, the ethyl ester enolate of **417** was readily formed and subsequently reacted with diphenyl diselenide, returning α -phenylselenide ester **418**. Alternatively, quenching the *t*-butyl ester enolate of **417** with phenylselenenylmethyl bromide yielded the corresponding α -(methylphenylselenenyl) ester **419**. Subsequent saponification of: (i) the ethyl ester with lithium hydroxide, and (ii) the *t*-butyl ester with TFA, afforded the corresponding carboxylic acids **420** and **421** in 92% and 98% yields, respectively (Scheme 54) [<2003JA5260>](#).

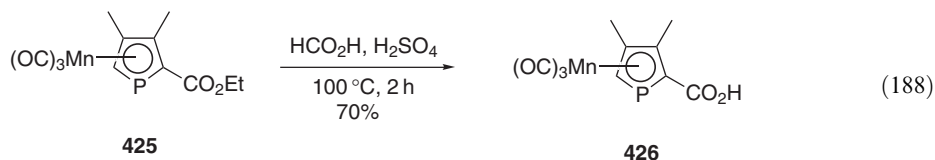


Scheme 54

A variety of 4,4-disubstituted selenobenzophenones, for example **422**, react as dienes in [4+2] hetero-Diels–Alder reactions with activated alkynes yielding 1-diarylmethylene-1*H*-2-benzoselenopyrans in poor-to-good yields (9–71%). The incorporation of propiolic acid **423** as the dienophile component afforded the corresponding carboxylic acid **424** in an 81% yield as the only product (Equation (187)) <2000JOC2090>.

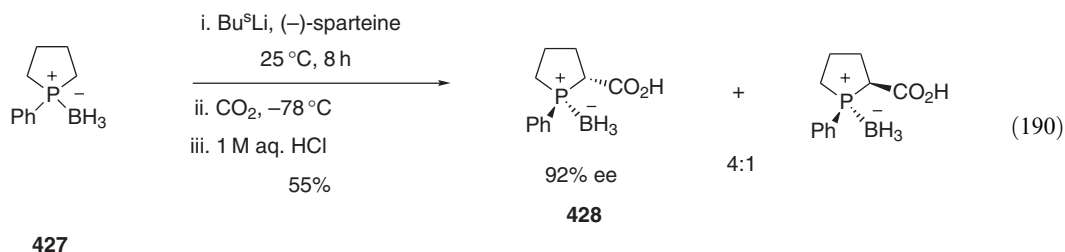
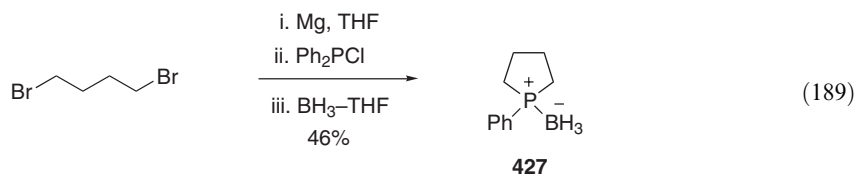


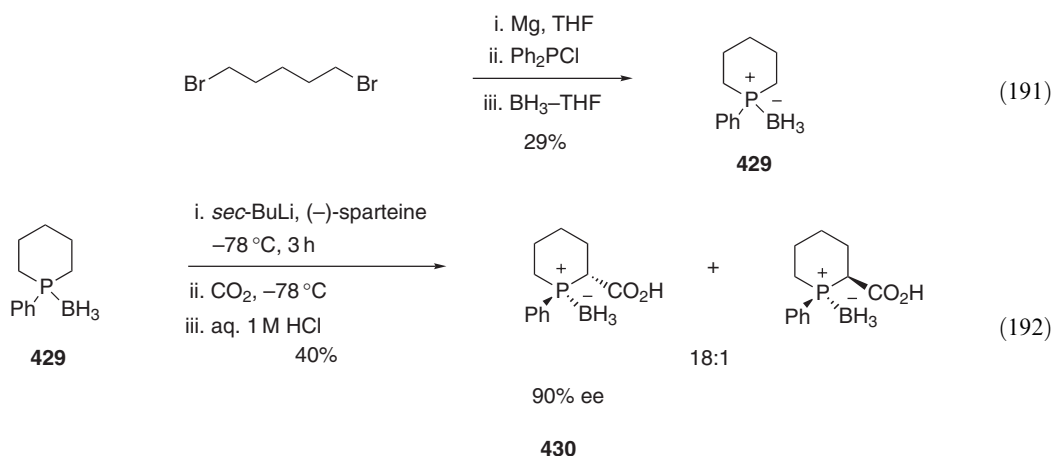
The hydrolysis of 1-phenyl-2-ethoxycarbonyl-3,4-dimethylphosphole **425** has been undertaken using a mixture of formic acid and sulfuric acid at 100 °C affording **426** in a 70% yield. The sensitivity of the phosphacymantrene to nucleophiles prohibited the use of basic condition for the ester hydrolysis (Equation (188)) <1999OM5688>.



5.02.2.7.2 By carbonation of organometallic reagents

The synthesis of an optically active 1-phenylphospholane-2-carboxylic acid–borane complex and a 1-phenylphosphorinane-2-carboxylic acid–borane complex, which are phosphorus analogs of proline and pipecolic acid has been accomplished. Synthesis of **427** in a 46% yield (Equation (189)) followed by enantioselective deprotonation using Bu^sLi/(–)-sparteine allowed the resulting enolate to be quenched with carbon dioxide affording carboxylic acid **428** in good ee (92%) and a 55% yield (Equation (190)). The synthesis of the corresponding pipecolic acid **429** was accomplished (Equation (191)) in a poorer yield (29%). Subsequent asymmetric deprotonation of **429** (Bu^sLi/(–)-sparteine) and quenching of the resulting anion with carbon dioxide afforded carboxylic acid **430** in high enantioselectivity (90%) and moderate 40% yield (Equation (192)) <2001TL7303>.



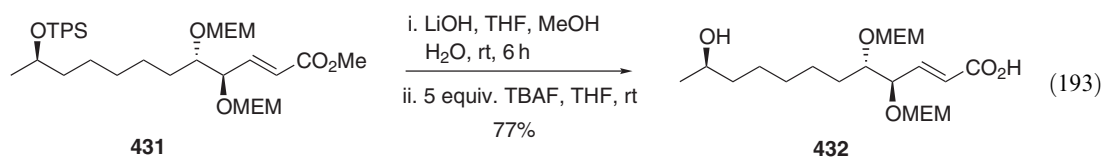


5.02.3 α,β -UNSATURATED ACIDS

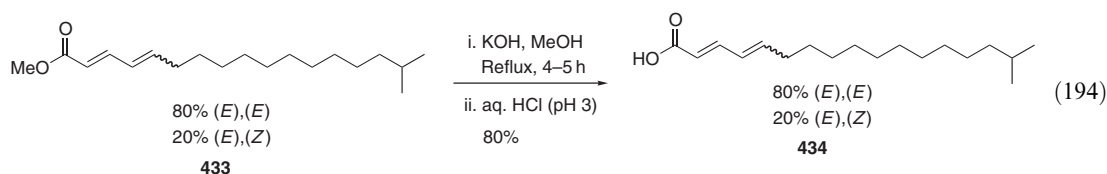
The synthesis of unsaturated acids via the Perkin reaction has been reviewed [\[1942OR\(1\)210, 1956CRV27, B-72MI502-01\]](#), likewise the Doebner reaction [\[1952JCS4521, B-1972MI502-01\]](#) for the synthesis of β -aryl- and β -alkyl- α,β -unsaturated carboxylic acids. The base condensation of diethyl succinate with ketones or aldehydes produces the monoesters of α -alkylidene or α -arylidene succinic acids [\[1949BSFD297, 1951OR\(61\)1, 1954OR\(8\)28, B-1972MI502-01\]](#).

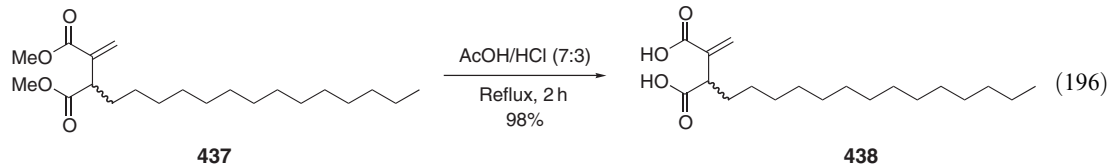
5.02.3.1 By hydrolysis reactions

The synthesis of α,β -unsaturated carboxylic acids via the hydrolysis of the corresponding ethyl esters has been achieved using group 1 alkali hydroxides. Using an aqueous methanolic solution of lithium hydroxide, the saponification of α,β -unsaturated methyl ester **431** was achieved affording **432** in a 77%. Appended *O*-MEM and *O*-TPS groups remained intact during the hydrolysis procedure (Equation (193)) [\[1995TA559\]](#). Aqueous sodium hydroxide has been utilized to transform a shikimic-acid-derived α,β -unsaturated ester to the corresponding α,β -unsaturated carboxylic acid [\[1998CC2033\]](#).



Hydrolysis of $\alpha,\beta,\gamma,\delta$ -unsaturated methyl ester **433** to give the corresponding unsaturated carboxylic acid **434** has been accomplished using potassium hydroxide in methanol at reflux (Equation (194)) [\[1997T15397\]](#). Exploiting a Baylis–Hillman reaction between *t*-butyl acrylate, DABCO, paraformaldehyde and 2-ethylhexanol as the solvent, returned α,β -unsaturated *t*-butyl ester **435** on a multigram scale and in good yield (77%). Subsequent hydrolysis of the *t*-butyl ester on **435** to the corresponding carboxylic acid **436** was performed with TFA in an excellent 96% yield (Equation (195)) [\[2003JA5351\]](#). The hydrolysis of α,β -unsaturated carboxylic acid esters to give the corresponding unsaturated carboxylic acids using TFA has been reported [\[1999BMC1625\]](#). The utilization of dilute aqueous mineral acids for the hydrolysis of esters is also viable; see, for example, the transformation of **437** to **438** (Equation (196)) [\[2002JOC7131, 2001OPRD498\]](#).





439

440

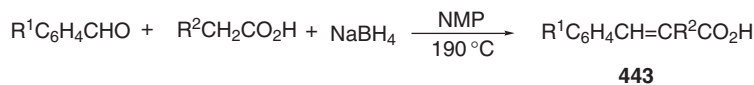
(197)

441

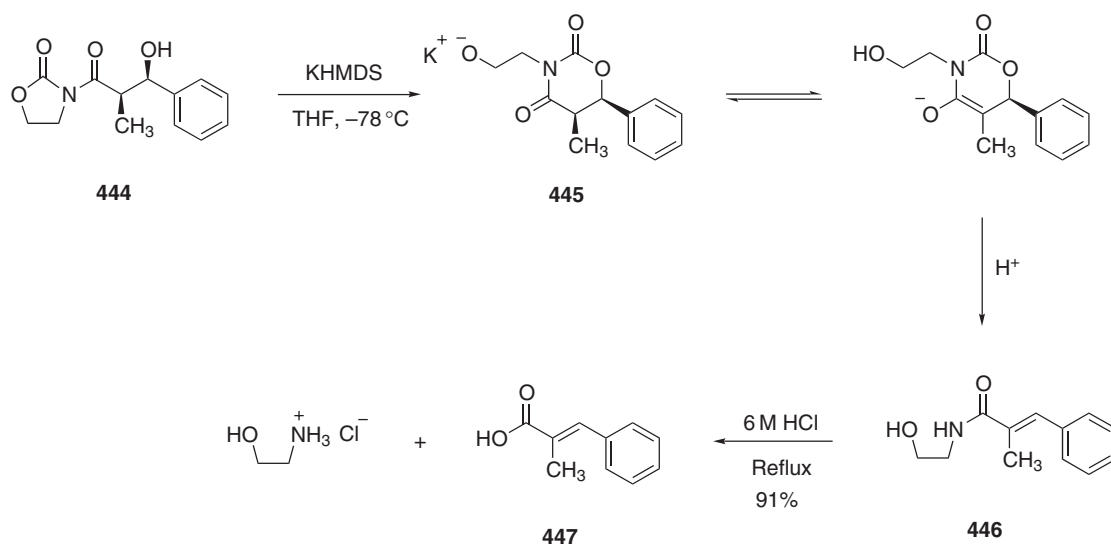
442

(198)

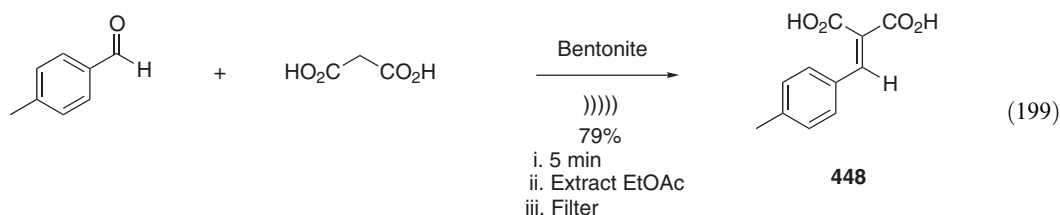
Few methods are available for the diastereoselective synthesis of α - and β -substituted (*E*)- α,β -unsaturated acids. Trisubstituted α,β -unsaturated acid derivatives are important synthetic targets serving as versatile substrates for the synthesis of a wide range of natural products. Potassium alkoxides of *N*-acyloxazolidin-2-ones, for example **445**, itself derived from the deprotonation of *syn*-aldolates **444** with KHMDS, underwent a clean elimination reaction affording the corresponding α,β -unsaturated carboxylic acids amides **446** in 67–99% yields and >90% de. The high diastereoselectivities are explained by invoking an intramolecular endocyclic cleavage mechanism. Refluxing the carboxylic acid amides **446** in 6 M hydrochloric acid afforded the corresponding carboxylic acids **447** in excellent yields (Scheme 55) <2003CC2184>.

Table 9 Synthesis of (*E*)-cinnamic acids from aromatic aldehydes and aliphatic acids

R^1	R^2	Time (h)	Yield (%)
<i>m</i> -Cl	H	10	74
<i>p</i> -H	H	12	66
<i>p</i> -Cl	H	9	83
<i>p</i> -NO ₂	H	9	86
<i>m</i> -NO ₂	H	10	81
<i>p</i> -CH ₃ O	H	12	59
<i>m</i> -Cl	CH ₃	10	72
<i>m</i> -NO ₂	CH ₃	10	77

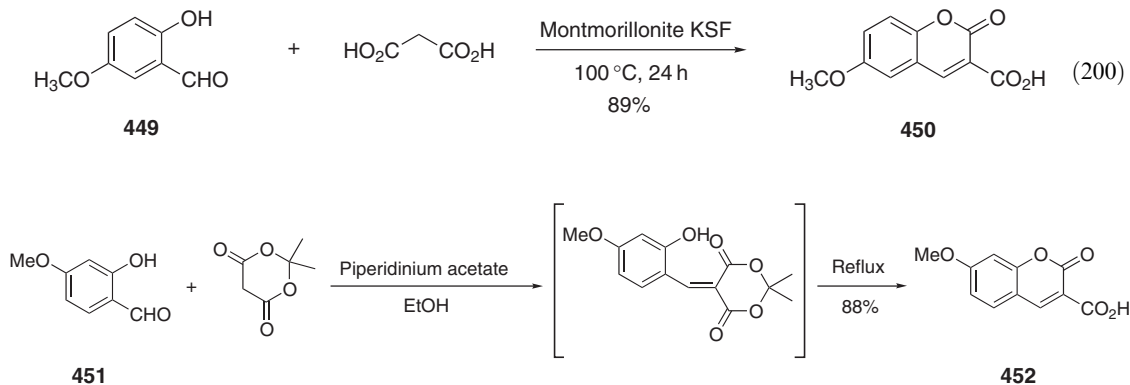


The application of solvent-free reaction conditions and microwave irradiation has been used for the synthesis of β -aryl- α,β -unsaturated dicarboxylic acids, for example **448**. In the presence of bentonite, the irradiation of a number of aryl aldehydes and malonic acid resulted in high yields (79–94%) of β -aryl- α,β -unsaturated dicarboxylic acids (Equation (199)). Smaller amounts of (*E*)-cinnamic acids were also produced <2001JCS(P1)1220>.

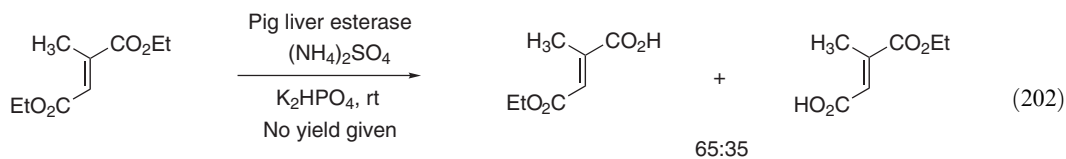
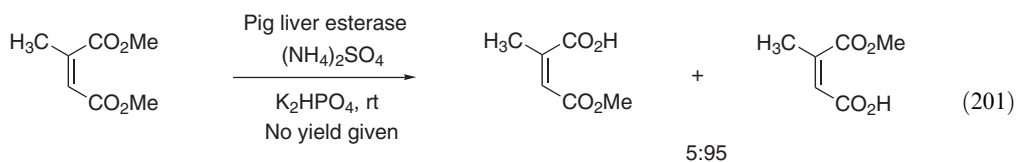


Coumarin-3-carboxylic acids, for example **450**, are traditionally synthesized via Knoevenagel condensations of *o*-hydroxyaryl aldehydes **449** and malonic acid derivatives. In an extension of this reaction the use of montmorillonite KSF and K10 as inorganic, water-stable, reusable catalysts has been reported, and of these the former was more active. Interestingly, the montmorillonite is proposed to act as a ditopic catalyst containing both basic and acidic sites, the former activating the Knoevenagel condensation and the latter inducing α -pyrone ring formation

(Equation (200)). The yields of the coumarin-3-carboxylic acids were excellent (93–95%). The montmorillonite catalyst was readily recycled via a simple procedure comprising a Büchner filtration, washing with methanol and drying, and returned a catalyst which could be used at least five times more without significant loss of activity <1999JOC1033>. The use of alternative heterogeneous catalysts in the Knoevenagel condensation reaction have been reported, and these include; cation-exchanged zeolites <1997TL1721>, alkali-containing MCM-41 <1995CC1005>, and bentonitic clay <1995SC753>. A novel, one-pot procedure for the synthesis of coumarin-3-carboxylic acid, for example **452**, in high yields (61–98%) and excellent purity (94–98%) using *o*-hydroxybenzaldehydes **451** and Meldrum's acid has been reported (Scheme 56). The procedure is convenient and straightforward with no further purification required in the majority of cases <2003TL1755>.



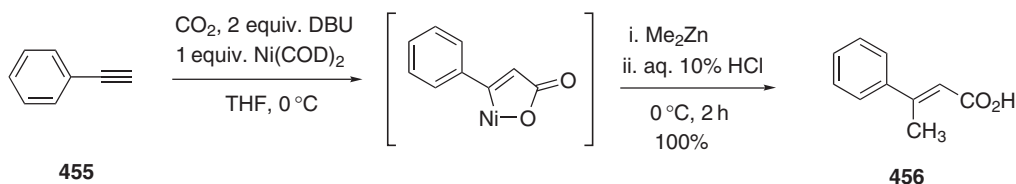
During recent years, the use of enzymes to accomplish stereoselective chemical transformations has become commonplace in the synthetic chemistry laboratory. Pig liver esterase (PLE) is perhaps one of the most extensively used enzymes for such purposes. The regioselective mono-hydrolysis of diesters of (*Z*)- and (*E*)-2-methyl-butenedioic acids has been achieved using PLE. Interestingly, of the dimethyl **453**, diethyl **454** and di-*n*-propyl esters used, the diethyl displayed the lowest regioselectivity for both the (*E*)- and (*Z*)-isomers (Equations (201) and (202), respectively) with the (*E*)-isomers tending to be hydrolyzed quicker than the (*Z*)-isomers <2001TL8543>.



5.02.3.2 By Carbonation of Organometallic Reagents

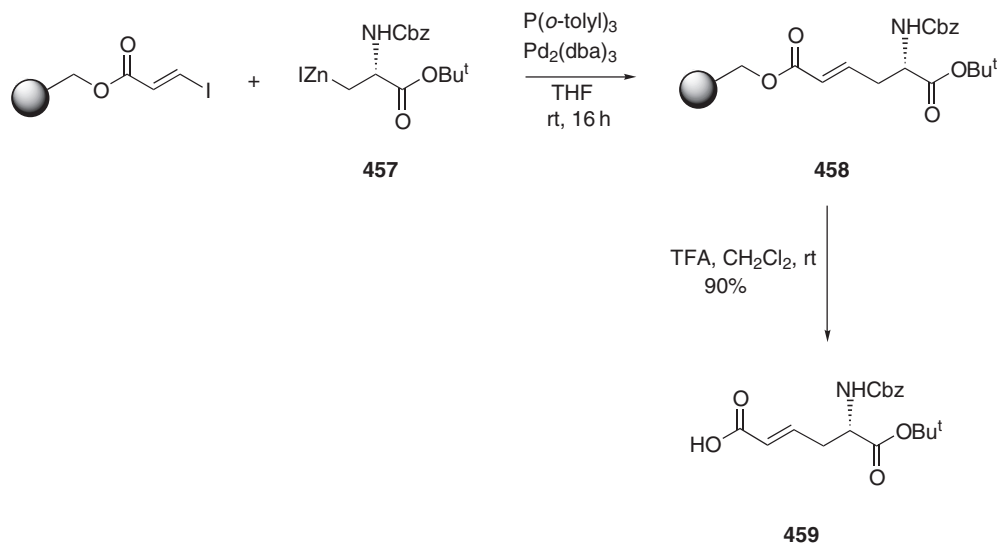
The regioselective carboxylation of nonactivated internal alkynes can be performed with carbon dioxide under atmospheric pressure using a simple procedure based on chemistry developed by Sato and co-workers using diisopropoxytitanacyclopropenes. Various polysubstituted vinyl-carboxylic acids have been prepared in this way <2003EJO1157>. The alkylative or arylative

carboxylation of terminal alkynes **455** can be undertaken using mild reaction conditions affording β,β -disubstituted unsaturated carboxylic acids **456** in a highly regio- and stereoselective manner (Scheme 57) in moderate-to-high yields (33–82%) <2001OL3345>.



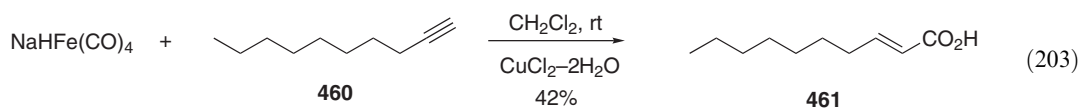
Scheme 57

Early solid-supported chemistry was directed toward the preparation of carbon–heteroatom bonds and it is only relatively recent that methods for the formation of C–C bonds have been explored. The advantages of using solid-phase synthetic techniques are widely recognized. For example, the ease of undertaking synthetic transformations can be enhanced when conducted on solid-support due to the fact that immobilized reactions are undertaken simply by shaking the support with the desired solvent(s) and reagents, filtering the mixture and subsequently washing the resin. Subsequent cleavage often returns the products in high yield and purity. Oates and co-workers have reported the synthesis of solid-supported optically enriched 3-substituted (*Z*)- or (*E*)-propenoic esters **458** using organozinc reagents **457**, derived from (*L*)-serine, and palladium catalysts in (generally) very good yields (37–99%). Cleavage of the Wang-, NovaSyn-, or Rink-derived propenoic esters yielding the corresponding carboxylic acids **459**, was undertaken using either 50% TFA, neat TFA or 1% TFA, respectively (Scheme 58) <2003OBC140>.



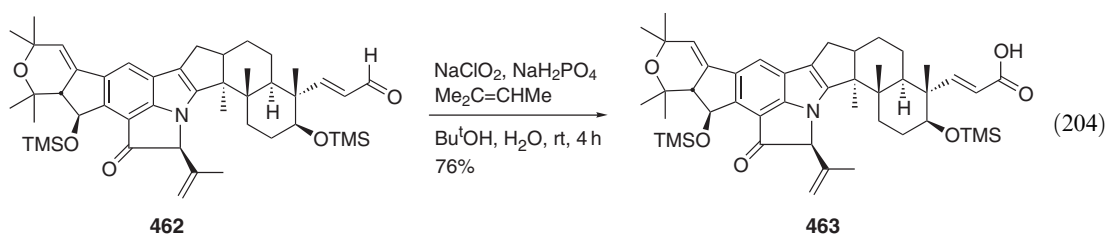
Scheme 58

There has been immense interest in the use of iron carbonyl reagents in organic synthesis over recent years <1995ACR414>. The synthesis of α,β -unsaturated carboxylic acids **461** via the hydrocarboxylation of terminal **460** and internal alkynes is possible using an *in situ* organoiron reagent produced by oxidation of $\text{NaHFe}(\text{CO})_4$ with copper(II) chloride (Equation (203)). The reaction proceeds efficiently at ambient temperatures and, interestingly, only one of the four possible regio- and stereoisomers is formed. Incorporating trimethylsilyl chloride into the reaction furnishes slightly higher yields (45–55%) of the (*E*)- α,β -unsaturated carboxylic acids <1998JOC4930>.



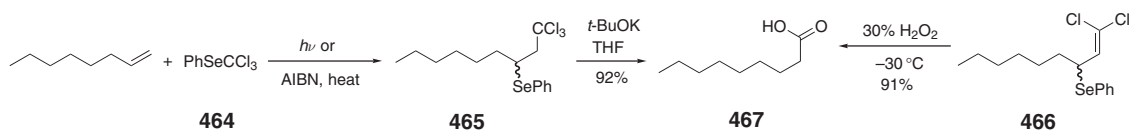
5.02.3.3 By Oxidation Reactions

The oxidation of unsaturated alcohols to the corresponding carboxylic acids can be undertaken using sodium ruthenate <1972CJC3741>. Reagents used for the oxidation of aldehydes to carboxylic acids include sodium chlorite and hydrogen peroxide <1986JOC567>, alkaline silver(I) oxide <1956CI(L)548> and Jones's reagent <1958JCS1313>. Oxidation of α,β -unsaturated aldehydes **462** to the corresponding α,β -unsaturated carboxylic acids **463** can be readily undertaken using sodium chlorite in a mixture of *t*-butanol and 2-methylbutene (Equation (204)). The carboxylic acids are produced in good yields, under mild reaction conditions that tolerate a wide selection of commonly used protecting groups <2002OL1291>.



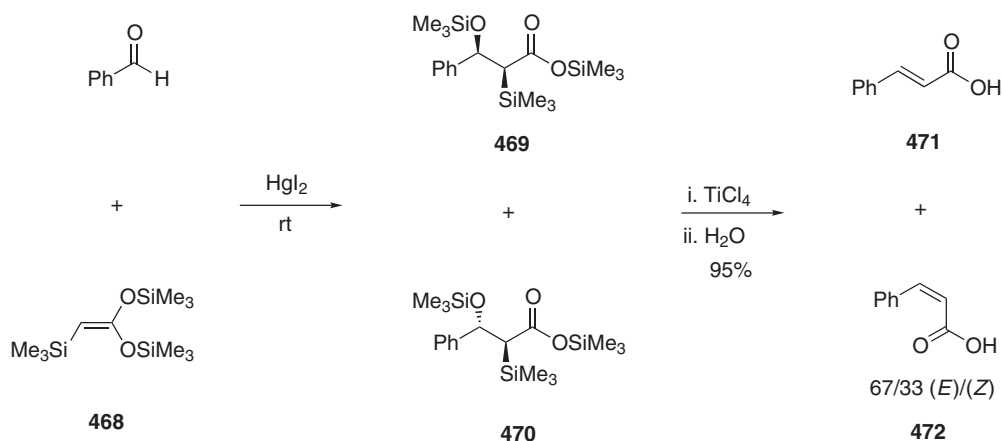
5.02.3.4 By Miscellaneous Reactions

The phenylselenenyl radical transfers to alkyl radicals with rates comparable to those observed for bromine atom transfers. This suggests that phenyl trichloromethyl selenide should undergo free-radical additions and, furthermore, that it may well behave like bromotrichloromethane. The free-radical addition of phenyl trichloromethyl selenide **464** to alkenes affords, for example, 2-phenylseleno-1-trichloromethylalkane **465** in moderate-to-good yields (43–88%). Subsequent treatment with base and oxidation of the phenylselenide complex **466** using hydrogen peroxide affords the α,β -unsaturated carboxylic acids **467** in good-to-excellent yields (60–91%, Scheme 59). Interestingly, the addition of phenyl trichloromethyl selenide to monosubstituted alkenes afforded a single adduct, although addition of the selenide to (*E*)- and (*Z*)-dec-5-ene returned a mixture of diastereomers (3.8:1 and 4.2:1, respectively). Therefore, the free-radical addition is highly regioselective but not particularly stereoselective <1997CC1759>.



Scheme 59

The condensation of *C,O,O*-tris(trimethylsilyl)ketene acetals, for example **468**, with aliphatic and aromatic aldehydes, in the presence of mercuric iodide yields at room temperature *syn*- and *anti*- β -trimethylsiloxy- α -trimethylsilylalkanoic acid silyl esters **469** and **470** in good yields (65–95%) and diastereoselectivities (67:33). Treating the diastereomeric mixture (**469** and **470**) with titanium tetrachloride and then quenching with water, returned a mixture of (*E*)- and (*Z*)- α,β -unsaturated carboxylic acids **471** and **472** with an (*E*)/(*Z*) ratio of 67:33, which matches that of the starting material β -siloxytrimethylsilyl esters (Scheme 60) <1998JOC8785, 2001JOC5054>.



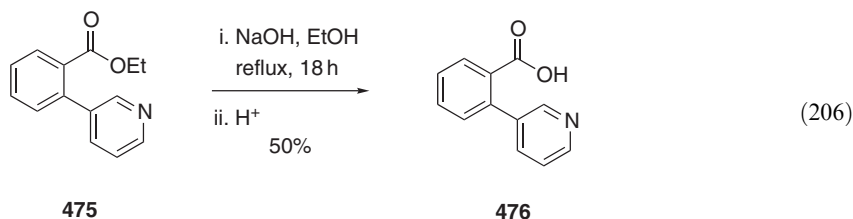
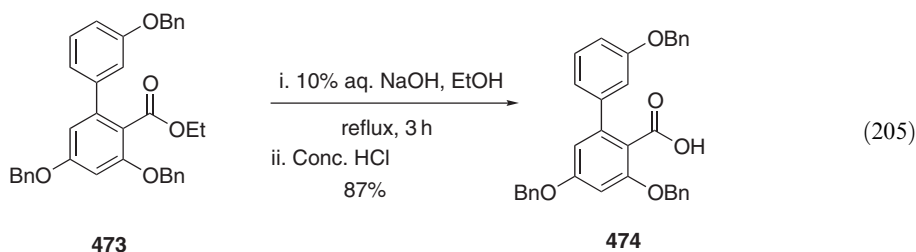
Scheme 60

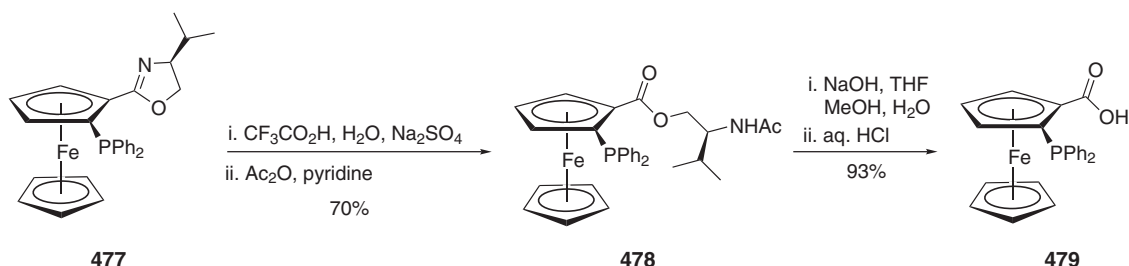
5.02.4 HOMO- AND HETEROAROMATIC ACIDS

A number of reviews have been published on the synthesis of aromatic and heteroaromatic carboxylic acids <B-1954MI502-01, B-1964MI502-03, B-1976MI502-03, 1981MI502-04>.

5.02.4.1 By Hydrolysis Reactions

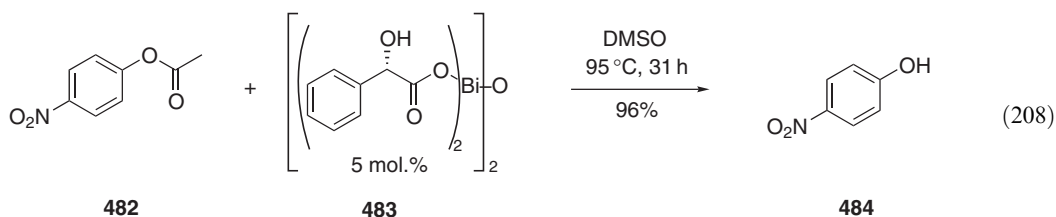
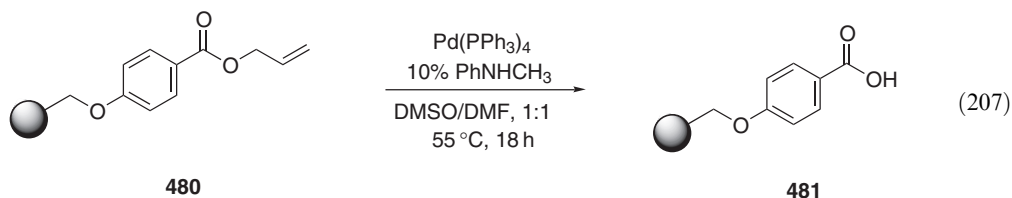
The hydrolysis of ester groups, appended to aromatic rings, to the corresponding carboxylic acids can be undertaken using a variety of basic or acidic reagents. Typical protocols utilising basic reagents for a variety of substrates are outlined. Heating at reflux an aqueous ethanolic solution of sodium hydroxide saponified the ethyl ester **473** affording the carboxylic acid **474** in high yield (Equation (205)) <2000JNP371, 2003BMC723>. In a similar procedure, utilizing neat ethanol as the solvent and sodium hydroxide as the base, hydrolysis of the ethyl ester **475** to the aryl carboxylic acid **476** was achieved (Equation (206)) <2003T4973>. The synthesis of optically active (S_p)-2-(diphenylphosphino)-ferrocenecarboxylic acid **479** (Scheme 61) has been reported by Stepnicka, who undertook the hydrolytic cleavage of (*S*)-valine-derived dihydrooxazole **477** and then submitted the resulting ester **478** to saponification using 1 M sodium hydroxide <2002NJC567>.



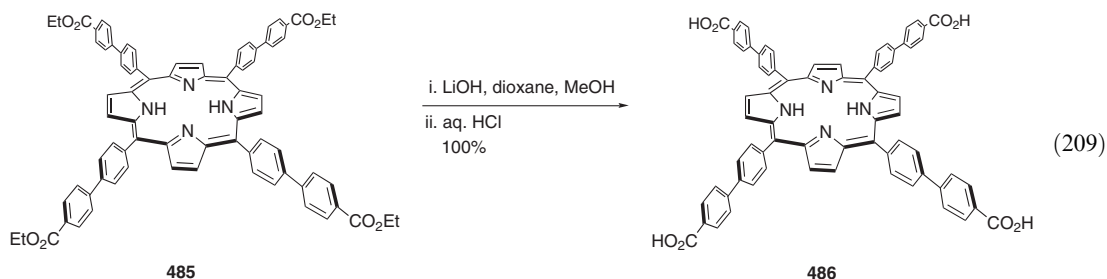


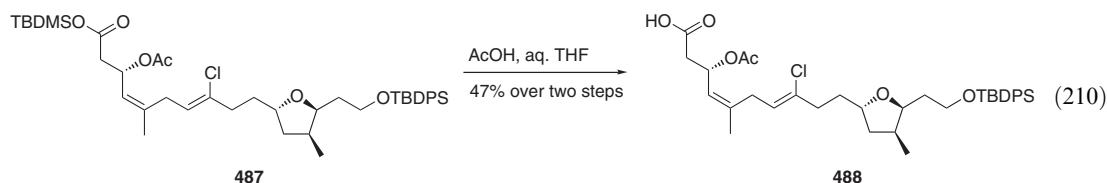
Scheme 61

The synthesis of a solid-supported (Wang resin) aryl carboxylic acid **481** was undertaken via a transition metal-mediated hydrolysis of allyl ester **480** (Equation (207)); the immobilized aryl carboxylic acid was incorporated into an ene-yne methathesis reaction for the synthesis of isoindoles [<1998TL6815>](#). The selective hydrolysis of aryl esters, for example **482**, affording aryl carboxylic acid **484** has been accomplished using catalytic quantities of bismuth(III) mandelate **483** or bismuth(III) salicylate (5 mol.%) in DMSO at 80 °C (Equation (208)). Catalyst **483** was readily synthesized from bismuth(III) oxide and (*L*)-mandelic acid by refluxing in water. Conducting the hydrolysis reaction under an atmosphere of oxygen (1 atm) increased the yields from 80% to 96%, whereas adding water dramatically decreased the catalytic activity. The reaction system shows high selectivity for aryl ester hydrolysis only, with alkyl esters unaffected; furthermore, electron-deficient aromatic esters were more reactive to hydrolysis than electron-rich ones [<1997TL2981>](#).



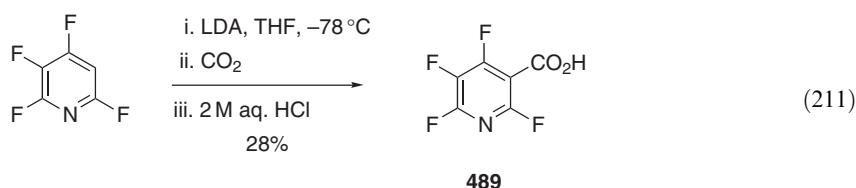
Hamilton and co-workers have described the synthesis of tetra-carboxylic acid-appended porphyrin **486** via hydrolysis of **485**. Hamilton employed acid **486** for subsequent appendage of a wide variety of amino acids and the resulting entities were used to target cell surface receptors (Equation (209)) [<2003BMCL2651>](#). Selective hydrolysis of an acyl-appended *O*-TBDMS group on **487** in the presence of a TBDMS-protected primary alcohol (Equation (210)) has been achieved using acetic acid in aqueous THF, affording carboxylic acid **488** [<2003OL957>](#).



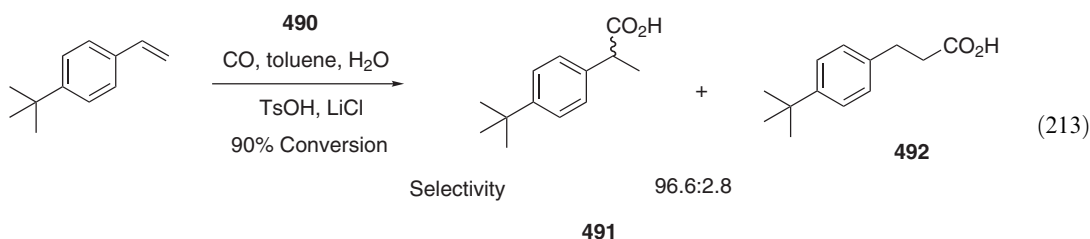
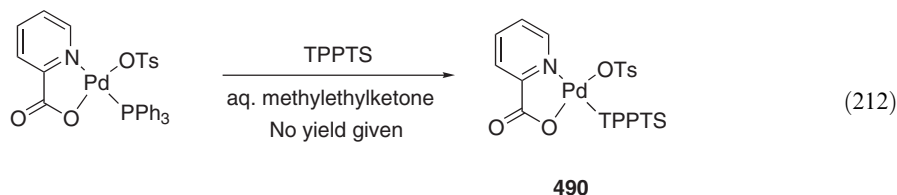


5.02.4.2 By Carbonation of Organometallic Reagents

A convenient method for the synthesis of aryl carboxylic acids proceeds via the corresponding organometallic reagent and carbon dioxide. However, it is interesting to note that the synthesis of fluoroarene carboxylic acid **489**, for example, tetrafluoronicotinic acid, via a carbonation reaction suffered from dramatic solvent effects, and on scale up (50 mmol) low yields (~10%), which were attributed to extensive polymerization (Equation (211)) <2000JFC(101)45>.

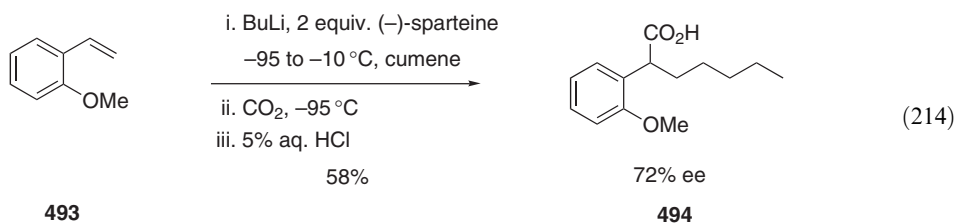


The novel water-soluble palladium(II) complex, comprising pyridine-2-carboxylate and tris(*m*-sulfophenyl)phosphine trisodium salt **490** (Equation (212)), yields a highly active catalyst (550 TOF/h⁻¹) for the selective carbonylation of vinyl aromatics under biphasic conditions affording racemic 2-arylpropanoic acids **491**. Varying amounts of the corresponding 3-arylpropanoic acids **492** were formed (Equation (213)) <2000CC1239>.



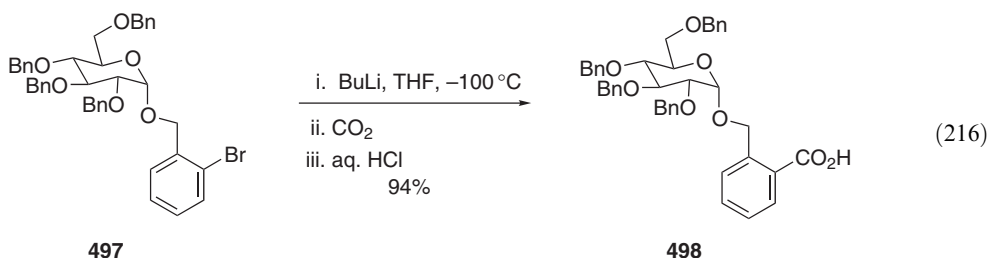
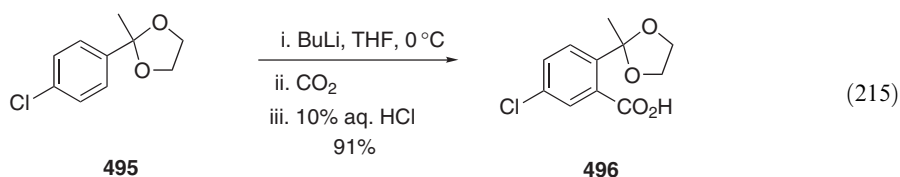
Radiolabeled ¹¹C-carboxylic acids are generally synthesized from the corresponding Grignard reagent and [¹¹C]-carbon dioxide. An alternative, mild and rapid synthetic procedure using an organohalide or triflate (most reactive) in the presence of [¹¹C]-carbon monoxide and tetrakis(triphenylphosphine)palladium(0) allows for the formation of a Pd-acyl complex, which was readily transformed into the corresponding [¹¹C]-carboxylic acid in the presence of a hydroxide source, for example, tetramethylammonium hydroxide. When aqueous sodium hydroxide or water are used no product is formed <2002JCS(P1)2256>.

The addition of BuⁿLi to styrene and its derivatives, allows the electrophilic trapping of the resulting benzyllithium species with a variety of reagents, for example, carbon dioxide, dimethyl disulfide, carbon disulfide and dimethyl carbamyl chloride. Conducting the reactions in the presence of (–)-sparteine affords chiral nonracemic reaction products with up to 30% ee, depending on the solvent employed, temperature, and electrophile used. With 2-substituted styrenes **493** the addition of BuⁿLi (cumene as solvent at –95 °C) followed by carboxylation (–95 °C) resulted in 2-arylheptanoic acids **494** with ee's up to 72% (Equation (214)) <1997TA665, 1996TL4209>.

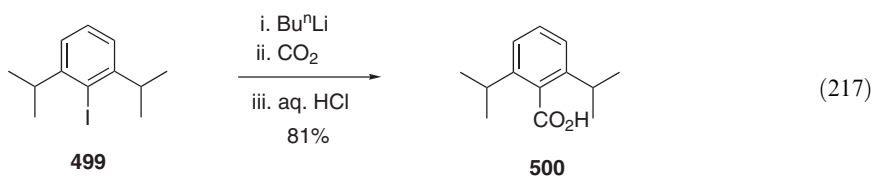


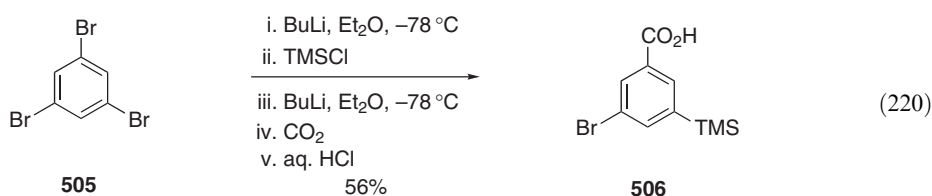
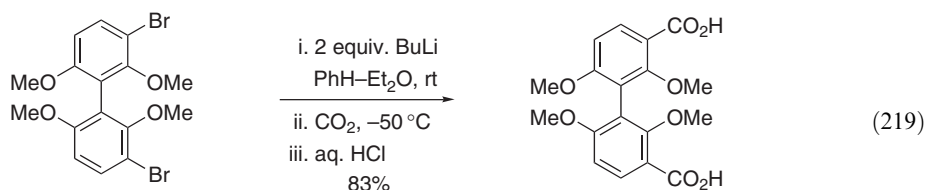
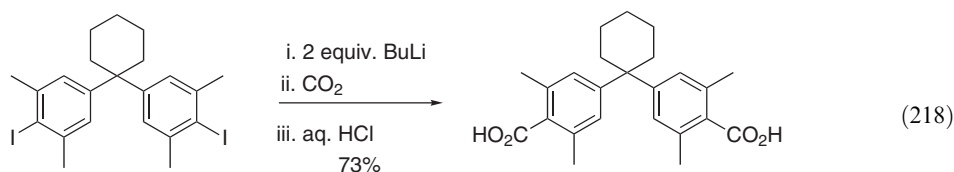
Aryl and allyl silanes are carboxylated with carbon dioxide with the aid of an aluminum-based Lewis acid, yielding aromatic and β,γ -unsaturated carboxylic acids in fair-to-good yields, respectively. Synthesis of the former was rationalized by invoking an aromatic electrophilic substitution reaction that incorporated a carbon dioxide molecule activated by a Lewis acid, while the latter, a nucleophilic addition of an *in situ* generated allylaluminum species to carbon dioxide <2003CL454>.

Ortho-lithiation of 2-(4-chlorophenyl)-2-methyl-1,3-dioxolane **495** using BuⁿLi in THF at 0 °C and subsequent quenching of the anion with a variety of electrophiles, for example carbon dioxide, returned the corresponding aryl carboxylic acid **496** (Equation (215)) in good to excellent yields (65–95%) <2003TL3211>. Metal–halogen exchange of the bromine on the aryl group within *O*-benzyl protected carbohydrate **497** using BuⁿLi at -100 °C afforded the expected organolithium species. Subsequent quenching of the anion with carbon dioxide returned, after work up, in excellent yield (94%), the corresponding *o*-carboxylic acid **498** (Equation (216)) <1999JOC1319>.

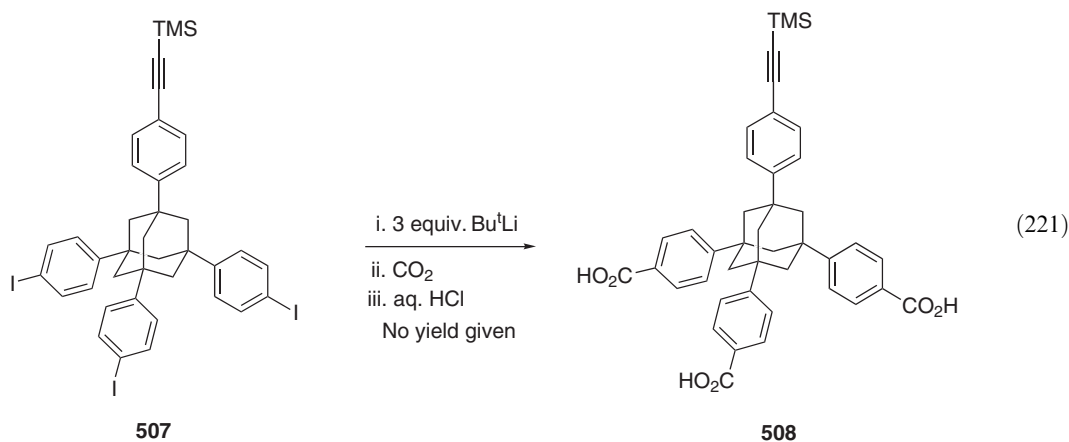


The transmetalation of an iodoarene **499** and diiodoarene **501** using BuⁿLi and then transformation into the corresponding carboxylic acid **500** and dicarboxylic acid **502** via quenching with carbon dioxide proceeded in high yields (Equations (217) and (218)) <2003CC1642>. The simultaneous metal–halide exchange of two bromine atoms contained within a racemic 3,3-dibromobiphenyl **503** has been undertaken, subsequent quenching of the anion was undertaken with a variety of electrophiles, including carbon dioxide, to afford **504** (Equation (219)) in moderate-to-good yields (41–83%) <2000TA4417>. The sequential transmetalation of two bromine groups on 1,3,5-tribromobenzene **505**, using BuⁿLi and the reaction of each organolithium species with, in the first instance trimethylsilyl chloride and subsequently carbon dioxide afforded 3-bromo-5-(trimethylsilyl)benzoic acid **506** in a 56% yield (Equation (220)) <2002JOC7761>.

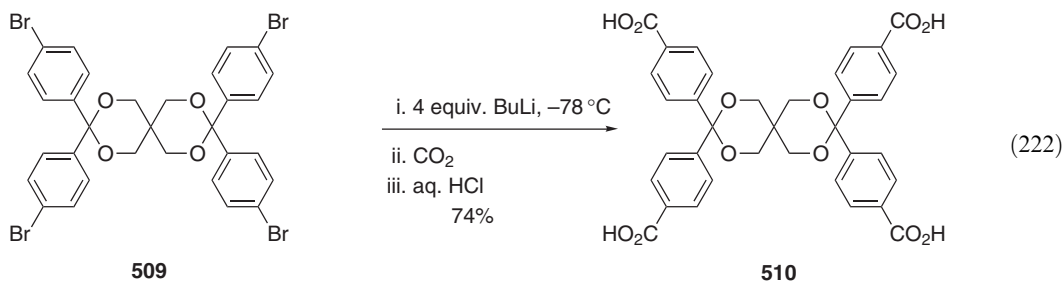




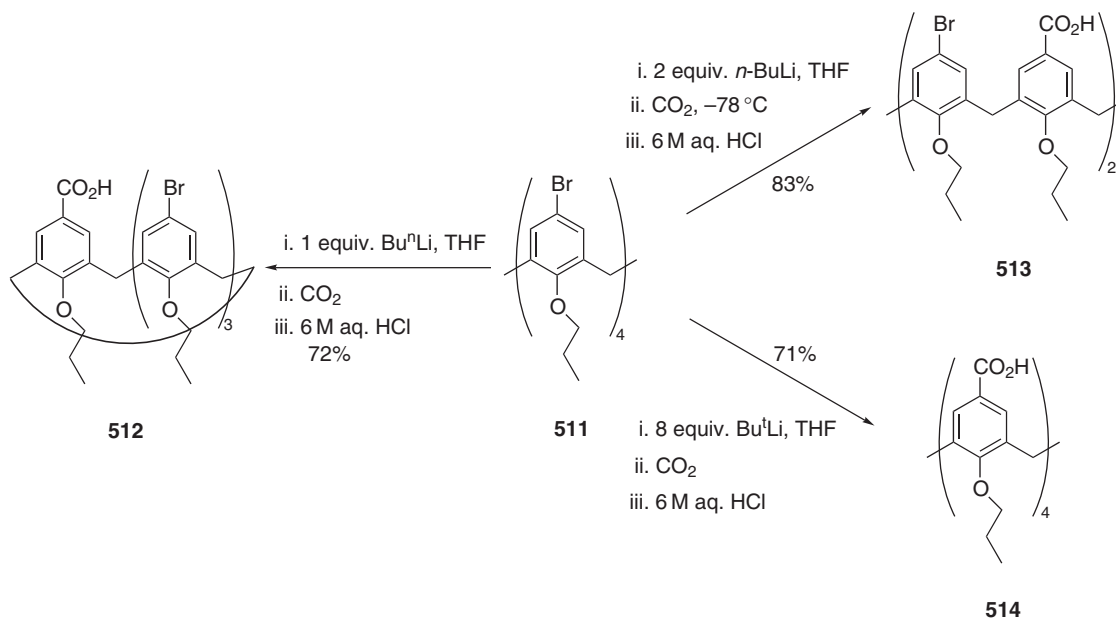
The transmetalation (Bu^tLi) of three iodoarene species attached to the adamantane skeleton **507** and their subsequent transformation into the corresponding tricarboxylic acid **508** has been reported (Equation (221)) <2000TL7419, 2002JA7801>.



Molecular tectonics uses structurally defined molecules for the synthesis of ordered structures that assemble in a defined manner. The synthesis of 2,4,8,10-tetraazaspiro[5.5]undecanes tetra-substituted at the 3 and 9 positions has been reported, and these molecules have shown promise as molecular tectonic building blocks. The tetralithiation of tetrabromide **509** using BuⁿLi at -78 °C afforded, after the addition of carbon dioxide, a 74% yield of the corresponding tetracarboxylic acid **510** (Equation (222)) <2003JOC240>.

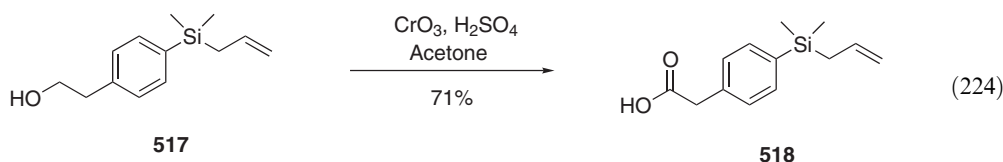
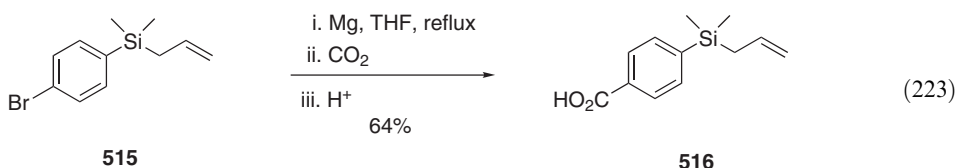


Larsen and co-workers have described a number of protocols for undertaking selective metal–halogen exchange reactions on bromine-substituted calix[4]arene **511** using either Bu^nLi or Bu^tLi in THF. Quenching the anion with a variety of anions, including carbon dioxide, returned the expected carboxylic acid reaction products, for example **512–514**, in good yields (Scheme 62) <1996JOC6651>.



Scheme 62

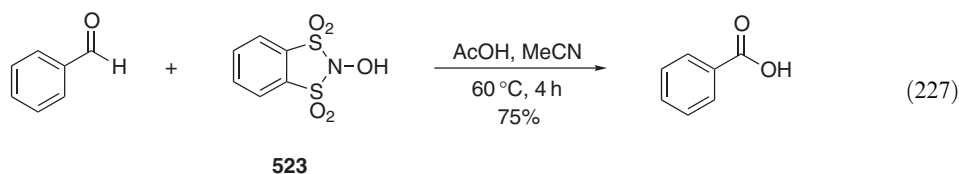
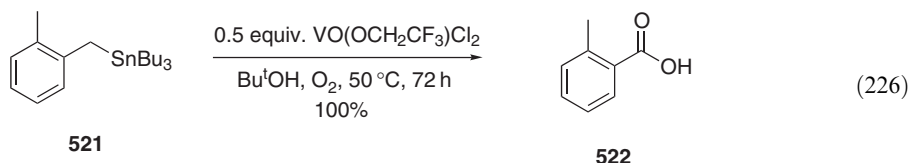
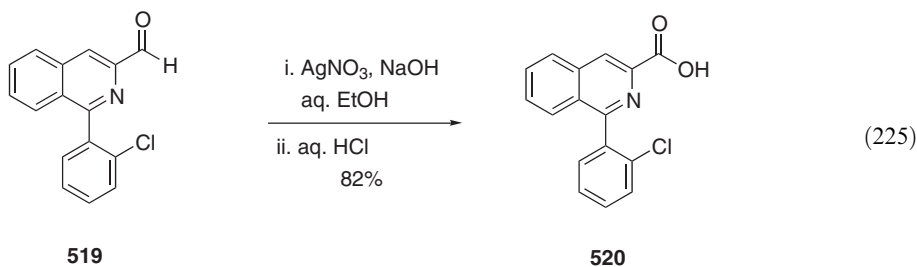
The synthesis of novel aryl silanes for use in the development of traceless linkers in combinatorial chemistry has been reported. The core starting material, 4-allyldimethylsilyl-1-bromobenzene **515**, efficiently underwent a metal–halogen exchange reaction using either Bu^tLi or magnesium. Subsequent quenching of the Grignard reagent with, for example, carbon dioxide, afforded aryl carboxylic acid **516** in a 64% yield (Equation (223)). Likewise, reacting the organolithium species with ethylene oxide and subsequently oxidizing the primary alcohol **517** (Jones's reagent) returned the homologated carboxylic acid **518** (Equation (224)) in good yield <2001T5339>.



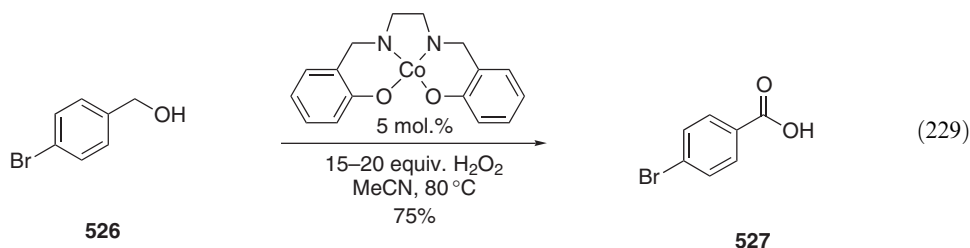
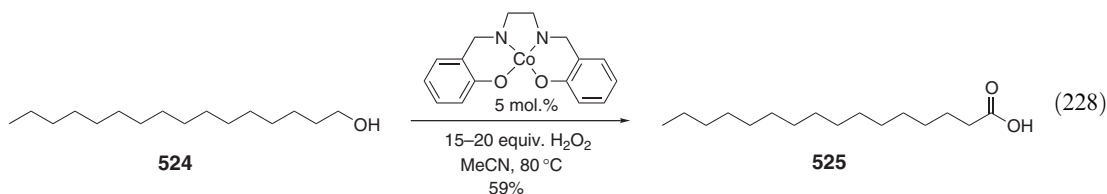
5.02.4.3 By Oxidation Reactions

The oxidation of aryl aldehyde **519** to the corresponding carboxylic acid **520** has been achieved in a good yield (82%) using silver nitrate in an ethanolic sodium hydroxide solution (Equation (225)), presumably forming, *in situ*, the active oxidant silver oxide <2002JCS(P1)529>. Benzylstannanes, for example **521**, are oxidized, under an atmosphere of oxygen, by an oxovanadium(V)

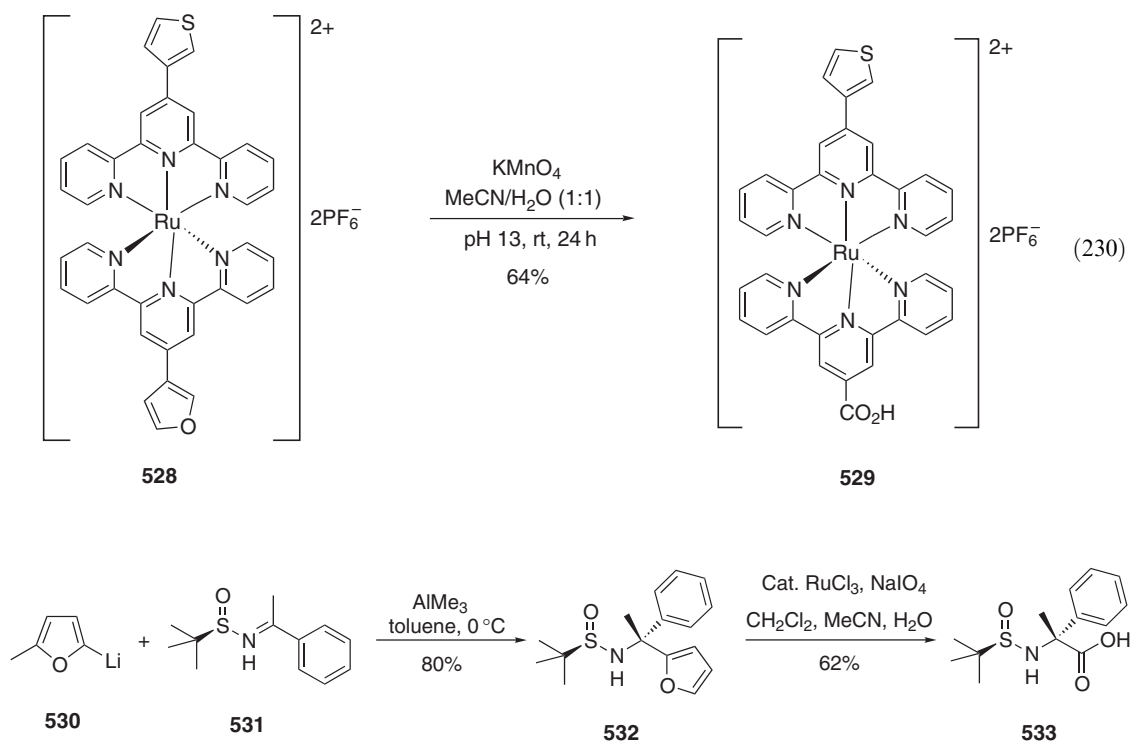
complex affording aromatic carboxylic acids **522** in poor-to-excellent yields (Equation (226)). The aryl carboxylic acids are produced from the corresponding aldehydes by further oxidation under the oxovanadium-O₂ conditions employed. The reaction is considered to proceed via an electron-transfer process <2001TL5073>. Recent years have seen an upsurge of interest in the development of metal-free, substrate-selective oxidizing agents. An example of a metal-free oxidizing agent is *N*-hydroxy-*o*-benzenedisulfonamide **523** (NHOBS) a useful and relatively selective oxidizing agent for transforming aryl aldehydes to the corresponding carboxylic acids (Equation (227)) in reasonable yields (22–75%) <1996JOC8762>. Although NHOBS was first synthesized in 1926, an improved protocol has been published <1981JOC2691>.



The oxidation of aliphatic **524** and aromatic alcohols **526** to the corresponding carboxylic acids **525** and **527** (Equations (228) and (229), respectively) has been carried out under mild reaction conditions using 30% hydrogen peroxide and catalytic amounts (5 mol.%) of a cobalt(II) salen complex in good yields (55–76%). It is noteworthy that no oxidation of the aromatic ring was observed, but attempted oxidation of cinnamyl alcohol afforded benzoic acid due to C=C bond cleavage <2003TL6033>.



The furan heterocycle can be used as a surrogate carboxylic acid, releasing the carboxylic acid when acted on by a suitable oxidising agent. Oxidation of the furan ring on **528** was achieved in good yields via a one-pot procedure using potassium permanganate in aqueous acetonitrile at pH 13, the corresponding carboxylic acid **529** being returned in a good yield (Equation (230)) <2003TL1767>. α,α -Disubstituted amino acids are key components in bioactive peptides, potential therapeutic agents, and natural products <1998TA3517>. Borg and co-workers have utilized the furan heterocycle as a surrogate carboxylic acid for the synthesis of optically enriched α,α -disubstituted amino acids. 5-Methylfuryllithium **530** was reacted with a variety of chiral non-racemic sulfinylketimines **531** in the presence of trimethylaluminum affording sulfonamides **532** in 75–97% yields and diastereoselectivities ranging from 75:25 to 99:1. Subsequent furan oxidation on, for example **532**, using a catalytic amount of ruthenium trichloride (1 mol.%)/sodium periodate (15 equiv.) afforded the *t*-butanesulfonyl protected α,α -disubstituted amino acids **533** in 62–69% yield (Scheme 63). Removal of the *t*-butanesulfonyl group was undertaken using triflic acid <2001TL1433>.




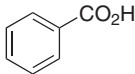
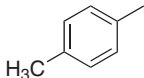
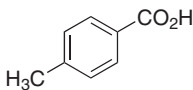
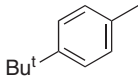
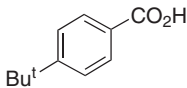
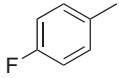
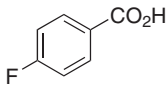
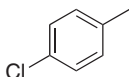
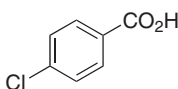
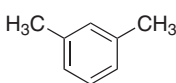
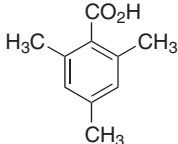
Scheme 63

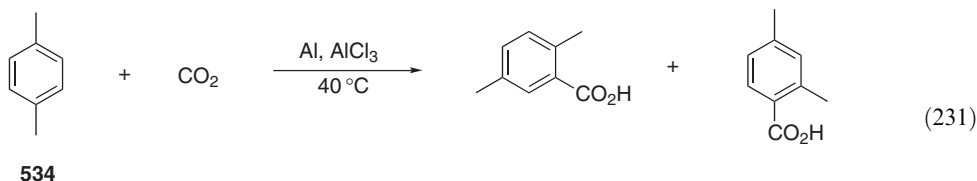
Magnesium monoperoxyphthalate is an effective reagent for the conversion of aryl aldehydes into the corresponding aryl carboxylic acids under mild reaction conditions and in good yields. Changing the oxidant to urea-hydrogen peroxide was shown to be an effective oxidizing agent for transforming isomeric methoxybenzaldehydes to their corresponding aryl carboxylic acids <2001TL163>.

5.02.4.4 By Miscellaneous Reactions

Aromatic carboxylic acids (Table 10) are obtained in good-to-excellent yields (46–92%) by the carbonylation of aromatic species **534** with carbon dioxide in the presence of stoichiometric amounts of aluminum chloride and aluminum. Although the reaction takes place using aluminum chloride on its own, the yields were higher when the reaction was conducted with metal additives (Equation (231)) <2002JA11379>.

Table 10 Carboxylation of benzene and substituted aromatics with CO₂/AlCl₃/Al

<i>Aromatic</i>	<i>Temperature (°C)</i>	<i>Product</i>	<i>Yield (%)</i>
	70		88
	60		69
	40		46
	40		47
	60		45
	40		92



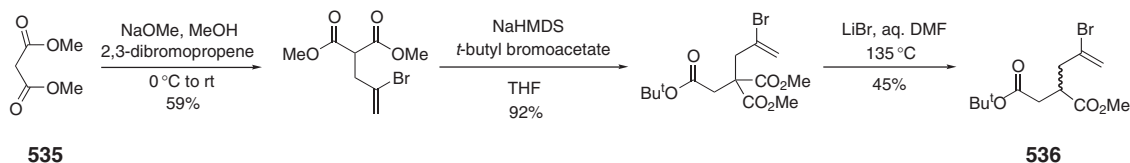
See Table 10

5.02.5 CARBOXYLIC ACIDS VIA BIOTRANSFORMATIONS

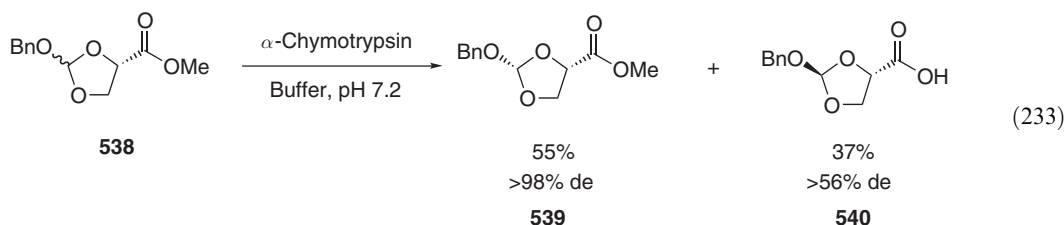
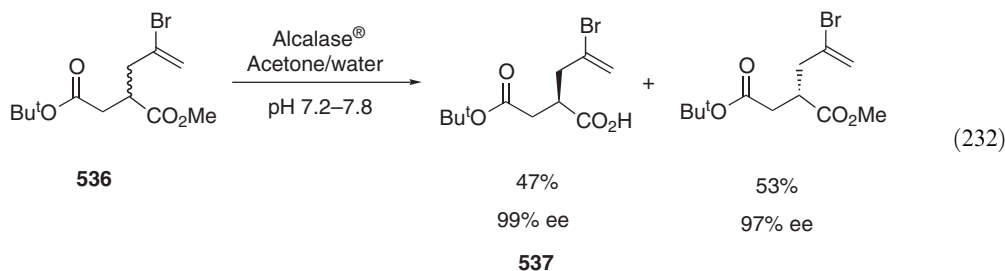
There have been tremendous developments in the use of enzymes in synthetic chemistry since the early 1990s, and as a consequence a large body of original research has been committed to books, reviews, and databases. A number of reviews have been published concerned with biocatalyzed deracemisations <1997S1>, use of lipases <1998AG(E)1609>, utilization of enzymes for the synthesis of amino acids and peptides <1997COC121>, and the asymmetric decarboxylation of α -aryl- α -methylmalonic acids <1997BCJ2895>. Roberts has published several general reviews on aspects of the literature concerned with preparative biotransformations <1998JCS(P1)157, 1999JCS(P1)1, 2000JCS(P1)611, 2001JCS(P1)1475>. An excellent overview on enantioselective synthesis using enzymes has been published <1996T3769>. A number of databases have also been established with many tens of thousands of biotransformation entries compiled.

The hydrolysis of esters using enzymes is relatively routine with many different varieties of enzyme available for this transformation. The use of enzymes for the hydrolytic resolution of racemic esters affording chiral nonracemic carboxylic acids is well established. Bailey and co-workers have utilized Alcalase, an enzyme preparation derived from *Subtilisin Carlsberg*, for

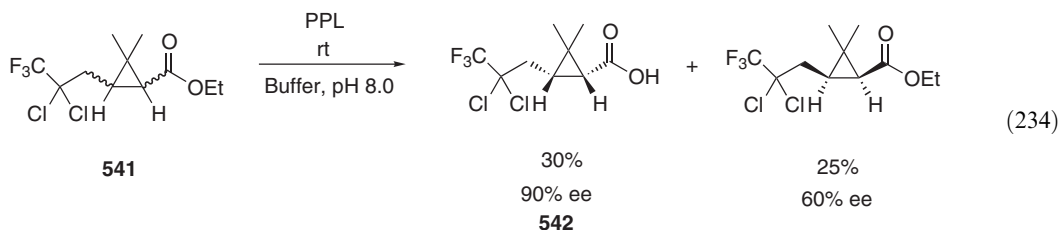
the enantio- and regioselective monohydrolysis of racemic 2-substituted succinate esters, affording the corresponding monoesters in modest to excellent enantioselectivity. The substituted succinate ester starting materials, for example **535**, were readily prepared in three steps, in multigram quantities and modest overall yields (e.g., 24% for the methyl ester), using dimethyl malonate **535** (Scheme 64). Performing the enantioselective hydrolysis reactions using ester **536** and Alcalase afforded the corresponding carboxylic acid **537** in good yield and excellent enantioselectivity (Equation (232)) <1999TA3285>. The separation of *cis*- and *trans*-dioxolane nucleosides, **539** and **540**, respectively, via ester hydrolysis of **538**, using the inexpensive and commercially available proteases, α -chymotrypsin (Equation (233)) and bovine pancreatic protease has been successfully undertaken <1999JOC9019>. The use of mixed anhydrides and lipase catalyzed resolutions of racemic carboxylic acids has been reported <1996TL4397>.

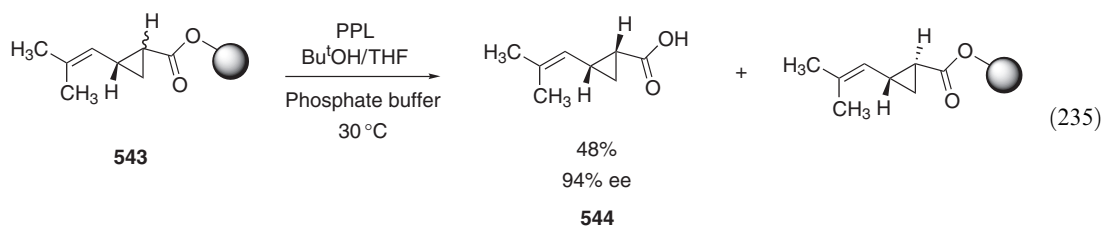


Scheme 64

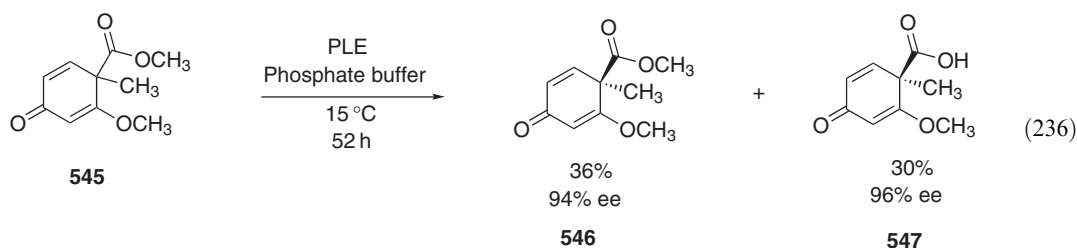


The enzymic hydrolytic resolution of a series of racemic *cis*-2,2-dimethylcyclopropane esters **541** using a variety of lipases has been reported. Porcine pancreas lipase afforded the corresponding chiral nonracemic cyclopropyl carboxylic acid **542** in a modest 30% yield and 90% enantioselectivity (Equation (234)) <1997TA2291>. The kinetic resolution of racemic 2-substituted cyclopropane carboxylic acids **543** anchored onto either Merrifield, Wang, or Tentagel resins is viable. Coupling the cyclopropane acids onto the resins was straightforward, and subsequent suspension of the beads in a THF/*t*-butanol solvent system allowed the kinetic resolution to be undertaken using porcine pancreas lipase. The corresponding (*R*)-carboxylic acid **544** was returned in a 48% yield and 94% ee when Merrifield resin was used as the immobilizing support (Equation (235)) <1999TL5905>.

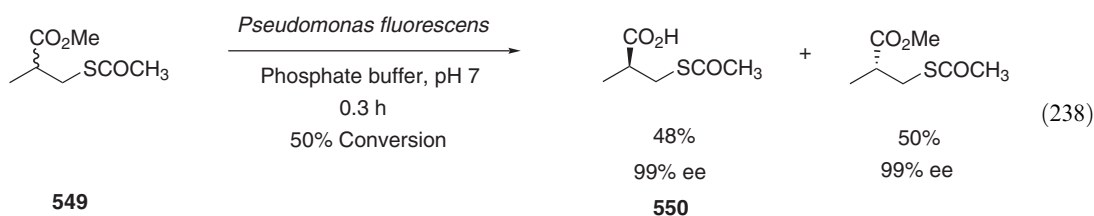
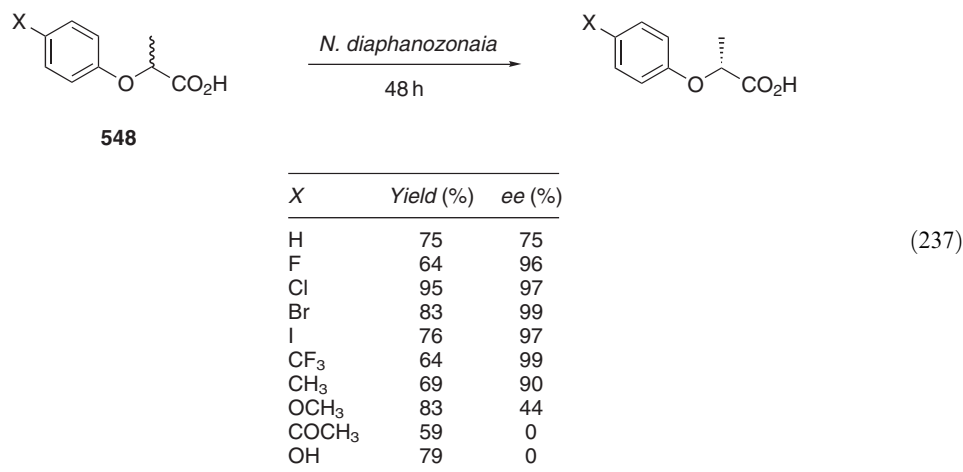




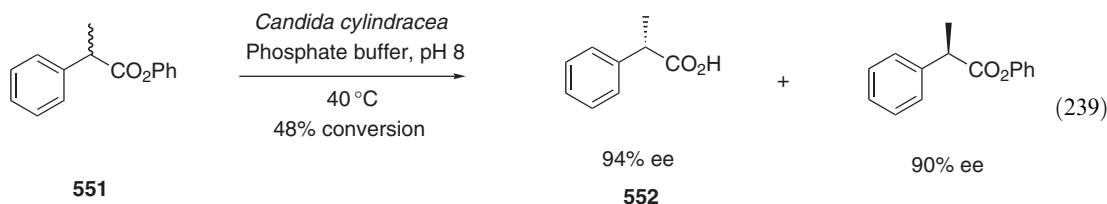
The enantioselective hydrolysis of racemic methyl 2-methoxy-1-methyl-2,5-cyclohexadiene-1-carboxylate and methyl 2-methoxy-1-methyl-2,5-cyclohexadiene-4-one-1-carboxylate **545** has been undertaken using the hydrolase enzymes PLE (Equation (236)) and HLE affording the corresponding enantiomerically enriched ester **546** and carboxylic acid **547** in 92–96% ee <1999TA1129>.



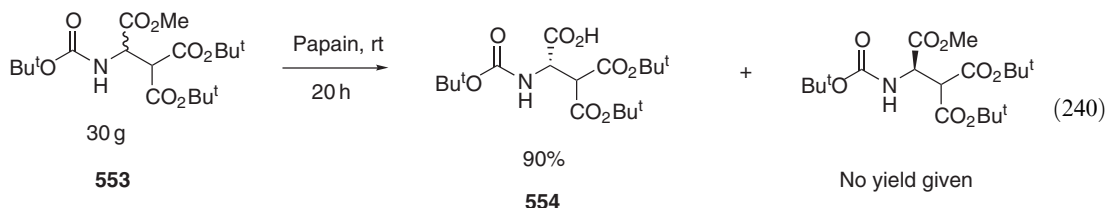
Using *Nocardia diaphanozonaria* Kato and co-workers have demonstrated the deracemization of *para*-substituted 2-phenoxypropanoic acids, for example **548**, to proceed in good yield and reasonable to excellent ee values (Equation (237)). Attempted deracemization of 2-arylpropanoic acids, α -substituted phenylacetic acids and 2-(chlorophenoxy)propanoic acids with *Nocardia diaphanozonaria* did not proceed as well, returning products of low enantioselectivity <2003JOC7234, 2002OL371>. A study by Kumar and co-workers established that the esterase, *Pseudomonas fluorescens* MTCC B10015 was able to performed an enantioselective hydrolysis of methyl 3-acetylsulfanyl-2-methylpropanoate **549**, affording the corresponding (*S*)-3-acetylsulfanyl-2-methylpropanoic acid **550** in an excellent 99% ee and 48% yield (Equation (238)) <1999OL207>.



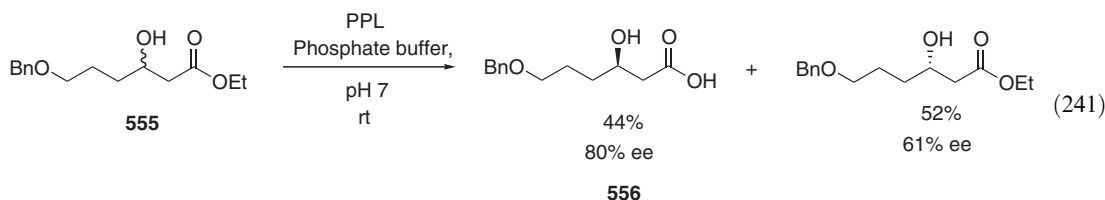
Williams and co-workers have reported a study using *Candida cylindracea* lipase (CCL) for the kinetic resolution of racemic 2-phenylpropanoic methyl and aryl esters, for example **551** (Equation (239)), affording the corresponding carboxylic acids **552** in excellent ee <1999TL749>.



The use of papain for the rapid deracemization of racemic α -amino acid, for example **553**, affording the corresponding chiral nonracemic amino acid **554** in an excellent ee (99.5% by HPLC) on a 30 g scale has been reported (Equation (240)) <1996TL417>. Similarly, the synthesis of chiral nonracemic methyl 2-aryloxypropionic acids has been undertaken using a two-phase aqueous organic solvent system incorporating *Candida rugosa* lipase. The ee values (36–96%) of the desired α -aryloxypropionic acids were dependent on the solvent system and the starting material employed <1999TA4599>.

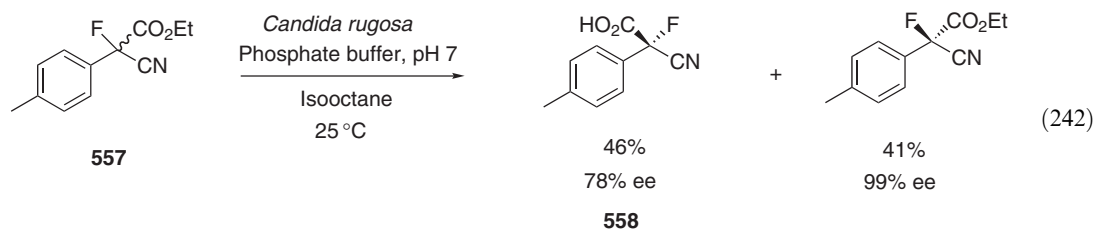


During the total synthesis of the piperidinol alkaloid (–)-(2*R*),3(*R*),6(*S*)-cassine, Oetting *et al.* established the viability of undertaking a lipase-catalyzed kinetic resolution on racemic β -hydroxy ester **555**. Using porcine pancreas lipase (PPL) the corresponding (3*R*)-hydroxycarboxylic acid **556** was returned in a 44% yield and 80% ee (Equation (241)). Subsequent treatment with (1*R*,2*S*)-ephedrine yielded the corresponding salt, which, when crystallized and liberated with mineral acid, afforded the enantiomerically pure (3*R*)-hydroxycarboxylic acid <1997TA477>.

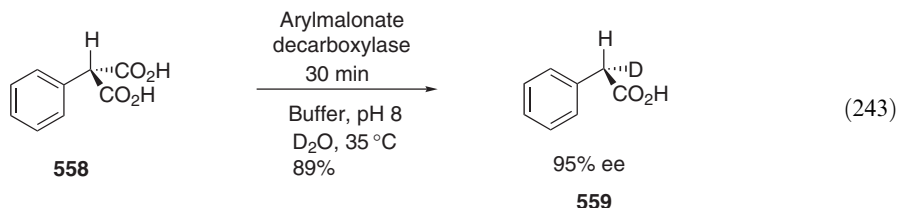


The hydrolysis of benzene-1,2-diacetic ester chromium tricarbonyl complexes with the lipase PLE, furnishes the corresponding planar chiral mono-carboxylic acid tricarbonyl complexes in 80–90% ee <1996TA95>.

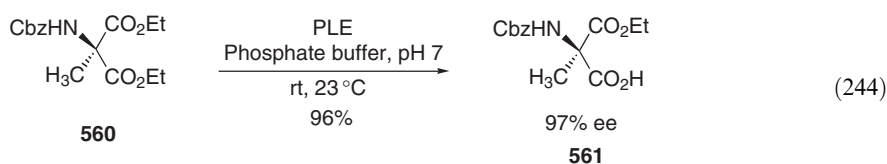
The synthesis of the chiral nonracemic derivatizing agent, α -cyano- α -fluoro-*p*-tolylacetic acid **558** has been undertaken, using a kinetic resolution procedure incorporating the enzyme *Candida rugosa* and the corresponding ethyl ester of α -fluorocarboxylic acid **557** (Equation (242)). The kinetic resolution procedure furnished the carboxylic acid in a 78% ee, and subsequent optical enrichment using (*R*)- α -phenethylamine and recrystallization and subsequent release with 1 M HCl afforded the desired, optically pure α -cyano- α -fluoro-*p*-tolylacetic acid <1998CC365>.



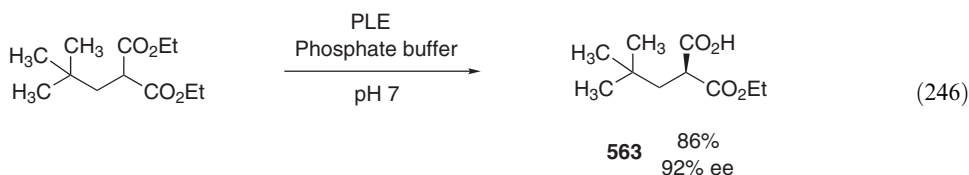
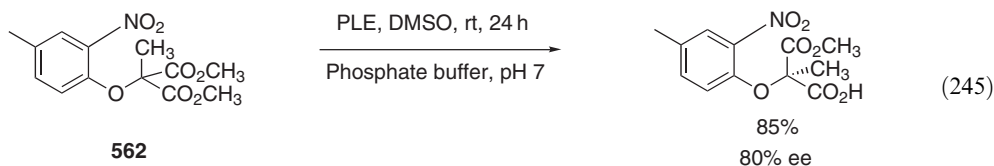
Arylmalonate decarboxylase (AMDase) has been used for the synthesis of optically enriched [α - ^2H]-phenylacetic acid **559**. Treating [α - ^2H]-phenylmalonic acid **558** with arylmalonate decarboxylase, catalyzed the enantioselective decarboxylation of the malonic acid yielding [α - ^2H]-phenylacetic acid in a 95% ee (Equation (243)) <2000CC1519>.



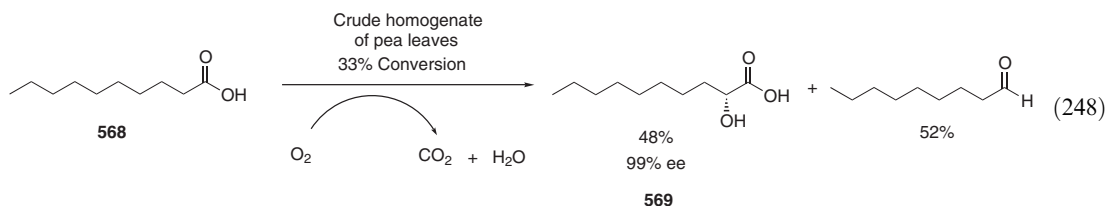
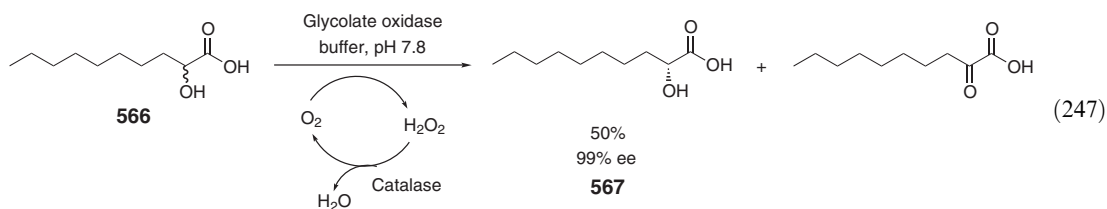
Pig liver esterase or rabbit liver esterase have been used for the enantioselective hydrolysis of prochiral *N*-Cbz protected diallyl, dibenzyl and diethyl α -aminomalonate **560**, affording the corresponding chiral nonracemic monocarboxylic acid **561** in 90–97% ee (Equation (244)) <1998TL5571>.



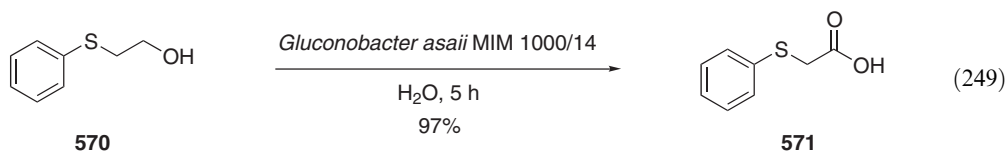
Pig liver esterase (PLE) has been used for the enantioselective hydrolysis of dimethyl and diethyl 2-methyl-2-(*o*-nitrophenoxy)malonate **562** to the corresponding (*R*)-monomethyl or (*R*)-monoethyl 2-methyl-2-(*o*-nitrophenoxy)malonic acids (Equation (245)) in moderate to good enantioselectivities (61–81% ee) <1997TA425>. In a similar protocol, PLE has been used for the enantioselective hydrolysis of *t*-alkylmalonic dimethyl and diethyl esters. The desired malonic monocarboxylic acid **563** were returned in high ee's and yields (Equation (246)) <1997TA1821>.



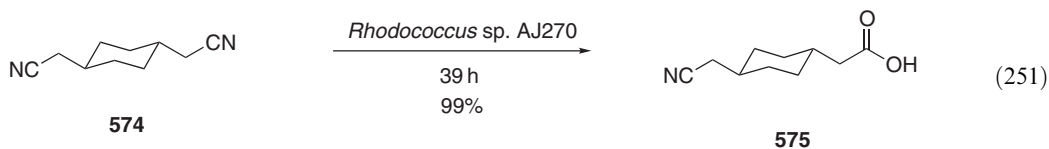
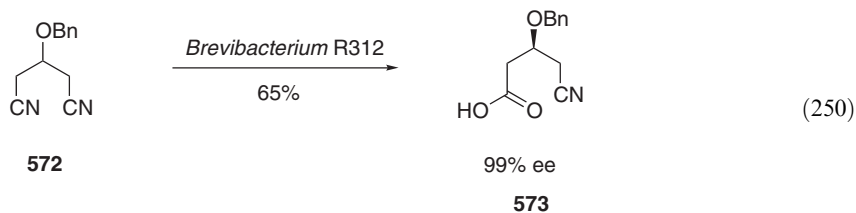
Chiral nonracemic α -hydroxy carboxylic acids are important building blocks in synthetic chemistry. Chadha and co-workers have reported that *Candida parapsilosis* performs a deracemization of ethyl-2-hydroxy-4-phenylbutanoic acid returning the corresponding (*S*)-2-hydroxy-4-phenylbutanoic acid in an excellent 99% ee and 85–90% yield. Extending the versatility of the reaction, racemic mandelic acid methyl and ethyl esters **564** were also deracemized, yielding the corresponding (*S*)-carboxylic acid **565** in excellent ee (99%) and yield <2002TA1461>. Using glycolate oxidase (EC 1.1.3.15) derived from spinach and molecular oxygen, Adam and co-workers have demonstrated that saturated **566** and unsaturated aliphatic derivatives of racemic 2-hydroxycarboxylic acids are enantioselectively oxidized to the corresponding 2-oxocarboxylic acids **567**. Thus, the glycolate oxidase-catalyzed kinetic resolution provides a convenient biocatalytic method for the preparation of enantiomerically pure (*R*)-2-hydroxy carboxylic acids (Equation (247)) <1997JOC7841>. The enantioselective α -oxidation of long chain (C-7 to C-16) carboxylic acids **568** using the crude homogenate of pea leaves and oxygen, has been shown by Adam and co-workers to proceed in reasonable conversion (10–86%), but excellent >99% enantioselectivity affording **569** (Equation (248)). Attempted α -oxidation of aliphatic acids with less than eight carbon atoms afforded very low conversions, typically <10% <1996TA2287>.



The oxidation of primary alcohols, for example **570**, to the corresponding carboxylic acids **571** (Equation (249)) has been undertaken using one of two strains of acetic acid bacteria, *Acetobacter* sp. ALEG MIM or *Gluconobacter asaii* MIM. Undertaking the oxidation reactions in water yielded the corresponding carboxylic acids; of the two bacteria *Acetobacter* sp. ALEG generally afforded higher yields <2001TL513>.

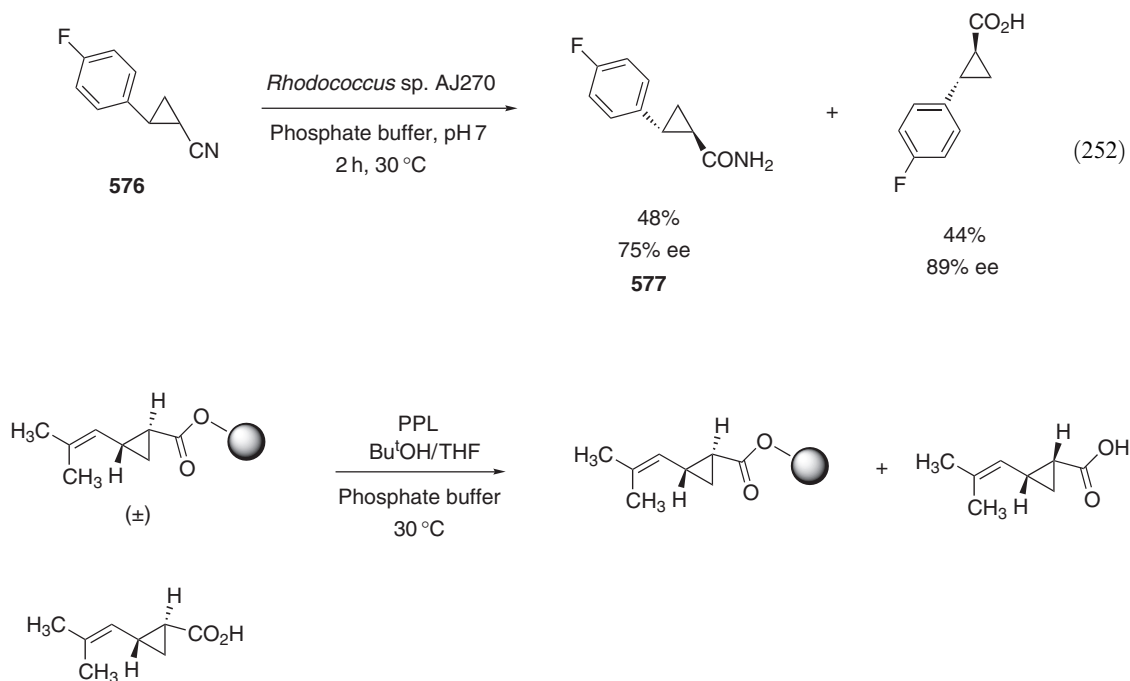


The enzyme-catalyzed hydrolysis of nitriles to amides and/or carboxylic acids has recently emerged as a synthetically useful transformation. By employing whole-cell systems that contain the required nitrile hydrolase and amidase enzymes it is possible to catalyze the hydrolysis of a wide range of substrates, under mild reaction conditions. Turner and co-workers utilized a whole-cell preparation of *Brevibacterium* R312 as a convenient source of nitrile hydratase enzyme. Using this enzyme, the enantioselective hydrolysis of multigram quantities of 3-(benzyloxy)glutaronitrile **572** yielded the desired 3-(*S*)-cyano carboxylic acid **573** in good yield (65%) and an 88% ee (Equation (250)) <1996TL6001>. The chemical hydrolysis of nitriles usually requires forceful reaction conditions. Using a whole-cell *Rhodococcus* sp. AJ270, Meth-Cohn *et al.* were able to hydrolyze a number of dinitriles, for example **574**, under mild reaction conditions affording the corresponding monocarboxylic acids **575** with excellent regioselectivity (Equation (251)) <1997JCS(P1)3197>.



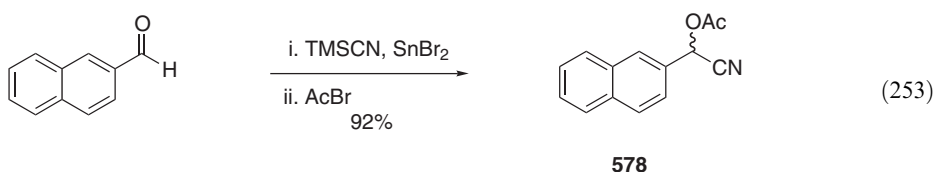
Wang and co-workers employed *Rhodococcus* sp. AJ270, as the whole-cell nitrile hydratase/amidase complex, for the enantioselective hydrolysis of both racemic *cis*- and *trans*-2-arylcyclopropanecarbonitriles **576**, affording the chiral nonracemic *cis*- or *trans*-2-arylcyclopropanecarboxylic acids **577** in excellent ee's (Equation (252)). The high enantioselectivity of the biotransformations results from the

combined effect of the nitrile hydratase and amidase enzyme components. The reaction rates and enantioselectivities observed for the hydrolysis of the nitriles were dependent on the substituents appended to the aryl ring and its substitution pattern (Scheme 65).



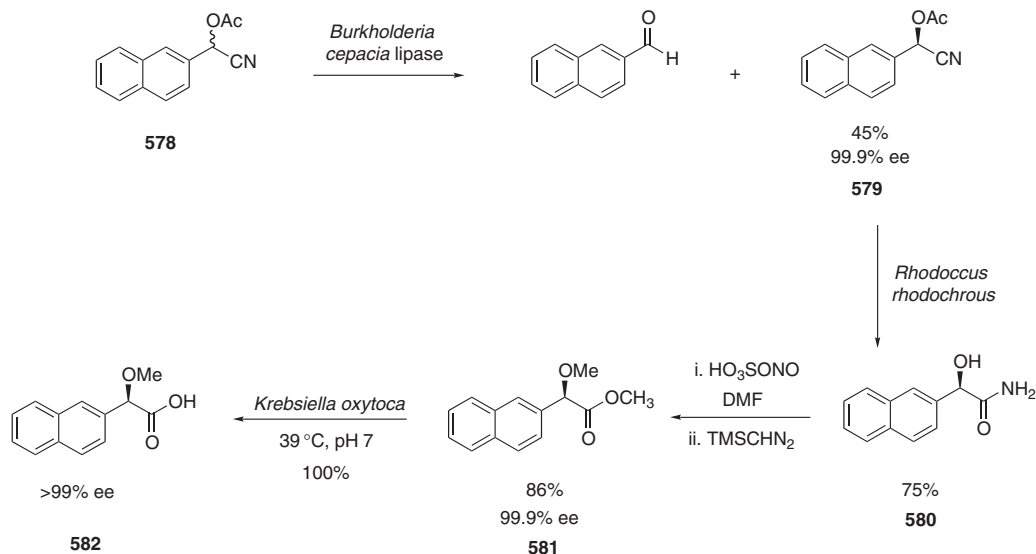
Scheme 65

Enantiomerically pure (*R*)-2-naphthylmethoxyacetic acid has been synthesized via a multistep chemo-enzymatic protocol. In a one-pot procedure, incorporating 2-naphthaldehyde, trimethylsilyl cyanide, tin(II) bromide and acetyl bromide, the synthesis of racemic α -acetoxy-2-naphthylacetonitrile **578** was achieved in a 92% yield (Equation (253)). Subjecting racemic nitrile **578** to the lipase *Burkholderia cepacia*, afforded the chiral non-racemic (*R*)- α -acetoxy-2-naphthylacetonitrile **579** in optically pure form (99.9%). Subjecting optically pure nitrile **579** to enzyme-mediated hydrolysis using *Rhodococcus rhodochrous* did not afford the desired carboxylic acid but the corresponding amide **580** in a 75% yield. Hydrolysis of the amide on **580** to the carboxylic acid was undertaken using nitrosylsulfuric acid which, concomitantly cleaved the acetyl group returning, after exhaustive methylation, the α -methoxy ester **581**. Hydrolysis of the methyl ester **581** to the desired chiral non-racemic carboxylic acid **582** was achieved using the esterase *Krebsiella oxytoca* (Scheme 66) <2002TA1059>.

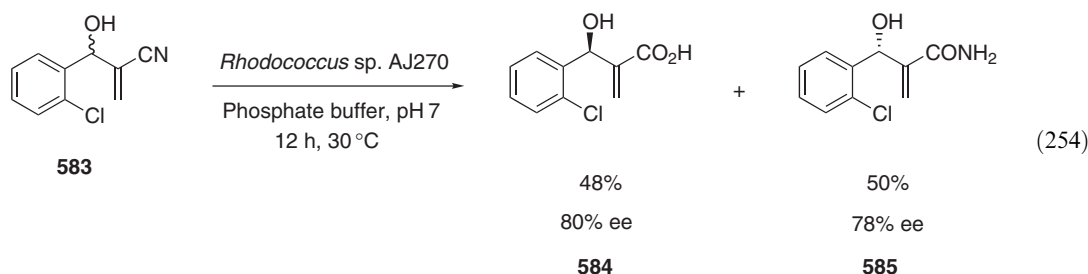


The Baylis–Hillman reaction between electron-deficient alkenes and aldehydes, catalyzed by DABCO, affords racemic α -methylene- β -hydroxycarbonyl or -nitrile adducts. Wang and co-workers have investigated the possibility of using *Rhodococcus* sp. AJ270 cells for the enantioselective hydrolysis of the nitrile function group to the corresponding chiral non-racemic β -hydroxycarboxylic acid. Subjecting a number of β -hydroxynitriles **583** to enzymatic hydrolysis afforded

the corresponding optically active β -hydroxycarboxylic acids **584** in reasonable yields (26–63%) and ee values (27–80%). Varying amounts of optically enriched β -hydroxy amides **585** were also formed (Equation (254)) <2003OBC535>.

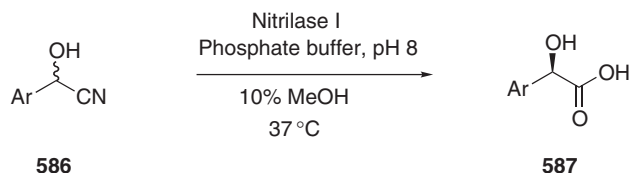


Scheme 66



The enzyme-catalyzed hydrolysis of nitriles has been shown to proceed through two distinct pathways. Nitrilase enzymes convert a nitrile directly into the corresponding carboxylic acid and ammonia, whereas nitrile hydratases catalyze hydration of the nitrile to the amide, which is then transformed into a carboxylic acid by the action of an amidase. In an attempt to expand on the number of nitrilases currently available DeSantis and co-workers created large genomic libraries by extracting DNA from environmental samples. Using these they identified and characterized over 200 new nitrilases, all of which possessed the conserved catalytic triad Glu-Lys-Cys characteristic of this class of enzyme. Cyanohydrins are well known to racemize under basic conditions through reversible loss of HCN; incorporating nitrilases DeSantis and co-workers investigated the possibility of synthesising chiral nonracemic α -hydroxy carboxylic acids from the corresponding cyanohydrins via a dynamic kinetic resolution.

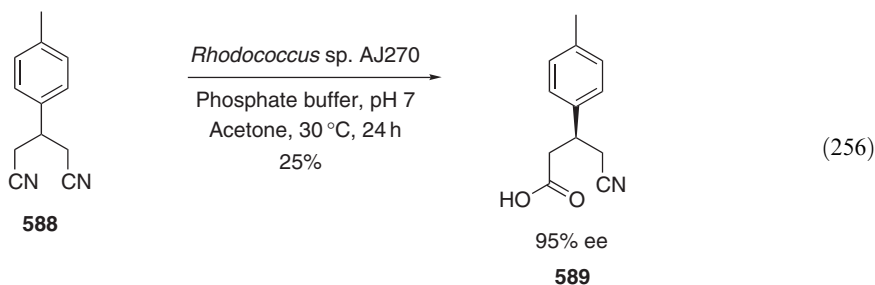
Preliminary results using mandelonitrile **586** revealed that one enzyme, nitrilase I, was particularly efficient affording mandelic acid **587** in high yield (86%) and ee (98%). A broad range of mandelic acid derivatives as well as aromatic and heteroaromatic α -hydroxy carboxylic acids can be synthesized in high enantioselectivities (Equation (255)) <2002JA9024>.



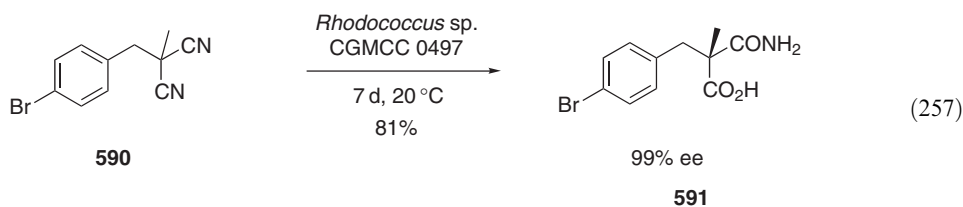
Ar	ee (%)
C ₆ H ₅	98
2-Cl-C ₆ H ₄	97
2-Br-C ₆ H ₄	96
2-CH ₃ -C ₆ H ₄	95
3-Cl-C ₆ H ₄	98
3-Br-C ₆ H ₄	99
4-F-C ₆ H ₄	99
1-naphthyl	95
2-naphthyl	98
3-pyridyl	97
3-thienyl	95

(255)

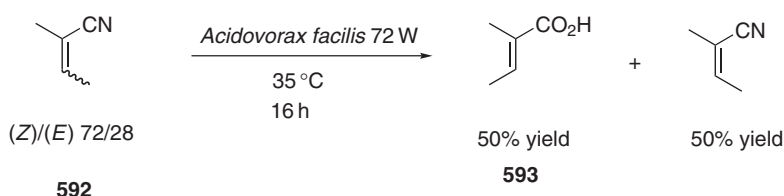
The enantioselective hydrolysis of 3-alkyl and 3-arylglutaronitriles, for example **588**, catalyzed by *Rhodococcus* sp. AJ270 returned the corresponding chiral nonracemic (*S*)-3-substituted 4-cyanobutanoic acids, for example, **589**. Augmenting the reaction medium with additives such as toluene, hexane, and in particular, acetone significantly increased the enantioselectivity of the desymmetrization process, yielding reaction products with ee values up to 95% (Equation (256)) <2001TA3367>. The application of *Rhodococcus* sp. CGMCC 0497 for the enantioselective hydrolysis of α,α -disubstituted malonitriles **590** afforded the corresponding (*R*)- α,α -disubstituted malonamic acids, for example **591**, in excellent ee values (97% to >99%) and poor-to-excellent yields (31–96%). Interestingly, lowering the temperature from 30 °C to 20 °C increased the enantiomeric excess of the returned malonamic acids (Equation (257)) <2003CC386>. The regioselective hydrolysis of ((*E*),(*Z*))-2-methyl-2-butenenitrile **592** using the nitrilase containing *Acidovorax facilis* 72W afforded only (*E*)-2-methyl-2-butenic acid **593** with no detectable hydrolysis of the (*Z*)-2-methyl-2-butenenitrile regioisomer (Scheme 67). The (*E*)-carboxylic acid was isolated as its ammonium salt in good yield <2004T577>.



(256)

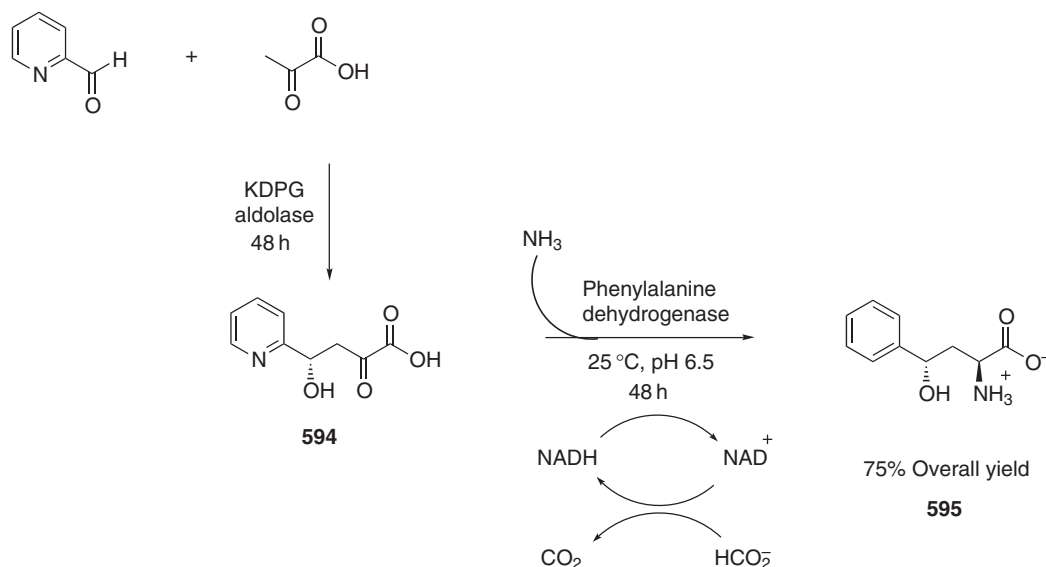


(257)



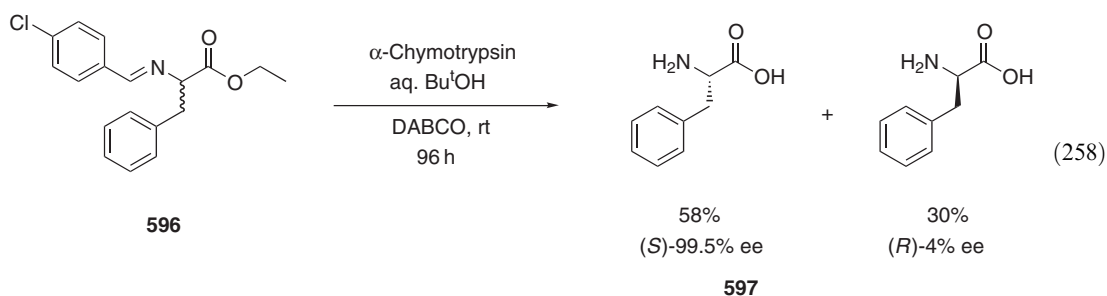
Scheme 67

Henderson and co-workers have demonstrated the feasibility of using KDPG aldolase in a pyruvate aldol condensation reaction affording 4-substituted 4-hydroxy-2-ketobutyrate products. Subsequent transformation of the α -ketocarboxylic acid **594** into the desired α -amino acid using phenylalanine dehydrogenase from *Bacillus sphaericus* SCRC-R79 afforded the *N*-terminal amino acid moiety of nikkomycin K_X and K_Z **595**, via a two-step procedure in a 75% yield (Scheme 68) <1997JOC7911>.

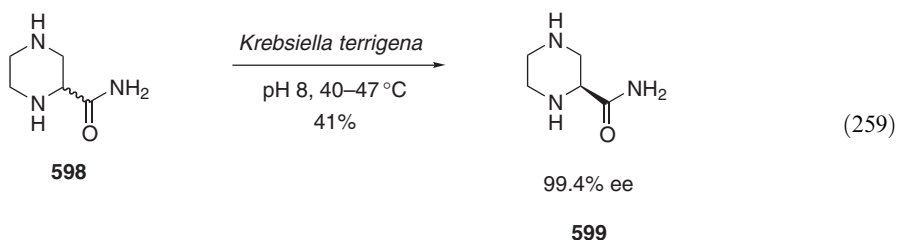


Scheme 68

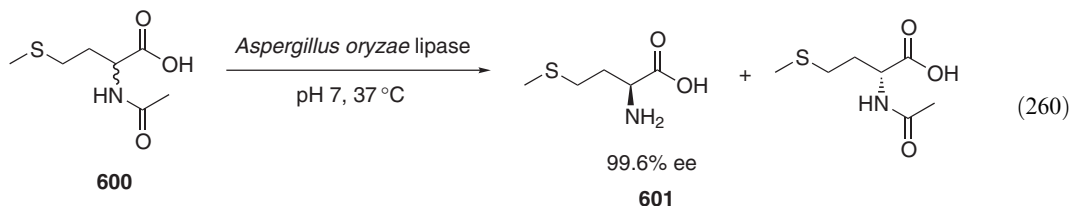
Parmer and co-workers investigated the possibility of using a variety of lipases and α -chymotrypsin for their ability to asymmetrically hydrolyze Schiff bases, for example **596**, derived from racemic α -amino acid esters and aromatic aldehydes. Hydrolyzing the Schiff bases in aqueous acetonitrile with, for example, α -chymotrypsin returned the corresponding (*S*)- α -amino acids **597** in high ee values and moderate yields (Equation (258)) <1996JOC1223>.



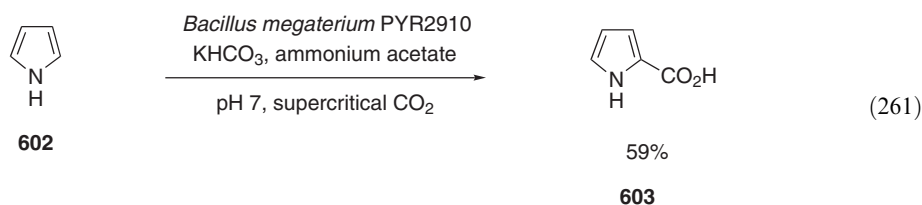
The efficient kinetic resolution of racemic piperazine-2-carboxamide **598** (Equation (259)) and piperidine-2-carboxamide to the corresponding enantiomerically pure carboxylic acids **599** has been performed using the whole cell bacteria, *Klebsiella terrigena* DSM 9174 and *Burkholderia* sp. DSM 9925. Both of the chiral non-racemic carboxylic acid heterocycles were returned in excellent enantioselectivity (99%) and moderate-to-reasonable yields, 44% and 22%, respectively <1997TA2533>.



A number of sulfur- and selenium-containing racemic *N*-acylamino acids **600** have been enantioselectively deracemised using the acylase from *Aspergillus oryzae*, affording the chiral nonracemic (*S*)-amino acid **601** in very good ee (Equation (260)) <1997TA3197>.



Matsuda and co-workers have demonstrated that pyrrole **602** can be converted into the corresponding pyrrole-2-carboxylate **603** in supercritical carbon dioxide using the cells of *Bacillus megaterium* PYR 2910, affording the corresponding carboxylic acid in a reasonable 59% yield (Equation (261)). Interestingly, conducting the reaction at atmospheric pressure afforded only a 6% yield of the desired acid <2001CC2194>.



REFERENCES

- 1879LA1
 1898JA648
 1905JCS747
 1909JCS1004
 1942OR(1)210
 B-1945MI502-02
 B-1947MI502-01
 B-1947MI502-02
 B-1948MI502-01
 1949BSFD297
 1951OR(6)1
 1951OR(61)1
 B-1951MI502-01
 1952JCS4521
 B-1952MI502-01
 B-1952MI502-2
 B-1954MI502-01
 1954OR(8)28
 1954OR(8)258
 1956CI(L)548
 1956CRV27
 1958JCS1313
 1959CB1608
 1959CRV89
 1960HCA113
 1961AG449
 1963OSC(4)919
 B-1964MI502-03
 1965JCS6655
 1966MI502-01
- L. Schreiner, *Justus Liebigs Ann. Chem.* **1879**, 1.
 J. A. Matthews, *J. Am. Chem. Soc.* **1898**, 20, 648–668.
 A. Findlay, W. E. S. Turner, *J. Chem. Soc.* **1905**, 747.
 A. Findlay, E. M. Hickmans, *J. Chem. Soc.* **1909**, 1004.
 J. R. Johnson, *Org. React.* **1942**, 1, 210.
 D. W. Knight, *Gen. Synth. Methods* **1945**, 11, 502.
 F. Salmon-Legagneur, in *Traite de Chimie Organique*, V. Grignard, C. Dupont, R. Lacquin, Eds., Masson et Cie, Paris, **1947**, Vol. 10, pp. 1–443.
 F. Salmon-Legagneur, in *Traite de Chimie Organique*, V. Grignard, C. Dupont, R. Lacquin, Eds., Masson et Cie, Paris, **1947**, Vol. 10, pp. 445–630.
 R. Truchet, in *Traite de Chimie Organique*, V. Grignard, C. Dupont, R. Lacquin, Eds., Masson et Cie, Paris, **1948**, Vol. 9, pp. 1–92, 145–687.
 D. A. Shirley, *Org. React.* **1949**, 8, 297.
 W. S. Johnson, G. H. Daub, *Org. React.* **1951**, 6, 1.
 D. A. Shirley, *Org. React.* **1951**, 61, 1.
 A. W. Johnson, C. E. Dalgliesh, J. Walker, in *Chemistry of Carbon Compounds*, E. H. Rodd, Ed., Elsevier, Amsterdam, **1951**, Vol. 1A, pp. 537–647.
 F. Bergmann, A. Kalmus, *J. Chem. Soc.* **1952**, 4521.
 C. E. Dalgliesh, A. N. Johnson, C. Buchannan, in *Chemistry of Carbon Compounds*, E. H. Rodd, Ed., Elsevier, Amsterdam, **1952**, Vol. 1B, pp. 950–1011.
 D. W. Knight, *Gen. Synth. Methods* **1952**, 11, 502.
 W. J. Hickinbottom, in *Chemistry of Carbon Compounds*, E. H. Rodd, Ed., Elsevier, Amsterdam, **1954**, Vol. 3A, pp. 541–601.
 D. A. Shirley, *Org. React.* **1954**, 8, 28.
 H. Gilman, J. W. Morton Jr., *Org. React.* **1954**, 8, 258.
 I. Bell, E. R. H. Jones, M. C. Whiting, *Chem. Ind. (London)*, **1956**, 548.
 P. H. Leake, *Chem. Rev.* **1956**, 56, 27.
 I. Bell, E. R. H. Jones, M. C. Whiting, *J. Chem. Soc.* **1958**, 1313.
 H. Böhme, H. Ellenberg, O.-E. Herboth, W. Lehnert, *Chem. Ber.* **1959**, 92, 2433.
 D. G. M. Diaper, A. Kuksis, *Chem. Rev.* **1959**, 59, 89.
 F. Elsinger, J. Schreiber, A. Eschenmoser, *Helv. Chim. Acta* **1960**, 43, 113.
 L. Jaenicke, *Angew. Chem.* **1961**, 73, 449.
 E. Campaigne, W. M. LeSuer, *Org. Synth., Coll. Vol.* **1963**, 4, 919.
 G. A. Olah, J. A. Olah, in *Acid Synthesis in Friedel–Crafts and Related Reactions*, G. A. Olah, Ed., Interscience, New York, **1964**, Vol. 3, pp. 1257–1317.
 P. D. G. Dean, *J. Chem. Soc.* **1965**, 6655.
 F. Salmon-Legagneur, *Ind. Chem. Belg.* **1966**, 31, 993.

- B-1968MI502-01 S. R. Sandler, W. Karo, *Organic Functional Group Preparations*, Academic Press, New York, **1968**, Vol. 12-I, p. 578.
- B-1969MI502-01 R. P. A. Sneeden, in *The Chemistry of Carboxylic Acids and Esters*, S. Patai, Ed., Wiley, New York, **1969**, chap. 4, pp. 137–173.
- B-1969MI502-02 V. F. Kuchеров, L. A. Yanovskaya, in *The Chemistry of Carboxylic Acids and Esters*, S. Patai, Ed., Wiley, New York, **1969**, chap. 5, pp. 175–209.
- B-1970MI502-01 C. A. Buehler, D. E. Pearson, *Survey of Organic Syntheses*, Wiley-Interscience, New York, **1970**, chap. 13, p. 744.
- 1970S615 B. Blagoev, D. Ivanov, *Synthesis* **1970**, 615.
- 1972CJC3741 D. G. Lee, D. T. Hall, J. H. Cleland, *Can. J. Chem.* **1972**, 50, 3741.
- 1972MI502-01 W. F. Brill, J. T. Baker, *High Polym.* **1972**, 27, 477.
- 1972MI502-02 J. K. Stille, M. E. Freeburger, W. B. Alston, E. L. Mainen, *High Polym.* **1972**, 27, 689.
- 1972S464 G. Fodor, J. P. Fumeaux, V. Sankaran, *Synthesis* **1972**, 464.
- B-1972MI501-01 S. Patai, Ed., *The Chemistry of Acyl Halides*, Interscience, New York, **1972**.
- B-1972MI502-01 H. O. House, in *Modern Synthetic Reactions*, W. A. Benjamin, Menlo Park, California, 2nd Ed., **1972**, chap. 10, pp. 629–733.
- 1973RCR939 B. I. Zapadinskii, B. I. Liogon'kii, A. A. Berlin, *Russ. Chem. Rev. (Engl. Transl.)* **1973**, 42, 939.
- 1974JOC600 G. E. Niznik, W. H. I. Morrison III, H. M. Walborsky, *J. Org. Chem.* **1974**, 39, 600.
- 1974S443 Y. Fukuyama, Y. Kawashima, T. Miwa, T. Tokoroyama, *Synthesis* **1974**, 443.
- 1975JOC1187 H. L. Vaughn, M. D. Robbins, *J. Org. Chem.* **1975**, 40, 1187–1189.
- B-1975MI502-01 B. Cornils, in *Ullmanns Encykl. Tech. Chem., 4. Arefl.*, E. Bartholome, E. Biekert, H. Hellmann, Eds., Weinheim, Germany, **1975**, Vol. 10, pp. 135–143.
- 1976AR(B)199 E. W. Colvin, *Annu. Rep. Prog. Chem., Sect. B* **1976**, 72, 199.
- 1976CC885 D. W. Knight, *Gen. Synth. Methods* **1976**, 11, 885.
- 1976JA1275 P. G. Gassman, P. K. G. Hodgson, R. J. Balchunis, *J. Am. Chem. Soc.* **1976**, 98, 1275–1276.
- B-1976MI502-03 J. Grimshaw, in *Rodd's Chemistry of Carbon Compounds*, S. Coffey, Ed., 2nd edn., Elsevier, Amsterdam, **1976**, Vol. 3, Part D, p. 141.
- B-1977MI502-01 C. A. Buehler, D. E. Pearson, *Survey of Organic Syntheses*, Wiley, New York, **1977**, chap. 13, p. 655.
- 1978GSM111 D. W. Knight, *Gen. Synth. Methods* **1978**, 1, 111.
- B-1978MI502-02 L. Eberson, K. Nyberg, in *Encyclopedia of Electrochemistry of the Elements*, A. J. Bard, Ed., Marcel Dekker, New York, **1978**, Vol. 12, pp. 261–328.
- B-1978MI502-03 J. Q. Chambers, in *Encyclopedia of Electrochemistry of the Elements*, A. J. Bard, Ed., Marcel Dekker, New York, **1978**, Vol. 12, pp. 329–502.
- 1979COC841 D. W. Knight, *Gen. Synth. Methods* **1979**, 11, 841.
- 1979COC(2)841 I. O. Sutherland, *Comp. Org. Chem.* **1979**, 2, 841.
- 1979GSM67 D. W. Knight, *Gen. Synth. Methods* **1979**, 2, 67.
- 1979MI502-01 L. M. Bova, *Khim. Prom-st. Rubezhom* **1979**, 31 (*Chem. Abstr.*, **1979**, 91, 74 139c).
- 1979MI502-02 M. Ohta, *Yushi* **1979**, 32, 50 (*Chem. Abstr.*, **1980**, 93, 25 800u).
- B-1979MI502-01 M. A. Ogliaruso, J. F. Wolfe, in *The Chemistry of Functional Groups, Supplement B. Part 1*, S. Patai, Ed., Wiley-Interscience, New York, **1979**, chap. 7, pp. 270–490.
- 1980GSM75 D. W. Knight, *Gen. Synth. Methods* **1980**, 3, 75.
- B-1980MI502-01 B. Kurtev, in *Organometalliches Fonct. Ambidends, Recl. Commun., Colloq. Fr.-Bulg.* Eds., B. Blagoev, F. Gaudemar-Bardone, M. Mladenova, Acad. Bulg. Sci., Inst. Chim. Org., Sofia, **1980**, p. 1. (*Chem. Abstr.*, **1981**, 95, 60 729r).
- 1980S243 S. Cacchi, D. Misiti, F. La Torre, *Synthesis* **1980**, 243.
- 1981GSM87 D. W. Knight, *Gen. Synth. Methods* **1981**, 4, 87.
- 1981MI502-04 V. V. Antonova, A. M. Bespalova, G. V. Krylova, V. K. Promonenkov, *Deposited Doc.* **1981**, SPSTL369 Khp-D81 (*Chem. Abstr.* **1983**, 98, 71 834j).
- 1982GSM100 D. W. Knight, *Gen. Synth. Methods* **1982**, 5, 100.
- 1982MI502-02 M. Hronec, J. Ilavsky, *Ropa Uhlie* **1982**, 24, 464 (*Chem. Abstr.*, **1982**, 97, 218 392d).
- 1983CC392 D. Wenkert, K. M. Eliasson, R. Rudisill, *J. Chem. Soc., Chem. Commun.* **1983**, 392.
- 1983GSM98 P. R. Jenkins, *Gen. Synth. Methods* **1983**, 6, 98.
- B-1983MI502-01 I. O. Sutherland, Ed., *General Organic Chemistry, Carboxylic Acids and Their Derivatives. Phosphorus Compounds*, Khimiya, Moscow, **1983**, Vol. 4 (*Chem. Abstr.* **1984**, 100, 138 213m).
- 1983S605 S. R. Ramadas, P. S. Srinivasan, J. Ramachandran, V. V. S. K. Sastry, *Synthesis* **1983**, 605.
- 1985GSM96 P. R. Jenkins, *Gen. Synth. Methods* **1985**, 7, 96.
- 1985S493 S. Randriamahefa, P. Deschamps, R. Gallo, *Synthesis* **1985**, 493–495.
- 1986GSM131 D. W. Knight, *Gen. Synth. Methods* **1986**, 11, 131.
- 1986JOC567 E. Dalcanele, F. Mantanari, *J. Org. Chem.* **1986**, 51, 567.
- 1987GSM130 D. W. Knight, *Gen. Synth. Methods* **1987**, 11, 130.
- 1988GSM75 D. W. Knight, *Gen. Synth. Methods* **1988**, 11, 75.
- 1989GSM89 D. W. Knight, *Gen. Synth. Methods* **1989**, 11, 89.
- 1989TL1197 P. Beak, W.-K. Lee, *Tetrahedron Lett.* **1989**, 30, 1197–1200.
- 1990GSM91 D. W. Knight, *Gen. Synth. Methods* **1990**, 12, 91.
- 1990TL3893 Y. H. Kim, K. Kim, Y. J. Park, *Tetrahedron Lett.* **1990**, 31, 3893–3894.
- B-1991MI502-01 M. A. Ogliaruso, J. F. Wolfe, in *Synthesis of Carboxylic Acids, Esters and Their Derivatives, Updates From the Chemistry of Functional Groups*, S. Patai, Z. Rappoport, Eds., Wiley-Interscience, New York, **1991**.
- 1992GSM79 D. W. Knight, *Gen. Synth. Methods* **1992**, 13, 79.
- 1992JOC2220 M. J. Chong, S. B. Park, *J. Org. Chem.* **1992**, 57, 2220–2222.
- 1992JOC3731 Y. Goldberg, H. Alper, *J. Org. Chem.* **1992**, 57, 3731–3732.

- 1993JA5953
1993JFC(60)179
1993JOC898

1993JOC1109
1993TL51
1994JOC1904
1995ACR414
1995CC1005
1995COFGT(5)23

1995TA559
1995JA7842
1995JA12342
1995JMC1140

1995JOC2792
1995JOC4449

1995JOC5378
1995JOC5763
1995JOC6148
1995S1003
1995SC753

1995SC1963
1995TA469
1995TA559
1995TL3469

1995TL8697

1996ACR552

1996ACS552

1996CC141
1996JFC(77)21

1996JOC1223

1996JOC1817
1996JOC6651
1996JOC8762
1996S1153
1996S1433
1996T157
1996T255
1996T3769
1996T6953
1996T8257
1996TA95

1996TA228

1996TA3545

1996TL417
1996TL1149

1996TL1781

1996TL2943
1996TL3663
1996TL4209
1996TL4397

1996TL6001

1996TL6603
- J. F. Marlier, *J. Am. Chem. Soc.* **1993**, *115*, 5953–5956.
V. Tolman, *J. Fluorine Chem.* **1993**, *60*, 179–183.
G. R. Newcome, S. Arai, F. R. Fronczek, C. N. Moorefield, X. Lin, C. D. Weis, *J. Org. Chem.* **1993**, *58*, 898–903.
P. Beak, W.-K. Lee, *J. Org. Chem.* **1993**, *58*, 1109–1117.
A. F. Burchat, J. M. Chong, S. B. Park, *Tetrahedron Lett.* **1993**, *34*, 51–54.
E. Bon, D. C. H. Bigg, G. Bertrand, *J. Org. Chem.* **1994**, *59*, 1904–1906.
H. Alper, K. Khumtaveeporn, *Acc. Chem. Res.* **1995**, *28*, 414–422.
K. R. Kloetstra, H. Van Bekkum, *J. Chem. Soc., Chem. Commun.* **1995**, 1005–1006.
M. A. Ogliaruso, J. Wolfe, Carboxylic Acids, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 23–120.
G. Solladié, A. Almario, *Tetrahedron Lett.* **1995**, *6*, 559–576.
T. A. Keating, R. W. Armstrong, *J. Am. Chem. Soc.* **1995**, *117*, 7842–7843.
M. Schlosser, D. Limat, *J. Am. Chem. Soc.* **1995**, *117*, 12342–12343.
F. Animato, F. M. Arcamone, M. R. Conte, P. Felicetti, A. Galeone, P. Lombardi, L. Mayol, L. G. Paloma, C. Rossi, *J. Med. Chem.* **1995**, *38*, 1140–1149.
J. Yoon, S. Hong, K. A. Martin, A. W. Czarnik, *J. Org. Chem.* **1995**, *60*, 2792–2795.
E. Aller, D. S. Brown, G. G. Cox, D. J. Miller, C. J. Moody, *J. Org. Chem.* **1995**, *60*, 4449–4460.
W. R. Dolbier Jr., R. Ocampo, *J. Org. Chem.* **1995**, *60*, 5378–5379.
R. E. Gawley, Q. Zhang, *J. Org. Chem.* **1995**, *60*, 5763–5769.
F. A. Reddy, G. V. Reddy, B.-C. Chen, A. Kumar, *J. Org. Chem.* **1995**, *60*, 6148–6153.
L. F. Titze, T. Neumann, M. Kajino, M. Pretor, *Synthesis* **1995**, 1003.
F. Delgado, J. Tamariz, G. Zepeda, M. Landa, R. Miranda, J. Garcea, *Syn. Commun.* **1995**, *25*, 753–759.
I. S. Byun, Y. H. Kim, *Syn. Comm.* **1995**, *25*, 1963–1969.
R. S. Ward, A. Pelter, D. Goubet, M. C. Pritchard, *Tetrahedron Asymmetry* **1995**, *6*, 469–498.
G. Solladié, A. Almario, *Tetrahedron Asymmetry* **1995**, *6*, 559–576.
C. P. Wilgus, S. Downing, E. Molitor, S. Bains, R. M. Pagni, G. W. Kabalka, *Tetrahedron Lett.* **1995**, *36*, 3469–3472.
Y. Yamamoto, T. Kimachi, Y. Kanaoka, S. Kato, K. Bessho, *Tetrahedron Lett.* **1996**, *37*, 7801–7804.
P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552.
P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552–560.
G.-J. Booms, A. Burton, S. Isles, *J. Chem. Soc., Chem. Commun.* **1996**, 141–142.
C. Dapremont-Avignon, P. Calas, C. Amatore, S. Bénéfice-Malouetm A. Commeyras, *J. Fluorine Chem.* **1996**, *77*, 21–26.
V. S. Parmar, A. Singh, K. S. Bisht, N. Kumar, Y. N. Belokon, K. A. Kochetkov, N. S. Ikonnikov, S. A. Orlova, V. I. Tararov, T. F. Saveleva, *J. Org. Chem.* **1996**, *61*, 1223–1227.
C. Schmitz, A. Rouanet-Dreyfuss, M. Tueni, J. Biellmann, *J. Org. Chem.* **1996**, *61*, 1817–1821.
M. Larsen, M. Jørgensen, *J. Org. Chem.* **1996**, *61*, 6651–6655.
M. Barbero, I. Degani, R. Fochi, P. Perracino, *J. Org. Chem.* **1996**, *61*, 8762–8764.
A. E. J. Nooy, A. C. Besemer, H. Van Bekkum, *Synthesis* **1996**, 1153–1174.
A. Trzeciak, W. Bannwarth, *Synthesis* **1996**, 1433–1434.
H. Fukuda, M. Tetsu, T. Kitazume, *Tetrahedron* **1996**, *52*, 157–164.
T. Ishihara, K. Ichihara, H. Yamanaka, *Tetrahedron* **1996**, *52*, 255–262.
E. Schöffers, A. Golebiowski, C. R. Johnson, *Tetrahedron* **1996**, *52*, 3769–3826.
V. A. Soloshonok, V. P. Kukhar, *Tetrahedron Lett.* **1996**, *52*, 6953–6964.
M. Schlosser, D. Michel, *Tetrahedron* **1996**, *52*, 8257–8262.
J. A. S. Howell, M. G. Palin, G. Jaouen, B. Malezieux, S. Top, J. M. Cense, *Tetrahedron Asymmetry* **1996**, *7*, 95–104.
W. Adam, M. Lazarus, B. Boss, C. R. Saha-Möller, P. Schreier, *Tetrahedron Asymmetry* **1996**, *7*, 2287–2292.
Y. Kokuryo, T. Nakatani, K. Kobayashi, Y. Tamura, K. Kawada, M. Ohtani, *Tetrahedron Asymmetry* **1996**, *7*, 3545–3551.
P. Clapes, I. Valverde, C. Jamie, J. L. Torres, *Tetrahedron Lett.* **1996**, *37*, 417–418.
A. M. Strocker, T. A. Keating, P. A. Tempest, R. W. Armstrong, *Tetrahedron Lett.* **1996**, *37*, 1149–1152.
J.-Y. Winum, M. Kamal, A. Leydet, J.-P. Roque, J.-L. Montero, *Tetrahedron Lett.* **1996**, *37*, 1781–1782.
A. M. M. Mjalli, S. Sarshar, T. J. Baiga, *Tetrahedron* **1996**, *37*, 2943–2946.
J. Lee, J. K. Cha, *Tetrahedron Lett.* **1996**, *37*, 3663–3666.
X. Wei, R. J. K. Taylor, *Tetrahedron Lett.* **1996**, *37*, 4209–4210.
E. Guibé-Jampe, Z. Chalecki, M. Bassir, M. Gelo-Pujic, *Tetrahedron Lett.* **1996**, *52*, 4397–4402.
S. J. Maddrell, N. J. Turner, A. Kerridge, A. J. Willetts, J. Crosby, *Tetrahedron Lett.* **1996**, *37*, 6001–6004.
J. S. Yadav, S. Chandrasekhar, G. Sumithra, R. Kache, *Tetrahedron Lett.* **1996**, *37*, 6603–6606.

- 1996TL7801 Y. Yamamoto, T. Kimachi, Y. Kanaoka, S. Kato, K. Beesho Takuyuki Matsumoto, T. Kusakabe, Y. Sugiura, *Tetrahedron Lett.* **1996**, 37, 7801–7804.
- 1996TL8899 K. Tomooka, A. Nagasawa, A.-Y. Wei, T. Nakai, *Tetrahedron Lett.* **1996**, 37, 8899–8900.
- 1996TL9237 N. Hashimoto, S. Kawamura, T. Ishizuka, T. Kunieda, *Tetrahedron Lett.* **1996**, 37, 9237–9240.
- 1997AA3 S. Kroeger, G. Haufe, *Amino Acids* **1997**, 12, 363–372.
- 1997AG(E)617 S. Matsubara, M. Yoshioka, K. Utimoto, *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 617–618.
- 1997AG(E)2283 L. Wesemann, *Angew. Chem., Int. Ed. Engl.* **1997**, 109, 2283–2284.
- 1997BCJ2895 H. Ohta, *Bull. Chem. Soc. Jpn.* **1997**, 70, 2895–2911.
- 1997BMC797 T. S. Morris, S. Frommann, S. Shechosky, C. Lowe, M. S. Lall, V. Gauss-Müller, R. H. Purcell, S. U. Emerson, J. C. Vederas, B. A. Malcom, *Biorg. Med. Chem.* **1997**, 5, 797–807.
- 1997BMCL2765 A. D. Baxter, R. Bhogal, J. B. Bird, G. M. Buckley, D. S. Gregory, P. C. Hedges, D. T. Manallack, T. Massil, K. J. Minton, J. G. Montana, S. Neidle, D. A. Owen, R. J. Watson, *Biorg. Med. Chem. Lett.* **1997**, 7, 2765–2770.
- 1997BMCL3053 J. R. Falck, Y. Y. Belosludtsev, K. K. Reddy, K. Malla Reddy, M. Shortt, K. Chauhan, J. H. Capdevilla, S. Wei, *Biorg. Med. Chem. Lett.* **1997**, 7, 3053–3056.
- 1997CC1759 T. G. Back, K. Minkszty, *J. Chem. Soc., Chem. Commun.* **1997**, 1759–1760.
- 1997COC121 N. J. Turner, *Curr. Org. Chem.* **1997**, 1, 21–36.
- 1997JA445 N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, 119, 445–446.
- 1997JA12386 K. Sato, M. Aoki, J. Takagi, R. Noyori, *J. Am. Chem. Soc.* **1997**, 119, 12386–12387.
- 1997JCS(P1)2989 M. Penny, S. M. Westaway, C. L. Willis, *J. Chem. Soc., Perkin Trans. 1* **1997**, 2989–2995.
- 1997JCS(P1)2997 F. Hong, J. Zaidi, Y.-P. Pang, B. Cusack, E. Richelson, *J. Chem. Soc., Perkin Trans. 1* **1997**, 2997–3003.
- 1997JCS(P1)3197 O. Meth-Cohn, M.-X. Wang, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3197–3204.
- 1997JFC(86)99 L. Xiao, T. Kitazume, *J. Fluorine Chem.* **1997**, 86, 99–104.
- 1997JOC234 C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1997**, 62, 234–235.
- 1997JOC967 K. Rück-Braun, A. Stamm, S. Engel, H. Kunz, *J. Org. Chem.* **1997**, 62, 967–975.
- 1997JOC1574 Y. S. Park, P. Beak, *J. Org. Chem.* **1997**, 62, 1574–1575.
- 1997JOC1594 Q. Xu, Y. Imamura, M. Fujiwara, Y. Souma, *J. Org. Chem.* **1997**, 62, 1594–1598.
- 1997JOC7679 K. M. Bertini Gross, Y. M. Jun, P. Beak, *J. Org. Chem.* **1997**, 62, 7679–7689.
- 1997JOC7841 W. Adam, M. Lazarus, B. Boss, C. R. Saha-Möller, H.-U. Humpf, P. Schreier, *J. Org. Chem.* **1997**, 62, 7841–7843.
- 1997JOC7911 D. P. Henderson, M. C. Shelton, I. C. Cotterill, E. J. Toone, *J. Org. Chem.* **1997**, 62, 7910–7911.
- 1997JOC8932 C.-J. Li, Y. Meng, X.-H. Yi, J. Ma, T.-H. Chan, *J. Org. Chem.* **1997**, 62, 8632–8633.
- 1997LA1201 S. Kroeger, G. Haufe, *Liebigs Ann. Chem.* **1997**, 12, 363–372.
- B-1997MI001 G. M. Coppola, H. F. Schuster, α -Hydroxy acids in enantioselective syntheses, Wiley VCH, Weinheim, **1997**.
- B-1997MI502-01 E. Juaristi, Ed., Enantioselective synthesis of β -amino acids, John Wiley, NY, **1997**.
- 1997S1 H. Stecher, K. Faber, *Synthesis* **1997**, 1–16.
- 1997T13149 P. C. P. Page, M. J. McKenzie, S. M. Allin, S. S. Klair, *Tetrahedron* **1997**, 53, 13149–13164.
- 1997T14031 M. Benedetti, L. Forti, F. Ghelfi, U. Pagnoni, R. Ronzoni, *Tetrahedron* **1997**, 53, 14031–14042.
- 1997T15397 W. Srisiri, Y.-S. Lee, T. M. Bondurant, D. F. O'Brien, *Tetrahedron* **1997**, 53, 15397–15414.
- 1997T16213 V. K. Aggarwal, A. Thomas, S. Schade, *Tetrahedron* **1997**, 53, 16213–16228.
- 1997T16463 N. A. Petasis, A. Goodman, I. A. Zavialov, *Tetrahedron Lett.* **1997**, 53, 16473–16470.
- 1997TA425 M. Breznik, D. Kikelj, *Tetrahedron Asymmetry* **1997**, 8, 425–434.
- 1997TA477 J. Oetting, J. Holzkamp, H. H. Meyer, A. Pahl, *Tetrahedron Asymmetry* **1997**, 8, 477–484.
- 1997TA665 X. Wei, R. J. K. Taylor, *Tetrahedron Asymmetry* **1997**, 8, 665–668.
- 1997TA1821 B. Klotz-Berendes, W. Kleemiß, U. Jegelka, H. J. Schäfer, S. Kotila, *Tetrahedron Asymmetry* **1997**, 8, 1821–1823.
- 1997TA2291 J. S. Yadav, A. B. Rao, Y. Ravindra Reddy, K. Venkata Rami Reddy, *Tetrahedron Asymmetry* **1997**, 8, 2291–2294.
- 1997TA2433 A. Rottmann, J. Liebscher, *Tetrahedron Asymmetry* **1997**, 8, 2433–2446.
- 1997TA2533 E. Eichhorn, J.-P. Roduit, N. Shaw, K. Heinzmann, A. Kiener, *Tetrahedron Asymmetry* **1997**, 8, 2533–2536.
- 1997TA3197 A. S. Bommarius, K. Drauz, K. Günther, G. Knaup, M. Schwarn, *Tetrahedron Asymmetry* **1997**, 8, 3197–3200.
- 1997TL317 R. J. Andersen, J. E. Coleman, *Tetrahedron Lett.* **1997**, 38, 317–320.
- 1997TL1721 T. I. Reddy, R. S. Varma, *Tetrahedron Lett.* **1999**, 38, 1721–1724.
- 1997TL2629 W. J. Hoekstra, M. N. Greco, S. C. Yabut, B. L. Hulshizer, B. E. Maryanoff, *Tetrahedron Lett.* **1997**, 38, 2629–2632.
- 1997TL2981 V. Le Boisselier, M. Postel, E. Dunach, *Tetrahedron Lett.* **1997**, 38, 2981–2984.
- 1997TL4721 R. Matthews Thomas, G. Hari. Mohan, D. S. Iyengar, *Tetrahedron Lett.* **1997**, 38, 4721–4724.
- 1997TL4861 P. Roussel, M. Bradley Ian Matthews, P. Kane, *Tetrahedron Lett.* **1997**, 38, 4861–4864.
- 1997TL6505 N. Voyer, J. Roby, S. Chénard, C. Barberis, *Tetrahedron Lett.* **1997**, 38, 6505–6508.
- 1997TL7547 F. Jeanjean, N. Perol, J. Gore, G. Fournet, *Tetrahedron Lett.* **1997**, 38, 7547–7550.
- 1998AG(E)1609 R. D. Schmid, R. Verger, *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 1608–1633.
- 1998CC365 Y. Takeuchi, M. Konishi, H. Hori, T. Takahashi, T. Kometani, K. L. Kirk, *J. Chem. Soc., Chem. Commun.* **1998**, 365–366.
- 1998CC649 H. Hsieh, Y. Wu, S. Chen, K. Wang, *J. Chem. Soc., Chem. Commun.* **1998**, 649–650.
- 1998CC761 S. H. Kang, S. B. Lee, *J. Chem. Soc., Chem. Commun.* **1998**, 761–762.
- 1998CC2033 K. Hiroya, K. Ogasawara, *J. Chem. Soc., Chem. Commun.* **1998**, 2033–2034.

- 1998CC2431 M. S. Goedheijt, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leewen, *J. Chem. Soc., Chem Commun.* **1998**, 2431–2432.
- 1998CC2519 M. M. Jones, J. M. J. Williams, *J. Chem. Soc., Chem. Commun.* **1998**, 2519–2520.
- 1998CL297 M. K. Nayak, A. K. Chakraborti, *Chem. Lett.* **1998**, 297–298.
- 1998JA1916 S. A. Hitchcock, C. N. Eid, J. A. Atkins, M. Zia-Ebrahimi, L. C. Blaszcak, *J. Am. Chem. Soc.* **1998**, *120*, 1916–1917.
- 1998JA4345 M. J. Burk, C. S. Kalberg, A. Pizzano, *J. Am. Chem. Soc.* **1998**, *120*, 4345–4353.
- 1998JA9228 B. M. Trost, G. D. Probst, A. Schoop, *J. Am. Chem. Soc.* **1998**, *120*, 9228–9236.
- 1998JCS(P1)157 S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1998**, 157–169.
- 1998JCS(P1)2451 A. S. Franklin, *J. Chem. Soc., Perkin 1* **1998**, 2451–2465.
- 1998JMC808 C. Balsamini, A. Bedini, G. Diamantini, G. Spadoni, A. Tontini, G. Tarzia, *J. Med. Chem.* **1998**, *41*, 808–820.
- 1998JOC3631 M. A. Blaskovich, G. Evindar, N. G. W. Rose, S. Wilkinson, Y. Luo, G. A. Lajoie, *J. Org. Chem.* **1998**, *63*, 3631–3646.
- 1998JOC4120 S. V. Pansare, R. G. Ravi, R. P. Jain, *J. Org. Chem.* **1998**, *63*, 4120–4124.
- 1998JOC4930 M. Periasamy, C. Rameshkumar, U. Radhakrishnan, J.-J. Brunet, *J. Org. Chem.* **1998**, *63*, 4930–4935.
- 1998JOC7990 H. Sajiki, K. Hattori, K. Hirota, *J. Org. Chem.* **1998**, *63*, 7990–7992.
- 1998JOC8785 M. Bellassoued, N. Lensen, M. Bakasse, S. Mouelhi, *J. Org. Chem.* **1998**, *63*, 8785–8789.
- 1998S145 N. C. M. E. Barendse, P. A. M. van der Klein, J. Verweij, H. A. Witkamp, W. J. van Zoest, E. de vroom, *Synthesis* **1998**, 145–147.
- 1998SC3 E. Chiozza, M. Desigaud, J. Greiner, E. Dulach, *Studies in surface science and catalysis* **1998**, *114*, 213–218.
- 1998T401 K. S. Webb, S. J. Ruskay, *Tetrahedron* **1998**, *54*, 401–410.
- 1998T2619 N. De Kimpe, M. Boeykens, *Tetrahedron* **1998**, *54*, 2619–2630.
- 1998T5929 G. Haufe, K. W. Laue, M. U. Triller, *Tetrahedron* **1998**, *54*, 5929–5938.
- 1998T9447 G. Guillena, B. Mancheno, C. Nájera, *Tetrahedron* **1998**, *54*, 9447–9456.
- 1998T14549 S. V. Pansare, R. G. Ravi, *Tetrahedron* **1998**, *54*, 14549–14564.
- 1998TA1641 B. Chen, M. S. Bednarz, O. R. Kocy, J. E. Sundeen, *Tetrahedron Lett.* **1998**, *9*, 1641–1644.
- 1998TA2065 P. Camps, F. Pérez, N. Soldevilla, *Tetrahedron Asymmetry* **1998**, *9*, 2065–2079.
- 1998TA3517 C. Cativiela, M. Dolores diaz-de-villegas, *Tetrahedron Asymmetry* **1998**, *9*, 3517–3599.
- 1998TA4109 N. W. Fadnavis, R. L. Babu, S. Kumara Vadivel, A. A. Deshpande, U. T. Bhalerao, *Tetrahedron Asymmetry* **1998**, *9*, 4109–4112.
- 1998TL1335 A. G. Myers, L. McKinstry, J. K. Barbay, J. L. Gleason, *Tetrahedron Lett.* **1998**, *39*, 1335–1338.
- 1998TL1409 J. M. Conellón, P. L. Bernad, J. A. Pérez-Andrés, *Tetrahedron Lett.* **1998**, *39*, 1409–1412.
- 1998TL3005 M. K. Basu, F.-T. Luo, *Tetrahedron Lett.* **1998**, *39*, 3005–3006.
- 1998TL4277 J. Thibonnet, V. Launay, M. Abarbri, A. Duchêne, J.-L. Parrain, *Tetrahedron Lett.* **1998**, *38*, 4277–4280.
- 1998TL4591 K. H. Bleicher, J. R. Wareing, *Tetrahedron Lett.* **1998**, *39*, 4591–4594.
- 1998TL4757 T. M. Heidelbaugh, B. Liu, A. Padwa, *Tetrahedron Lett.* **1998**, *39*, 4757–4760.
- 1998TL4871 B. Yu, B. Li, J. Zhang, Y. Hui, *Tetrahedron Lett.* **1998**, *39*, 4891.
- 1998TL5041 F. Tellier, M. Audouin, M. Baudry, R. Sauëvre, *Tetrahedron Lett.* **1998**, *39*, 5041–5044.
- 1998TL5323 M. Zhao, J. Li, Z. Song, R. Desmond, D. M. Tschaen, E. J. J. Grabowski, P. J. Reider, *Tetrahedron Lett.* **1998**, *39*, 5323–5326.
- 1998TL5501 Z. Wang, B. La, J. M. Fortunak, X. Meng, G. W. Kabalka, *Tetrahedron Lett.* **1998**, *39*, 5501–5504.
- 1998TL5571 S. Sano, K. Hayashi, T. Miwa, T. Ishii, M. Fujii, H. Mima, Y. Nagao, *Tetrahedron Lett.* **1998**, *39*, 5571–5574.
- 1998TL6815 D. A. Heerding, D. T. Takata, C. Kwon, W. F. Huffman, J. Samanen, *Tetrahedron Lett.* **1998**, *39*, 6815–6818.
- 1998TL7153 G. Pandley, P. Das, P. Y. Reddy, *Tetrahedron Lett.* **1998**, *39*, 7153–7154.
- 1998TL9621 L. H. Zhang, J. Duan, Y. Xu, W. R. Dolbier Jr., *Tetrahedron Lett.* **1998**, *39*, 9621–9622.
- 1999BCJ2287 K. Sato, M. Aoki, J. Takagi, K. Zimmermann, R. Noyori, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2287–2306.
- 1999BMC251 P. G. Baraldi, P. Cozzi, C. Geroni, N. Mongelli, R. Romagnoli, G. Spalluto, *Biorg. Med. Chem.* **1999**, *7*, 251–262.
- 1999BMC1625 P. Ciuffreda, S. Casti, E. Santaniello, *Bioorg. Med. Chem.* **1999**, *7*, 1625–1636.
- 1999CC187 M. Bellassoued, E. Chelain, J. Collot, H. Rudler, J. Vaissermann, *J. Chem. Soc., Chem Commun.* **1999**, 187–188.
- 1999CC245 A. D. Campbell, T. M. Raynham, R. J. K. Taylor, *J. Chem. Soc., Chem. Commun.* **1999**, 245–246.
- 1999CC555 A. Sutherland, J. F. Caplan, J. C. Vederas, *J. Chem. Soc., Chem. Commun.* **1999**, 555–556.
- 1999CC1067 S. Jayasree, A. Seayad, R. V. Chaudhari, *J. Chem. Soc., Chem. Commun.* **1999**, 1067–1068.
- 1999CC2063 H. P. Lesutis, R. Gläser, C. L. Liotta, C. A. Eckert, *J. Chem. Soc., Chem Commun.* **1999**, 2063.
- 1999JA54 D. L. Boger, C. W. Boyce, M. A. Labroli, C. A. Schon, Q. Jin, *J. Am. Chem. Soc.* **1999**, *121*, 54–62.
- 1999JA6816 D. A. Evans, D. H. B. Ripin, D. P. Halstead, K. R. Campos, *J. Am. Chem. Soc.* **1999**, *121*, 6816–6826.
- 1999JA9574 D. Stien, G. T. Anderson, C. E. Chase, Y.-H. Koh, S. M. Weinreb, *J. Am. Chem. Soc.* **1999**, *121*, 9574–9579.
- 1999JCS(P1)1 S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1–21.

- 1999JOC282 S. Yamazaki, T. Inoue, T. Hamada, T. Takada, K. Yamamoto, *J. Org. Chem.* **1999**, *64*, 282–286.
- 1999JOC293 J. B. Epp, T. S. Widlanski, *J. Org. Chem.* **1999**, *64*, 293–295.
- 1999JOC346 A. R. Katritzky, J. Yao, W. Bao, M. Qi, P. J. Steel, *J. Org. Chem.* **1999**, *64*, 346–350.
- 1999JOC1033 R. Maggi, G. Sartori, *J. Org. Chem.* **1999**, *64*, 1033–1035.
- 1999JOC1319 G. Scheffler, R. R. Schmidt, *J. Org. Chem.* **1999**, *64*, 1319–1325.
- 1999JOC2564 M. Zhao, J. L. Eüchi Mano, Z. Song, D. M. Tschaen, E. J. J. Grabowski, P. J. Reider, *J. Org. Chem.* **1999**, *64*, 2564–2566.
- 1999JOC9019 L. E. Janes, A. Cimpoaia, R. J. Kazlauskas, *J. Org. Chem.* **1999**, *64*, 9019–9029.
- 1999JOC9704 A. Chen, L. Ren, C. M. Crudden, *J. Org. Chem.* **1999**, *64*, 9704–9710.
- 1999JOM(572)93 I. D. Kostas, O. S. Akkerman, F. Bickelhaupt, N. Veldman, A. L. Spek, *J. Organomet. Chem.* **1999**, *572*, 93–104.
- 1999OL207 I. Kumar, R. S. Jolly, *Org. Lett.* **1999**, *1*, 207–209.
- 1999OL459 A. Seayad, S. Jayasree, R. V. Chaudhari, *Org. Lett.* **1999**, *1*, 459–461.
- 1999OL2061 J. Chang, D. Jang, B. Uang, F. Liao, S. Wang, *Org. Lett.* **1999**, *1*, 2061–2063.
- 1999OM5688 B. Deschamps, L. Ricard, F. Mathey, *Organometallics* **1999**, *18*, 5688–5690.
- 1999TA1129 C. Tanyeli, B. Sezen, A. S. Demir, R. Brondi Alves, S. Arseniyadis, *Tetrahedron Asymmetry* **1999**, *10*, 1129–1133.
- 1999TA2945 K. Matsuyama, M. Ikunaka, *Tetrahedron Asymmetry* **1999**, *10*, 2945–2950.
- 1999TA3285 M. D. Bailey, T. Halmos, D. Adamson, J. Bordeleau, C. Grand-Maitre, *Tetrahedron Asymmetry* **1999**, *10*, 3285–3295.
- 1999TA4331 T. P. Keenan, D. Yaeger, D. A. Holt, *Tetrahedron Lett.* **1999**, *10*, 4331–4341.
- 1999TA4463 M. D. Miquel-Serrano, A. Aghmiz, M. Diéguez, A. M. Masdeu-Bultó, C. Claver, D. Sinou, *Tetrahedron Asymmetry* **1999**, *10*, 4463–4467.
- 1999TA4599 A. Cipiciani, F. Bellezza, F. Fringuelli, M. Stillitano, *Tetrahedron Asymmetry* **1999**, *10*, 4599–4605.
- 1999TL749 P. M. Dinh, J. M. J. Williams, W. Harris, *Tetrahedron Lett.* **1999**, *40*, 749–752.
- 1999TL5905 S. Nanda, A. Bhaskar, J. S. Yadav, *Tetrahedron Lett.* **1999**, *40*, 5905–5908.
- 1999TL6809 N. Komine, L. Wang, K. Tomooka, T. Nakai, *Tetrahedron Lett.* **1999**, *40*, 6809–6812.
- 2000BiotechProg B. Hwang, H. B. Lee, Y. G. Kim, B. Kim, *Biotechnol. Prog.* **2000**, *16*, 973–978.
- 2000CC1239 S. Jayasree, A. Seayad, R. V. Chaudhari, *J. Chem. Soc., Chem. Commun.* **2000**, 1239–1240.
- 2000CC1519 K. Matoishi, S. Hanzawa, H. Kakidani, M. Suzuki, T. Sugai, H. Ohta, *J. Chem. Soc., Chem. Commun.* **2000**, 1519–1520.
- 2000JA11340 S. Nakamura, R. Nakagawa, Y. Watanabe, T. Toru, *J. Am. Chem. Soc.* **2000**, *122*, 11340–11347.
- 2000JCS(P1)611 S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1* **2000**, 611–633.
- 2000JFC(101)5 V. Tolman, P. Sedmera, *J. Fluorine Chem.* **2000**, *101*, 5–10.
- 2000JFC(101)45 P. L. Coe, A. J. Rees, *J. Fluorine Chem.* **2000**, *101*, 45–60.
- 2000JMC(A)93 A. M. Trzeciak, J. J. Ziolkowski, *J. Mol. Catal.* **2000**, *154*, 93–101.
- 2000JNP371 C.-Z. Wang, U. H. Maier, M. H. Zenk, *J. Am. Chem. Soc.* **2003**, *63*, 371–374.
- 2000JOC2090 K. Okuma, Y. Koga, K. Kojima, K. Shioji, H. Matsuyama, Y. Yokomori, *J. Org. Chem.* **2000**, *65*, 2090–2095.
- 2000JOC5469 J. Czombos, W. Aelterman, A. Tkachev, J. C. Martins, D. Tourwé, A. Péter, G. Tóth, F. Fülöp, N. De Kimpe, *J. Org. Chem.* **2000**, *65*, 5469–5475.
- 2000OL203 S. Jayasree, R. V. Chaudhari, *Org. Lett.* **2000**, *2*, 203–206.
- 2000OL747 V. A. Soloshonok, C. Cai, V. R. Hruby, *Org. Lett.* **2000**, *2*, 747–750.
- 2000OL799 L. A. Barnhurst, Y. Wan, A. G. Kutateladze, *Org. Lett.* **2000**, *2*, 799–801.
- 2000OL1569 P. Klán, M. Zabadal, D. Heger, *Org. Lett.* **2000**, *2*, 1569–1571.
- 2000OL2165 M. T. Crimmins, K. A. Emmitte, J. D. Katz, *Org. Lett.* **2000**, *2*, 2165–2167.
- 2000OL3789 A. R. Katritzky, S. Zhang, Y. Fang, *Org. Lett.* **2000**, *2*, 3789–3791.
- 2000OM4715 J. Real, E. Prat, S. González-Cabello, M. Pagès, A. Polo, *Organometallics* **2000**, 4715–4719.
- 2000T9305 C. Alemany, J. Bach, J. Garcia, M. López, A. B. Rodríguez, *Tetrahedron* **2000**, *56*, 9305–9312.
- 2000TA889 F. Tranel, G. Haufe, *Tetrahedron Asymmetry* **2000**, *11*, 889–896.
- 2000TA1015 R. Badorrey, C. Cativiela, M. D. Diaz-de-Villegas, José. A. Gálvez, *Tetrahedron Asymmetry* **2000**, *11*, 1015.
- 2000TA2125 H. Schedel, P. J. L. M. Quaedflieg, Q. B. Broxterman, W. Bisson, A. L. L. Duchateau, I. C. H. Maes, R. Herzschuh, K. Burger, *Tetrahedron Asymmetry* **2000**, *11*, 2125.
- 2000TA4105 J. Guo, D. W. Knapp, S. Boegeman, *Tetrahedron Asymmetry* **2000**, *11*, 4105–4111.
- 2000TA4417 G. Delogu, D. Fabbri, M. A. Dettori, A. Forni, G. Casalone, *Tetrahedron Asymmetry* **2000**, *11*, 4417–4427.
- 2000TL2729 R. L. Harding, T. D. H. Bugg, *Tetrahedron Lett.* **2000**, *41*, 2729–2731.
- 2000TL3209 F. J. Aladro, F. M. Guerra, F. J. Moreno-Dorado, J. M. Bustamante, Z. D. Jorge, G. M. Massanet, *Tetrahedron Lett.* **2000**, *41*, 3209–3213.
- 2000TL6121 K. Tomooka, L. Wang, F. Okazaki, T. Nakai, *Tetrahedron Lett.* **2000**, *41*, 6121–6125.
- 2000TL7419 W. Guo, E. Galoppini, G. Rydja, G. Pardi, *Tetrahedron Lett.* **2000**, *41*, 7419–7421.
- 2001CC2194 T. Matsuda, Y. Ohashi, T. Harada, R. Yanagihara, T. Nagusawa, K. Nakamura, *J. Chem. Soc., Chem. Commun.* **2001**, 2194–2195.
- 2001JA5602 C. Palomo, M. Oiarbide, F. Dias, A. Oritz, A. Linden, *J. Am. Chem. Soc.* **2001**, *123*, 5602–5603.
- 2001JA7207 A. G. Myers, J. K. Barbay, B. Zhong, *J. Am. Chem. Soc.* **2001**, *123*, 7207–7219.
- 2001JCS(P1)221 N. Baba, M. K. Alam, Y. Mori, S. S. Haider, M. Tanaka, S. Nakajima, S. Shimizu, *J. Chem. Soc., Perkin Trans 1* **2001**, 221–223.

- 2001JCS(P1)508 O. Westerhoff, A. Lützen, W. Maison, M. Kosten, J. Martens, *J. Chem. Soc., Perkin Trans 1* **2001**, 508–513.
- 2001JCS(P1)1220 A. Loupy, S.-J. Song, S.-M. Sohn, Y.-M. Lee, T.-W. Kwon, *J. Chem. Soc., Perkin Trans 1* **2001**, 1220–1222.
- 2001JCS(P1)1475 S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1475–1499.
- 2001JCS(P1)2217 J. F. Caplan, A. Sutherland, J. C. Vederas, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2217–2220.
- 2001JOC11 M. Adamczyk, D. D. Johnson, R. E. Reddy, *J. Org. Chem.* **2001**, 66, 11–19.
- 2001JOC2884 J. C. Martins, K. Van Rompaey, G. Wittmann, C. Tömböly, G. Tóth, N. De Kimpe, D. Tourwe, *J. Org. Chem.* **2001**, 66, 2884–2886.
- 2001JOC3597 H.-S. Lee, P. R. LePlae, E. A. Porter, S. H. Gellman, *J. Org. Chem.* **2001**, 66, 3597–3599.
- 2001JOC5054 M. Bellassoued, S. Mouelhi, N. Lensen, *J. Org. Chem.* **2001**, 66, 5054–5057.
- 2001JOC5606 A. R. Katritzky, S. Zhang, A. H. M. Hussein, Y. Fang, *J. Org. Chem.* **2001**, 66, 5606–5612.
- 2001OL3345 M. Takimoto, K. Shimizu, M. Mori, *Org. Lett.* **2001**, 3, 3345–3348.
- 2001OPRD498 J. A. Ragan, J. A. Murry, M. J. Castaldi, A. K. Conrad, B. P. Jones, B. Li, T. W. Makowski, R. McDermott, B. J. Sitter, T. D. White, *Org. Process Res. Dev.* **2001**, 5, 498–507.
- 2001S1830 M. Schlosser, A. Zellner, F. Leroux, *Synthesis* **2001**, 1830–1836.
- 2001S1873 J. Jensen, K. Warnmark, *Synthesis* **2001**, 1873–1877.
- 2001SL1555 T. Takemoto, K. Yasuda, S. V. Ley, *Synlett* **2001**, 1555–1556.
- 2001SL1941 S.-K. Lee, S. Y. Lee, Y. S. Park, *Synthetic Letters* **2001**, 12, 1941–1943.
- 2001T545 A. Avenoza, C. Cativiela, J. H. Busto, M. A. Fernández-Recio, *Tetrahedron* **2001**, 57, 545–548.
- 2001T2121 A. S. Lee, Y. Hu, S. Chu, *Tetrahedron* **2001**, 57, 2121–2126.
- 2001T2781 A. Salgado, T. Huybrechts, A. Eeckhaut, J. Van Der Eycken, Z. Szakonyi, F. Fülöp, A. Tkachev, N. De Kimpe, *Tetrahedron* **2001**, 57, 2781–2786.
- 2001T2965 C. Barberis, N. Voyer, J. Roby, S. Chénard, M. Tremblay, P. Labrie, *Tetrahedron* **2001**, 57, 2965–2972.
- 2001T5073 T. Hirao, C. Morimoto, T. Takada, H. Sakurai, *Tetrahedron* **2001**, 57, 5073–5079.
- 2001T5339 Y. Lee, R. B. Silverman, *Tetrahedron* **2001**, 57, 5339–5342.
- 2001T6383 R. Warmuth, T. E. Munsch, R. A. Stalker, B. Li, A. Beatty, *Tetrahedron* **2001**, 57, 6383–6397.
- 2001T6417 E. Bunuel, A. M. Gil, M. D. Diaz-de-Villegas, C. Cativiela, *Tetrahedron* **2001**, 57, 6417–6427.
- 2001T6579 R. Ling, I. V. Ekhatov, J. R. Rubin, D. J. Wustrow, *Tetrahedron* **2002**, 57, 6579–6588.
- 2001T6589 S. Caddick, C. A. M. Afonso, A. X. Candeias, P. B. Hitchcock, K. Jenkins, M. D. Pardoe, A. Gil Santos, N. R. Treweek, R. Weaving, *Tetrahedron* **2001**, 57, 6589–6605.
- 2001TA279 F. Effenberger, S. Obwald, *Tetrahedron Asymmetry* **2001**, 12, 279–285.
- 2001TA347 J. M. Andrés, M. A. Martínez, R. Pedrosa, A. Pérez-Encabo, *Tetrahedron Asymmetry* **2001**, 12, 347–353.
- 2001TA3367 M.-X. Wang, C.-S. Liu, J.-S. Li, *Tetrahedron Asymmetry* **2001**, 12, 3367–3373.
- 2001TL513 R. Gandolfi, N. Ferrara, F. Molinari, *Tetrahedron Lett.* **2001**, 42, 513–514.
- 2001TL1433 G. Borg, M. Chino, J. A. Ellman, *Tetrahedron Lett.* **2001**, 42, 1433–1436.
- 2001TL1835 H. Yu, C. E. Ballard, B. Wang, *Tetrahedron Lett.* **2001**, 42, 1835–1838.
- 2001TL2665 F. Tellier, M. Audouin, R. Sauévre, *Tetrahedron Lett.* **2001**, 42, 2665–2667.
- 2001TL3563 R. Roers, G. L. Verdine, *Tetrahedron Lett.* **2001**, 42, 3563–3565.
- 2001TL5163 R. W. Jackson, *Tetrahedron Lett.* **2001**, 42, 5163–5165.
- 2001TL5525 S. Bhattacharya, M. Thomas, *Tetrahedron Lett.* **2001**, 42, 5525–5528.
- 2001TL6607 H. Heaney, A. J. Newbold, *Tetrahedron Lett.* **2001**, 42, 6607–6609.
- 2001TL7163 B. Liu, K. D. Moeller, *Tetrahedron Lett.* **2001**, 42, 7163–7165.
- 2001TL7303 S. Kobayashi, N. Shiraishi, W. W.-L. Lam, K. Manabe, *Tetrahedron Lett.* **2001**, 42, 7303–7306.
- 2001TL8713 J. J. Turner, M. A. Leeuwenburgh, G. A. van der Marcel, J. H. van Boom, *Tetrahedron Lett.* **2001**, 42, 8713–8719.
- 2002Ag(E)623 H. Oka, S. Yamago, J. Yoshida, O. Kajimoto, *Angew. Chem., Int. Ed. Engl.* **2002**, 41, 623–625.
- 2002BMC913 M. Lee, D. H. Kim, *Biorg. Med. Chem.* **2002**, 10, 913–922.
- 2002BMCL2439 G. M. Coppola, R. E. Damon, J. Bruce Eskesen, D. S. France, J. R. Paterniti Jr., *Biorg. Med. Chem. Lett.* **2002**, 12, 2439–2442.
- 2002CC224 A. Sutherland, J. C. Vederas, *J. Chem. Soc., Chem. Commun.* **2002**, 224–225.
- 2002CC1116 K. S. Kim, Y. Joo, Lee, J. H. Kim, D. K. Sung, *J. Chem. Soc., Chem. Commun.* **2002**, 1116–1117.
- 2002CC1748 F. Stieber, H. Waldmann, *J. Chem. Soc., Chem. Commun.* **2002**, 1748–1749.
- 2002CC2380 D. L. J. Clive, M. Yu, *J. Chem. Soc., Chem. Commun.* **2002**, 2380–2381.
- 2002EJO1690 S. Nakamura, A. Furutani, T. Toru, *Eur. J. Org. Chem.* **2002**, 1690–1695.
- 2002JA2259 J. F. Mata-Segreda, *J. Am. Chem. Soc.* **2002**, 124, 2245–2258.
- 2002JA2870 L. Tang, L. Deng, *J. Am. Chem. Soc.* **2002**, 124, 2870–2871.
- 2002JA7801 E. Galoppini, W. Guo, W. Zhang, P. G. Hoertz, P. Qu, G. J. Meyer, *J. Am. Chem. Soc.* **2002**, 124, 7801–7811.
- 2002JA9024 G. DeSantis, Z. Zhu, W. A. Greenberg, K. Wong, J. Chaplin, S. R. Hanson, B. Farwell, L. W. Nicholson, C. L. Rand, D. P. Weiner, D. E. Robertson, M. J. Burk, *J. Am. Chem. Soc.* **2002**, 124, 9024–9025.
- 2002JA9692 K. Mukhopadhyay, B. R. Sarkar, R. V. Chaudhari, *J. Am. Chem. Soc.* **2002**, 124, 9692–9693.
- 2002JA11870 M. J. Dearden, C. R. Firkin, J. R. Hermet, P. O'Brien, *J. Am. Chem. Soc.* **2002**, 124, 11870–11871.
- 2002JA11379 G. A. Olah, B. Török, J. P. Joschek, I. Bucsi, P. M. Esteves, G. Rasui, G. K. S. Prakash, *J. Am. Chem. Soc.* **2002**, 124, 11379–11391.

- 2002JCS(P1)529 Y. L. Janin, E. Roulland, A. Beurdeley-Thomas, D. Decaudin, C. Monneret, M.-F. Poupon, *J. Chem. Soc., Perkin Trans. 1.* **2002**, 529–532.
- 2002JCS(P1)1024 K. Yasuda, S. V. Ley, *J. Chem. Soc., Perkin Trans. 1.* **2002**, 1024–1025.
- 2002JCS(P1)1159 Y. Six, *J. Chem. Soc., Perkin Trans. 1.* **2002**, 1159–1160.
- 2002JCS(P1)2256 F. Karimi, B. Långström, *J. Chem. Soc., Perkin Trans. 1.* **2002**, 2256–2259.
- 2002JFC(113)167 F. Tellier, M. Audouin, R. Sauévre, *J. Fluorine Chem.* **2002**, 113, 167–175.
- 2002JFC(113)211 J. Kvicala, R. Hrabal, J. Czernek, I. Bartosová, O. Paleta, A. Pelter, *J. Fluorine Chem.* **2002**, 113, 211–218.
- 2002JMC1535 A. Friese, K. Hell-Momeni, T. Winckler, T. Dingermann, G. Dannhardt, *J. Med. Chem.* **2002**, 45, 1535–1542.
- 2002JOC72 R. Ocampo, W. R. Dolbier Jr., K. A. Abboud, F. Zuluaga, *J. Org. Chem.* **2002**, 67, 72–78.
- 2002JOC2192 Z. Szakonyi, F. Fülöp, D. Tourwé, N. De Kimpe, *J. Org. Chem.* **2002**, 67, 2192–2196.
- 2002JOC2509 Z. Zhao, H.-W. Liu, *J. Org. Chem.* **2002**, 67, 2509–3514.
- 2002JOC3468 B. Dolensky, K. L. Kirk, *J. Org. Chem.* **2002**, 67, 3468–3473.
- 2002JOC3933 L. J. Charbonnière, N. Weibel, R. F. Ziessel, *J. Org. Chem.* **2002**, 67, 3933–3936.
- 2002JOC5440 N. F. Badham, W. L. Mendelson, A. Allen, A. M. Diederich, D. S. Eggleston, J. J. Filan, A. J. Freyer, L. B. Killmer, C. J. Kowalski, L. Liu, V. J. Novack, F. G. Vogt, K. S. Webb, J. Yang, *J. Org. Chem.* **2002**, 67, 5440–5443.
- 2002JOC6008 J. Jensen, J. Tejler, K. Wärnmark, *J. Org. Chem.* **2002**, 67, 6008–6014.
- 2002JOC7131 A. Kar, N. P. Argade, *J. Org. Chem.* **2002**, 67, 7131–7134.
- 2002JOC7741 T. Konoike, K. Matsumura, T. Yorifuji, S. Shinomoto, *J. Org. Chem.* **2002**, 67, 7741–7749.
- 2002JOC7761 C.-H. Lin, J. Tour, *J. Org. Chem.* **2002**, 67, 7761–7768.
- 2002NJCS567 P. Stepnicka, *New J. Chem.* **2002**, 26, 567–575.
- 2002OL371 D. Kato, S. Mitsuda, H. Ohta, *Org. Lett.* **2002**, 4, 371–373.
- 2002OL1291 P. K. Chakravarty, S. Tyagarajan, T. L. Shih, S. Salva, C. Snedden, M. J. Wyvratt, M. H. Fisher, P. T. Meinke, *Org. Lett.* **2002**, 4, 1291–1294.
- 2002OL3549 M. B. Andus, E. L. Meredith, B. L. Simmons, B. B. V. Soma Sekhar, E. J. Hicken, *Org. Lett.* **2002**, 4, 3549–3552.
- 2002T7391 G. A. Kraus, H. Ogutu, *Tetrahedron* **2002**, 58, 7391–7395.
- 2002TA975 H. Boussac, J. Crassous, J. Dutasta, L. Grosvalet, A. Thozet, *Tetrahedron Asymmetry* **2002**, 13, 975–981.
- 2002TA1059 M. Kimura, A. Atsuhito, T. Sugai, *Tetrahedron Asymmetry* **2002**, 13, 1059–1068.
- 2002TA1461 A. Chadha, B. Baskar, *Tetrahedron Asymmetry* **2002**, 13, 1461–1464.
- 2002TL4439 J. Matulic-Adamic, M. Sanseverino, L. Beigelman, *Tetrahedron Lett.* **2002**, 43, 4439–4441.
- 2002TL4973 A. S. Kende, H.-Q. Dong, X. Liu, F. H. Ebetino, *Tetrahedron Lett.* **2002**, 43, 4973–4976.
- 2002TL5555 F. Chemat, *Tetrahedron Lett.* **2002**, 43, 5555–5557.
- 2002TL7135 Y. Liu, G. W. Gribble, *Tetrahedron Lett.* **2002**, 43, 7135–7137.
- 2002TL7179 H. Ji, T. Mizugaki, K. Ebitani, K. Kaneda, *Tetrahedron Lett.* **2002**, 43, 7179–7183.
- 2002TL7871 H. Mori, A. Mori, Q. Xu, Y. Souma, *Tetrahedron Lett.* **2002**, 43, 7871–7874.
- 2002TL8253 J. Nam, S. Lee, K. Y. Kim, Y. S. Park, *Tetrahedron Lett.* **2002**, 43, 8253–8255.
- 2003BMC723 J. B. Laursen, C. G. Jorgensen, J. Neilsen, *Biorg. Med. Chem.* **2003**, 11, 723–731.
- 2003BMCL2413 B. Raju, K. Mortell, S. Anandan, H. O'Dowd, H. Gao, M. Gomez, C. Hackbarth, C. Wu, W. Wang, Z. Yuan, R. White, J. Trias, D. V. Patel, *Biorg. Med. Chem. Lett.* **2003**, 13, 2413–2418.
- 2003BMCL2651 T. Aya, A. D. Hamilton, *Biorg. Med. Chem. Lett.* **2003**, 13, 2651–2654.
- 2003BMCL2659 M. Flipo, I. Florent, P. Grellier, C. Sergheraert, R. Deprez-Poulain, *Biorg. Med. Chem. Lett.* **2003**, 13, 2659–2662.
- 2003CC386 Z.-L. Wu, Z.-Y. Li, *J. Chem. Soc., Chem. Commun.* **2003**, 386–387.
- 2003CC536 B. Jiang, F. Zhang, W. Xiong, *J. Chem. Soc., Chem. Commun.* **2003**, 536–537.
- 2003CC1642 C. A. Hunter, P. S. Jones, P. M. N. Tiger, S. Tomas, *J. Chem. Soc., Chem. Commun.* **2003**, 1642–1643.
- 2003CC2184 F. J. P. Feuillet, D. E. J. E. Robinson, S. D. Bull, *J. Chem. Soc., Chem. Commun.* **2003**, 2184–2186.
- 2003CL454 T. Hattori, Y. Suzuki, S. Miyano, *Chemistry Letters* **2003**, 32, 454–455.
- 2003EJO1157 Y. Six, *Eur. J. Org. Chem.* **2003**, 1157–1171.
- 2003JA4996 T. Chatterji, M. Kizil, K. Keerthi, G. Chowdhury, T. Pospisil, K. S. Gates, *J. Am. Chem. Soc.* **2003**, 125, 4996–4997.
- 2003JA5260 N. Miranda, P. Daublain, J. H. Horner, M. Newcomb, *J. Am. Chem. Soc.* **2003**, 125, 5260–5261.
- 2003JA5351 H. M. Jung, K. E. Price, D. T. McQuade, *J. Am. Chem. Soc.* **2003**, 125, 5351–5355.
- 2003JA6149 M. R. Pratt, C. R. Bertozzi, *J. Am. Chem. Soc.* **2003**, 125, 6149–6159.
- 2003JMC978 K. Dzierzbicka, P. Trozonkowski, P. Sewerynek, A. Mysliwaki, *J. Med. Chem.* **2003**, 46, 978–986.
- 2003JMC1811 R. J. Cherney, J. J.-W. Duan, M. E. Voss, L. Chen, L. Wang, D. T. Meyer, Z. R. Wasserman, K. D. Hardman, R.-Q. Liu, M. B. Covington, M. Qian, S. Mandleskar, D. D. Christ, J. M. Trzaskos, R. C. Newton, R. L. Magolda, R. R. Wexler, C. P. Decicco, *J. Med. Chem.* **2003**, 46, 1811–1823.
- 2003JOC240 H. Sauriat-Dorizon, T. Maris, J. D. Wuest, *J. Org. Chem.* **2003**, 68, 240–246.
- 2003JOC621 M. Wang, G. Feng, *J. Org. Chem.* **2003**, 68, 621–624.
- 2003JOC4574 G. V. M. Sharma, C. G. Reddy, P. R. Krishna, *J. Org. Chem.* **2003**, 68, 4574–4575.
- 2003JOC4973 T. K. Ellis, V. M. Hochla, V. A. Soloshonok, *J. Org. Chem.* **2003**, 68, 4973–4976.
- 2003JOC4999 L. De Luca, G. Giacomelli, S. Masala, A. Porcheddu, *J. Org. Chem.* **2003**, 68, 4999–5001.

- 2003JOC7234 D. Kato, S. Mitsuda, H. Ohta, *J. Org. Chem.* **2003**, 68, 7234–7242.
2003JOC7479 J. Shen, D. Qun, H. Zhang, Z. Yao, *J. Org. Chem.* **2003**, 68, 7479–7484.
2003JOC7544 Z. Jian, Y. Qin, F. Quing, *J. Org. Chem.* **2003**, 68, 7544–7547.
2003JOC7555 X. Jiang, L. Song, Y. Long, *J. Org. Chem.* **2003**, 68, 7555–7558.
2003NewJournalChem387 E. Teoh, E. M. Campi, W. R. Jackson, A. J. Robinson, *New J. Chem.* **2003**, 27, 387–394.
2003OBC140 L. J. Oates, R. F. W. Jackson, M. H. Block, *Organic and Biomolecular Sciences* **2003**, 140–144.
2003OBC535 M.-X. Wang, Y. Wu, *Organic and Biomolecular Chemistry* **2003**, 535–540.
2003OBC1308 H. Emtenäs, M. Carlsson, J. S. Pinker, S. J. Hultgren, F. Almqvist, *Organic and Biomolecular Chemistry* **2003**, 1, 1308–1314.
2003OBC1707 R. Hovland, A. J. Aasen, J. Klaveness, *Organic and Biomolecular Chemistry* **2003**, 1, 1707–1710.
2003OBC2531 E. Bunel, S. D. Bull, S. G. Davies, A. C. Garner, E. D. Savory, A. D. Smith, R. J. Vickers, D. J. Watkin, *Organic and Biomolecular Chemistry* **2003**, 1, 2531–2542.
2003OL71 C. Ma, M. G. Steinmetz, Q. Cheng, V. Jayaraman, *Org. Lett.* **2003**, 5, 71–74.
2003OL101 S. Limura, K. Manabe, S. Kobayashi, *Org. Lett.* **2003**, 5, 101–103.
2003OL957 H. Kigoshi, M. Kita, S. Ogawa, M. Itoh, D. Uemura, *Org. Lett.* **2003**, 5, 957–960.
2003OL4469 W. N. Atemnkeng, L. D. Louisiana II, P. K. Yong, B. Vottero, A. Banerjee, *Org. Lett.* **2003**, 5, 4469–4471.
2003OPRD198 D. Ainge, D. Ennis, M. Gidlund, M. Stefinovic, L. Vaz, *Org. Process Res. Dev.* **2003**, 7, 198–201.
2003T2007 R. J. Bergeron, G. Huang, R. E. Smith, N. Bharti, J. S. McManis, A. Butler, *Tetrahedron* **2003**, 59, 2007–2014.
2003T4973 A.-S. Rebstock, F. Mongin, F. Trécourt, G. Quéguiner, *Tetrahedron* **2003**, 59, 4973–4977.
2003T5241 L. Patiny, J.-F. Guichou, M. Keller, O. Turpin, T. Rückle, P. Lhote, T. M. Buetler, U. T. Rugg, R. M. Wenger, M. Mutter, *Tetrahedron* **2003**, 59, 5241–5249.
2003TL695 N. M. Howarth, L. P. G. Wakelin, D. M. Walker, *Tetrahedron Lett.* **2003**, 44, 695–698.
2003TL769 N. Al-Haq, A. C. Sullivan, J. R. H. Wilson, *Tetrahedron Lett.* **2003**, 44, 769–771.
2003TL1611 J. S. Choi, Y. Lee, E. Kim, N. Jeong, H. Yu, H. Han, *Tetrahedron Lett.* **2003**, 44, 1611–1614.
2003TL1755 A. Song, X. Wang, K. S. Lam, *Tetrahedron Lett.* **2003**, 44, 1755–1758.
2003TL1767 J. Husson, M. Beley, G. Kirsch, *Tetrahedron Lett.* **2003**, 44, 1767–1770.
2003TL3211 G. Lukács, M. Porcs-Makkay, G. Simig, *Tetrahedron Lett.* **2003**, 44, 3211–3214.
2003TL3381 K. Wright, M. Crisma, C. Toniolo, R. Török, A. Péter, M. Wakselman, J.-P. Mazaleyrat, *Tetrahedron Lett.* **2003**, 44, 3381–3384.
2003TL3579 C. I. Chiriac, F. Tanasa, M. Onciu, *Tetrahedron Lett.* **2003**, 44, 3579–3580.
2003TL6033 S. Das, T. Punniyamurthy, *Tetrahedron Lett.* **2003**, 44, 6033.
2003TL7011 M.-P. Brun, A.-S. Martin, C. Garbay, L. Bishoff, *Tetrahedron Lett.* **2003**, 44, 7011–7013.
2003TL7663 P. Allevi, M. Anastasia, *Tetrahedron Lett.* **2003**, 44, 7663–7665.
2004T11 Neil F. Badham, *Tetrahedron* **2004**, 60, 11–42.
2004T13 N. F. Badham, *Tetrahedron* **2004**, 60, 11–42.
2004T577 E. C. Hann, A. E. Sigmund, S. F. Fager, F. B. Cooling, J. E. Gavagan, M. G. Bramucci, S. Chauhan, M. S. Payne, R. DiCosimo, *Tetrahedron* **2004**, 60, 577–581.

Biographical sketch

Dr. Sean P. Bew. Following his Ph.D., he undertook postdoctoral research at the Universities of Nottingham and Cardiff with Professor D. W. Knight and at Oxford University with Professor S. G. Davies. He took up his present position as a Lecturer in Organic Chemistry at University of East Anglia in 2000. His research interests include: synthesis of cell-surface receptor binding calixarenes, the development of methodology for the asymmetric synthesis of aziridines, asymmetric heterocyclic intramolecular Diels–Alder reactions, development of potential β -turn mimics based on Trögers base and the synthesis of novel multidentate P,N-ligands for use in asymmetric catalysts.

5.03

Carboxylic Esters and Lactones

B. R. BUCKLEY

Loughborough University, Loughborough, UK

5.03.1	CARBOXYLIC ESTERS VIA ESTERIFICATION REACTIONS	128
5.03.1.1	Direct Esterification Using Carboxylic Acids and Alcohols	128
5.03.1.2	Esterification by Carboxylic Group-activated Intermediates (Mixed Anhydrides or Activated Esters)	130
5.03.1.3	Esterification of Alcohols with Acid Halides and Anhydrides	131
5.03.1.4	Esterification via Hydroxyl Group Activation	134
5.03.1.5	Alkylation of Carboxylate Anions	136
5.03.1.6	Transesterification	136
5.03.1.7	Enzymatic Transesterification	138
5.03.1.8	Monoacylation of Polyols	139
5.03.2	ESTERS WITH POLYFUNCTIONAL ALCOHOL COMPONENTS	140
5.03.2.1	1- and 2-Haloalkyl Esters	140
5.03.2.2	Nitrogen-substituted Alcohol Components	140
5.03.3	ESTERS VIA OXIDATION REACTIONS	141
5.03.3.1	Without Changing the Number of Carbons	141
5.03.3.2	Esters via Ozonolytic Cleavage of Double Bonds	144
5.03.3.3	Esters via Baeyer–Villiger Oxidation	144
5.03.4	ESTERS VIA ONE CARBON CHAIN ELONGATION	145
5.03.4.1	Alkoxyacylation	145
5.03.4.2	Arndt–Eistert Homologation	146
5.03.5	ESTERS OF PARTICULAR CARBOXYLIC ACIDS	148
5.03.5.1	Esters of Cycloalkanoic Acids	148
5.03.5.2	α - and β -C-Branched Alkenoic Acids	150
5.03.5.2.1	Enolate alkylation	150
5.03.5.2.2	Conjugate addition to α,β -enoates	151
5.03.5.3	α,β -Unsaturated Esters	154
5.03.5.3.1	α,β -Unsaturated esters via redox reactions	154
5.03.5.3.2	α,β -Unsaturated esters via alkenation	155
5.03.5.3.3	α,β -Unsaturated esters via Heck coupling or alkoxyacylation	156
5.03.5.4	β,γ -Unsaturated Esters	157
5.03.5.4.1	β,γ -Unsaturated esters via alkoxyacylation	157
5.03.5.4.2	β,γ -Unsaturated esters via S_N2' reaction	157
5.03.5.5	γ,δ -Unsaturated Esters	157
5.03.5.5.1	γ,δ -Unsaturated esters via Tsuji–Trost reaction	157
5.03.5.5.2	γ,δ -Unsaturated esters via Claisen–Johnson rearrangement	157
5.03.5.6	α,β -Alkynoic Esters	158
5.03.6	LACTONES	158
5.03.6.1	β -Lactones	159
5.03.6.2	γ -Lactones	161
5.03.6.2.1	γ -Lactones by direct cyclodehydration of γ -hydroxycarboxylates	161
5.03.6.2.2	γ -Lactones by enolate additions	162
5.03.6.2.3	γ -Lactones from β,γ -, and γ,δ -ene-carboxylates	163
5.03.6.2.4	Ring enlargement of β -lactones	164
5.03.6.2.5	Carbonylation reactions	164
5.03.6.2.6	γ -Lactones via redox reactions	164
5.03.6.3	δ -Lactones	165
5.03.6.4	Macrolactones	166

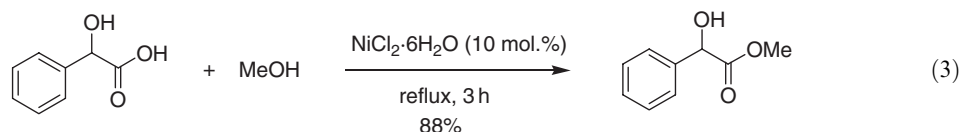
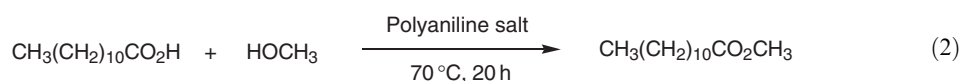
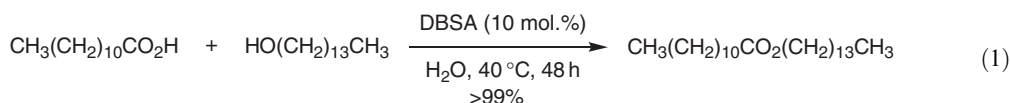
5.03.1 CARBOXYLIC ESTERS VIA ESTERIFICATION REACTIONS

This subject has been covered by a number of reviews which were outlined in <1995COFGT(5)121> and more recently in references <1997COS309, 1998JCS(P1)2451, 1999JCS(P1)3537, 2001AG(E)2044>. There are numerous methods for the synthesis of esters and lactones; this chapter therefore offers an overview of the most important and commonly used methods.

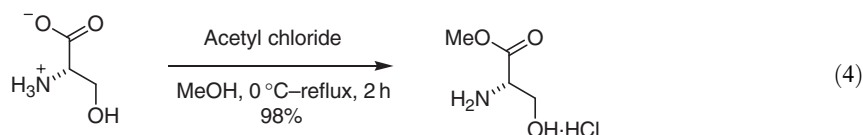
5.03.1.1 Direct Esterification Using Carboxylic Acids and Alcohols

This is the most general and least expensive method for carboxylic ester synthesis. A carboxylic acid and alcohol are mixed together in a suitable solvent and treated with a Brønsted or Lewis acid. Equations (1)–(12) show a selection of examples.

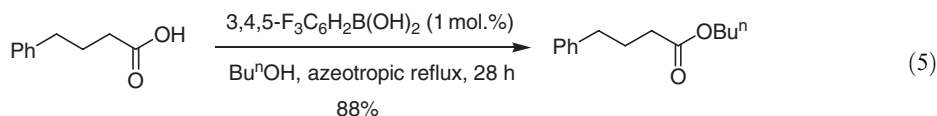
Surfactant-type Brønsted acid-catalyzed direct esterification of carboxylic acids with alcohols can occur in water <2001JA10102>. Excellent product yields have been achieved using 4-dodecylbenzenesulfonic acid (DBSA) with 1:1 carboxylic acid and alcohol ratios (Equation (1)). Esterification of carboxylic acids with alcohols can also be achieved with catalytic polyaniline salts (Equation (2)) <2002GC53>. Esterification of carboxylic acids has been accomplished using catalytic $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ giving the corresponding carboxylic esters in excellent yields (Equation (3)) <1997T7335>.



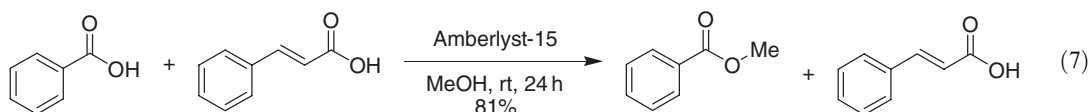
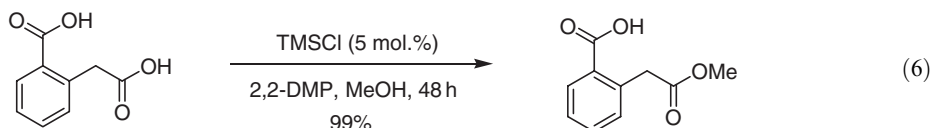
The use of acetyl chloride and methanol or ethanol leads to the *in situ* generation of HCl, which promotes the formation of methyl or ethyl esters in 57–100% yield <1998SC471>. This method is particularly useful in the preparation of methyl or ethyl esters of amino acids, in which no racemization is observed (Equation (4)) <1998S1707>.



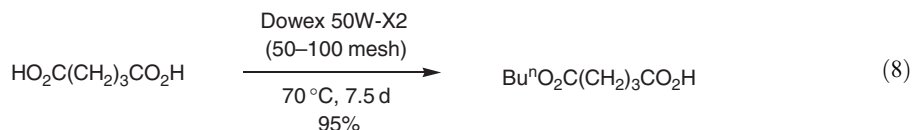
The conditions used for boron-catalyzed amidation reactions have been found to be useful for esterification. Using 1 mol. % of 3,4,5-trifluorobenzeneboronic acid and 1-butanol, effective esterification of 4-phenylbutyric acid was observed (Equation (5)) <1996JOC4197>.



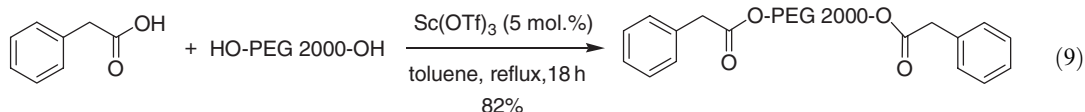
A selective method for the preparation of aliphatic methyl esters in the presence of aromatic carboxylic acids has been reported. A mixture of 2,2-dimethoxypropane/methanol in the presence of anhydrous HCl generated *in situ* from TMSCl, selectively esterified aliphatic over aromatic carboxylic acids (Equation (6)) <1998TL8563>. Selective esterification of nonconjugated carboxylic acids in the presence of conjugated or aromatic carboxylic acids can be achieved under mild conditions using the Amberlyst-15 resin (Equation (7)) <1999JCR(S)378>.



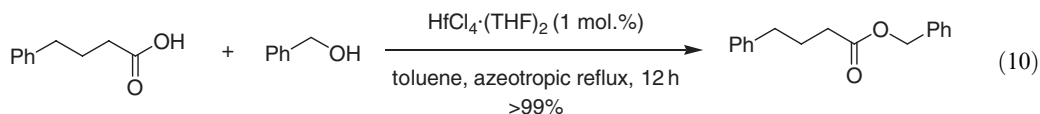
Selective monoesterification of symmetric diacids has been reported and is catalyzed by the Dowex 50W-X2 ion-exchange resin, with excellent yields (Equation (8)) <1996TL6733>.



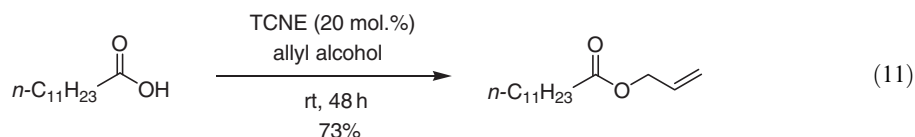
To avoid environmental waste it is highly desirable that both the carboxylic acid and alcohol are used in stoichiometric amounts, and this is also important if the substrates are scarce, expensive, or obtained after multistep synthesis. Therefore, development of new procedures wherein stoichiometric amounts of carboxylic acids and alcohols are sufficient is particularly desirable. Some very good procedures have been reported recently <2000TL5249, 2000S290>. A variety of carboxylic acids have been directly condensed with polyethylene glycols catalyzed by $\text{Sc}(\text{OTf})_3$ (Equation (9)) <2002TL8335>.



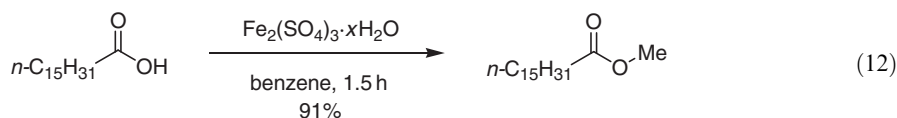
Hafnium(IV) and zirconium(IV) salts have also been explored as effective catalysts for direct ester condensation from carboxylic acids and alcohols with stoichiometric ratios of 1:1 (Equation (10)) <2002T8179>.



Tetracyanoethylene (TCNE) has been found to catalyze several reactions including the esterification of carboxylic acids. The catalytic π -acid affords good yields of a variety of functionalized esters and is reported to tolerate both *N*-Cbz and *N*-*t*-BOC groups under what are essentially neutral and mild conditions (Equation (11)) <1997CL55>.

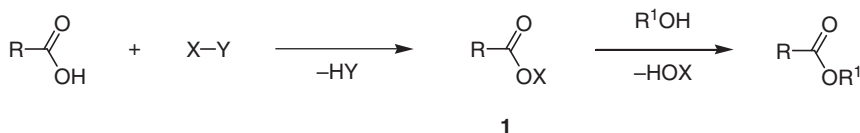


Another mild process is catalyzed by iron(III) sulfate, where a range of aliphatic mono- and bis-carboxylic acids can be esterified in excellent yields (Equation (12)) <1998SC1159>.



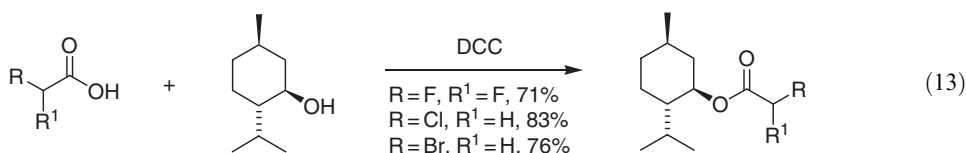
5.03.1.2 Esterification by Carboxylic Group-activated Intermediates (Mixed Anhydrides or Activated Esters)

This is one of the most important methods when stoichiometric amounts of acid and alcohol are employed, and sensitive functionality is present in either component. The mechanism of the reaction involves the formation of a carboxyl group-activated (CGA) intermediate **1** from the carboxylic acid and an activation agent X—Y (Scheme 1). The species **1** then acts as the acylating agent for the alcohol. In effect X—Y is transformed into H—Y and HOX during the reaction.

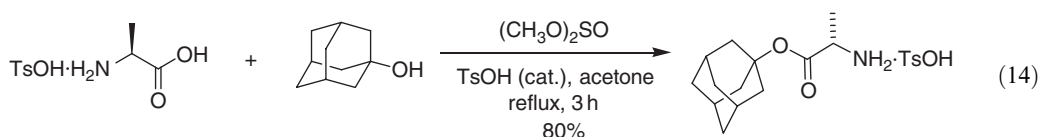


Scheme 1

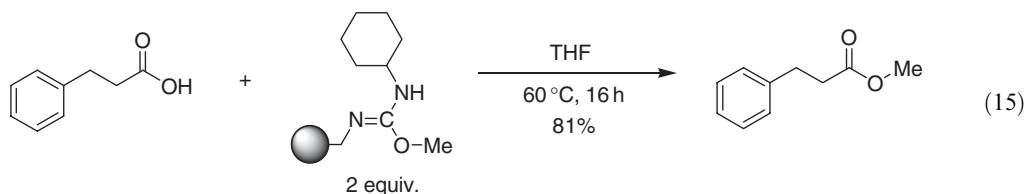
Dicyclohexylcarbodiimide (DCC) is an important reagent used to form activated esters and there is a wide range of methods, which utilize this reagent many of which were reviewed in <1995COFGT(5)121>. More recently Streinz has investigated the use of DCC in the esterification of carboxylic acids containing α -halogen atoms. Classical DCC methods were found to be incompatible with these substrates, hence a new system was developed which employs a reaction medium that is both solvent-free and base-free. DCC and the alcohol are mixed, and once solidified the acid is added and the reaction heated to 100 °C. Excellent yields of the corresponding esters can be achieved (Equation (13)) <2001SL809>.



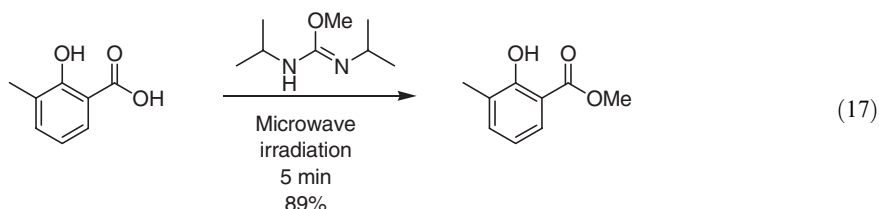
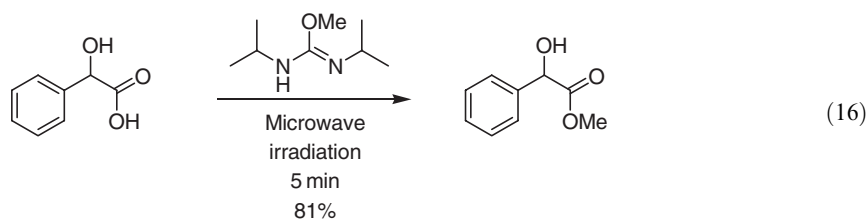
Carboxylic acids are often converted into trialkylmethyl esters, which are then employed as carboxy-protected derivatives; the *t*-butyl group typically represents this class of protecting group. Tricyclic tertiary 1-adamantanol is known to generate a carbenium ion at the bridgehead position that is more stable than the corresponding *t*-butylcarbenium ion, which is free to undergo alkene-forming side reactions. Adamantyl esters of α -amino acids are acid-labile but more stable than their *t*-butyl analogs. Iossifidou and Froussios have reported a practical synthesis for these hindered esters with good yields of adamantyl esters being reported (Equation (14)) <1996S1355>.



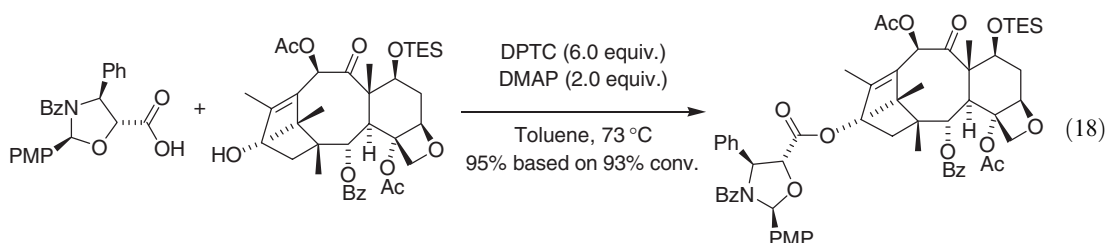
The use of polymer-supported reagents has proven to be extremely useful and many solid-supported reagents allow for a single filtration/evaporation sequence in order to isolate the desired product in good yield and purity. To this end several reagents for esterification have been developed. Polymer-supported *O*-methyl, *O*-benzyl, and *O*-allyl isoureas are able to convert a series of carboxylic acids to the corresponding methyl, benzyl, or allyl esters in good yield and purity (Equation (15)) <2002OL1035, 2003OL853>.



Modification of the traditional solution-phase reaction conditions, employing microwave irradiation, has resulted in a large rate of acceleration in the *O*-alkylation of carboxylic acids using isoureas. For example, esterification of the compounds shown in Equations (16) and (17) with conventional heating has been reported to require 3–4 h at 60 °C, while Crosignani and co-workers <2002OL2961> report complete conversion and excellent yields in just 5 min using microwave energy.



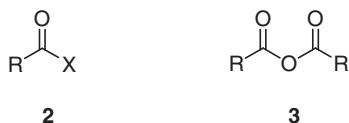
A combined reagent of *O,O'*-di(2-pyridyl)thiocarbonate (DPTC) and 4-(dimethylamino)-pyridine (DMAP) has proven to be effective in the formation of carboxylic esters when compared to the conventional combination of DCC and DMAP, *N*-alkyl-2-alkoxypyridinium salts with trialkylamines, di(2-pyridyl)carbonate (DPC), etc. as reported in <1995COFGT(5)121>. A large range of substrates was screened and excellent yields of esters were obtained, the mild reaction conditions being exemplified by the use of this system in the total synthesis of taxol. The side chain, a protected phenylisoserine, was coupled with 7-TES baccatin III in excellent yield (Equation (18)) <1998CL1, 1998CL3, 1998CL679>.



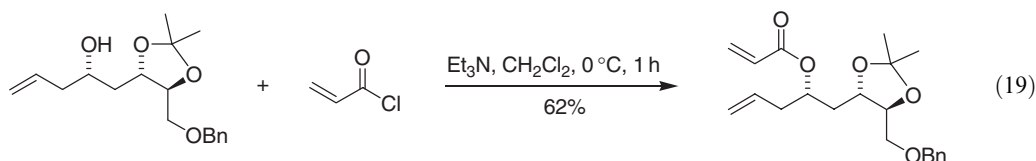
5.03.1.3 Esterification of Alcohols with Acid Halides and Anhydrides

This esterification method makes use of preformed CGA species **2** and **3** to which the alcohol is added. The formation of acid chlorides requires strong Lewis acids such as thionyl or oxalyl chloride, which may react with acid-sensitive functions in the molecule and also cause

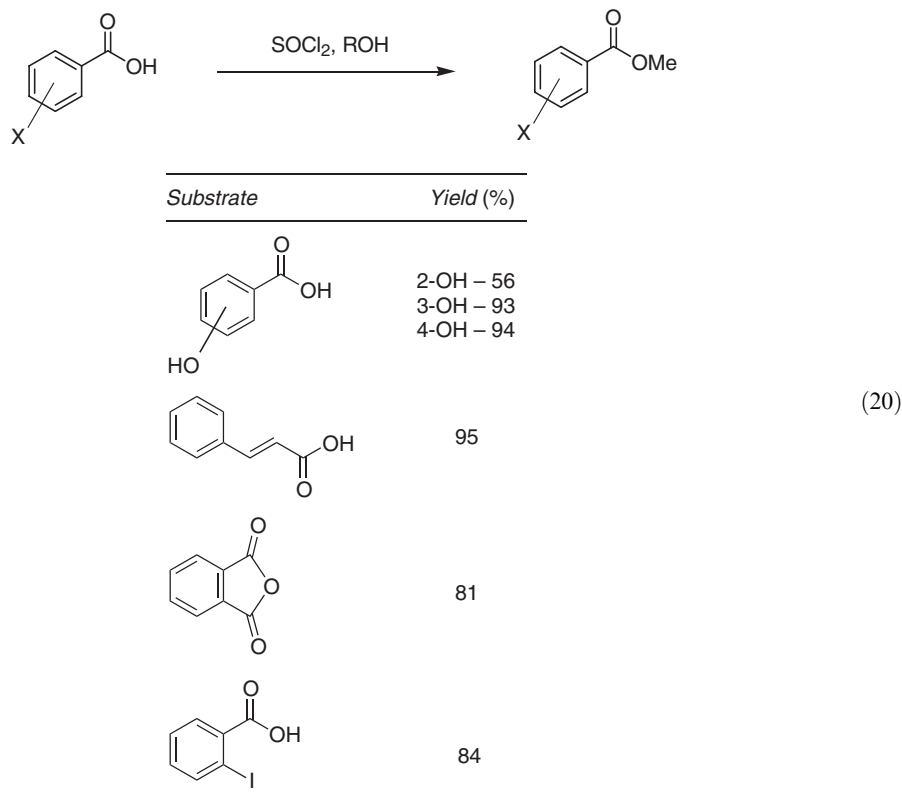
epimerization of chiral α -centers. Alternatively, using symmetrical anhydrides for esterification means the loss of 1 equiv. of acid. Thus, both **2** and **3** should preferably be used for inexpensive carboxylic acids with a low degree of functionalization.



Using this methodology the enantioselective synthesis of the C₁–C₉ segment of the antitumor agent macrolide peloruside has been accomplished. Reaction of the alcohol in [Equation \(19\)](#) with acryloyl chloride and triethylamine affords the desired acrylate ester in good yield. <2003TL3967>.

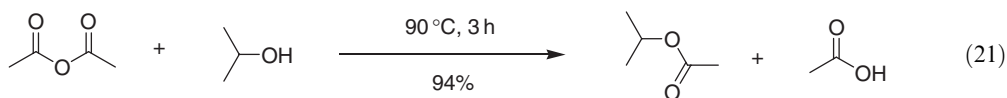


An efficient general method for esterification of aromatic carboxylic acids has been reported using thionyl chloride. [Equation \(20\)](#) illustrates the generality of this method, as phenolic hydroxy groups, amino groups, and olefinic double bonds are unaffected under these reaction conditions. This method is equally as effective for dicarboxylic acids, anhydrides, and halogenated aromatic carboxylic acids, in general; however, a reduction in yield is observed for *o*-substituted aromatics <1996TL6375>.

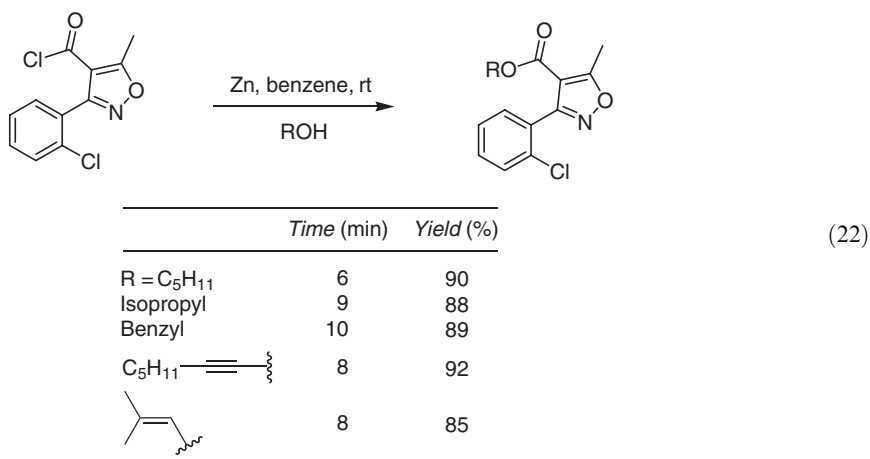


Esters of secondary and tertiary alcohols have been synthesized from alcohols and anhydrides in the absence of both solvent and catalyst in high yield. The alcohol and anhydride are mixed together in a 1:3 molar ratio and heated to the desired temperature ([Equation \(21\)](#))

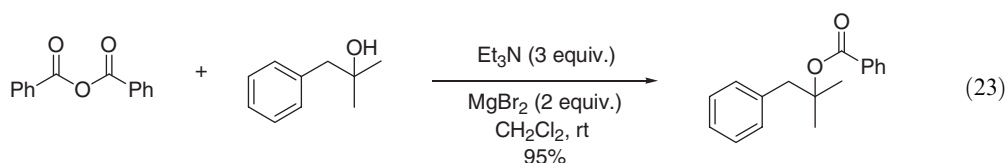
<1997SC2777>. Another report of solvent-free conditions utilizes DABCO, with aliphatic and aromatic esters being synthesized from acid chlorides and alcohols <2002SC23>.



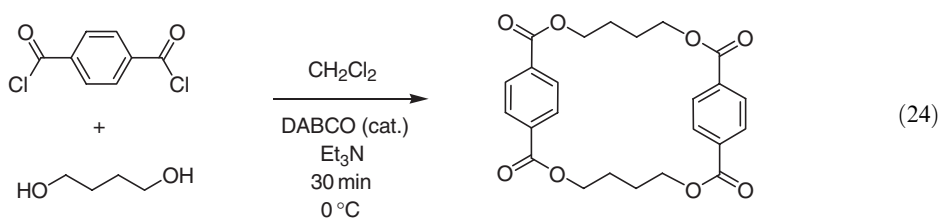
Zinc-promoted esterification of acid chlorides with alcohols has been achieved, affording a variety of esters in excellent yields (Equation (22)) <1998SC2337>. The efficiency of the reaction is explained by the fact that the polar groups complex to the surface of zinc and increase the electrophilic character of the acyl groups.



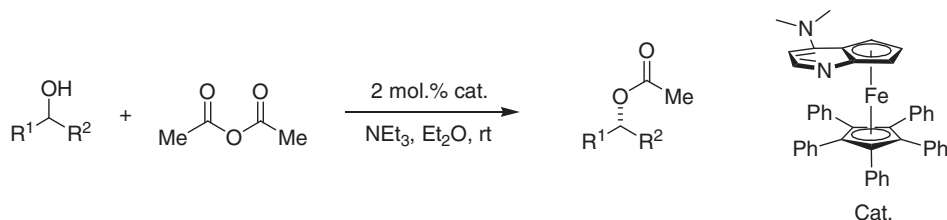
A novel method for ester synthesis involving dual activation affords good yields in reactions between hindered alcohols and anhydrides using magnesium bromide and a tertiary amine (Equation (23)) <1996JOC5702>.



Brunelle and co-workers <1997PP381> have reported the amine-catalyzed reaction of acid chlorides with diols (Equation (24)). The yield of the cyclic oligomers is strongly dependent on the structure of the amine catalyst, with the highest yields obtained with sterically unhindered amines such as quinuclidine. Optimization studies eventually led to a process, which uses catalytic amounts of DABCO in conjunction with stoichiometric quantities of triethylamine, producing up to 85% yields of poly(butylene terephthalate) (PBT) cyclic oligomers. Brittain and co-workers <1996MM8304> have also reported their progress in this area and a detailed mechanistic study on this process <1998JOC677>.



Fu and co-workers have reported the effective kinetic resolution of a range of propargylic <1999JA5091> and secondary alcohols <1997JA1492, 1998JOC2794, 2000ACR412>, by acetylation using a planar chiral analog of DMAP. Excellent enantioselectivity is observed for the unreacted alcohols (Equation (25)).



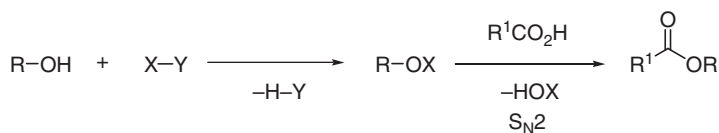
Unreacted alcohol, major enantiomer	Unreacted alcohol (%) ee	Conversion
	R = Me 95.2	62
	Et 98.8	62
	Pr ⁱ 97.7	55
	Bu ^t 92.2	51
	CH ₂ Cl 98.9	69
	99.7	63
	99.1	67
	96.0	58
	95.0	64
	95.0	66
	94.0	69

(25)

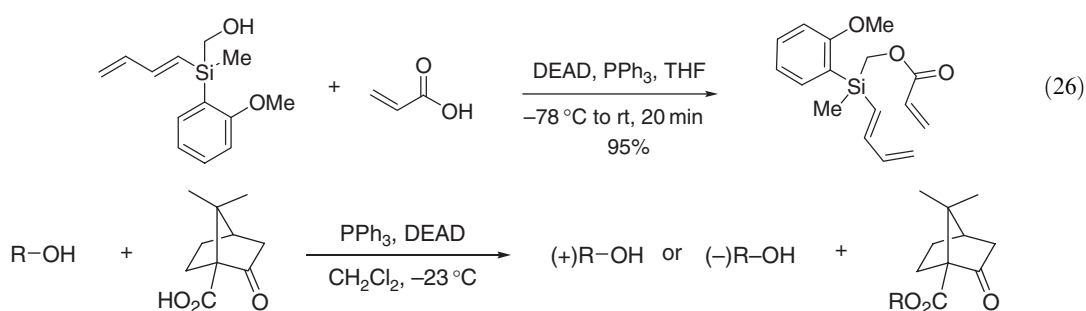
5.03.1.4 Esterification via Hydroxyl Group Activation

The mechanism of hydroxyl group activation (HGA) esterification is shown in Scheme 2. The alcohol first reacts with a reagent X—Y under HY-elimination to form a hydroxyl group-activated species, which is attacked by the carboxylate under S_N2 substitution. Using this mechanism, the esterification typically proceeds under the formation of an *O*-alkyl bond under S_N2 inversion of the configuration at R. This means that R should be primary or secondary, and

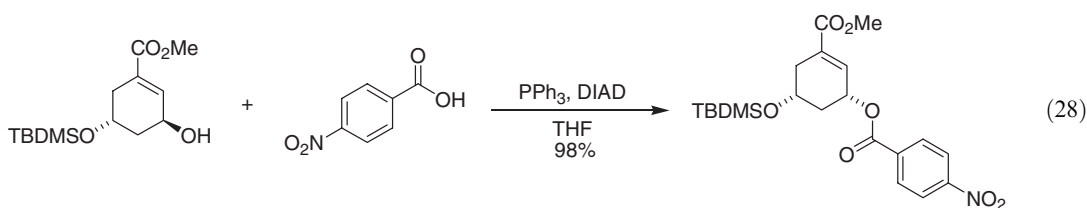
preferentially a benzylic or allylic alkyl residue. Typical HGA esterifications are those with amidinium ion activation, Appel-type, or Mitsunobu-type reactions as shown in <1995COFGT(5)121>. Recent reports utilizing the Mitsunobu reaction <1999JCS(P1)2249, 1999JOC4353> are shown in Equations (26) <2003T2451>, (27) <2002TA615>, and (28) <2000TL775>, under the conditions outlined in <2002TA615>; dynamic kinetic resolution of alcohols is also possible; no further advances have occurred in this area since the publication of chapter 5.03.14 in <1995COFGT(5)121>.



Scheme 2



Alcohol	Unreacted starting material		Product	
	Yield (%)	ee (%)	Yield (%)	de (%)
		70	42	95
	44	90	37	87
	38	82	41	76
	44	90	41	95
	40		42	95
	40	90	40	78

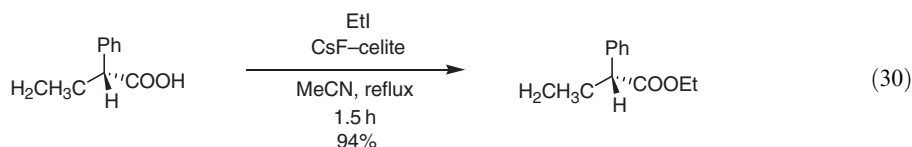


5.03.1.5 Alkylation of Carboxylate Anions

These esterifications are similar to the HGA esterification described in [Section 5.03.1.4](#). The carboxylic acids are used in the form of sodium, potassium, or caesium salts and are treated with alkyl halides ([Equation \(29\)](#)). The alkylating agent $\text{R}^1\text{--X}$ must show high- $\text{S}_{\text{N}}2$ reactivity.

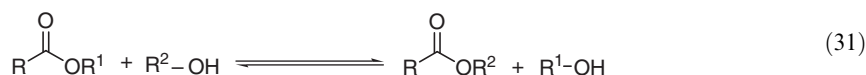


An improved method for the preparation of carboxylic esters using caesium fluoride–celite has been reported. The solid base has been shown to give excellent yields of a variety of esters including aromatic, aliphatic, and heteroaromatic esters. The work-up simply consists of filtration of the inorganic salts avoiding aqueous alkaline wash. Chiral α -substituted carboxylic acids were also tolerated under these conditions with no loss in stereochemical integrity ([Equation \(30\)](#)) [<1998SC2021>](#). No further advances have occurred in this area since the publication of chapter 5.03.15 in [<1995COFGT\(5\)121>](#).

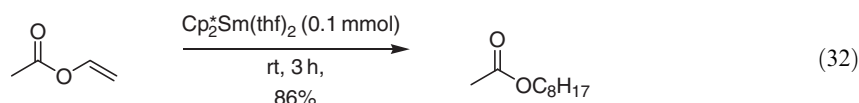


5.03.1.6 Transesterification

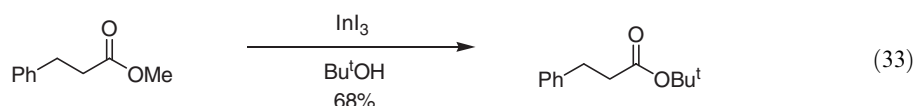
Transesterification represents a mild and versatile alternative to esterification reactions between an acid and an alcohol. This transformation takes place via an alkoxy moiety exchange between an ester and an alcohol ([Equation \(31\)](#)). This is more useful if one of the reaction components is inexpensive as the equilibrium mixtures formed require a large excess of one of the reagents in order to shift the equilibrium to the product side. A catalyst has to be added which may be any acid or base. The transesterification of an ester by exchange of an alkoxy moiety has been efficiently achieved using enol esters as acylating agents. Conversion of the liberated enolate to an aldehyde or ketone subsequently drives the transesterification equilibrium in the desired direction.



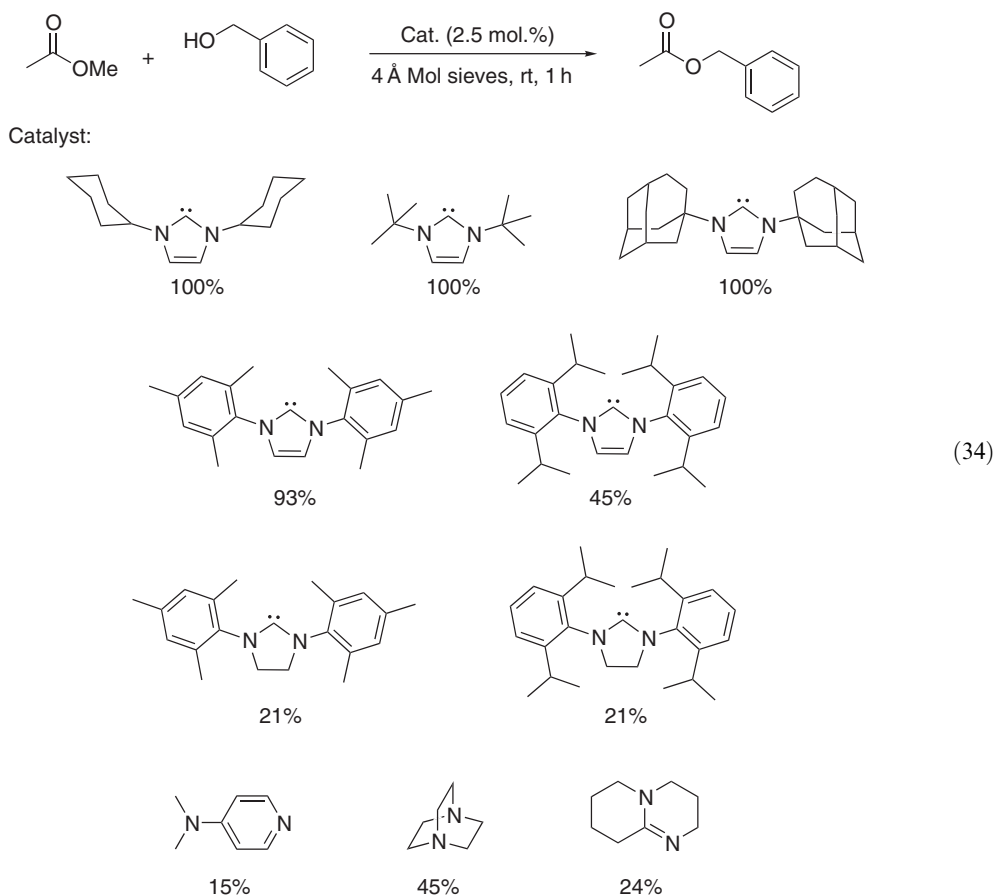
Samarium complexes such as $\text{Cp}_2^*\text{Sm}(\text{thf})_2$ have been used in transesterification reactions and are effective for acylation of alcohols using enol esters as acylating reagents ([Equation \(32\)](#)) [<1996JOC3088>](#).



Yttrium–salen complexes have been found to catalyze the acylation of secondary alcohols in excellent yields <1999CSR85>. Distannoxane has been used to promote the transesterification of enol esters with primary alcohols in excellent yields; this is a mild process and is therefore useful if sensitive substrates are required <1998JOC2420, 2003CC1428>. Butylstannonoic acid affords good yields in the transesterification of some highly functionalized substrates under reaction conditions in which no loss of stereochemical information is observed <1998TL2257>. Superbases have been found to catalyze transesterification with both primary and secondary alcohols <1999JOC9063>. A range of menthyl esters has been synthesized via titanium(IV) oxide-catalyzed transesterification <1998TL4223>. TCNE and dicyanoketene dimethyl acetal have been reported to mediate transesterification of methyl laurate with a range of substituted alcohols <1997CL55>. Indium halides have also been employed as transesterification catalysts. InI_3 , although not reactive enough to be used catalytically, offers the advantage of favoring tertiary over primary alcohols (Equation (33)) <1998JOC6027>.

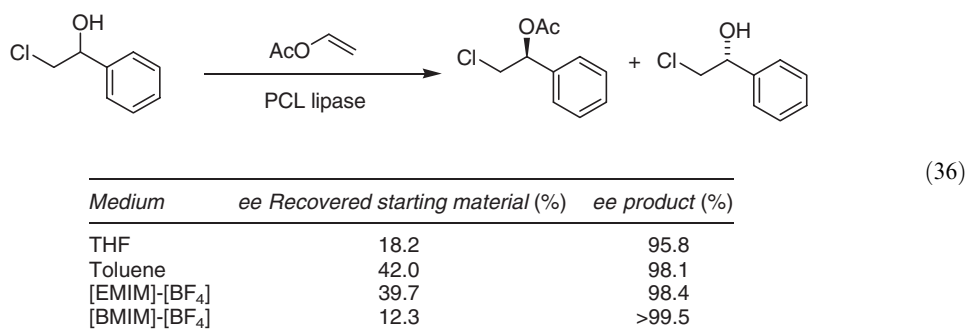
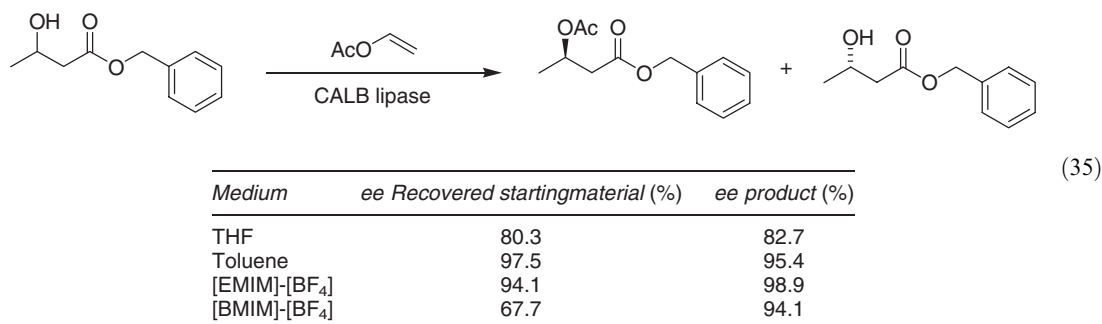


Nucleophilic *N*-heterocyclic carbene (NHC) catalysts have been found to catalyze transesterification <2002OL3583, 2002OL3587, 2003JOC2812>. It has been found that traditional strongly nucleophilic amines, such as DMAP, DABCO, and DBU do not perform as well as NHC catalysts in the transesterification reaction of methyl acetate with benzyl alcohol (Equation (34)).



5.03.1.7 Enzymatic Transesterification

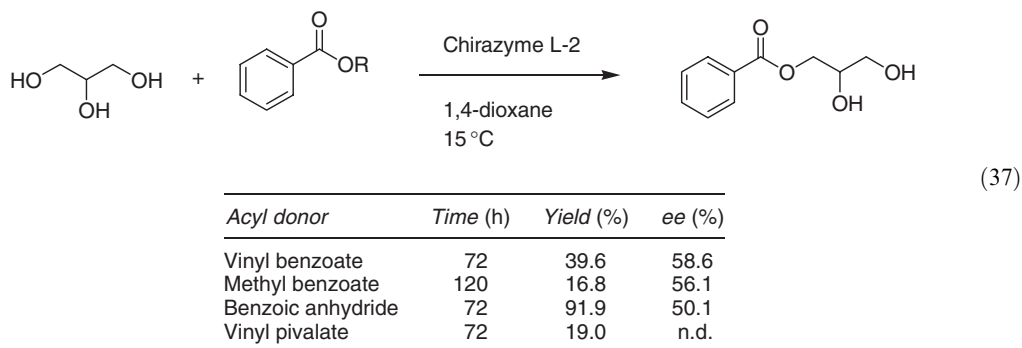
Enzymatic transesterification has gained considerable attention over the last couple of decades, in particular for the optical resolution of carboxylic acids or (more frequently) of alcohols. Lipases have found broad application within organic chemistry due to their availability, stability, and cost; they also tend to have low-substrate selectivity, i.e., they accept unnatural substrates <1999TA1223>. Recently it has been observed that lipases can be up to 25 times more enantioselective in ionic liquids than in conventional organic solvents <2001OL1507>. Two ionic liquids, [EMIM]-[BF₄] ([EMIM] = 1-ethyl-3-imidazolium) and [BMIM]-[BF₄] ([BMIM] = 1-butyl-3-imidazolium), were tested as media for lipase-catalyzed transesterification and compared with two organic solvents, THF and toluene (Equations (35) and (36)). The evaluation of enzyme enantioselectivity was carried out with a range of alcohols in the presence of vinyl acetate and one of either *Candida antarctica* lipase B (CALB) or *Pseudomonas cepacia* lipase.



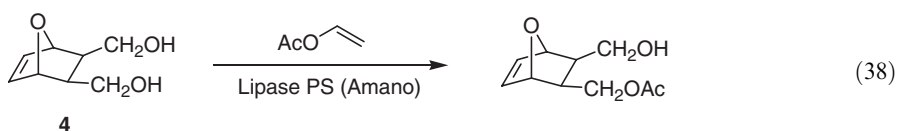
Enzymatic transesterification in ionic liquids has also been reported for the selective acylation of glycosides <2003JMC(B)115> and the impact of ionic liquid physical properties on lipase activity and stability has been studied <2003JA4125>.

Enzymatic transesterification utilizing vinyl acetate as acyl donor, a range of lipases and substrates has been reported: in the acylation of protected 1,3-propane diols, with product ee values of up to 98% <2001TA3223>; in the selective transesterification of 4-hydroxytetralone and 3-hydroxyindanone, with ee values of up to 96% <2001TA2283>; in the transesterification of intermediates in the synthesis of isoprostane and iridoid lactones <2001TA1779>, of β -hydroxyisoxazoles <2000TA2565>, of intermediates for the synthesis of (+)-albicanol and (+)-albicanol acetate <2000T1899>, of phenylalkane diols <1999T14947>, of (\pm)-4-cyano-4-phenyl-1-hexanol, a key intermediate in the synthesis of (*R*)-(+)-aminogluthethimide <2003JMC(B)185>, of racemic 2-arylpropionic acids <2003JMC(B)43>, of β -hydroxy ketones <2003JMC(B)151>, and in the chemoenzymatic synthesis of 2-substituted 2-fluoro-1,3-dioxygenated chiral building blocks <1999TA1223>.

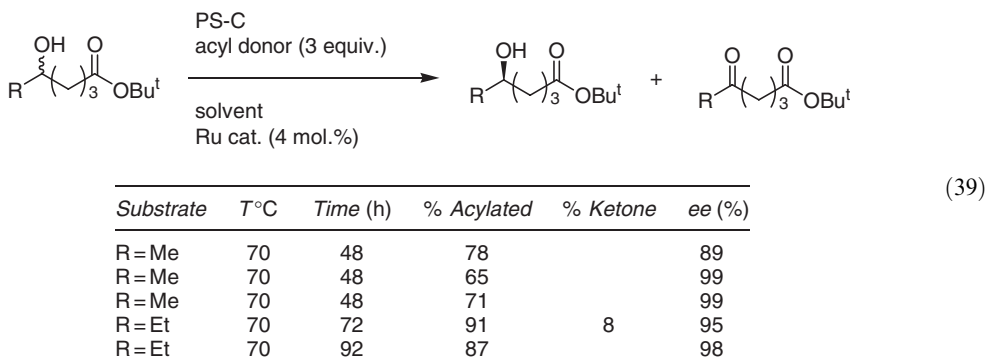
The transesterification of glycerol has been reported in the synthesis of optically active α -monobenzoylglycerol (Equation (37)) <2000JMC(B)193>.



Several key intermediates in the synthesis of natural products have been prepared by the lipase-mediated transesterification of diol **4** with vinyl acetate (Equation (38)) <1995SL339, 1997TA3665, 1997T17079>.



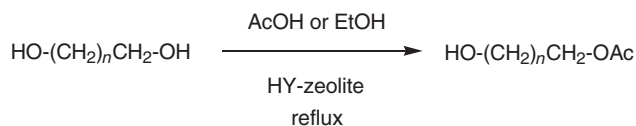
Dynamic kinetic resolution has also been reported and the transesterification of δ -hydroxy esters has been efficiently achieved using *Pseudomonas cepacia* lipase (PS-C), 4-chlorophenyl acetate as acyl donor, and a ruthenium catalyst for alcohol racemization (Equation (39)) <2002JOC1261>.



Similar systems for dynamic resolution of allylic alcohols <2000OL2377> and secondary alcohols <1999JA1645> have also been developed.

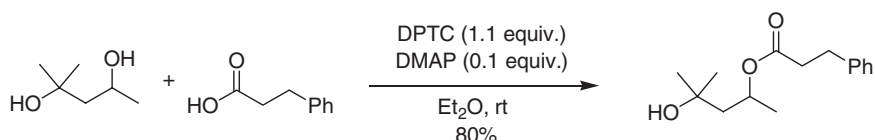
5.03.1.8 Monoacylation of Polyols

Selective protection of multiple identical functional groups is extremely important in organic synthesis and is one of the central problems in many natural product syntheses. HY-zeolite has been found to be an efficient and reusable catalyst for selective monoacylation of symmetrical diols (Equation (40)) <2003SL2419>. Selective monoacetylation of a secondary over a primary alcohol has been achieved using the DPTC and DMAP method (Equation (41)) <1998CL679>.



Diol $\text{HO}(\text{CH}_2)_n\text{OH}$	Acyating agent	Time (h)	Yield (%)
$n=2$	HOAc	2	90
	EtOAc	3.5	83
$n=4$	HOAc	3	98
	EtOAc	5	91
$n=10$	HOAc	4	94
	EtOAc	7	85
$n=16$	HOAc	6	92
	EtOAc	8	78
$\text{HOCH}_2\text{CH}=\text{CHCH}_2\text{OH}$	HOAc	3.5	93
	EtOAc	5	95

(40)

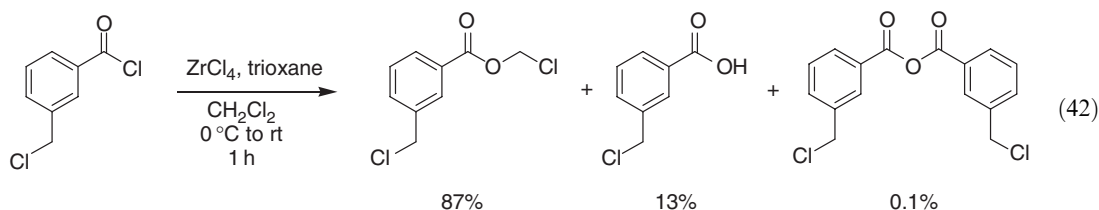


(41)

5.03.2 ESTERS WITH POLYFUNCTIONAL ALCOHOL COMPONENTS

5.03.2.1 1- and 2-Haloalkyl Esters

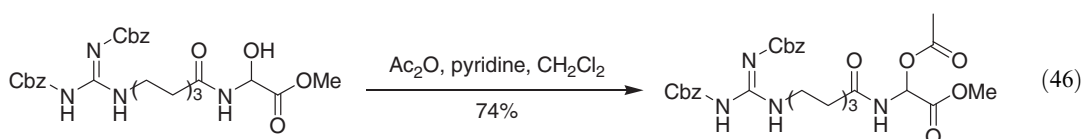
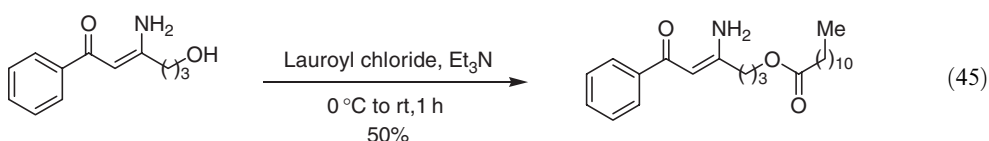
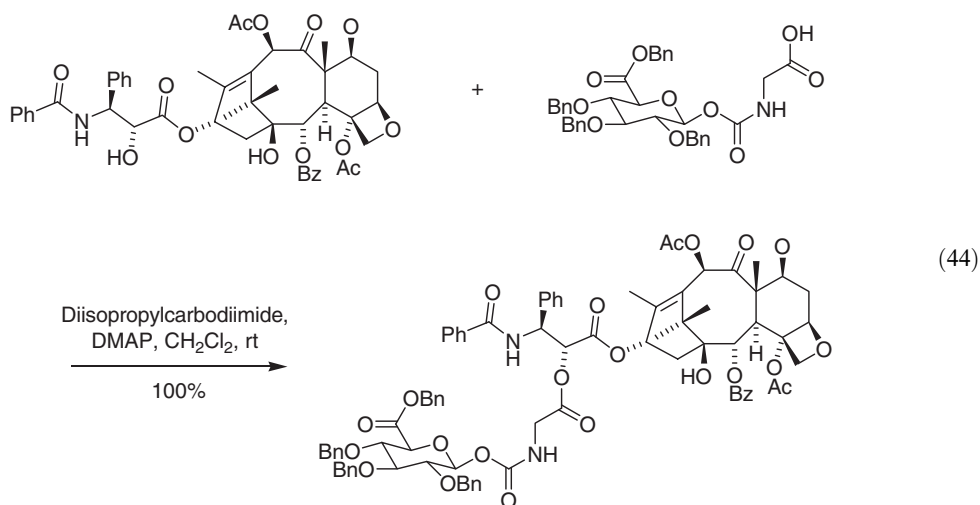
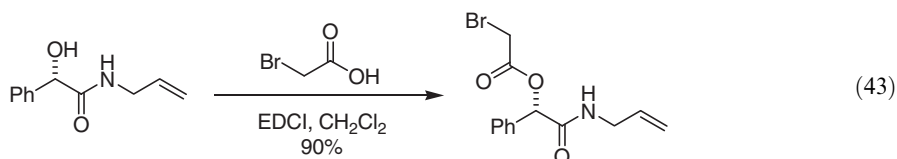
1-Chloroalkyl esters have been prepared from acyl chlorides and aldehydes, presumably via *O*-acylation of the aldehyde and subsequent addition of the chloride ion to the oxonium carbon. A mild procedure for the synthesis of chloromethyl esters has been developed from acid chlorides and trioxane employing zirconium tetrachloride as Lewis acid. Excellent yields of chloromethyl esters are reported and unlike earlier reports suppression of the problematic dimer formation is achieved (Equation (42)) <2002TL6317>. 2-Haloalkyl esters are prepared in two ways as described in <1995COFGT(5)121>. No further advances have occurred in this area since the publication of chapter 5.03.2.1 in <1995COFGT(5)121>.



(42)

5.03.2.2 Nitrogen-substituted Alcohol Components

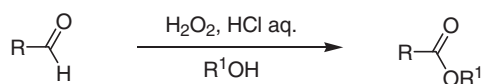
There are a large number of methods for the synthesis of amino esters. Equations (43) <2003T6291>, (44) <1997BMC405>, (45) <2000BMC2195>, and (46) <2000TA3665> show just a few methods. Equation (44) highlights the versatility of the carbodiimide coupling method in the synthesis of paclitaxel prodrugs <1997BMC405>.



5.03.3 ESTERS VIA OXIDATION REACTIONS

5.03.3.1 Without Changing the Number of Carbons

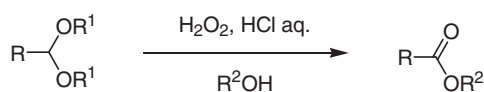
Direct oxidation of alcohols to the corresponding carboxylic acids and *in situ* esterification of these acids with unreacted alcohol, and related procedures, were reported in [<1995COFGT\(5\)121>](#), as was the oxidation of aldehydes to esters in the presence of an alcohol. More recently this transformation has been achieved using hydrogen peroxide, hydrochloric acid, and an alcohol ([Equation \(47\)](#)) [<1997SL1149>](#).



Aldehyde	Alcohol	Yield (%)
$\text{CH}_3(\text{CH}_2)_7\text{CH}_2\overset{\text{O}}{\parallel}\text{C}-\text{H}$	MeOH	90
$\text{Ph}-\overset{\text{O}}{\parallel}\text{C}-\text{H}$	MeOH	82

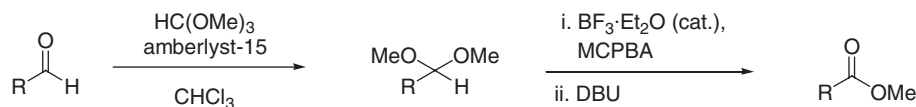
(47)

Under the same reaction conditions effective oxidation of acetals can be achieved generating the corresponding esters in generally good yield (Equation (48)) <1997SL1149>. A similar one-pot process, starting from the aldehyde, generates the dimethyl acetal *in situ* and subsequent oxidation affords a range of methyl esters (Scheme 3) <1998TL1365>.



Acetal	Alcohol	Yield (%)
$\text{CH}_3(\text{CH}_2)_7\text{CH}_2\overset{\text{O}-\text{Me}}{\underset{\text{O}-\text{Me}}{\text{C}}}$	MeOH	96
$\text{Ph}-\overset{\text{O}-\text{Me}}{\underset{\text{O}-\text{Me}}{\text{C}}}$	MeOH	95
$\text{Ph}-\text{CH}=\text{CH}-\overset{\text{O}-\text{Me}}{\underset{\text{O}-\text{Me}}{\text{C}}}$	MeOH	14
$\text{CH}_3(\text{CH}_2)_7\text{CH}_2\text{C}(\text{OCH}_2)_2$	MeOH	98
	EtOH	99
	Pr ⁱ OH	64

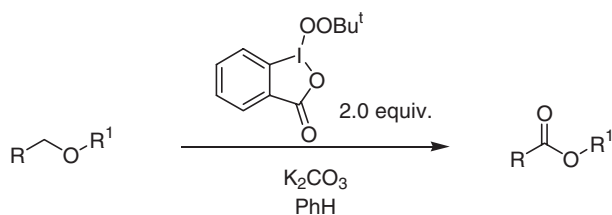
(48)



Aldehyde	Product	Yield (%)
$\text{C}_6\text{H}_5\text{CHO}$	$\text{C}_6\text{H}_5\text{CO}_2\text{Me}$	95
$4\text{-MeC}_6\text{H}_4\text{CHO}$	$4\text{-MeC}_6\text{H}_4\text{CO}_2\text{Me}$	96
$4\text{-MeOC}_6\text{H}_4\text{CHO}$	$4\text{-MeOC}_6\text{H}_4\text{CO}_2\text{Me}$	93
$4\text{-O}_2\text{NC}_6\text{H}_4\text{CHO}$	$4\text{-O}_2\text{NC}_6\text{H}_4\text{CO}_2\text{Me}$	65
$2\text{-HOC}_6\text{H}_4\text{CHO}$	$2\text{-HOC}_6\text{H}_4\text{CO}_2\text{Me}$	68
$\text{C}_6\text{H}_5\text{CH}_2\text{CHO}$	$\text{C}_6\text{H}_5\text{CH}_2\text{CO}_2\text{Me}$	89
$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	$\text{CH}_3(\text{CH}_2)_2\text{CO}_2\text{Me}$	87
$\text{CH}_3(\text{CH}_2)_4\text{CHO}$	$\text{CH}_3(\text{CH}_2)_4\text{CO}_2\text{Me}$	85
$\text{CH}_3(\text{CH}_2)_5\text{CHO}$	$\text{CH}_3(\text{CH}_2)_5\text{CO}_2\text{Me}$	87
$(E)\text{-PhCH=CH-CHO}$	$E\text{-PhCH=CH-CO}_2\text{Me}$	83
$(E)\text{-PhCH=CMe-CHO}$	$E\text{-PhCH=CMe-CO}_2\text{Me}$	85

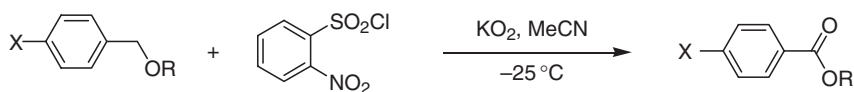
Scheme 3

The synthesis of carboxylic esters by direct oxidation of ethers with a variety of oxidants has also been reported (Equations (49)–(51)) <1996JA7716, 1997BCSJ2561, 1998JCS(P1)633>.



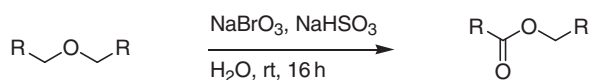
Ether	Time (h)	Yield (%)
Ph-CH ₂ -O-R ¹		
R ¹ = Me	30	78
Et	36	84
Pr ⁱ	36	71
Bu ⁿ	48	76
Bu ^s	50	63
Bu ^t	24	80
<i>o</i> -C ₅ H ₉	34	58
<i>o</i> -C ₆ H ₁₁	48	79
	30	74
R = 4-MeO	36	95
4-Me	31	82
4-Cl	51	94
3-Cl	56	98
	86	90
	96	62
	72	73
	28	62
	51	72

(49)



X	R	Time (h)	Yield (%)
H	Me	6	83
H	Et	6	85
H	Pr	6	87
H	<i>o</i> -C ₆ H ₁₁	6	87
H	CH ₃ (CH ₂) ₇	6	85
Cl	CH ₃ (CH ₂) ₇	6	87
OCH ₃	CH ₃ (CH ₂) ₇	4	81
OCH ₃	CH ₃ (CH ₂) ₇	6	93
OCH ₃	CH ₃ (CH ₂) ₇	8	93

(50)



Ether	Product	Yield (%)
$(n\text{-C}_6\text{H}_{13})_2\text{O}$	$n\text{-C}_5\text{H}_{11}\text{CO}_2n\text{-C}_6\text{H}_{13}$	82
$(n\text{-C}_{11}\text{H}_{23})_2\text{O}$	$n\text{-C}_{10}\text{H}_{21}\text{CO}_2n\text{-C}_{11}\text{H}_{23}$	78
$n\text{-C}_8\text{H}_{17}\text{OC}_2\text{H}_5$	$n\text{-C}_7\text{H}_{15}\text{CO}_2\text{C}_2\text{H}_5$	44

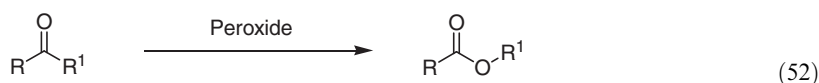
(51)

5.03.3.2 Esters via Ozonolytic Cleavage of Double Bonds

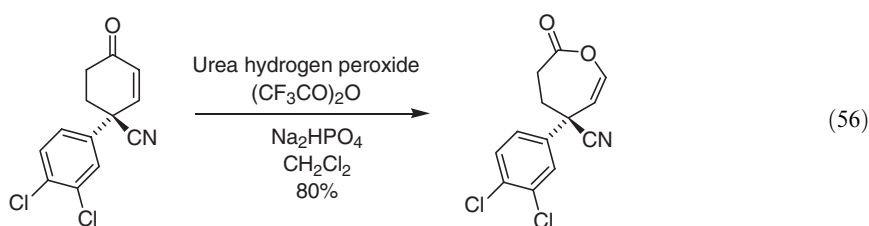
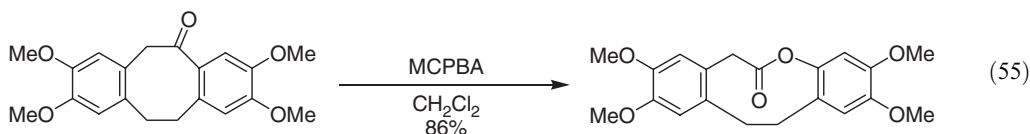
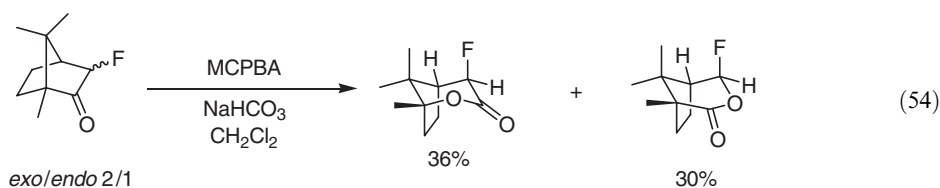
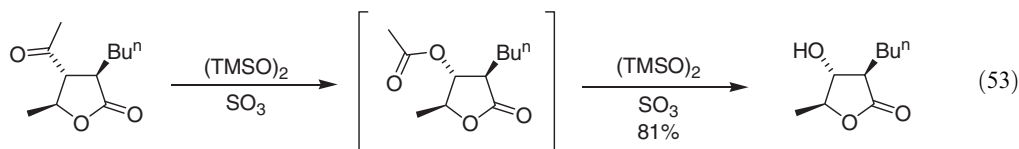
This is a very mild and general access to esters, however, no major advances have occurred in this area since the publication of chapter 5.03.3.2 in <1995COFGT(5)121>.

5.03.3.3 Esters via Baeyer–Villiger Oxidation

This reaction starts from symmetrical or unsymmetrical ketones to furnish esters, while cyclic ketones give lactones (Equation (52)). For unsymmetrical ketones the correct relative migratory aptitude is essential for the formation of the desired product. The residue that migrates faster becomes the alcohol part of the ester. Equations (53)–(56) show some recent examples <1997TL6621, 2003TA2883, 1996T8063, 2001T8193>.



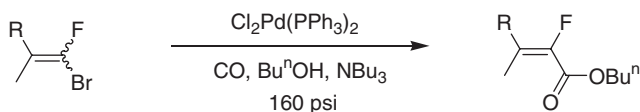
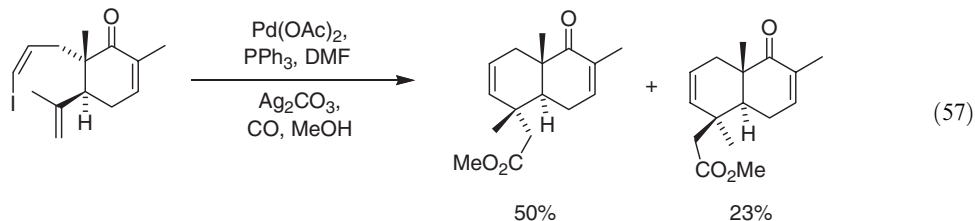
Migratory aptitude: *t*-alkyl > cyclohexyl > *sec*-alkyl > aryl > *n*-alkyl > Me



5.03.4 ESTERS VIA ONE CARBON CHAIN ELONGATION

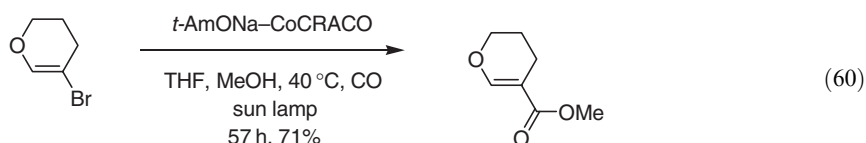
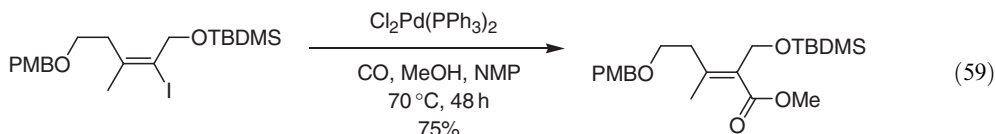
5.03.4.1 Alkoxycarbonylation

Alkoxycarbonylation can be performed with haloalkenes, carbon monoxide, an alcohol that is also used as solvent, and a transition metal complex. Examples are shown in Equations (57)–(60) <2000T7389, 2002OL831, 2003T2781, 1995JOC8339>.

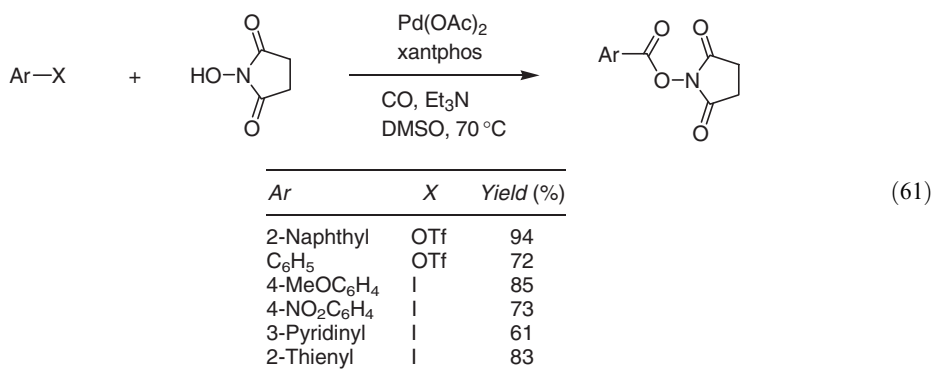


<i>R</i>	(<i>E</i>)/(<i>Z</i>) of reactant	Temp (°C)	Time (h)	(<i>E</i>)/(<i>Z</i>) of product	Yield (%)
Ph	88:12	rt	57	1:99	72
2-ClC ₆ H ₄	82:18	rt	96	1:99	78
4-MeOC ₆ H ₄	81:19	rt	258	0:100	73
PhC(CH ₃)H	83:17	45	115	2:98	56
Ph	0:100	70	180	100:0	90
2-ClC ₆ H ₄	0:100	70	125	100:0	94
4-MeOC ₆ H ₄	0:100	70	155	98:2	79
PhC(CH ₃)H	0:100	70	161	100:0	92

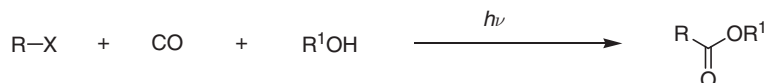
(58)

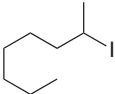
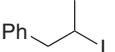
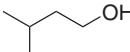

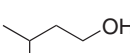


There is also a wide variety of methods for the transition metal-catalyzed alkoxycarbonylation of aryl halides <1995JOC8339, 2002S2171, 2003S501, 1996JMC(A)L187, 1998T15861, 1997JCS(P1)2273>. Aryl tosylates have also been used <1998SL183>, and Lou and co-workers <2003TL2477> report the synthesis of *N*-hydroxysuccinimido esters using aryl triflates and halides (Equation (61)).



Ryu and Sonoda have shown that the alkoxyacylation transformation can also be accomplished in the absence of a transition metal, and can be carried out under photoirradiation conditions, affording the desired products in good yield (Equation (62)) <1997JA5465>.

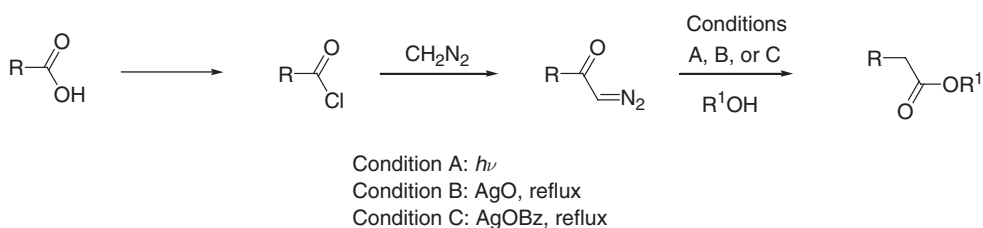


Alkyl halide	Alcohol	Conditions	Yield (%)
	Ph-CH ₂ -OH	30 atm, 12 h	87
		55 atm, 33 h	60
		40 atm, 18 h	68

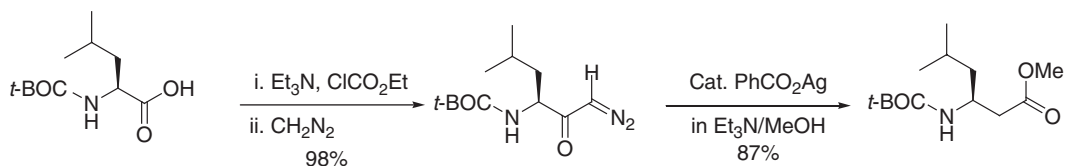
(62)

5.03.4.2 Arndt-Eistert Homologation

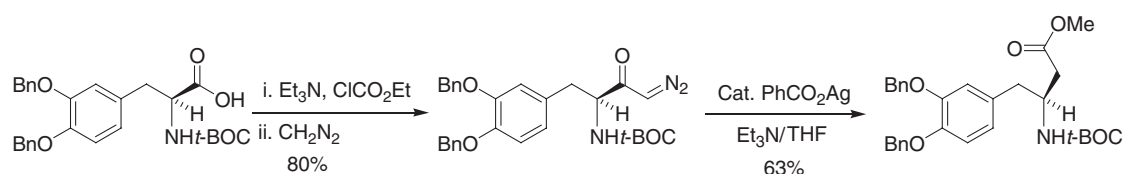
The general protocol of this reliable and well-established homologation is outlined in Scheme 4. A carboxylic acid is converted into the chloride and then treated with diazomethane to give the diazoketone, which is submitted to a Wolff rearrangement under either photolytic conditions or thermal conditions using silver(I) catalysis. All homologations proceed with retention of configuration, and two recent examples are shown in Schemes 5 and 6 <1996HCA913, 2002TL8241>. This procedure for the synthesis of β -amino acids has also been reviewed <2002T7991>.



Scheme 4

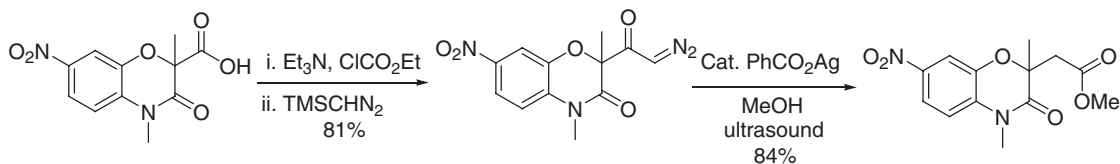


Scheme 5



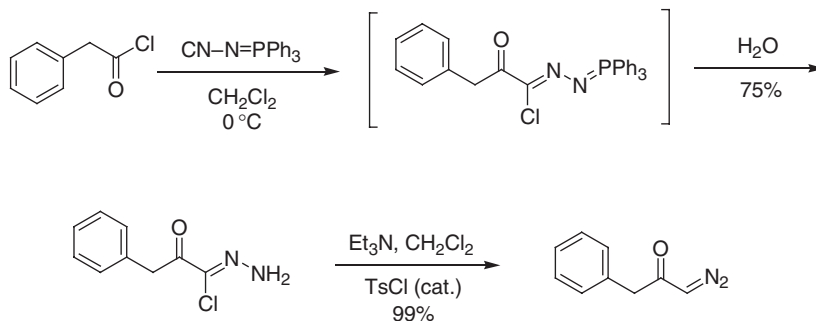
Scheme 6

Since diazomethane is highly toxic, labile, and potentially explosive, much effort has been put into finding a less hazardous substitute. Trimethylsilyldiazomethane (TMSCHN₂) has been successfully used in numerous reactions previously dominated by diazomethane and the application of TMSCHN₂ in the classical Arndt–Eistert reaction has been achieved (Scheme 7) <2001TL7099>.

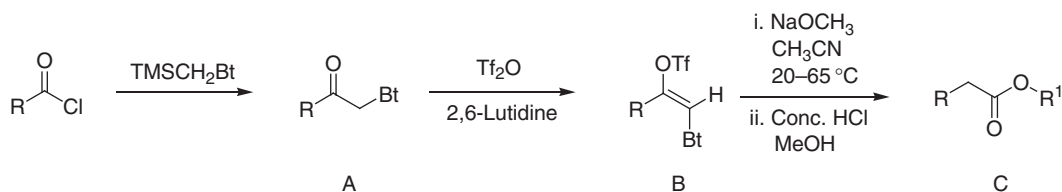


Scheme 7

Diazomethane has also been successfully replaced with *N*-isocyanotriphenyliminophosphorane (Scheme 8) <2000SL526>. An alternative procedure for the homologation of carboxylic acids via benzotriazole methyl ketones has been reported (Scheme 9) <2000OL3789>.



Scheme 8



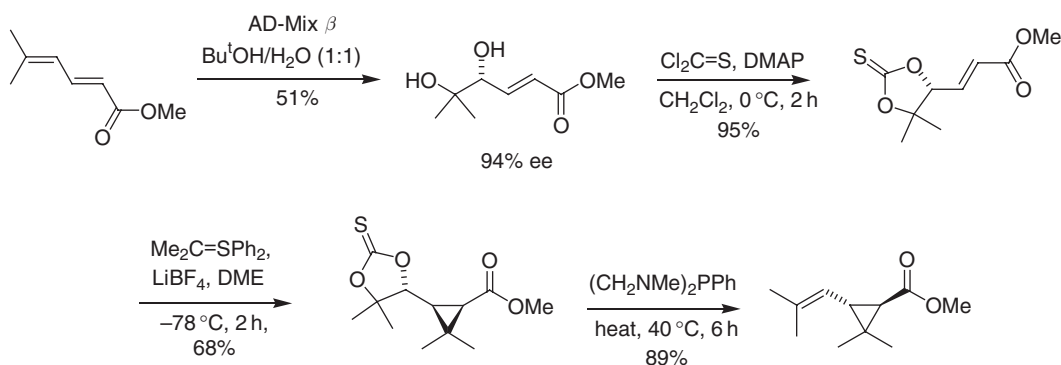
R	Yield (%)		
	A	B	C
C ₆ H ₅	85	95	89
4-ClC ₆ H ₄	90	95	98
4-CH ₃ C ₆ H ₄	91	90	92
CH ₃	83	88	55
(CH ₃) ₃ CCH ₂	95	95	45
<i>n</i> -CH ₃ (CH ₂) ₆	95	90	49

Scheme 9

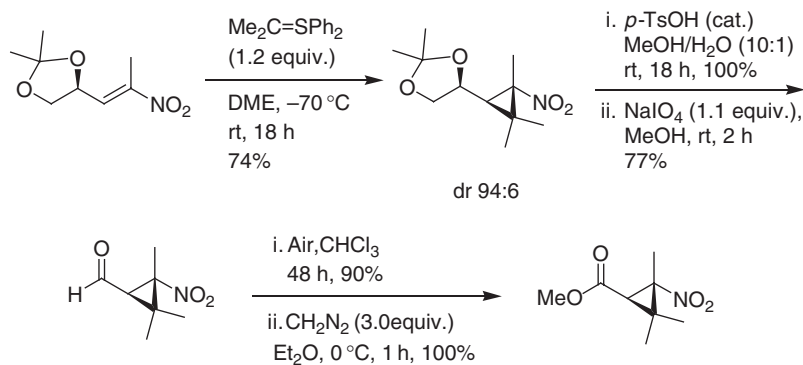
5.03.5 ESTERS OF PARTICULAR CARBOXYLIC ACIDS

5.03.5.1 Esters of Cycloalkanoic Acids

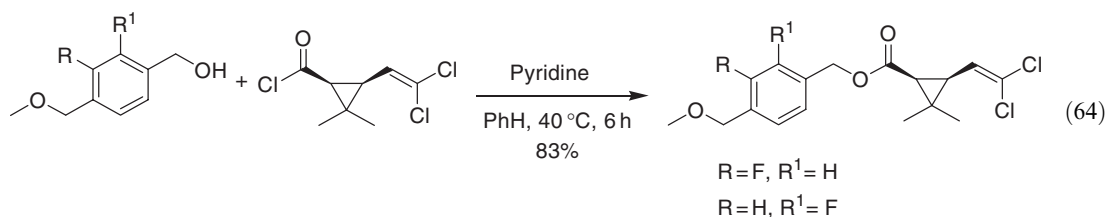
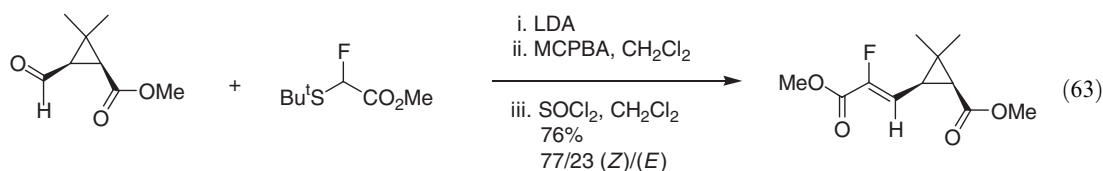
Cyclopropanoic esters have tremendous importance as insecticides (pyrethroids). There is a variety of procedures for the synthesis of such compounds, some of which were reviewed in <1995COFGT(5)121>. More recent examples are shown in Schemes 10, 11, and Equations (63)–(65). The enantioselective synthesis of (*R*)-*trans*-chrysanthemate using asymmetric dihydroxylation methodology has been achieved (Scheme 10) <2002TL7881>. The preparation of nitro-substituted cyclopropanic esters was reported in the synthesis of a range of unnatural amino acids (Scheme 11) <2002T10485>. Several fluorine-substituted pyrethroid analogs have been synthesized (Equation (63)) <2002T4759>. Equation (64) highlights the synthesis of 4-methoxymethylbenzyl permethrinates <2002JFC173>, where interestingly it was found that the fluorine atom increased biological activity but its position on the aromatic ring had little effect.

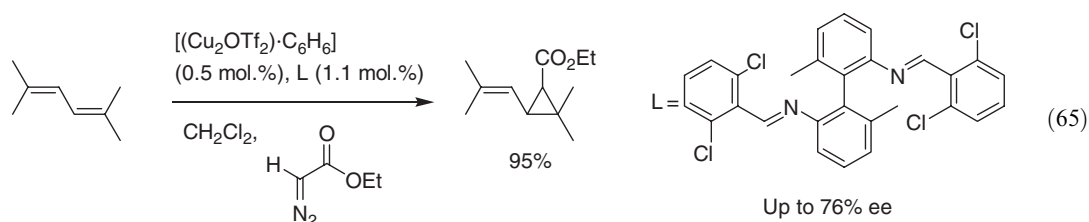


Scheme 10

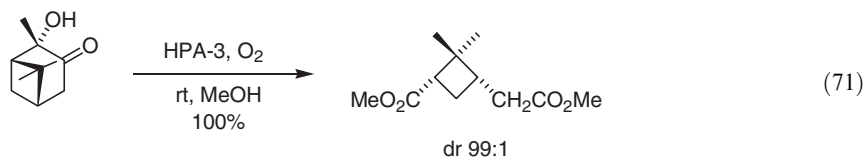
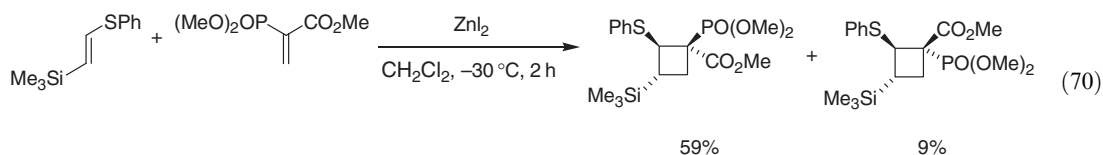
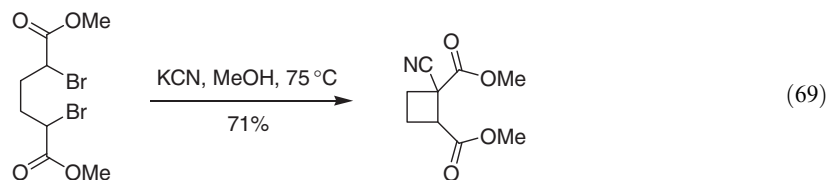
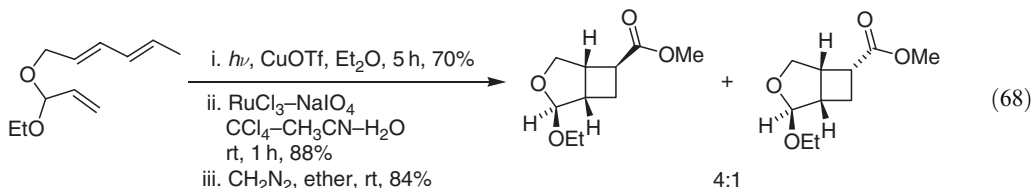
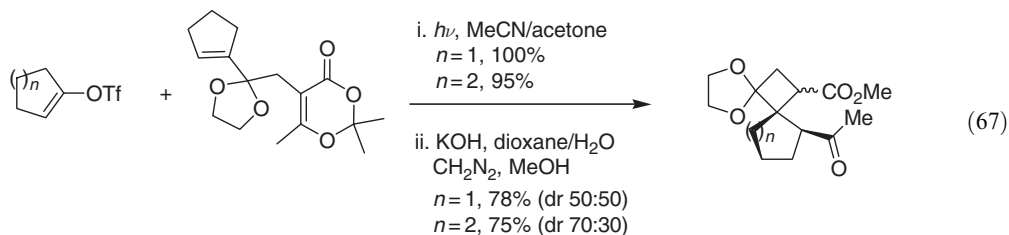
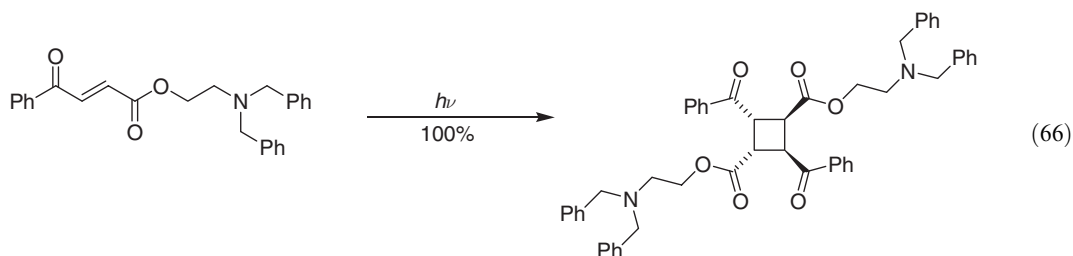


Scheme 11

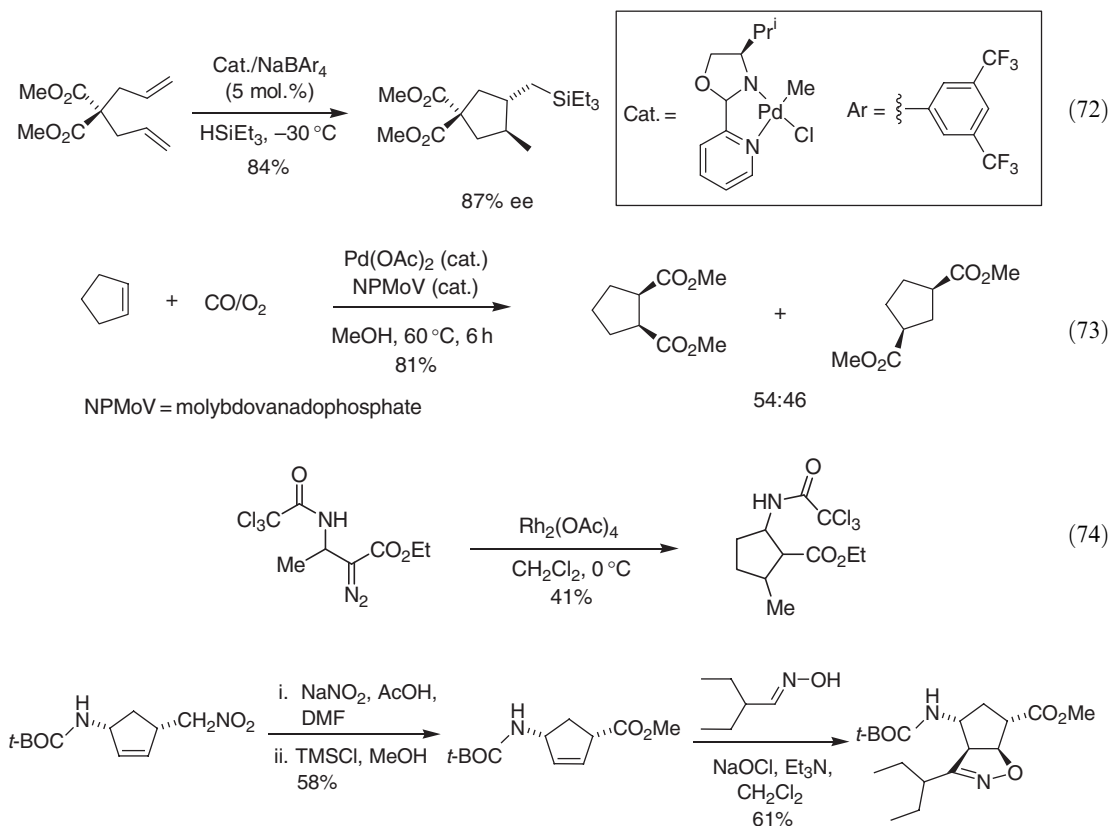




In general, cyclobutanoic esters are prepared in good yield by [2+2]-photocycloaddition reactions, some examples of which are shown in [Equations \(66\)–\(69\)](#) <2001JCS(P1)3025, 2001JOC233, 2001JCS(P1)3013, 2003TA127>. Lewis acid-mediated [2+2]-cycloadditions have also been reported ([Equation \(70\)](#)) <2001JOC5915>. Selective catalytic oxidative cleavage of α -hydroxy ketones, using vanadium-based heteropolyanions and dioxygen, affords enantiomerically pure cyclobutanoic esters ([Equation \(71\)](#)) <2001CC2218>.

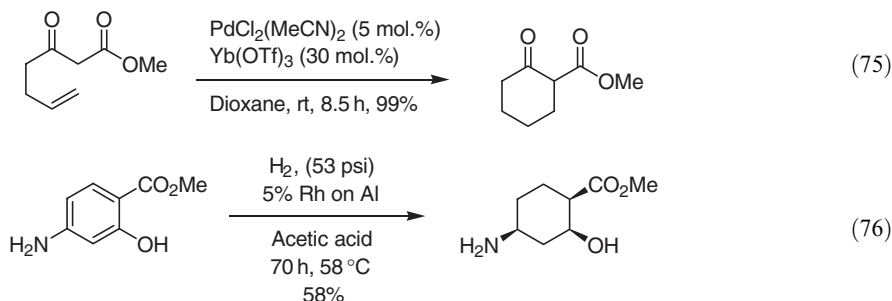


There are many ways to generate cyclopentanoic esters, and a variety of methods were highlighted in <1995COFGT(5)121>. Some more recent examples are shown in Equations (72)–(74) <2001JOC7639, 2002JOC5005, 2003OL2243> and Scheme 12 <2003JOC6591>.



Scheme 12

There is a variety of methods for the synthesis of cyclohexanoic esters. Two examples are shown in Equation (75) <2003OL2869> and Equation (76) <2003BMCL3597>, where reduction of the aromatic ring affords a key intermediate for the synthesis of novel CCR3 antagonists.

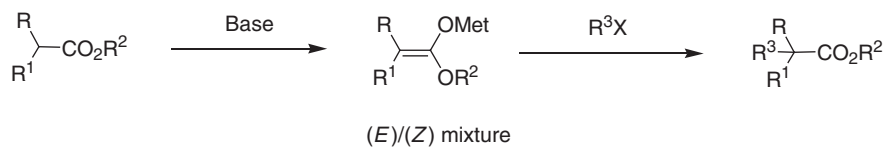


5.03.5.2 α - and β -C-Branded Alkenoic Acids

5.03.5.2.1 Enolate alkylation

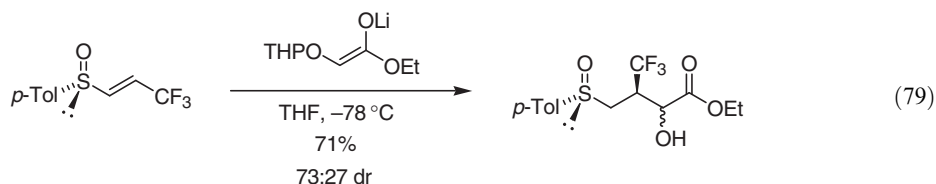
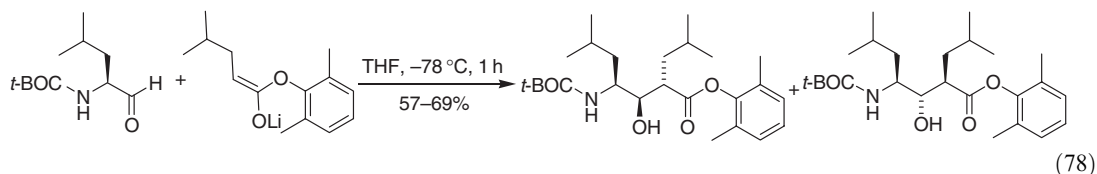
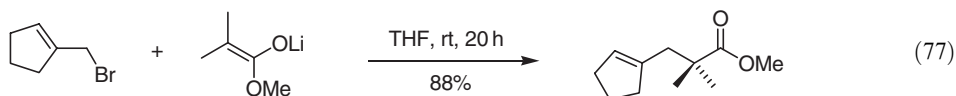
The general procedure for enolate alkylation is shown in Scheme 13. The ester is α -deprotonated with a strong-hindered base such as lithium diisopropylamide (LDA), lithium cyclohexylisopropylamide (LICA), or potassium hexamethyldisilazide (KHMDs) to the enolate, as a mixture

of (*E*)- and (*Z*)-diastereoisomers which is then treated with an alkylating reagent to form the α -branched ester. The yields are generally good if reactive alkylating reagents are used. A number of methods utilizing enolate alkylation were reported in <1995COFGT(5)121>.



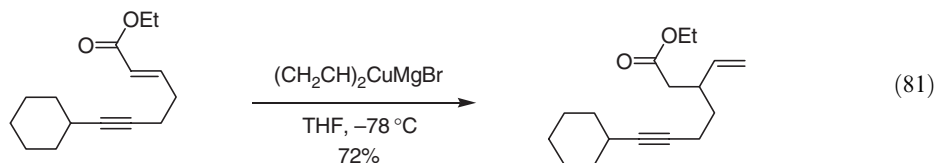
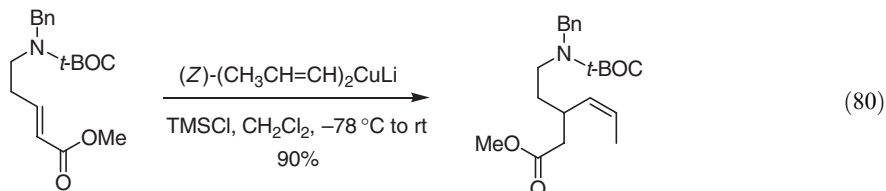
Scheme 13

More recently, lithium enolates have been alkylated with a variety of electrophiles. Equation (77) highlights just one example of alkylation with an alkyl halide, the product of which was then utilized in the construction of (+)-15-nor-pentalenene <1997JOC4851>. 2-Substituted statines have been synthesized by addition of a lithium enolate to an aldehyde (Equation (78)) <2001OL2725>. Michael addition of the anion from hydroxy-protected glycolate to a vinyl sulfone containing a trifluoromethyl group proceeds with reasonable diastereoselectivity (Equation (79)) <1996T199>. Interestingly, no reaction occurred when the Michael addition of the dianion from glycolate to the vinyl sulfone was attempted.

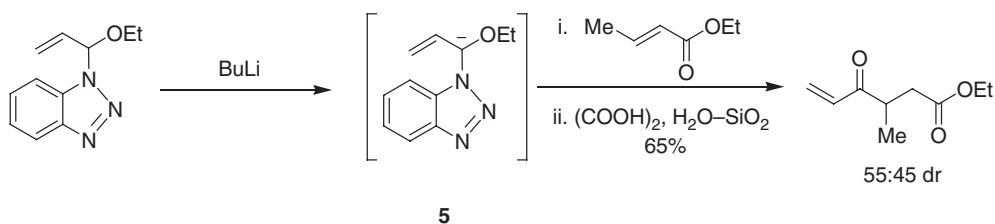


5.03.5.2.2 Conjugate addition to α,β -enoates

Conjugate additions of organocuprates to α,β -enoates are widely applicable versatile C—C bond-forming reactions in organic synthesis, and there are a vast number of procedures available, some of which were reported in <1995COFGT(5)121>. Addition of vinylcuprates to α,β -enoates affords the desired products in good yield (Equations (80) and (81)) <1995JA9139, 1998JOC5507>. Equation (80) formed part of Overman's total synthesis of (+)-19-epi-ajmalicine.

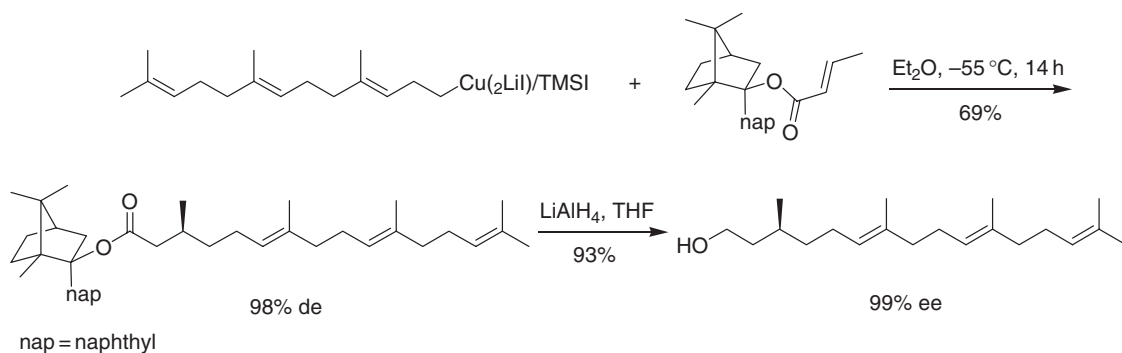


Katritzky has shown that reaction of a sterically congested anion, such as **5**, results in solely 1,4-addition. It was also found that both the alkylation and quenching of the reaction must be carried out at -78°C ; higher temperatures do not result in isolation of the desired products (Scheme 14) <1995JOC7589>.

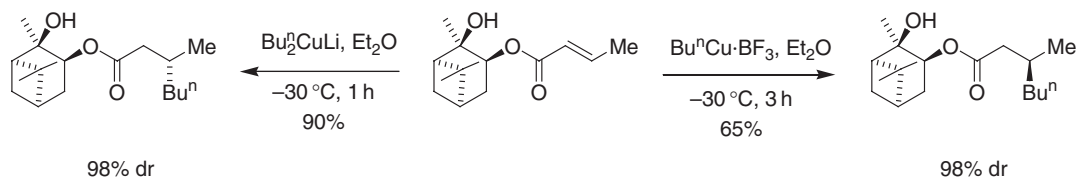


Scheme 14

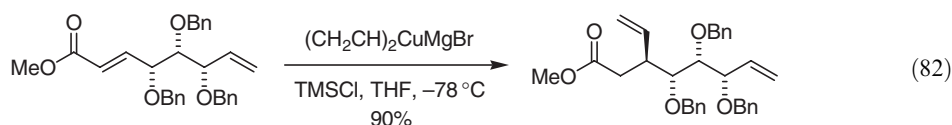
The stereochemistry of the cuprate addition may be controlled by several factors and there are many excellent methods for highly enantioselective syntheses. Scheme 15 <1996TL7127>, Scheme 16 <2002TA2513>, and Equation (82) <1998JOC7920> represent just three of these procedures, illustrating the use of chiral esters and chirality in the acid portion.



Scheme 15

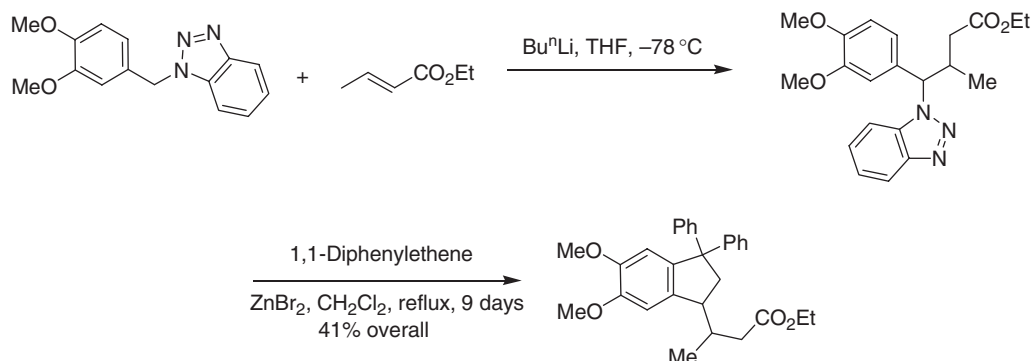
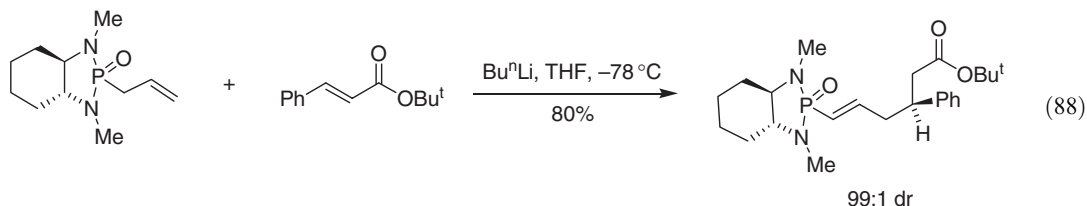
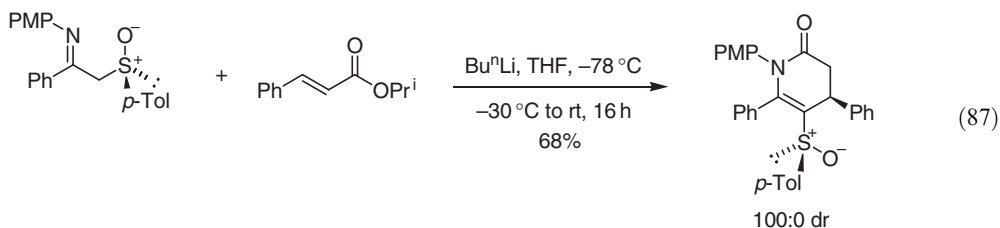
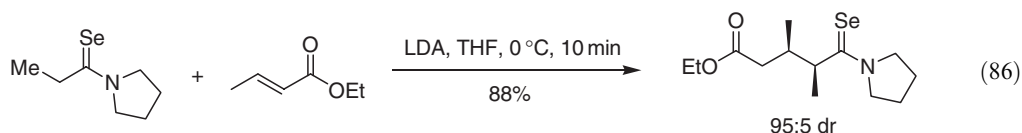
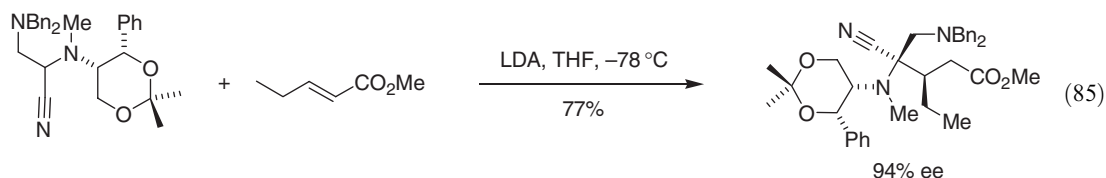
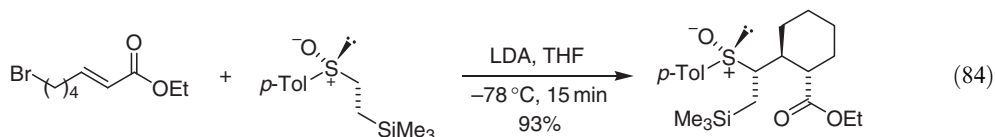
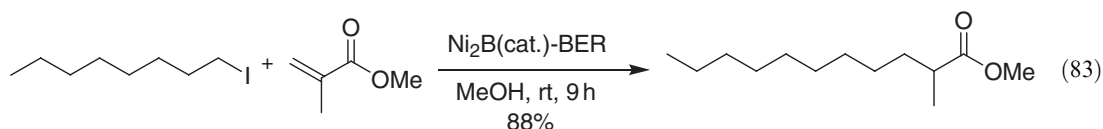


Scheme 16

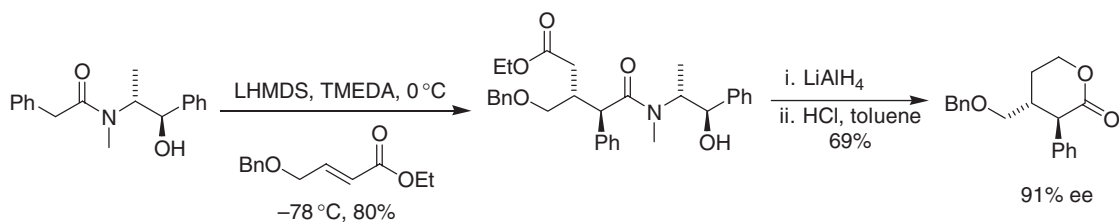


Conjugate addition to α,β -enoates is not just limited to organocuprates and there is a wide variety of other methods for successful 1,4-addition. Nickel boride–borohydride exchange resin (BER) has been found to act as a useful mediator for conjugate addition with alkyl halides (Equation (83)) <1996TL3137, 1997JOC2357>. LDA has been used many times as a base for 1,4-addition. Equations (84)–(86) <1997SL449, 2000JOC1758, 1999JCS(P1)1617, 2000OL311> highlight some recent examples, showing that several types of functional group can be tolerated under the reaction conditions. *n*-Butyllithium has also been found as a useful mediator for this reaction, as illustrated in Equation (87) <2001TA3173>, in which the ester is subsequently involved in a

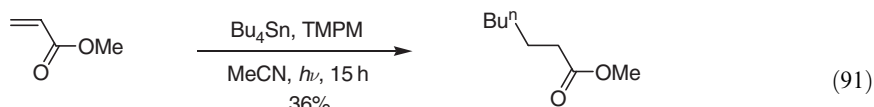
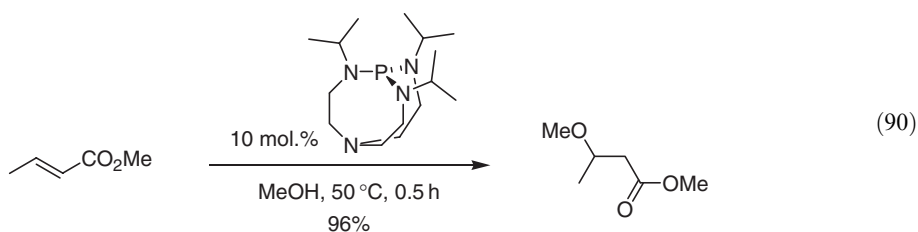
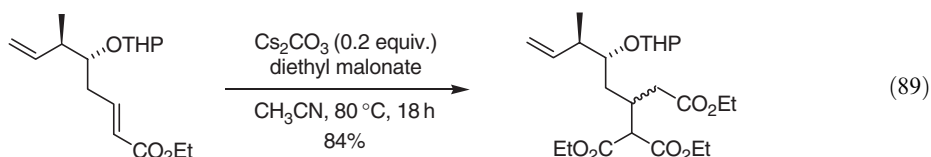
cyclization, Equation (88) <2000JOC5623> and Scheme 17 <1997SC2467>. LHMDs (Scheme 18) <2002OL1963>, Cs_2CO_3 (Equation (89)) <2001SL769>, and $\text{P}(\text{Pr}^i\text{NCH}_2\text{CH}_2)_3\text{N}$ (Equation (90)) <2002JOC3555> have also been found to be useful promoters of conjugate addition. Electron-transfer-photosensitized conjugate addition has been achieved; however, addition to α,β -enoates proceeds with poor yield (Equation (91)) <1998JOC4026>.



Scheme 17



Scheme 18

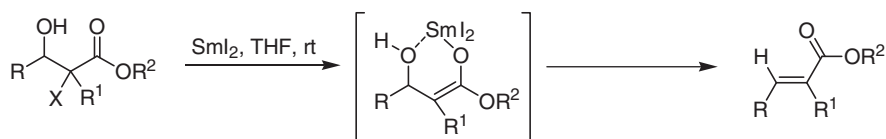


TMPM = tetramethyl pyromellitate

5.03.5.3 α,β -Unsaturated Esters

5.03.5.3.1 α,β -Unsaturated esters via redox reactions

Only a few methods for the synthesis of α,β -unsaturated esters via redox reactions were reported in [<1995COFGT\(5\)121>](#), and apart from [Scheme 19 <2000AG\(E\)2773>](#), no major advances have occurred in this area since the publication of chapter 5.03.5.3.1 in [<1995COFGT\(5\)121>](#).

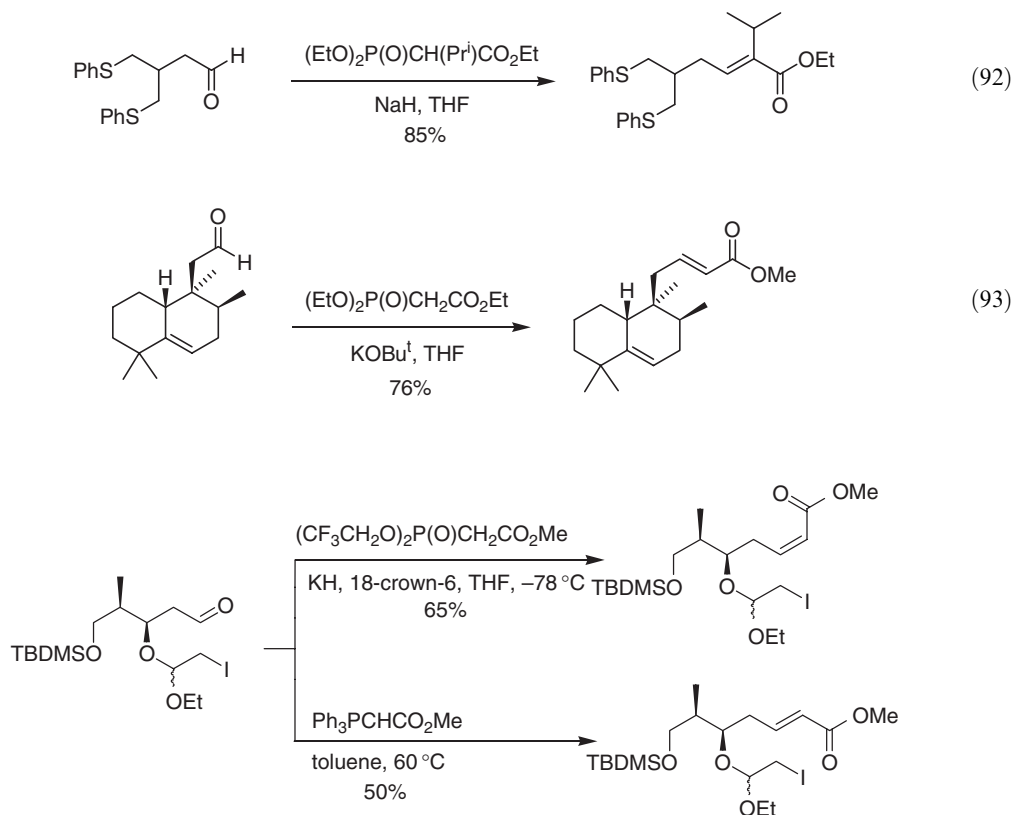


R	R^1	R^2	X	(E)/(Z) ratio	Yield (%)
C_7H_{15}	Me	Et	Cl	>98:2	75
Cyclohexyl	Me	Et	Cl	>98:2	90
4- ClC_6H_4	H	Bu^t	Cl	>98:2	72
Ph	Bu^n	Et	Br	>98:2	86
4- CNC_6H_4	Me	Et	Cl	>98:2	84
4- MeOC_6H_4	Me	Et	Cl	>98:2	91
(E)- $\text{MeCH}=\text{CH}$	C_6H_{13}	Et	Br	>98:2	90

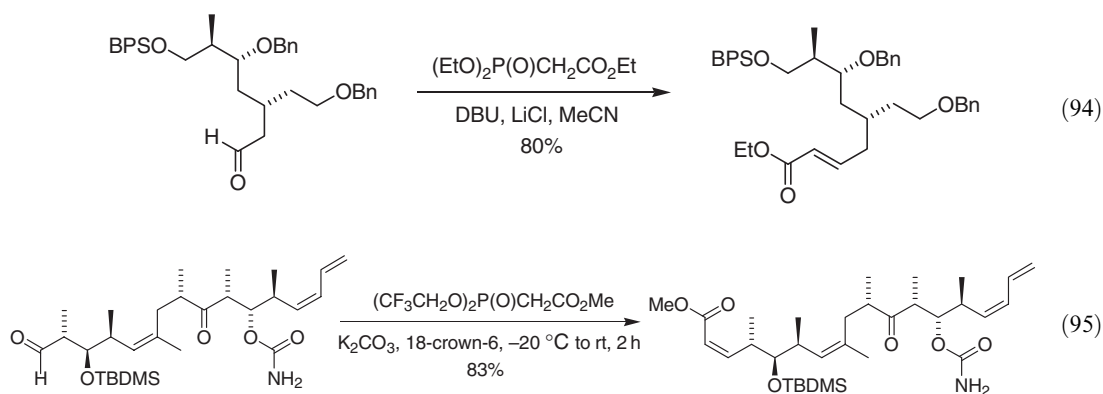
Scheme 19

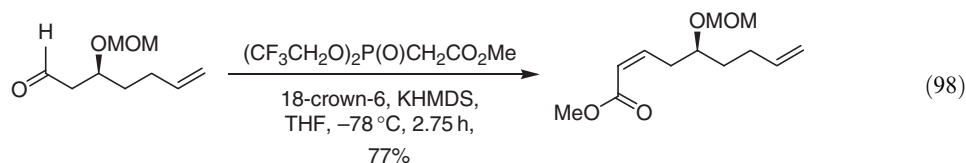
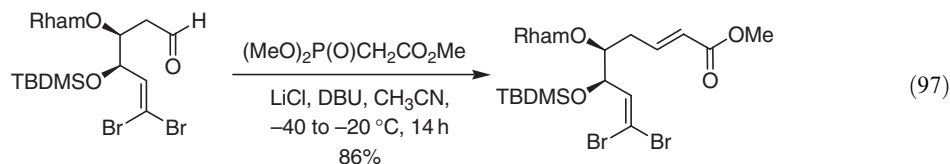
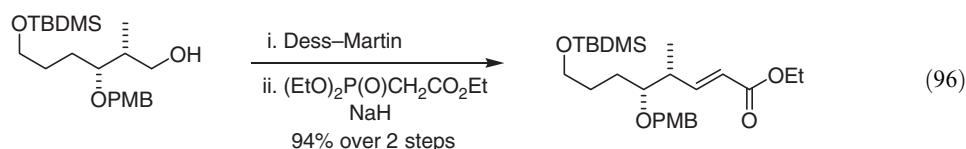
5.03.5.3.2 α,β -Unsaturated esters via alkenation

Wittig or Horner alkenations are extremely useful and versatile for the synthesis of α,β -enoates (Equation (92)) <2002OL4705>, and many of the reported syntheses use the products of alkenation in the synthesis of a range of complex natural products. Examples include: Equation (93) in the total synthesis of (–)-cacospongionolide <2003OL991>, Scheme 20 <2002JOC7750> and Equation (94) <2003JOC4215> in the total synthesis of the antitumor macrolide rhizoxin D, Equations (95) and (96) in the formal synthesis of (+)-discodermolide <2003OL1233> and of discodermolide/dictyostatin hybrids <2002OL4443>, Equation (97) toward the synthesis of the spinosyn A tricyclic nucleus <2002OL3157>, and Equation (98) in the determination of the relative configuration of the C2–C1'-fragment of cytostatin <2002S2096>. The geometry of the double bond can be controlled by an appropriate choice of reagents and solvent, as exemplified in Scheme 20 <2002JOC7750>.



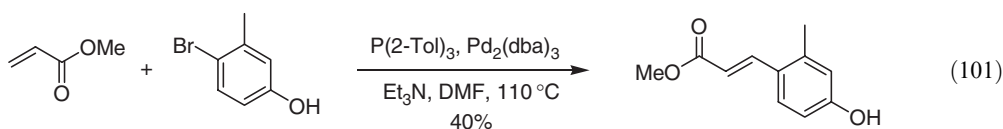
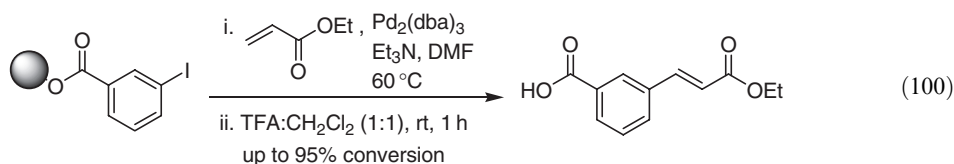
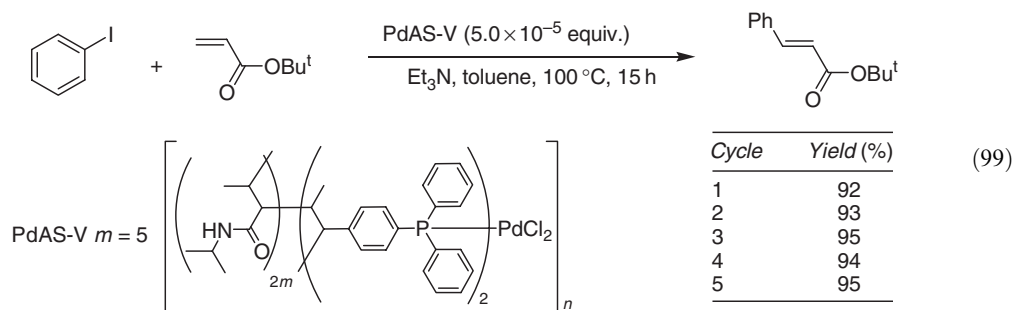
Scheme 20

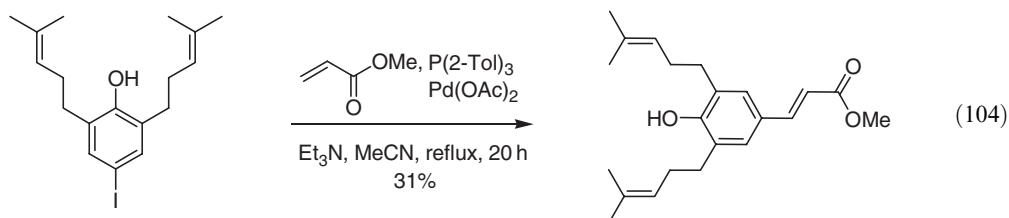
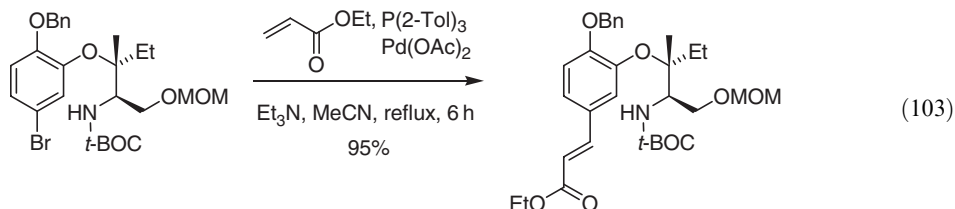
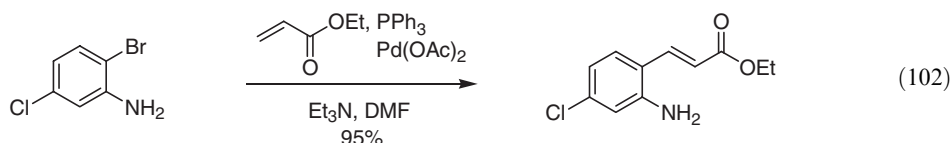




5.03.5.3.3 α,β -Unsaturated esters via Heck coupling or alkoxy carbonylation

The Heck reaction is a reliable method for the synthesis of cinnamic esters with (*E*)-configuration <2002TL8475, 2000OL1287, 2003JMC1580, 2003OL3209, 2002SL439>. Some recent examples are highlighted in Equation (99), where a useful recyclable catalyst has been developed <2003TL2379>; in Equation (100), where the use of solid-phase synthesis allows for the easy isolation of the desired α,β -unsaturated ester <2002TL5973>; and in Equation (101), where the synthesis of small molecule agonists has been achieved by further manipulation of the α,β -unsaturated ester formed <2003BOMCL1517>. Equation (102) also highlights an intermediate in the synthesis of a novel COX-2 inhibitor <2003JOC4104>. Equations (103) and (104) feature intermediates formed in the total synthesis of ustiloxin D <2002JA520> and artemillin C <2002JOC2355>, respectively. There have been no further advances in alkoxy carbonylation since the publication of chapter 5.03.5.3.3 in <1995COFGT(5)121>.





5.03.5.4 β,γ -Unsaturated Esters

5.03.5.4.1 β,γ -Unsaturated esters via alkoxy carbonylation

Allylic acetates and dienes have been shown to be converted into β,γ -enoates; however, there have been no major advances in this type of alkoxy carbonylation since the publication of chapter 5.03.5.4.1 in <1995COFGT(5)121>.

5.03.5.4.2 β,γ -Unsaturated esters via S_N2' reaction

In <1995COFGT(5)121> it was shown that γ,δ -dihydroxy- α,β -enoates could undergo stereoselective S_N2' reactions with cuprates to form β,γ -enoates stereoselectively. However, there have been no major advances in this area since the publication of chapter 5.03.5.4.2 in <1995COFGT(5)121>.

5.03.5.5 γ,δ -Unsaturated Esters

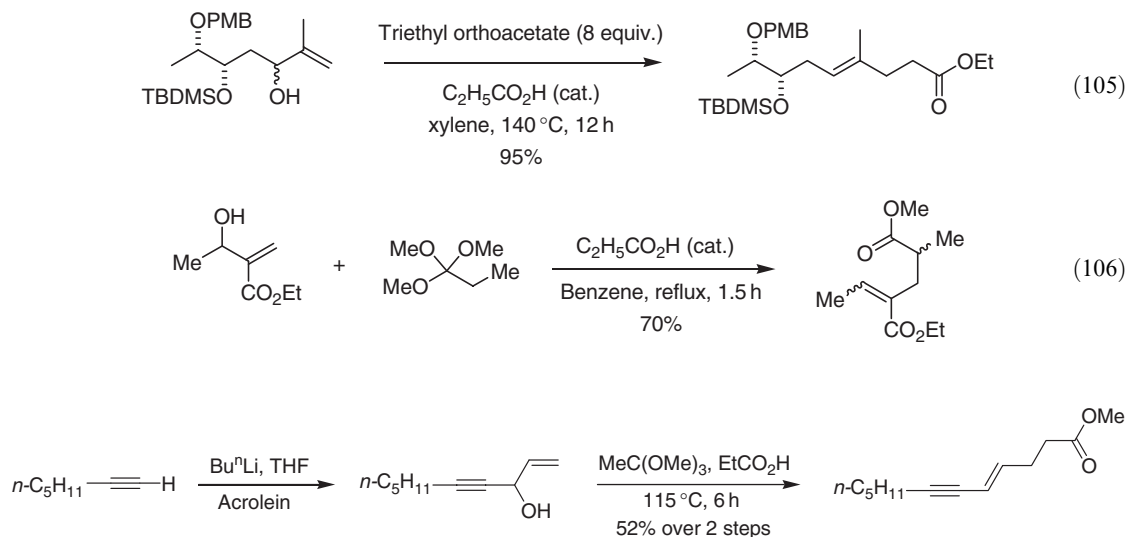
5.03.5.5.1 γ,δ -Unsaturated esters via Tsuji–Trost reaction

In <1995COFGT(5)121> the mild variant of S_N2 displacement reactions with malonate anions under Pd catalysis developed by Tsuji and Trost was reported. Since the publication of chapter 5.03.5.4.2 in <1995COFGT(5)121> there have been no major advances in this area.

5.03.5.5.2 γ,δ -Unsaturated esters via Claisen–Johnson rearrangement

Claisen–Johnson rearrangement is the most efficient and stereochemically most reliable synthesis of γ,δ -unsaturated esters. A variety of syntheses were reported in <1995COFGT(5)121>: some more recent examples are shown in Equation (105), synthesis of an intermediate in the synthesis of epothilone B <2000AG(E)581>; Equation (106), synthesis of an intermediate in the synthesis of

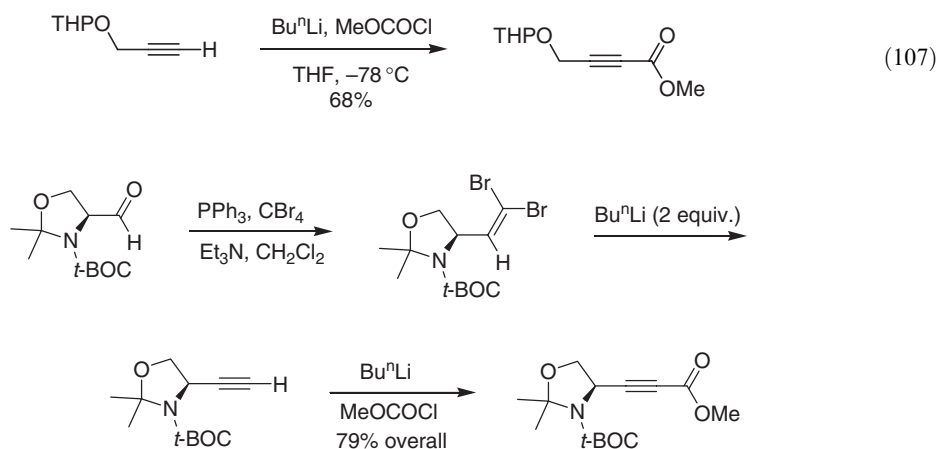
alkyl- α -ketoglutaric acids <1999TL6577>; and in Scheme 21, preparation of an intermediate for the formal synthesis of (Z),(Z)-dodeca-3,-6-dien-1-ol (trail pheromone mimic of the subterranean termite *Reticulitermes virginicus*) <1998JCR(S)706>.



Scheme 21

5.03.5.6 α,β -Alkynoic Esters

α,β -Alkynoic esters can be synthesized by the treatment of protected propargyl alcohol with *n*-butyllithium at low temperature and subsequent exposure to methyl chloroformate to give the desired product in good yield (Equation (107)) <1995T2129>. As mentioned in <1995COFGT(5)121> the Corey–Fuchs sequence is extremely useful for the synthesis of α,β -alkynoic esters, and a more recent example is shown in Scheme 22 <1995TL8275, 1996CC733, 1997JOC6187, 1998T10217>.



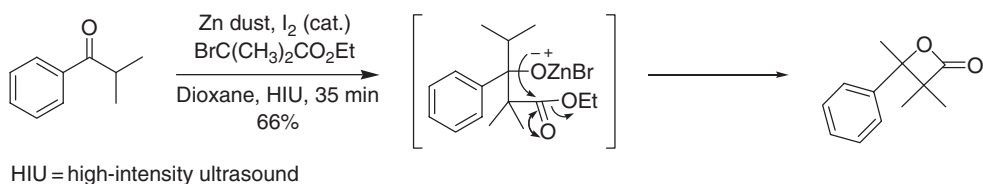
Scheme 22

5.03.6 LACTONES

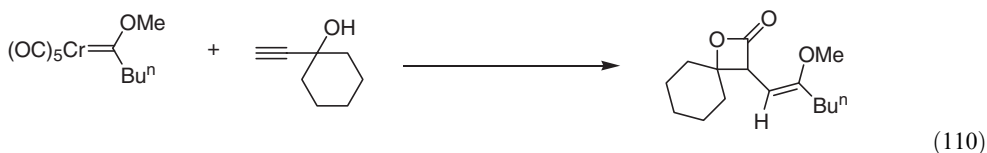
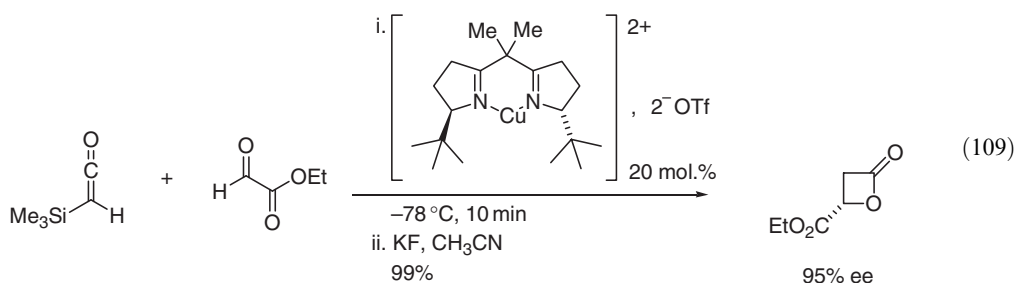
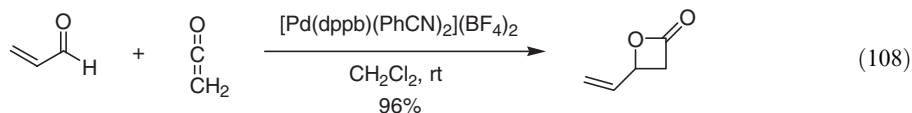
In general lactones, except β -lactones, may be synthesized from cycloalkanones via Baeyer–Villiger oxidation. Other methods are presented in Section 5.03.6.1.

5.03.6.1 β -Lactones

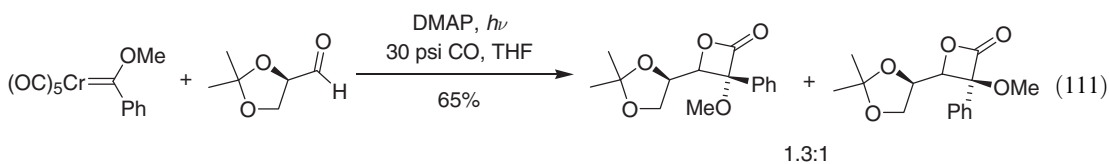
The smallest lactone rings that are synthetically useful are the β -lactones, and a wide range of methods for the production of β -lactones was reported in <1995COFGT(5)121>. More recently a large number of reports describe various procedures for the formation of β -lactones; Scheme 23 and Equations (108)–(120) highlight just a few examples. High intensity ultrasound (HIU) has been used to form β -lactones in good yield <2003JOC360> (Scheme 22). Ketenes have been used extensively for the synthesis of β -lactones (Equation (108)) <2002T5215>, and high enantioselectivities can be achieved (Equation (109)) <2001OL2125>. Chromium alkyl(alkoxy)carbene complexes have been found as useful reagents (Equation (110)) <1999TL3485, 1999TL3481> and Equation (111) <2003JOC6056>. A highly enantioselective and stereoselective synthesis of β -lactones has been developed by Nelson and co-workers (Equation (112)) <2000OL1883>, and the products formed are used in the total synthesis of several natural products including (–)-malyngolide <2000JA10470> and (–)-lailimalide <2002JA13654>. A variety of methods for lactonization for the synthesis of β -lactones have been reported (Equations (113) <2000T3921>, (114) <2003CC114>, and (115) <2002BMC2553, 2002JOC1536, 2002OL711>), with Equation (116) highlighting the total synthesis of (–)-ebelactone A <2002OL2043>. Other methods include the tandem Mukaiyama aldol-lactonization (Equation (117)) <1997TL6537, 1998BMC1255, 2002OL3231>, the palladium-catalyzed carbonylation of tertiary allylic alcohols (Equation (118)) <2002JFC177>, the carbonylation of epoxides (Equation (119)) <2001JOC5424>, and radical cyclization (Equation (120)) <2003OL757>.

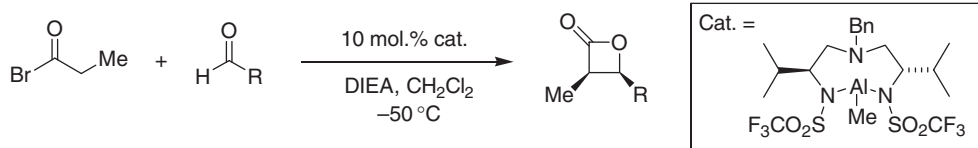


Scheme 23



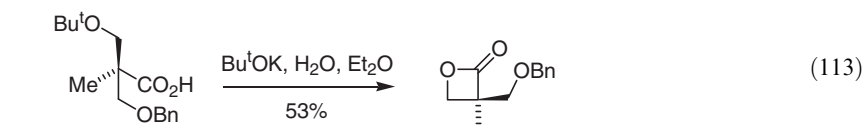
Conditions	Time (h)	Yield (%)
THF, reflux	1.0	65
Benzene, γ), Et ₃ N	1.5	57



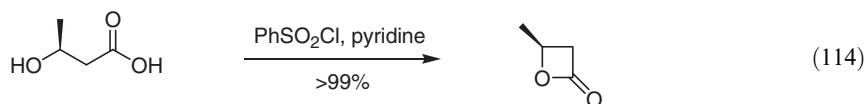


<i>R</i>	<i>ee</i> (%)	<i>cis:trans</i>	<i>Yield</i> (%)
CH ₂ OBn	94	88:12	78
C≡CCH ₂ OBn	94	91:9	85
C≡CCH ₂ CH ₂ OPMB	90	87:13	86
C≡CC ₅ H ₁₁	93	98:2	85
C≡CCMe ₃	90	>99:1	90
C≡CSiMe ₃	93	>99:1	90
C≡CPh	91	>99:1	83
4-O ₂ NC ₆ H ₄	>98	>99:1	90

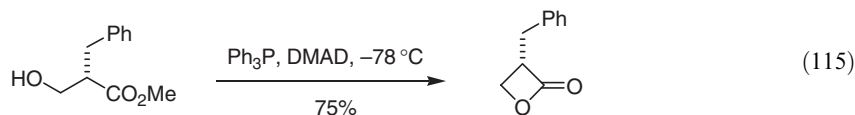
(112)



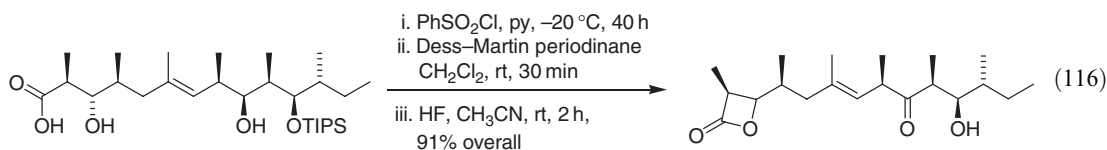
(113)



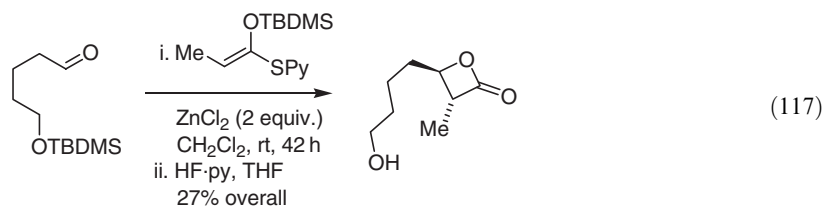
(114)



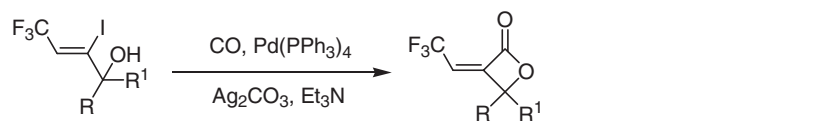
(115)



(116)

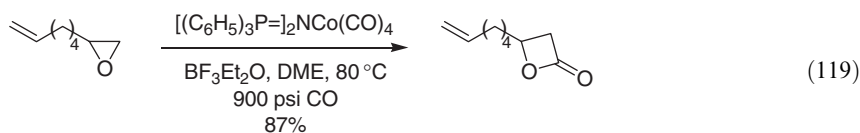


(117)

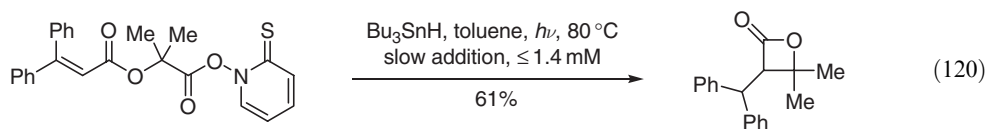


(118)

<i>R</i>	<i>R</i> ¹	<i>Yield</i> (%)
-(CH ₂) ₅ -		86
-(CH ₂) ₄ -		77
CH ₃	CH(CH ₃) ₂	71
C ₂ H ₅	<i>n</i> -C ₇ H ₁₅	62



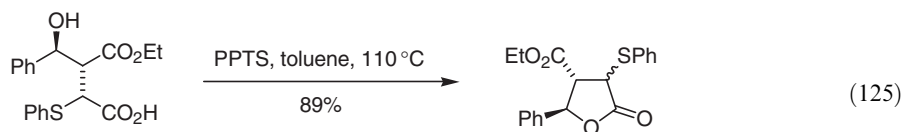
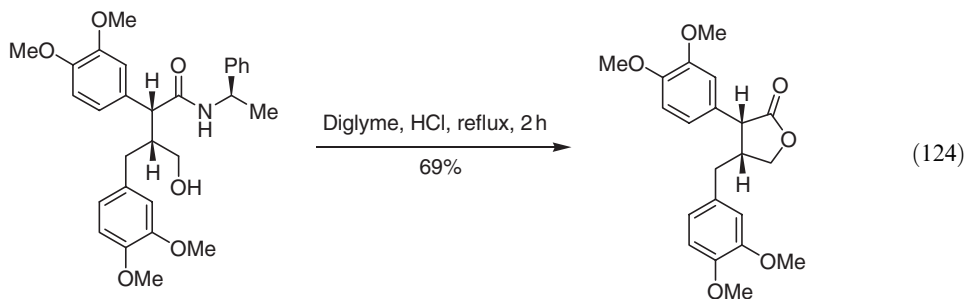
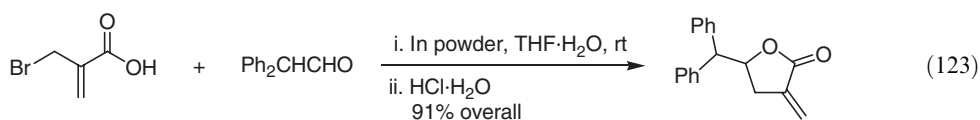
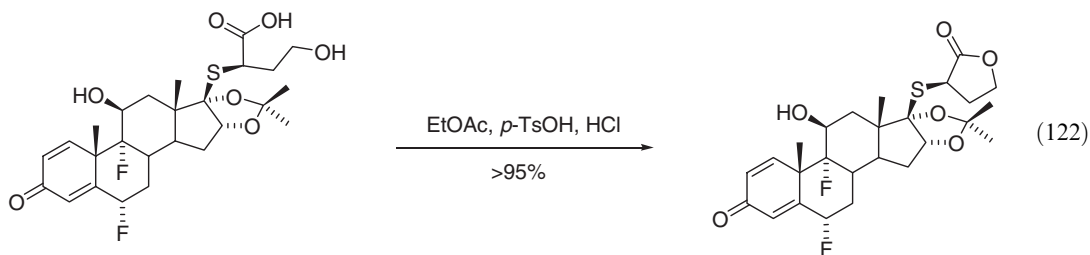
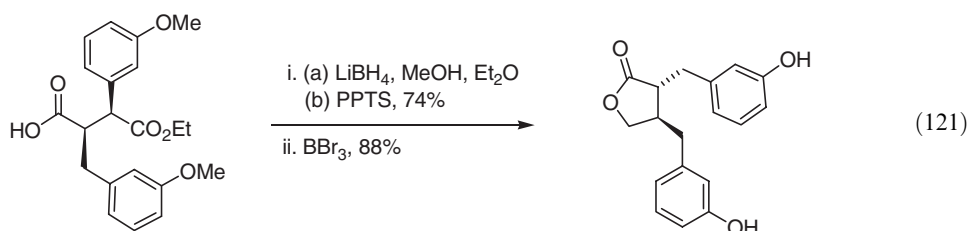
(119)



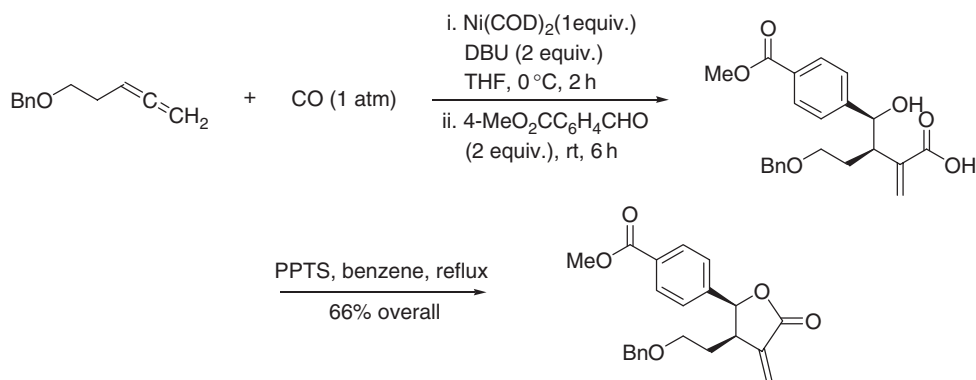
5.03.6.2 γ -Lactones

5.03.6.2.1 γ -Lactones by direct cyclodehydration of γ -hydroxycarboxylates

Aside from the most hindered systems, γ -hydroxycarboxylates spontaneously cyclize to lactones, especially in the presence of a mineral acid. A plethora of syntheses were reported in [<1995COFGT\(5\)121>](#), and [Equations \(121\) <2002JOC1738>](#), [\(122\) <2001JMC602>](#), [\(123\) <1998TL3581>](#), [\(124\) <1996T12799>](#), [\(125\) <2001TL8497>](#), and [Scheme 24 <2003OL2599>](#) represent some more recent reports utilizing this extremely useful method.



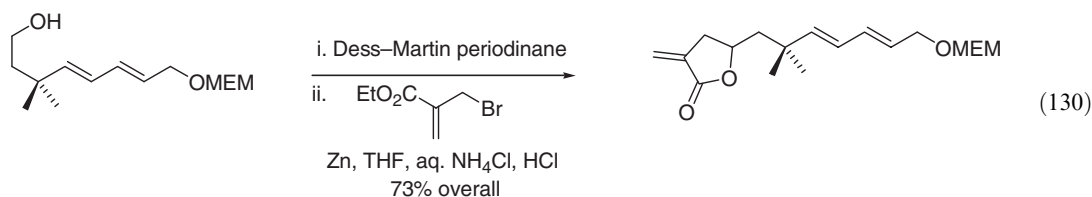
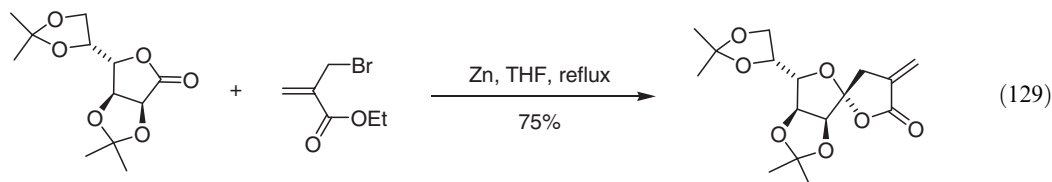
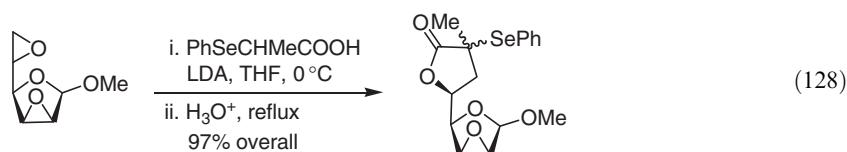
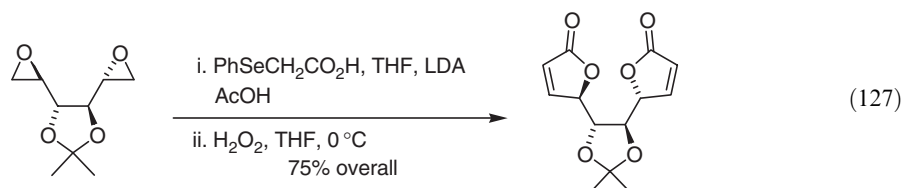
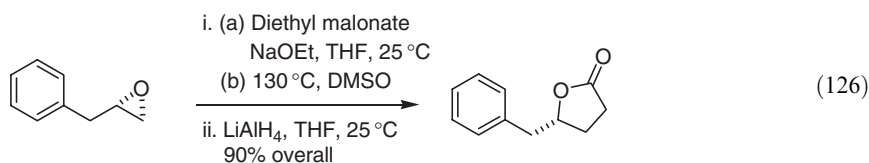
4,5-*cis*/4,5-*trans* 86/14

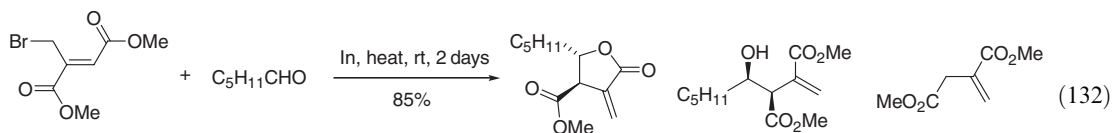
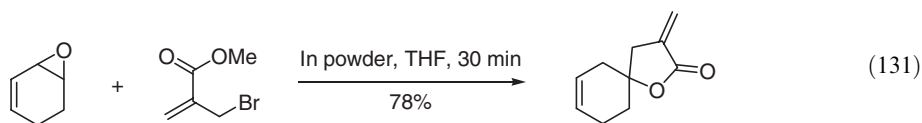


Scheme 24

5.03.6.2.2 γ -Lactones by enolate additions

In many cases the γ -hydroxycarboxylate is generated by enolate addition, for example epoxides are opened by stabilized enolate anions to form γ -hydroxycarboxylates which can cyclize (Equation (126)) <2003JA10219>. Exposure of epoxides to the anion of phenylseleno acids affords γ -lactones in good yield (Equation (127) <2003JOC2437> and Equation (128) <2001TA1131>). The Reformatsky addition is an extremely useful tool in the preparation of spirocyclic systems such as in Equation (129) <2001TA1131> and in the synthesis of γ -lactones (Equation (130) <2002JOC2474>). Indium-mediated Reformatsky-type addition has also been reported (Equation (131) <2003TL2911> and Equation (132) <2001TL3511>).

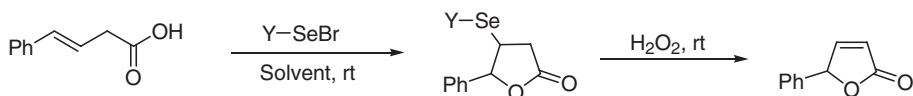
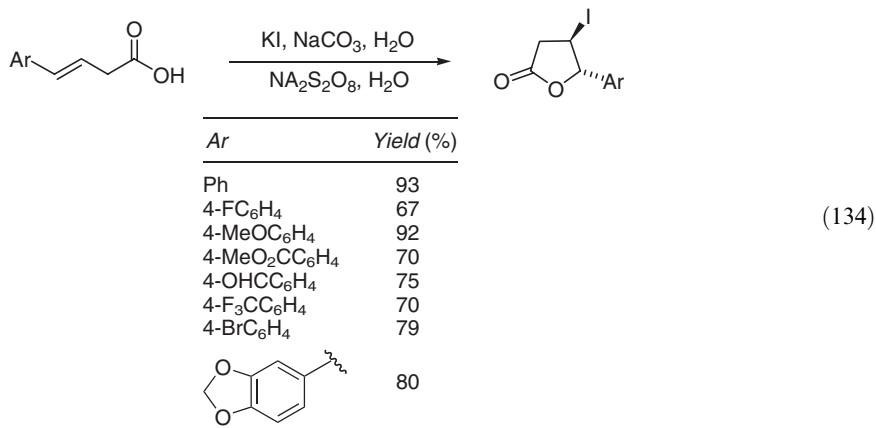
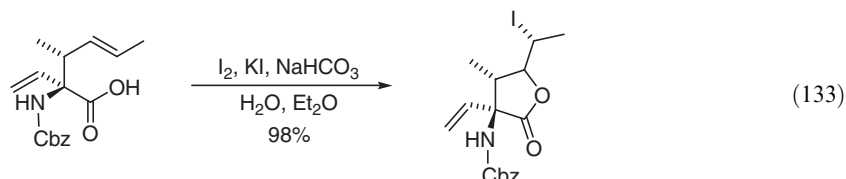




40:45:15

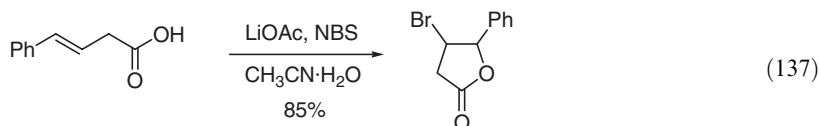
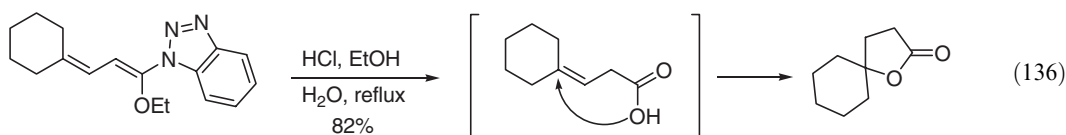
5.03.6.2.3 γ -Lactones from β -, γ -, and γ - δ -ene-carboxylates

Direct lactonization of unsaturated carboxylic acids is a well-established method for the synthesis of γ -lactones. Iodolactonization is highlighted in Equation (133) <1996TL5351> and Equation (134) <1996TL7507>. There are a variety of methods for selenolactonization <2000TL3241, 1997T2029> and this procedure has been modified to run on solid support (Equation (135)) <2003TL3793>. Acid hydrolysis of benzotriazole derivatives affords γ -lactones in good yield (Equation (136)) <1997JOC4131>. β -Halo- γ -lactones can be synthesized from but-2-enoic acids by treatment with catalytic lithium acetate and *N*-halosuccinimides (Equation (137)) <1997JOC199>.



	Yield (%) of deselenylated product	
	H ₂ O	CH ₂ Cl ₂
PhSeBr	38	90
	59	46
	62	44

(135)



5.03.6.2.4 Ring enlargement of β -lactones

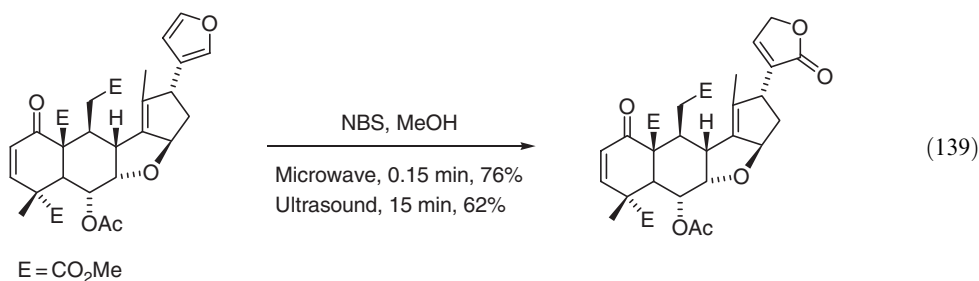
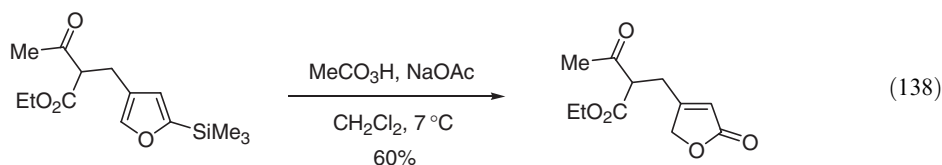
It has been shown that under the influence of Lewis acids, β -lactones can undergo stereocontrolled dyotropic ring enlargement to γ -lactones; however, there have been no further advances in this type of reaction since the publication of chapter 5.03.6.2.4 in <1995COFGT(5)121>.

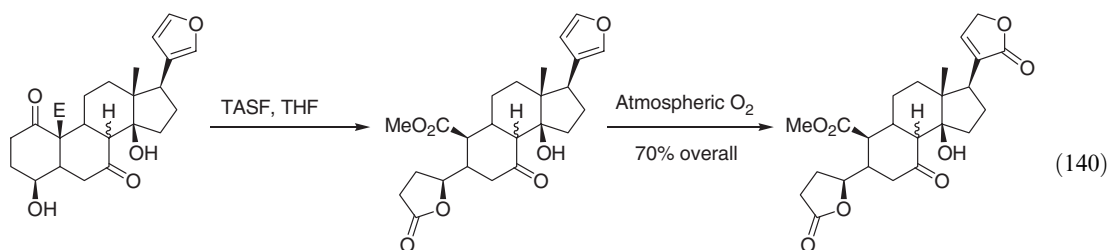
5.03.6.2.5 Carbonylation reactions

In <1995COFGT(5)121> it was shown that γ -lactones could be synthesized by palladium-catalyzed carbonylation reactions. However, there have been no further advances in this area since the publication of chapter 5.03.6.2.5 in <1995COFGT(5)121>.

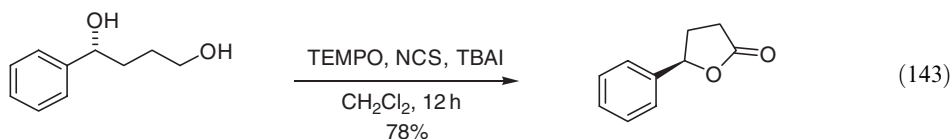
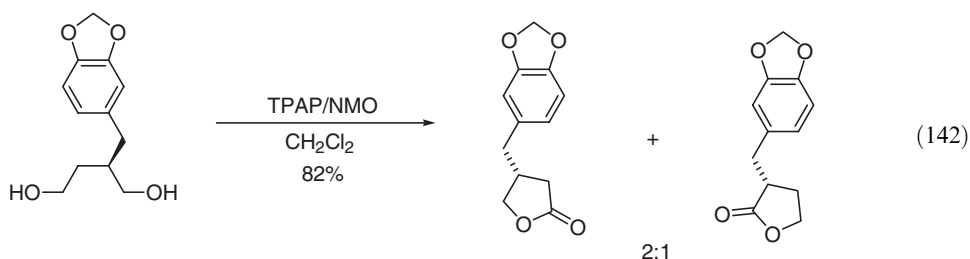
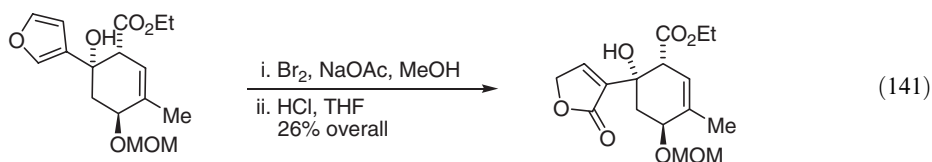
5.03.6.2.6 γ -Lactones via redox reactions

Butenolides can be synthesized by an oxidation–reduction sequence through the formal addition of water to furans. The choice of reagent determines the regiochemical control of the reaction. Peracid/sodium acetate gives the β -product (Equation (138) <1996T12137>) and NBS gives the α -product <1995COFGT(5)121>. The NBS method has been extended with the use of microwave or ultrasound techniques (Equation (139)) <2001TL6577>. Another procedure utilizes atmospheric oxygen (Equation (140)) <2002JOC5669>, and bromine/NaOAc has also been reported for this transformation (Equation (141)) <1997JCS(P1)381>. Butane-1,4-diols undergo oxidative cyclization to γ -lactones, which was originally reported with Fetizon's reagent (Ag₂CO₃/celite) <1995COFGT(5)121>, and can now be carried out with TPAP/NMO (Equation (142)) <2002SL77> or TEMPO (Equation (143)) <2003TA1575>.



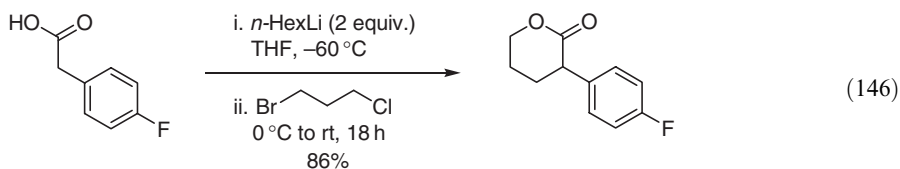
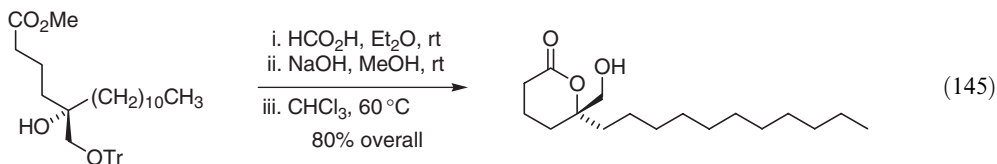
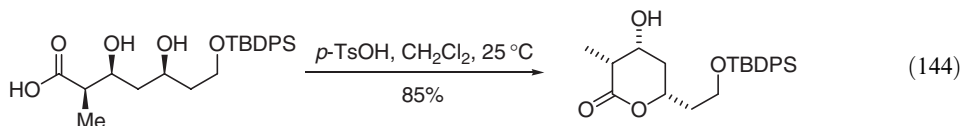
E = CO₂Me

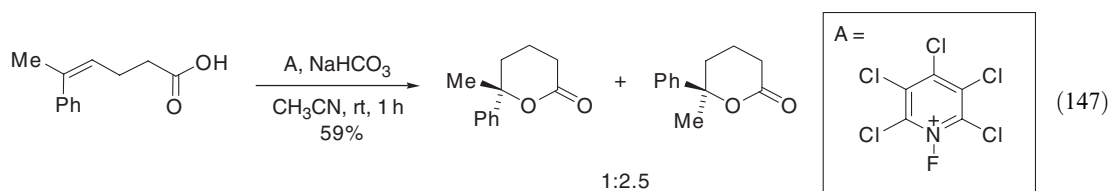
TASF = tris(Dimethylamino)sulfonium difluorotrimethyl silicate



5.03.6.3 δ -Lactones

The synthesis of δ -lactones is very similar to that of γ -lactones. Therefore, direct cyclization of δ -hydroxy acids is quite common, an example of which is shown in Equation (144) <2003SL1500>. Addition of alkoxides to esters is also a popular method, and Equation (145) highlights the total synthesis of (+)-tanikolide <2003TL2513>. Intramolecular addition of carboxylic acid enolates to alkyl halides can afford γ -lactones in good yield (Equation (146)) <2003TL365>, and direct lactonization can also be achieved from unsaturated carboxylic acids (Equation (147)) <1997JFC157>.





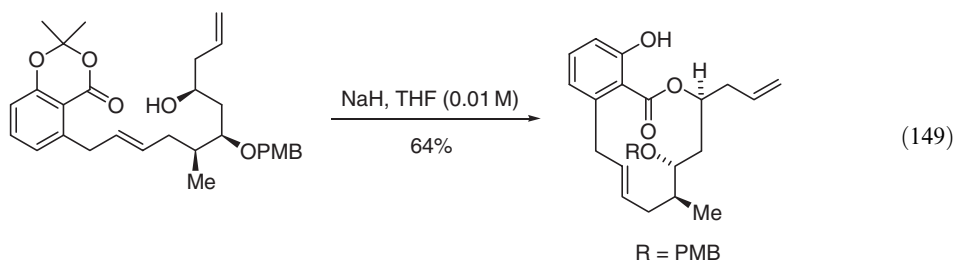
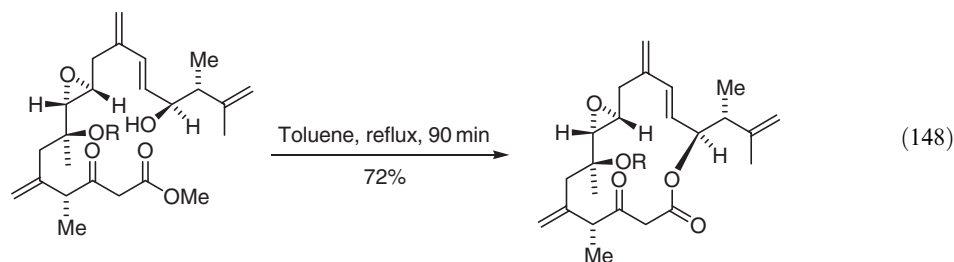
5.03.6.4 Macrolactones

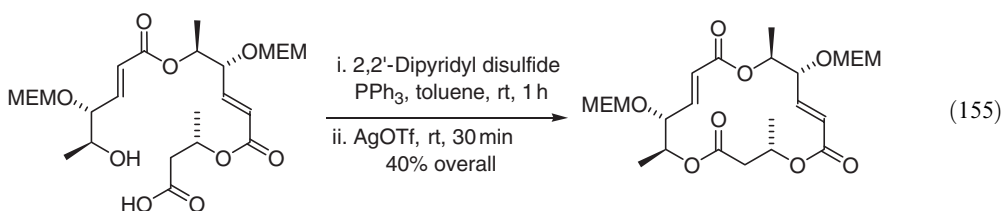
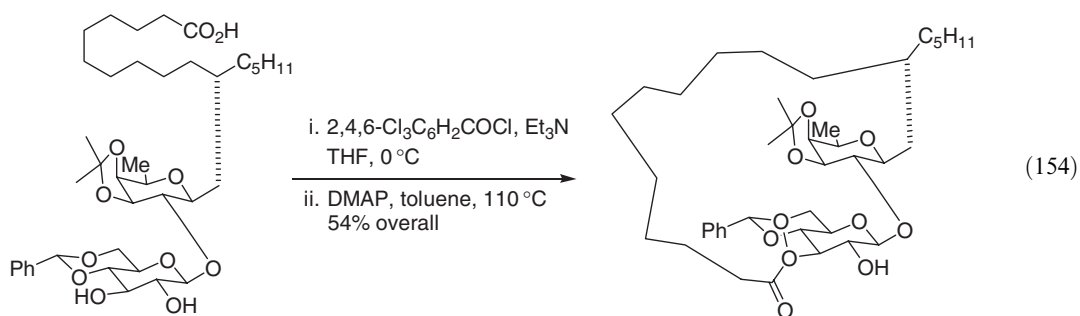
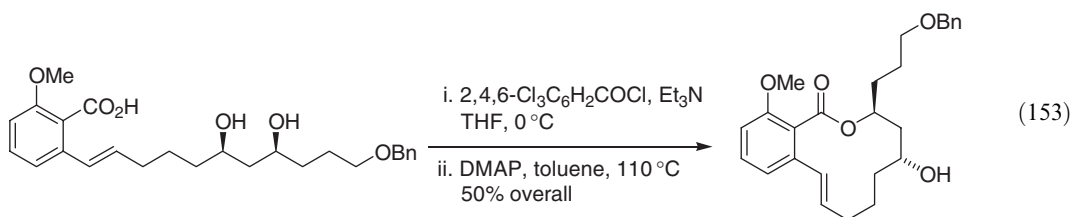
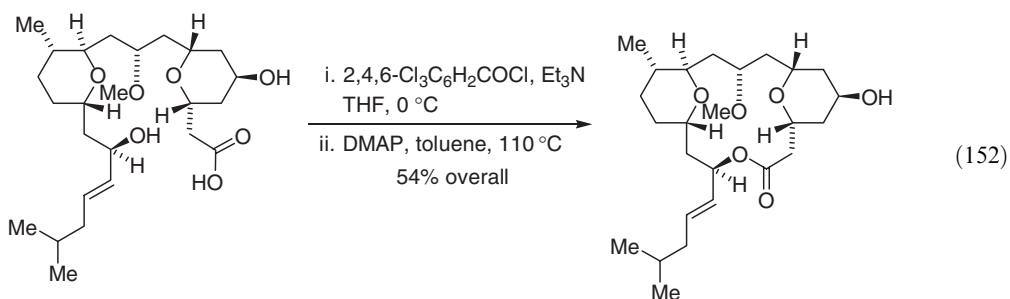
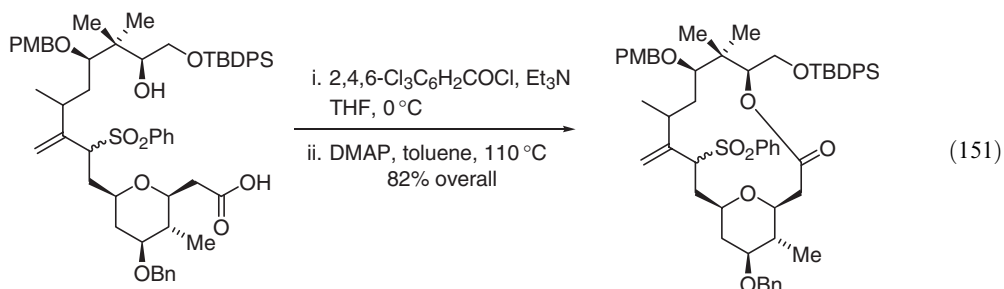
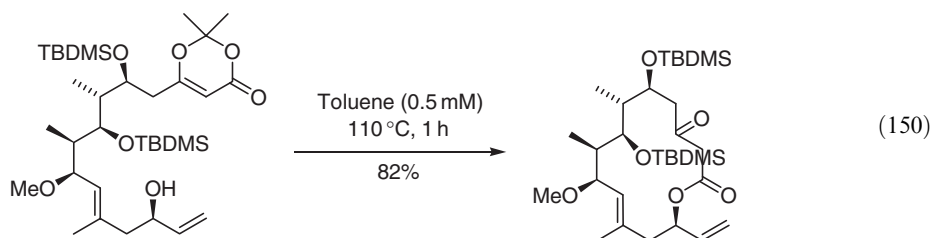
Macrolactones are of enormous importance in natural product synthesis. Consequently, a variety of lactonization methods have been developed, many of which were reviewed in [<1995COFGT\(5\)121>](#). The main problem encountered with this technique is the competition between macrolactonization and polymerization. Thus, reactions are generally performed under high dilution and lactone ring sizes from 12 upward are accessible. Since the publication of [<1995COFGT\(5\)121>](#), major advances in the synthesis of macrolactones have been achieved by use of ring-closing metathesis (RCM), and a wide variety of natural products—e.g., [17]- and [18]-dehydrodesoxyepothilones B [<2002JOC7750>](#), (+)-aspicilin, and the macrolide core of migrastatin [<2002TL9039>](#) have been synthesized.

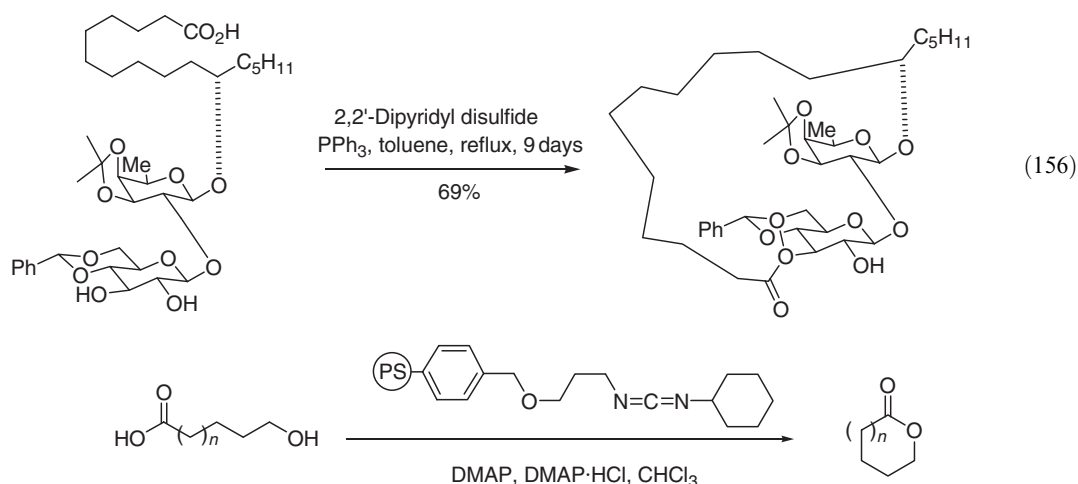
Lactonizations may be subdivided into CGA and HGA procedures; some alternative methods are available, but they do not appear as generally applicable.

5.03.6.4.1 Carboxylic group-activated methods

The most reliable results are generally observed using this methodology. A wide variety of CGA reagents have been introduced, with the simplest being esters. For example, in the synthesis of (–)-amphidinolide (Equation (148)) [<2000OL945>](#), salicylhalamides A and B (Equation (149)) [<2003JOC2200>](#), and in the synthesis of callipeltoside A (Equation (150)) [<2002JA10396>](#). The most applicable CGA method is Yamaguchi's procedure, using 2,4,6-trichlorobenzoyl chloride and DMAP, examples of which were shown in [<1995COFGT\(5\)121>](#). More recently this method has been used to synthesize (–)-polycarveroside A (Equation (151)) [<1999JA4542>](#), (+)-leucascandrolide A (Equation (152)) [<2003OL4641>](#), the core of apicularen A (Equation (153)) [<2002OL643>](#), and in the total synthesis of tricolorin A (Equation (154)) [<1997JOC8406>](#). Corey's thiol ester method, also reported in [<1995COFGT\(5\)121>](#), has found recent application in the synthesis of macrosphelide A (Equation (155)) [<2003TL8857>](#) and in a separate total synthesis of tricolorin A (Equation (156)) [<1997JOC8400>](#). A polymer-supported DCC reagent has been reported for the synthesis of a range of lactone ring sizes (Equation (157)) [<2000TL8673>](#).



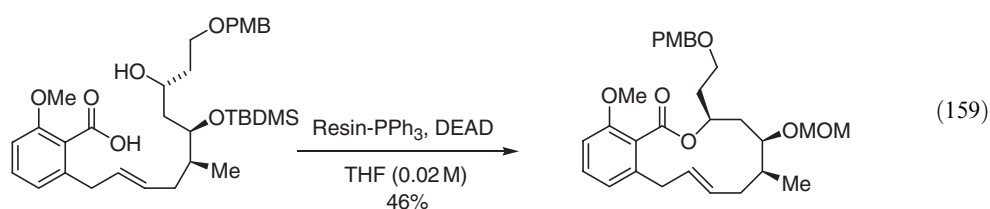
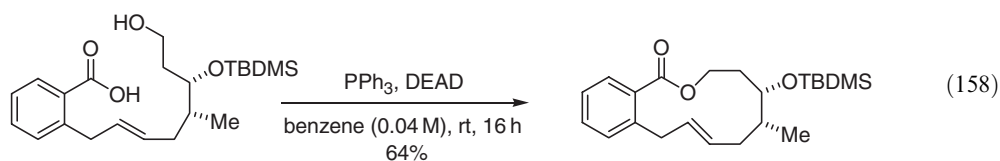




Lactone	Yield (%)	Lactone	Yield (%)
	52		97
	77		96

5.03.6.4.2 Hydroxyl group-activation methods

The Mitsunobu reagent is the most suitable reagent for macrolactonization via the HGA approach, and a variety of methods were shown in [<1995COFGT\(5\)121>](#). Two more recent examples are illustrated here, used in the synthesis of salicylhalamides (Equation (158) [<2000TL8569>](#) and Equation (159) [<2003JOC8129>](#)).



5.03.6.4.3 Special methods

No major progress has been made in this area since the publication of chapter 5.03.6.4.3 in <1995COFGT(5)121>.

REFERENCES

- 1995COFGT(5)121 J. Mulzer, Carboxylic esters and lactones, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, p. 121–180.
- 1995JA9139 M. Lögers, L. E. Overman, G. S. Welmaker, *J. Am. Chem. Soc.* **1995**, *117*, 9139–9150.
- 1995JOC7589 A. R. Katritzky, G. Zhang, J. Jiang, *J. Org. Chem.* **1995**, *60*, 7589–7596.
- 1995JOC8339 J. Marchal, J. Bodiguel, Y. Fort, P. Caubere, *J. Org. Chem.* **1995**, *60*, 8336–8340.
- 1995T2129 G. Reginato, A. Capperucci, A. Degl'Innocenti, A. Mordini, S. Pecchi, *Tetrahedron* **1995**, *51*, 2129–2136.
- 1995TL8275 G. Reginato, A. Mordini, A. Degl'Innocenti, M. Caracciolo, *Tetrahedron Lett.* **1995**, *36*, 8275–8278.
- 1995SL339 C. Cinquin, I. Shaper, G. Mandville, R. Bloch, *Synlett* **1995**, 339–340.
- 1996CC733 M. T. Reetz, T. J. Strack, J. Kanand, R. Goddard, *J. Chem. Soc., Chem. Commun.* **1996**, 733–734.
- 1996HCA913 D. Seebach, M. Overhand, F. N. M. Kühnle, B. Martinoni, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1996**, *79*, 913–925.
- 1996JA7716 M. Ochiai, T. Ito, H. Takahashi, A. Nakanishi, M. Toyonari, T. Sueda, S. Goto, M. Shiro, *J. Am. Chem. Soc.* **1996**, *118*, 7716–7730.
- 1996JMC(A)L187 Y. Kubota, T. Hanaoka, K. Takeuchi, Y. Sugi, *J. Mol. Catal. A: Chemical* **1996**, *111*, L187–L192.
- 1996JOC3088 Y. Ishii, M. Takeno, Y. Kawasaki, A. Muromachi, Y. Nishiyama, S. Sakaguchi, *J. Org. Chem.* **1996**, *61*, 3088–3092.
- 1996JOC4197 K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196–4197.
- 1996JOC5702 E. Vedejs, O. Daugulis, *J. Org. Chem.* **1996**, *61*, 5702–5703.
- 1996MM8304 P. Hubbard, W. J. Brittain, W. J. Simonsick Jr., C. W. Ross III, *Macromolecules* **1996**, *29*, 8304–8307.
- 1996S1355 S. M. Iossifidou, C. C. Froussios, *Synthesis* **1996**, 1355–1358.
- 1996T199 T. Konno, T. Yamazaki, T. Kitazume, *Tetrahedron* **1996**, *52*, 199–208.
- 1996T8063 I. W. Elliott, M. J. Sloan, E. Tate, *Tetrahedron* **1996**, *52*, 8063–8072.
- 1996T12137 E. S. Wang, Y. M. Choy, H. N. C. Wong, *Tetrahedron* **1996**, *52*, 12137–12158.
- 1996T12799 R. S. Ward, A. Pelter, M. I. Edwards, *Tetrahedron* **1996**, *52*, 12799–12814.
- 1996TL3137 T. B. Sim, J. Choi, N. M. Yoon, *Tetrahedron Lett.* **1996**, *37*, 3137–3140.
- 1996TL5351 U. Kazmaier, *Tetrahedron Lett.* **1996**, *37*, 5351–5354.
- 1996TL6375 B. D. Hosangadi, R. H. Dave, *Tetrahedron Lett.* **1996**, *37*, 6375–6378.
- 1996TL6733 M. Saitoh, S. Fujisaki, Y. Ishii, T. Nishiguchi, *Tetrahedron Lett.* **1996**, *37*, 6733–6736.
- 1996TL7127 A. Johansson, T. Olsson, G. Bergström, *Tetrahedron Lett.* **1996**, *37*, 7127–7128.
- 1996TL7507 J. Thibonnet, M. Abarbri, J.-L. Parrain, A. Duchêne, *Tetrahedron Lett.* **1996**, *37*, 7507–7510.
- 1997BCSJ2561 S. Sakaguchi, D. Kikuchi, Y. Ishii, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2561–2566.
- 1997BMC405 D. S. A. de Bont, R. G. G. Leenders, H. J. Haisma, I. van der Meulen-Muileman, H. W. Scheeren, *Biorg. Med. Chem.* **1997**, *5*, 405–414.
- 1997CL55 Y. Masakai, N. Tanaka, T. Miura, *Chem. Lett.* **1997**, 55–56.
- 1997COS309 T. Ladduwahetty, *Contemp. Org. Synth.* **1997**, *4*, 309–325.
- 1997JA1492 J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 1492–1493.
- 1997JA5465 K. Nagahara, I. Ryu, M. Komatsu, N. Sonoda, *J. Am. Chem. Soc.* **1997**, *119*, 5465–5466.
- 1997JCS(P1)381 E. R. Parmee, S. V. Mortlock, N. A. Stacey, E. J. Thomas, O. S. Mills, *J. Chem. Soc., Perkin Trans. I* **1997**, 381–390.
- 1997JCS(P1)2273 M.-Z. Cai, C.-S. Song, X. Huang, *J. Chem. Soc., Perkin Trans. I.* **1997**, 2273–2274.
- 1997JFC157 M. Okada, Y. Nakamura, H. Horikawa, T. Inoue, T. Taguchi, *J. Fluorine Chem.* **1997**, *82*, 157–161.
- 1997JOC199 S. Chowdhury, S. Roy, *J. Org. Chem.* **1997**, *62*, 199–200.
- 1997JOC2357 T. B. Sim, J. Choi, M. J. Joung, N. M. Yoon, *J. Org. Chem.* **1997**, *62*, 2357–2361.
- 1997JOC4131 A. R. Katritzky, D. Feng, H. Lang, *J. Org. Chem.* **1997**, *62*, 4131–4136.
- 1997JOC4851 J. Tormo, A. Moyano, M. A. Pericàs, A. Riera, *J. Org. Chem.* **1997**, *62*, 4851–4856.
- 1997JOC6187 G. Reginato, A. Mordini, M. Caracciolo, *J. Org. Chem.* **1997**, *62*, 6187–6192.
- 1997JOC8400 S.-F. Lu, Q. O'yang, Z.-W. Guo, B. Yu, Y.-Z. Hui, *J. Org. Chem.* **1997**, *62*, 8400–8406.
- 1997JOC8406 D. P. Larson, C. H. Heathcock, *J. Org. Chem.* **1997**, *62*, 8406–8418.
- 1997PP381 D. J. Brunelle, J. E. Bradt, J. Serth-Guzzo, T. Takekoshi, T. L. Evans, J. Pearce, *Polym. Prepr.* **1997**, *38*, 381–383.
- 1997SC2467 A. R. Katritzky, G. Zhang, L. Xie, *Synth. Commun.* **1997**, *27*, 2467–2478.
- 1997SC2777 N. Kammoun, Y. Le Bigot, M. Delmas, B. Boutevin, *Synth. Commun.* **1997**, *27*, 2777–2781.
- 1997SL449 T. Toru, S. Nakamura, H. Takemoto, Y. Ueno, *Synlett* **1997**, 449–450.
- 1997SL1149 T. Takeda, H. Watanabe, T. Kitahara, *Synlett* **1997**, 1149–1150.
- 1997T2029 K. Fujita, K. Murata, *Tetrahedron* **1997**, *53*, 2029–2048.
- 1997T7335 R. N. Ram, I. Charles, *Tetrahedron* **1997**, *53*, 7335–7340.
- 1997T17079 G. Mandville, C. Girard, R. Bloch, *Tetrahedron* **1997**, *53*, 17079–17088.
- 1997TA3665 G. Mandville, C. Girard, R. Bloch, *Tetrahedron: Asymmetry* **1997**, *8*, 3665–3673.
- 1997TL6537 C. Zhao, D. Romo, *Tetrahedron Lett.* **1997**, *38*, 6537–6540.
- 1997TL6621 P. A. Jacobi, P. Herradura, *Tetrahedron Lett.* **1997**, *38*, 6621–6624.
- 1998BMC1255 D. Romo, P. H. M. Harrison, S. I. Jenkins, R. W. Riddoch, K. Park, H. W. Yang, C. Zhao, G. D. Wright, *Biorg. Med. Chem.* **1998**, *6*, 1255–1272.

- 1998CL1
1998CL3
1998CL679
1998JCR(S)706
1998JCS(P1)633
1998JCS(P1)2451
1998JOC677
1998JOC2420
1998JOC2794
1998JOC4026
1998JOC5507
1998JOC6027
1998JOC7920
1998S1707
1998SC471

1998SC1159
1998SC2021
1998SC2337
1998SL183
1998T10217

1998T15861
1998TL1365
1998TL2257
1998TL3581
1998TL4223
1998TL8563
1999CSR85
1999JA1645
1999JA4542
1999JA5091
1999JCR(S)378
1999JCS(P1)1617
1999JCS(P1)2249

1999JCS(P1)3537
1999JOC4353
1999JOC9063
1999T14947
1999TA1223
1999TL3481

1999TL3485
1999TL6577
2000ACR412
2000AG(E)581
2000AG(E)2773

2000BMC2195

2000JA10470
2000JMC(B)193
2000JOC1758
2000JOC5623
2000OL311
2000OL945
2000OL1883
2000OL2377
2000OL3789
2000S290
2000SL526
2000T1899
2000T3921
2000T7389
2000TA2565
2000TA3665
2000TL775
2000TL3241

2000TL5249

I. Shiina, H. Iwadare, H. Sakoh, M. Hasegawa, Y. Tani, T. Mukaiyama, *Chem. Lett.* **1998**, 1–2.
I. Shiina, K. Saitoh, I. Fréchet-Ortuno, T. Mukaiyama, *Chem. Lett.* **1998**, 3–4.
K. Saitoh, I. Shiina, T. Mukaiyama, *Chem. Lett.* **1998**, 679–680.
A. A. Vasil'ev, L. Engman, E. P. Serebryakov, *J. Chem. Res. (S)* **1998**, 706–707.
Y.-H. Kim, Y. I. Kim, J. Y. Kim, *J. Chem. Soc., Perkin Trans. 1* **1998**, 633–634.
A. S. Franklin, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2451–2465.
P. Hubbard, W. J. Brittain, *J. Org. Chem.* **1998**, 63, 677–683.
A. Orita, A. Mitsutome, J. Otera, *J. Org. Chem.* **1998**, 63, 2420–2421.
J. C. Ruble, J. Tweddell, G. C. Fu, *J. Org. Chem.* **1998**, 63, 2794–2795.
M. Fagnoni, M. Mella, A. Albini, *J. Org. Chem.* **1998**, 63, 4026–4033.
G. A. Molander, W. H. Retsch, *J. Org. Chem.* **1998**, 63, 5507–5516.
B. C. Ranu, P. Dutta, A. Sarkar, *J. Org. Chem.* **1998**, 63, 6027–6028.
F. E. Ziegler, Y. Wang, *J. Org. Chem.* **1998**, 63, 7920–7930.
A. D. Campbell, T. M. Raynham, R. J. K. Taylor, *Synthesis* **1998**, 12, 1707–1709.
A. Nudelman, Y. Nechor, E. Falb, B. Fischer, B. A. Wexler, A. Nudelman, *Synth. Commun.* **1998**, 28, 471–474.
G.-S. Zhang, *Synth. Commun.* **1998**, 28, 1159–1162.
J. C. Lee, Y. Choi, *Synth. Commun.* **1998**, 28, 2021–2026.
J. S. Yadav, G. S. Reddy, D. Srinivas, K. Himabindu, *Synth. Commun.* **1998**, 28, 2337–2342.
Y. Y. Kubota, S. Nakada, Y. Sugi, *Synlett* **1998**, 183–185.
G. Reginato, A. Mordini, A. Capperucci, A. Degl'Innocenti, S. Manganiello, *Tetrahedron* **1998**, 54, 10217–10226.
K. Takatori, M. Nishihara, Y. Nishiyama, M. Kajiura, *Tetrahedron* **1998**, 54, 15861–15869.
H. Rhee, J. Y. Kim, *Tetrahedron Lett.* **1998**, 39, 1365–1368.
R. L. E. Furlán, E. G. Mata, O. A. Mascaretti, *Tetrahedron Lett.* **1998**, 39, 2257–2260.
P. K. Choudhury, F. Foubelo, M. Yus, *Tetrahedron Lett.* **1998**, 39, 3581–3584.
P. Krasik, *Tetrahedron Lett.* **1998**, 39, 4223–4226.
A. Rodriguez, M. Nomen, B. W. Spur, *Tetrahedron Lett.* **1998**, 39, 8563–8566.
C. Laetitia, D. C. Sherrington, *Chem. Soc. Rev.* **1999**, 28, 85–93.
B. A. Persson, A. L. E. Larsson, M. Le Ray, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1999**, 121, 1645–1650.
L. A. Paquette, L. Barriault, D. Pissarnitski, *J. Am. Chem. Soc.* **1999**, 121, 4542–4543.
B. Tao, J. C. Ruble, D. A. Hoic, G. C. Fu, *J. Am. Chem. Soc.* **1999**, 121, 5091–5092.
R. C. Anand, Vimal, A. Milhotra, *J. Chem. Res. (S)* **1999**, 378–379.
D. Enders, J. P. Shilvock, G. Raabe, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1617–1619.
A. Marchand, T. Lioux, C. Mathe, J. L. Imbach, G. Gosselin, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2249–2254.
A. S. Franklin, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3537–3554.
C. Cabrele, M. Langer, A. G. Beck-Sickinger, *J. Org. Chem.* **1999**, 64, 4353–4361.
P. Ilankumar, J. G. Verkade, *J. Org. Chem.* **1999**, 64, 9063–9066.
A. Rumero, I. Borreguero, J. Sinisterra, A. R. Alcántara, *Tetrahedron* **1999**, 55, 14947–14960.
E. Narisano, R. Riva, *Tetrahedron: Asymmetry* **1999**, 10, 1223–1242.
J. J. Caldwell, J. P. A. Harrity, N. M. Heron, W. J. Kerr, S. McKendry, D. Middlemiss, *Tetrahedron Lett.* **1999**, 40, 3481–3484.
J. J. Caldwell, W. J. Kerr, S. McKendry, *Tetrahedron Lett.* **1999**, 40, 3485–3486.
V. Helaine, J. Rossi, J. Bolte, *Tetrahedron Lett.* **1999**, 40, 6577–6580.
G. C. Fu, *Acc. Chem. Res.* **2000**, 33, 412–420.
H. J. Martin, M. Drescher, J. Mulzer, *Angew., Chem. Int. Ed. Engl.* **2000**, 39, 581–583.
J. M. Concellón, J. A. Pérez-Andrés, H. Rodríguez-Solla, *Angew., Chem. Int. Ed. Engl.* **2000**, 39, 2773–2775.
S. Batra, S. Srivastava, K. Singh, R. Chander, A. K. Khanna, A. P. Bhaduri, *Biorg. Med. Chem.* **2000**, 8, 2195–2209.
Z. Wan, S. G. Nelson, *J. Am. Chem. Soc.* **2000**, 122, 10470–10471.
Y. Kato, I. Fujiwara, Y. Asano, *J. Mol. Catal. B: Enzymatic*, **2000**, 9, 193–200.
S. Nakemura, Y. Watanabe, T. Toru, *J. Org. Chem.* **2000**, 65, 1758–1766.
S. Hanessian, A. Gomtsyan, N. Malek, *J. Org. Chem.* **2000**, 65, 5623–5631.
T. Murai, A. Suzuki, T. Ezaka, S. Kato, *Org. Lett.* **2000**, 2, 311–313.
D. R. Williams, B. J. Meyers, L. Mi, *Org. Lett.* **2000**, 2, 945–948.
S. G. Nelson, Z. Wan, *Org. Lett.* **2000**, 2, 1883–1886.
D. Lee, E. A. Huh, M.-J. Kim, H. M. Jung, J. H. Koh, J. Park, *Org. Lett.* **2000**, 2, 2377–2379.
A. R. Katritzky, S. Zhang, Y. Fang, *Org. Lett.* **2000**, 2, 3789–3791.
K. Ishihara, S. Ohara, H. Yamamoto, *Science* **2000**, 290, 1140–1142.
E. Aller, P. Molina, A. Lorenzo, *Synlett* **2000**, 526–528.
A. T. Anilkumar, U. Sudhir, S. Joly, M. S. Nair, *Tetrahedron* **2000**, 56, 1899–1903.
F.-R. Alexandre, S. Legoupy, F. Huet, *Tetrahedron* **2000**, 56, 3921–3926.
D. H. Hua, K. Takasu, X. Huang, G. S. Millward, Y. Chen, J. Fan, *Tetrahedron* **2000**, 56, 7389–7398.
J. A. Fuentes, A. Maestro, A. M. Testera, J. M. Báñez, *Tetrahedron: Asymmetry* **2000**, 11, 2565–2577.
X. Wang, J. Thottathil, *Tetrahedron: Asymmetry* **2000**, 11, 3665–3669.
M. Díaz, M. Ferrero, S. Fernández, V. Gotor, *Tetrahedron Lett.* **2000**, 41, 775–779.
M. Tiecco, L. Testaferri, L. Bagnoli, F. Marini, A. Temperini, C. Tomassini, C. Santi, *Tetrahedron Lett.* **2000**, 41, 3241–3245.
K. Wakasugi, T. Misaki, K. Yamada, Y. Tanabe, *Tetrahedron Lett.* **2000**, 41, 5249–5252.

- 2000TL8569 J. T. Feutrill, G. A. Holloway, F. Hilli, H. M. Hügel, M. A. Rizzacasa, *Tetrahedron Lett.* **2000**, *41*, 8569–8572.
- 2000TL8673 G. E. Keck, C. Sanchez, C. A. Wager, *Tetrahedron Lett.* **2000**, *41*, 8673–8676.
- 2001AG(E)2044 J. Otera, *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 2044–2045.
- 2001CC2218 L. El Aakel, F. Launay, A. Atlamsani, J.-M. Brégeault, *J. Chem. Soc., Chem. Commun.* **2001**, 2218–2219.
- 2001JA10102 K. Manabe, X.-M. Sun, S. Kobayashi, *J. Am. Chem. Soc.* **2001**, *123*, 10101–10102.
- 2001JCS(P1)3013 J. Panda, S. Ghosh, S. Ghosh, *J. Chem. Soc., Perkin Trans. 1* **2001**, 3013–3016.
- 2001JCS(P1)3025 T. Hasegawa, K. Ikeda, Y. Yamazaki, *J. Chem. Soc., Perkin Trans. 1* **2001**, 3025–3028.
- 2001JMC602 P. A. Procopiu, K. Biggadike, A. F. English, R. M. Farrell, G. N. Hagger, A. P. Hancock, M. V. Haase, W. R. Irving, M. Sareen, M. A. Snowden, Y. E. Solanke, C. J. Tralau-Stewart, S. E. Walton, J. A. Wood, *J. Med. Chem.* **2001**, *44*, 602.
- 2001JOC233 R. H. Blaauw, J.-F. Brière, R. de Jong, J. C. J. Benningshof, A. E. van Ginkel, J. Fraanje, K. Goubitz, H. Schenk, F. P. J. T. Rutjes, H. Hiemstra, *J. Org. Chem.* **2001**, *66*, 233–242.
- 2001JOC5424 J. T. Lee, P. J. Thomas, H. Alper, *J. Org. Chem.* **2001**, *66*, 5424–5426.
- 2001JOC5915 S. Yamazaki, Y. Yanase, K. Kamimoto, K. Yamada, *J. Org. Chem.* **2001**, *66*, 5915–5918.
- 2001JOC7639 T. Pei, R. A. Widenhoefer, *J. Org. Chem.* **2001**, *66*, 7639–7645.
- 2001OL1507 K.-W. Kim, B. Song, M.-Y. Choi, M.-J. Kim, *Org. Lett.* **2001**, *3*, 1507–1509.
- 2001OL2125 D. A. Evans, J. M. Janey, *Org. Lett.* **2001**, *3*, 2125–2128.
- 2001OL2725 J. M. Travins, M. G. Bursavich, D. F. Verber, D. H. Rich, *Org. Lett.* **2001**, *3*, 2725–2728.
- 2001SL769 M.-A. N'Zoutani, A. Pancrazi, J. Ardisson, *Synlett* **2001**, 769–722.
- 2001SL809 L. Streinz, B. Koutek, D. Šaman, *Synlett* **2001**, 809–811.
- 2001TL8193 G. Allan, A. J. Carnell, M. L. E. Hernandez, A. Pettman, *Tetrahedron* **2001**, *57*, 8193–8202.
- 2001TA1131 A. P. Rauter, J. Figueiredo, M. Isnael, T. Canda, J. Font, M. Figueredo, *Tetrahedron: Asymmetry* **2001**, *12*, 1131–1146.
- 2001TA1779 G. Zanon, F. Agnelli, A. Meriggi, G. Vidari, *Tetrahedron: Asymmetry* **2001**, *12*, 1779–1784.
- 2001TA2283 S. Joly, M. S. Nair, *Tetrahedron: Asymmetry* **2001**, *12*, 2383–2387.
- 2001TA3173 H. Acherki, C. Alvarez-Ibarra, A. de Dios, M. Gutiérrez, M. L. Quiroga, *Tetrahedron: Asymmetry* **2001**, *12*, 3173–3183.
- 2001TA3223 J. S. Yadav, S. Nanda, *Tetrahedron: Asymmetry* **2001**, *12*, 3223–3234.
- 2001TL3511 T.-P. Loh, P.-L. Lye, *Tetrahedron Lett.* **2001**, *42*, 3511–3514.
- 2001TL6577 G. Gopalakrishnan, N. D. P. Singh, V. Kasinath, M. S. R. Krishnan, R. Malathi, S. S. Rajan, *Tetrahedron Lett.* **2001**, *42*, 6577–6579.
- 2001TL7099 J. Cesar, M. S. Dolenc, *Tetrahedron Lett.* **2001**, *42*, 7099–7102.
- 2001TL8497 A. Kamimura, F. Kawahara, Y. Omata, N. Murakami, R. Morita, H. Otake, H. Mitsudera, M. Shirai, A. Kakehi, *Tetrahedron Lett.* **2001**, *42*, 8497–8500.
- 2002BMC2553 D. H. Kim, J. Park, S. J. Chung, J. D. Park, N.-K. Park, J. H. Han, *Bioorg. Med. Chem.* **2002**, *10*, 2553–2560.
- 2002GC53 S. Palaniappan, M. S. Ram, *Green Chem.* **2002**, *4*, 53–55.
- 2002JA520 B. Cao, H. Park, M. M. Joullie, *J. Am. Chem. Soc.* **2002**, *124*, 520–521.
- 2002JA10396 B. M. Trost, J. L. Gunzner, O. Dirat, Young h. Rhee, *J. Am. Chem. Soc.* **2002**, *124*, 10396–10415.
- 2002JA13654 S. G. Nelson, W. S. Cheung, A. J. Kassick, M. A. Hilfiker, *J. Am. Chem. Soc.* **2002**, *124*, 13654–13655.
- 2002JFC173 X. Zou, Z. Qiu, *J. Fluorine Chem.* **2002**, *116*, 173–179.
- 2002JFC177 F.-L. Qing, X.-X. Jiang, *J. Fluorine Chem.* **2002**, *114*, 177–180.
- 2002JOC1261 O. Pàmies, J.-E. Bäckvall, *J. Org. Chem.* **2002**, *67*, 1261–1265.
- 2002JOC1536 M. S. Lall, Y. K. Ramtohl, M. N. G. James, J. C. Vederas, *J. Org. Chem.* **2002**, *67*, 1536–1547.
- 2002JOC1738 M. P. Sibi, P. Liu, J. Ji, S. Hajra, J.-X. Chen, *J. Org. Chem.* **2002**, *67*, 1738–1745.
- 2002JOC2355 Y. Uto, A. Hirata, T. Fujita, S. Takubo, H. Nagasawa, H. Hori, *J. Org. Chem.* **2002**, *67*, 2355–2357.
- 2002JOC2474 F. Richter, M. Bauer, C. Perez, C. Maichle-Mössmer, Martin E. Maier, *J. Org. Chem.* **2002**, *67*, 2474–2480.
- 2002JOC3555 P. B. Kisanga, P. Ilankumaran, B. M. Fetterly, J. G. Verkade, *J. Org. Chem.* **2002**, *67*, 3555–3560.
- 2002JOC5005 T. Yokota, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2002**, *67*, 5005–5008.
- 2002JOC5669 D. Chapdelaine, J. Belzile, P. Deslongchamps, *J. Org. Chem.* **2002**, *67*, 5669–5762.
- 2002JOC7750 J. D. White, P. R. Blakemore, N. J. Green, E. B. Hauser, M. A. Holoboski, L. E. Keown, C. S. N. Kolz, B. W. Phillips, *J. Org. Chem.* **2002**, *67*, 7750–7760.
- 2002OL643 S. M. Kühnert, M. E. Maier, *Org. Lett.* **2002**, *4*, 643–646.
- 2002OL711 S. V. Ley, A. Priour, C. Heusser, *Org. Lett.* **2002**, *4*, 711–714.
- 2002OL831 J. Xu, D. J. Burton, *Org. Lett.* **2002**, *4*, 831–833.
- 2002OL1035 S. Crosignani, P. D. White, B. Linclau, *Org. Lett.* **2002**, *4*, 1035–1037.
- 2002OL1963 J. H. Smitrovich, G. N. Boice, C. Qu, L. Dimichele, T. D. Nelson, M. A. Huffman, J. Murry, J. McNamara, P. J. Reider, *Org. Lett.* **2002**, *4*, 1963–1966.
- 2002OL2043 A. K. Mandal, *Org. Lett.* **2002**, *4*, 2043–2045.
- 2002OL2961 S. Crosignani, P. D. White, B. Linclau, *Org. Lett.* **2002**, *4*, 2961–2963.
- 2002OL3157 D. J. Mergott, S. A. Frank, W. R. Roush, *Org. Lett.* **2002**, *4*, 3157–3160.
- 2002OL3231 Y. Wang, D. Romo, *Org. Lett.* **2002**, *4*, 3231–3234.
- 2002OL3583 G. A. Grasa, R. M. Kissling, S. P. Nolan, *Org. Lett.* **2002**, *4*, 3583–3586.
- 2002OL3587 G. W. Nyce, J. A. Lamboy, E. F. Connor, R. M. Waymouth, J. L. Hedrick, *Org. Lett.* **2002**, *4*, 3587–3590.
- 2002OL4443 Y. Shin, N. Choy, R. Balachandran, C. Madiraju, B. W. Day, D. P. Curran, *Org. Lett.* **2002**, *4*, 4443–4446.
- 2002OL4705 J. Colucci, D. Lee, M.-C. Wilson, A. Chau, *Org. Lett.* **2002**, *4*, 4705–4708.

- 2002S2096 L. Bialy, M. Lopez-Canet, H. Waldmann, *Synthesis* **2002**, 2096–2104.
 2002S2171 C. Ramesh, Y. Kubota, M. Miwa, Y. Sugi, *Synthesis* **2002**, 2171–2173.
 2002SC23 A. R. Hajipour, G. Mazloumi, *Synth. Commun.* **2002**, 32, 23–30.
 2002SL77 S. Kamlage, M. Sefkow, N. Zimmermann, M. G. Peter, *Synlett* **2001**, 77–80.
 2002SL439 G. Battistuzzi, S. Cacchi, G. Fabrizi, *Synlett* **2002**, 439–442.
 2002T4759 D. Chevrie, T. Lequeux, J.-C. Pommelet, *Tetrahedron* **2002**, 58, 4759–4767.
 2002T5215 T. Hattori, Y. Suzuki, Y. Ito, D. Hotta, S. Miyano, *Tetrahedron* **2002**, 58, 5215–5223.
 2002T7991 M. Liu, M. P. Sibi, *Tetrahedron* **2002**, 58, 7991–8035.
 2002T8179 K. Ishihara, M. Nakayama, S. Ohara, H. Yamamoto, *Tetrahedron* **2002**, 58, 8179–8188.
 2002T10485 J. Hübner, J. Liebscher, M. Pätz, *Tetrahedron* **2002**, 58, 10485–10500.
 2002TA615 S. Chandrasekhar, G. Kulkarni, *Tetrahedron: Asymmetry* **2002**, 13, 615–619.
 2002TA2513 S. Pinheiro, S. F. Pedraza, M. A. Peralta, R. C. Teixeira, F. M. de Farias, V. F. Ferreira, P. R. R. Costa, *Tetrahedron: Asymmetry* **2002**, 13, 2513–2517.
 2002TL5973 J. R. Morphy, Z. Ranovic, M. York, *Tetrahedron Lett.* **2002**, 43, 5973–5975.
 2002TL6317 B. Mudryk, S. Rajaraman, N. Soundararajan, *Tetrahedron Lett.* **2002**, 43, 6317–6318.
 2002TL7881 A. Krief, L. Provins, A. Froidbise, *Tetrahedron Lett.* **2002**, 43, 7881–7882.
 2002TL8241 A. Gaucher, O. Barbeau, W. Hamchaoui, L. Vandromme, K. Wright, M. Wakselman, Jean-Paul Mazaleyrat, *Tetrahedron Lett.* **2002**, 43, 8241–8244.
 2002TL8335 S. Chandrasekhar, S. S. Sultana, C. Narsihmula, J. S. Yadav, R. Gee, J. C. Guillemin, *Tetrahedron Lett.* **2002**, 43, 8335–8337.
 2002TL8475 A. Ceccon, L. Crociani, S. Santi, A. Venzo, A. Biffis, G. Boccaletti, *Tetrahedron Lett.* **2002**, 43, 8475–8478.
 2002TL9039 C. Gaul, S. J. Danishefsky, *Tetrahedron Lett.* **2002**, 43, 9039–9042.
 2003BMCL1517 M. L. Szaidman, C. D. Haffner, P. R. Maloney, A. Fivush, E. Chao, D. Goreham, M. L. Sierra, C. LeGrumec, H. E. Xu, V. G. Montana, M. H. Lambert, T. M. Willson, W. R. Oliver Jr., D. D. Sterback, *Biorg. Med. Chem. Lett.* **2003**, 13, 1517–1521.
 2003BMCL3597 L. Gong, J. H. Hogg, J. Collier, R. S. Wilhelm, C. Soderberg, *Biorg. Med. Chem. Lett.* **2003**, 13, 3597–3600.
 2003CC114 Y. Kashiwagi, F. Kurashima, S. Chiba, J. Anzai, T. Osa, J. M. Bobbitt, *J. Chem. Soc., Chem. Commun.* **2003**, 114–115.
 2003CC1428 B. Jousseume, C. Laporte, M.-C. Rasle, T. Toupance, *J. Chem. Soc., Chem. Commun.* **2003**, 1428–1429.
 2003JA4125 J. L. Kaar, A. M. Jesionowski, J. A. Berberich, R. Moulton, A. J. Russell, *J. Am. Chem. Soc.* **2003**, 125, 4125–4131.
 2003JA10219 G. Hoge, *J. Am. Chem. Soc.* **2003**, 125, 10219–10227.
 2003JMC1580 L. Ye, Y.-L. Li, K. Mellström, C. Mellin, L.-G. Bladh, K. Koehler, N. Garg, A. M. G. Collazo, C. Litten, B. Husman, K. Persson, J. Ljunggren, G. Grover, P. G. Sleph, R. George, J. Malm, *J. Med. Chem.* **2003**, 46, 1580–1588.
 2003JMC(B)43 J. Ceynowa, M. Rauchfleisch, *J. Mol. Catal. B: Enzymatic* **2003**, 23, 43–51.
 2003JMC(B)115 M.-J. Kim, M. Y. Choi, J. K. Lee, Y. Ahn, *J. Mol. Catal. B: Enzymatic* **2003**, 26, 115–118.
 2003JMC(B)151 S. Joly, M. S. Nair, *J. Mol. Catal. B: Enzymatic* **2003**, 22, 151–160.
 2003JMC(B)185 D. S. Im, C. S. Cheong, S. H. Lee, Y. K. Jung, I. H. Jeong, *J. Mol. Catal. B: Enzymatic* **2003**, 26, 185–191.
 2003JOC360 N. A. Ross, R. A. Bartsch, *J. Org. Chem.* **2003**, 68, 360–366.
 2003JOC2200 G. A. Holloway, H. M. Hügel, M. A. Rizzacasa, *J. Org. Chem.* **2003**, 68, 2200–2204.
 2003JOC2437 P. de March, M. Figueredo, J. Font, J. Raya, A. Alvarez-Larena, *J. Org. Chem.* **2003**, 68, 2437–2447.
 2003JOC2812 G. A. Grasa, T. Güveli, R. Singh, S. P. Nolan, *J. Org. Chem.* **2003**, 68, 2812–2819.
 2003JOC4104 S. Caron, E. Vazquez, R. W. Stevens, K. Nakao, H. Koike, Y. Murata, *J. Org. Chem.* **2003**, 68, 4104–4107.
 2003JOC4215 J. A. Lafontaine, D. P. Provencal, C. Gardelli, J. W. Leahy, *J. Org. Chem.* **2003**, 68, 4215–4234.
 2003JOC6056 C. A. Merlic, B. C. Doroh, *J. Org. Chem.* **2003**, 68, 6056–6059.
 2003JOC6591 T. Mineno, M. J. Miller, *J. Org. Chem.* **2003**, 68, 6591–6596.
 2003JOC8129 C. Herb, M. E. Maier, *J. Org. Chem.* **2003**, 68, 8129–8135.
 2003OL757 K. Castle, C.-S. Hau, J. B. Sweeney, C. Tindall, *Org. Lett.* **2003**, 5, 757–759.
 2003OL853 S. Crosignani, P. D. White, R. Steinauer, B. Linclau, *Org. Lett.* **2003**, 5, 853–856.
 2003OL991 D. Demeke, C. J. Forsyth, *Org. Lett.* **2003**, 5, 991–994.
 2003OL1233 C. Francavilla, W. Chen, F. R. Kinder, Jr., *Org. Lett.* **2003**, 5, 1233–1236.
 2003OL2243 W. Shi, N. Jiang, S. Zhang, W. Wu, D. Du, J. Wang, *Org. Lett.* **2003**, 5, 2243–2246.
 2003OL2599 M. Takimoto, M. Kawamura, M. Mori, *Org. Lett.* **2003**, 5, 2599–2601.
 2003OL2869 D. Yang, J.-H. Li, Q. Gao, Y.-L. Yan, *Org. Lett.* **2003**, 5, 2869–2871.
 2003OL3209 S. B. Park, H. Alper, *Org. Lett.* **2003**, 5, 3209–3212.
 2003OL4641 M. T. Crimmins, P. Siliphaivanh, *Org. Lett.* **2003**, 5, 4641–4644.
 2003S501 C. Ramesh, R. Nakamura, Y. Kubota, M. Miwa, Y. Sugi, *Synthesis* **2003**, 501–504.
 2003SL1500 T. Deba, F. Yakushiji, M. Shindo, K. Shishido, *Synlett* **2003**, 1500–1502.
 2003SL2419 K. V. N. S. Srinivas, I. Mahender, B. Das, *Synlett* **2003**, 2419–2421.
 2003T2451 P. J. Coelho, L. Blanco, *Tetrahedron Lett.* **2003**, 44, 2451–2456.
 2003T2781 F. Bilodeau, L. Dubé, P. Deslongchamps, *Tetrahedron* **2003**, 59, 2781–2791.
 2003T6291 A. Kamimura, Y. Omata, K. Tanaka, M. Shirai, *Tetrahedron* **2003**, 59, 6291–6299.
 2003TA127 A. M. Daly, D. G. Gilheany, *Tetrahedron: Asymmetry* **2003**, 14, 127–137.
 2003TA1575 A. Kamal, M. Sandbhor, A. A. Shaik, *Tetrahedron: Asymmetry* **2003**, 14, 1575–1580.
 2003TA2883 P. Garner, Ö. Şeşenoğlu, H. Burgoon, *Tetrahedron: Asymmetry* **2003**, 14, 2883–2887.
 2003TL365 J. D. Rosen, T. D. Nelson, M. A. Huffman, J. M. McNamara, *Tetrahedron Lett.* **2003**, 44, 365–368.

- 2003TL2379 Y. M. A. Yamada, K. Takeda, H. Takahashi, S. Ikegami, *Tetrahedron Lett.* **2003**, *44*, 2379–2382.
2003TL2477 R. Lou, M. VanAlstine, X. Sun, M. P. Wentland, *Tetrahedron Lett.* **2003**, *44*, 2477–2480.
2003TL2513 A. E. Koumbis, K. M. Dieti, M. G. Vikentiou, J. K. Gallos, *Tetrahedron Lett.* **2003**, *44*, 2513–2516.
2003TL2911 B. K. Oh, J. H. Cha, Y. S. Cho, K. I. Choi, H. Y. Koh, M. H. Chang, A. N. Pae, *Tetrahedron Lett.* **2003**, *44*, 2911–2913.
2003TL3793 K. Fujita, S. Hashimoto, A. Oishi, Y. Taguchi, *Tetrahedron Lett.* **2003**, *44*, 3793–3795.
2003TL3967 A. K. Ghosh, J.-H. Kim, *Tetrahedron Lett.* **2003**, *44*, 3967–3969.
2003TL8857 S. Kusaka, S. Dohi, T. Doi, T. Takahashi, *Tetrahedron Lett.* **2003**, *44*, 8857–8859.

Biographical sketch

Benjamin R. Buckley was born in Nottingham, studied at Manchester Metropolitan University, where he obtained a B.Sc. in 1999 and Loughborough University where he obtained his Ph.D. in 2003 under the supervision of Professor Philip C. Bulman Page. Following this he worked as Postdoctoral Research Associate with Professor Philip C. Bulman Page for a further year and took up his present position as a Postdoctoral Research Fellow in the Page group at Loughborough University in January 2004. His scientific interests include all aspects of asymmetric synthesis, in particular asymmetric organocatalysis.

5.04

Other Acyloxy Compounds

Due to factors beyond the editors' control, the manuscript for this chapter was not available in time for publication.

5.05

Acylsulfur, -selenium, or -tellurium Functions

A. P. DOBBS and K. M. WINDEATT

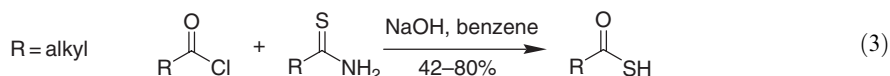
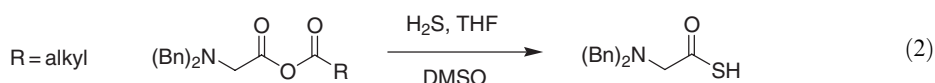
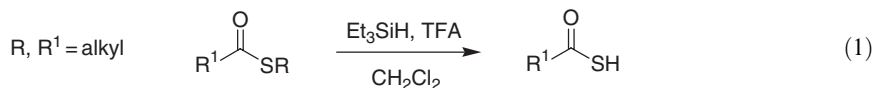
University of Exeter, Exeter, UK

5.05.1	THIOCARBOXYLIC ACIDS AND THEIR SELENIUM ANALOGS	178
5.05.1.1	Thiocarboxylic Acids	178
5.05.1.2	Selenocarboxylic Acids	178
5.05.2	THIOCARBOXYLIC ESTERS AND THEIR SELENIUM AND TELLURIUM ANALOGS	179
5.05.2.1	Thiocarboxylic Esters	179
5.05.2.1.1	<i>From acyl halides</i>	179
5.05.2.1.2	<i>From carboxylic acids</i>	180
5.05.2.1.3	<i>From esters</i>	181
5.05.2.1.4	<i>From thiocarboxylic esters</i>	181
5.05.2.1.5	<i>From carbon monoxide</i>	183
5.05.2.1.6	<i>From anhydrides</i>	183
5.05.2.1.7	<i>From thiocarboxylic acids</i>	183
5.05.2.1.8	<i>Miscellaneous</i>	184
5.05.2.2	Selenocarboxylic Esters	186
5.05.2.2.1	<i>From acyl halides</i>	186
5.05.2.2.2	<i>From carboxylic acids</i>	187
5.05.2.2.3	<i>From esters</i>	187
5.05.2.2.4	<i>From selenocarboxylates</i>	187
5.05.2.2.5	<i>Miscellaneous</i>	187
5.05.2.3	Tellurocarboxylic Esters	188
5.05.3	BIS(ACYL) SULFIDES AND THEIR SELENIUM AND TELLURIUM ANALOGS	188
5.05.3.1	Bis(acyl) Sulfides	188
5.05.3.2	Bis(acyl) Selenides	189
5.05.3.3	Bis(acyl) Tellurides	189
5.05.4	ACYLSULFENYL HALIDES	189
5.05.4.1	Acylsulfenyl Chlorides	189
5.05.4.2	Acylsulfenyl Bromides	189
5.05.4.3	Acylsulfenyl Iodides	190
5.05.5	ACYLSULFENIC ETHERS	190
5.05.6	ACYL-SUBSTITUTED DICHALCOGENIDES	190
5.05.6.1	Monoacyl-substituted Dichalcogenides	190
5.05.6.1.1	<i>Monoacyl-substituted disulfides</i>	190
5.05.6.1.2	<i>Acylsulfenyl selenides</i>	191
5.05.6.1.3	<i>Acylsulfenyl tellurides</i>	192
5.05.6.1.4	<i>Acylselenenyl sulfides</i>	192
5.05.6.1.5	<i>Monoacyl-substituted diselenides</i>	192
5.05.6.1.6	<i>Acylselenenyl tellurides</i>	192
5.05.6.1.7	<i>Acyltellurenyl sulfides</i>	192
5.05.6.2	Bis(acyl) Dichalcogenides	192
5.05.6.2.1	<i>Bis(acyl) disulfides</i>	192
5.05.6.2.2	<i>Bis(acyl) diselenides</i>	193
5.05.6.2.3	<i>Bis(acyl) ditellurides</i>	194
5.05.7	ACYLSULFENAMIDES	194
5.05.8	ACYLTHIOSILANES AND THEIR SELENIUM AND TELLURIUM ANALOGS	194

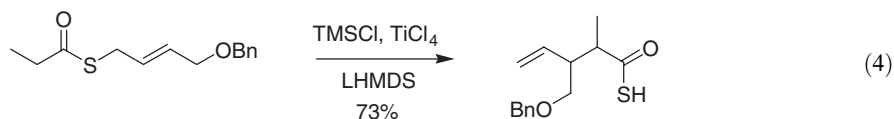
5.05.1 THIOCARBOXYLIC ACIDS AND THEIR SELENIUM ANALOGS

5.05.1.1 Thiocarboxylic Acids

There have been a number of syntheses of thiocarboxylic acids from a variety of precursors and the methods reported in the previous edition are still relevant <1995COFGT(5)231>. In general, they are prepared from esters (or thiocarboxylic esters) <2003JA7754> (Equation (1)), anhydrides <2001HCA786> (Equation (2)), or acid chlorides <2003PS1661> (Equation (3)), <2000JAN1086>.

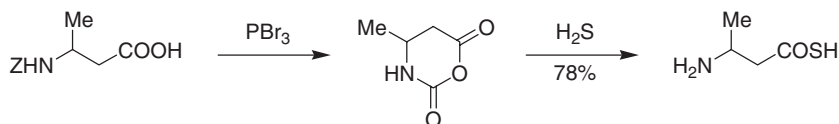


More specifically, Koch and co-workers have developed a diastereoselective Lewis acid-promoted Claisen–Ireland rearrangement of esters and thiocarboxylic esters to give carboxylic and thiocarboxylic acids, respectively <2002TL4837>. It uses catalytic amounts of Lewis acids to yield *erythro*-thiocarboxylic acids (Equation (4)).

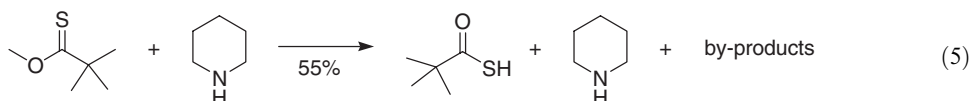


Thio- β -alanine has been prepared in a novel one-pot synthesis via the homo-Leuchs anhydride by treatment of the *Z*-protected β -amino acid with PBr_3 <2002TL6897> (Scheme 1).

2,2-Dimethylthiopropionic acid has been prepared by the reaction of piperidine with an *O*-methyl ester <1995MI166> (Equation (5)).



Scheme 1



5.05.1.2 Selenocarboxylic Acids

There are no further reports for the synthesis of these compounds; the reader is referred to COFGT (1995).

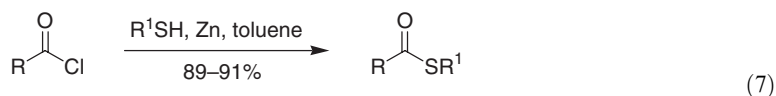
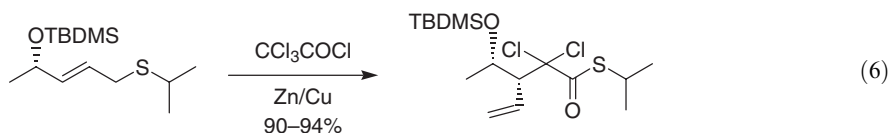
5.05.2 THIOCARBOXYLIC ESTERS AND THEIR SELENIUM AND TELLURIUM ANALOGS

5.05.2.1 Thiocarboxylic Esters

5.05.2.1.1 From acyl halides

As reported in COFGT (1995), still one of the most common ways to synthesize thiocarboxylic esters is from the reaction of a thiol with an acyl halide (usually chloride) in the presence of a tertiary amine (typically pyridine, triethylamine) <1999T1005, 2002OL3859, 2002JOC6902>.

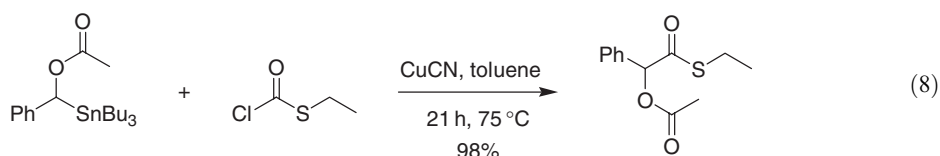
There have been many reports of new, improved promoters in the reaction of acyl chlorides with thiols. In the presence of activated zinc, the reaction of thiols and acyl chlorides has afforded excellent yields of thiocarboxylic esters. Zinc and copper have been used to promote the Claisen rearrangement of allyl thioethers with acyl chlorides <1997HCA876>. This process proceeds diastereoselectively with a high preference for *syn*-derivatives (Equation (6)). Zinc has also been used to promote a more general synthesis from acyl chlorides and thiols where the recovery and subsequent reuse of zinc makes the procedures very economical <1998SL877> (Equation (7)). Zinc has also been used with ZrCl_4 to reduce S—S bonds to produce sulfur anions, which can then react with acyl halides and thus afford thiocarboxylic esters in reasonable yields (62–65%) <2002JCR(S)582>.



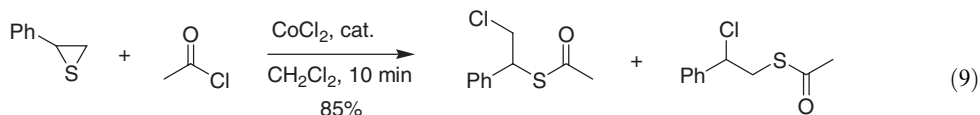
R = alkyl or aryl
R¹ = alkyl or aryl

The treatment of sulfides with carboxylic acid chlorides and AgBF_4 as a promotor in dichloromethane affords the corresponding thiocarboxylic esters in high yields, thus allowing the sulfide to be used as a sulphydryl protective group, since they are easily prepared and stable to many reaction conditions <1999TL1811>.

Copper(I) cyanide (CuCN) has been found to catalyze the cross-coupling of various tributylstannanes with allylic bromides in fair yields. The addition of a proximal thio-substituent on either species enhances yields and reaction rates substantially and has been used to synthesize a number of protected α -amino acids. The reaction proceeds with complete retention of configuration via a stabilized organocopper intermediate <1995JA5973> (Equation (8)).

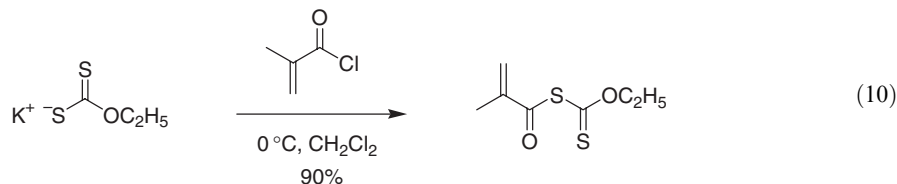


Cobalt(II) chloride has also been used as a catalyst for the synthesis of thiocarboxylic esters. It catalyzes the ring-opening of thiranes with acetyl chloride to afford vicinal chlorothiocarboxylic esters in good yields <2003SC2321> (Equation (9)).



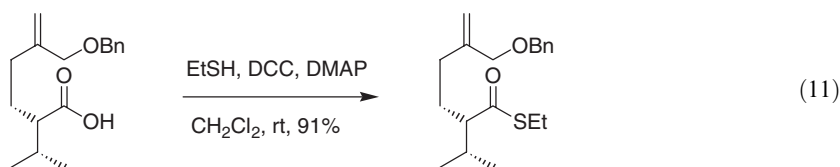
The reaction of excess trichloroacetyl chloride with various thiols in a solvent-free environment resulted in the corresponding thiocarboxylic esters in excellent yields (90–100%). These were then further functionalized to *S*-alkyl carbamates in a novel one-pot synthesis <2003JOC3733>.

The slow addition of potassium *O*-ethyl xanthates to methacryloyl chloride in dichloromethane at 0 °C yields 90% of the corresponding thioester derivative, used as a photoinitiator <1999JA6599> (Equation (10)).



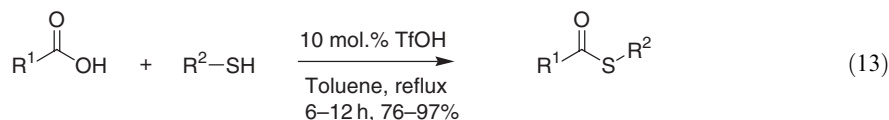
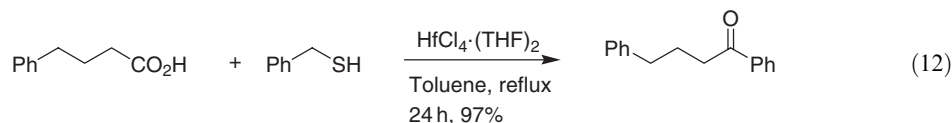
5.05.2.1.2 From carboxylic acids

The use of dicyclohexylcarbodiimide (DCC) and other coupling reagents is still a very well-reported method for the generation of thiocarboxylic esters in moderate-to-excellent yields from carboxylic acids and thiols <2001OL1721, 2003TL1571, 2002JOC4993> (Equation (11)).

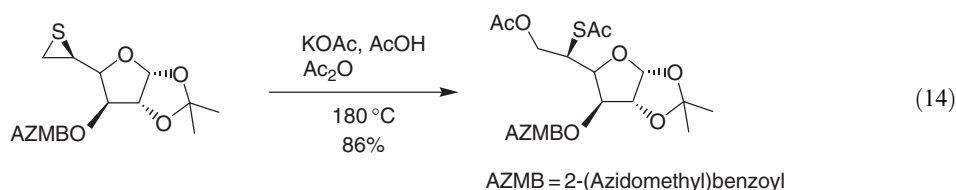


1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) has been used to couple a thiol and a carboxylic acid to synthesize a thiocarboxylic ester in the total synthesis of cobalamin-linked β -cyclodextrin <1997TL5763>.

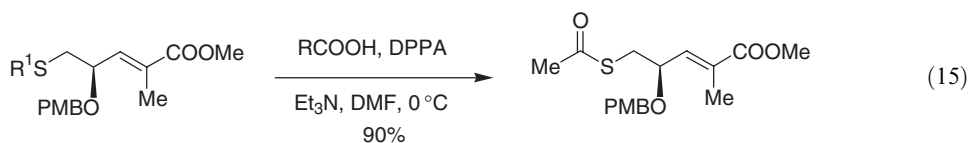
It has been found that thiols and carboxylic acids in equimolar amounts will undergo esterification reactions using catalytic amounts of either $\text{HfCl}_4 \cdot (\text{THF})_2$ <2002T8179> (Equation (12)) or trifluoromethanesulfonic acid <2002CC94> (Equation (13)). This negates the need to use large excesses of one of the reactants or stoichiometric amounts of condensing reagents, thus limiting environmental waste.



The ring opening of a thiirane and subsequent reaction with a carboxylic acid affords the thiocarboxylic ester in a good yield <2002SC3347> (Equation (14)).



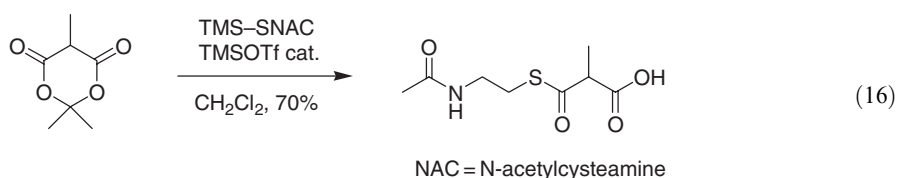
Formation of thiocarboxylic esters via azide formation using diphenylphosphoryl azide (DPPA) has also been reported <2003OL1287> (Equation (15)).



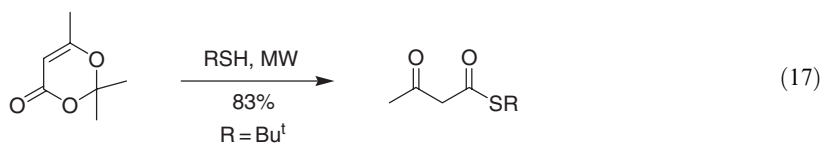
5.05.2.1.3 From esters

As reported in COFGT (1995), aluminum sulfides react easily with a variety of esters to produce thiocarboxylic esters in very good yields <2002TL3621>. Trimethylaluminum has also been employed with a thiol and carboxylic ester <1997JOC4746> or lactone <2003OL621> to produce the corresponding thiocarboxylic ester in fair yields.

A number of thiocarboxylic esters have been synthesized from the ring-opening of 1,3-dioxane-4,6-dione (Meldrum's acid) derivatives using a variety of conditions <2000AG224>. 2,2,5-Tri-methyl-1,3-dioxane-4,6-dione, when treated with a catalytic amount of TMSOTf in dichloro-methane in the presence of a thiol-containing species, will ring-open to undergo conversion into the corresponding thiocarboxylic ester, an analog of methylmalonyl CoA <1998JA11206> (Equation (16)).



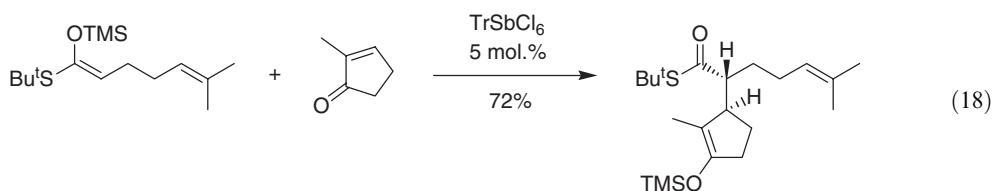
Microwave techniques have been used in the ring-opening of 2,2,6-trimethyl-1,3-dioxin-4-one and subsequent reaction with a number of thiols to yield thiocarboxylic esters in excellent yields (92–97%) <2000SC1725> (Equation (17)). The microwave technique is advantageous in short-ening reaction times (1–4 min), minimizing waste, and gaining, in general, higher yields.

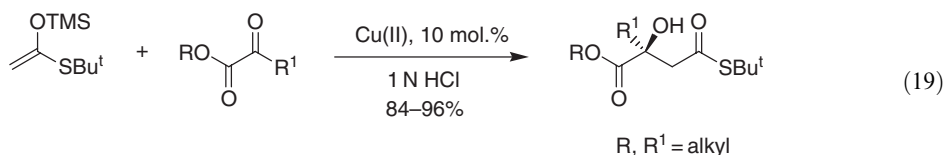


5.05.2.1.4 From thiocarboxylic esters

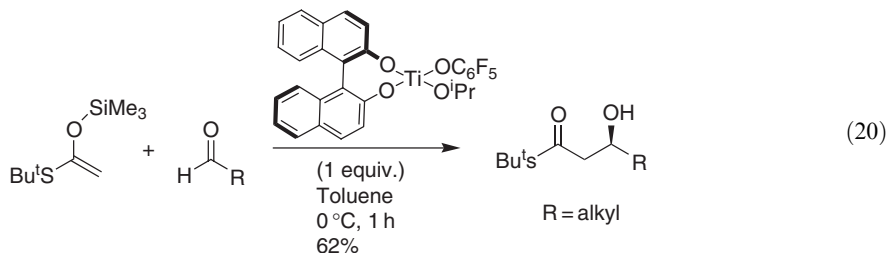
Silyl enol ether derivatives of thiocarboxylic esters react with a variety of carbonyl compounds in an aldol reaction in the presence of Lewis acid catalysts to afford thiocarboxylic esters. Of late, attention has focused on asymmetric reactions, as discussed below.

Ketones react with silyl enol ethers to yield thiocarboxylic esters using Lewis acids as catalysts. 2-Methylcyclopent-2-en-1-one reacts with a ketene thioacetal in the presence of trityl hexachloro-antimonate (TrSbCl₆) to afford the thiocarboxylic ester in the total synthesis of 25-hydroxy-vitamin D₃ <2002EJO2727> (Equation (18)). A polymer-bound bisoxazolidine copper(II) complex has proved to be a highly efficient catalyst for the Mukaiyama aldol reaction, catalyzing the formation of thiocarboxylic esters from methyl pyruvate and ketene thioacetal <2001AG2519>. Copper(II) complexes have also proved to be excellent chiral Lewis acid catalysts in the enantioselective aldol additions of enol silanes to pyruvate esters <1997JA7893> (Equation (19)).

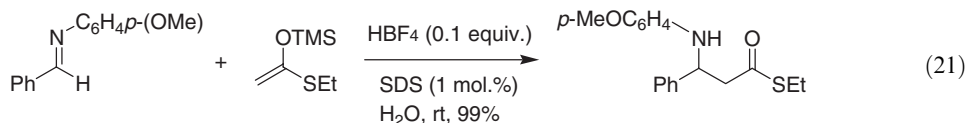




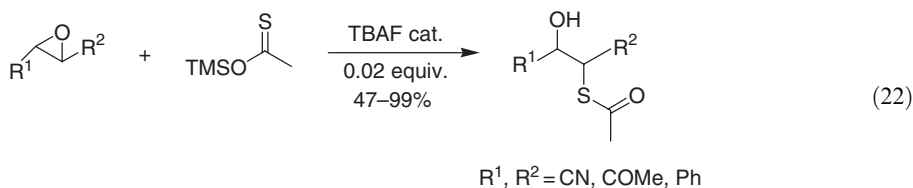
Asymmetric Mukaiyama aldol reactions between aldehydes and silyl enol ethers are catalyzed by a variety of chiral Lewis acid complexes employing, for example, boron [<2002T8237>](#), zinc, and copper with bis(oxazolidine) (box) ligands [<1996TL7481>](#), zirconium [<2002JA3292, 2000JA5403>](#), and tin [<1995TA2565>](#). Using perfluorophenol as an effective achiral ligand for a binaphthol (BINOL)-derived titanium(IV) catalyst in the Mukaiyama aldol reaction affords thiocarboxylic esters, via a cyclic transition state, in good yields with excellent enantioselectivity [<1995TA2571>](#) (Equation (20)).



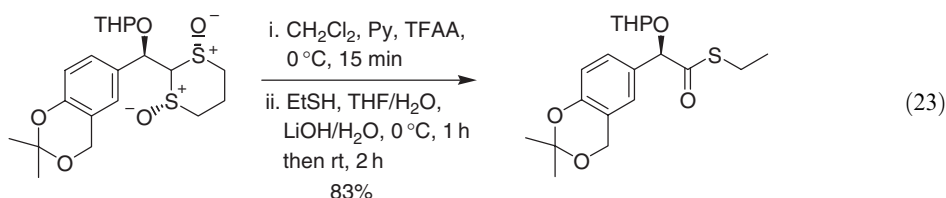
Asymmetric Mannich-type reactions between silyl enol ethers, aldehydes, and amines or imines can also be catalyzed, with good yields and enantioselectivity, by chiral Lewis acid complexes which incorporate, for example, zirconium ($\text{Zr}(\text{OBu}^t)_4$) [<2001TL7863>](#), hafnium ($\text{Hf}(\text{OTf})_4$) [<1997SL1099>](#) and a number of lanthanides (e.g., $\text{Yb}(\text{OTf})_4$) [<1996TL3731>](#). Brønsted acids have also been found to catalyze Mannich-type reactions [<2003CC1644>](#). HBF_4 , in the presence of sodium dodecyl sulfate (SDS), catalyzes the reaction between an imine and a silyl enol ether to afford a thiocarboxylic ester in excellent yields [<2002SL1269>](#) (Equation (21)).



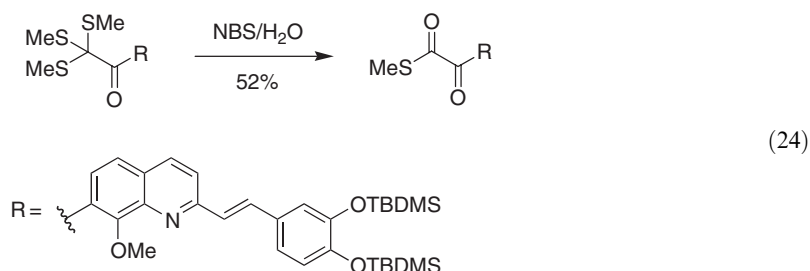
The regioselective ring opening of oxiranes by isothiocyanatotrimethylsilane proceeds under mild conditions promoted by catalytic tetrabutylammonium fluoride (TBAF) [<1997JCS\(P1\)671>](#) (Equation (22)).



Within the total synthesis of (*R*)-Salbutamol, a dithiane dioxide was transformed into the thiocarboxylic ester by a Pummerer rearrangement followed by exchange of thiol esters [<2002JOC8618>](#) (Equation (23)).

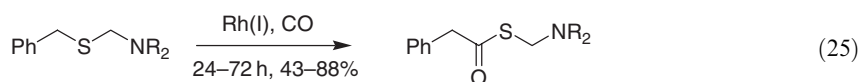


The treatment of α -oxo trithioorthoesters with NBS in water or THF/water affords thiocarboxylic esters as shown in Equation (24) [<2001TL8189, 1996S467, 1997JOC7228>](#).

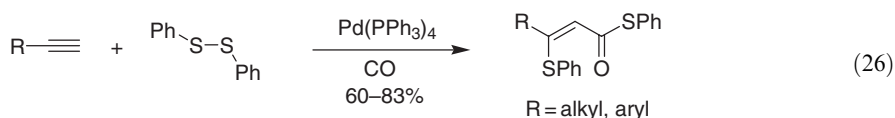


5.05.2.1.5 From carbon monoxide

In the presence of a rhodium(I) catalyst, carbon monoxide at atmospheric pressure can react with diaryl sulfides to afford thiocarboxylic esters in fair-to-good yields [<1995JOC5579>](#) (Equation (25)).

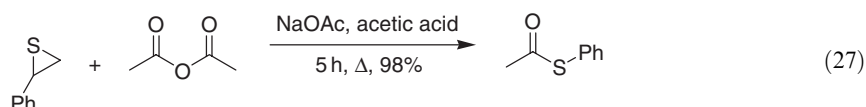


Other transition metal complexes have been used to catalyze the reaction between thiols (or diaryl disulfides), terminal alkenes, and alkynes to form thiocarboxylic esters, e.g., palladium ($\text{Pd}(\text{OAc})_2/\text{PPh}_3$) [<2001JOC6229, 1998JOC2609>](#), platinum ($\text{Pt}(\text{Ph}_3)_4$), and cobalt ($\text{Co}_2(\text{CO})_8$) [<1997JA12380>](#) (Equation (26)).

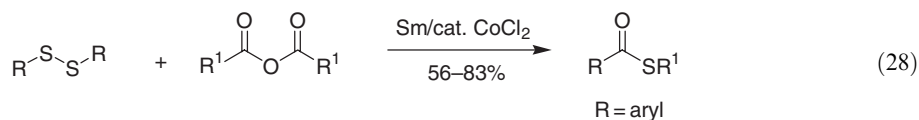


5.05.2.1.6 From anhydrides

Anhydrides can react with sulfur species to yield thiocarboxylic esters. A variety of thiiranes react with acetic anhydride in acetic acid in the presence of a base to form the corresponding thiocarboxylic esters in excellent yields (>98%) [<1996CPB4645, 1996T12677>](#) (Equation (27)).



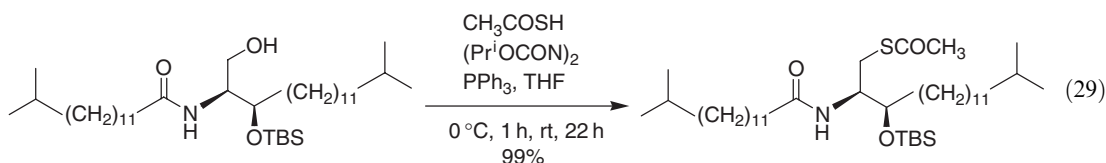
The reaction may also take place in the presence of a catalyst, e.g., vanadyl triflate ($\text{V}(\text{O})(\text{OTf})_2$) [<2001OL3729>](#) or copper triflate ($\text{Cu}(\text{OTf})_2$) [<1999TL2611>](#). The Sm/cat. CoCl_2 system promotes disulfides to react with symmetrical anhydrides in mild, neutral conditions to afford thiocarboxylic esters in good yields [<1999SC3699>](#) (Equation (28)). Zinc along with a Lewis acid (essential for reaction) also promotes the reaction of a disulfide with a symmetrical anhydride to form the thiocarboxylic ester [<2001JCR\(S\)22>](#).



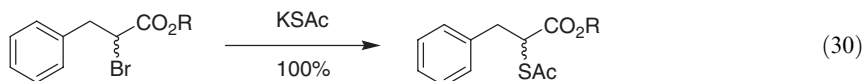
5.05.2.1.7 From thiocarboxylic acids

Thiocarboxylic acids can be converted into thiocarboxylic esters by a number of modern methodologies. Reports on the Mitsunobu reaction of thiocarboxylic acids with alcohols are common, and most of them record excellent yields [<2002JCS\(P1\)831, 2003OBC2958>](#).

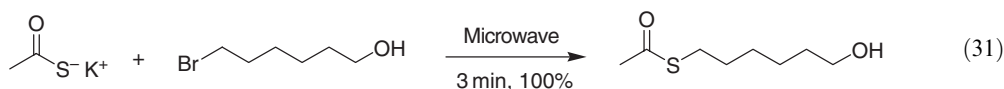
The reaction has been used within the total synthesis of natural compounds such as (-)-cylindrocyclophanes A and F <2001JA5925>, Sulfolobacin A and B <1998TL5793, 1998TL5797> (Equation (29)) and (±)-calicheamicinone <1998JA10332>.



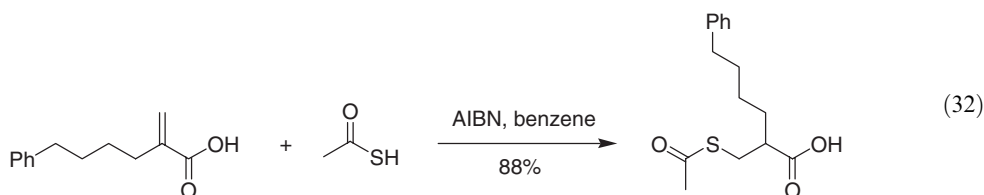
The addition of a potassium or sodium base to a thiocarboxylic acid gives a quantitative yield of the corresponding thiocarboxylic ester <2003CEJ1909, 1998BMCL3683>. The synthesis of (*S*)-2-acetylthio-3-phenylpropanoic acid contains the said reaction <2002TL7585> (Equation (30)).



Microwave technology can vastly reduce the time of the reaction to 3 min, whilst maintaining an excellent quantitative yield <1996CL635> (Equation (31)).

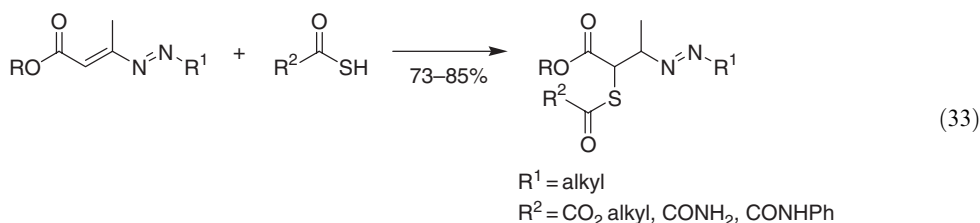


Sulfur reacts well under radical conditions, so unsurprisingly, a popular method for the synthesis of thiocarboxylic esters in fair-to-excellent yields is the radical addition of thiocarboxylic acids to a terminal alkene <2002JA806, 1998JOC7552, 1999JOC2346, 2000TL4247, 2002JMC911> (Equation (32)).



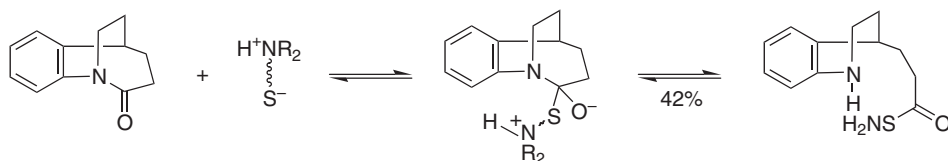
This methodology has also been used in the synthesis of functionalized carbosilane dendrimers <2001TL3327> and *N,N'*-bis(acrylamido)acetic acid-based T-antigen glycodendrimers <2001JA1809>.

The addition of thiocarboxylic acids to conjugated azoalkenes results in the synthesis of thiocarboxylic esters <1996T1579> (Equation (33)).



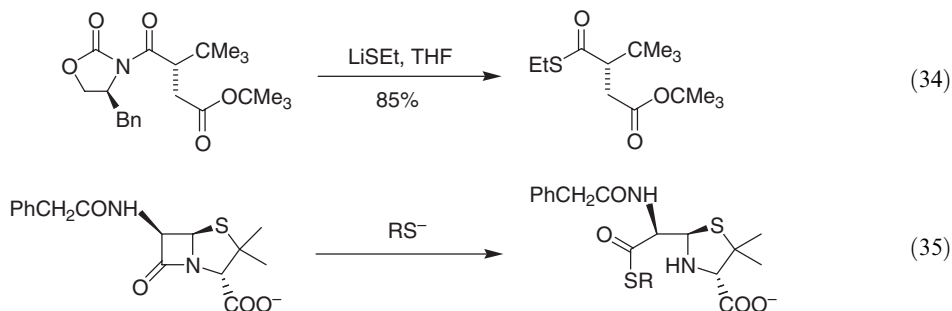
5.05.2.1.8 Miscellaneous

Amides have also been used as precursors to thiocarboxylic esters as illustrated in Scheme 2 <1996JA10829>. A chiral *N*-acyloxazolidinone imide can be reacted with a thiol in the presence

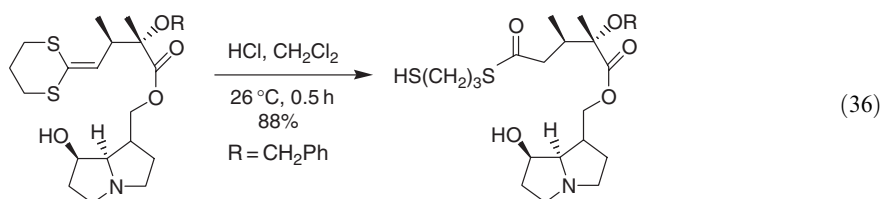


Scheme 2

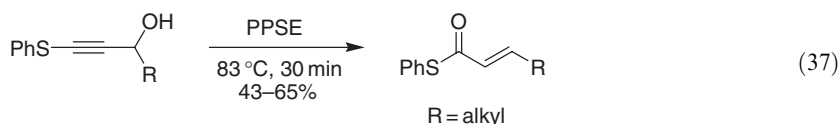
of Bu^nLi to afford the thiocarboxylic ester in good yields <1999JOC6411> (Equation (34)). The presence of a thiol will also catalyze the hydrolysis of the lactam in benzylpenicillin <2000JCS(P2)1521> (Equation (35)). Trifluoroacetic acid (TFA)-induced ring opening of β -lactams and subsequent reaction with a thiol yielded thiocarboxylic esters <1997T8439>.



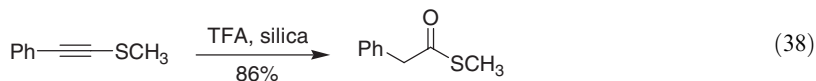
The conversion of a dithiane derivative into a thiocarboxylic ester occurs under acidic conditions <1996JOC1473> (Equation (36)).



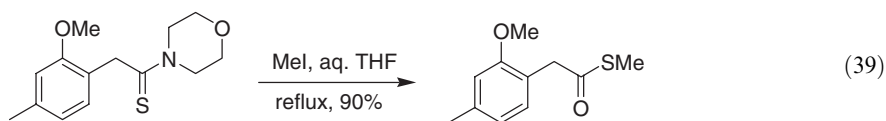
The Meyer–Schuster rearrangement of γ -sulfur-substituted propargyl alcohols in the presence of polyphosphoric acid trimethylsilyl ester (PPSE) affords α,β -unsaturated thiocarboxylic esters in reasonable yields <1995JOC4798> (Equation (37)).



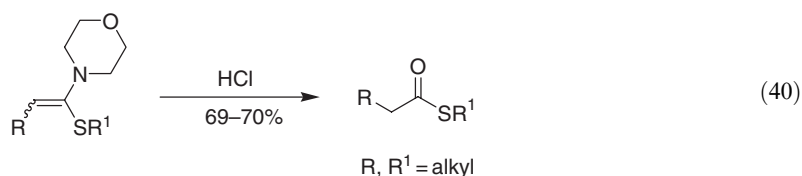
The reaction of thioacetylenes with TFA in dichloromethane in the presence of silica affords the thiocarboxylic esters in good yields (80–86%) <2001T3297, 1998TL3395> (Equation (38)). Ozonolysis of thioacetylenes and subsequent hydrolysis in presence of oxygen affords the thiocarboxylic ester in a 73% yield <2000HCA1611>.



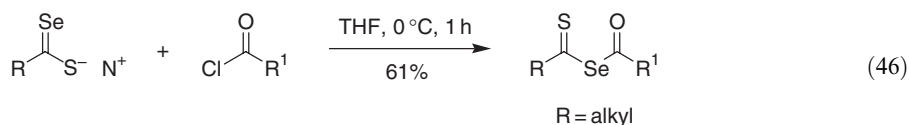
Simultaneous alkylation and hydrolysis of a thioamide affords the thiocarboxylic ester in very good yields <1999TL4443, 1999T1187> (Equation (39)).



S,N-Ketene acetals undergo selective hydrolysis to the corresponding (*S*)-thiocarboxylic esters under mildly acidic conditions <1996T11095> (Equation (40)).

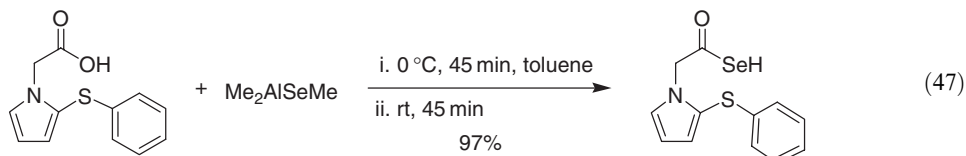


selenothioic acid salts with acid chlorides gave the corresponding selenocarboxylic esters <2000JA9850> (Equation (46)).



5.05.2.2.2 From carboxylic acids

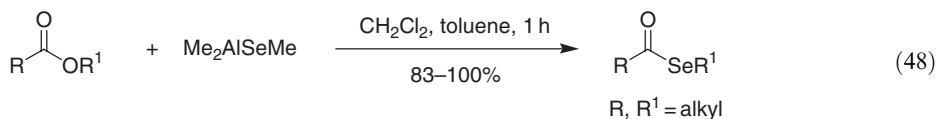
Selenocarboxylic acids have been prepared from the reaction of a carboxylic acid with dimethylaluminum methaneselenolate in excellent yields <1998JMC3763> (Equation (47)).



For other syntheses, refer to COFGT (1995).

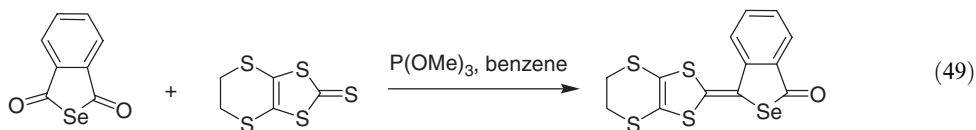
5.05.2.2.3 From esters

Similarly to the recent synthesis from carboxylic acids, the reaction of the aluminum selenium species with an ester will yield a selenocarboxylic ester <1997SL179, 1996T4817, 2002JOC2323> (Equation (48)).



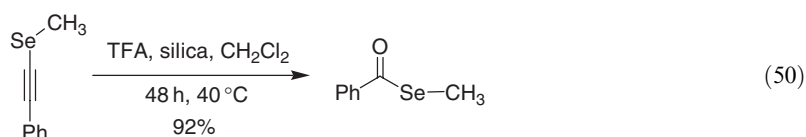
5.05.2.2.4 From selenocarboxylates

The reaction of selenosuccinic anhydride with 2 equiv. of a dithiine-2-thione affords the corresponding selenocarboxylic ester <1997JMC2375, 1996CL1001> (Equation (49)).

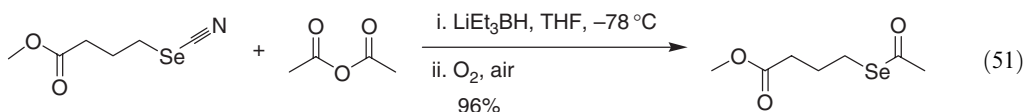


5.05.2.2.5 Miscellaneous

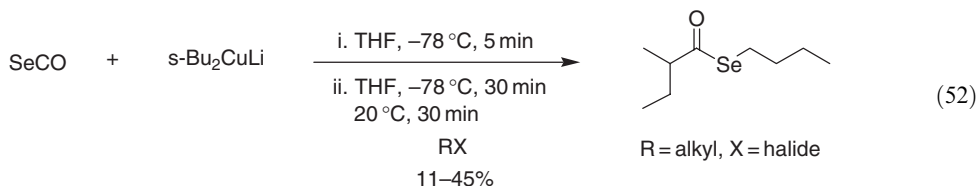
Selenocarboxylic esters can also be prepared by the reaction of selenothioic acid salts with acetic anhydride (see reaction with acyl chlorides) <2001JOC8101>. By reacting chalcogenoacetylenes with TFA in dichloromethane and in the presence of silica, selenocarboxylic esters were formed <2001T3297> in good yields (Equation (50)).



The reaction of acetic anhydride with selenocyanato ester species <1995TL5711> (Equation (51)) and selenocarbohydrate residues <2000MI781> affords selenocarboxylic esters in reasonable-to-good yields.

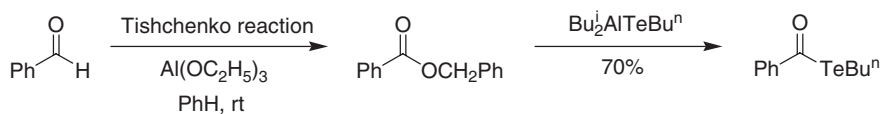


Selenocarbonyl compounds are prone to undergo selenophilic addition when treated with organolithium or Grignard reagents; however, the selecarboxylation of organocopper reagents with SeCO occurs via carbophilic addition <1998JOC1724> (Equation (52)).



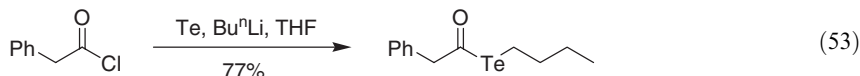
5.05.2.3 Tellurocarboxylic Esters

The methods reported in the previous edition are still used for the synthesis of tellurocarboxylic esters: (i) acylation of tellurolate anions with acyl halides and (ii) alkylation of tellurocarboxylate anions with alkyl halides. There are still few methods available for the synthesis of these compounds; however, one novel method has been reported by Inoue and co-workers: the reaction of an aldehyde with diisobutylaluminum tellurate affords the tellurocarboxylic acid in good yields via a Tishchenko-type reaction <1994JOC5824> (Scheme 3).



Scheme 3

There are few recent examples of the first method using acyl chlorides. Tellurocarboxylic esters are afforded from the reaction of elemental tellurium with BuⁿLi and phenylacetyl chloride in THF <1994JOC8209> (Equation (53)).

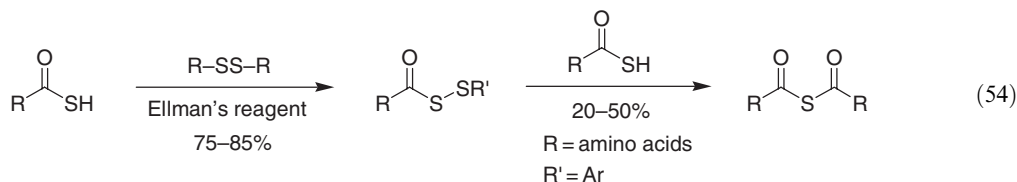


For examples of the latter method, the reader is referred to COFGT (1995).

5.05.3 BIS(ACYL) SULFIDES AND THEIR SELENIUM AND TELLURIUM ANALOGS

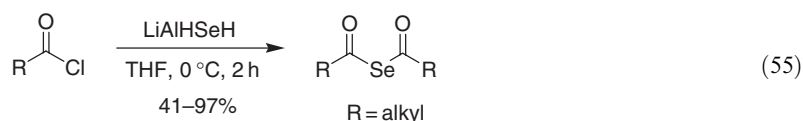
5.05.3.1 Bis(acyl) Sulfides

The procedures reported in COFGT (1995) are still the main methods for preparing bis(acyl) sulfides. A more recent example of the acylations of thiocarboxylic acids is reported by Zhang and co-workers. The coupling of thiocarboxylic acids with dialkyl disulfides produced acyl disulfides; these were then coupled again with the thiocarboxylic acid to yield bis(acyl) sulfides <1997TL3> (Equation (54)).

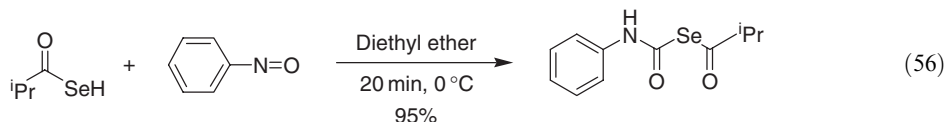


5.05.3.2 Bis(acyl) Selenides

Bis(acyl) selenides are relatively difficult to obtain because of their instability, but they have been prepared from the reaction of 2 equiv. of various acyl chlorides with LiAlHSeH in a one-step, very high-yielding process <2002JCS(P1)737> (Equation (55)).

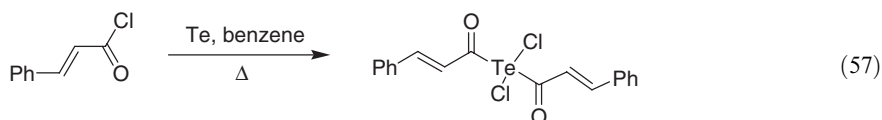


Alternatively, they may be prepared by the reaction of selenocarboxylic acids with isocyanatobenzene in diethyl ether <2001HAC250> (Equation (56)).



5.05.3.3 Bis(acyl) Tellurides

Kulkarni and co-workers have prepared bis(acyl) tellurides from the reaction of an acyl chloride with tellurium in benzene <1995IJC261> (Equation (57)).

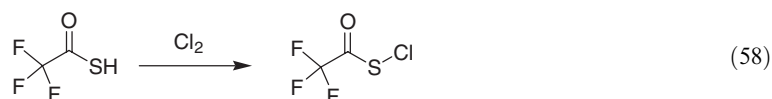


No further new syntheses have been reported; the reader is referred to COFGT (1995) for relevant examples.

5.05.4 ACYLSULFENYL HALIDES

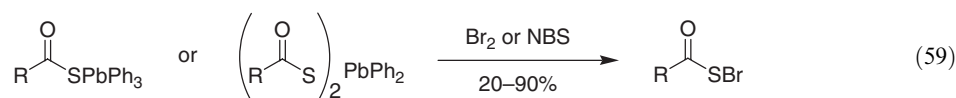
5.05.4.1 Acylsulfenyl Chlorides

There are few new syntheses of acylsulfenyl chlorides; the reader is referred to COFGT (1995) for other examples. Ulic *et al.* have prepared perfluoroacetyl sulfenyl chloride from the reaction of trifluorothioacetic acid with chlorine gas <1997JST171> (Equation (58)).



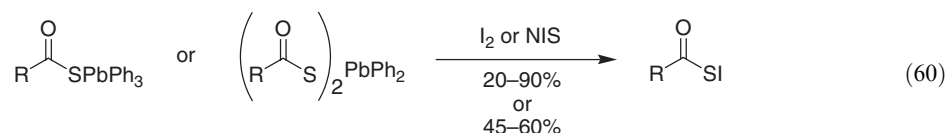
5.05.4.2 Acylsulfenyl Bromides

The method previously reported for the synthesis of acylsulfenyl chlorides (see COFGT (1995)) by the reaction of diacetyl sulfide and thionyl chloride cannot be extended to acylsulfenyl bromides or iodides due to the difficulty in obtaining thionyl bromide and iodide. Methods of preparation reported in COFGT (1995) are still relevant. A new method employing lead thiocarboxylates and *N*-bromosuccinimide has been reported <1999PS319>. The reaction proceeds in dichloromethane/hexane at 0°C to give the corresponding acylsulfenyl bromides in a 20–90% yield when starting from triphenyllead thiocarboxylates and a 45–60% yield when starting from diphenyllead bis(thiocarboxylates) (Equation (59)).



5.05.4.3 Acylsulfenyl Iodides

The only recent reported preparation of acylsulfenyl iodides is analogous to that for acylsulfenyl bromides using triphenyllead thiocarboxylates or diphenyllead bis(thiocarboxylates), which afford acylsulfenyl iodides in yields of 20–90% and 45–60%, respectively <1999PS319> (Equation (60)).



5.05.5 ACYLSULFENIC ETHERS

There are no new reported syntheses of acylsulfenic ethers; the reader is referred to COFGT (1995).

5.05.6 ACYL-SUBSTITUTED DICHALCOGENIDE

5.05.6.1 Monoacyl-substituted Dichalcogenides

5.05.6.1.1 Monoacyl-substituted disulfides

As reported in COFGT (1995), the two main methods for the synthesis of monoacyl-substituted disulfides are: (i) reaction of acylsulfenyl chlorides with thiols and (ii) reaction of thiocarboxylic acids or esters with R^2SX (Figure 1).

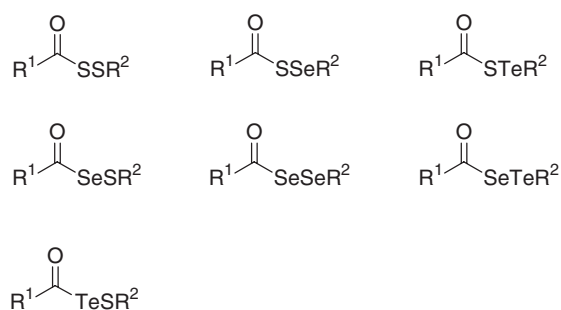
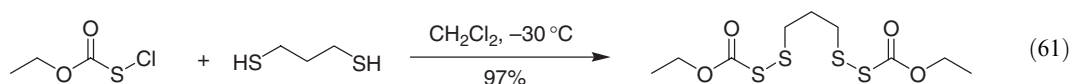


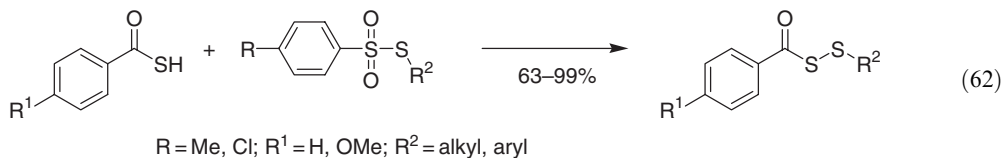
Figure 1 Monoacyl-substituted dichalcogenides.

The former reaction has been carried out using a 2:1 ratio of thiol to acylsulfenyl chloride in dichloromethane to afford the required product <1997JCS(P1)3575> (Equation (61)), <1997JMAC647>.

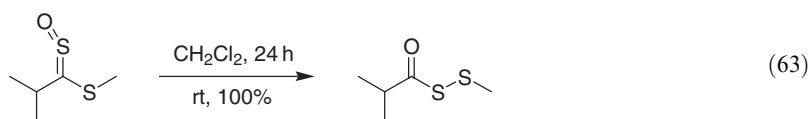


This reaction has been further utilized by many groups to functionalize and synthesize biologically active molecules <1999BMCL2095, 2000CPB740> such as amino acids <1997JMC864> and transferase inhibitors as demonstrated by Yang and co-workers <1999JOC242>; a monoacyl disulfide was synthesized in an intermediate step by treating a thiazolidinyl function with NaOAc·H₂O in acetic acid to yield the required product in 92–97% yields.

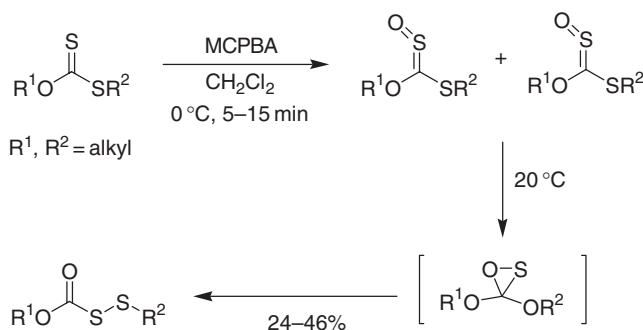
Using solvent-free conditions, Fujiki and co-workers have synthesized various benzoyl disulfides in good yields (61–82%) at room temperature from the reaction of thiosulfonates with thiocarboxylic *S*-acids in a ratio of 1.2:1 <2001S1035>. They have performed the reaction both in the absence and presence of an amine. When the *p*-toluenethiosulfonate contained an electron-donating group such as a methoxy group at the *p*-position (R¹), the reaction was rapid (1 min). In contrast to this, when a *p*-nitro or *p*-chloro species was used, the reaction time was increased to over 1.5 h, even in the presence of an amine to activate the thiol and trap the liberated sulfinic acid (Equation (62)).



Thiosulfines have been found to rearrange to acyl disulfides under ambient temperature over many days or by heating for less time. The rearrangement takes place in fair-to-excellent yields (28–100%) <1995BSF67, 1995RTC91> (Equation (63)).



Acyl disulfides can also be prepared from the reaction of xanthates with *m*-chloroperoxybenzoic acid via sulfines (which spontaneously convert into thiocarbonates at ambient temperatures) <1997JCS(P1)2019> (Scheme 4) <2001JOC320>.

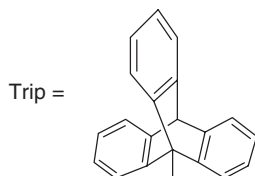
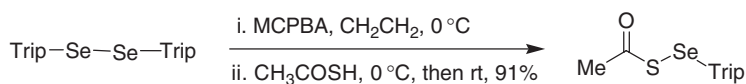


Scheme 4

The synthesis and functionalization of peptide nucleic acid oligomers has also been achieved by the reaction of mercaptoethanol with resin-supported precursors <1999JOC7281>.

5.05.6.1.2 Acylsulfenyl selenides

In addition to the methods reported in COFGT (1995), acylsulfenyl selenides can be prepared from diselenides and thioacetic acid <2002CC2810>. Di-9-triptycyl diselenide was treated with MCPBA and then with thioacetic acid to give acetyltriptycene-9-thioselenate (Equation (64)).



(64)

5.05.6.1.3 Acylsulfenyl tellurides

The procedures reported in COFGT (1995) are still the main methods employed to prepare the title compounds. Takaguchi and co-workers have also prepared acylsulfenyl tellurides from a tellurobenzoic acid derivative. A spirobi-benzoxatellurole when reacted with a thio species in toluene at 100 °C afforded the spirobi-benzthiatellurole equivalent, albeit in low yields (17%) <1996CL859>.

5.05.6.1.4 Acylselenenyl sulfides

There are no new reported syntheses of acylselenenyl sulfides; the reader is referred to COFGT (1995).

5.05.6.1.5 Monoacyl-substituted diselenides

There are no new reported syntheses of monoacyl-substituted diselenides; the reader is referred to COFGT (1995).

5.05.6.1.6 Acylselenenyl tellurides

There are no new reported syntheses of acylselenenyl tellurides; the reader is referred to COFGT (1995).

5.05.6.1.7 Acyltellurenyl sulfides

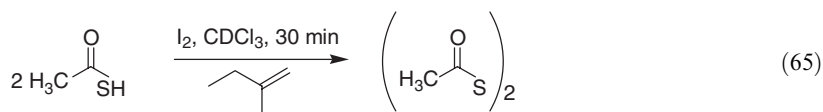
There are no new reported syntheses of acyltellurenyl sulfides; the reader is referred to COFGT (1995).

5.05.6.2 Bis(acyl) Dichalcogenides

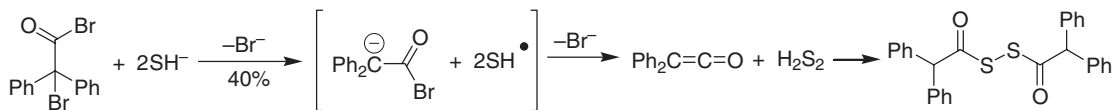
5.05.6.2.1 Bis(acyl) disulfides

There are many examples that use methods reported in the previous edition to synthesize bis(acyl) disulfides; the acylations of disulfide anions with acyl halides is a method which is of continued use <1998CJC2867, 1995SC889>. Tamami and co-workers have employed Amberlyst A-26 (OH)[−] resin and sulfur rather than the more common use of sodium disulfide <1998SC1275>.

The oxidation of 2 equiv. of thioacetic acid in the presence of iodine and 2-methylbutene in deuterated chloroform yielded diacetyldisulfane <2000OL369> (Equation (65)).

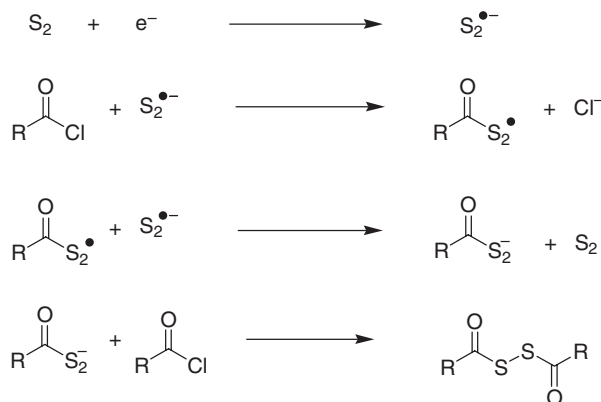


Bromodiphenylacetyl bromide was reacted with diphenylketene and tetraethylammonium hydrosulfide to form bisdiphenylacetyldisulfane <1996T1259> (Scheme 5).



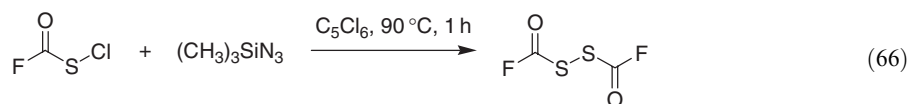
Scheme 5

The reaction of various acid chlorides with Li_2S_6 or by electrolysis with S_8 in *N,N*-dimethylacetamide gave the corresponding bis(acyl)disulfanes <1997JCS(P2)1759, 1997JCS(P2)473> (Scheme 6).



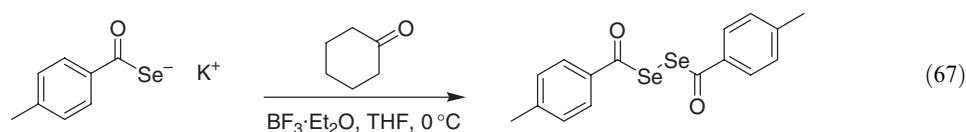
Scheme 6

Bis(fluorocarbonyl)disulfane is produced from the reaction of carbonofluoridic hypochlorous thioanhydride and $(\text{CH}_3)_3\text{SiN}_3$ in 1,2,3,4,5,5-hexachloro-cyclopenta-1,3-diene; it is, however, very volatile and difficult to isolate <1995JCS(F)231> (Equation (66)).



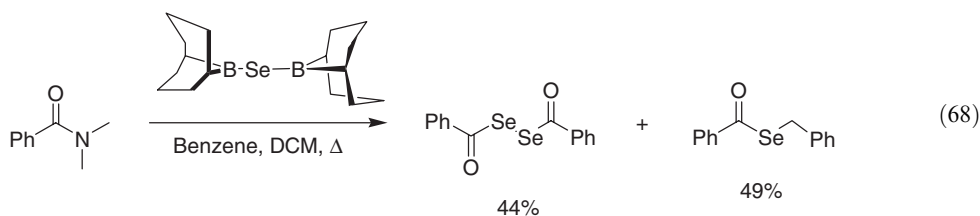
5.05.6.2.2 Bis(acyl) diselenides

The methods reported in COFGT (1995) are still relevant and further examples have been published more recently. The reaction of potassium salts of selenocarboxylic acids with BF_3 etherate and cyclohexanone in THF yields the corresponding bis(acyl) diselenides (Ishihara and co-workers) <1998CL1287> (Equation (67)). As an extension to the synthesis of bis(acyl) selenides, Koketsu and co-workers have also produced bis(acyl) diselenides from the reaction of acid chlorides with LiAlHSeH and further reaction with iodine and potassium iodide <2002JCS(P1)737> as shown in Scheme 32 in COFGT (1995).



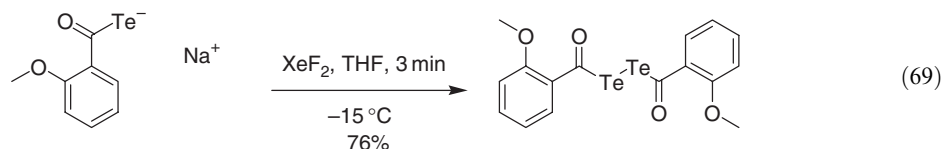
Employing the method previously reported, which uses sodium hydroxide to selectively reduce elemental selenium to produce Se_2^{2-} , Wang and co-workers have further advanced this to yield a number of iodo- and bromobenzyl-substituted bis(acyl) diselenides using microwave irradiation in the first step [<2000SC971>](#).

The treatment of carboxylic acid derivatives with bis(1,5-cyclooctanedimethylboryl) selenides produces bis(acyl) diselenides along with other selenocarbonyl compounds [<1997BCJ197>](#) (Equation (68)).



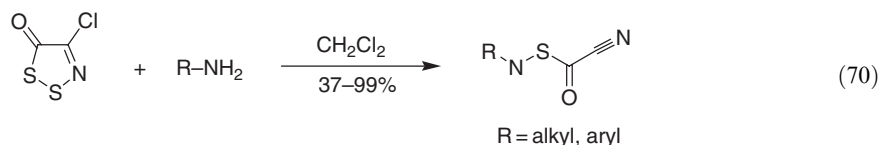
5.05.6.2.3 Bis(acyl) ditellurides

Bis(acyl) ditellurides are extremely unstable and therefore difficult to isolate. Since the first isolation in 1987 there have been few recent reports on their synthesis, and so the methods reported in the previous edition are still relevant. In an effort to demonstrate the unusual planar nature of diacyl ditellurides compared with their selenium and sulfur analogs, Niyomura and co-workers have used a new method to synthesize such molecules. They have employed a method that involves alkali-metal tellurocarboxylates and XeF_2 as an oxidizing agent in an oxidative dimerization. The oxidation of sodium 2-methoxybenzenecarbotelluroate with XeF_2 gave bis(2-methoxybenzoyl)ditelluride [<2000JA2132>](#) (Equation (69)).



5.05.7 ACYLSULFENAMIDES

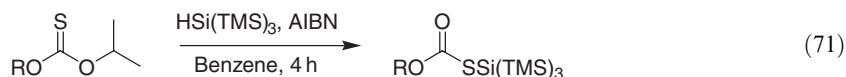
The reaction of 4-chloro-5*H*-1,2,3-dithiazo-5-one with various amines produces the corresponding acylsulfenamide derivative [<1997PS229>](#) (Equation (70)).



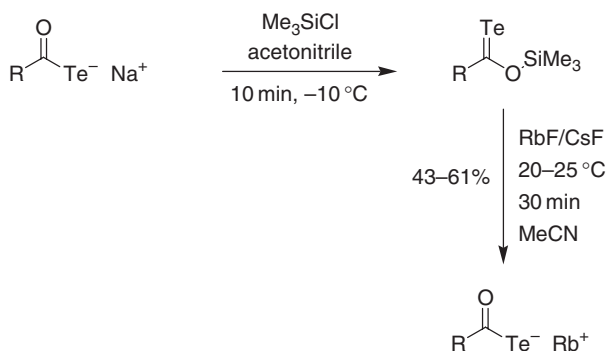
There have been no further reports regarding the syntheses of acylsulfenamides; the reader is, therefore, referred back to COFGT (1995) for other examples of syntheses.

5.05.8 ACYLTHIOSILANES AND THEIR SELENIUM AND TELLURIUM ANALOGS

The methods for preparation of acylthiosilanes reported in the previous edition are still relevant. Crich and co-workers have prepared acylthiosilanes in quantitative yields from the radical reaction of a thioester with excess tris(trimethylsilyl)silane in benzene, employing AIBN as the radical initiator [<1995JA8757>](#) (Equation (71)).



Tellurocarboxylates are formed via silylation of the tellurosilyl ester and then isomerization of the corresponding *O*-silyl ester <1995CL87>. The reaction of sodium tellurocarboxylates with trimethylsilyl chloride in acetonitrile at -10°C gave *O*-silyl telluroesters, which were then reacted with rubidium or caesium fluoride to yield the corresponding alkali-metal tellurocarboxylates in good yields <1995BCJ3507> (Scheme 7).



Scheme 7

REFERENCES

- 1994JOC8209 T. Inoue, N. Kambe, I. Ryu, N. Sonoda, *J. Org. Chem.* **1994**, 59, 8209–8214.
 1994JOC5824 T. Inoue, T. Takeda, N. Kambe, A. Ogawa, I. Ryu, N. Sonoda, *J. Org. Chem.* **1994**, 59, 5824–5827.
 1995BCJ3507 Y. Kawahara, S. Kato, T. Kanda, T. Murai, M. Ebihara, *Bull. Chem. Soc. Jpn.* **1995**, 68, 3507–3518.
 1995BSF67 F. Cerreta, A.-M. Nocher, C. Leriverend, P. Metzner, *Bull. Soc. Chim. Fr.* **1995**, 132, 67–74.
 1995CL87 Y. Kawahara, S. Kato, T. Kanda, T. Murai, *Chem. Lett.* **1995**, 2, 87–88.
 1995COFGT(5)231 A. Ogawa, N. Sonoda, Acylsulfur, -selenium, or -tellurium functions, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 231–256.
 1995IJC261 Y. D. Kulkarni, A. Rani, A. Bishnoi, R. L. Shukla, Z. K. Khan, *J. Indian Chem. Soc.* **1995**, 72, 261–262.
 1995JA5973 J. R. Falck, R. K. Bhatt, J. Ye, *J. Am. Chem. Soc.* **1995**, 117, 5973–5982.
 1995JA8757 D. Crich, A. L. J. Beckwith, C. Chen, Q. Yao, I. G. E. Davison, *J. Am. Chem. Soc.* **1995**, 117, 8757–8768.
 1995JCS(F)231 C. O. Della Védova, H.-G. Mack, *J. Chem. Soc., Faraday Trans.* **1995**, 91, 231–235.
 1995JOC5579 C. M. Crudden, H. Alper, *J. Org. Chem.* **1995**, 60, 5579–5587.
 1995JOC4798 M. Yoshimatsu, M. Naito, M. Kawahigashi, H. Shimizu, T. Kataoka, *J. Org. Chem.* **1995**, 60, 4798–4802.
 1995MI166 Y. E. Klimko, S. D. Isaev, A. G. Yurchenko, *Russ. J. Org. Chem.* **1995**, 32, 166–170.
 1995RTC91 J. B. van der Linden, J. L. Timmermans, L. Johan, B. Zwaneburg, *Recl. Trav. Chim. Pays-Bas* **1995**, 114, 91–96.
 1995SC889 J.-X. Wang, W. Cui, Y. Hu, K. Zhao, *Synth. Commun.* **1995**, 25, 889–898.
 1995TA2565 S. Kobayashi, M. Horibe, *Tetrahedron Asymmetry* **1995**, 6, 2565–2569.
 1995TA2571 S. Matsukawa, K. Mikami, *Tetrahedron Asymmetry* **1995**, 6, 2571–2574.
 1995TL5711 P. Salama, C. Bernard, *Tetrahedron Letters* **1995**, 36, 5711–5714.
 1996CL1001 K. Takahashi, T. Ise, T. Mori, H. Mori, S. Tanaka, *Chem. Lett.* **1996**, 11, 1001–1002.
 1996CL635 P. Kumar, K. C. Gupta, *Chem. Lett.* **1996**, 8, 635–636.
 1996CL859 Y. Takaguchi, N. Furukawa, *Chem. Lett.* **1996**, 10, 859–860.
 1996CPB4645 Y. Tsuda, Y. Sato, K. Kanemitsu, S. Hosoi, K. Shibayama, *Chem. Pharm. Bull.* **1996**, 44, 1456.
 1996JA10829 B. A. Kellogg, A. A. Neverov, A. M. Aman, R. S. Brown, *J. Am. Chem. Soc.* **1996**, 118, 10829–10837.
 1996JOC1473 W.-C. Chou, J.-M. Fang, *J. Org. Chem.* **1996**, 61, 1473–1477.
 1996S467 I. Degani, S. Dughera, R. Fochi, A. Gatti, *Synthesis* **1996**, 467–469.
 1996T11095 P. A. Otten, N. Oskam, A. van der Gen, *Tetrahedron* **1996**, 52, 11095–11104.
 1996T12677 W. Schroth, S. Dunger, F. Billig, R. Spitzner, R. Herzschuh, A. Vogt, T. Jende, G. Israel, J. Barche, D. Ströhl, *Tetrahedron* **1996**, 52, 12677–12698.

- 1996T4817 A. Fernández-Mateos, G. P. Coca, R. R. González, C. T. Hernández, *Tetrahedron* **1996**, 52, 4817–4828.
- 1996T1579 o. a. Attamasi, S. Buratti, P. Filippone, C. Fiorucci, E. Foresti, D. Giovagnoli, *Tetrahedron* **1996**, 5, 1579–1596.
- 1996T1259 J. I. Lozano, F. Barba, *Tetrahedron* **1996**, 52, 1259–1266.
- 1996T2839 T. Murai, K. Kakami, N. Itoh, T. Kanda, S. Kato, *Tetrahedron* **1996**, 52, 2839–2846.
- 1996TL7481 D. A. Evans, M. C. Kozlowski, J. S. Tedrow, *Tetrahedron Lett.* **1996**, 37, 7481–7484.
- 1996TL8209 H.-J. Wu, S.-H. Tsai, W.-S. Chung, *Tetrahedron Lett.* **1996**, 37, 8209–8212.
- 1996TL3731 S. Kobayashi, H. Ishitani, S. Komiyama, D. C. Oniciu, A. R. Katritzky, *Tetrahedron Lett.* **1996**, 37, 3731–3734.
- 1997BCJ197 K. Shimada, N. Jin, M. Michiko, K. Dobashi, Y. Nagano, M. Fujimura, E. Kudoh, T. Kai, N. Saito, J. Masuda, M. Iwaya, H. Fujisawa, S. Aoyagi, Y. Takikawa, *Bull. Chem. Soc. Jpn.* **1997**, 20, 197–206.
- 1997HCA876 B. Ernst, J. Gonda, R. Jeschke, U. Nubbemeyer, R. Oehrlin, D. Bellus, *Helv. Chim. Acta* **1997**, 80, 876–891.
- 1997JA12380 A. Ogawa, J. Kawakami, M. Mihara, T. Ikeda, N. Sonoda, T. Hirao, *J. Am. Chem. Soc.* **1997**, 119, 12380–12381.
- 1997JA7893 D. A. Evans, M. C. Kozlowski, C. S. Burgey, D. W. C. MacMillan, *J. Am. Chem. Soc.* **1997**, 119, 7893–7894.
- 1997JCS(P1)3575 R. L. Meline, R. L. Elsenbaumer, *J. Chem. Soc. Perkin Trans. 1* **1997**, 24, 3575–3576.
- 1997JCS(P1)2019 E. Marriere, D. Chevie, P. Metzner, *J. Chem. Soc. Perkin Trans. 1* **1997**, 14, 2019–2020.
- 1997JCS(P1)671 Y. Tanabe, K. Mori, Y. Yoshida, *J. Chem. Soc. Perkin Trans. 1* **1997**, 671–675.
- 1997JCS(P2)1759 J. Robert, M. Anouti, M. Abarbri, J. Paris, *J. Chem. Soc. Perkin Trans. 2* **1997**, 9, 1759–1764.
- 1997JCS(P2)473 J. Robert, M. Anouti, J. Paris, *J. Chem. Soc. Perkin Trans. 2* **1997**, 3, 473–478.
- 1997JMC2375 K. Takahashi, T. Shirahata, K. Tomitani, *J. Mater. Chem.* **1997**, 7, 2375–2379.
- 1997JMAC647 A. G. S. Blommaert, H. Dhotel, B. Ducos, C. Durieux, N. Goudreau, *J. Med. Chem.* **1997**, 40, 647–658.
- 1997JMC864 L. Chen, I. Zoulikova, J. Slaninova, G. Barany, *J. Med. Chem.* **1997**, 40, 864–876.
- 1997JOC4746 C. Gennari, M. Carcano, M. Donghi, N. Mongelli, E. Vanotti, A. Vulpetti, *J. Org. Chem.* **1997**, 62, 4746–4755.
- 1997JOC7228 I. Degani, S. Dughera, R. Fochi, S. Gazzetto, *J. Org. Chem.* **1997**, 62, 7228–7233.
- 1997JST171 S. E. Ulic, K. I. Gobato, C. O. Vedova, *J. Mol. Struct.* **1997**, 407, 171–176.
- 1997PS229 K. Kim, *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, 120, 229–244.
- 1997SL179 J. Josefina, C. Escolano, J. Bonjoch, *Syn. Lett.* **1997**, 2, 179–180.
- 1997SL1099 S. Kobayashi, S. Iwamoto, S. Nagayama, *Synlett* **1997**, 1099–1101.
- 1997T8439 S. Pippich, H. Bartsch, W. Holzer, *Tetrahedron* **1997**, 53, 8439–8446.
- 1997TL5763 M. Rezac, R. Breslow, *Tetrahedron Lett.* **1997**, 38, 5763–5766.
- 1997TL3 L. Zhang, J. P. Tam, *Tetrahedron Lett.* **1997**, 38, 3–6.
- 1998BMCL3683 T. D. Owens, J. E. Semple, *Bioorg. Med. Chem. Lett.* **1998**, 8, 3683–3688.
- 1998JC2867 A. Ahrika, M. Anouti, J. E. Robert, J. L. Paris, *Can. J. Chem.* **1998**, 76, 1867–1874.
- 1998CL1287 H. Ishihara, K. Yosimura, M. Kouketsu, *Chem. Lett.* **1998**, 12, 1287–1288.
- 1998JA11206 N. L. Pohl, R. S. Gokhale, D. E. Cane, C. Khosla, *J. Am. Chem. Soc.* **1998**, 120, 11206–11207.
- 1998JA10332 D. L. J. Clive, Y. Bo, Y. Tao, S. Daigneault, Y.-J. Wu, G. Meignan, *J. Am. Chem. Soc.* **1998**, 120, 10332–10349.
- 1998JMC3763 G. Campiani, V. Nacci, S. Bechalli, S. M. Ciani, A. Garofalo, *J. Med. Chem.* **1998**, 41, 3763–3772.
- 1998JOC2609 W.-J. Xiao, G. Vasapollo, H. Alper, *J. Org. Chem.* **1998**, 63, 2609–2612.
- 1998JOC7552 B. T. Houseman, M. Mrksich, *J. Org. Chem.* **1998**, 63, 7552–7555.
- 1998JOC2397 W. A. Reinert, J. M. Tour, *J. Org. Chem.* **1998**, 63, 2397–2400.
- 1998JOC1724 S. Fujiwara, A. Asai, T. Shin-ike, N. Kambe, N. Sonoda, *J. Org. Chem.* **1998**, 63, 1724–1726.
- 1998SC1275 B. Tamami, A. R. Kiasat, *Synth. Commun.* **1998**, 28, 1275–1280.
- 1998SL877 H. M. Meshram, G. S. Reddy, K. H. Bindu, J. S. Yadav, *Synlett* **1998**, 877–878.
- 1998TL5797 N. Irako, T. Shioiri, *Tetrahedron Lett.* **1998**, 39, 5797–5798.
- 1998TL5793 N. Irako, T. Shioiri, *Tetrahedron Lett.* **1998**, 39, 5793–5796.
- 1998TL3395 A. L. Braga, O. E. D. Rodrigues, E. de Avila, C. C. Silveira, *Tetrahedron Lett.* **1998**, 39, 3395–3396.
- 1999BMCL2095 C. E. O'Connell, K. Ackermann, C. A. Rowell, A. M. Garcia, M. D. Lewis, C. E. Schwartz, *Bioorg. Med. Chem. Lett.* **1999**, 9, 2095–2100.
- 1999JA6599 A. Ajayaghosh, R. Francis, *J. Am. Chem. Soc.* **1999**, 121, 6599–6606.
- 1999JA6197 D. L. Boger, H. Keim, B. Oberhauser, E. P. Schreiner, C. A. Foster, *J. Am. Chem. Soc.* **1999**, 121, 6197–6205.
- 1999JOC242 H. Yang, X. C. Sheng, E. M. Harrington, K. Ackermann, A. M. Garcia, M. D. Lewis, *J. Org. Chem.* **1999**, 64, 242–251.
- 1999JOC7281 M. Planas, E. Bardaji, K. J. Jensen, G. Barany, *J. Org. Chem.* **1999**, 64, 7281–7289.
- 1999JOC6411 D. A. Evans, L. D. Wu, J. J. N. Wiener, J. S. Johnson, D. H. B. Ripin, J. S. Tedrow, *J. Org. Chem.* **1999**, 64, 6411–6417.
- 1999JOC2346 C. Wang, G. A. Russell, *J. Org. Chem.* **1999**, 64, 2346–2352.
- 1999PS319 S. Kato, N. Sugiura, T. Kanda, *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, 153–154, 319–320.
- 1999SL569 H. Xian, J.-H. Jun, *Synlett* **1999**, 5, 569–570.
- 1999SL893 H. Oberhauser, K. Baumann, B. Grohmann, H. Sperner, *Synlett* **1999**, S1, 893–896.
- 1999T1005 T. Yamaguchi, N. Harada, K. Ozaki, M. Hayashi, H. Arakawa, T. Hashiyama, *Tetrahedron* **1999**, 55, 1005–1016.
- 1999T1187 D. C. Harrowven, M. C. Lucas, P. D. Howes, *Tetrahedron* **1999**, 55, 1187–1196.
- 1999TL4443 D. C. Harrowven, M. C. Lucas, P. D. Howes, *Tetrahedron Lett.* **1999**, 40, 4443–4444.
- 1999TL1811 H. Grundberg, M. Andergran, U. J. Nilsson, *Tetrahedron Lett.* **1999**, 40, 1811–1814.

- 1999SC3699 R. Chen, Y. Zhang, *Synth. Commun.* **1999**, 29, 3699–3704.
1999TL2611 P. Saravanan, V. K. Singh, *Tetrahedron Lett.* **1999**, 40, 2611–2614.
2000AG224 C. E. Anson, M. J. Bibb, K. I. Booker-Milburn, C. Clissold, P. J. Haley, D. A. Hopwood, K. Ichinose, W. P. Revill, G. R. Stephenson, C. M. Surti, *Angew. Chem. Int. Ed.* **2000**, 39, 224–225.
2000CPB740 C. E. O'Connell, C. A. Rowell, K. Ackermann, A. M. Garcia, M. D. Lewis, J. J. Kowalczyk, *Chem. Pharm. Bull.* **2000**, 48, 740–742.
2000HCA1611 K. Schank, H. Bech, F. Werner, *Helv. Chim. Acta.* **2002**, 83, 1611–1624.
2000JA9850 T. Murai, T. Kamoto, S. Kato, *J. Am. Chem. Soc.* **2000**, 122, 9850–9851.
2000JA5403 H. Ishitani, Y. Yamashita, H. Shimizu, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, 122, 5403–5404.
2000JA2132 O. Niyomura, S. Kato, S. Inagaki, *J. Am. Chem. Soc.* **2000**, 122, 2132–2133.
2000JAN1086 F. M. Arcamone, M. Altamura, E. Perrotta, A. Crea, S. Manzini, D. Poma, A. Salimbeni, A. Triolo, C. A. Maggi, *J. Antibiot.* **2000**, 53, 1086–1095.
2000JCS(P2)1521 A. Llinás, J. Donoso, B. Vilanova, J. Frau, F. Muñoz, M. I. Page, *J. Chem. Soc., Perkin Trans. 2* **2000**, 1521–1525.
2000MI781 O. Schulze, S. Bruns, J. Voss, G. Adiwidjaja, *Carbohydr. Res.* **2000**, 329, 781–790.
2000OL369 M. Stephanie, P. Abada, M. Koreeda, *Org. Lett.* **2000**, 2, 369–372.
2000SC971 J.-X. Wang, L. Bai, Z. Liu, *Synth. Commun.* **2000**, 30, 971–978.
2000SC1725 M. Gianotti, G. Martelli, G. Spunta, E. Campana, M. Panunzio, M. Mendoza, *Synth. Commun.* **2000**, 30, 1725–1730.
2000TL4247 K. W. Gano, D. C. Myles, *Tetrahedron Lett.* **2000**, 41, 4247–4250.
2001AG2519 S. Orlandi, A. Mandoli, D. Pini, P. Salvadori, *Angew. Chem. Int. Ed.* **2001**, 40, 2519–2521.
2001HAC250 H. Kageyama, K. Tani, S. Kato, T. Kanda, *Heteroat. Chem.* **2001**, 12, 250–258.
2001HCA786 R. A. Brietenmoser, H. Heimgartner, *Helv. Chim. Acta.* **2001**, 84, 786–796.
2001JA5925 A. B. Smith III, C. M. Adams, S. A. Kozmin, D. B. Paone, *J. Am. Chem. Soc.* **2001**, 123, 5925–5937.
2001JA1809 R. Roy, M.-G. Baek, K. Rittenhouse-Olson, *J. Am. Chem. Soc.* **2001**, 123, 1809–1816.
2001JCR(S)22 B. Movassagh, M. M. Lakouraj, Z. Fadaei, *J. Chem. Res. (S)* **2001**, 22–23.
2001JOC6229 W.-J. Xiao, H. Alper, *J. Org. Chem.* **2001**, 66, 6229–6233.
2001JOC8101 T. Murai, S. Hayakawa, S. Kato, *J. Org. Chem.* **2001**, 66, 8101–8105.
2001JOC320 B. Batanero, O. Picazo, F. Barba, *J. Org. Chem.* **2001**, 66, 320–322.
2001OL1721 P. Chiu, B. Chen, K. F. Cheng, *Org. Lett.* **2001**, 3, 1721–1724.
2001OL3729 C.-T. Chen, J.-H. Kuo, C.-H. Li, N. B. Barhate, S.-W. Hon, T.-W. Li, S.-D. Chao, C.-C. Liu, Y.-C. Li, I.-H. Chang, J.-S. Lin, C.-J. Liu, Y.-C. Chou, *Org. Lett.* **2001**, 3, 3729–3732.
2001S1035 K. Fujiki, S. Akieda, H. Yasuda, Y. Sasaki, *Synthesis* **2001**, 7, 1035–1042.
2001T3297 A. L. Braga, T. L. C. Martins, C. C. Silveira, O. E. D. Rodrigues, *Tetrahedron* **2001**, 57, 3297–3300.
2001TL7863 M. Ueno, H. Kitagawa, H. Ishitani, S. Yasuda, K. Hanada, S. Kobayashi, *Tetrahedron Lett.* **2001**, 42, 7863–7865.
2001TL8189 F. Zouhiri, D. Desmaele, J. d'Angelo, M. Ourevitch, J.-F. Mouscadet, H. Leh, M. Le Bret, *Tetrahedron Lett.* **2001**, 42, 8189–8192.
2001TL3327 K. Matsuoka, H. Oka, T. Koyama, Y. Esumi, D. Terunuma, *Tetrahedron Lett.* **2001**, 42, 3327–3330.
2002CC94 S. Iimura, K. Manabe, S. Kobayashi, *Chem. Commun.* **2002**, 94–95.
2002CC2810 A. Ishii, T. Takeshi, A. Tawata, A. Furukawa, H. Oshida, J. Nakayama, *Chem. Comm.* **2002**, 2810–2811.
2002EJO2727 I. Prowotorow, W. Stepaneko, J. Wicha, *Eur. J. Org. Chem.* **2002**, 2727–2735.
2002JA806 Y. Kwon, M. Krksich, *J. Am. Chem. Soc.* **2002**, 124, 806–811.
2002JA3292 Y. Yamashita, H. Ishitani, H. Shimizu, S. Kobayashi, *J. Am. Chem. Soc.* **2002**, 124, 3292–3302.
2002JCR(S)582 F. Tian, Y. M. Zhu, S. Zhang, Y. Wang, *J. Chem. Res. (S)* **2002**, 582–583.
2002JCS(P1)737 M. Koketsu, F. Nada, S. Hiramatsu, H. Ishihara, *J. Chem. Soc., Perkin Trans. 1* **2002**, 737–740.
2002JCS(P1)831 R. M. Angell, K. Biggadike, R. M. Farrell, S. S. Flack, A. P. Hancock, W. R. Irving, S. M. Lynn, P. A. Procopiou, *J. Chem. Soc., Perkin Trans. 1* **2002**, 831–839.
2002JMC911 J. D. Park, D. H. Kim, *J. Med. Chem.* **2002**, 45, 911–918.
2002JOC2323 J. Quirante, X. Vila, C. Escolano, J. Bonjoch, *J. Org. Chem.* **2002**, 67, 2323–2328.
2002JOC4993 M. B. Soellner, B. L. Nilsson, R. T. Raines, *J. Org. Chem.* **2002**, 67, 4993–4996.
2002JOC8618 V. K. Aggarwal, B. N. Esquivel-Zamora, *J. Org. Chem.* **2002**, 67, 8618–8621.
2002JOC6902 M. Völkert, S. Koul, G. H. Müller, M. Lehnig, H. Waldmann, *J. Org. Chem.* **2002**, 67, 6902–6910.
2002OL3859 J. M. McFadden, G. L. Frehywot, C. A. Townsend, *Org. Letts.* **2002**, 4, 3859–3862.
2002SC3347 H. Matsuda, M. Hashimoto, T. Okuno, *Synth. Commun.* **2002**, 32, 3347–3355.
2002SL1269 T. Akiyama, J. Itoh, K. Fuchibe, *Synlett* **2002**, 8, 1269–1272.
2002T8179 K. Ishihara, M. Nakayama, S. Ohara, H. Yamamoto, *Tetrahedron* **2002**, 58, 8179–8188.
2002T8237 S. Itsuno, K. Komura, *Tetrahedron* **2002**, 58, 8237–8246.
2002TL3621 H. Usuda, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2002**, 43, 3621–3624.
2002TL9129 Y. Arroyo, J. F. Rodriguez, M. A. Sanz-Tejedor, M. Santos, *Tetrahedron Lett.* **2002**, 43, 9129–9132.
2002TL6897 J. Klob, B. Beck, A. Dömling, *Tetrahedron Lett.* **2002**, 43, 6897–6901.
2002TL4837 G. Koch, P. Janser, G. Kottersch, E. Romero-Giron, *Tetrahedron Lett.* **2002**, 43, 4837–4840.
2002TL7585 J. Zhu, L. You, S. X. Zhao, B. White, J. G. Chen, P. M. Skonezny, *Tetrahedron Lett.* **2002**, 43, 7585–7587.
2003CC1644 S. Iimura, D. Nobutou, K. Manabe, S. Kobayashi, *Chem. Commun.* **2003**, 1644–1645.
2003CEJ1909 A. G. Barrientos, J. M. de la Fuente, T. C. Rojas, A. Fernández, S. Penadés, *Chem. Eur. J.* **2003**, 9, 1909–1921.
2003JA7754 N. Shangguan, S. Katukojvala, R. Greenberg, L. J. Williams, *J. Am. Chem. Soc.* **2003**, 125, 7754–7755.
2003JOC3733 J. H. Wynne, S. D. Jensen, A. W. Snow, *J. Org. Chem.* **2003**, 68, 3733–3735.
2003OBC2958 K. E. Elson, I. D. Jenkins, W. A. Loughlin, *Org. Biomol. Chem.* **2003**, 1, 2958–2965.

- 2003OL621 T. M. Gierasch, Z. Shi, G. L. Verdine, *Org. Lett.* **2003**, 5, 621–624.
2003OL1287 J. Chen, C. J. Forsyth, *Org. Lett.* **2003**, 5, 1281–1283.
2003PS1661 M. Toriyama, H. Kamijo, S. Motohashi, T. Takido, K. Itabashi, *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, 178, 1661–1666.
2003PS319 T. Toshio, T. Masaharu, Y. Kentaro, S. Tomoyuki, S. Manabu, *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, 178, 319–326.
2003SC2321 N. Iranpoor, H. Firouzabadi, A. A. Jafari, *Synth. Comm.* **2003**, 33, 2321–2327.
2003TL1571 H. R. Plake, T. B. Sundberg, A. R. Woodward, S. F. Martin, *Tetrahedron Lett.* **2003**, 44, 1571–1574.

Biographical sketch



Adrian Dobbs was born in Bromley, Kent, and studied at King's College London, obtaining a B.Sc. in 1992 and a Ph.D. in 1996, working under the guidance of Dr. Keith Jones. He then undertook postdoctoral research for two years with Professor Istvan Markó at the Université Catholique de Louvain, in Louvain-la-Neuve, Belgium, under a Royal Society Research Fellowship. On returning to the UK, he joined the process chemistry department of Glaxo SmithKline (Tonbridge, Kent), before taking up his first academic position at the Open University at the end of 1999. He moved to his current position as Lecturer in Organic Chemistry at the University of Exeter in 2001. His research interests encompass the development of new synthetic methodologies for the synthesis of complex heterocyclic systems and their application to the total synthesis of natural products.



Kim Windeatt was born in Brixham, Devon, and studied at the University of Exeter where she gained a B.Sc. in Biological Medicinal Chemistry. She has recently completed a Ph.D. at Exeter, under the supervision of Dr. Mark Wood. Her research interests include free radical chemistry and amino acids.

5.06

Amides

P. D. BAILEY, T. J. MILLS, R. PETTECREW, and R. A. PRICE
UMIST, Manchester, UK

5.06.1	GENERAL METHODS	202
5.06.1.1	Introduction	202
5.06.1.1.1	Structure of the review	204
5.06.1.1.2	Types of amides	204
5.06.1.1.3	Overview of major recent developments	206
5.06.1.2	Acylation of Amines	207
5.06.1.2.1	Directly from carboxylic acids	208
5.06.1.2.2	From simple esters	209
5.06.1.2.3	From active esters	212
5.06.1.2.4	From acid anhydrides	217
5.06.1.2.5	From acyl halides	219
5.06.1.2.6	From acyl azides	221
5.06.1.2.7	Using in situ coupling reagents	221
5.06.1.2.8	Other acylation methods	225
5.06.1.3	Hydrolysis of Nitriles	229
5.06.1.3.1	Enzymic hydrolysis of nitriles	230
5.06.1.3.2	Nonenzymic hydrolysis of nitriles	233
5.06.1.4	Rearrangement Reactions	234
5.06.1.4.1	Beckmann rearrangement	234
5.06.1.4.2	Schmidt rearrangement	235
5.06.1.4.3	Claisen rearrangement	235
5.06.1.4.4	Wolff rearrangement	236
5.06.1.4.5	Willgerodt rearrangement	237
5.06.1.4.6	Oxaziridine rearrangements	238
5.06.1.4.7	Other rearrangement processes	238
5.06.1.5	Other General Methods	239
5.06.1.5.1	Special routes to β -lactams	239
5.06.1.5.2	Other routes to "normal" amides	240
5.06.2	AMIDES OF ALKANOIC ACIDS	241
5.06.2.1	N-Unsubstituted Alkanoamides	241
5.06.2.1.1	Methods from simple esters	241
5.06.2.1.2	Methods from active esters	242
5.06.2.1.3	Methods using phosphorus reagents	242
5.06.2.1.4	Hydrolysis of nitriles	242
5.06.2.2	N-Alkylalkanoamides	246
5.06.2.2.1	Methods from carboxylic acids	246
5.06.2.2.2	Methods from simple esters	246
5.06.2.2.3	Methods from active esters	247
5.06.2.2.4	Methods from acid anhydrides	249
5.06.2.2.5	Methods from acyl halides	249
5.06.2.2.6	Methods using diimides	249
5.06.2.2.7	Methods using phosphorus reagents	250
5.06.2.2.8	Methods using uronium salts	251
5.06.2.2.9	Methods using iminium salts	254
5.06.2.2.10	Other acylation methods	257
5.06.2.2.11	Rearrangement reactions	260

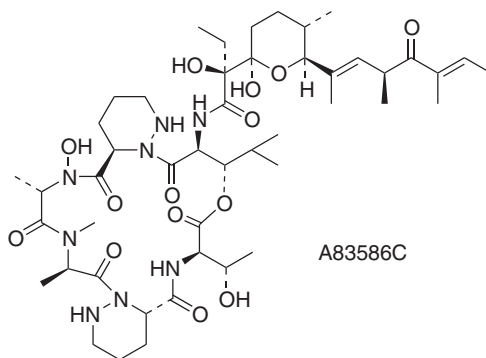
5.06.2.2.12	<i>β</i> -Lactams	262
5.06.2.2.13	Other methods	262
5.06.2.3	<i>N</i> -Alkenylalkanoamides (Enamides)	263
5.06.2.3.1	Acylation methods	263
5.06.2.3.2	Rearrangement reactions	263
5.06.2.4	<i>N</i> -Aryl- and <i>N</i> -Heteroaryl-alkanoamides	264
5.06.2.4.1	Methods from carboxylic acids	264
5.06.2.4.2	Methods from simple esters	265
5.06.2.4.3	Methods from active esters	265
5.06.2.4.4	Methods from acid anhydrides	266
5.06.2.4.5	Methods from acyl halides	266
5.06.2.4.6	Other acylation methods	267
5.06.2.4.7	Beckmann rearrangement reactions	267
5.06.3	AMIDES OF ALKENOIC ACIDS	268
5.06.3.1	<i>N</i> -Unsubstituted Alkenoamides	268
5.06.3.1.1	Hydrolysis of nitriles	268
5.06.3.2	<i>N</i> -Alkylalkenoamides	269
5.06.3.2.1	Methods from carboxylic acids	269
5.06.3.2.2	Methods from simple esters	269
5.06.3.2.3	Methods from active esters	269
5.06.3.2.4	Methods from acid anhydrides	270
5.06.3.2.5	Rearrangement reactions	270
5.06.3.2.6	<i>β</i> -Lactams	272
5.06.3.2.7	Other methods	272
5.06.3.3	<i>N</i> -Alkenylalkenoamides	273
5.06.3.4	<i>N</i> -Aryl- and <i>N</i> -Heteroaryl-alkenoamides	273
5.06.3.4.1	Other methods	273
5.06.4	AMIDES OF AROMATIC AND HETEROAROMATIC ACIDS	273
5.06.4.1	<i>N</i> -Unsubstituted Arylamides	273
5.06.4.1.1	Methods from active esters	273
5.06.4.1.2	Hydrolysis of nitriles	273
5.06.4.2	<i>N</i> -Alkylarylamides	275
5.06.4.2.1	Methods from carboxylic acids	275
5.06.4.2.2	Methods from simple esters	275
5.06.4.2.3	Methods from active esters	275
5.06.4.2.4	Methods from acyl halides	277
5.06.4.2.5	Methods using diimides	277
5.06.4.2.6	Methods using phosphorus reagents	277
5.06.4.2.7	Methods using uronium salts	277
5.06.4.2.8	Methods using iminium salts	278
5.06.4.2.9	Other acylation methods	279
5.06.4.2.10	Rearrangement reactions	280
5.06.4.2.11	<i>β</i> -Lactams	281
5.06.4.2.12	Other methods	281
5.06.4.3	<i>N</i> -Alkenylarylamides	281
5.06.4.3.1	Rearrangement reactions	281
5.06.4.4	<i>N</i> -Arylarylamides	283
5.06.4.4.1	Methods from active esters	283
5.06.4.4.2	Methods from acid anhydrides	283
5.06.4.4.3	Methods from acyl halides	283
5.06.4.4.4	Methods using diimides	283
5.06.4.4.5	Methods using iminium salts	284
5.06.4.4.6	Other acylation methods	285
5.06.4.4.7	Rearrangement reactions	286
5.06.4.4.8	Other methods	287
5.06.5	AMIDES OF ALKYNIC ACIDS	287
5.06.5.1	<i>N</i> -Alkylarylamides	287
5.06.5.1.1	Methods using iminium salts	287

5.06.1 GENERAL METHODS

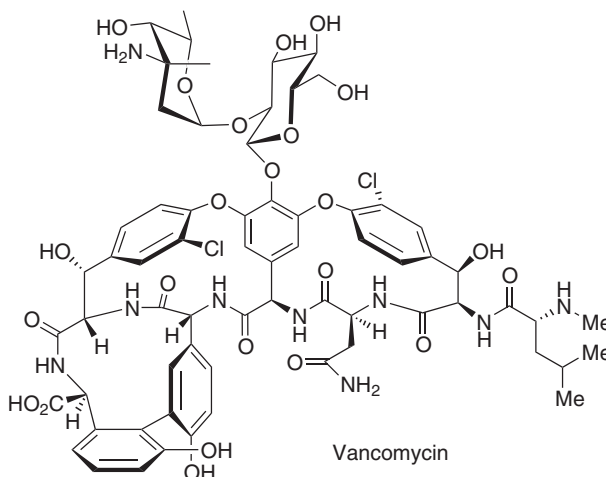
5.06.1.1 Introduction

The amide functional group is one of the most important subunits in both natural products and man-made compounds. It is a core feature of peptides and proteins, and is also present in a large number of other nitrogenous natural compounds. Moreover, many drug compounds also contain the amide functional group, and it is also frequently used as a linking unit to generate chimeric compounds, such as the peptide nucleic acids. Another major development has been the use of combinatorial chemistry

in order to produce large libraries of compounds; peptides are especially well suited to this methodology because of the reliability with which solid-phase peptide synthesis has been developed since its introduction in the 1960s. In parallel with the continued importance of amides and interest in their synthesis has been an astonishing evolution in the types of coupling reagents that are being used for the *in situ* coupling of amines with carboxylic acids. Many of these reagents had been introduced in the 1990s (or even earlier), but it is since the 1990s that they have truly come to dominate the field of amide synthesis in general, and peptide synthesis in particular. The power of these reagents has perhaps encouraged synthetic research groups to tackle target molecules that would have appeared far too ambitious in the early 1990s, spurred on by the confidence that the coupling reagents available should allow the synthesis of complex peptides and depsipeptides to be accomplished, provided the constituent building blocks could be prepared. The aim of this review is not to provide examples of complex syntheses, but to offer a summary of the main methods by which the amide bond might be constructed. Nevertheless, it is illustrative of the power of the modern coupling procedures that targets such as the antibiotics A83586C [<1997CC2319>](#) and vancomycin [<1999AG\(E\)240>](#), both requiring the introduction of six amide bonds, have been successfully synthesized.



A83586C



Vancomycin

Since the 1990s, really substantial changes have taken place in the reagents used to form peptides, and the vast majority of amides are now made using reagents which are different from those that dominated their synthesis in the mid-1990s. Interestingly, most of the reagents in common use in early 2000s were, in fact, introduced at least a decade prior to that, but it took an intervening time for them to become established as the reagents of choice, or for the reaction conditions to be modified so that the yields became high and reliable. It is also worth adding that the availability of these reagents at reasonable prices obviously influences their uptake by the community, so that the very best reagents could conceivably be little-used if they were unavailable commercially or prohibitively expensive.

The layout of this review follows the structure of that in COFGT (1995) [<1995COFGT\(5\)257>](#), but the weighting of the various sections is dramatically different, reflecting the major developments in reagents that have led to changes in the way that the amide bond is

prepared. The following three subsections therefore outline the structure of this review; a brief reminder of the various types of amides that are targeted; and an overview of the major developments in amide synthesis since the publication of COFGT (1995).

5.06.1.1.1 *Structure of the review*

In COFGT (1995), the functional groups are categorized in a systematic and rigorous way, which readily enables readers to locate the specific features for which they are searching. However, developments in amide chemistry since the mid-1990s have focused very much on the design of new methods for tackling rather general issues that relate to amide bond formation. The two dominant issues have been the formation of amides that are highly hindered (whatever their systematic substitution might be), and matters relating to stereocontrol, in particular the retention of optical integrity of chiral groups adjacent to the carbonyl or the amide.

The bulk of this review (Section 5.06.1) therefore focuses on the new methods that have been developed recently, with an indication of the ways in which they can be exploited in the synthesis of amides for which there are particular problems. The main categories under which the new methods are presented are identical to those in <1995COFGT(5)257>, so that correlation between the reviews should be relatively straightforward.

In the sections thereafter (5.06.2–5.06.5), detailing the synthetic routes to particular substitution patterns in amides, the key publications are tabulated to indicate the substructures for which the methodology has proved to be successful. It is clear that much of the methodology could be applied to a wide range of substitution patterns, so many of the general methods (Section 5.06.1) will often be applicable to substructures that were not explicitly covered in the publications. This approach should be of maximum use to those who are attempting to find the best procedure for synthesizing a particular amide, whilst trying to cope with the almost unmanageable number of procedures that are recommended in the literature.

5.06.1.1.2 *Types of amides*

In the previous review, the amides were briefly classified as *N*-unsubstituted amides, peptides, acyl-protected amines, and cyclic amides. These were overarching categories identified in order to indicate the specific problems that the synthetic methods were addressing for the various classes of amides. Because of the ways in which the reagents have developed since, a brief overview is provided below, but the categories have been modified in order to reflect more usefully the developments that have taken place.

(i) *N*-Unsubstituted amides

There is a substantial number of target molecules of the general type alkyl-CONH₂ or ArCONH₂, which are unsubstituted on the amide nitrogen. Like many functional groups, their apparent simplicity often belies problems that can occur during synthesis. Nevertheless, there have not been fundamental developments recently concerning the synthesis of unsubstituted amides, as adequate processes were largely in place already in the mid-1990s. Because of the relatively low reactivity of the amide group, simple unsubstituted amides also have the advantage that they can often be introduced at any one of several stages in a complex synthesis, and this allows one to select the most appropriate time to establish that functional group. However, as will become apparent later in this review, *N*-unsubstituted amides are now often prepared using enzymic hydrolysis conditions, and this allows enantioselective syntheses of amides in many cases.

(ii) *Unhindered amides*

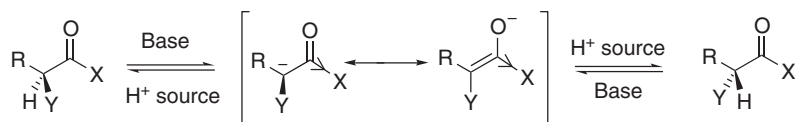
Many amides are most obviously synthesized by the acylation of an amine, and when the two components are both relatively unhindered, then almost any coupling reagent would yield the desired amide in reasonable yield.

(iii) *Hindered amides*

This group of compounds—typically in which the nitrogen is trisubstituted in the final amide, or there is branching immediately adjacent to the carbonyl group (or both)—comprises systems for which amide bond formation can be astonishingly difficult. The majority of the newly developed coupling reagents have been designed to address this specific problem. It is worth emphasizing that problems can ensue when the carbonyl group is very strongly activated, particularly when the carbon atom next to the carbonyl group is a chiral center, and epimerization is to be minimized. This has led to the design of specific reagents, or of important additives, to minimize the unwanted side-reactions.

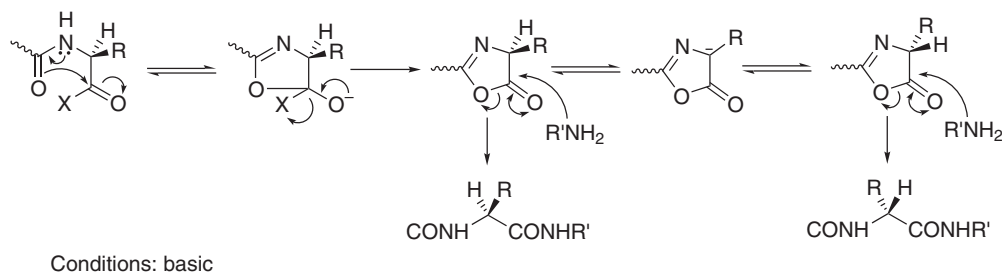
(iv) *Enolizable chiral centers*

As indicated above, the presence of a chiral group adjacent to the carbonyl of an amide can be a serious problem when the carbonyl group is activated. There are several mechanisms by which epimerization can take place, depending on the precise nature of the carboxy component. As indicated in [Scheme 1](#), the base which is usually present to ensure that the amine is always available in its nonprotonated nucleophilic form can lead to epimerization by direct proton extraction, for which the electron-withdrawing group introduced to activate the carbonyl unit is able to stabilize the negatively charged enolate intermediate.



Scheme 1

For peptides, a further problematic mechanism is known to be involved, in which the carbonyl group from the preceding residue (or as a protecting group on the nitrogen) is able to participate in the formation of a five-membered oxazolone ring, from which a planar aromatic intermediate allows epimerization to take place ([Scheme 2](#)).



Scheme 2

Assessing the degree of epimerization from various reagents has been one of the dominant aspects of amide bond formation in the literature in recent years; this is unquestionably because of the enormous number of peptides that are synthesized routinely using solid-phase methodology, and for which the stereochemical integrity of the final target peptides is of paramount importance.

(v) *Stereocontrolled formation of amides*

Since the early 1990s, asymmetric synthesis has been one of the dominant themes of organic synthesis. This did not impinge particularly strongly on the synthesis of amides up until the mid-1990s, as the asymmetric methodology then available could be used to prepare chiral carboxylic

acids in high ee, for which simple coupling reactions could then be used to generate the desired amides, provided that problems of epimerization could be avoided. In more recent years, methods of directly generating amides have started to emerge in which the relative or absolute stereochemistry of new chiral centers could be controlled.

(vi) *Cyclic amides, including β -lactams*

In general, the synthesis of cyclic amides is relatively straightforward when five- to seven-membered rings are being prepared. For larger rings, the problem is essentially the same as that for hindered amides, for which the reactivity of the carbonyl group must be such that the entropically unfavorable approach of the amine is almost certain to lead to amide bond formation. Therefore, the reagents that have been developed to maximize the yields in the formation of hindered amides are generally also suitable for the formation of larger-ring amides. β -Lactams, however, are difficult to prepare by the cyclization of β -amino acids, and in general alternative syntheses have been developed. The synthetic routes to β -lactams are discussed under the other methods in [Section 5.06.1.5.1](#).

5.06.1.1.3 Overview of major recent developments

Amide bond formation continues to be an area in which there is an almost overwhelming number of publications. During the early 1990s through early 2000s, concerning the synthesis of peptides alone, there have been over 500 reviews published, over half of which were looking at methods of synthesis (as distinct from summaries of the peptides that had been synthesized). For peptides, the synthetic methodology involves strategy, protection, coupling procedures, and a range of other factors such as disulfide bond formation and solid-phase issues. Nevertheless, there have been around 50 reviews looking simply at coupling reagents, which emphasizes the importance of this approach to the synthesis of peptides in particular, and of amides in general.

Four main areas of synthetic methodology have produced a disproportionate number of publications in recent years, indicating that these are indeed major areas in which significant developments have taken place:

(i) The use of enzymes in the synthesis of amides, both to induce the coupling of amines with carboxylic acids or esters, and also the use of nitrilases in the selective hydrolysis of nitriles. The importance of enzymes has come to the fore because of the requirement to achieve asymmetric syntheses of compounds of medicinal importance. The techniques needed to handle these enzymes successfully were really established only in the 1990s, which is why this area has recently come to such prominence.

(ii) The selective hydrolysis of nitriles has also dominated the literature both through enzymic hydrolysis, and through the use of other nonbiological reagents which have been found to generate amides without further hydrolysis to the corresponding carboxylic acid. The discovery that a range of transition metal-based reagents, and more particularly environmentally friendly clays, can catalyze the selective hydrolysis has led to their widespread use in the synthesis of unsubstituted amides, helped by the ready accessibility of many nitriles.

(iii) The third major development, but perhaps the most outstandingly important one, has been the development of new coupling reagents. For around 20 years, the carbodiimides completely dominated the *in situ* procedures for the coupling of carboxylic acids with amines. These reagents had a number of known disadvantages but, in combination with a range of additives, they had led to reliable procedures that were hard to replace by the newer alternatives. As more challenging amide targets were selected, it became apparent that the diimides would never drive the coupling of highly hindered carboxylic acids with amines, and a series of more reactive coupling reagents was developed. Foremost amongst these have been the uronium salts; these are now often the coupling method of choice, being capable of achieving efficient syntheses of both unhindered and significantly crowded amides. Alongside these rather general reagents, some of the phosphonium and iminium salts have also proved popular, but perhaps most surprising has been the resurgence in the use of acid chlorides and acid fluorides in the synthesis of peptides; the former were, of course, used in the very earliest syntheses of peptides around 100 years ago, but problems of racemization had led them to being almost entirely dropped until Carpino resurrected them in conjunction with the Fmoc protecting group [<1996ACR268>](#). With more challenging synthetic

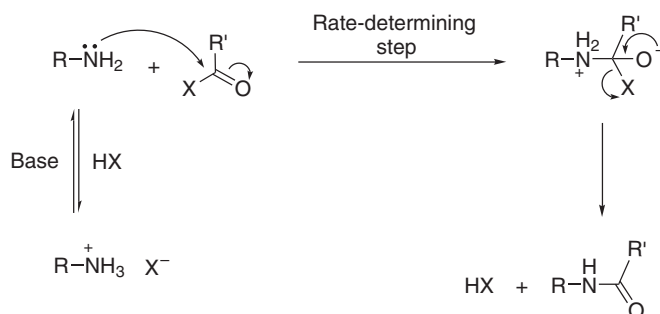
targets in mind, highly reactive derivatives, such as the acyl halides have been re-explored, and it has been found that, under appropriate conditions, they often have the capability of achieving the desired coupling when other reagents have failed.

(iv) The final major development concerns the use of immobilized supports, reagents, or scavengers in the synthesis of amides. The excellent review by Ley's group includes a list of immobilized reagents and catalysts for amide bond formation (table 3.7.1, pp. 3908–3918 of <2000JCS(P1)3815>); in addition, because peptides are often prepared using solid-phase methodology, the RSC *Annual Reviews of Amino Acids, Peptides and Proteins* contain a section on solid-phase synthesis. As combinatorial chemistry has become more and more important, peptides have been obvious targets for the synthesis of large arrays. This review, however, only highlights aspects of immobilization that have a significant impact on the synthetic methodology.

Most of the other general methods for preparing amides that were identified in <1995COFGT(5)257> have received modest attention since, with rearrangement reactions continuing to be a significant route to amides. The only group of amides to have received noticeably less synthetic attention has been the β -lactams, perhaps because such a huge range of other antibiotics have been identified; moreover, the majority of synthetic approaches had already been developed by the mid-1990s, so that no major developments in methodology were needed in order to continue the synthesis of these four-membered cyclic amides in more recent times.

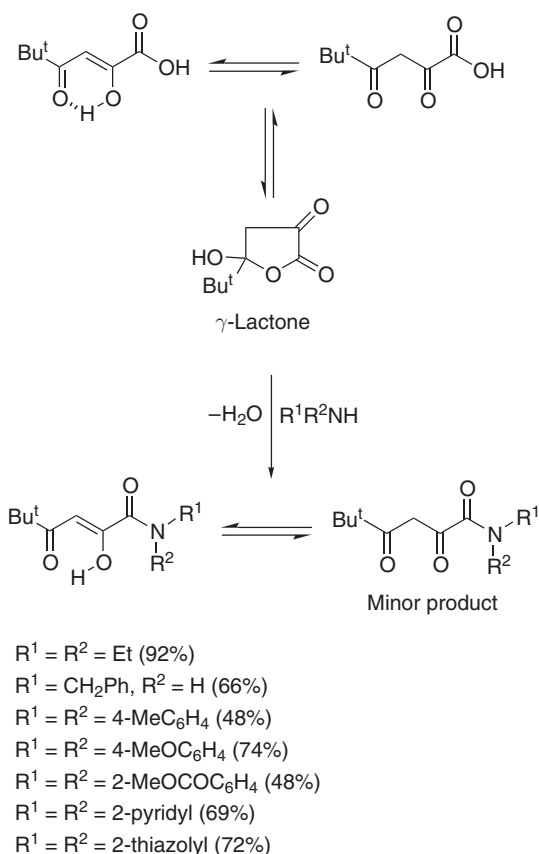
5.06.1.2 Acylation of Amines

The acylation of amines is the most widely used method of preparing amides, and no other approach comes even remotely close in terms of usage. It is worth summarizing the key mechanistic features relating to the acylation of amines, for these have influenced the ways in which the new reagents and additives have been designed and developed since 1994 (see Scheme 3).



Scheme 3

The first key feature to note is that the rate-determining step in the acylation of amines usually involves attack on the carbonyl group, so that the more powerful the electron-withdrawing nature of the leaving group, the faster will the reaction occur. A second key factor is that the acylation of amines runs the risk of slowing down almost to a complete halt at the halfway stage, unless a base is also present that can remove the protons generated during the reaction, and so prevent the protonation (and hence deactivation) of unreacted amine. The combinations of leaving group, other additives, and base have been the key features in the design of new coupling procedures. One major problem is that each new reagent that is announced by a particular research group is usually compared with alternative reagents that are already well established, and it is almost invariably reported that the new reagent has substantial advantages over its predecessors. Perhaps familiarity with one's own reagents leads to improved experimental technique, and therefore higher yields or greater purity in the products. In the end, it is the adoption of specific reagents or procedures by the community in general (particularly those involved in the synthesis of specific targets, rather than in the niceties of methodology) that indicates when a reagent has indeed been found to have significant advantages over the alternatives. Excellent summaries of the developments in methodology can be found in the *Annual Reviews of Amino Acids, Peptides and Proteins* which are published by the Royal Society of Chemistry, and which always include a chapter on peptide synthesis. Because these reviews both summarize synthetic methodology, and provide a



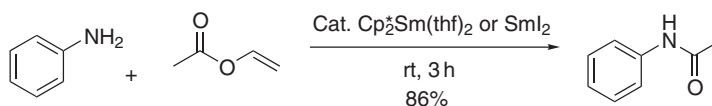
Scheme 5

aromatic amines using acetic acid [<2003JMOC\(A\)141>](#). It seems certain that other transition metal-based supported catalysts will be developed over the next few years. Finally, the use of enzymes continues to be of some value in the synthesis of amides from the amine and the acid. In practice, this transformation is not the one that has great generality, but the lipase-catalyzed acylation of sugar derivatives has been reported by Monsan's group [<1997T7587>](#); the use of hexane as the solvent produced a hydrophobic environment, and helped to drive the reaction in the reverse direction to the norm for this enzyme, allowing the group to achieve the synthesis of acylated glucosamine derivatives. The same group has also used this methodology to prepare biodegradable surfactants in which the acylating unit is a long-chain carboxylic acid [<1998JMOC\(B\)13>](#).

5.06.1.2.2 From simple esters

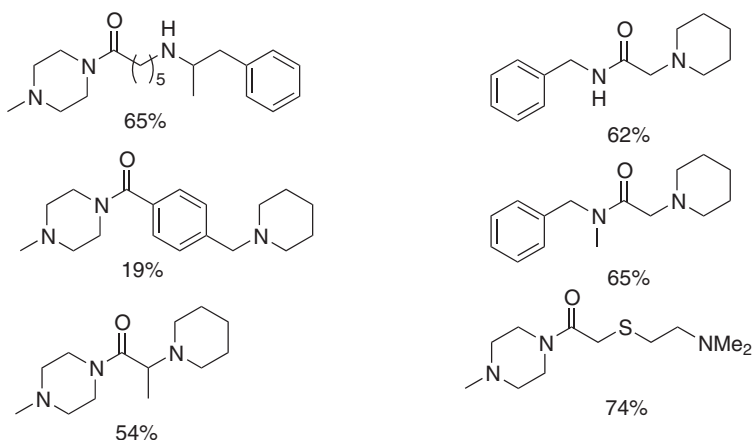
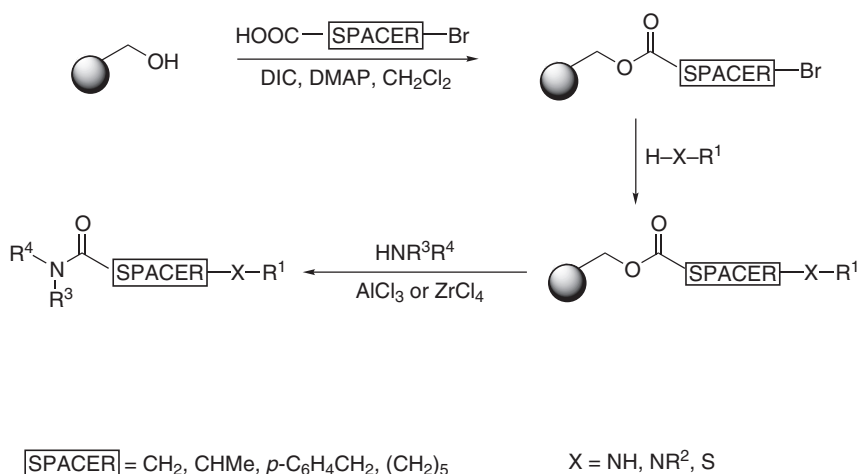
The synthesis of amides from simple esters normally requires substantial heating, unless the reaction leads to the formation of five- to seven-membered rings. For example, the formation of diketopiperazines from the dipeptide ester precursors is a relatively facile process. There have been relatively few developments in this straightforward process since [<1995COFGT\(5\)257>](#), although some useful catalysts have been developed that allow the reaction to be carried out at lower temperatures. For example, Ishii's group [<1996JOC3088>](#) has developed the use of samarium catalysts, which allow the acetylation of amines using vinyl acetate at room temperature; the chemistry appears to work well for primary and secondary aliphatic amines (Scheme 6).

Alternatively, primary aliphatic amines, can be acetylated using ethyl acetate at reflux with indium triiodide as the catalyst [<2000JCS\(P1\)2223>](#). The lack of reactivity of secondary or aromatic amines suggests that this might be a useful procedure for the selective acylation of primary amines when other amino groups are present. On the solid-phase front, benzyl esters attached to Wang or Tentagel resins could be cleaved from the support, with the concomitant



Scheme 6

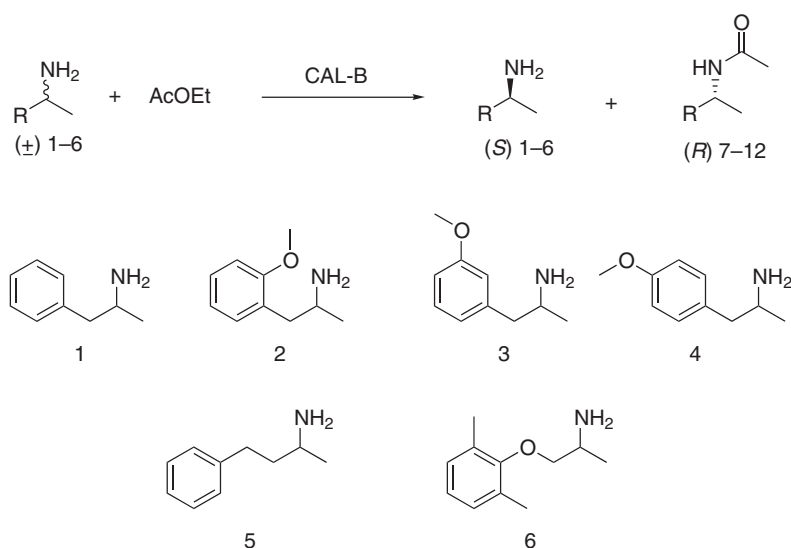
formation of the amide, by treatment with the corresponding amine at room temperature in the presence of aluminum trichloride or zirconium tetrachloride as the catalyst [<1996TL3213>](#); surprisingly, other Lewis acid catalysts gave little or none of the desired product (Scheme 7).



Scheme 7

The term “simple esters” has been used in this review to indicate ones that were not sufficiently activated for spontaneously acylation at room temperature to occur at a reasonable rate, but simple esters can sometimes be more reactive than one might expect. For example, dihydrocoumarins react smoothly with amines at room temperature over a period of several hours, and this was used by Bussolari's group [<2001OL279>](#) to prepare a range of cinnamyl amides, for which a neat solid-phase quench procedure facilitated the synthesis. On the borderline of simple and active esters are the trifluoroacetyl derivatives, and it has been found that ethyl trifluoroacetate can be reacted with amines at 0°C for a period of ~ 10 min with excellent selectivity for the acylation of primary amines over secondary amines [<1995TL7357>](#). This is an example of a recurring theme, in which reagents are developed that show good selectivity for one amino group over another without the requirement for protecting groups.

Perhaps the major development in the use of simple esters for the synthesis of amides has been the increased utilization of enzymes to catalyze these reactions. Lipases are particularly useful, and the ability to carry out resolution using the enzymes is especially attractive. Lipases from *Candida antarctica* (CAL) and *Pseudomonas* species are particularly common, and there is an excellent review by Rantwijk and co-workers <2000M549>. For example, it was found that (1,1'-binaphthyl)amines could be resolved using lipase-catalyzed amidation, provided the binaphthyl unit was separated from the amino group by one or two methylene units. The acylating reagent had to be tuned to the particular reaction, although butyrates were generally most successful <2002TL5529>. Whilst the previous reaction utilized a *Pseudomonas* enzyme, it has been found that the CAL-B-catalyzed reaction of pharmacologically interesting β -aminopropyl and γ -aminobutyl aromatic derivatives could be accomplished using ethyl acetate as the acetylating agent (Scheme 8); this selective acylation was in line with Kazlauskas' rule, which conveniently allows access to the (*R*)-amides <2002TA1315>.



Amine	Amide	Time (h)	Substrate [(S)-1-6]		Product [(R)-7-12]	
			Yield (%)	ee (%)	Yield (%)	ee (%)
1	7	7	75	73	90	89
2	8	8	95	93	98	92
3	9	11	88	96	97	89
4	10	22	97	99	99	82
5	11	4	76	90	99	86
6	12	21	81	99	94	92

Scheme 8

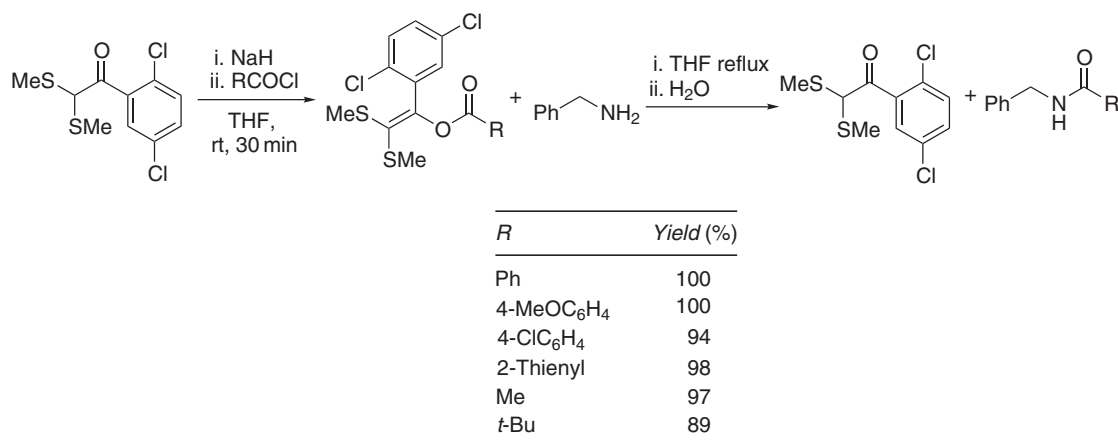
The importance of enzymes in the synthesis of pharmaceuticals is discussed in a short but interesting mini-review by Gotor <2002OPRD420>, in which the use of CAL enzymes is one of the specific examples, this time leading to the formation of primary amides using ammonia itself as the nucleophile <1999TA721>. The importance of these enzymes to industry is illustrated by the number of patents in this area that have been lodged over the last few years <2001USP6271005>.

Acylases have also proved to be popular enzymes for the resolution of amines, as exemplified by the formation of pent-4-enoyl derivatives of amines using subtilisin as the catalyst <1996TL6287>. As with many of the lipase reactions, these appear to be most successful when there is an aromatic group a short distance away from the amine, and Sheldon's group has demonstrated that, even when constrained by additional rings, aminoacylases are able to catalyze this type of reaction using a range of acyl donors <2001TA3267>. The increasing importance of acylases is exemplified by the use of *Aspergillus* species as a source of acylase <1995SL599>; further examples of

enzyme-catalyzed amide bond formation include the use of clostripain in the formation of amide derivatives of arginine <2000JOC1672>, and the use of quite different guanidine-based acyl transfer agents in the formation of secondary aliphatic amides <2000CEJ463>. Further useful examples of subtilisin-based enzyme catalysis include the use of thiosubtilisin (a chemically modified enzyme) as the catalyst for simple acetylation of amino acids using ethyl acetate <2002MI24>. Even enzymes such as horse liver acetonc powder (HLAP) are now being used <1995BSB161>, whilst the penicillin G amidase enzyme has been patented for its use in the formation of acyl penicillin derivatives, which are clearly still of substantial commercial importance <2001MI0107438>.

5.06.1.2.3 From active esters

Active esters have traditionally been used very extensively in the formation of amides, as they offer the advantage that they can often be relatively easily prepared from the acid and an appropriate alcohol, and the reactivity can be controlled by the choice of the alcohol to minimize side-reactions and maximize the yield of the amide formed upon the addition of an amine. This has led to active esters being studied very extensively over the years, but they suffer the disadvantage that they require an additional step in their formation, which many other procedures can avoid. There has therefore been relatively little improvement of active ester methodology since the 1990s, although the bis(methylsulfanyl)vinyl esters <1999S1200> are rather different from the traditional forms (which most often utilize aryl groups that can delocalize a negative charge), and were found to be effective benzoylating reagents with a wide range of amines (Scheme 9).

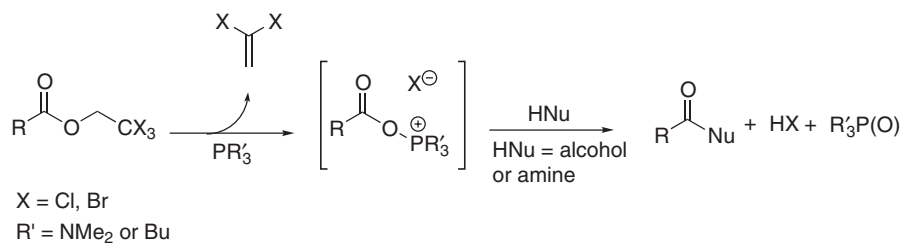


Scheme 9

A rather different tactic was developed by Burke's group, in which 2,2,2-trihaloethyl esters were activated *in situ* by the addition of phosphorus(III) reagents, which could be trapped by amines to generate amides in good yield <2000JOC2114> (Scheme 10).

Active esters have, however, been adapted quite extensively since the 1990s to create solid-supported variants, which are of considerable use in the preparation of combinatorial libraries. These have for the most part used active esters in which an aryl group is able to stabilize the negative charge of the oxygen leaving group, thereby facilitating the formation of the amide bond. For example, immobilized 2-nitrophenyl ester derivatives have been developed by several groups <1984JOC922, 1990JOC251, 1997JOC2594, 1998T1243>; this approach was utilized by Kim's group in order to acylate some very unreactive aryl amines in high yield (Scheme 11) <1999SL1957>, and they also reported the beneficial use of immobilized BEMP as a basic catalyst <1985C269, 1998BMCL1089>.

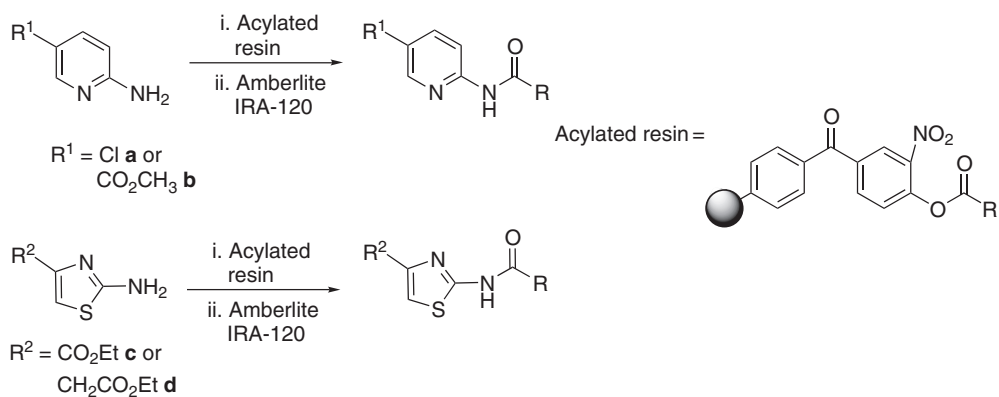
Hydroxamic esters have also been employed as acylating agents, and the use of arylhydroxamic acids allows simple attachment to a polymethacrylate <1997MI863> or polystyrene <1997MI169> support, as summarized in Scheme 12. These acylating agents are particularly suitable for reaction with aryl amines.



Using $P(NMe_2)_3$

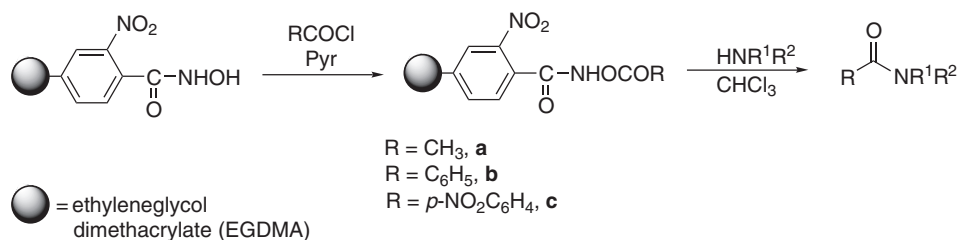
<i>R</i>	<i>Amine</i>	<i>Yield (%)</i>
Ph	HNEt ₂	76
Ph	HCl·GlyOEt	77
<i>c</i> -Hex	BuNH ₂	88
<i>c</i> -Hex	HNEt ₂	57
(<i>S</i>)-BOC-NH-CH(CH ₃)	HCl·AlaOEt	70

Scheme 10



<i>R</i>	<i>Amine</i>	<i>Yield (%)</i>
	a	15
	c	94
	a	21
	c	74
	b	23
	d	43
	b	12
	d	60

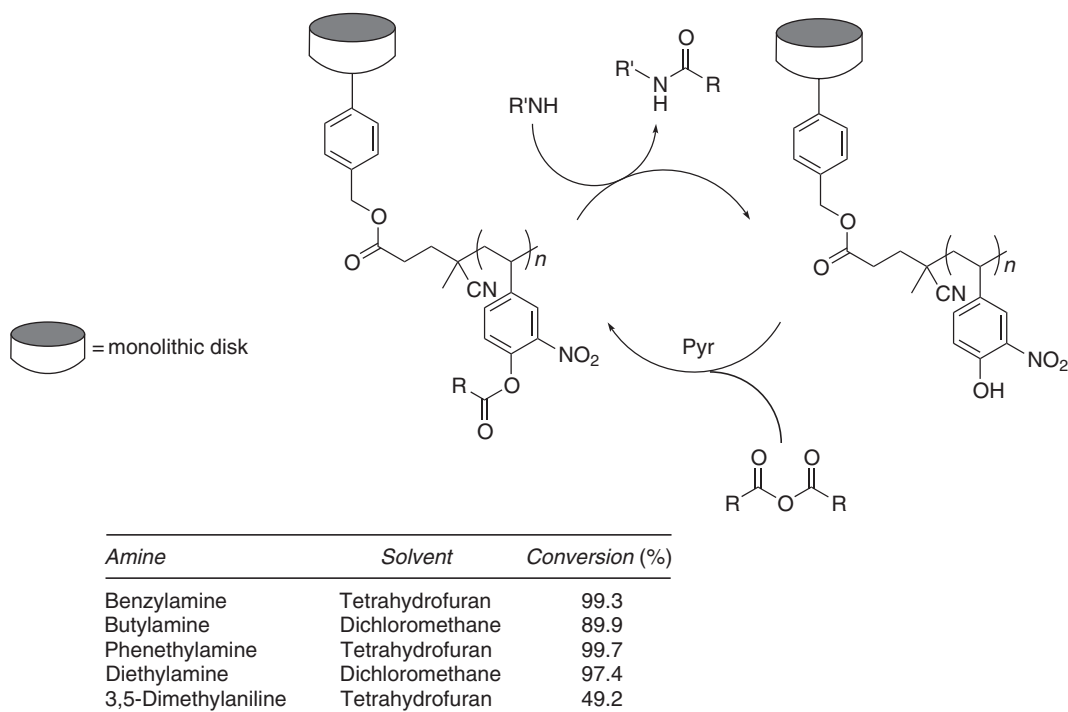
Scheme 11



Amine	Solvent	Yield (%) using		
		a	b	c
Aniline	CHCl_3	66	70	76
<i>o</i> -Toluidine	CHCl_3	70	76	83
<i>m</i> -Toluidine	CHCl_3	62	69	77
<i>p</i> -Toluidine	CHCl_3	67	71	79
Glycine	Dioxane:water (1:1)	64	69	78
Methylamine	Dioxane	73	85	94

Scheme 12

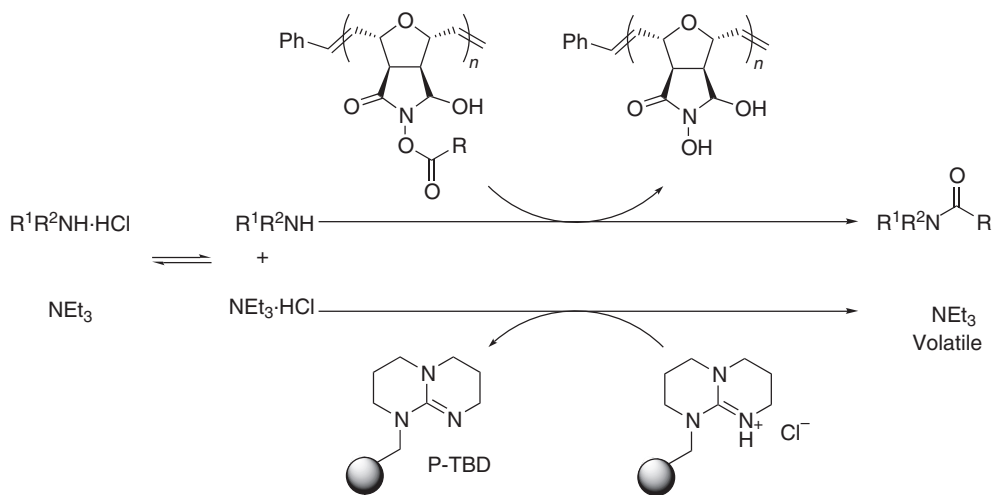
Besides the chemistry of such transformations, some groups have also looked in detail at the engineering required to facilitate high-throughput processes or continuous-flow methodology. Concerning the latter, macroporous polymer disks have been developed by Fréchet's group [\[2001JCO604\]](#), and adapted for *o*-nitrophenoxy (Scheme 13) or tetrachlorophenoxy leaving groups. The researchers focused on understanding the practical details relating to such disks, which are constructed from cylindrical polymeric rods, and they studied a small but quite diverse range of alkyl and aryl amines.



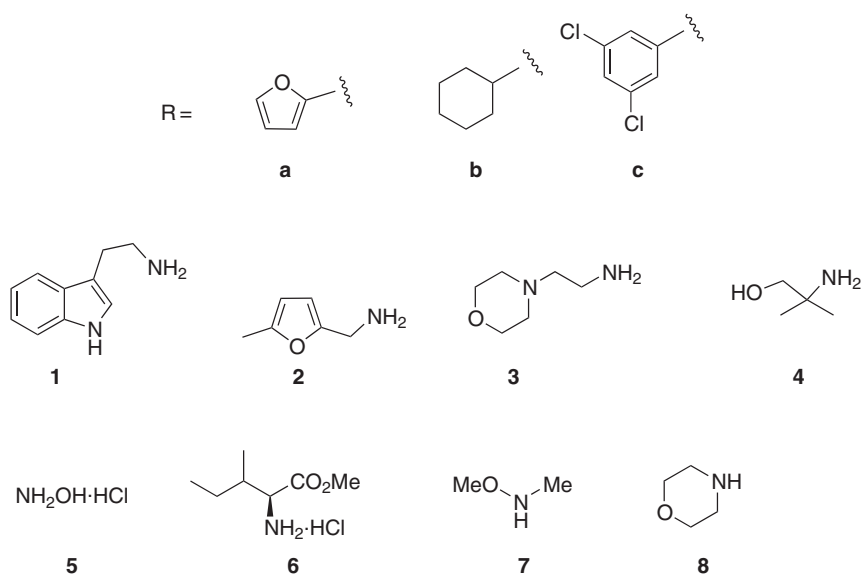
Scheme 13

Whilst Fréchet's work is based on polystyrene-type polymers, Barrett and co-workers have published the use of ROMP-type catalysts, using *N*-hydroxysuccinimide active esters for the acylation step <2000OL261>; they also used an immobilized guanidine base in order to catalyze these reactions, which were shown to work for a range of primary and secondary alkyl amines (Scheme 14).

Other examples of immobilized active esters include acyloxypyrimidine derivatives <2002H369>, which were used for the formation of a small but diverse library of compounds;

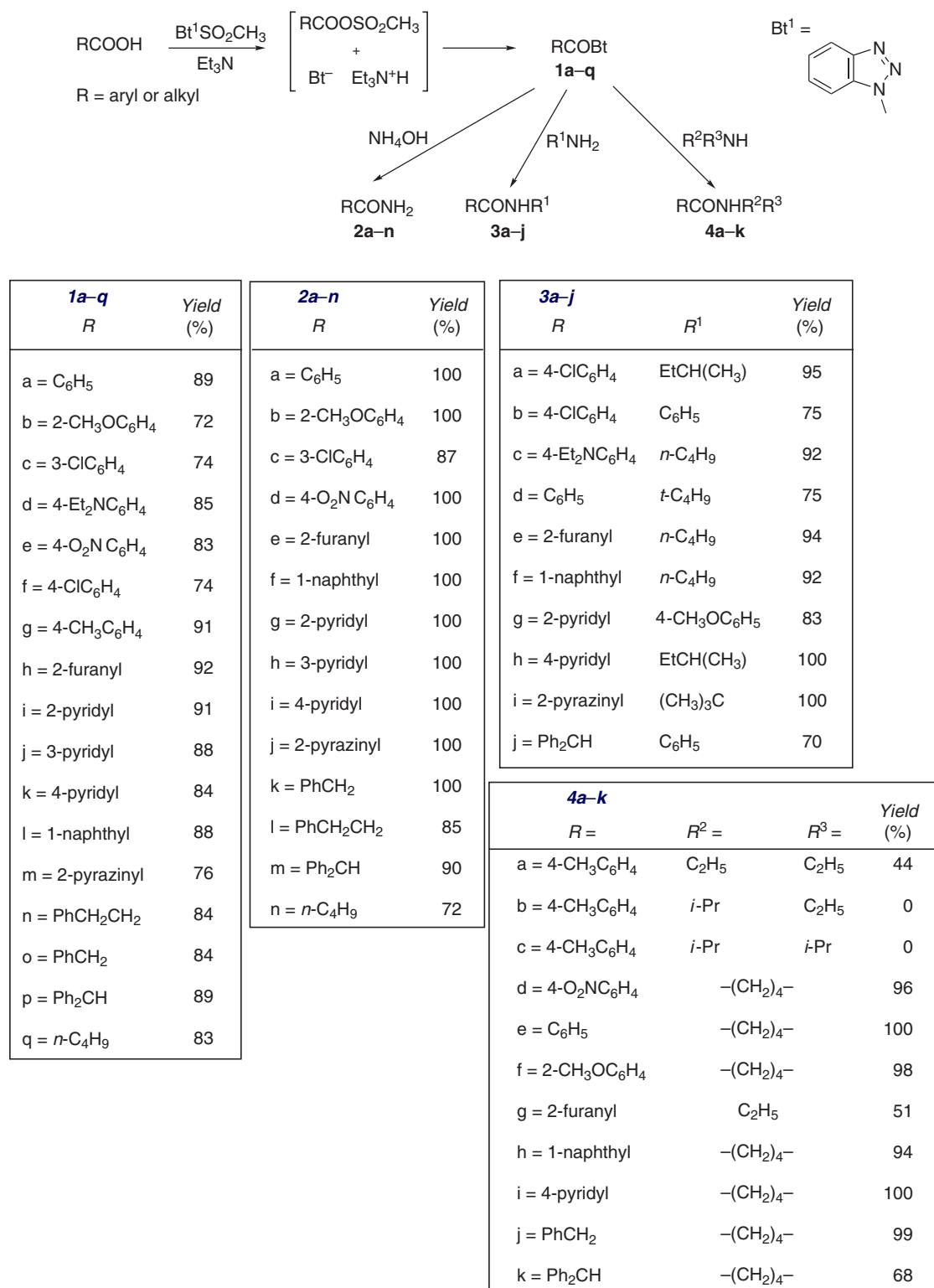


Isolated yields	a	b	c
1	95	90	97
2	97	93	97
3	97	97	98
4	89	90	80
5	91	90	96
6	96		98
7	95	93	98
8	95	98	96



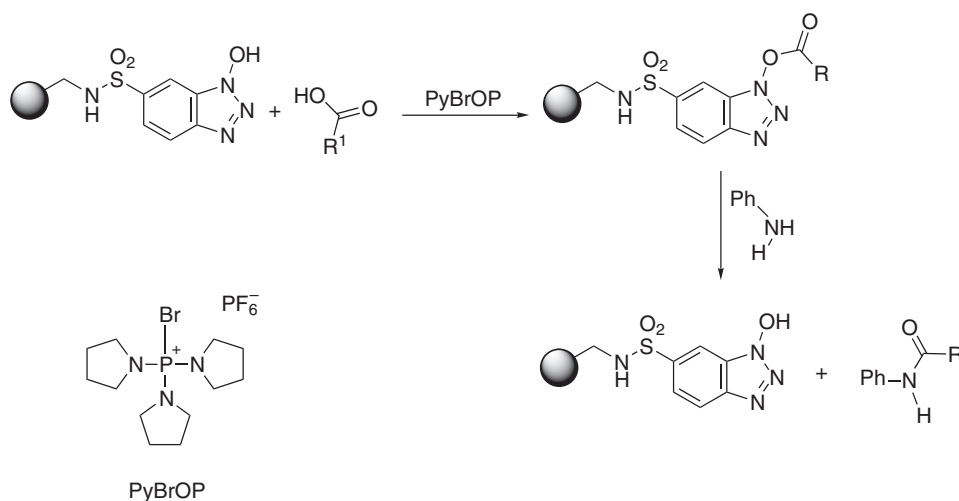
Scheme 14

this chemistry can be accelerated using microwave irradiation <2002TL6507>. Katritzky's group <2002BMCL1809, 2000JOC8210> has continued to develop the use of benzotriazoles as acylating agents, providing access to primary, secondary, and tertiary amides (Scheme 15).



Scheme 15

1-Hydroxybenzotriazole derivatives have also been found to be effective acyl transfer agents, particularly for rather less reactive aryl or tertiary carboxylic acid derivatives, and can be conveniently immobilized through a sulfonamide linkage (Scheme 16) <1997JOC2594>.



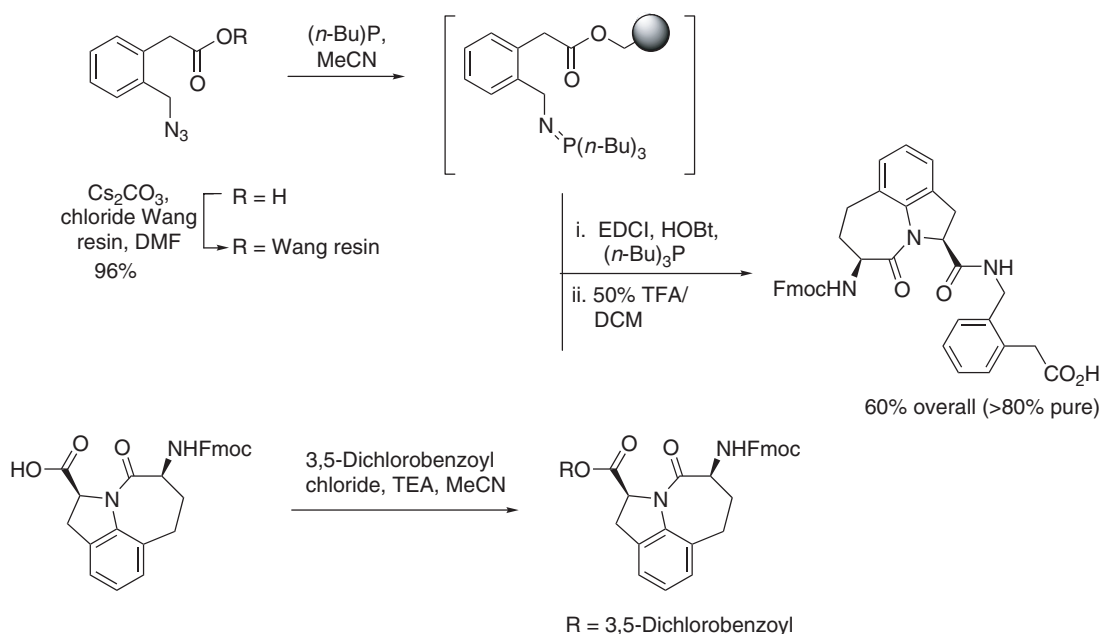
Amine	R	Yield (%)
Ph-CH ₂ -NH ₂		84
		87
		50

Scheme 16

Sometimes problems are encountered when the undesired formation of a δ -lactam can prevent an amine from forming the required amide bond. Pelletier's group <1998TL4773> overcame this by the use of iminophosphoranes, generated by reaction of azides with tributylphosphine (Scheme 17). In their examples, they were generating pharmacologically interesting polycycles using a solid-phase approach, but clearly the methodology should be applicable to solution-phase examples as well.

5.06.1.2.4 From acid anhydrides

The developments in this area of amide bond formation have not been restricted to the design of new acid anhydrides, but have included variations in the conditions under which these reactions take place, or the catalysts required in order to accelerate the processes. For example, it has been found that solvent-free conditions can be very efficient for the acetylation of amines <2003GC44>, although the research concentrated more on the formation of esters rather than amides; nevertheless, the solvent-free approach has distinct advantages from an environmental



RCO_2H	Solvent/Temp	Yield (%)	Purity (%)
	MeCN, 0 °C	69	82
	MeCN, 0 °C	100	79
FmocGly	1,4-Dioxane, 20 °C	92	80
FmocAla	1,4-Dioxane, 20 °C	82	80
Benzoic acid	1,4-Dioxane, 20 °C	100	91
Propionic acid	1,4-Dioxane, 20 °C	86	82

Scheme 17

standpoint. The deployment of catalysts to effect acylation using anhydrides under mild conditions has included the use of yttria–zirconia-based Lewis acid catalysts [\[2002JMOC\(A\)207, 2001SL206\]](#), the use of vanadyl triflate as catalyst [\[2001OL3729\]](#), the use of copper triflate as catalyst [\[1999TL2611\]](#), and the use of Mn(III) salen complexes [\[2001JMOC\(A\)69\]](#). Concerning microporous catalysts, the use of montmorillonite clays has also been reported [\[1998JCS\(P1\)1913\]](#), and tetrafluoroboric acid adsorbed on silica has also been claimed to be effective [\[2003TL3521\]](#). Almost all of these examples focus on the acceleration of acetylation using acetic anhydride for the formation of esters, but in all cases a small number of examples are

also given, illustrating the formation of amides, and it would appear that the use of such catalysts might have more widespread applicability.

In the formation of acetanilides, one possible approach is by reduction of the corresponding nitro compound, followed by an acylation step; the reduction and acylation steps can be carried out in a one-pot procedure using indium metal and a variety of Lewis acid catalysts, and the conditions can be modified to yield the acylated amine predominantly, or the diacetylated hydroxy amine. Although very specific examples, these compounds obviously have a subunit that is commonly seen in pharmaceuticals, and the results are therefore quite interesting <2001SC3577>. Finally, the acylation of lactams is reported in a patent, employing routine tertiary amines such as triethylamine in the presence of lithium salts; the lithium salt presumably helps stabilize the amide anion, and the chemistry is most efficient for four-, five-, and six-membered lactams <1997USP5594134>.

5.06.1.2.5 From acyl halides

Acyl halides were some of the earliest acylating agents used in the formation of amides, but had largely fallen out of favor because they cannot usually be purified readily, and their high reactivity often leads to side reactions. Although acid chlorides have regained favor for difficult couplings, it is the acyl fluorides that have found greater utility in this regard.

For amino acid-derived acid chlorides, the rapidity with which they can form oxazolones (which are less reactive, and readily racemized) had been a major problem in peptide chemistry <1998T241>, but Fmoc acid chlorides can be generated *in situ* using bis(trichloromethyl) carbonate for solid-phase peptide synthesis <1999MI507>, whilst Fmoc peptidyl chlorides have been successfully used in solution <1999SC79>. Practical issues relating to the ease of purification of the resulting amide have turned out to be quite important, as have processes that simplify the actual formation of the acyl chlorides. For example, it was found that sodium 2-ethyl hexanoate could be used as a mild base scavenger in the acylation of prolinamide, for which the standard Schotten–Baumann conditions created problems due to the water solubility of starting materials and products; the new modified procedure allowed acylation to be carried out in tetrahydrofuran (THF) <1998TL6991> and was extended to other amino acid derivatives. The formation of acid chlorides *in situ* has been accomplished using trichloroacetonitrile and triphenylphosphine <2002TL6039>, thereby allowing an immobilized amine to be acylated using a free carboxylic acid, with the co-reagents being added *in situ*; this reagent combination was found to be far superior to the widely utilized HBTU (Section 5.06.1.2.7).

Concerning specific classes of nonpeptidic compounds for which the use of acyl chlorides was beneficial, it was found that bis-acetylation of imidazolines <1998S1463> and the formation of macrocycles in which two amide bonds are formed simultaneously <1999JHC601> were both most effectively achieved using the acid chlorides. In general, acid chlorides are not used where high selectivity is required, but chiral secondary anilines can undergo kinetic resolution with a suitable acid chloride under conditions in which the acyl chloride is not racemized (Scheme 18) <2002MC27>.

Although this example is unusual in the use of an acid chloride for the resolution, processes that lead to the formation of single enantiomers or diastereoisomers have featured highly in the literature since the 1990s.

The use of acyl fluorides for amide formation has, perhaps unexpectedly, come back to the fore. It should be remembered that the rate-determining step in the formation of an amide by acylation is usually the attack of the nucleophile on the carbonyl group, rather than the subsequent reformation of the π -bond and displacement of the leaving group (Scheme 3). Therefore, the strongly electron-withdrawing fluorine atom is able to stabilize the transition state and the tetrahedral intermediate, and its poor leaving group ability is of little energetic importance in the subsequent formation of the stable amide bond. Importantly, acyl fluorides are much less reactive toward oxygen nucleophiles than their acid chloride counterparts (hence, the latter are readily hydrolyzed, and form oxazolones easily), but of similar high reactivity with amines. Acyl fluorides have had a resurgence of attention in the peptide field, as they often allow the generation of amide bonds that otherwise would be extremely sluggish to form. Their use has been promoted by Carpino and co-workers <1996ACR268>, who discovered that the urethane-protected amino acid fluorides suffered much less tendency to form oxazolones than their acid chloride counterparts.

Rather neatly, α -azidocarboxylic acids can also be activated as their acyl fluorides <1995TL6013> and used for coupling to highly hindered amines and hydrazides, without racemization at the α -center; the azides can of course be subsequently reduced to the corresponding amine, for further elaboration. One slight problem with the use of acyl fluorides is that the HF generated in the reaction can cause problems, such as trace amounts of fluoride ion being present in the products, although this can be overcome by the addition of silazanes during work-up <1996EUP709366>.

5.06.1.2.6 From acyl azides

Traditionally, acyl azides were important acylating agents for coupling reactions in which the carbonyl component might be expected to be particularly susceptible to racemization. Developments since the early 1990s have almost entirely superseded the use of azides, which are sluggish in their formation of the amide bond, and commonly lead to the generation of a number of side-products. Acyl azides can be prepared by classical nitrosation of acid hydrazides using an $[\text{NO}]^+$ source such as $\text{Bu}_4\text{N}^+\text{NO}_2^-$ <1995MI109>, by treatment of acid anhydrides or chlorides with NaN_3 <2000JCS(P1)4328>, or *in situ* from the carboxylic acid using diphenylphosphoryl azide (DPPA) <1972JA6203>. However, the development of improved conditions for a whole range of acylating agents (discussed in earlier sections), and the enormous advances in the range of *in situ* coupling reagents that can affect acylation with minimal racemization, has meant that acyl azides are now rarely used for the formation of amides.

5.06.1.2.7 Using *in situ* coupling reagents

The early days of peptide chemistry used mainly acid chlorides and acid anhydrides as the acylating agents for amide bond formation. In the 1960s and 1970s, the *in situ* diimide coupling reagents had largely superseded the cumbersome two-step procedures, but as solid-phase peptide synthesis became more and more common, problems associated with use of *in situ* coupling reagents started to become apparent. In particular, there were side-reactions that, whilst rarely producing significant problems, could lead to the accumulation of substantial amounts of by-products as an extended solid-phase synthesis progressed. Although significant improvements were made in the use of *in situ* coupling reagents, particularly the use of additives that led to the formation of transient active esters, it started to become more and more attractive to prepare and purify activated intermediates whose reactivity could be fine-tuned to ensure relatively speedy peptide coupling, whilst minimizing unwanted side-reactions. Since the early 1990s, there has been a massive resurgence in the use of *in situ* coupling reagents, and they have come to dominate the formation of amides using the acylation of amines. Because of their importance, the majority of the reagents have been developed with peptide chemistry in mind, and with the concerns of the peptide chemist to the fore. In particular, the potential epimerization of chiral centers adjacent to an activated carbonyl group has been a major consideration, as has also the simplicity with which the final amide product can be readily isolated from by-products or impurities.

The *Specialist Periodic Reports on Amino Acids, Peptides, and Proteins*, published by the Royal Society of Chemistry, provide a very clear picture of the ways in which peptide synthesis has been evolving <1997MI110, 1998MI126, 1999MI111, 2000MI120, 2001MI107, 2002MI183>. From these it can be seen that diimides and phosphorus reagents continue to be important, but it is the use of uronium salts that has really started to dominate the peptide coupling field. The use of iminium salts, which in some ways are partway between diimides and uronium salts, has produced a number of interesting publications, which suggest that they may start to dominate the peptide coupling field in the not-too-distant future. There is an excellent detailed review covering the period up to 2000 <2001OPP203>, in which the preparation of a range of *in situ* coupling reagents, their mechanisms of action, and their use in the synthesis of peptides is discussed at some length. One problem when reading publications reporting new coupling reagents is that authors invariably manage to demonstrate that their reagents are superior to any others, concerning either the yield of the coupling step, or the degree of racemization that takes place. In practice, the establishment of a new reagent for the routine preparation of peptides comes about when many groups discover that it can address specific problems; for example, when coupling steps are extremely sluggish or racemization is a particularly serious problem, then alternative

(i) Diimides

Whilst the use of the water-soluble diimide EDCI **1** [$\text{Me}_2\text{N}-(\text{CH}_2)_3-\text{N}=\text{C}=\text{N}-\text{Et}$] <1973JA875> continues to be widespread, because of the ease with which the resulting urea by-product can be washed out with water at the end of the coupling, it is the development of immobilized diimide reagents to facilitate purification that has dominated this area since 1990s. For example, the immobilized PS-carbodiimide **2** that is commercially available was found to be highly efficient for the preparation of a range of amides <2001TL6703> and, with the simultaneous use of an immobilized base, the purification became quite simple. Similarly, Mosher's amides could be readily prepared using the polystyrene-immobilized form of EDCI <1996TL7171>. Additives to carbodiimide couplings also provide a tremendously sensitive way of fine-tuning the reagent; the use of 1-hydroxy-7-azabenzotriazole (HOAt) in place of HOBt is now widespread as a diimide additive <1993JA4397>, whilst Ramage's group has demonstrated that ethyl 1-hydroxy-1*H*-1,2,3-triazole-4-carboxylate **3** (HOCT) is an excellent additive when diisopropylcarbodiimide is used as the coupling reagent, and is particularly effective at reducing racemization to an extremely low level <1999T2713>. Nevertheless, traditional dicyclohexylcarbodiimide is still useful, and is sufficiently selective to allow the kinetic resolution of a range of amines using a protected proline as chiral resolving agent in the coupling step <2001TL2617>; this procedure has been cleverly extended to resolution using active esters of proline that are immobilized onto a solid-phase support. The DCC/HOBt combination is one of the most traditional reagent mixtures, but the simple removal of the triazole catalyst at the end of the synthesis can now be achieved by immobilizing it onto a polystyrene support <1998CC499>. Interestingly, in a comparison of a range of coupling reagents that included uronium and phosphonium salts, it was found that solid-phase peptide synthesis in the reverse ($\text{N} \rightarrow \text{C}$) direction proceeded with minimum racemization when diisopropylcarbodiimide was used in conjunction with the copper salt of 1-hydroxybenzotriazole <2000OL1815>. The use of carbodiimides, therefore, continues to be an important method for forming amides, particularly combinatorial libraries such as those prepared for the discovery of peptides with selective metal-binding properties <2002JCO329>. Despite the extent to which diimides have been superseded by other reagents, the well-known peptide research groups of Sakakibara <1999MI279> and Carpino <1999T6813> advocate the continued use of diimides as one of the important methods for the *in situ* coupling of amines and acids.

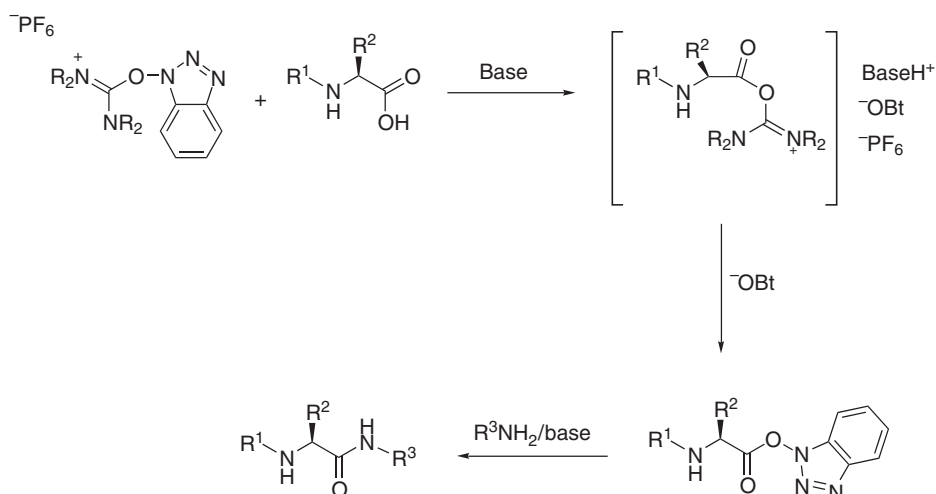
(ii) Phosphorus reagents

The triazaphosphonium salts of BOP **4** and PyBOP **5** continue to be frequently employed as coupling reagents in peptide synthesis, and can be used to form peptides, or even simple unsubstituted amides by using ammonium chloride as the source of NH_2 <1999TL2501>. The latter simple procedure works with other coupling reagents, but serves to highlight that simple primary amides are often tricky to prepare; their synthesis usually needs more than one step, and involves the use of either liquid ammonia (awkward) or aqueous ammonia (where water is a competitive nucleophile). New phosphorus coupling reagents have not really dominated the literature, but examples have been published that include phosphates (DEPBT **6**, DOPBT **7**) and their aza-analogs (DEPBO **8**, DOPBO **9**) <B-1999MI337, 1996SC1455>.

(iii) Uronium salts

These have now come to dominate the field of *in situ* peptide coupling, with HBTU **10a** and HATU **11** the most important. An enormous range of alkyl substituents has been attached to the uronium substructure in order to modify the reactivity. Interestingly, the supposed uronium structure of HBTU has in fact been shown to be the *N*-oxide **10b**, based on an X-ray crystal structure <1994MI57>. Nevertheless, it is possible that the uronium salt is indeed the active component in solution, and they are almost always called "uronium salts" in the literature. A distinction between uronium and iminium salts has been drawn, although both obviously depend on the same basic mechanism, as outlined in Scheme 21.

Useful comparisons of uronium and other coupling reagents have been provided by Sabatino's group <2002MI119>, in which the efficiency in the synthesis of a difficult decapeptide sequence was compared using a range of coupling reagents under solid-phase conditions, and in a subsequent paper <2002MI125> uronium salts were compared concerning their propensity to cause racemization of the carbonyl component. Many new uronium salts have been presented in the literature in the 1990s,



Scheme 21

including the 6-chloro derivative of HBTU <2002MI119>, polycyclic uronium salts <B-2001MI273>, and 2-mercaptopyridone-1-oxide based uronium salts <1999JOC8936>, as well as a range of other examples. The use of uronium salts is now of course being extended well beyond that of peptides, and it would appear to be an excellent coupling reagent for a large number of hindered and difficult amide bond-forming reactions, including those in which racemization of the acyl component is a concern. Their use is exemplified by the formation of oligonucleotide–peptide chimeras <2002HCA2409> utilizing HBTU/HOBt as the coupling mixture, and of course immobilized versions of these reagents are beginning to appear, as exemplified by the polystyrene-bound derivative of TBTU <2000TL2463>. Whilst some fine-tuning may be possible in the next few years, it would seem that the uronium salts have probably been virtually optimized for efficiency of coupling and minimization of racemization, although as more and more ambitious targets are undertaken, the small advantages of one reagent over another may start to become important.

(iv) Iminium salts

The use of iminium salts as peptide coupling reagents has been extensively explored, and the CIP reagent **12** is useful for couplings involving hindered amino acids, especially in the presence of the additive HOAt <1996JOC3350>. More recently, a range of new iminium coupling reagents has been developed by Li and Xu <2000T4437, 2000T8119, 2000MI456>, and the comparison of these and other coupling reagents in the synthesis of cyclosporine O <2000JOC2951> provides an opportunity to compare the practical merits of the different coupling reagents. They report the synthesis and properties of several other iminium-type salts <1999TL8301, 2000TL721, 2000MI110, 2000T9949>, but it has yet to be seen whether these reagents will be considered by the general community to be more efficient than the alternatives that are currently available. Iminium salts related to the Vilsmeier reagent have also been developed <2002TL7597> (e.g., CMPA **13**), and ones based on thiazolium salts <2003TL4393> are also receiving attention (e.g., BMTB **14**).

(v) Other methods

The possibility of using alternative electrophilic centers attached to the oxygen of (for example) 1-hydroxybenzotriazole has been achieved by using a sulfinate derivative N-NSBt **15**, and this is a nice example of logical design in reagent development, although others have not taken up this reagent since then <1996JCR(S)200>. A completely novel approach would appear to be the use of NO and oxygen to trigger coupling reactions from carbamoyl amino acid derivatives. The gaseous reactants are known to cause loss of the carbamoyl unit, liberating the free NH_2 group in peptides that are protected in this way, and leading to the formation of *N*-carboxyanhydrides (NCAs) under these conditions <2002EJO1026>. These cyclic anhydrides are effectively both

activated on the carbonyl group and protected on the nitrogen, and under suitable conditions can undergo efficient amide bond formation with external nitrogen nucleophiles.

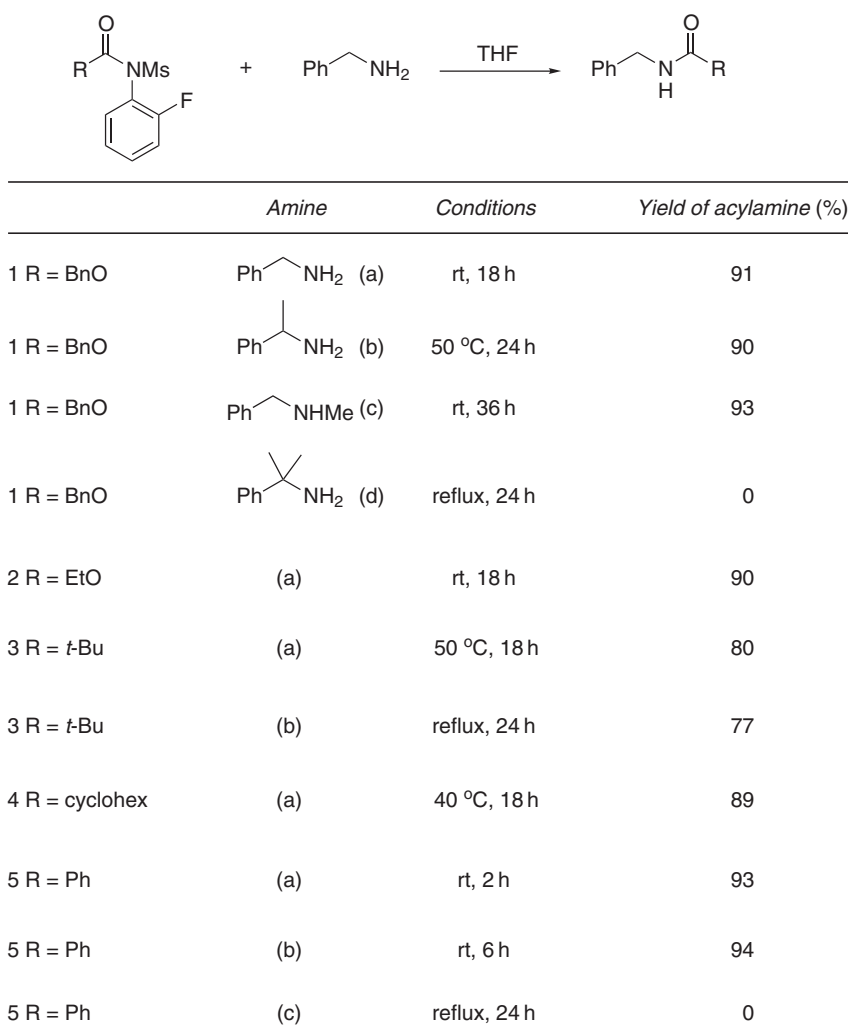
5.06.1.2.8 Other acylation methods

An astonishing array of other leaving groups has been explored as carboxylic acid derivatives in amide bond formation. For this review, they have been divided into those with nitrogen leaving groups, those with sulfur, and others.

(i) N-Leaving groups

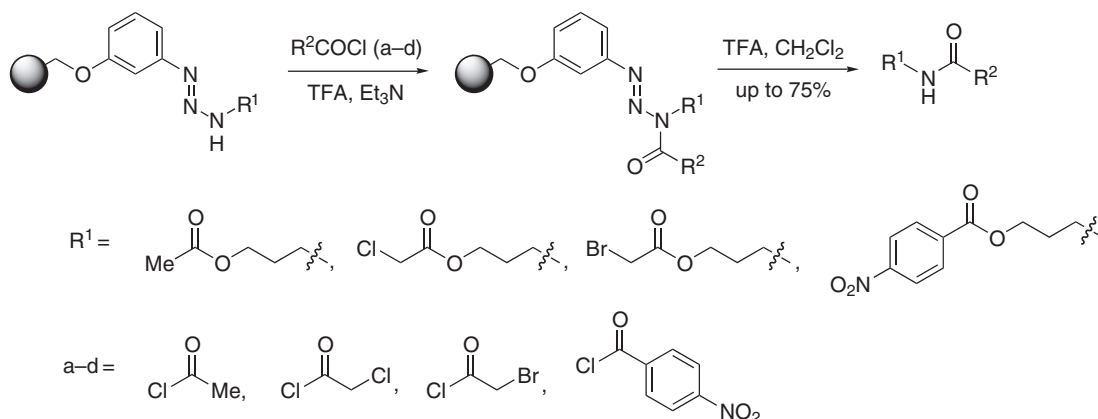
(a) *Sulfonamides*. Simple sulfonamides can be used to acylate amines (acetylation or benzoxylation), but temperatures of over 100 °C are required <1995IJC(B)1102>. However, Murakami has developed some much more active sulfonamides <1998JCS(P1)2973, 2000T5843> that effect efficient acylation of aliphatic amines in THF (Scheme 22).

(b) *Triazenes*. Triazenes have also been developed as leaving groups. Diaryltriazenes are readily accessible via diazonium intermediates, and can be acylated to generate derivatives that react with amines on timescales of 2–84 h at room temperature with a wide range of amines



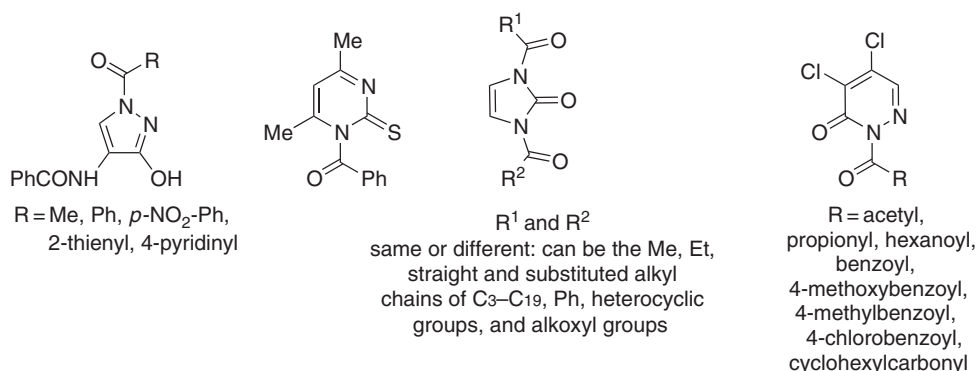
Scheme 22

<2001TL6659>. In contrast, triazene chemistry has been applied to the synthesis of amide libraries <2000JCO710>, in which the acyltriazene is created on an immobilized polymeric support, and directly released by the addition of TFA (Scheme 23).

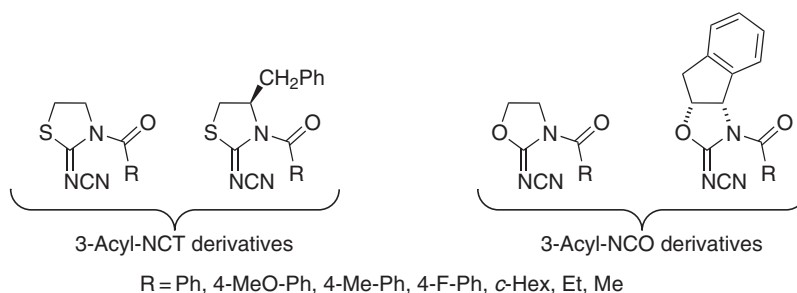


Scheme 23

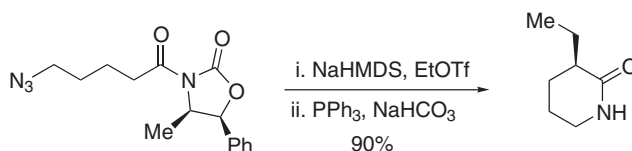
(c) *N*-Heterocyclic leaving groups. The feature of these systems is the ability to delocalize the negative charge of the leaving group over several atoms, often (but not always) into aromatic systems. A range of *N*-heterocyclic acyl derivatives <1998MI455, 2001MI43, 1999USP5994557> has been developed, whose structures are shown below.



Unfortunately, their sluggish reactivity will probably mean that they have modest uptake in synthesis, although the photochemically activated acylnitroindolines offer greater reactivity under unusual conditions <1996JCR(S)200>. Modest reactivity can, however, be exploited for selectivity; Tanaka's NCT/NCO derivatives acylate primary amines over timescales of many hours, and chiral versions of these can achieve enantioselective acylation of amines with reasonable ee <2001T9309> (see structures below).

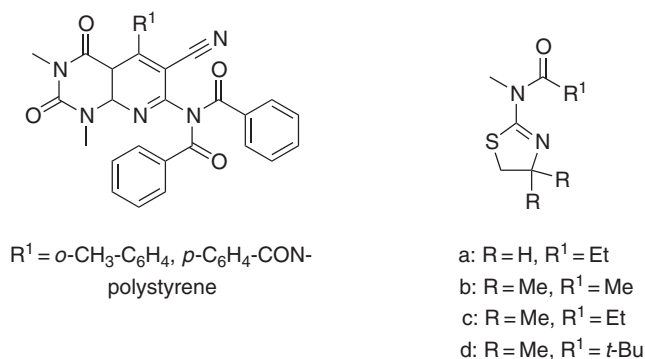


In an elegant utilization of the Evans auxiliary, Suh's group have prepared δ -lactams by using the auxiliary itself as a leaving group (Scheme 24) <B-1999MIOGRN-147>; as discussed earlier, the formation of five- to seven-membered lactams is much easier than most other amides, and so this approach should be viable for many chiral lactams of this size.

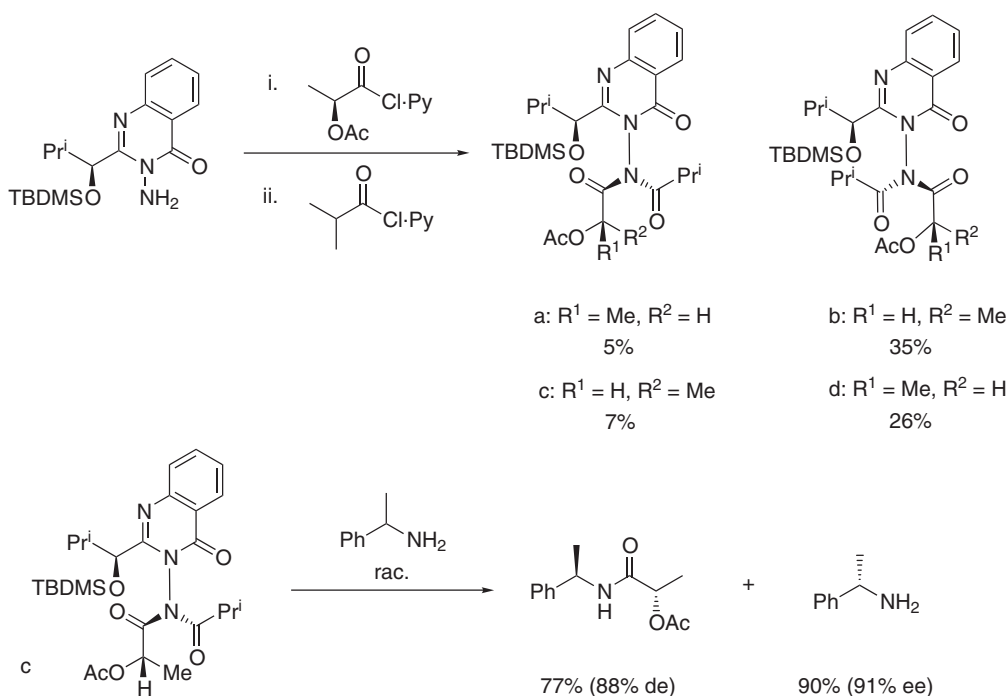


Scheme 24

(d) *Other N-leaving groups.* There are a few other examples of *N*-leaving groups that are attached to heterocyclic rings, as exemplified below <2002BMCL1799, 2002TL9553>.



The most impressive developments in this area are the axially chiral 3-acylaminoquinazolin-4(3*H*)-ones. The axial chirality can be controlled by a second chiral center <1996JCS(P1)1047> and has been improved to give diacyl derivatives <2000JCS(P1)4413, 2000TL2239, 2000CC43>, which can be used for the resolution of chiral amines (Scheme 25).

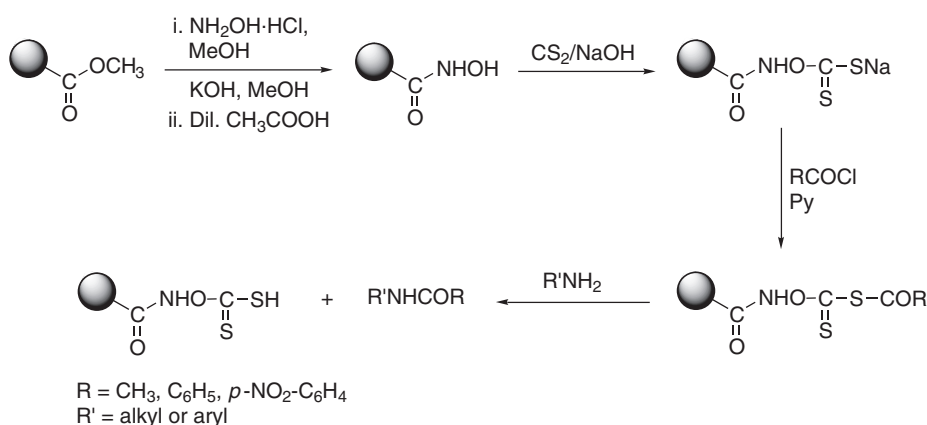


Scheme 25

Enzymes have featured strongly in this review, generally catalyzing the coupling of acids or esters with amines. Penicillin acylase is a specific enzyme which unusually can induce NH_2^- to be a leaving group in amide bond formation; using this enzyme, phenylacetamide can be reacted with a range of amines <2000TA4593>, and this chemistry can be used to effect the resolution of racemic amines <2001TA1645, 2002MI0220821>.

(ii) *S-Leaving groups*

Sulfur leaving groups that are structurally similar to the *N*-derivatives described above have been used <1998JCR(S)268, 1997MI442>, and the dithiobenzoic anhydrides developed by Sreekumar are worth considering (reaction time of ~ 2 h with a range of amines). The main attraction of these reagents, however, is that they can be readily immobilized on polystyrene <1995PIA51, 1997PIA49, 2000MI161>, with the acyl transfer unit remaining immobilized after formation of the amide (Scheme 26).



Examples use PMMA resins crosslinked with DVB

Amine	Solvent	$R = \text{CH}_3$	$R = \text{C}_6\text{H}_5$	$R = p\text{-NO}_2\text{-C}_6\text{H}_4$
Aniline	Chloroform	18	55	64
α -Toluidine	Chloroform	54	61	71
<i>m</i> -Toluidine	Chloroform	50	57	66
<i>p</i> -Toluidine	Chloroform	52	59	69
<i>m</i> -Chloroaniline	Chloroform	41	45	49
<i>p</i> -Chloroaniline	Chloroform	43	48	52
α -Aminophenol	Chloroform	46	52	58
Glycine	Dioxane/water (1:1)	43	46	50
Methylamine	Dioxane	58	69	75

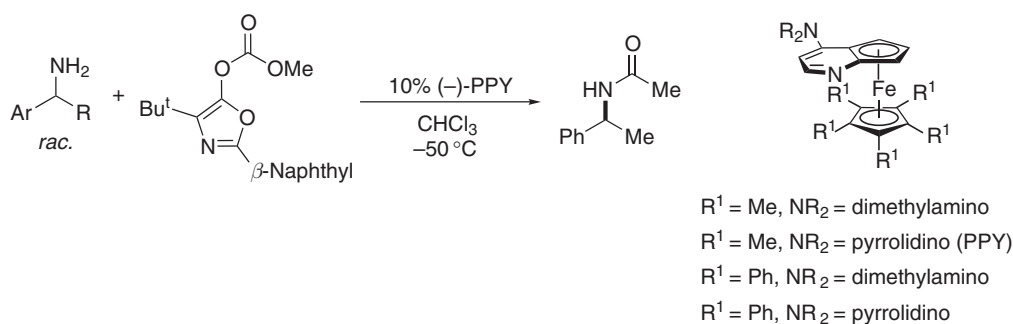
Scheme 26

(iii) *Other acylating systems*

DMAP has long been used as an acyl transfer catalyst, and Fu's group has developed chiral ferrocenyl derivatives such as (–)-PPY that have been used for the resolution of α -alkylaryl-amines with great success (Scheme 27) <2000CC119, 2001AG(E)647>.

Other useful developments include acyloxyphosphonium salts <1997TL5359>, which are readily prepared *in situ*, and the use of sulfinylanilines in a mild, intramolecular amide bond-forming step <2000TL6017>.

In some instances, amides are synthetically accessible via protected amines, for which the protecting group can then be removed. Cleavage of the N–O bond of *N*-acylhydroxylamines



Amine	Selectivity factor (s)
	12
	27
	16
	11

Amine	Selectivity factor (s)
	13
	22
	16
	11

Scheme 27

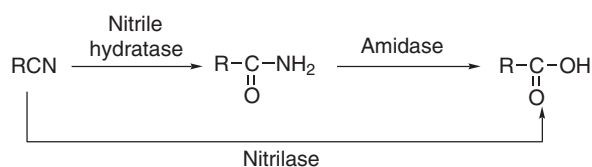
with SmI_2 has been used by two groups [<1996JOC359, 1999T11755>](#), and this allows nitrones and hydroxamic acid precursors to be used in the synthesis of amides. In a rather different vein, Roush [<1998JOC2062>](#) has found that Teoc derivatives of amines can be acylated and then deprotected, under conditions in which the free amine undergoes unwanted side-reactions; this is a useful trick that could have widespread use. Finally, a review of selectivity in acyl transfer agents, generally of the type discussed earlier in this section (*N*- and *S*-leaving groups linked to heterocycles), provides useful references [<2000MI39>](#).

5.06.1.3 Hydrolysis of Nitriles

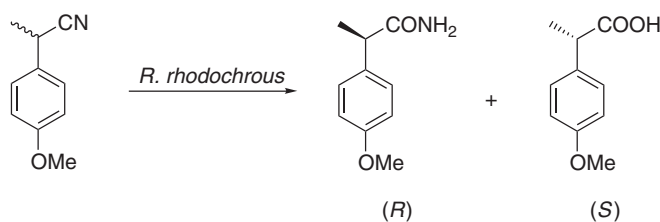
There has been an enormous amount of research since the 1990s on the hydrolysis of nitriles as a route to amides, opening up a wide range of synthetic strategies to a variety of targets. For example, the formation of anions adjacent to primary/secondary amides is difficult, whereas the formation of anions adjacent to the nitrile unit is well documented and relatively straightforward, and subsequent hydrolysis to the amide can be carried out. Two other factors have led to the importance of nitriles in the synthesis of amides; first, there has been a big increase in the range of enzymes that are able to effect this hydrolysis and, second, a wide range of Lewis acid catalysts have been devised for the hydrolysis, many of which have green technology in mind. The hydrolysis of nitriles is, therefore, considered first under the heading of biocatalysis, and then nonenzymic hydrolytic methods.

5.06.1.3.1 Enzymic hydrolysis of nitriles

The developments in this area are emphasized by the number of major reviews on the enzymic hydrolysis of nitriles. Several of these provide excellent guidance as to the types of nitrile that can be hydrolyzed, and the range of appropriate organisms <2002MI699, 1997MI1419, 1999MI373>. Others emphasize the biotechnological potential, and the relevance of the enzymic hydrolysis of nitriles to the commercial synthesis of amides <1999MI925, 1998MI89, 1999CI(M)1305, 1996C434>. One of the major problems is finding enzymes that will hydrolyze nitriles to amides without further hydrolyzing them to the carboxylic acid; however, a significant advantage of the enzymic hydrolysis is that products with high enantiomeric excesses can often be obtained using these methods (Schemes 28 and 29) <1996C434>. The specific type of enzyme that leads to the formation of amides is a nitrile hydratase, and the most widely used ones are derived from *Rhodococcus* and *Pseudomonas* organisms.



Scheme 28



Reaction time (h)	Yield (%) / ee (%)	
	(R)	(S)
6	45/99	47/99
24	37/>99	59/53

Scheme 29

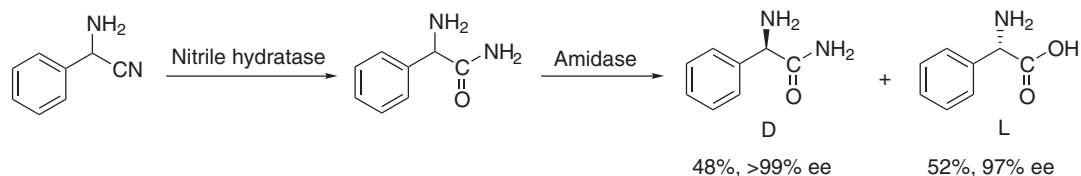
The enzymic hydrolysis of nitriles is most conveniently divided into the categories of compounds for which the enzymes are active, for which the major developments in the 1990s are as follows.

(i) Amino acids

Sheldon's group has successfully isolated *Rhodococcus* enzymes that have proved very useful for the synthesis of optically enriched amino acids. In particular, these have turned out to be extremely valuable for the synthesis of phenylglycine, which is a non-DNA-encoded amino acid that is widely employed, but for which there are no natural sources (Scheme 30) <2001JMOC(B)249, 2002MI356>.

Other organisms have also been found to effect the hydrolysis of the nitrile precursor of phenylglycine, even more impressive is work that has shown that a whole range of arylglycinamides can also be synthesized using *Rhodococcus* organisms, and that they also effect the hydrolysis of nonaryl amino acids, although in general with very poor enantiomeric excesses.

One feature of these enzyme systems is that they generally use crude cell extracts, which contain both nitrile hydratases and amidases; the consequence is that the nitriles are generally hydrolyzed

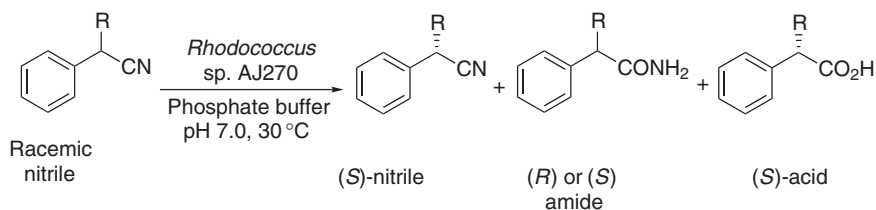


Scheme 30

to the amides, only half of which is then further hydrolyzed to the corresponding carboxylic acids. This means that the products are generally the D-amino acid amides that are generated together with the corresponding L-amino acids.

(ii) 2-Arylacetonitriles

It transpires that the amino group of the phenylglycines is not required for effective hydratase activity from the *Rhodococcus* cultures, so that other 2-arylacetonitriles can be successfully hydrolyzed (Scheme 31). This is very useful as it extends enormously the range of substrates that can be hydrolyzed. Again, the microbial extracts tend to generate the *R*-amide and the *S*-acid, which can be readily separated and then both used in subsequent syntheses. Key publications in this area all utilize the *Rhodococcus* organisms <2001TA3305, 2000TA1123, 2001JMOC(B)77, 2002TA1695, 2002TL6617>.



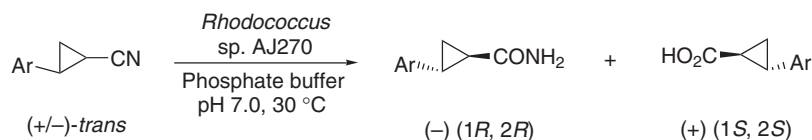
R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, MeO, MeS

<i>R</i>	Time	Recovered nitrile (%)	Config. ee (%)	Amide (%)	Config. ee (%)	Acid (%)	Config. ee (%)
Me	10			42	<i>R</i> , >99	48	<i>S</i> , 90
Me	13.5			36	<i>R</i> , >99	58	<i>S</i> , 67
Et	70			58	<i>R</i> , 35	39	<i>S</i> , >99
Et	96			34	<i>R</i> , 96	40	<i>S</i> , >99
<i>n</i> -Pr	150	55	<i>S</i> , 24	27	<i>S</i> , 41	8	<i>S</i> , >99
<i>n</i> -Pr	214	33	<i>S</i> , 28	40	<i>S</i> , 13	13	<i>S</i> , >99
<i>n</i> -Pr	120			47	<i>R</i> , >99	46	<i>S</i> , >99
<i>n</i> -Bu	300	36	<i>S</i> , 36	34	<i>S</i> , 20	23	<i>S</i> , 98
MeO	46			78	0		
MeO	72			56	0		
MeS	120			64	<i>R</i> , 15	10	<i>S</i> , 96

Scheme 31

(iii) Nitriles attached to three-membered rings

Wang's group has been a major contributor to work on the enzymic hydrolysis of nitriles. Most of their work have focused on cyclopropyl derivatives, and clearly the constraints of this ring allow the substrates to be accepted by the enzymes, provided that there is an aryl group vicinal to the nitrile—effectively 3-arylpropanonitriles. They have produced nice examples of this chemistry as exemplified in Scheme 32 <2002MI1575, 2001MI113> and they have also illustrated its application to the synthesis of chrysanthemic acid <2003JOC621>, which shows that the presence of methyl groups does not interfere with the enzymic hydrolysis. They have demonstrated that a wide range of aryl groups are accepted, and furthermore that the cyclopropane ring can be replaced by an oxirane ring without compromising the efficiency of the enzyme <2003JOC4570>.



Ar	Time (h)	(-) (1R, 2R)		(+) (1S, 2S)	
		Yield (%)	ee (%)	Yield (%)	ee (%)
C ₆ H ₅	2	47	51	53	33
C ₆ H ₅	4	22	77	77	8
4-ClC ₆ H ₄	4	52	58	47	44
4-ClC ₆ H ₄	6	37	68	59	20
4-MeC ₆ H ₄	6	54	57	42	59
4-MeOC ₆ H ₄	8	55	2	32	13

Scheme 32

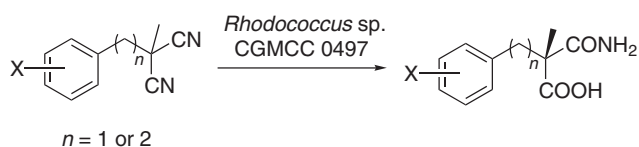
(iv) Dinitriles

Dinitriles often offer the possibility of desymmetrization as a route to generating optically pure products from a starting material that contains a plane of symmetry. Particularly useful has been work by Li's group on the hydrolysis of derivatives of malononitriles, again generally with aryl groups in the 3-position (Scheme 33) <2003JOC2479, 2003CC386>.

This rather elegantly extends the chemistry from allowing synthesis of α -arylglycines to phenylalanine derivatives, in which a range of substituted phenyl groups can be introduced. The chemistry works well with quaternary derivatives in which there is a methyl group on the α -position (which, of course, helps prevent racemization), and simple chemical manipulations can be used to exploit this chemistry to generate either the *R*- or the *S*-amino acid derivatives at the end of a synthetic sequence. The hydrolysis of other dinitriles to give mono- or diamides has also been studied <1998MI165, 1995TL8657>, including a detailed study of the hydrolysis of cyclohexano-1,2-dinitriles that are readily generated from Diels–Alder chemistry <1998TA1097>.

(v) Other nitrile hydratase substrates

Other examples of the use of hydratases, generally from *Rhodococcus* sources, include the hydrolysis of benzonitrile derivatives <1995TL9561, 1997JCS(P1)1099>, of β -hydroxynitriles, <2003JMOC(B)105> and of an unsaturated variant <2003OBC535>. All of these examples



Substrate	X	Yield (%)	ee (%)
$n = 1$	<i>p</i> -CH ₃	58	>99
	<i>p</i> -F	80	>99
	<i>p</i> -Cl	83	>99
	<i>p</i> -Br	81	>99
	<i>p</i> -MeO	58	>99
	<i>m</i> -Cl	85	98
	<i>o</i> -Cl	65	99
$n = 2$	H	96	>99

Conditions: 7 days at 20 °C.

Scheme 33

help to indicate that the range of substrates for which the use of hydratases might be worthwhile is perhaps very much larger than might have been thought, and it is undoubtedly worthwhile considering this approach when primary amides are the target.

5.06.1.3.2 Nonenzymic hydrolysis of nitriles

The selective hydrolysis of nitriles to amides has always suffered from the problem of over-hydrolysis, and the use of hydrogen-peroxide-based systems has traditionally been widespread. Whilst there have been developments in this and some other methods of selective nitrile hydrolysis, it has been the identification of Lewis acid catalysts that has really dominated the published literature since the early 1990s.

(i) Lewis acid-catalyzed selective hydrolysis of nitriles

Hydrolysis of nitriles has been well documented, particularly that by transition metal catalysts. To a large extent, this is because the systems have been of interest mechanistically, but relatively few of them have generated synthetic methods that can rival the alternative more traditional ones. A review on the hydration/hydrolysis by solid acids has a useful section on the hydration of nitriles, which gives a valuable summary up to 1997 of successful methods of generating amides <1997MI371>.

The use of platinum-containing catalysts has been studied in some detail by Parkin's group <1995TL8657, 1996MI169, 1996JOC45>. This has led to improvements to the catalysts so that a range of common substrates can now be hydrolyzed to the amide in high yield and with good turnover frequencies. It seems clear that these and other platinum-based catalysts <2000TL2467> are efficient enough for them to be of value in the commercial synthesis of amides. Alternative late transition metal catalysts that have been successfully employed include iridium complexes <1999MI535>, ruthenium complexes <1997MI297, 1995POL3111, 2002JCC587>, molybdenum complexes <2003OM1203>, and first-row transition metal catalysts, such as manganese dioxide supported on silica <2002SC1731> and zinc systems <2002IC4798>. The use of zeolites <2000MI118> and alumina catalysts <1995TL3469> has also been explored and may become a viable alternative.

(ii) Oxidative hydrolysis of nitriles

Fine-tuning of the traditional conditions of basic hydrogen peroxide hydrolysis has allowed improvements in the yield of amides from nitriles <1996MI767>, and this traditional hydrolytic method is still used in important syntheses <1999M1167>. It has been found that dimethyldioxirane can also be used in the hydrolysis of nitriles to amides, and clearly this reagent may be of particular value when basic hydrolysis of other functional groups is a competing problem <1997SC3119>. Supported reagents have also been used to simplify the hydrolysis of nitriles, such as amberlyst-immobilized hydroperoxide <1999IJC(B)974>, whilst more intriguing, and perhaps of greater practical use, is the employment of microwaves to accelerate the hydrolysis of nitriles to amides using aqueous sodium perborate <2001SC431>. All of these methods tend to focus on the commonest nitriles, for which the authors believe that the methodology would be of greatest value; there has been little attempt to explore the range and limitations of these hydrolytic methods, and a more systematic and extensive survey is required.

(iii) Other methods of selectively hydrolyzing nitriles to amides

Unfortunately, the selective hydrolysis of nitriles to amides often requires the testing of a range of reagents and conditions in order to find the best. For example, HBr in acetic acid gave an excellent 94% yield of a sugar-based amide, whereas transition metal-catalyzed hydrolysis gave only poor yields <2000TA1719>. The use of tetrachlorosilane/ethanol has also been found to be worthwhile <1997MI139>, as has the use of a silanolate <2000TL3747>. The hydrolysis of nitriles under much milder conditions can sometimes be achieved if there is anchimeric assistance <1996TL4569, 2001AG(E)2507>, whilst hydrolysis by water is beginning to be used, as exemplified by the photochemical hydrolysis <1995TL8941>, alkaline hydrolysis under microwave conditions <1995SC3007>, and the hydrolysis of nitriles in water at a high temperature <1997MI2048>. None of these methods would probably provide conditions of choice for the hydrolysis of nitriles, for which an enormous range of possible reagents are available, but they indicate that it is highly likely that very efficient conditions can ultimately be discovered provided a wide range is explored, and some of these may turn out to be of genuine commercial value and be important in laboratory syntheses as well.

5.06.1.4 Rearrangement Reactions

There has appeared a remarkable amount of published literature on the rearrangement routes to amides, probably because of the commercial value of many of the amide products that are generated. In only a relatively small number of examples is the methodology applied to a really wide range of substrates, and it is not always clear, therefore, whether the methodology is more widely applicable. Most of the examples cited here have been demonstrated to work on a reasonable range of substrates, and they are categorized under the main rearrangement processes involved.

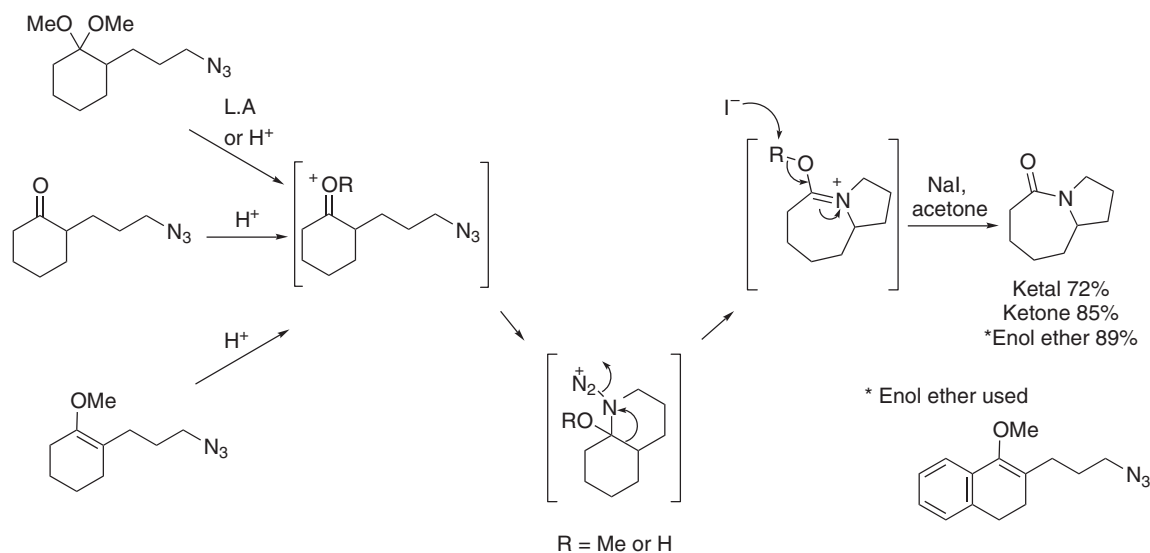
5.06.1.4.1 Beckmann rearrangement

The Beckmann rearrangement has been studied using nonmetallic and metal-based reagents, and in the former category the use of 2,4,6-trichloro[1,3,5]triazine has proved to be very efficient for a simple range of aryl oximes, and oximes derived from cyclohexanone derivatives <2002JOC6272>. Other nonmetallic reagents include triphenylphosphine and *N*-chlorosuccinimide <2002SC2535>, metaboric acid <2002TL2455>, and chloral <2003TL755>. Strong heating of simple oximes can also lead to the Beckmann rearrangement <2001TL8123>, and the use of microwaves to accelerate the reaction has also proved popular <2000JCR(S)482, 1998MI795, 1995SL1259>.

An enormous number of metal-catalyzed processes have been developed for the Beckmann rearrangement, most notably the use of rhodium catalysts <2001OL311>, perrhenate <1995BCJ373>, ytterbium triflate <2002JCR(S)236>, aluminum chloride <1998SC2275>, and zeolites <1998MI267, 2002SL625>.

5.06.1.4.2 Schmidt rearrangement

The Schmidt rearrangement requires the use of azides, and a simple modification is to use dimethoxyethane as the solvent in place of chlorinated solvents, which can be hazardous <1996T1609>. An elegant use of the Schmidt rearrangement has been developed by Aubé, in which an enolate is used to introduce an azide side-chain, which is then triggered to undergo the intramolecular Schmidt rearrangement reaction from the ketone, ketal, or enol ether (Scheme 34) <1995JA8047, 1995JA10449, 1996T3403>.



Scheme 34

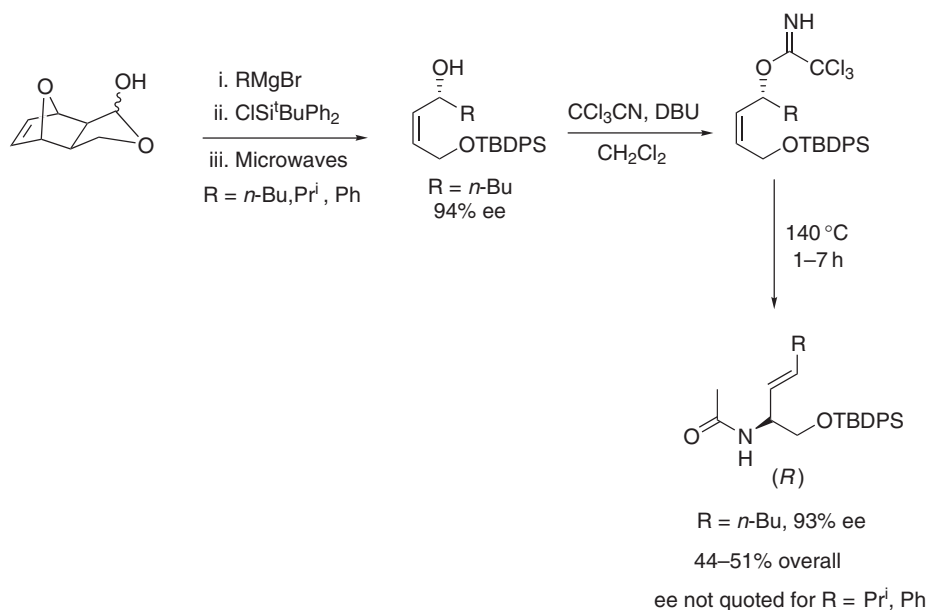
5.06.1.4.3 Claisen rearrangement

Claisen rearrangements come under three main classifications for the synthesis of amides; those in which an imino intermediate is within the rearranging “ring” transition state, those in which the imino group is exocyclic to the transition state, and those which do not possess an imino nitrogen. For imino-Claisen arrangements, the stereocontrol possible has been well illustrated by Bloch’s group (Scheme 35), <1999TL3735> and the trichloroacetimidates have also been exploited in the synthesis of nucleosides <1995TL4311>.

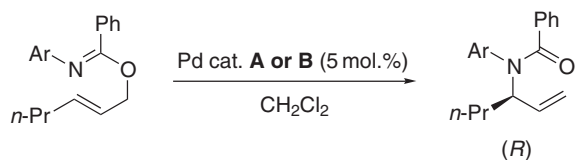
Overman’s group has perhaps made the greatest contribution to imino-Claisen rearrangements, with the development of a range of palladium catalysts that allow achiral precursors to undergo the rearrangement reaction to give chiral products <1997TL8837, 1998TA3213, 1999JA2933>; similar catalysts have also been developed by others (Scheme 36) <2002TL9509, 1998TA1065>.

More widespread are Claisen rearrangements involving imidates, which are then deprotonated in order to generate the rearrangement precursor. Asymmetric versions of this reaction have been developed by Metz’s group (Scheme 37) <1997JOC4442> and chiral auxiliaries on nitrogen have also been used (Scheme 38) <2002OL1383>.

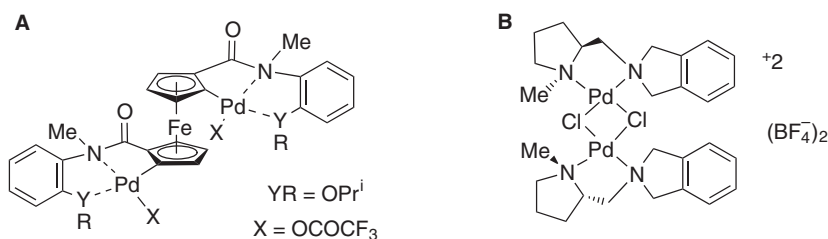
An enormously diverse range of structures is accessible by this Claisen rearrangement route <2000T9949, 2002SL411, 1995CC2325>. Examples also include cases in which the nitrogen is within the rearranging ring but not directly involved in the enolate intermediate, such as amide enolates (Scheme 39) <2003TL3521, 1999AG(E)3545> and ammonium enolates (Scheme 40) <1995JOC3773, 2002S242>. Aryl acetamides can be accessed through the Claisen rearrangement of aryl amidates <1998H367>, and the methodology has been used toward very complex targets such as porphyrin-related intermediates <1995LA1509>.



Scheme 35



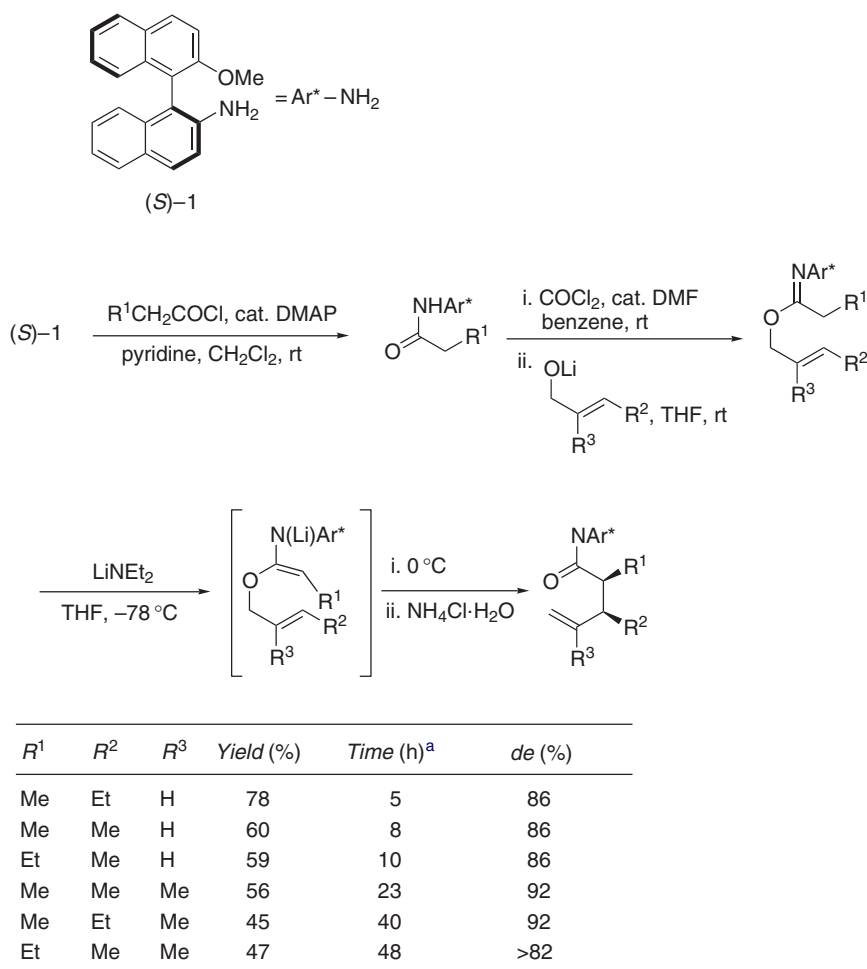
Ar = 4-CF₃C₆H₄; yield = 69%, 55% ee; 40 °C
 Ar = *p*-MeOC₆H₄; yield = 91%, 92% ee; 0.5 h, rt



Scheme 36

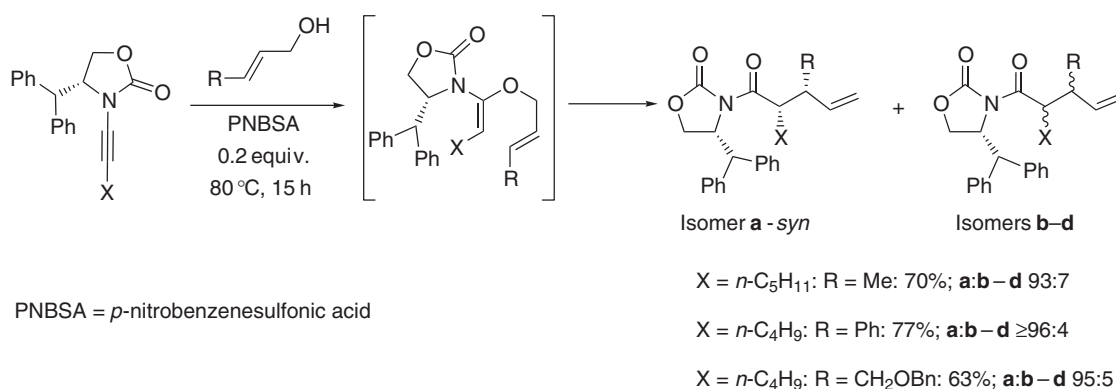
5.06.1.4.4 Wolff rearrangement

The Wolff rearrangement (see Section 5.06.1.4.4 in COFGT (1995) <1995COFGT(5)257>) involves the use of diazoketones to generate ketene intermediates that can be trapped by amines. Seebach's group has used this methodology to generate oligonucleopeptides <1997HCA1>. Other studies involving the photochemical Wolff rearrangement include both target synthesis <1995JOC3249> and more mechanistic studies <2001JOC5016, 2002JA13790>.



^a Rearrangement time (0 °C) after deprotonation.

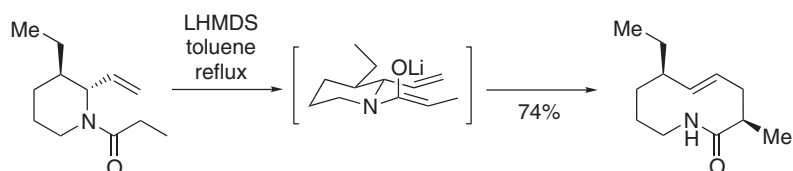
Scheme 37



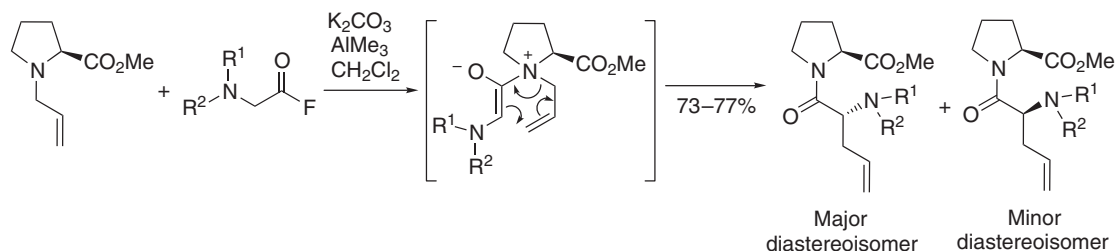
Scheme 38

5.06.1.4.5 Willgerodt rearrangement

Two examples of the Willgerodt rearrangement (see [Section 5.06.1.4.5](#) in COFGT (1995) <1995COFGT(5)257>) are typical of developments that have taken place since the early 1990s: the use of microwaves to accelerate this reaction <1995JOC2456>, and its inclusion in a review of combinatorial approaches <1999MI83>.



Scheme 39

(a) $R^1 = t\text{-BOC}$, $R^2 = \text{CH}_2\text{CH}(\text{OEt})_2$ dr = 15:1(b) $R^1, R^2 = \text{Pht}$ (c) $R^1, R^2 = \text{N}_2$ dr = 9.5:1 (at -20°C)

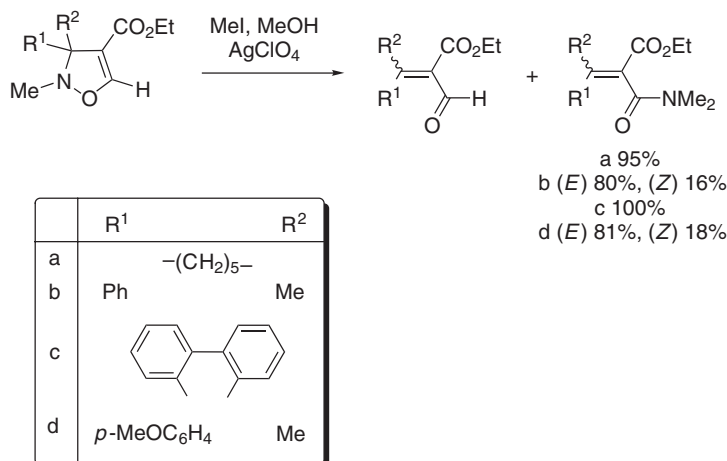
Scheme 40

5.06.1.4.6 Oxaziridine rearrangements

Reviews on the oxaziridine rearrangement [<1997CSR269>](#) and the chemistry of perfluorinated oxaziridines [<1996CRV1809>](#) are a rich source of information for oxaziridine rearrangements (see chapter 5.06.1.4.6 in COFGT (1995) [<1995COFGT\(5\)257>](#)). Developments in this area include the use of sodium perborate [<1997T3805>](#), and the photochemical accessibility of aziridines by this route [<2001OL3067>](#).

5.06.1.4.7 Other rearrangement processes

The photochemical rearrangement of enamides can be useful synthetically [<1996T2405>](#), whilst isoxazoline derivatives can be alkylated and ring opened to generate α,β -unsaturated amides [<2003JOC3718>](#) (Scheme 41).

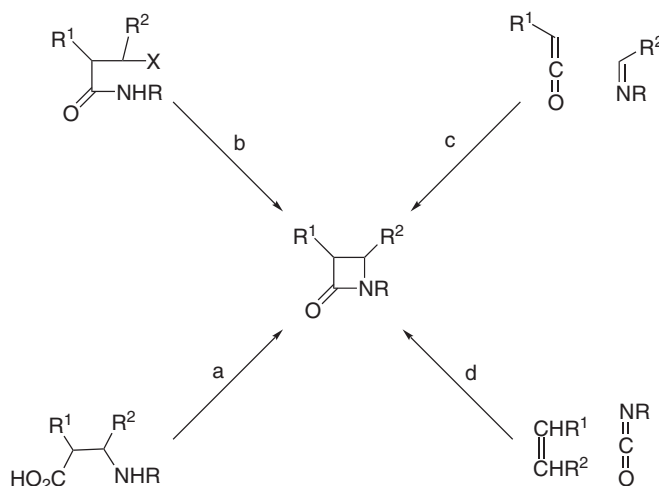


Scheme 41

5.06.1.5 Other General Methods

5.06.1.5.1 Special routes to β -lactams

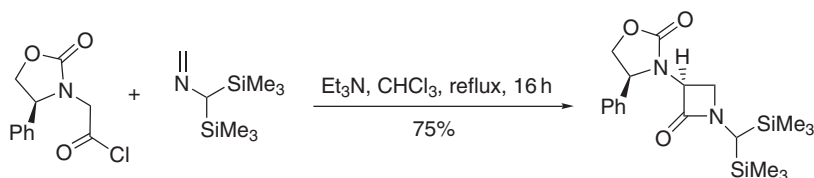
β -Lactams are usually prepared by one of four routes, as summarized in [Scheme 42](#). There have in fact been relatively few major developments in the synthesis of β -lactams since the early 1990s, although clearly the methodology has been refined and improved during this period.



Scheme 42

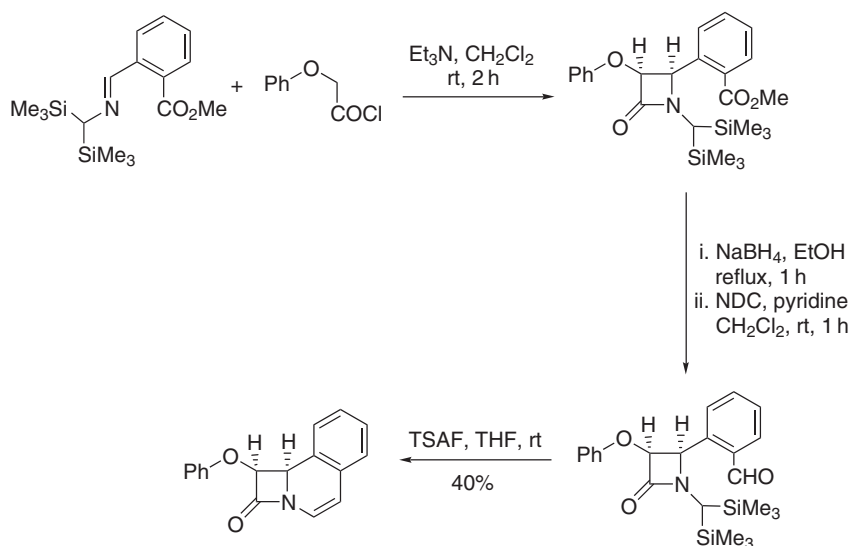
Importantly, Miller has utilized route b via the displacement of chloride or mesylate in order to generate β -lactams that were subsequently derivatized using Mn(III) in free-radical cyclization reactions [<1995H691>](#).

More developments have taken place using [2 + 2]-cycloaddition reactions, particularly the Staudinger reaction between a ketene and an imine. As in much of amide chemistry, the development of asymmetric versions has proved to be important, as outlined in the mini review by Palomo and co-workers [<1999EJO3223>](#). An improvement in the Staudinger chemistry has been facilitated by the use of bis(trimethylsilyl)methylamine, which not only helps to generate β -lactams in high yield ([Scheme 43](#)), but also generates a convenient protecting group on the nitrogen that can be readily elaborated and removed in the synthesis of more complex targets ([Scheme 44](#)) [<2000CJC1363>](#). The generality of the Staudinger approach is illustrated by the ferrocene-containing β -lactams prepared by Bonini's group [<2001SL1092>](#).



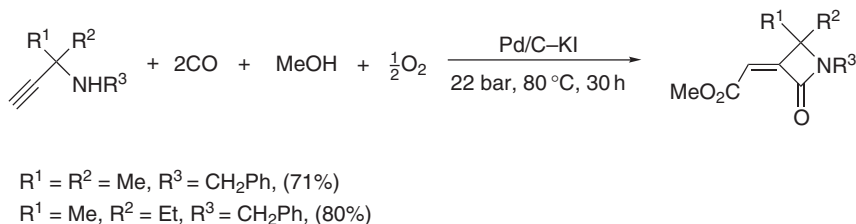
Scheme 43

The alternative [2 + 2]-cycloaddition process involves an ester enolate condensing with an imine, and a major review of this chemistry was published in 1996 [<1996MI119>](#). Kise's group has shown this with more recent synthetic work [<1999JOC7511>](#), in which an imine carbamate



Scheme 44

is generated *in situ* following an anodic oxidation. Other routes to β -lactams include the sulfur-directed radical cyclization [<1995JOC1276>](#), and a one-pot process, in which an alkynyl-amine is condensed with an alcohol and carbon monoxide under catalytic oxidative conditions (Scheme 45) [<1995TL7495>](#).

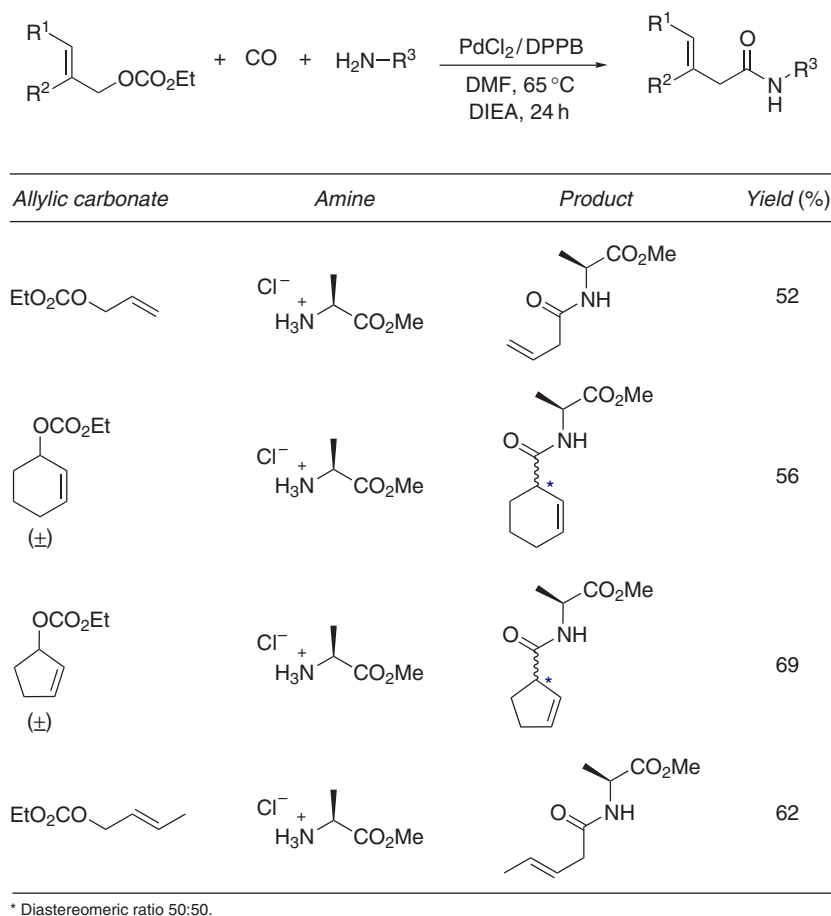


Scheme 45

5.06.1.5.2 Other routes to “normal” amides

A handful of completely different methods have been published for synthesis of amides. For example, α,β -unsaturated carbonates can be reacted with amines in the presence of carbon monoxide and a palladium(II) catalyst to generate β,γ -unsaturated intermediates (Scheme 46) [<1999TL2649, 2003OBC541>](#).

The classical Ugi-type condensation also continues to be widely used, not least because of the ease with which combinatorial libraries can be generated [<2002TL8467>](#). β -Aryl- α,β -unsaturated amides can be prepared using carbonyl condensation chemistry [<2001SC1201>](#) and α,β -unsaturated systems can also be prepared using 3,3,3-trifluoro-1-propynylamines with carbonyl compounds [<1999CL855>](#), whilst carbamoyl chlorides can be reacted selectively with Grignard reagents to give amides in good yield [<2000TL9997>](#). Acyliminium ion chemistry has been developed by Kobayashi [<2001JCO401>](#) and used with a solid phase catalyst; in this chemistry, the amide is effectively already in place, and activates the $\text{N}=\text{C}$ system to nucleophilic attack, thereby allowing a range of substituents to be introduced. Problems associated with synthesizing enamides might be overcome by isomerization chemistry, in which a remote double bond is moved into conjugation using organometallic reagents such as iron pentacarbonyl [<2003HCA750>](#).



Scheme 46

In Sections 5.06.2–5.06.5, the synthetic routes to the various patterns of substituted amides are summarized in tables, subdivided into reaction types for easy reference to Section 5.06.1. The absence of a table relating to a particular pattern of amide or type of reagent indicates that no key synthetic methods relating to this specific transformation have been selected for this review. However, as stressed in the introduction (Section 5.06.1.1), it is highly likely that other methods that have been shown to work for one type of amide will be applicable to another.

5.06.2 AMIDES OF ALKANOIC ACIDS

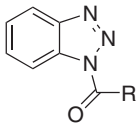
5.06.2.1 *N*-Unsubstituted Alkanoamides

5.06.2.1.1 *Methods from simple esters*

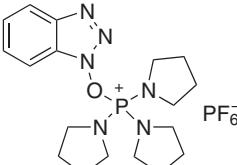
Reagent/catalyst/conditions	Reference	Cross-reference	Comments
CAL-B/NH ₃			
	<2002OPRD420>	E	93% and 98% ee

E = enzymic.

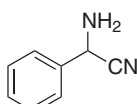
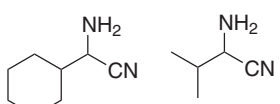
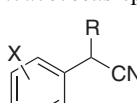
5.06.2.1.2 *Methods from active esters*

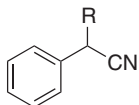
Reagent/catalyst/conditions	Reference	Cross-reference	Comments
 R = <i>n</i> -Bu, Bn, PhCH ₂ CH ₂	<2000JOC8210>		Three examples, yields 75%, 85%, and 100%

5.06.2.1.3 *Methods using phosphorus reagents*

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
 pyBOP	<1999TL2501>		Four examples, yields 85–95%

5.06.2.1.4 *Hydrolysis of nitriles*

Reagent/catalyst/conditions	References	Cross-references	Comments
<i>Rhodococcus</i> sp. <i>R/S</i> -phenylglycine nitrile 	<2001JOC(B)249>	E/KR	D-PhGly 48%, >98% ee, L-PhGly 52%, 97% ee
<i>R. rhodochrous</i> MAWE Penicillin G acylase (E.C. 3.5.1.11) D-Phenylglycine nitrile <i>R/S</i> -Phenylglycine nitrile <i>Rhodococcus</i> sp. AJ270	<2002MI356> <2002TA2629>	E E/KR	Tandem one-pot reaction Various enzymes used
	<2002JOC6542>	E/KR	Two aliphatic nitriles used, amides, 45%, 88% ee, and 48%, 22% ee
<i>Rhodococcus</i> sp. CGMCC 0497  R = Me, Et, <i>n</i> -Pr X = X, NO ₂ , OMe at various positions	<2001TA3305>	E/KR	10 examples studied, amide yields >40%, most ee values >98% by HPLC

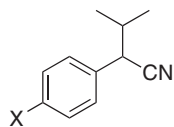
Rhodococcus sp. AJ270

R = Me, Et, *i*-Pr, *n*-Pr,
n-Bu, MeO, MeS

<2000TA1123>

E/KR

Seven substituted benzene
examples for R = Me, *i*-Pr,
yields >36%, ee values >99%

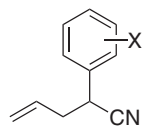
Rhodococcus sp. AJ270

X = H, F, Cl, Br, OMe

<2001JMOC(B)77>

E/KR

Five substituted benzyl
examples, three amide
yields >39%, ee values >99%

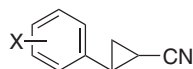
Rhodococcus sp. AJ270

X = H, F, Cl, OMe, Me
at various positions

<2002TA1695>

E/KR

Seven benzyl substituted
examples, five yields >44%,
ee values >99%

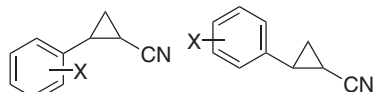
Rhodococcus sp. AJ270

X = H, F, Cl, OMe, Me
at various positions

<2002TL6617>

E/KR

Seven benzyl substituted
examples, five yields >44%,
ee values >99%

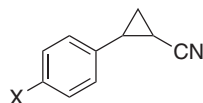
Rhodococcus sp. AJ270

X = H, F, Cl, OMe, Me
at various positions

<2002MI1575>

E/KR

Seven benzyl substituted
examples, five yields >29%,
all five ee values >99%

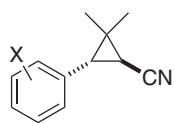
Rhodococcus sp. AJ270

X = H, F, Cl, OMe, or Me

<2001MI113>

E/KR

Five benzyl substituted
examples, three yields >38%,
all five ee values >99%

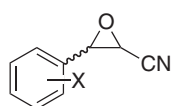
Rhodococcus sp. AJ270

X = H, F, Cl, OMe, Me
at various positions

<2003JOC621>

E/KR

Seven benzyl substituted
compounds studied

Rhodococcus sp. AJ270

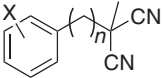
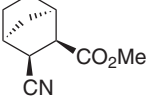
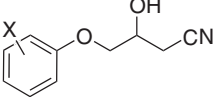
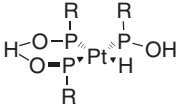
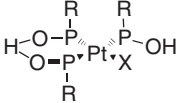
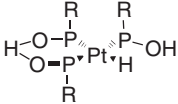
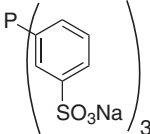
X = H, F, Cl, Me
at various positions

<2003JOC4570>

E/KR

Five benzyl substituted
compounds studied,
four yields >42%,
ee values >99%

Continued

Reagent/catalyst/conditions	References	Cross-references	Comments
Rhodococcus sp. CGMCC 0497			
 <p>X = F, Cl, Br, OMe, Me at various positions and n = 1 or 2</p>	<2003CC386>	E/KR	Eight aryl substituted examples studied, five yields >80%, ee values >99%
Rhodococcus rhodochrous IFO 15564			
	<1998TA1097>	E/KR	Low yields and ee values
Rhodococcus sp. CGMCC 0497			
 <p>X = Br, NO₂, OMe, t-Bu at various positions</p>	<2003JMO(B)105>	E/KR	Six aryl substituted examples studied, yields varied, 9–64%, ee values varied, 35–87%
Acetonitrile Na ₂ PdCl ₄	<1997MI371>		Conversion 23%
Acetonitrile Zn(OAc) ₂	<1997MI371>		
Succinonitrile Nb ₂ O ₃	<1997MI371>		Conversion 70%
 <p>R = Me₂</p>	<1995TL8657>		Amide yield 91%
Acetonitrile			
 <p>R = Ph₂, X = H, or Cl R = Me₂, X = H, or Cl R = -(CH₂)₄-, X = Cl</p>	<2000JMO(A)249>		Amide yield 91%
Acetonitrile			
 <p>R = Me₂</p>	<2000TL2467>		Six amine “traps” used, 3° amides formed, all yields >51%
Ir (H)(CO)(TPPTS) ₃ where TPPTS is			
	<1999MI535>		Five examples, yields 38–89% by NMR
For R-CN where R = Me, Hex, CH ₂ Cl, and NC(CH ₂) _n CN where n = 2 or 4			
[Cp' Mo(μ-OH) ₂ Mo Cp'] ₂ (OTs) ₂ (where Cp' = η ⁵ -CH ₃ C ₅ H ₄)	<2003OM1203>		Four alkyl examples, all yields >90%

$\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}:$ in 1:4 ratio	<2002IC4798>		Seven aliphatic compounds studied, six yields 46–86%, other catalysts surveyed
NaY zeolite succinonitrile	<2000MI118>	C	Yield 35%
Unactivated alumina	<1995TL3469>	C	Five simple alkyl compounds, all yields >60%
$\text{H}_2\text{O}_2/\text{conc. NH}_3$	<1996MI767>		$\text{CH}_3\text{CHNH}_2\text{CN}$ only, kinetic model study
DMDO 2-Chloroacetonitrile	<1997SC3119>		Yield 55%
Amberlyst A26(OH [−]) H_2O_2	<1999IJC(B)974>	SPS	Six examples, three dinitriles, yields 85–97%
$\text{NaBO}_3/\text{microwave}$			
 	<2001SC431>		Three examples, yields 87–92%
HBr/AcOH			
	<2000TA1719>		Yield 83%, no racemization
KOSiMe_3	<2000TL3747>		Three examples, 32%, 67%, 69%, simple work-up
$\text{HCl(g)}/\text{Et}_2\text{O}/\text{H}_2\text{O}$			
	<1996TL4569>		All high yields, substrate specific
Where R^2 is H or Me and R^1 is Me, Et, <i>n</i> -Pr, <i>t</i> -Bu			
$\text{BF}_3 \cdot \text{OEt}_2$			
	<2001AG(E)2507>		All high yields
Where R^1 is H, <i>n</i> -Bu and R^2 is H, Me, Et, <i>n</i> -Bu and R^3 is H or Me			
	<1995TL8941>		Only two examples
R = H or Me			
$\lambda > 280 \text{ nm}/\text{MeOH}$			
$\text{H}_2\text{O}/\text{high T/P}$	<1997MI2048>		Only MeCN, kinetic study

KR = kinetic resolution, E = enzymic, C = clays/zeolites, SPS = solid-phase synthesis/reagent.

5.06.2.2 *N*-Alkylalkanoamides

5.06.2.2.1 *Methods from carboxylic acids*

Reagent/catalyst/conditions	References	Cross-references	Comments
Δ /sublimation Pivaloyl pyruvic acid H–Y zeolite/AcOH	<2001JCS(P2)522>	C	Only one example Only four examples Six examples, most benzylic amines, five yields >95%
Fe^{3+} /K-10 montmorillonite	<2003JOC1165>	C	Seven examples, most benzylic amines, yields 87–95%
Fe^{3+} /K-10 montmorillonite AcOH/propionic acid/ butyric acid	<2001MI207>	C	Nine examples, most benzylic amines, eight yields >97%
AcOH/propionic acid/butyric acid Fe^{3+} (other metal ions claimed) K-10 montmorillonite	<2001USP6215024>	C	Nine examples, seven yields >95%
Fe_2O_3 /C amberlyst IRC-50	<2003JMOC(A)141>	C	Three examples, yields >95%
Lipozyme [®] /hexane	<1997T7587>	E	Only one example
Lipozyme [®] /novozym hexane/ <i>t</i> -butanol	<1998JMOC(B)13>	E	Only one example

E = enzymic, C = clays/zeolites.

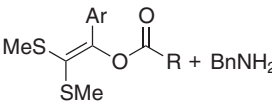
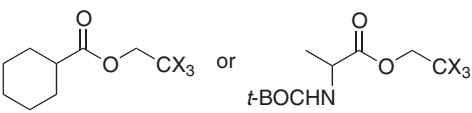
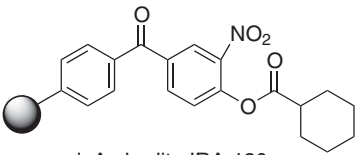
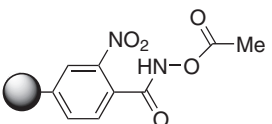
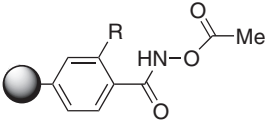
5.06.2.2.2 *Methods from simple esters*

Reagent/catalyst/ conditions	References	Cross-references	Comments
$\text{Cp}^*_2\text{Sm}(\text{THF})_2$ Acyl Donor	<1996JOC3088>		Vinyl acetate best several amines used
In + I_2 “ InI_3 ” Ethyl Acetate	<2000JCS(P1)2223>		Only 7 examples, yields >80%
AlCl_3 or ZrCl_4	<1996TL3213>	SPS	11 Examples, 7 yields >45%, All purities >84%
Coumarin/WA21J resin	<1999TL1241>	SPS	Good diversity of amines used most yields 65–97%
$\text{CF}_3\text{CO}_2\text{Et}$ Bis amine	<1995TL7357>		GC yields only
Acyl donor/LIP-300 or LPL-311	<2002TL5529>	E Res	Variable ee's, most benzylic amines
CAL-B/EtOAc	<2002TA1315>	E Res	Yields 90%, ees >98%
Novozym [®] 435/ $\text{MeOCH}_2\text{CO}_2\text{Me}$ (<i>Candida antarctica</i>)	<2002USP6387692>	E Res	Mostly benzylic amines
Amano P or DSM 8246/ $\text{MeOCH}_2\text{CO}_2\text{Et}$ (<i>Pseudomonas</i> lipase)	<1998USP5728876>	E Res	
Novozym [®] 435/ $\text{ROCH}_2\text{RCO}_2\text{R}$	<2001USP6214608>	E Res	
Aminoacylase I (E.C. 3.5.1.14) methyl methoxyacetate (<i>Aspergillus melleus</i>)	<2001TA3267>	E	Mostly benzylic amines, ees 12–72%
Aminoacylase I (E.C. 3.5.1.14) Vinyl acetate	<1995SL599>	E	Variable yields, ees 66–98%

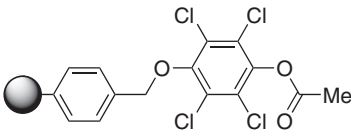
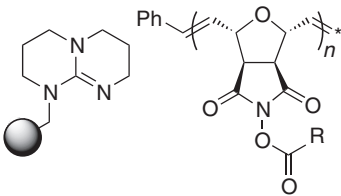
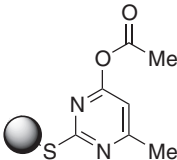
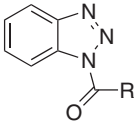
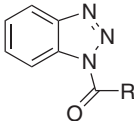
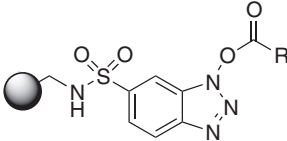
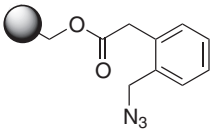
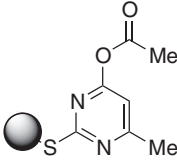
Reagent/catalyst/ conditions	References	Cross-references	Comments
Clostripain Protease (E.C. 3.4.22.8)/ Bz-Arg-OEt	<2000JOC1672>	E	Many Amines used No yields given
Clostripain Protease (E.C. 3.4.22.8)	<2000MI463>	E	2 Acyl donor examples
Subtilisin Carlsberg (E.C.3.4.21.14)/ Vinyl butyrate	<2002JA1871>	E	V. specific example
Thiolsubtilisin/EtOAc	<2002MI24>	E	Low conversions Amino acids and amines used, no ees given
Horse Liver Acetonic Powder (PAFC)/butyl butyrate	<1995BSB161>	E	Only cyclic 2° amines used
Penicillin G Amidase/Methyl Phenoxyacetate	WO01/07438	E	V. specific for <i>cis</i> β -lactams

E = Enzymic, E Res = Enzymic Resolution, SPS = Solid Phase Synthesis/Reagent.

5.06.2.2.3 Methods from active esters

Reagent/catalyst/conditions	References	Cross-references	Comments
 R = Me or <i>t</i> -Bu	<1999S1200>		Four examples, yields 84–97%
 X = Cl or Br (Me ₂ N) ₃ P	<2000JOC2114>		Three examples, yields 57–88%
 i. Amberlite IRA-120 ii. BEMP support/ polymeric trisamine	<1999SL1957>	SPS	Two Acids, five amines, yields 33–97%, purities 63–99%
	<1997MI863>	SPS	Three Resins used, two examples, yields 42–72%
 R = H or NO ₂	<1997MI169>	SPS	Four Resins used, two examples, yields 43–73%

Continued

Reagent/catalyst/conditions	References	Cross-references	Comments
	<2001JCO604>	SPS	Four alicyclic anhydrides, used conversion 93–100%
 <p>R = Cy or FMOCAIa</p>	<2000OL261>	SPS	Two acylation reagents with eight amines, yields 90–98%, purity >95% by GCMS
	<2002H369>	SPS	Four amine examples, yields 74–90%, no purities given
 <p>R = C₅H₁₁ or <i>t</i>-BOCAIa</p>	<2002BMCL1809>	SPS	Two examples, six amines, HPLC yields 40–95%
 <p>R = Bn or Ph₂CH</p>	<2000JOC8210>	SPS	12° and 23° amides made, yields, 70%, 68%, and 98%
 <p>R = various alkyl</p>	<1997JOC2594>	SPS	Nine examples, all yields >64%
	<1998TL4773>	SPS	Five acid examples, yields 69–100%, purities 79–82%
 <p>Microwave</p>	<2002TL6507>	SPS	Only one acid example, yield 47%

SPS = solid-phase synthesis/reagent.

5.06.2.2.4 Methods from acid anhydrides

Reagent/catalyst/conditions	References	Section/cross-references	Comments
Neat amine/excess anhydride			Cyclohexylamine, 79%
Yttria–zirconia catalyst	<2002JMOC(A)207>		Aminoethanol, 94%
Yttria–zirconia catalyst	<2001SL206>		Three examples, one 3° amide, yields 91–99%
V(O)(OTf) ₂	<2001OL3729>		Diisopropylamine only, yield 97%
Cu(OTf) ₂	<1999TL2611>		<i>t</i> -Butylamine only, yield 92%
Mn(III) salen	<2001JMOC69>		Phenylethylamine only, yield 96%
Montmorillonite K-10 or KSF	<1998JCS(P1)1913 ^a >	C	Diisopropylamine only, yield 98%
Ac ₂ O/HBF ₄ /SiO ₂	<2003TL3521>	C	One example, 90%
LiBr or LiCl/anhydride	<1997USP5594134>		No yields given
Cycloalkyl amide			

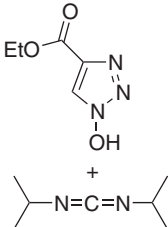
C = clays/zeolites, ^a see also <2003TL3521>.

5.06.2.2.5 Methods from acyl halides

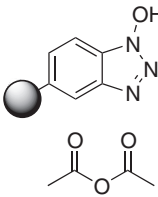
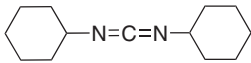
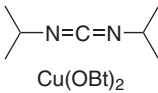
Reagent/catalyst/conditions	References	Cross-references	Comments
Prolinamide/RCOCl	<1998TL6991>		Three examples, yields >80%
sodium 2-ethylhexanoate			
Prolinamide/RCOCl	<2001USP6211384>		Three examples, yields >80%
sodium 2-ethylhexanoate			
EtCOCl/Pyr	<1998S1463>		Three examples, yields 53–73%
RCOF/hydrazide/BTSA ^a	<1995TL6013>		Three examples reported, yields 44%, 46%, and 64%
RCOF/silane or silazane	<1996EUP709366>		

SPS = solid-phase synthesis/reagent, ^a BTSA = bistrimethylacetamide.

5.06.2.2.6 Methods using diimides

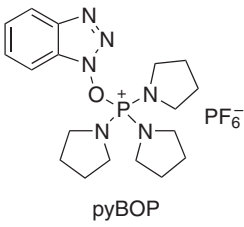
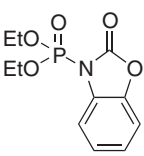
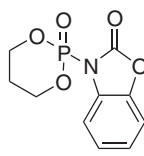
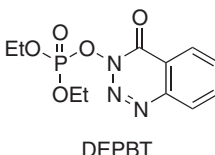
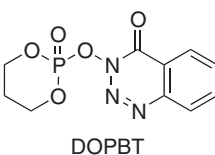
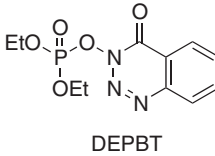
Reagent/catalyst/conditions	References	Cross-references	Comments
PS-carbodiimide/MP-carbonate	<2001TL6703>	SPS	Three examples, one amine used, yields 88–99%, purities 85–94%
PS-DMAP			
SS-EDC/Mosher's acid amino acid	<1996TL7171>	SPS	12 Examples, yields 71–95%, no purity data
	<1999T2713>	SPS	Low racemization
DCC/acid/amine	<2001TL2617>	SPS-KR	

Continued

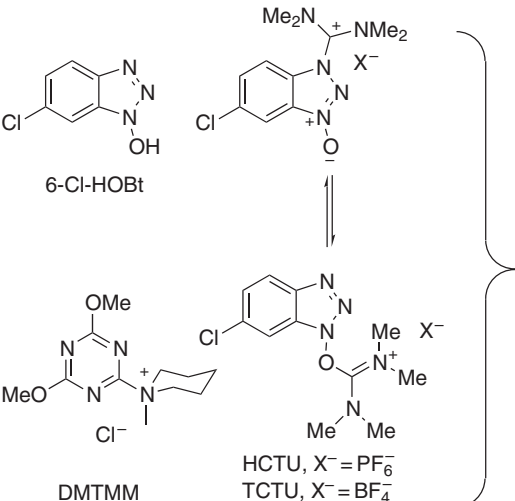
Reagent/catalyst/conditions	References	Cross-references	Comments
	<1998CC499>	SPS	11 Examples, yields 83–99%
			
	<2000OL1815>	SPS	One example, low racemization
Diisopropylcarbodiimide/ 2-bromoacetic acid/Rink amide	<2002JCO329>	SPS	Library synthesis

SPS = solid-phase synthesis/reagent, KR = kinetic resolution.

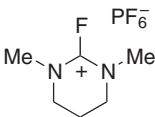
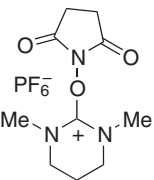
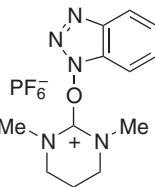
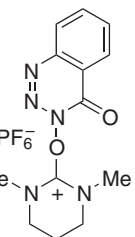
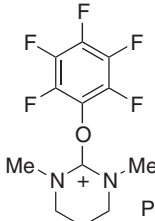
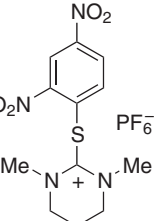
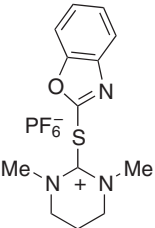
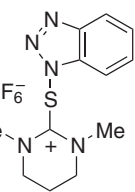
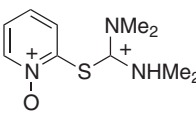
5.06.2.2.7 Methods using phosphorus reagents

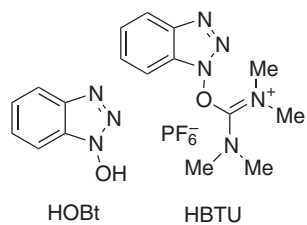
Reagent/catalyst/conditions	References	Cross-references	Comments
	<1999TL2501>		Five examples, yields 85–95%
			
			
			
			
	<1996SC1455>		Seven examples, yields 66–94%, solution synthesis

5.06.2.2.8 Methods using uronium salts

Reagent/catalyst/conditions	References	Cross-references	Comments
 <p>6-Cl-HOBt</p> <p>DMTMM</p> <p>HCTU, $X^- = PF_6^-$ TCTU, $X^- = BF_4^-$</p>	<p><2002MI119></p> <p><2002MI125></p>	<p>SPS</p> <p>SPS</p>	<p>All combinations used, TCTU/6-Cl-HOBt best</p> <p>Low racemization with 6-Cl-HOBt</p>

Continued

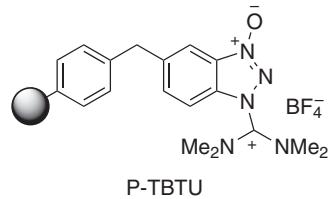
Reagent/catalyst/conditions	References	Cross-references	Comments			
 <p>HDPyF</p>	 <p>HDPyOSu</p>	 <p>HDPyOBt</p>	 <p>HDPyDhBt</p>			
 <p>HDPyOPfp</p>	 <p>HDPySDnp</p>	 <p>HDPySBox</p>	 <p>HDPySBt</p>	<1999MI273>	SPS	
 <p>HOTT X⁻ = PF₆⁻ TOTT X⁻ = BF₄⁻</p>	<1999JOC8936>	SPS	23 Examples, 10 peptides prepared, 17 yields >68%			



<2002HCA2409>

SPS

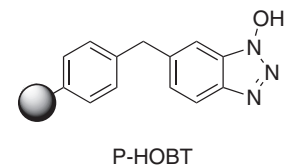
14 Examples
reported, HPLC
yields 75–99%,
purities 53–90%



<2000TL2463>

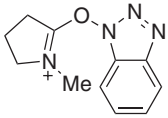
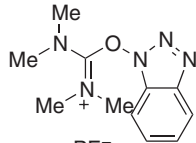
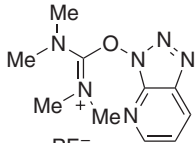
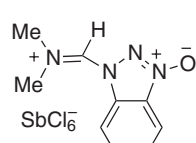
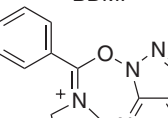
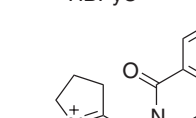
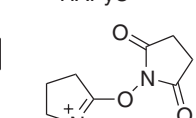
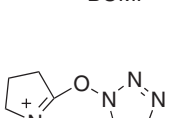
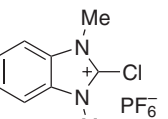
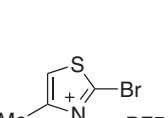
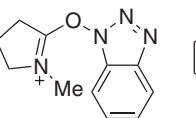
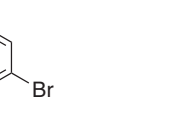
SPS

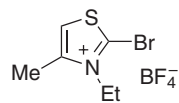
12 Peptides prepared,
seven yields >70%



SPS = solid-phase synthesis/reagent.

5.06.2.2.9 Methods using iminium salts

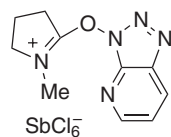
Reagent/catalyst/conditions	References	Cross-references	Comments			
 SbCl ₆ ⁻ BDMP	 PF ₆ ⁻ HBPYU	 PF ₆ ⁻ HAPyU	 SbCl ₆ ⁻ BOMI			
 SbCl ₆ ⁻ BPMP	 SbCl ₆ ⁻ DOMP	 SbCl ₆ ⁻ SOMP	 SbCl ₆ ⁻ AOMP	 <2000T4437> 		BPMP gave highest yield, with model peptide (96%)
 PF ₆ ⁻ CMBI				 <2000T9949> 		10 Examples reported, CMBI with N-MeAAs, 8 yields >90%
 BF ₄ ⁻ BEMT	 SbCl ₆ ⁻ BDMP	 BF ₄ ⁻ BEP		 <2000JOC2951> 	SPS	BEP/BEMT w/HOAt, low racemization used in solution



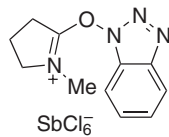
BEMT

<1999TL8301>

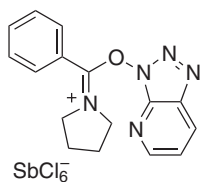
Seven AAs prepared,
all yields >86%



AOMP

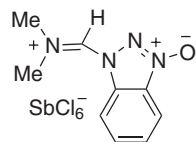


BDMP



BPMP

<2000TL721>

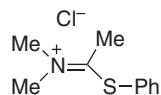


BOMI

<2000MI110>

SPS

Eight peptides
prepared, all
yields >85%

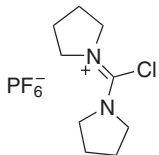
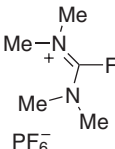
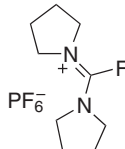
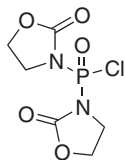
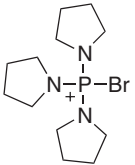
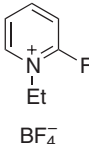
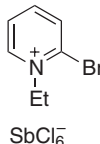
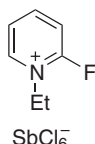
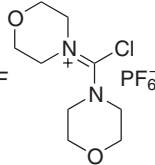


CPMA

<2002TL7595>

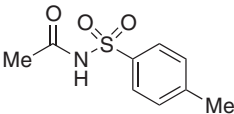
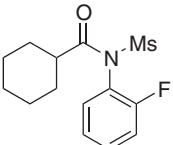
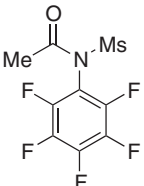
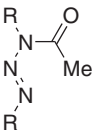
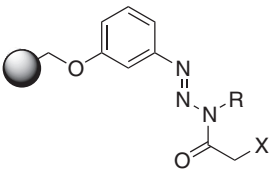
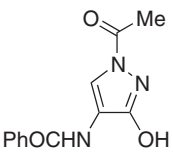
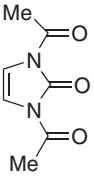
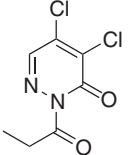
One example, 100%

Continued

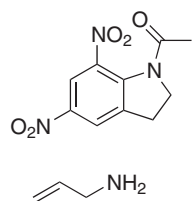
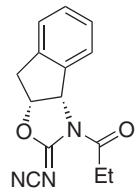
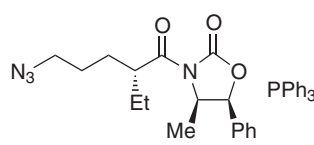
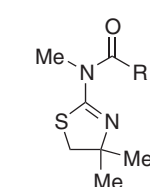
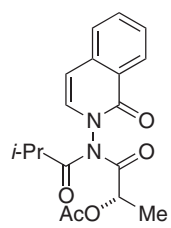
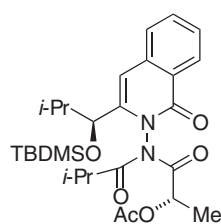
Reagent/catalyst/conditions	References	Cross-references	Comments			
 PyCIU	 TFFH	 BTFFH	 BOP-Cl			
 PyBroP	 FEP	 BEPH	 FEPH	 CMMM	<p><2000MI456></p>	One peptide example comparison of reagents

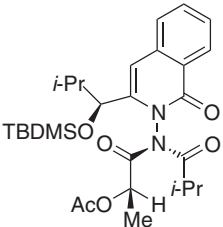
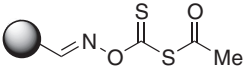
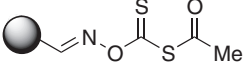
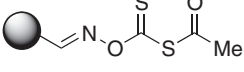
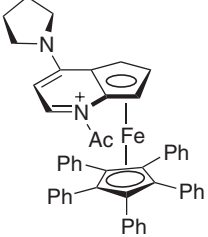
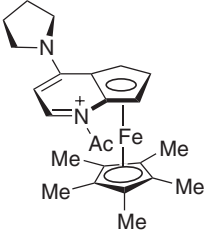
SPS = solid-phase synthesis/reagent.

5.06.2.2.10 Other acylation methods

Reagent/catalyst/conditions	References	Cross-references	Comments
	<1995IJC(B)1102>		Two examples of 2° amides, yields 30–45%
	<1998JCS(P1)2973>		Seven examples, five yields 76–91%
	<2000T5843>		Seven examples, 2°/3° amides, five yields 76–92%
	<2001TL6659>		Five triazenes, 14 amines, 24 yields 81–98%
 <p>X = H, Cl, or Br</p>	<2000JCO710>	SPS	Three acids used, library synthesis
	<1998MI455>		One example 67%
	<1999USP5994557>		Ten examples given, all yields >90%
	<2002S733>		Four examples, all yields 84–98%

Continued

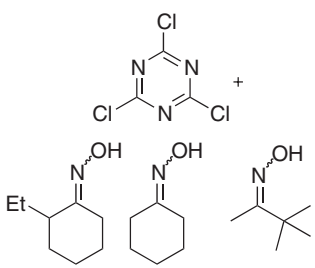
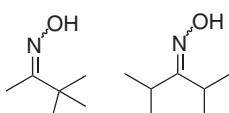
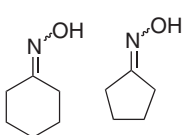
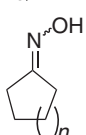
Reagent/catalyst/conditions	References	Cross-references	Comments
	<2001SL1968>		Eight amine examples, six alkyl acids, 10 yields 81–100%
	<2001T9309>	KR	Four examples, best yield 87%, best ee 65%
	<1999AG(E)3545>		One example, 74%
 <p>R = Me, Et, and <i>t</i>-Bu</p>	<2002TL9553>		Four examples tested, with three amines, nine yields >81%
	<1996JCS(P1)1047>		Chiral acylation, two examples moderate, selectivities
	<2000JCS(P1)4413>		Chiral acylation

Reagent/catalyst/conditions	References	Cross-references	Comments
	<2000MI43>	KR	Two amines resolved, yields >77% de values >88%
		SPS	Three resins tested, only two simple amines used, yields 48–58%
	<1997PIA49>	SPS	Three resins tested, only two simple amines used, yields 48–58%
	<2000MI161>	SPS	Three resins tested, one acid, two simple amines used, yields 43–64%
	<2000MI119>	KR	Only benzylic amines used, ee values 66–91%
	<2000AG(E)234>	KR	Only benzylic amines tested, selectivities 11–27%
PPh ₃ /NBS	<1997TL5539>		10 Examples reported, nine yields >81%
SmI ₂	<1996JOC359>		Four sugar substrates, yields 69–85%
SmI ₂ /TFAA or Ac ₂ O	<1999T11755>		10 Benzylic amines used, six yields >80%
LiHMDS/RCOCl, R = alkyl	<1998JOC2062>		Six examples, five yields >70%
Penicillin acylase pH11 (E.C. 3.5.1.11) phenylacetamide	<2000TA4593>	E	
Penicillin acylase pH10 (E.C. 3.5.1.11) phenylacetamide	<2001TA1645>	E	All amines contain Ph Group, ee values >96%
Penicillin G acylase	<WO0220821>	E	
Penicillin G acylase	<WO0220820>	E	

SPS = solid-phase synthesis/reagent, KR = kinetic resolution.

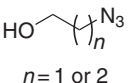
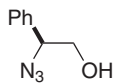
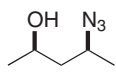
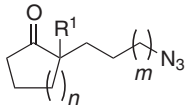
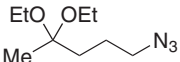
5.06.2.2.11 Rearrangement reactions

(i) Beckmann rearrangement

Reagent/catalyst/conditions	References	Cross-references	Comments
	<2002JOC6272>		12 Examples, yields 60–100%
NCS/PPh ₃ oxime/amide	<2002SC2535>		One example 82%, nitrile side-reaction
Ketoxime/(HBO ₂) _n cyclohexanone oxime	<2002TL2455>		One example, yield 62%
Chloral cyclohexanone oxime	<2003TL755>		One example, yield 67%
Ketoxime·HCl salt/Δ cyclohexanone oxime	<2001TL8123>		One example, yield 72%
Ketone/NH ₂ OH·HCl NaHSO ₄ /SiO ₂ microwave	<2000JCR(S)482>		Cyclohexanone oxime yield 85%
Ketone/NH ₂ OH·HCl HCO ₂ H/SiO ₂ microwave	<1998MI795>		Two examples, yields 40% and 52%
K10 Montmorillonite oxime/microwave	<1995SL1259>		Cyclohexanone oxime yield 21%
[RhCl(COD)] ₂ /CF ₃ SO ₃ H P(<i>p</i> -Tol) ₃ /Δ			
	<2001OL311>		Two examples, yields 71% and 30%
Bu ₄ NReO ₄ /pTsOH/Δ ketone/NH ₂ OH·HCl or oxime	<1995BCJ373>		Four examples, all yields >84%, oximes best
Oxime/Yb(OTf) ₃ /Δ			
	<2002JCS(S)236>		Yields 78% and 83%
AlCl ₃ /oxime/Δ			
	<1998SC2275>		Four examples, yields ~100%
For <i>n</i> = 1, 2, or 3			
H-Beta zeolites or H-ZSM-5 zeolite	<1998MI267>	C	Solid or liquid phase, two examples
Ketone/NH ₂ OH·HCl HY zeolite/microwave	<2002SL625>	C	Cyclohexanone oxime only, yield 95%

C = clays or zeolites.

(ii) Schmidt rearrangement

Reagent/catalyst/conditions	References	Cross-references	Comments
NaN ₃ /McSO ₃ H/DME	<1996T1609>		Five ketones/ β -keto esters, three yields >79%
 $n = 1 \text{ or } 2$			
	<1995JA8047>		Many cyclic ketones and Lewis acids studied, seven yields >80%
			
			
R ¹ = H, Me, CO ₂ Me/Et $n = 0, 1, 2, 3, 4, 8$ $m = 0, 1, 2, 3$ Lewis acid, e.g., TFA	<1995JA10449>		Several fused bicyclic lactams formed
	<1996T3403>		Four examples, yields 68–95%
TFA/TMSOTf			

(iii) Claisen rearrangement

Reagent/catalyst/conditions	Reference	Cross-references	Comments
CH ₃ C(OMe) ₂ NMe ₂ or CH ₂ C(OEt)(NMe ₂)/ Δ	<1998H367>		Only 1 example, low yield

(iv) Wolff rearrangement

Reagent/catalyst/conditions	References	Cross-references	Comments
α -diazoketone/h ν or Ag + LiCl or LiClO ₄	<1997HCA1>		Method appears general, only 2 amino acids used, yields 75–93%
α -diazoketone/h ν /amine	<1995JOC3249>		1 example 87%



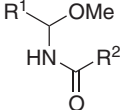
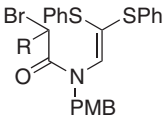
(v) Willgerodt rearrangement

Reagent/catalyst/conditions	References	Cross-references	Comments
PhCOMe or styrene S ₈ /py/NH ₃ Microwave reactor	<1995JOC2456>		Only 2 examples, need high P/T
p-Hydroxyacetophenone or styrene/S ₈ /py/NH ₃ Microwave reactor	<1999AJC83>		Other microwave, uses discussed

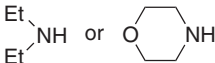
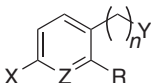
(vi) Oxaziridine rearrangement

Reagent/catalyst/conditions	References	Cross-references	Comments
Aldimine/ $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ /TFA	<1997T3805>		6 Alkyl examples reported, formamide products, 3 yields 53–59%
Diag of substrates here	<2001OL3067>		3 Examples, yields 45–50%

5.06.2.2.12 β -Lactams

Reagent/catalyst/conditions	References	Cross-references	Comments
 $\text{X} = \text{OH or Cl}$  Ti(iPrO) ₄ /TiCl ₄ or Ti(iPrO) ₃ Cl/LDA	<2001SL1092>		Three methods used, yields variable, good <i>cis</i> -selectivity
 $\text{R}^4\text{O}-\text{C}(=\text{O})-\text{CH}_2-\text{R}^3$ $n\text{-Bu}_3\text{SnH/AIBN}$	<1999JOC7511>		Yields 42–80%, catalyst affects, product ratios
 $\text{R} = \text{H or Et}$	<1996JOC1276>		Poor selectivity, mix of products

5.06.2.2.13 Other methods

Reagent/catalyst/conditions	References	Cross-references	Comments
$\text{R-MgX} + \text{CO}_2 + \text{NiCl}_2(\text{PPh}_3)_2$   Where $\text{X} = \text{H, F, Cl, OMe, NO}_2$ $\text{Z} = \text{CH or N, Y} = \text{Br or I, } n = 0 \text{ or } 1$ $^{11}\text{CO/Pd(PPh}_3)_4$	<2000TL9997>		Five Grignards used, two amine traps, yields 32–82%
	<2003OBC541>		Eight examples, yields 77–98%

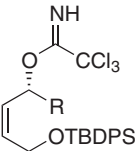
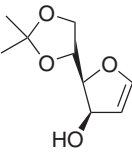
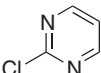
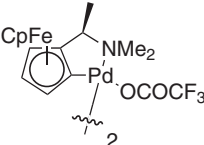
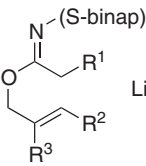
5.06.2.3 *N*-Alkenylalkanoamides (Enamides)

5.06.2.3.1 Acylation methods

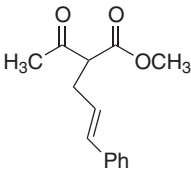
Reagent/catalyst/conditions	Reference	Cross-reference	Comments
Diag of Reagent here	<2001SL1968>		1 Example, 57%

5.06.2.3.2 Rearrangement reactions

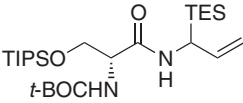
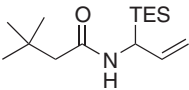
(i) Claisen rearrangement

Reagent/catalyst/conditions	References	Cross-references	Comments
 <p>R = <i>n</i>-Bu, <i>i</i>-Pr, Ph toluene/Δ</p>	<1999TL3735>		Three examples, yields 74–79%
 <p>NaH/CCl₃CN or </p>	<1995TL4311>		Yields 78% or 61%
	<1997TL8837>		NMR yield 39%, 8% ee
 <p>LiNEt₂</p>	<1997JOC4442>		High <i>anti:syn</i> ratios, yields 45–78%, six examples in study

(ii) Schmidt rearrangement

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
 $\text{NaN}_3/\text{MeSO}_3\text{H}/\text{DME}$	<1996T1609>		One example, yield 79%

(iii) Other rearrangements

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
  Toluene/ Δ	<2002AG(E)512>		Four examples only, two yields, 52% and 72%

5.06.2.4 N-Aryl- and N-Heteroaryl-alkanoamides

5.06.2.4.1 Methods from carboxylic acids

Reagent/catalyst/conditions	References	Cross-references	Comments
Pivaloyl pyruvic acid H-Y zeolite/AcOH		C	Only four examples Good for anilines and benzylic amines
Fe^{3+} /K-10 montmorillonite	<2003JOC1165>	C	Good for anilines and benzylic amines
Fe^{3+} /K-10 montmorillonite AcOH/propionic acid/butyric acid	<2001MI207>	C	General method, all yields >95%
AcOH/propionic acid/butyric acid Fe^{3+} (other metal ions claimed) K-10 montmorillonite	<2001USP6215024>	C	General method, all yields >95%
$\text{Fe}_2\text{O}_3/\text{C}$ amberlyst IRC-50	<2003JMOC(A)141>	C	General method, all yields >95%

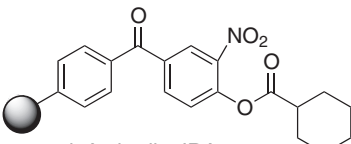
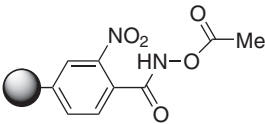
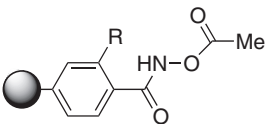
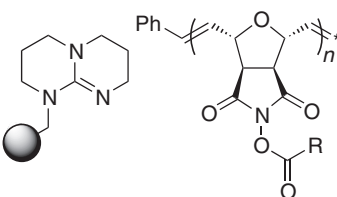
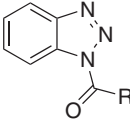
E = enzymic, C = clays/zeolites.

5.06.2.4.2 Methods from simple esters

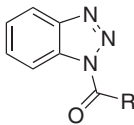
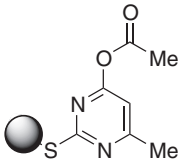
Reagent/catalyst/conditions	References	Cross-references	Comments
Acyl donor/LIP-300 or LPL-311 ChiroCLEL-PC/EtOAc (<i>Pseudomonas cepacia</i> lipase)	<2002TL5529> <2001USP6271005>	E Res E Res	Variable ee values Amino tetralins

E Res = enzymic resolution.

5.06.2.4.3 Methods from active esters

Reagent/catalyst/conditions	References	Cross-references	Comments
 i. Amberlite IRA-120 ii. BEMP-support/ polymeric trisamine	<1999SL1957>	SPS	Yields 34–58%
	<1997MI863>	SPS	Three resins used, nine examples, yields 50–94%
 R = H or NO ₂	<1997MI169>	SPS	Four resins used, nine examples, yields 44–94%
 R = Cy or FmocAla	<2000OL261>	SPS	Two acylation reagents with two amines, yields 95–97%, purity >95% by GCMS
 R = C ₅ H ₁₁ or N- <i>t</i> -BOCAla	<2002BMCL1809>	SPS	Two examples, two amines, HPLC yields 42% and 76%

Continued

Reagent/catalyst/conditions	References	Cross-references	Comments
 R = Bn, Ph ₂ CH, or PhCH ₂ CH ₂	<2000JOC8210>	SPS	Only 1° amides made, two examples, 72% and 85%
 Microwave	<2002TL6507>	SPS	Only one acid example, and yield 47%

SPS = solid-phase synthesis/reagent.

5.06.2.4.4 Methods from acid anhydrides

Reagent/catalyst/conditions	References	Cross-references	Comments
Neat amine/excess anhydride			One example, yield 93%
Yttria–Zirconia catalyst	<2002JMOC(A)207>		Two examples, 92% and 93%
V(O)(OTf) ₂	<2001OL3729>		Naphthyl amine only, yield 99%
Cu(OTf) ₂	<1999TL2611>		Three amine examples, yields 91–98%
Mn (III) salen	<2001JMOC69>		Three amines examples, all yields >93%
Montmorillonite K-10 or KSF	<1998JCS(P1)1913> ^a	C	Three aniline examples, yields 72–98%
Ac ₂ O/HBF ₄ /SiO ₂	<2003TL3521>	C	Two anilines used, yields 80% and 98%
In/InCl ₃	<2001SC3577>		Eight nitrobenzenes used, five yields >81%
nitroaryl compound			No yields given
LiBr or LiCl/anhydride	<1997USP5594134>		
cycloalkyl amide			

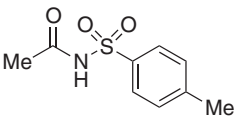
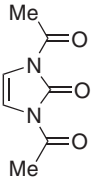
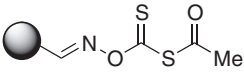
C = clays/zeolites. ^a See also <2003TL3521>.

5.06.2.4.5 Methods from acyl halides

Reagent/catalyst/conditions	References	Cross-references	Comments
(COCl) ₂ /MgO/silica gel	<1999JHC601>		Three examples, yields 51–56%, macrocycle method
(S)-Naproxen acetyl chloride	<2002MC27>	KR	Only two examples reported, yields 75%, ee values 76–78%

KR = kinetic resolution.

5.06.2.4.6 Other acylation methods

Reagent/catalyst/conditions	References	Cross-references	Comments
	<1995IJC(B)1102>		Seven examples of 2° amides, five yields 70–83%
	<1999USP5994557>		Four examples given, all yields >90%
	<2000MI161>	SPS	Three resins tested, one acid, seven anilines used, yields 41–59%

SPS = solid-phase synthesis/reagent.

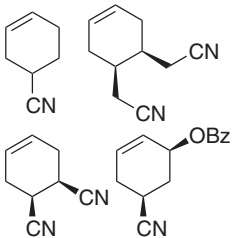
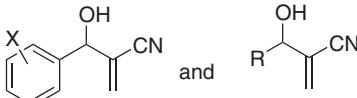
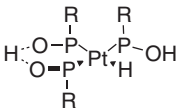
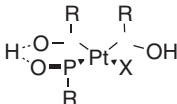
5.06.2.4.7 Beckmann rearrangement reactions

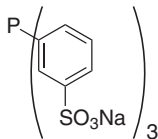
Reagent/catalyst/conditions	References	Cross-references	Comments
Ketoxime/(HBO ₂) _n	<2002TL2455>		Two examples, yields 85% and 87%
Oxime/chloral	<2003TL755>		Eight examples, yields 74–98%
Ketoxime·HCl salt/Δ	<2001TL8123>		Two examples, yields 83–90%
Ketone/NH ₂ OH·HCl NaHSO ₄ /SiO ₂ microwave	<2000JCR(S)482>		Eight examples, seven yields 85–94%
Ketone/NH ₂ OH·HCl HCO ₂ H/SiO ₂ microwave	<1998MI795>		Three examples, yields 35%, 60% and 70%
K10 montmorillonite oxime/microwave	<1995SL1259>		Four examples, yield 68–96%
[RhCl(COD)] ₂ /CF ₃ SO ₃ H P(pTol) ₃ /Δ	<2001OL311>		Eight examples, yields 52–88%
Bu ₄ NReO ₄ /pTsOH/Δ ketone/NH ₂ OH·HCl or oxime	<1995BCJ373>		One example, yield 94%
Oxime/Yb(OTf) ₃ /Δ H-Beta zeolites or H-ZSM-5 zeolite	<2002JCS(S)236> <1998MI267>		One example yields 90% Acetophenone oxime only
Ketone/NH ₂ OH·HCl HY zeolite/microwave	<2002SL625>	C	Four examples, yields 82–95%

C = clays or zeolites.

5.06.3 AMIDES OF ALKENOIC ACIDS

5.06.3.1 *N*-Unsubstituted Alkenoamides5.06.3.1.1 *Hydrolysis of nitriles*

Reagent/catalyst/conditions	References	Cross-references	Comments
<i>Rhodococcus</i> sp. C3II <i>Rhodococcus erythropolis</i> MP50 <i>Rhodococcus rhodochrous</i> IFO 15564	<1998MI165>	E/KR	
	<1998TA1097>	E/KR	Low yields and ee values
<i>Rhodococcus</i> sp. AJ270			
 X = H, Cl, Me, or OMe at various positions R = Et or <i>i</i> -Pr	<2003OBC535>	E/KR	10 Examples, nine yields 43–64%, nine ee values 19–80%
Acrylonitrile plus Cu/Ru/Rh/Fe/Cr catalysts	<1997MI371>		Conversions 65–98%
Methacrylonitrile LiOH	<1997MI371>		Conversion 35%
 R = Me ₂	<1995TL8657>		Acrylonitrile only, yield 93%
 R = Ph ₂ , X = H, or Cl R = Me ₂ , X = H, or Cl R = -(CH ₂) ₄ -, X = Cl	<2000JMO(A)249>		Acrylonitrile only, yield 93%

Reagent/catalyst/conditions	References	Cross-references	Comments
Ir(H)(CO)(TPPTS) ₃ where TPPTS is 	<1999MI535>		Four examples, yields 31–91%
Cp ² Mo(μ-OH) ₂ MoCp ² [(OTs) ₂] (where Cp' = η ⁵ -CH ₃ C ₅ H ₄) Amberlyst A26(OH ⁻) H ₂ O ₂ KOSiMe ₃	<2003OM1203> <1999IJC(B)974> <2000TL3747>	SPS	Acrylonitrile, yield 83% Acrylonitrile, yield 76% One example, 68%, simple work-up

SPS = solid-phase synthesis/reagent, KR = kinetic resolution, E = enzymic.

5.06.3.2 N-Alkylalkenoamides

5.06.3.2.1 Methods from carboxylic acids

Reagent/catalyst/conditions	References	Cross-references	Comments
Lipozyme [®] Hexane	<1997T7587>	E	N-Me glucamine
Lipozyme [®] /Novozym Hexane/ <i>t</i> -butanol	<1998JMOC(B)13>	E	N-Me glucamine

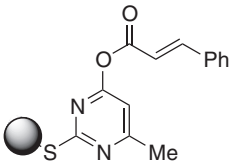
E = enzymic.

5.06.3.2.2 Methods from simple esters

Reagent/catalyst/conditions	References	Cross-references	Comments
Cp ² Sm(THF) ₂ Acyl donor Subtilisin Carlsberg/ cyanomethyl pen-4-enoate	<1996JOC3088> <1996TL6287>	E	Octylamine, yield 86% Two examples, yield 43%, 97% ee yield 30%, 83% ee

E = enzymic.

5.06.3.2.3 Methods from active esters

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
 Microwave	<2002TL6507>	SPS	One example, yield 50%

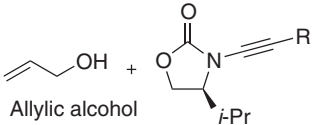
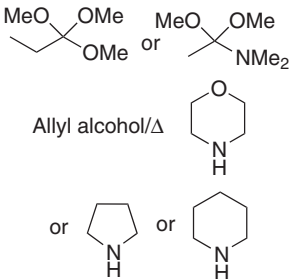
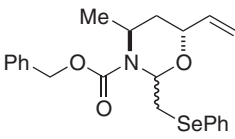
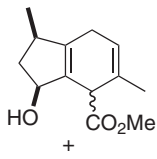
SPS = solid-phase synthesis/reagent.

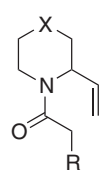
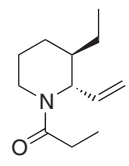
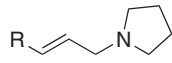
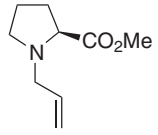
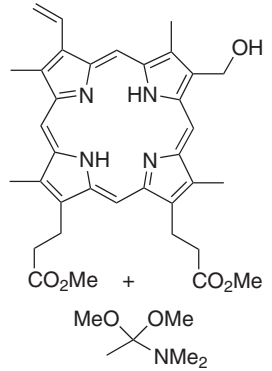
5.06.3.2.4 Methods from acid anhydrides

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
LiBr or LiCl/anhydride cycloalkyl amide	<1997USP5594134>		Several acids used

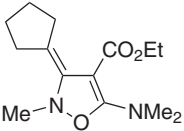
5.06.3.2.5 Rearrangement reactions

(i) Claisen rearrangement

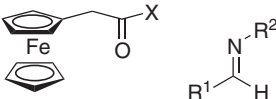
Reagent/catalyst/conditions	References	Cross-references	Comments
 Allylic alcohol p-Nitrobenzenesulfonic acid/ toluene sealed tube	<2002OL1383>		16 varied examples, all yields >60%
 Allyl alcohol/ Δ	<2002SL411>		10+ examples, can be a one-pot process, most yields >73%
 Allyl alcohol/ $\text{CH}_3\text{C}(\text{OMe})_2$ NMe_2 xylene/ Δ	<1995JCS(P1)2325>		One example, three products
 Allyl alcohol/ $\text{CH}_3\text{C}(\text{OMe})_2$ NMe_2 xylene/ Δ	<2001OL279>		Very specific example, yield 50%

Reagent/catalyst/conditions	References	Cross-references	Comments
 <p>X = CH₂ or NBn R = H, Me, or OMe LiHMDS/toluene/Δ</p>	<1996SC1675>		Six compounds studied, four yields >75%
 <p>LiHMDS/toluene/Δ</p>	<1999AG(E)3545>		One example, yield 74%
 <p>AcCl or PrCOCl K₂CO₃/Me₃Al</p>	<1995JOC3773>		Many analogs used, all yields >73%
 <p>K₂CO₃/Me₃Al</p>	<2002S242>		Most yields >70%, good <i>syn:anti</i> ratios
 <p>MeO-C(OMe)(NMe₂)-OMe</p>	<1995LA1509>		One example, yield 17%

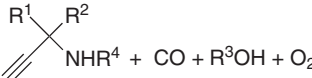
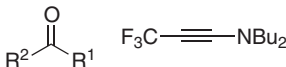
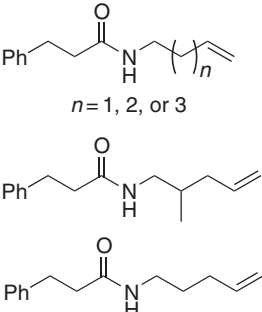
(ii) Other rearrangements

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
 MeI/MeOH	<2003JOC3718>		One example, yield 95%

5.06.3.2.6 β -Lactams

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
 X = OH or Cl	<2001SL1092>		Three methods used, good yields and <i>cis</i> -selectivity

5.06.3.2.7 Other methods

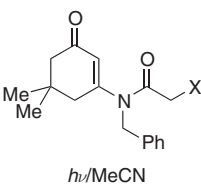
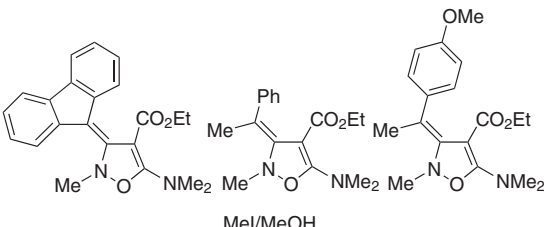
Reagent/catalyst/conditions	References	Cross-references	Comments
L-Ala-OMe·HCl allyl carbonate/DIPEA CO/DPPB/PdCl ₂	<1999TL2649>		Varied substrates, four examples, yields 52% and 69%
 R ¹ , R ² = H, H, or H, Me R ³ = MeOH, R ⁴ = Bn	<1995TL7495>		One example, yield 71%
BF ₃ ·OEt ₂ /4A MS  R ¹ = H or Me R ² = Ph, ArX, alkyl, vinyl	<1999CL855>		Two aldehydes and one ketone, yields 71%, 88%, and 95%
[Fe(CO) ₅]/Δ  n = 1, 2, or 3	<2003HCA750>		N-(But-3-enyl) amides best substrates

5.06.3.3 *N*-Alkenylalkenoamides

No methods for this specific transformation have been selected for this review.

5.06.3.4 *N*-Aryl- and *N*-Heteroaryl-alkenoamides

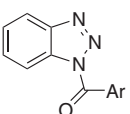
5.06.3.4.1 Other methods

Reagent/catalyst/conditions	References	Cross-references	Comments
 $h\nu/\text{MeCN}$	<1996T2405>		Two examples, yields 55% and 72%
 MeI/MeOH	<2003JOC3718>		Three examples, yields 96–100%

5.06.4 AMIDES OF AROMATIC AND HETEROAROMATIC ACIDS

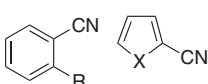
5.06.4.1 *N*-Unsubstituted Arylamides

5.06.4.1.1 Methods from active esters

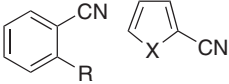
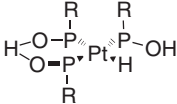
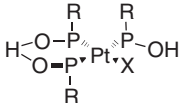
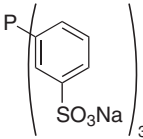
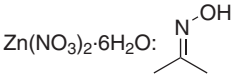
Reagent/catalyst/conditions	Reference	Cross-reference	Comments
	<2000JOC8210>	SPS	10 (Hetero)aryl acids 1° amides formed, nine yields 100%

SPS = solid-phase synthesis/reagent.

5.06.4.1.2 Hydrolysis of nitriles

Reagent/catalyst/conditions	References	Cross-references	Comments
<i>Rhodococcus</i> sp. C3II <i>Rhodococcus erythropolis</i> MP50 <i>Rhodococcus rhodochrous</i> AJ270	<1998MI165>	E/KR	Two examples
 $\text{R} = \text{Me, OMe, OH, NO}_2, \text{NH}_2$ $\text{X} = \text{O or S}$	<1995TL9561>	E/KR	12 Examples, eight yields 80–98%

Continued

Reagent/catalyst/conditions	References	Cross-references	Comments
<i>Rhodococcus rhodochrous</i> AJ270			
 <p>R = Me, OMe, OH, NO₂, NH₂ X = O or S</p>	<1997JCS(P1)1099>	E/KR	Short times best, 14 examples, yields 63–98%
Benzonitrile PhCO ₂ NH ₄	<1997MI371>		92% Conversion
 <p>R = Me₂</p>	<1995TL8657>		One example, yield 86%
 <p>R = Ph₂, X = H, or Cl R = Me₂, X = H, or Cl R = -(CH₂)₄-, X = Cl</p>	<2000JMO(A)249>		One example, yield 86%
Ir (H)(CO)(TPPTS) ₃ where TPPTS is			
	<1999MI535>		One example, yield 54%
[(terpy)(bipy)Ru ^{II} - (4-pyrCN)Ru ^{II} (NH ₃) ₅](PF ₆) ₄	<1995POL3111>		One example, no yield given
[Ru ^{II} (tpy)(bpy)NCPh](PF ₆) ₂ PhCN only	<2002JCC587>		Kinetic study
Cp ₂ Mo(μ-OH) ₂ MoCp' ₂ (OTs) ₂ (where Cp' = η ⁵ -CH ₃ C ₅ H ₄)	<2003OM1203>		Two compounds, yields 63% and 78%
MnO ₂ /SiO ₂	<2002SC1731>	C	Nine examples, five yields 66–99%
 <p>in 1:4 ratio</p>	<2002IC4798>		Two examples, yields 65–90%, other catalysts used.
Na Y zeolite	<2000MI118>	C	Six examples, four yields 87–92%

Reagent/catalyst/conditions	References	Cross-references	Comments
Unactivated alumina	<1995TL3469>	C	Four examples, yields 82–92%
NaOH/H ₂ O ₂	<1999M1167>		Nucleosides, two examples, yield 87%
DMDO	<1997SC3119>		Six examples, yields 61–83%
Amberlyst A26(OH [−]) H ₂ O ₂	<1999IJC(B)974>	SPS	Five examples, short times, all yields >95%
NaBO ₃ /microwave	<2001SC431>		Five examples, yields 83–97%
KOSiMe ₃	<2000TL3747>		Five examples, yields 78–82%, simple work-up
H ₂ O/High T/P	<1997MI2048>		Only PhCN, kinetic study

SPS = solid-phase synthesis/reagent, KR = kinetic resolution, E = enzymic, C = clays/zeolites.

5.06.4.2 *N*-Alkylarylamides

5.06.4.2.1 *Methods from carboxylic acids*

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
Fe ³⁺ /K-10 montmorillonite	<2003JOC1165>	C	Five examples, yields 91–95%

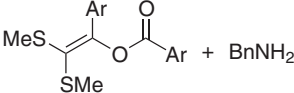
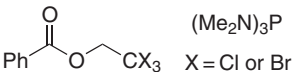
C = clays/zeolites.

5.06.4.2.2 *Methods from simple esters*

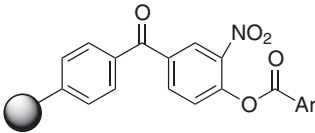
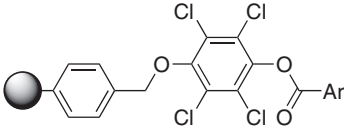
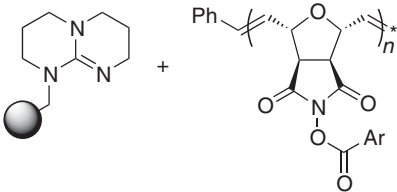
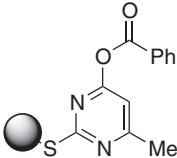
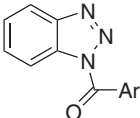
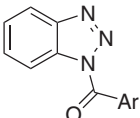
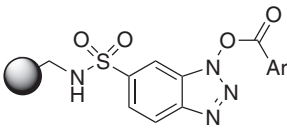
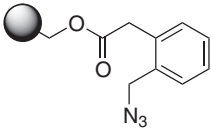
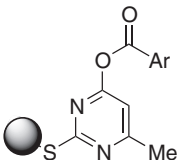
Reagent/catalyst/conditions	References	Cross-references	Comments
Cp ₂ Sm(THF) ₂ acyl donor	<1996JOC3088>		Vinyl benzoate, yield 98%, only two examples
AlCl ₃ or ZrCl ₄	<1996TL3213>	SPS	One example, yield 19%, purity 85%

SPS = solid-phase synthesis/reagent.

5.06.4.2.3 *Methods from active esters*

Reagent/catalyst/conditions	References	Cross-references	Comments
	<1999S1200>		Seven examples, yields 84–100%
	<2000JOC2114>		Two examples, yields 76% and 77%

Continued

Reagent/catalyst/conditions	References	Cross-references	Comments
 i. Amberlite IRA-120 ii. BEMP support/ polymeric trisamine	<1999SL1957>	SPS	Three acids used, five amines, yields 35–95%, all purities >95%
	<2001JCO604>	SPS	One anhydride used, conversion 100%
	<2000OL261>	SPS	Two anhydrides used, yields/purity >95%
	<2002H369>	SPS	Four examples, yields 82–98%
	<2002BMCL1809>	SPS	Five (hetero)aryl acids, four amines used, 17 yields 60–95%
	<2000JOC8210>	SPS	Seven examples 2°, six yields >92%, seven examples 3°, five yields >94%
	<1997JOC2594>	SPS	11 Examples, most yields >70%
	<1998TL4773>	SPS	One example, yield 100% purity 91%
	<2002TL6507>	SPS	Six acids used, four yields >75%
Microwave			

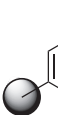
SPS = solid-phase synthesis/reagent.

5.06.4.2.4 *Methods from acyl halides*

Reagent/catalyst/conditions	References	Cross-references	Comments
Prolinamide/PhCOCl	<1998TL6991>		Two examples, yields >80%
sodium 2-ethylhexanoate			
Prolinamide/ArCOCl	<2001USP6211384>		Two examples, yields >80%
sodium 2-ethylhexanoate			
ArCO ₂ H/Cl ₃ CCN/PPh ₃	<2002TL6039>	SPS	FMPE best, 10 examples, seven yields >60%, all purities >83%
MAMP or FMPE resin			Three examples, yields 50–76%
PhCOCl/Pyr diamine	<1998S1463>		
ArCOF/silane or silazane	<1996EUP709366>		

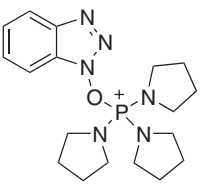
SPS = solid-phase synthesis/reagent.

5.06.4.2.5 *Methods using diimides*

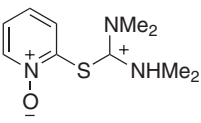
Reagent/catalyst/conditions	References	Cross-references	Comments
PS-carbodiimide/MP-carbonate	<2001TL6703>	SPS	Five examples, only two acids used, yields 88–89%, purities 81–95%
PS-DMAP			
	<1998CC499>	SPS	Two acids, 11 examples, eight yields >79%
DCC/AcOH			
Diisopropylcarbodiimide/2-bromoacetic acid/Rink amide	<2002JCO329>	SPS	Library synthesis

SPS = solid-phase synthesis/reagent.

5.06.4.2.6 *Methods using phosphorus reagents*

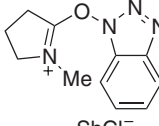
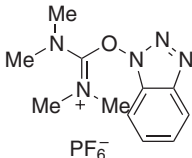
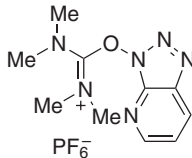
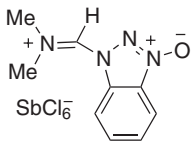
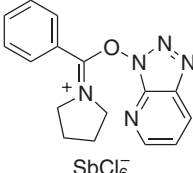
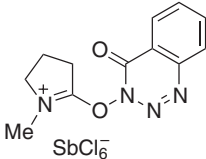
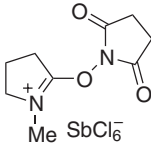
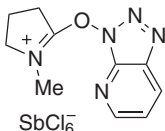
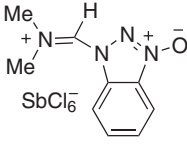
Reagent/catalyst/conditions	Reference	Cross-reference	Comments
	<1999TL2501>		Two examples, yields >90%
pyBOP			

5.06.4.2.7 *Methods using uronium salts*

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
	<1999JOC8936>	SPS	Eight examples, nine yields 83–95%
HOTT X [−] = PF ₆ [−]			
TOTT X [−] = BF ₄ [−]			

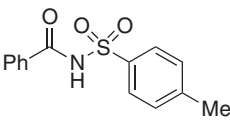
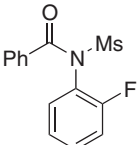
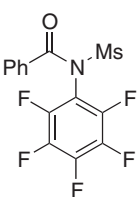
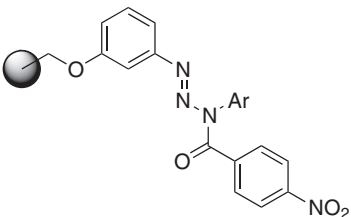
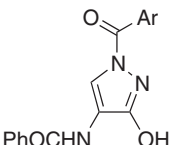
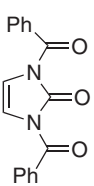
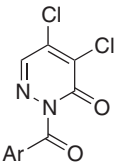
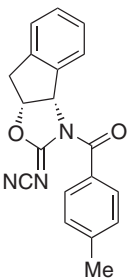
SPS = solid-phase synthesis/reagent.

5.06.4.2.8 Methods using iminium salts

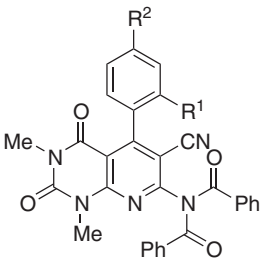
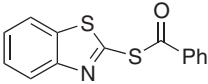
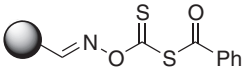
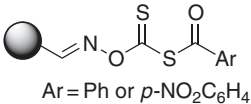
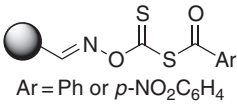
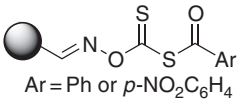
Reagent/catalyst/conditions	References	Cross-reference	Comments			
 BDMP SbCl_6^-	 HBPYU PF_6^-	 HAPYU PF_6^-	 BOMI SbCl_6^-			
 BPMP SbCl_6^-	 DOMP SbCl_6^-	 SOMP SbCl_6^-	 AOMP SbCl_6^-	<2000T4437>		Two examples with BOMI HPLC, yields 76% and 79%
 BOMI SbCl_6^-	<2000MI110>	SPS			Two peptides prepared BOMI, yields >75%	

SPS = solid-phase synthesis/reagent.

5.06.4.2.9 Other acylation methods

Reagent/catalyst/conditions	References	Cross-references	Comments
	<1995IJC(B)1102>		Two examples, 2°/3° amide, yields 40% and 30%
	<1998JCS(P1)2973>		Five examples, 2°/3° amides, four yields 92–94%
	<2000T5843>		Eight examples, 2°/3° amides, all yields 89–99%
	<2000JCO710>	SPS	One acid used, library synthesis
	<1998MI455>		Four examples, yields 59–87%
	<1999USP5994557>		Patent covers aryl acids, no examples reported
	<2002S733>		Two aryl acids tested, five examples given, yields 72–98%
	<2001T9309>	KR	12 examples with benzylic amines, best yield 85%, best ee 85%

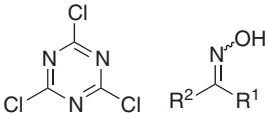
Continued

Reagent/catalyst/conditions	References	Cross-references	Comments
 <p>R¹ = H, R² = CON-polymer or R¹ = Me, R² = H</p>	<2002BMCL1799>	SPS	1°/2° Hindered examples, six solution yields 100%, six SPS yields 88–98%
	<1997MI442>		11 Examples, 2°/3° amides, yields 92–99%
	<1995PIA51>	SPS	Two examples simple amines, yields 68% and 82%
 <p>Ar = Ph or <i>p</i>-NO₂C₆H₄</p>		SPS	Three resins tested, two acids, two simple amines used, yields 48–68%
 <p>Ar = Ph or <i>p</i>-NO₂C₆H₄</p>	<1997PIA49>	SPS	Two resins tested, four acids, two simple amines used, yields 49–84%
 <p>Ar = Ph or <i>p</i>-NO₂C₆H₄</p>	<2000MI161>	SPS	Three resins tested, two acids, two simple amines used, yields 46–92%
SmI ₂ /benzoyl chloride	<1999T11755>		Two examples, yields 62%, 86%, and 93%
LiHMDS/benzoyl chloride	<1998JOC2062>		Two examples, yields both 84%

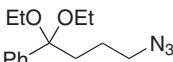
SPS = solid-phase synthesis/reagent, KR = kinetic resolution.

5.06.4.2.10 Rearrangement reactions

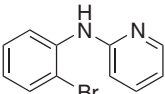
(i) Beckmann rearrangement

Reagent/catalyst/conditions	References	Cross-reference	Comments
	<2002JOC6272>		One example, yield 91%
Ketoxime·HCl salt/Δ	<2001TL8123>		One example, yield 96%
Ketone/NH ₂ OH·HCl	<2000JCR(S)482>		One example, yield 96%
NaHSO ₄ /SiO ₂			
microwave			
Oxime/Yb(OTf) ₃ /Δ	<2002JCS(S)236>		One example, yield 70%
AlCl ₃ /oxime/Δ	<1998SC2275>		Two examples, yields 100%

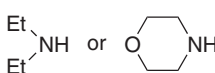
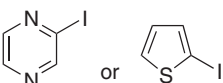
(ii) Schmidt rearrangement

Reagent/catalyst/conditions	References	Cross-reference	Comments
 TFA/TMSOTf	<1996T3403>		Two examples, yields 77% and 89%

5.06.4.2.11 β -Lactams

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
 $^{11}\text{CO}/\text{Pd}(\text{PPh}_3)_4$	<2003OBC541>		One example, yield 79%

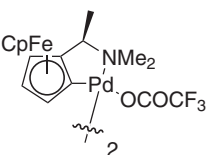
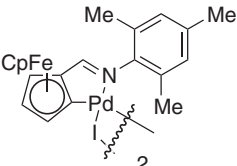
5.06.4.2.12 Other methods

Reagent/catalyst/conditions	References	Cross-references	Comments
$\text{R-MgX} + \text{CO}_2 + \text{NiCl}_2(\text{PPh}_3)_2$ 	<2000TL9997>		Two examples, only two amines, yields 72–96%
RMgX ($\text{X} = \text{Br}, \text{Cl}$) PBu_3 or $\text{NiCl}_2(\text{PPh}_3)_2$ 	<2003OBC541>		Two examples, yields 31% and 83%

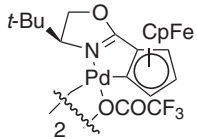
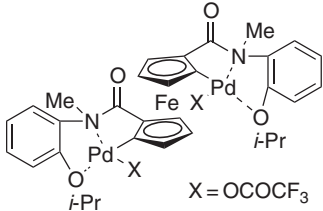
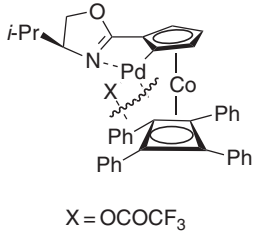
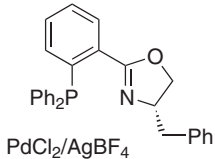
5.06.4.3 *N*-Alkenylarylamides

5.06.4.3.1 Rearrangement reactions

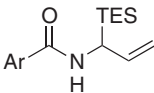
(i) Claisen rearrangement

Reagent/catalyst/conditions	References	Cross references	Comments
	<1997TL8837>		Seven examples, five yields 69–97%, six ee values 46–61%
	<1998TA3213>		Four examples, five catalysts used, yields 45–94%, ee range 43–73%

Continued

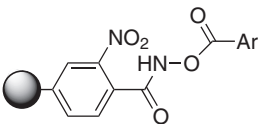
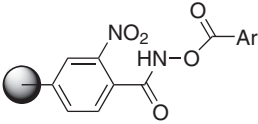
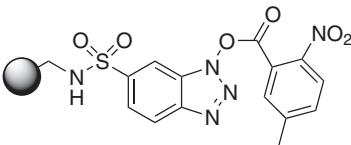
Reagent/catalyst/conditions	References	Cross references	Comments
	<1999JA2933>		13 Imidates tested, nine yields 77–97%, ee range 63–96%
	<2002TL9509>		Eight imidates tested, three catalysts used, 12 yields 65–91%, 11 ee values range 67–95%
	<2003TA415>		Five imidates tested, three catalysts used, 14 yields 70–97%, 11 ee values range 83–96%
	<1998TA1065>		Three imidates tested, many catalysts tested, best yield 88%, best ee 81%

(ii) Other rearrangements

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
 <p>Toluene/Δ</p>	<2002AG(E)512>		Three examples, yields 67–81%

5.06.4.4 *N*-Arylarylamides

5.06.4.4.1 *Methods from active esters*

Reagent/catalyst/conditions	References	Cross-references	Comments
	<1997MI863>	SPS	Three resins used, two acids, yields 52–97%
	<1997MI169>	SPS	Four resins used, two acids, yields 44–94%
	<1997JOC2594>	SPS	Four examples, one yield 91%

SPS = solid-phase synthesis/reagent.

5.06.4.4.2 *Methods from acid anhydrides*

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
Montmorillonite K-10 or KSF	<1998JCS(P1)1913>	C	Two examples, yields >90%

C = clays/zeolites.

5.06.4.4.3 *Methods from acyl halides*

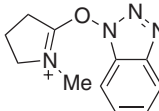
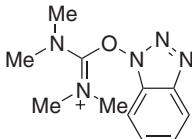
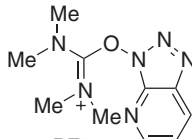
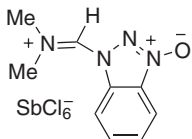
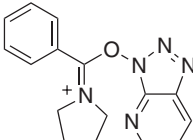
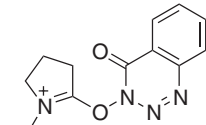
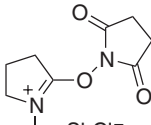
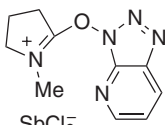
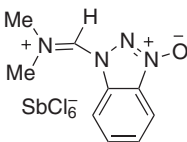
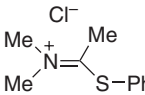
Reagent/catalyst/conditions	Reference	Cross-reference	Comments
Ar(COCl) ₂ /MgO/silica gel	<1999JHC601>		Three examples, all yields 51–54%, macrocyclic compounds

5.06.4.4.4 *Methods using diimides*

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
PS-carbodiimide/MP-carbonate PS-DMAP	<2001TL6703>	SPS	Five examples, only two acids used, yields 88–89%, purities 81–95%

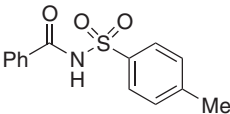
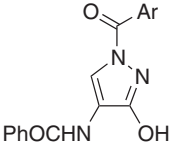
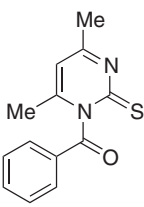
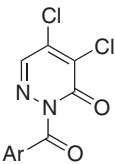
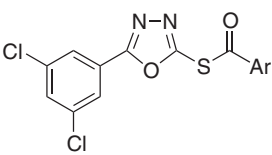
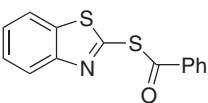
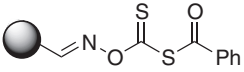
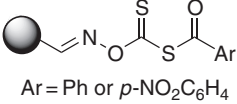
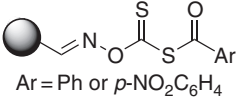
SPS = solid-phase synthesis/reagent.

5.06.4.4.5 Methods using iminium salts

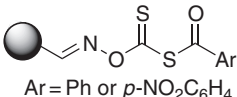
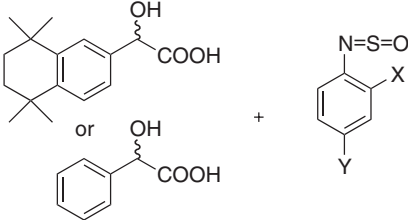
Reagent/catalyst/conditions	References	Cross-references	Comments			
 SbCl_6^- BDMP	 PF_6^- HBPpyU	 PF_6^- HAPpyU	 SbCl_6^- BOMI			
 SbCl_6^- BPMP	 SbCl_6^- DOMP	 SbCl_6^- SOMP	 SbCl_6^- AOMP	 <2000T4437> 		Two examples with BOMI HPLC, yields 87% and 90%
 SbCl_6^- BOMI				 <2000MI110> 	SPS	One peptide prepared, yield 90%
 Cl^- CPMA	 <2002TL7595> 					Only benzoic acid, yield 100%

SPS = solid-phase synthesis/reagent.

5.06.4.4.6 Other acylation methods

Reagent/catalyst/conditions	References	Cross-references	Comments
	<1995IJC(B)1102>		Four examples, all 2° amides, three yields 70–85%
	<1998MI455>		One example, yield 77%
	<2001MI43>		13 Anilines used 12 yields 87–98%
	<2002S733>		Two aryl acids tested, eight examples given, yields 84–99%
	<1998JCR(S)268>		14 Examples, only anilines used, yields 76–90%
	<1997MI442>		11 Examples, 2°/3° amides, yields 92–99%
	<1995PIA51>	SPS	Seven examples with anilines, yields 68–84%
 <p>Ar = Ph or <i>p</i>-NO₂C₆H₄</p>		SPS	Three resins tested, 10 anilines used, yields 41–68%
 <p>Ar = Ph or <i>p</i>-NO₂C₆H₄</p>	<1997PIA49>	SPS	Two resins tested, four acids, 10 anilines used, yields 41–80%

Continued

Reagent/catalyst/conditions	References	Cross-references	Comments
 Ar = Ph or <i>p</i> -NO ₂ C ₆ H ₄	<2000MI161>	SPS	Three resins tested, two acids, seven anilines used, yields 46–92%
 R/S Mandelic Acid X = F, Y = CO ₂ Me X = H, Y = NO ₂ X = Cl, Y = Cl	<2000TL6017>		Five examples, three acids, yields 77–90%

SPS = solid-phase synthesis/reagent.

5.06.4.4.7 Rearrangement reactions

(i) Beckmann rearrangement

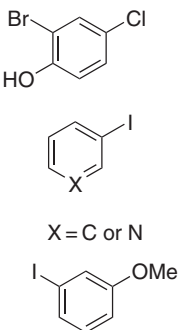
Reagent/catalyst/conditions	References	Cross reference	Comments
NCS/PPh ₃ oxime/amide	<2002SC2535>		One example, yield 75%, nitrile side-reaction
Ketoxime/(HBO ₂) _n	<2002TL2455>		One example, yield 92%
Ketone/NH ₂ OH·HCl NaHSO ₄ /SiO ₂ microwave	<2000JCR(S)482>		One example, yield 96%
Ketone/NH ₂ OH·HCl HCO ₂ H/SiO ₂ microwave	<1998MI795>		One example, yield 85%, benzophenone
K10 montmorillonite oxime/microwave	<1995SL1259>		One example, yield 96%
[RhCl(COD)] ₂ /CF ₃ SO ₃ H P(pTol) ₃ /Δ	<2001OL311>		Four examples, yields 91–99%
Bu ₄ NReO ₄ /pTsOH/Δ Ketone/NH ₂ OH·HCl or oxime	<1995BCJ373>		One example, yield 98%
Oxime/Yb(OTf) ₃ /Δ	<2002JCS(S)236>		10 Examples, yields 71–90%
Ketone/NH ₂ OH·HCl HY zeolite/microwave	<2002SL625>	C	One example, yield 95%

C = clays or zeolites.

(ii) Schmidt rearrangement

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
NaN ₃ /MeSO ₃ H/DME	<1996T1609>		One example, yield 57%

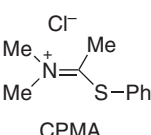
5.06.4.4.8 Other methods

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
 <p>X = C or N</p>	<2003OBC541>		10 Examples, six yields >76%
$^{11}\text{CO}/\text{Pd}(\text{PPh}_3)_4$			

5.06.5 AMIDES OF ALKYNOLIC ACIDS

5.06.5.1 N-Alkylarylamides

5.06.5.1.1 Methods using iminium salts

Reagent/catalyst/conditions	Reference	Cross-reference	Comments
 <p>CPMA</p>	<2002TL7595>		Phenylpropionic acid, yield 100%

REFERENCES

- 1972JA6203 T. Shiori, K. Ninomiya, S. Yamada, *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205.
 1973JA875 J. C. Sheehan, S. L. Ledis, *J. Am. Chem. Soc.* **1973**, *95*, 875–879.
 1984JOC922 B. J. Cohen, H. Karoly-Hafeli, A. Patchornik, *J. Org. Chem.* **1984**, *49*, 922–924.
 1985C269 R. Schwesinger, *Chimia* **1985**, *39*, 269–272.
 1990JOC251 L. A. Carpino, B. J. Cohen, Y. Z. Lin, K. E. Stephens Jr., S. A. Triolo, *J. Org. Chem.* **1990**, *55*, 251–259.
 1993JA4397 L. A. Carpino, *J. Am. Chem. Soc.* **1993**, *115*, 4397–4398.
 1994MI57 I. Abdelmoty, F. Albericio, L. A. Carpino, B. M. Foxman, S. A. Kates, *Letters in Peptide Science* **1994**, *1*, 57–67.
 1995BCJ373 H. Kusama, Y. Yamashita, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 373–377.
 1995BSB161 Z. Djeghaba, H. Deleuze, B. Maillard, B. De Jeso, *Bull. Soc. Chim. Belg.* **1995**, *104*, 161–164.
 1995CC2325 P. A. Evans, A. B. Holmes, I. Collins, P. R. Raithby, K. Russell, *J. Chem. Soc., Chem. Commun.* **1995**, 2325–2326.
 1995COFGT(5)257 P. D. Bailey, I. D. Collier, K. M. Morgan, Amides, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 257–307.
 1995H691 P. J. Crocker, U. Karlsson-Andreasson, B. T. Lotz, M. J. Miller, *Heterocycles* **1995**, *40*, 691–716.
 1995IJC(B)1102 S. H. Mashraqui, S. S. Nirantar, M. M. Biswas, *Indian J. Chem., Sect. B* **1995**, *34B*, 1102–1104.
 1995JA10449 G. L. Milligan, C. J. Mossman, J. Aube, *J. Am. Chem. Soc.* **1995**, *117*, 10449–10459.
 1995JA8047 V. Gracias, G. L. Milligan, J. Aube, *J. Am. Chem. Soc.* **1995**, *117*, 8047–8048.
 1995JCS(P1)2325 *J. Chem. Soc., Perkin Trans. 1* **1995**, 2325.

- 1995JOC1276 H. Ishibashi, C. Kameoka, H. Iriyama, K. Kodama, T. Sato, M. Ikeda, *J. Org. Chem.* **1995**, *60*, 1276–1284.
- 1995JOC2456 K. D. Raner, C. R. Strauss, R. W. Trainor, J. S. Thorn, *J. Org. Chem.* **1995**, *60*, 2456–2460.
- 1995JOC3249 I. Pendrak, P. A. Chambers, *J. Org. Chem.* **1995**, *60*, 3249–3251.
- 1995JOC3773 U. Nubbemeyer, *J. Org. Chem.* **1995**, *60*, 3773–3780.
- 1995LA1509 B. Gerlach, F.-P. Montforts, *Liebigs Ann. Chem.* **1995**, 1509–1514.
- 1995MI109 L. Y. Alfeeva, L. A. Andreeva, V. N. Nezavibat'ko, *Letters in Peptide Science* **1995**, *2*, 109–111.
- 1995PIA51 K. A. Kumari, K. Sreekumar, *Proc. -Indian Acad. Sci., Chem. Sci.* **1995**, *107*, 51–58.
- 1995POL3111 N. Lis De Katz, F. Fagalde, N. E. Katz, *Polyhedron* **1995**, *14*, 3111–3114.
- 1995SC3007 D. Barbry, C. Pasquier, C. Faven, *Synth. Commun.* **1995**, *25*, 3007–3013.
- 1995SL1259 A. I. Bosch, P. de la Cruz, E. Diez-Barra, A. Loupy, F. Langa, *Synlett* **1995**, 1259–1260.
- 1995SL599 B. Herradon, S. Valverde, *Synlett* **1995**, 599–602.
- 1995TL3469 C. P. Wilgus, S. Downing, E. Molitor, S. Bains, R. M. Pagni, G. W. Kabalka, *Tetrahedron Lett.* **1995**, *36*, 3469–3472.
- 1995TL4311 P. L. Armstrong, I. C. Coull, A. T. Hewson, M. J. Slater, *Tetrahedron Lett.* **1995**, *36*, 4311–4314.
- 1995TL6013 H.-O. Kim, B. Gardner, M. Kahn, *Tetrahedron Lett.* **1995**, *36*, 6013–6016.
- 1995TL7357 D. Xu, K. Prasad, O. Repic, T. J. Blacklock, *Tetrahedron Lett.* **1995**, *36*, 7357–7360.
- 1995TL7495 A. Bonardi, M. Costa, B. Gabriele, G. Salerno, G. P. Chiusoli, *Tetrahedron Lett.* **1995**, *36*, 7495–7498.
- 1995TL8657 T. Ghaffar, A. W. Parkins, *Tetrahedron Lett.* **1995**, *36*, 8657–8660.
- 1995TL8941 Q. Lu, P. Bovonsombat, W. C. Agosta, *Tetrahedron Lett.* **1995**, *36*, 8941–8944.
- 1995TL9561 O. Meth-Cohn, M.-X. Wang, *Tetrahedron Lett.* **1995**, *36*, 9561–9564.
- 1996ACR268 L. A. Carpino, M. Beyermann, H. Wenschuh, M. Bienert, *Acc. Chem. Res.* **1996**, *26*, 268–274.
- 1996C434 H. Ohta, *Chimia* **1996**, *50*, 434–436.
- 1996CRV1809 V. A. Petrov, G. Resnati, *Chem. Rev.* **1996**, *96*, 1809–1823.
- 1996EUP709366 Matsuda, T.; Sato, S.; Koike, N. European Patent 709366 (1996) CAN 125:57924.
- 1996JCR(S)200 B. Kundu, K. C. Agarwal, *J. Chem. Res., Synop.* **1996**, 200–201.
- 1996JCS(P1)1047 R. S. Atkinson, E. Barker, P. J. Edwards, G. A. Thomson, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1047–1055.
- 1996JOC3088 Y. Ishii, M. Takeno, Y. Kawasaki, A. Muromachi, Y. Nishiyama, S. Sakaguchi, *J. Org. Chem.* **1996**, *61*, 3088–3092.
- 1996JOC3350 K. Akaji, N. Kuriyama, Y. Kiso, *J. Org. Chem.* **1996**, *61*, 3350–3357.
- 1996JOC359 J. L. Chiara, C. Destabel, P. Gallego, J. Marco-Contelles, *J. Org. Chem.* **1996**, *61*, 359–360.
- 1996JOC45 J. E. Johnson, E. C. Riesgo, I. Jano, *J. Org. Chem.* **1996**, *61*, 45–50.
- 1996MI119 M. Panunzio, P. G. Cozzi, C. M. Kretz, E. Bandini, G. Martelli, *Topics in Heterocyclic Systems: Synthesis, Reactions and Properties*, **1996**, *1*, 119–140.
- 1996MI169 A. W. Parkins, *Platinum Metals Review* **1996**, *40*, 169–174.
- 1996MI285 C. Kaduk, H. Wenschuh, M. Beyermann, K. Forner, L. A. Carpino, M. Bienert, *Letters in Peptide Science* **1996**, *2*, 285–288.
- 1996MI767 J.-C. Rossi, L. Garrel, J. Taillades, A. Commeyras, *C. R. l'Academie. Sci., Ser. II Univers* **1996**, *322*, 767–773.
- 1996SC1455 C.-X. Fan, X.-L. Hao, Y.-H. Ye, *Synth. Commun.* **1996**, *26*, 1455–1460.
- 1996SC1675 *Synth. Commun.* **1996**, 1675.
- 1996T1609 N. Galvez, M. Moreno-Manas, R. M. Sebastian, A. Vallribera, *Tetrahedron* **1996**, *52*, 1609–1616.
- 1996T2405 A. Amougay, O. Letsch, J.-P. Pete, O. Piva, *Tetrahedron* **1996**, *52*, 2405–2420.
- 1996T3403 C. J. Mossman, J. Aube, *Tetrahedron* **1996**, *52*, 3403–3408.
- 1996TL3213 D. R. Barn, J. R. Morphy, D. C. Rees, *Tetrahedron Lett.* **1996**, *37*, 3213–3216.
- 1996TL4569 J. L. G. Ruano, A. M. M. Castro, J. H. R. Ramos, *Tetrahedron Lett.* **1996**, *37*, 4569–4572.
- 1996TL5483 H. Wenschuh, M. Beyermann, R. Winter, M. Bienert, D. Ionescu, L. A. Carpino, *Tetrahedron Lett.* **1996**, *37*, 5483–5486.
- 1996TL6287 S. Takayama, W. J. Moree, C.-H. Wong, *Tetrahedron Lett.* **1996**, *37*, 6287–6290.
- 1996TL7171 M. Adamczyk, J. R. Fishpaugh, *Tetrahedron Lett.* **1996**, *37*, 7171–7172.
- B-1996MI515 S. A. Kates, E. Dickmann, A. El-Faham, L. W. Herman, D. Ionescu, B. F. McGuinness, S. A. Triolo, F. Albericio, L. A. Carpino, in *Techniques in Protein Chemistry VII, [Symposium of the Protein Society]*, 9th, Boston, July 8-12, 1995, **1996**, pp. 515–523.
- 1997CC2319 K. J. Hale, J. Cai, *Chem. Comm.* **1997**, 2319–2320.
- 1997CSR269 J. Aube, *Chem. Soc. Rev.* **1997**, *26*, 269–278.
- 1997HCA1 C. Guibourdenche, D. Seebach, F. Natt, *Helv. Chim. Acta* **1997**, *80*, 1–13.
- 1997JCS(P1)1099 O. Meth-Cohn, M.-X. Wang, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1099–1104.
- 1997JOC2594 I. E. Pop, B. P. Deprez, A. L. Tartar, *J. Org. Chem.* **1997**, *62*, 2594–2603.
- 1997JOC4442 P. Metz, B. Hungerhoff, *J. Org. Chem.* **1997**, *62*, 4442–4448.
- 1997MI110 D. T. Elmore, *Amino Acids, Peptides, and Proteins* **1997**, *28*, 110–165.
- 1997MI139 S. S. Elmorsy, A. A. S. El-Ahl, F. M. Motty, F. A. Amer, *Egypt. J. Chem.* **1997**, *40*, 139–147.
- 1997MI1419 T. Sugai, T. Yamazaki, M. Yokoyama, H. Ohta, *Biosci., Biotechnol., Biochem.* **1997**, *61*, 1419–1427.
- 1997MI169 P. N. Sophiamma, K. Sreekumar, *Reactive & Functional Polymers* **1997**, *35*, 169–177.
- 1997MI2048 B. Izzo, C. L. Harrell, M. T. Klein, *AIChE J.* **1997**, *43*, 2048–2058.
- 1997MI297 Z. N. da Rocha, G. Chiericato Jr., E. Tfouni, *Advances in Chemistry Series* **1997**, *253*, 297–313.
- 1997MI371 Y. Izumi, *Catal. Today* **1997**, *33*, 371–409.
- 1997MI442 J. H. Lee, J. D. Kim, *Bull. Korean Chem. Soc.* **1997**, *18*, 442–444.
- 1997MI863 P. N. Sophiamma, K. Sreekumar, *Eur. Polym. J.* **1997**, *33*, 863–867.
- 1997PIA49 P. N. Sophiamma, K. Sreekumar, *Proc. -Indian Acad. Sci., Chem. Sci.* **1997**, *109*, 49–59.
- 1997SC3119 D. S. Bose, S. M. Baquer, *Synth. Commun.* **1997**, *27*, 3119–3123.

- 1997T3805 P. Nongkunsarn, C. A. Ramsden, *Tetrahedron* **1997**, 53, 3805–3830.
 1997T7587 T. Maugard, M. Remaud-Simeon, D. Petre, P. Monsan, *Tetrahedron* **1997**, 53, 7587–7594.
 1997TL5359 P. Froyen, *Tetrahedron Lett.* **1997**, 38, 5359–5362.
 1997TL8837 T. K. Hollis, L. E. Overman, *Tetrahedron Lett.* **1997**, 38, 8837–8840.
 1997USP5594134 Ho, G.-j.; Mathre, D. J. US Patent 5594134 (**1997**) CAN 126:157392.
 1998BMCCL1089 W. Xu, R. Mohan, M. M. Morrissey, *Biorg. Med. Chem. Lett.* **1998**, 8, 1089–1092.
 1998CC499 K. Dendrinis, J. Jeong, W. Huang, A. G. Kalivretenos, *Chem. Comm.* **1998**, 499–500.
 1998H367 T. Kawasaki, H. Ohtsuka, A. Mihira, M. Sakamoto, *Heterocycles* **1998**, 47, 367–373.
 1998JCR(S)268 B. N. Goswami, N. Borthakur, A. C. Ghosh, *J. Chem. Res., Synop.* **1998**, 268–269.
 1998JCS(P1)1913 T.-S. Li, A.-X. Li, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1913–1918.
 1998JCS(P1)2973 K. Kondo, E. Sekimoto, K. Miki, Y. Murakami, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2973–2974.
 1998JMOC(B)13 T. Maugard, M. Remaud-Simeon, D. Petre, P. Monsan, *J. Mol. Catal. B: Enz.* **1998**, 5, 13–17.
 1998JOC2062 W. R. Roush, L. A. Pfeifer, *J. Org. Chem.* **1998**, 63, 2062–2063.
 1998MI89 A. W. Bunch, *Antonie van Leeuwenhoek* **1998**, 74, 89–97.
 1998MI126 D. T. Elmore, *Amino Acids, Peptides, and Proteins* **1998**, 29, 126–174.
 1998MI165 F. Effenberger, B. W. Graef, *J. Biotechnol.* **1998**, 60, 165–174.
 1998MI267 M. A. Camblor, A. Corma, H. Garcia, V. Semmer-Herledan, S. Valencia, *J. Catal.* **1998**, 177, 267–272.
 1998MI455 V. Kepe, S. Polanc, M. Kocivar, *Acta Chim. Slov.* **1998**, 45, 455–462.
 1998MI795 J. C. Feng, B. Liu, L. Dai, N. S. Bian, *Chin. Chem. Lett.* **1998**, 9, 795–796.
 1998S1463 I. Coldham, P. M. Houdayer, R. A. Judkins, D. R. Witty, *Synthesis* **1998**, 1463–1466.
 1998SC2275 M. Ghiaci, G. H. Imanzadeh, *Synth. Commun.* **1998**, 28, 2275–2280.
 1998T241 L. A. Carpino, D. Ionescu, A. El-Faham, P. Henklein, H. Wenschuh, M. Bienert, M. Beyermann, *Tetrahedron Lett.* **1998**, 39, 241–244.
 1998T1243 J. F. Reichwein, R. M. J. Liskamp, *Tetrahedron Lett.* **1998**, 39, 1243–1246.
 1998TA1065 Y. Uozumi, K. Kato, T. Hayashi, *Tetrahedron: Asymmetry* **1998**, 9, 1065–1072.
 1998TA1097 K. Matoishi, A. Sano, N. Imai, T. Yamazaki, M. Yokoyama, T. Sugai, H. Ohta, *Tetrahedron: Asymmetry* **1998**, 9, 1097–1102.
 1998TA3213 F. Cohen, L. E. Overman, *Tetrahedron: Asymmetry* **1998**, 9, 3213–3222.
 1998TL4773 Z. Tang, J. C. Pelletier, *Tetrahedron Lett.* **1998**, 39, 4773–4776.
 1998TL6991 J. Fitt, K. Prasad, O. Repic, T. J. Blacklock, *Tetrahedron Lett.* **1998**, 39, 6991–6992.
 1998USP5728876 U.S. Pat. **1998**, 5728876.
 B-1999MI337 Ye, Y.-H.; Fan, C.-X.; Zhang, D.-Y.; Xie, H.-B.; Hao, X.-L.; Tian, G.-L. *Peptides: Frontiers of Peptide Science, Proceedings of the American Peptide Symposium, 15th, Nashville, June 14-19, 1997*, **1999**, 337–338.
 B-1999MIORGN-147 Y.-G. Suh, S.-A. Kim, J.-K. Jung, D.-Y. Shin, K.-H. Min, B.-A. Goo, in *Book of Abstracts, 218th ACS National Meeting, New Orleans, Aug. 22-26, 1999*, ORGN-147
 1999AG(E)240 K. C. Nicolaou, H. J. Mitchell, N. F. Jain, N. Winssinger, R. Hughes, T. Bando, *Angew. Chem. Int. Ed.* **1999**, 38, 240–244.
 1999AG(E)3545 Y.-G. Suh, S.-A. Kim, J.-K. Jung, D.-Y. Shin, K.-H. Min, B.-A. Koo, H.-S. Kim, *Angew. Chem., Int. Ed. Engl.* **1999**, 38, 3545–3547.
 1999AJC83 *Aust. J. Chem.* **1999**, 83.
 1999CI(M)1305 D. Bianchi, A. Bosetti, E. Battistel, *Chim. Ind. (Milan)* **1999**, 81, 1305–1308.
 1999CL855 T. Mantani, K. Shiomi, T. Ishihara, H. Yamanaka, *Chem. Lett.* **1999**, 855–856.
 1999EJO3223 C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Eur. J. Org. Chem.* **1999**, 3223–3235.
 1999IJC(B)974 M. M. Lakouraj, K. Bahrami, *Indian J. Chem., Sect. B* **1999**, 38B, 974–975.
 1999JA2933 Y. Donde, L. E. Overman, *J. Am. Chem. Soc.* **1999**, 121, 2933–2934.
 1999JHC601 H. Sharghi, K. Niknam, A. R. Massah, *J. Heterocycl. Chem.* **1999**, 36, 601–606.
 1999JOC7511 N. Kise, N. Ueda, *J. Org. Chem.* **1999**, 64, 7511–7514.
 1999JOC8936 M. A. Bailen, R. Chinchilla, D. J. Dodsworth, C. Najera, *J. Org. Chem.* **1999**, 64, 8936–8939.
 1999MI83 C. R. Strauss, *Aust. J. Chem.* **1999**, 52, 83–96.
 1999MI111 D. T. Elmore, *Amino Acids, Peptides, and Proteins* **1999**, 30, 111–162.
 1999MI153 B. Falkiewicz, *Nucleic Acids Symp. Ser.* **1999**, 42, 153–154.
 1999MI279 S. Sakakibara, *Biopolymers* **1999**, 51, 279–296.
 1999MI373 T. Sugai, *Curr. Org. Chem.* **1999**, 3, 373–406.
 1999MI507 E. Falb, T. Yechezkel, Y. Salitra, C. Gilon, *Journal of Peptide Research* **1999**, 53, 507–517.
 1999MI535 C. S. Chin, S. Y. Kim, K.-S. Joo, G. Won, D. Chong, *Bull. Korean Chem. Soc.* **1999**, 20, 535–538.
 1999MI925 C. Ramakrishna, H. Dave, M. Ravindranathan, *J. Sci. Ind. Res.* **1999**, 58, 925–947.
 1999MI1167 J. S. Larsen, M. A. Zahran, E. B. Pedersen, C. Nielsen, *Monatsh. Chem.* **1999**, 130, 1167–1173.
 1999SC79 V. V. S. Babu, K. Gayathri, H. N. Gopi, *Synth. Commun.* **1999**, 29, 79–91.
 1999S1200 I. Degani, S. Dughera, R. Fochi, E. Serra, *Synthesis* **1999**, 1200–1208.
 1999SL1957 K. Kim, K. Le, *Synlett* **1999**, 1957–1959.
 1999T2713 N. Robertson, L. Jiang, R. Ramage, *Tetrahedron* **1999**, 55, 2713–2720.
 1999T6813 L. A. Carpino, A. El-Faham, *Tetrahedron* **1999**, 55, 6813–6830.
 1999TA721 E. Garcia-Urdiales, F. Rebollo, V. Gotor, *Tetrahedron: Asymmetry* **1999**, 10, 721–726.
 1999TL2501 W. Wang, J. S. McMurray, *Tetrahedron Lett.* **1999**, 40, 2501–2504.
 1999TL2611 P. Saravanan, V. K. Singh, *Tetrahedron Lett.* **1999**, 40, 2611–2614.
 1999TL2649 T.-P. Loh, G.-Q. Cao, Z. Yin, *Tetrahedron Lett.* **1999**, 40, 2649–2652.
 1999TL3735 C. Martin, M. Bortolussi, R. Bloch, *Tetrahedron Lett.* **1999**, 40, 3735–3736.
 1999TL8301 P. Li, J. C. Xu, *Tetrahedron Lett.* **1999**, 40, 8301–8304.
 1999T11755 G. E. Keck, T. T. Wager, S. F. McHardy, *Tetrahedron* **1999**, 55, 11755–11772.
 1999USP5994557 Kim, C. S.; Cha, K. S. US Patent 5994557 (**1999**) CAN 132:3112.

- 2000AG(E)234
2000CC119
2000CC43
2000CEJ463
2000CJC1363
2000GC104
2000JCO710
2000JCR(S)482
2000JCS(P1)2223
2000JCS(P1)3815

2000JCS(P1)4328
2000JCS(P1)4413

2000JOC1672
2000JOC2114
2000JOC2951
2000JOC8210
2000M549
2000MI110
2000MI118

2000MI120
2000MI1552

2000MI161
2000MI39
2000MI41
2000MI456
2000MI463
2000OL1815
2000OL261
2000T4437
2000T5843
2000T8119
2000T9949
2000TA1123

2000TA1719
2000TA4593

2000TL2239
2000TL2463
2000TL2467

2000TL3747
2000TL6017

2000TL721
2000TL9997
2001AG(E)2507
2001AG(E)647
2001JCO401
2001JCO604
2001JCS(P2)522
2001JMOC(A)69

2001JMOC(B)249

2001JMOC(B)77
2001JOC5016
2001MI0107438

2001MI107
2001MI113
2001MI207

2001MI43
2001OL279
2001OL3067
- X. X. XXXX, *Angew. Chem. Int. Ed. Engl.* **2000**, 234.
Y. Ie, G. C. Fu, *Chem. Comm.* **2000**, 119–120.
A. G. Al-Sehemi, R. S. Atkinson, J. Fawcett, D. R. Russell, *Chem. Comm.* **2000**, 43–44.
R. Gunther, F. Bordusa, *Chem. Eur. J.* **2000**, 6, 463–467.
J.-P. Picard, *Can. J. Chem.* **2000**, 78, 1363–1379.
N. Narendar, P. Srinivasu, S. J. Kulkarni, K. V. Raghavan, *Green Chem.* **2000**, 2, 104–105.
S. Braese, S. Dahmen, M. Pfefferkorn, *J. Comb. Chem.* **2000**, 2, 710–715.
B. Das, N. Ravindranath, B. Venkataiah, P. Madhusudhan, *J. Chem. Res., Synop.* **2000**, 482–483.
B. C. Ranu, P. Dutta, A. Sarkar, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2223–2225.
S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, S. J. Taylor, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195.
V. V. S. Babu, K. Ananda, G.-R. Vasanthakumar, *J. Chem. Soc., Perkin Trans. 1* **2000**, 4328–4331.
A. G. Al-Sehemi, R. S. Atkinson, J. Fawcett, D. R. Russell, *J. Chem. Soc., Perkin Trans. 1* **2000**, 4413–4421.
R. Gunther, A. Stein, F. Bordusa, *J. Org. Chem.* **2000**, 65, 1672–1679.
J. J. Hans, R. W. Driver, S. D. Burke, *J. Org. Chem.* **2000**, 65, 2114–2121.
P. Li, J. C. Xu, *J. Org. Chem.* **2000**, 65, 2951–2958.
A. R. Katritzky, H.-Y. He, K. Suzuki, *J. Org. Chem.* **2000**, 65, 8210–8213.
F. Van Rantwijk, M. A. P. J. Hacking, R. A. Sheldon, *Monatsh. Chem.* **2000**, 131, 549–569.
P. Li, J. C. Xu, *Journal of Peptide Research* **2000**, 55, 110–119.
D. R. Millic, D. M. Opsenica, b. Adnadevic, B. A. Solaja, *Molecules [Electronic Publication]* **2000**, 5, 118–126.
D. T. Elmore, *Amino Acids, Peptides, and Proteins* **2000**, 31, 120–173.
V. O. Koz'minykh, N. M. Igidov, E. S. Berezina, E. N. Koz'minykh, Y. S. Kasatkina, *Russ. Chem. Bull. (Translation of Izvestiya Akademii Nauk, Seriya Khimicheskaya)* **2000**, 49, 1552–1556.
P. N. Sophiamma, K. Sreekumar, *Designed Monomers and Polymers* **2000**, 3, 161–170.
C. S. Cheong, S. H. Lee, *Kor. J. Med. Chem.* **2000**, 10, 39–51.
V. V. S. Babu, K. Ananda, *Letters in Peptide Science* **2000**, 7, 41–46.
P. Li, J.-C. Xu, *Chin. J. Chem.* **2000**, 18, 456–466.
R. Gunther, F. Bordusa, *Chem. Eur. J.* **2000**, 6, 463–467.
N. Thieriet, F. Guibe, F. Albericio, *Org. Lett.* **2000**, 2, 1815–1817.
A. G. M. Barrett, S. M. Cramp, R. S. Roberts, F. J. Zecri, *Org. Lett.* **2000**, 2, 261–264.
P. Li, J.-C. Xu, *Tetrahedron* **2000**, 56, 4437–4445.
K. Kondo, E. Sekimoto, J. Nakao, Y. Murakami, *Tetrahedron* **2000**, 56, 5843–5856.
P. Li, J.-C. Xu, *Tetrahedron* **2000**, 56, 8119–8131.
P. Li, J. C. Xu, *Tetrahedron* **2000**, 56, 9949–9955.
M.-X. Wang, G. Lu, G.-J. Ji, Z.-T. Huang, O. Meth-Cohn, J. Colby, *Tetrahedron: Asymmetry* **2000**, 11, 1123–1135.
L. Somsak, V. Nagy, *Tetrahedron: Asymmetry* **2000**, 11, 1719–1727.
L. M. van Langen, N. H. P. Oosthoek, D. T. Guranda, F. van Rantwijk, V. K. Svedas, R. A. Sheldon, *Tetrahedron: Asymmetry* **2000**, 11, 4593–4600.
A. G. Al-Sehemi, R. S. Atkinson, J. Fawcett, D. R. Russell, *Tetrahedron Lett.* **2000**, 41, 2239–2242.
R. Chinchilla, D. J. Dodsworth, C. Najera, J. M. Soriano, *Tetrahedron Lett.* **2000**, 41, 2463–2466.
C. J. Cobley, M. Van den Heuvel, A. Abbadi, J. G. De Vries, *Tetrahedron Lett.* **2000**, 41, 2467–2470.
K. J. Merchant, *Tetrahedron Lett.* **2000**, 41, 3747–3749.
R. Chidambaram, J. Zhu, K. Penmetsa, D. Kronenthal, J. Kant, *Tetrahedron Lett.* **2000**, 41, 6017–6020.
P. Li, J.-C. Xu, *Tetrahedron Lett.* **2000**, 41, 721–724.
L. Lemoucheux, J. Rouden, M. C. Lasne, *Tetrahedron Lett.* **2000**, 41, 9997–10001.
J. L. G. Ruano, M. C. Garcia, N. M. Laso, A. M. M. Castro, J. H. R. Ramos, *Angew. Chem., Int. Ed. Engl.* **2001**, 40, 2507–2509.
S. Arai, S. Bellemin-Laponnaz, G. C. Fu, *Angew. Chem., Int. Ed. Engl.* **2001**, 40, 647.
S. Kobayashi, H. Kitagawa, R. Matsubara, *J. Comb. Chem.* **2001**, 3, 401–403.
J. A. Tripp, F. Svec, J. M. J. Frechet, *J. Comb. Chem.* **2001**, 3, 604–611.
A. J. Kirby, I. V. Komarov, N. Feeder, *J. Chem. Soc., Perkin Trans. 2* **2001**, 522–529.
B. M. Choudary, M. L. Kantam, B. Bharathi, C. R. Venkat Reddy, *J. Mol. Catal. A: Chem.* **2001**, 168, 69–73.
M. A. Wegman, U. Heinemann, F. van Rantwijk, A. Stolz, R. A. Sheldon, *J. Mol. Catal. B: Enz.* **2001**, 11, 249–253.
M. X. Wang, J. J. Li, G. J. Ji, J. S. Li, *J. Mol. Catal. B: Enz.* **2001**, 14, 77–83.
N. C. de Lucas, J. C. Netto-Ferreira, J. Andraos, J. C. Scaiano, *J. Org. Chem.* **2001**, 66, 5016–5021.
Crichfield, K. S.; Hart, J. E.; Vaid, R. K.; Verral II, D. E. *Int. Pat.* 0107438 (**2001**) CAN 134:131366.
D. T. Elmore, *Amino Acids, Peptides, and Proteins* **2001**, 32, 107–162.
G.-Q. Feng, M.-X. Wang, *Chin. J. Chem.* **2001**, 19, 113–115.
B. M. Choudary, V. Bhaskar, M. L. Kantam, K. K. Rao, K. V. Raghavan, *Catal. Lett.* **2001**, 74, 207–211.
E. Purushothaman, M. P. Rajan, T. T. Marykutty, *Indian J. Het. Chem.* **2001**, 11, 43–46.
T.-P. Loh, Q.-Y. Hu, *Org. Lett.* **2001**, 3, 279–281.
E. Bourguet, J.-L. Baneres, J.-P. Girard, J. Parello, J.-P. Vidal, X. Lusinchi, J.-P. Declercq, *Org. Lett.* **2001**, 3, 3067–3070.

- 2001OL311 M. Arisawa, M. Yamaguchi, *Org. Lett.* **2001**, 3, 311–312.
2001OL3729 C.-T. Chen, J.-H. Kuo, C.-H. Li, N. B. Barhate, S.-W. Hon, T.-W. Li, S.-D. Chao, C.-C. Liu, Y.-C. Li, I. H. Chang, J.-S. Lin, C.-J. Liu, Y. C. Chou, *Org. Lett.* **2001**, 3, 3729–3732.
2001OPP203 F. Albericio, R. Chinchilla, D. J. Dodsworth, C. Najera, *Org. Prep. Proced. Int.* **2001**, 33, 203–303.
2001SC1201 H.-J. Ren, Y.-G. Wang, *Synth. Commun.* **2001**, 31, 1201–1204.
2001SC3577 B. H. Kim, J. W. Cheong, R. Han, Y. M. Jun, W. Baik, B. M. Lee, *Synth. Commun.* **2001**, 31, 3577–3586.
2001SC431 A. Sharifi, F. Mohsenzadeh, M. M. Mojtahedi, M. R. Saidi, S. Balalaie, *Synth. Commun.* **2001**, 31, 431–434.
2001SL1092 B. F. Bonini, C. Femoni, M. Comes-Franchini, M. Fochi, G. Mazzanti, A. Ricci, G. Varchi, *Synlett* **2001**, 1092–1096.
2001SL206 P. Kumar, R. K. Pandey, M. S. Bodas, M. K. Dongare, *Synlett* **2001**, 206–209.
2001SL1968 *Synlett* **2001**, 1968.
2001T9309 N. Maezaki, A. Furusawa, S. Uchida, T. Tanaka, *Tetrahedron* **2001**, 57, 9309–9315.
2001TA1645 D. T. Guranda, L. M. van Langen, F. van Rantwijk, R. A. Sheldon, V. K. Svedas, *Tetrahedron: Asymmetry* **2001**, 12, 1645–1650.
2001TA3267 M. I. Youshko, F. van Rantwijk, R. A. Sheldon, *Tetrahedron: Asymmetry* **2001**, 12, 3267–3271.
2001TA3305 Z.-L. Wu, Z.-Y. Li, *Tetrahedron: Asymmetry* **2001**, 12, 3305–3312.
2001TL2617 D. D. Diaz, S. Yao, M. G. Finn, *Tetrahedron Lett.* **2001**, 42, 2617–2619.
2001TL6659 B. Stefane, U. Cernigoj, M. Kocevar, S. Polanc, *Tetrahedron Lett.* **2001**, 42, 6659–6662.
2001TL6703 M. Lannuzel, M. Lamothe, M. Perez, *Tetrahedron Lett.* **2001**, 42, 6703–6705.
2001TL8123 S. Chandrasekhar, K. Gopalaiah, *Tetrahedron Lett.* **2001**, 42, 8123–8125.
2001USP6211384 *U.S. Pat.* **2001**, 6211384.
2001USP6214608 *U.S. Pat.* **2001**, 6214608.
2001USP6215024 Choudary, B. M.; Bhaskar, V.; Kantam, M. L.; Rao, K. K.; Raghavan, K. V. US Patent 6215024 (2001) CAN 134:280522.
2001USP6271005 Khumtaveeporn, K.; Cosway, T. C.; Yeh, W.-l. US Patent 6271005 (2001) CAN 135:151710.
B-2001MI273 H. Echner, W. Voelter, in *Innovation and Perspectives in Solid Phase Synthesis & Combinatorial Libraries: Peptides, Proteins and Nucleic Acids—Small Molecule Organic Chemistry Diversity, Collected Papers, International Symposium, 6th, York, United Kingdom, Aug. 31–Sept. 4, 1999*, **2001**, 273–276.
2002AG(E)512 *Angew. Chem. Int. Ed. Engl.* **2002**, 512.
2002BMCL1799 R. B. Nicewonger, L. Ditto, D. Kerr, L. Varady, *Biorg. Med. Chem. Lett.* **2002**, 12, 1799–1802.
2002BMCL1809 A. R. Katritzky, B. V. Rogovoy, N. Kirichenko, V. Vvedensky, *Biorg. Med. Chem. Lett.* **2002**, 12, 1809–1811.
2002EJO1026 O. Lagrille, J. Taillades, L. Boiteau, A. Commeyras, *Eur. J. Org. Chem.* **2002**, 1026–1032.
2002H369 M. Botta, F. Corelli, E. Petricci, C. Seri, *Heterocycles* **2002**, 56, 369–377.
2002HCA2409 A. V. Kachalova, D. A. Stetsenko, E. A. Romanova, V. N. Tashlitsky, M. J. Gait, T. S. Oretskaya, *Helv. Chim. Acta* **2002**, 85, 2409–2416.
2002IC4798 M. N. Kopylovich, V. Kukushkin, Yu. M. Haukka, J. R. Frausto da Silva Joao, A. J. L. Pombeiro, *Inorg. Chem.* **2002**, 41, 4798–4804.
2002JA1871 *J. Am. Chem. Soc.* **2002**, 1871.
2002JA13790 A. W. Acton, A. D. Allen, L. M. Antunes, A. V. Fedorov, K. Najafian, T. T. Tidwell, B. D. Wagner, *J. Am. Chem. Soc.* **2002**, 124, 13790–13794.
2002JCC587 F. Fagalde, N. D. Lis De Katz, N. E. Katz, *J. Coord. Chem.* **2002**, 55, 587–593.
2002JCO329 M. C. Pirrung, K. Park, L. N. Tumey, *J. Comb. Chem.* **2002**, 4, 329–344.
2002JCR(S)236 J. S. Yadav, B. V. S. Reddy, A. V. Madhavi, Y. S. S. Ganesh, *J. Chem. Res., Synop.* **2002**, 236–238.
2002JMOC(A)207 P. Kumar, R. K. Pandey, M. S. Bodas, S. P. Dagade, M. K. Dongare, A. V. Ramaswamy, *J. Mol. Catal. A: Chem.* **2002**, 181, 207–213.
2002JOC6272 L. De Luca, G. Giacomelli, A. Porcheddu, *J. Org. Chem.* **2002**, 67, 6272–6274.
2002MC27 V. P. Krasnov, G. L. Levit, I. N. Andreeva, A. N. Grishakov, V. N. Charushin, O. N. Chupakhin, *Mendeleev Commun.* **2002**, 27–28.
2002MI0220821 Svedas, V.-J. K.; Guranda, D. T.; Khimiouk, A. I.; Sheldon, R. A.; Van Rantwijk, F.; Van Langen, L. M. *Int. Pat.* 0220821 (2002) CAN 136:231356.
2002MI119 G. Sabatino, B. Mulinacci, M. C. Alcaro, M. Chelli, P. Rovero, A. M. Papini, *Letters in Peptide Science* **2002**, 9, 119–123.
2002MI125 A. Di Fenza, P. Rovero, *Letters in Peptide Science* **2002**, 9, 125–129.
2002MI1575 M.-X. Wang, G.-Q. Feng, *New J. Chem.* **2002**, 26, 1575–1583.
2002MI24 D.-F. Tai, W.-C. Liaw, *FEBS Lett.* **2002**, 517, 24–26.
2002MI356 M. A. Wegman, L. M. Van Langen, F. Van Rantwijk, R. A. Sheldon, *Biotechnol. Bioeng.* **2002**, 79, 356–361.
2002MI699 B. Schulze, in *Enzyme Catalysis in Organic Synthesis, (2nd Edition)*, Wiley-VCH Verlag GmbH & Co, Weinheim, **2002**, Vol. 2, pp. 699–715.
2002MI83 D. T. Elmore, *Amino Acids, Peptides, and Proteins* **2002**, 33, 83–134.
2002OL1383 J. A. Mulder, R. P. Hsung, M. O. Frederick, M. R. Tracey, C. A. Zifcsak, *Org. Lett.* **2002**, 4, 1383–1386.
2002OPRD420 V. Gotor, *Org. Process Res. Dev.* **2002**, 6, 420–426.
2002S242 N. Zhang, U. Nubbemeyer, *Synthesis* **2002**, 242–252.
2002S733 *Synthesis* **2002**, 733.
2002SC1731 B. M. Khadilkar, V. R. Madyar, *Synth. Commun.* **2002**, 32, 1731–1734.
2002SC2535 N. Iranpoor, H. Firouzabadi, G. Aghapour, *Synth. Commun.* **2002**, 32, 2535–2541.
2002SL411 S. N. Gradl, J. J. Kennedy-Smith, J. Kim, D. Trauner, *Synlett* **2002**, 411–414.

- 2002SL625 K. V. N. S. Srinivas, E. B. Reddy, B. Das, *Synlett* **2002**, 625–627.
2002TA1315 J. Gonzalez-Sabin, V. Gotor, F. Rebollo, *Tetrahedron: Asymmetry* **2002**, 13, 1315–1320.
2002TA1695 M.-X. Wang, S.-M. Zhao, *Tetrahedron: Asymmetry* **2002**, 13, 1695–1702.
2002TA2629 M. Hensel, S. Lutz-Wahl, L. Fischer, *Tetrahedron: Asymmetry* **2002**, 13, 2629–2633.
2002TL2455 S. Chandrasekhar, K. Gopalaiah, *Tetrahedron Lett.* **2002**, 43, 2455–2457.
2002TL5529 N. Aoyagi, T. Izumi, *Tetrahedron Lett.* **2002**, 43, 5529–5531.
2002TL6039 I. Vago, I. Greiner, *Tetrahedron Lett.* **2002**, 43, 6039–6041.
2002TL6507 E. Petricci, M. Botta, F. Corelli, C. Mugnaini, *Tetrahedron Lett.* **2002**, 43, 6507–6509.
2002TL6617 M.-X. Wang, S.-M. Zhao, *Tetrahedron Lett.* **2002**, 43, 6617–6620.
2002TL7597 L. Gomez, S. Ngouela, F. Gellibert, A. Wagner, C. Mioskowski, *Tetrahedron Lett.* **2002**, 43, 7597–7599.
2002TL8467 E. Campian, B. Lou, H. Saneii, *Tetrahedron Lett.* **2002**, 43, 8467–8470.
2002TL9509 J. Kang, K. H. Yew, T. H. Kim, D. H. Choi, *Tetrahedron Lett.* **2002**, 43, 9509–9512.
2002TL9553 T. H. Kim, G.-Y. Yang, *Tetrahedron Lett.* **2002**, 43, 9553–9557.
2002USP6387692 U.S. Pat. **2002**, 6387692.
2003CC386 Z.-L. Wu, Z.-Y. Li, *J. Chem. Soc., Chem. Commun.* **2003**, 386–387.
2003GC44 B. C. Ranu, S. S. Dey, A. Hajra, *Green Chem.* **2003**, 5, 44–46.
2003HCA750 S. A. Sergeev, M. Hesse, *Helv. Chim. Acta* **2003**, 86, 750–755.
2003JOC(A)141 B. Sreedhar, V. Bhaskar, C. Sridhar, T. Srinivas, L. Kotai, K. Szentmihalyi, *J. Mol. Catal. A: Chem.* **2003**, 191, 141–147.
2003JOC(B)105 Z.-L. Wu, Z.-Y. Li, *J. Mol. Catal. B: Enz.* **2003**, 22, 105–112.
2003JOC1165 K. V. N. S. Srinivas, B. Das, *J. Org. Chem.* **2003**, 68, 1165–1167.
2003JOC2479 Z.-L. Wu, Z.-Y. Li, *J. Org. Chem.* **2003**, 68, 2479–2482.
2003JOC3718 U. Chiacchio, A. Rescifina, M. A. Chiacchio, G. Romeo, R. Romeo, *J. Org. Chem.* **2003**, 68, 3718–3720.
2003JOC4570 M.-X. Wang, S.-J. Lin, C.-S. Liu, Q.-Y. Zheng, J.-S. Li, *J. Org. Chem.* **2003**, 68, 4570–4573.
2003JOC621 M.-X. Wang, G.-Q. Feng, *J. Org. Chem.* **2003**, 68, 621–624.
2003OBC535 M.-X. Wang, Y. Wu, *Org. Biomed. Chem.* **2003**, 1, 535–540.
2003OBC541 F. Karimi, B. Langstrom, *Org. Biomed. Chem.* **2003**, 1, 541–546.
2003OM1203 K. L. Breno, M. D. Pluth, D. R. Tyler, *Organometallics* **2003**, 22, 1203–1211.
2003TL3521 A. K. Chakraborti, R. Gulhane, *Tetrahedron Lett.* **2003**, 44, 3521–3525.
2003TL4393 R. Wischnat, J. Rudolph, R. Hanke, R. Kaese, A. May, H. Theis, U. Zuther, *Tetrahedron Lett.* **2003**, 44, 4393–4394.
2003TL755 S. Chandrasekhar, K. Gopalaiah, *Tetrahedron Lett.* **2003**, 44, 755–756.

Biographical sketch



Patrick Bailey was born in Derbyshire. He undertook his B.A. (1980) and D.Phil. degrees in chemistry at Oxford, the latter on peptide chemistry under the supervision of Dr. G.T. Young. He took up a lectureship at York in 1983, before moving to the chair of organic chemistry at Heriot-Watt University (Edinburgh) in 1992, and then on to his current position as Chair of Organic Chemistry at UMIST in 2001. His research has been focused on three main themes: developing new methods for preparing heterocyclic molecules of medicinal interest; studies on the synthesis and properties of peptides; and work on protein mechanisms. He has received a Yorkshire Cancer Research Campaign Career Development Award (1986–1991), the Zeneca Research Award for Organic Chemistry in 1994, and was elected to the Royal Society of Edinburgh in 1999. His teaching has been recognized by RSC HE and Nyholm awards (1998, 2000), and the BAAS Lord Kelvin Lectureship in 1999.



Timothy Mills was born in Harlow. He received his B.A. in chemistry at Hull (1993), before moving to Nottingham/Strathclyde to carry out free-radical synthetic research for his Ph.D. (1997) with Professor J. Murphy. He then took synthetic posts in industry with Unilever and Avecia, before moving back to university research in 2000 when he joined Professor P. D. Bailey's research group. Initially based at Heriot-Watt University, working on indole alkaloid chemistry, he moved with the research group to UMIST in 2001, and is currently studying the mechanism of the PepT1 peptide transporter protein as part of a multidisciplinary project funded by the Wellcome Trust.



Rachel Pettecrew was born in Bolton. She took an HND in chemistry with computing at Portsmouth (1994), before joining Ackros Chemicals in 1994, moving to the British Textiles Technology Group in 1995, and then on to Ciba Speciality Chemicals in 1998. Between then and 2001, she took a part-time B.Sc. in applied chemistry with materials science at Manchester Metropolitan University, before joining Professor P. D. Bailey's research group at UMIST in 2001, to undertake a Ph.D. on the synthesis of peptidic analogs for probing the mechanism of action of the PepT1 peptide transporter protein. She is currently completing her Ph.D., and has started work on exploiting PepT1 for drug delivery.



Richard Price was born in Hayes. He worked at Amersham International for a couple of years before taking his first degree in chemistry at the University of Sussex (1989). He then joined Ciba Pharmaceuticals in Horsham, before taking up an EPSRC Overseas Scholarship in 1994, which allowed him to undertake a synthetic Ph.D. at UBC, Vancouver under the supervision of Dr. E. Piers. After completing his Ph.D. in 1999, he joined Professor P. D. Bailey's group at Heriot-Watt University to work on the total synthesis of indole alkaloids, moving with the group to UMIST in 2001, where he is still based. He is now exploring the commercialization of a peptidic drug-transport system, under the Wellcome Trust "University Translation Award" scheme.

5.07

N-Heterosubstituted Amides

M. A. WILSON

University of East Anglia, Norwich, UK

5.07.1	AMIDES SUBSTITUTED BY FLUORINE, CHLORINE, BROMINE, OR IODINE	297
5.07.1.1	<i>N</i> -Fluoroamides	297
5.07.1.1.1	<i>From amino acid derivatives</i>	297
5.07.1.2	<i>N</i> -Fluoroimides	297
5.07.1.3	<i>N,N</i> -Difluoroamides	297
5.07.1.4	<i>N</i> -Chloroamides	297
5.07.1.4.1	<i>From amides</i>	298
5.07.1.5	<i>N</i> -Chloroimides	298
5.07.1.6	<i>N,N</i> -Dichloroamides	298
5.07.1.7	<i>N</i> -Hetero- <i>N</i> -chloroamides	298
5.07.1.7.1	<i>From hydroxamates</i>	299
5.07.1.7.2	<i>From ethoxycarbonylhydrazines</i>	299
5.07.1.8	<i>N</i> -Bromoamides	299
5.07.1.8.1	<i>From amides</i>	299
5.07.1.8.2	<i>Using t-butyl N,N-dibromocarbamate</i>	300
5.07.1.9	<i>N</i> -Bromoimides	300
5.07.1.9.1	<i>From imides</i>	300
5.07.1.9.2	<i>From N-metalimides</i>	300
5.07.1.10	<i>N,N</i> -Dibromoamides	300
5.07.1.10.1	<i>From carbamates</i>	301
5.07.1.11	<i>N</i> -Iodo(I) Amides	301
5.07.1.12	<i>N</i> -Iodo(I) Imides	301
5.07.1.13	<i>N,N</i> -Diiodoamides	301
5.07.1.14	<i>N</i> -Iodo(III) Amides	301
5.07.1.15	<i>N</i> -Iodo(III) Imides	301
5.07.2	AMIDES SUBSTITUTED BY OXYGEN	301
5.07.2.1	Hydroxamic Acids	301
5.07.2.1.1	<i>From acylation of hydroxylamines</i>	301
5.07.2.1.2	<i>From the addition of isocyanates to hydroxylamines</i>	305
5.07.2.1.3	<i>From the ring opening of cyclic acid anhydrides</i>	305
5.07.2.1.4	<i>From N-substituted phthalimides</i>	306
5.07.2.1.5	<i>From nitrile oxides</i>	306
5.07.2.1.6	<i>From oximes</i>	306
5.07.2.1.7	<i>From O-acyl to N-acyl transfer</i>	307
5.07.2.1.8	<i>From solid-phase synthesis</i>	307
5.07.2.2	Hydroxamates	308
5.07.2.2.1	<i>From acylation of alkoxyamines</i>	308
5.07.2.2.2	<i>From addition of hydroxylamines to isocyanates</i>	308
5.07.2.2.3	<i>From methylketenes</i>	308
5.07.2.2.4	<i>From oxidation of O-alkylhydroxamates</i>	308
5.07.2.2.5	<i>From N-chloro-O-alkylhydroxamates</i>	309
5.07.2.2.6	<i>From the formylation of hydroxylamines</i>	309
5.07.2.2.7	<i>From the addition of hydroxylamines to esters</i>	310
5.07.2.2.8	<i>Formation of Weinreb amides</i>	310
5.07.2.2.9	<i>From the reaction of hydroxylamines with succinic anhydride</i>	310
5.07.2.2.10	<i>From the ring opening of pyrrolidinones</i>	311
5.07.2.2.11	<i>From fragmentation of imides</i>	311

5.07.2.2.12	From 2-imino-1,3-oxathiolanes	311
5.07.2.2.13	From ozonolysis of O-alkyloximes	311
5.07.2.2.14	From palladium-catalyzed reactions of N-methoxy-N-methylcarbamoylechloride	312
5.07.2.2.15	From palladium-catalyzed carbonylation reactions	312
5.07.2.2.16	From reactions with isatoic anhydride	312
5.07.2.2.17	From rearrangement of N-protected diazo ketones	313
5.07.2.2.18	From ring opening of gem-dicyano epoxides	313
5.07.2.2.19	From N-methoxy-N-methylurea	313
5.07.2.2.20	From alkyl halides	314
5.07.2.2.21	From aryl halides	314
5.07.3	AMIDES SUBSTITUTED BY SULFUR, SELENIUM, OR TELLURIUM	314
5.07.3.1	Amide Derivatives: Oxidation State +2, Dicoordinate	314
5.07.3.1.1	From amides	314
5.07.3.1.2	From sulfenamides	315
5.07.3.1.3	From acylation of ammonium thiocyanate	315
5.07.3.1.4	From sulphenyl chlorides	315
5.07.3.1.5	From ring opening of imino-phthalides	316
5.07.3.2	Amide Derivatives: Oxidation State +4, Tricoordinate	316
5.07.3.2.1	From sulfinamides	316
5.07.3.3	Amide Derivatives: Oxidation State +6, Tetracoordinate	317
5.07.3.3.1	From acylation of sulfonamides	317
5.07.3.3.2	From sulfonylation of amides	320
5.07.3.3.3	From sulfonyl isocyanates	321
5.07.3.3.4	From sulfonyl azides	321
5.07.3.3.5	From oxidation of N-acylsulfinamides	322
5.07.3.3.6	From 1-acyl-2-(alkylsulfonyl)hydrazines	322
5.07.4	AMIDES SUBSTITUTED BY NITROGEN	323
5.07.4.1	Acylhydrazine Derivatives	323
5.07.4.1.1	From acylation of hydrazine and its derivatives	323
5.07.4.1.2	From acylation of N-silylhydrazines	332
5.07.4.1.3	From acylation of t-butoxycarbonylhydrazines	332
5.07.4.1.4	From reaction of alcohols, ethers, and thioethers	332
5.07.4.1.5	From alkyl and aryl halide compounds	334
5.07.4.1.6	From reduction of hydrazones	335
5.07.4.1.7	From ring opening of aziridinium ion species	335
5.07.4.1.8	From malonamic acid derivatives	337
5.07.4.1.9	From arylation of hydrazides	337
5.07.4.1.10	From 1-amino-5-hydroxytriazole derivatives	337
5.07.4.2	N-Nitrosoamides	338
5.07.4.2.1	From amides	338
5.07.4.3	N-Nitroamides	338
5.07.4.3.1	From amides	338
5.07.4.4	Acylhydrazones	338
5.07.4.4.1	From acylation of hydrazones	338
5.07.4.4.2	From acylhydrazines	339
5.07.4.4.3	From thiosemicarbazides	340
5.07.4.4.4	From vinyl esters	341
5.07.4.5	N,N-Diacylhydrazones	341
5.07.4.6	N-Acyl Triazenes	341
5.07.4.7	N-Acyl-N-(4-nitrobenzenesulfonyl) Triazenes	342
5.07.4.7.1	From diazo-transfer to lactones	342
5.07.5	AMIDES SUBSTITUTED BY PHOSPHORUS, ANTIMONY, ARSENIC, OR BISMUTH	342
5.07.5.1	Amide Derivatives: Oxidation State +3, Tricoordinate	342
5.07.5.1.1	From amides	342
5.07.5.1.2	From silylamides	343
5.07.5.2	Amide Derivatives: Oxidation State +3, Tetracoordinate	344
5.07.5.3	Amide Derivatives: Oxidation State +5, Tetracoordinate	344
5.07.5.3.1	From amides	344
5.07.5.3.2	From N-chloroamides	344
5.07.5.3.3	From acylation of phosphoramines	344
5.07.5.3.4	From isocyanates	346
5.07.5.3.5	From acyl azides	346
5.07.5.3.6	From ring-opening reactions	347
5.07.6	AMIDES SUBSTITUTED BY SILICON	347
5.07.6.1	N-Silylamide Derivatives	347
5.07.6.1.1	From silylation of amides	347
5.07.6.1.2	From acylation of N-silylamines	348
5.07.6.1.3	From ring opening of oxazolines	349
5.07.6.1.4	From hydrosilylation reactions	350
5.07.7	AMIDES SUBSTITUTED BY BORON OR ALUMINUM	350
5.07.8	AMIDES SUBSTITUTED BY METALS	350

This chapter provides an update regarding the chemistry of *N*-heterosubstituted amides detailing recent literature since the publication of COFGT (1995) <1995COFGT(5)309>.

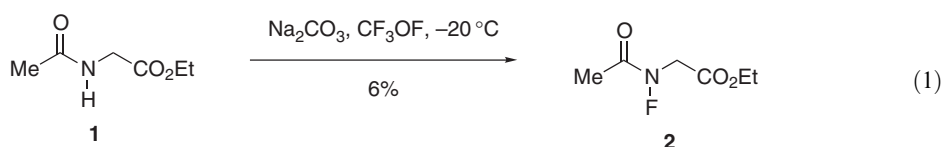
5.07.1 AMIDES SUBSTITUTED BY FLUORINE, CHLORINE, BROMINE, OR IODINE

5.07.1.1 N-Fluoroamides

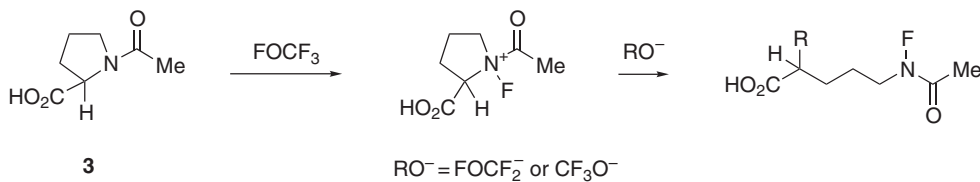
The synthesis of *N*-fluoroamides from amides and lactams, *O*-silyl enol ethers, perfluoromethanimine, and fluoroamines has been reviewed in COFGT (1995). There have been no significant advances with regard to the synthesis of *N*-fluoroamides.

5.07.1.1.1 From amino acid derivatives

The reaction of trifluoromethyl hypofluorite (CF_3OF) with *N*-acetylamino acid esters **1** provides the corresponding fluoroamides **2** in low yields (Equation (1)) <1996JFC1>.



It was observed that the fluorination of the nitrogen atom of *N*-acetylproline **3** using CF_3OF resulted in the formation of a large number of ring-opened fluorinated species (Scheme 1) <1996JFC1>.



Scheme 1

5.07.1.2 N-Fluoroimides

The fluorination of imides to provide the corresponding *N*-fluoroimides has been previously described in COFGT (1995). There have been no major advances with regard to the synthesis of *N*-fluoroimides.

5.07.1.3 N,N-Difluoroamides

The synthesis of *N,N*-difluoroamides from α -diketones and fluorinated acyl fluorides has been reviewed in COFGT (1995). There have been no significant advances with regard to the synthesis of *N,N*-difluoroamides.

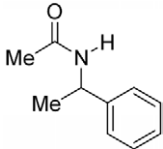
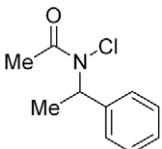
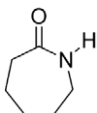
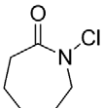
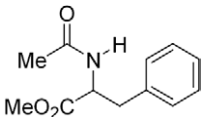
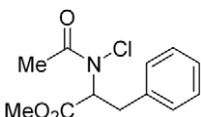
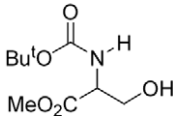
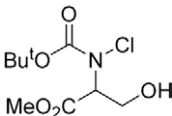
5.07.1.4 N-Chloroamides

The synthesis of *N*-chloroamides from both the chlorination of amides and the addition to imines has been documented in COFGT (1995). There have been no major advances with regard to the synthesis of *N*-chloroamides.

5.07.1.4.1 From amides

Treatment of amides with potassium hydrogen monopersulfate (Oxone[®]) supported on wet alumina in the presence of sodium chloride provides the corresponding *N*-chloroamides (Table 1) <2000SL813>. This protocol is applicable to a variety of *N*-acylamino acid derivatives, including serine-derived compounds.

Table 1 Chlorination of amides and lactams

$ \begin{array}{ccc} \text{R}^1-\text{C}(=\text{O})-\text{N}(\text{H})\text{R}^2 & \xrightarrow[\text{Al}_2\text{O}_3 \text{ wet, CHCl}_3]{\text{Oxone}^{\text{®}}, \text{NaCl}} & \text{R}^1-\text{C}(=\text{O})-\text{N}(\text{Cl})\text{R}^2 \\ & 45\text{ }^{\circ}\text{C, 2-5 h} & \end{array} $		
R^1CONHR^2	$\text{R}^1\text{CONH}(\text{Cl})\text{R}^2$	Yield (%)
		93
		97
		82
		96

5.07.1.5 N-Chloroimides

The chlorination of imides to provide the corresponding *N*-chloroimides has been previously described in COFGT (1995). There have been no significant advances with regard to the synthesis of *N*-chloroimides.

5.07.1.6 N,N-Dichloroamides

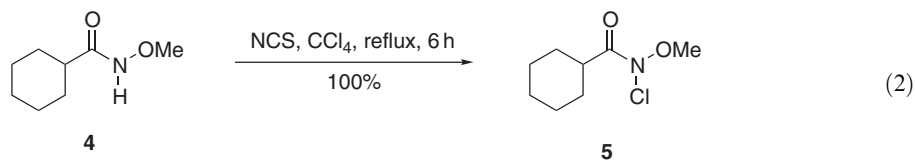
The synthesis of *N,N*-dichloroamides from amides and perfluoroacyliminosulfur difluorides has been reviewed in COFGT (1995). There have been no major advances with regard to the synthesis of *N,N*-dichloroamides.

5.07.1.7 N-Hetero-N-chloroamides

The synthesis of *N*-alkoxy-*N*-chloroamides from hydroxamates and *N*-acyl-*N*-chlorohydrazines from acylhydrazines has been documented in COFGT (1995).

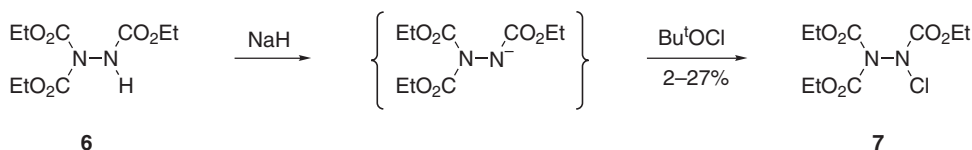
5.07.1.7.1 From hydroxamates

O-Methylcyclohexanohydroxamate **4** reacts with *N*-chlorosuccinimide (NCS) to provide *N*-chloro-*O*-methylcyclohexanohydroxamic acid **5** (Equation (2)) <1995JA4870>.



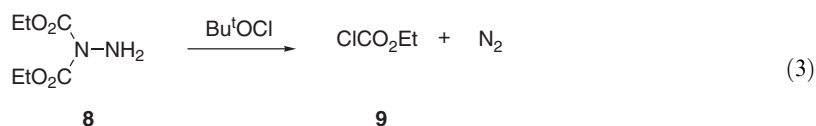
5.07.1.7.2 From ethoxycarbonylhydrazines

The treatment of *N,N,N'*-tris(ethoxycarbonyl)hydrazine **6** with sodium hydride followed by the addition of *t*-butyl hypochlorite (Bu^tOCl) provides *N*-chloro-*N,N,N'*-tris(ethoxycarbonyl)hydrazine **7** (Scheme 2) <2002T2085>. The reaction does not take place in the absence of sodium hydride.



Scheme 2

Chlorination of *N,N*-bis(ethoxycarbonyl)hydrazine **8** using Bu^tOCl did not provide *N,N*-dichloro-*N,N'*-bis(ethoxycarbonyl)hydrazine; instead, ethyl chloroformate **9** was formed exclusively (Equation (3)) <2002T2085>.

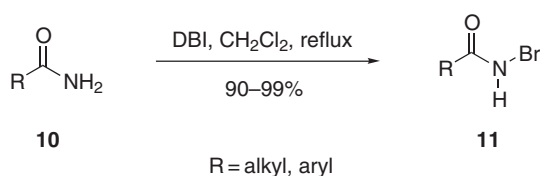


5.07.1.8 N-Bromoamides

The bromination of amides to provide the corresponding *N*-bromoamides has been previously described in COFGT (1995).

5.07.1.8.1 From amides

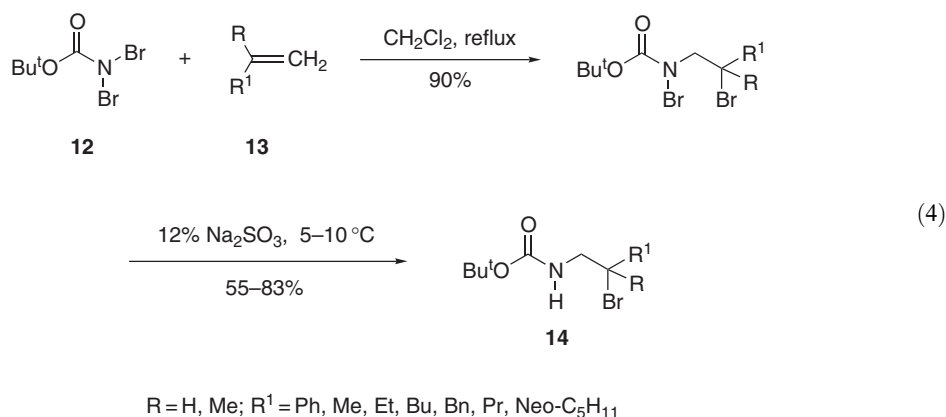
Sharpless has shown that dibromoisocyanuric acid (DBI) is an excellent agent for the bromination of amides **10**. Reactions take place under mild conditions and provide high yields of the corresponding *N*-bromoamides **11** (Scheme 3) <2000OL2221>, see also <1975M611>.



Scheme 3

5.07.1.8.2 Using *t*-butyl *N,N*-dibromocarbamate

The reaction of *t*-butyl *N,N*-dibromocarbamate (BBC) **12** with terminal alkenes **13** proceeds in an anti-Markovnikov fashion to provide β -bromo-*N*-(*t*-BOC)-amines **14** in good yields following reduction employing aqueous sodium sulfite (Equation (4)) <2001TL4539>.

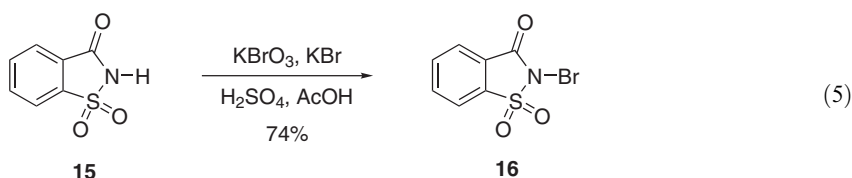


5.07.1.9 N-Bromoimides

The synthesis of *N*-bromoimides from imides and *N*-heteroimides has been reviewed in COFGT (1995).

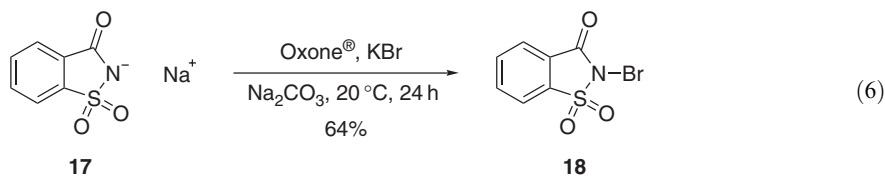
5.07.1.9.1 From imides

The bromination of imides has been achieved by the treatment of imide **15** with potassium bromate to provide in good yield the corresponding *N*-bromoimide **16** (Equation (5)) <1999SC1779>.



5.07.1.9.2 From *N*-metalimides

The reaction of the sodium salt of saccharin **17** with potassium bromide and Oxone[®] in water provides pure *N*-bromosaccharin **18** in moderate yield (Equation (6)) <2003SC935>.

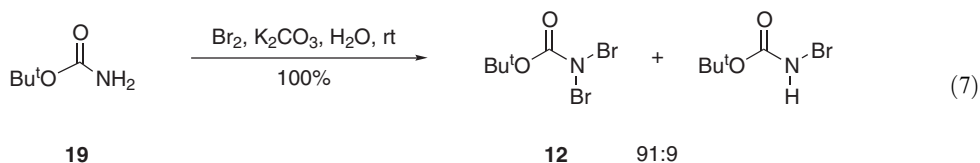


5.07.1.10 *N,N*-Dibromoamides

The synthesis of *N,N*-dibromoamides from amides has been reviewed in COFGT (1995).

5.07.1.10.1 From carbamates

Bromination of *t*-butyl carbamate **19** using a combination of bromine and aqueous potassium carbonate at ambient temperature provides *t*-butyl *N,N*-dibromocarbamate **12** in high yield with the monobromocarbamate as an impurity (~9%) (Equation (7)) <2001TL4539>.



5.07.1.11 N-Iodo(I) Amides

The synthesis of *N*-iodo(I) amides from amides and *N*-bromoamides has been reviewed in COFGT (1995). There have been no significant advances with regard to the synthesis of *N*-iodo(I) amides.

5.07.1.12 N-Iodo(I) Imides

The preparation of *N*-iodo(I) imides from *N*-metalimides, *N*-haloimides, and imides has been previously described in COFGT (1995). There have been no major advances with regard to the synthesis of *N*-iodo(I) imides.

5.07.1.13 N,N-Diiodoamides

The treatment of amides with iodine to form the corresponding *N,N*-diiodoamides has been documented previously in COFGT (1995). There have been no significant advances with regard to the synthesis of *N,N*-diiodoamides.

5.07.1.14 N-Iodo(III) Amides

The synthesis of *N*-iodo(III) amides from amides and *N*-silylamides has been reviewed in COFGT (1995). There have been no major advances with regard to the synthesis of *N*-iodo(III) amides.

5.07.1.15 N-Iodo(III) Imides

The preparation of *N*-iodo(III) imides has been previously described in COFGT (1995). There have been no significant advances with regard to the synthesis of *N*-iodo(III) imides.

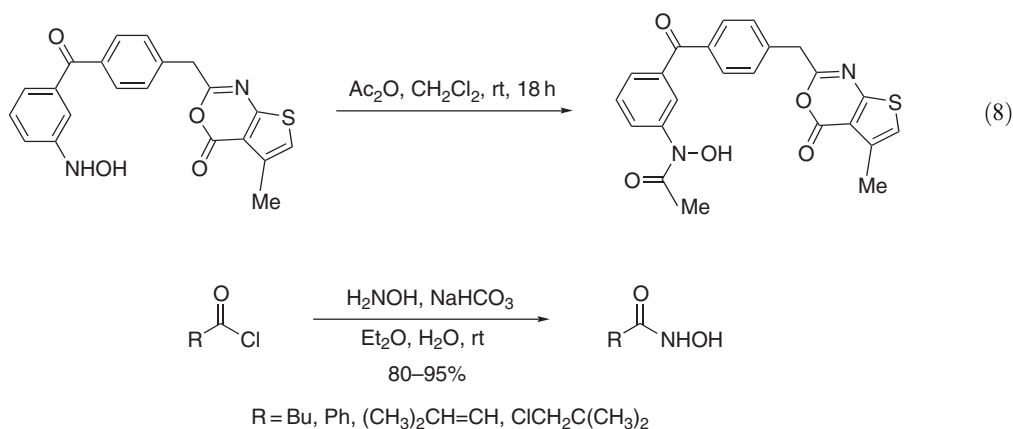
5.07.2 AMIDES SUBSTITUTED BY OXYGEN

The majority of amides substituted by oxygen are either hydroxamic acids, that is, *N*-hydroxy amides, or the analogous hydroxamates, that is, *O*-substituted derivatives. The early chemistry of these types of compounds has been reviewed in COFGT (1995).

5.07.2.1 Hydroxamic Acids

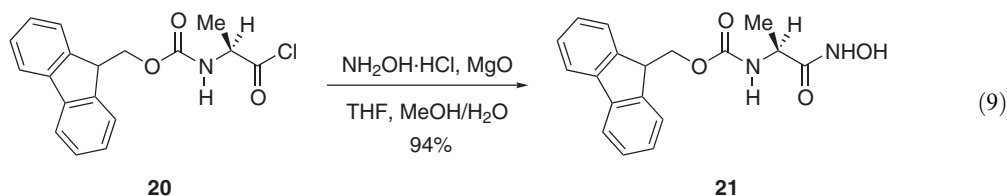
5.07.2.1.1 From acylation of hydroxylamines

The acylation of hydroxylamines to form the corresponding hydroxamic acids can be successfully carried out using traditional acylating agents such as acid anhydrides (Equation (8)) <1999BMCL3137> and acid chlorides (Scheme 4) <1998TL6227>.

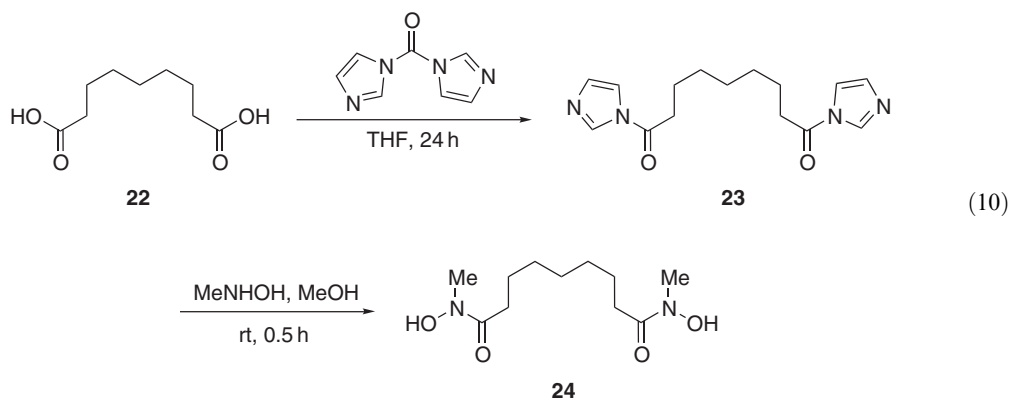


Scheme 4

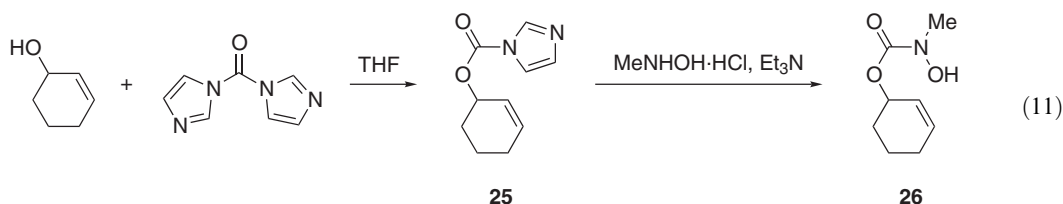
A simple and efficient method for the synthesis of Fmoc-protected amino hydroxamic acids **21** using Fmoc-amino acid chlorides **20**, hydroxylamine and magnesium oxide has been reported (Equation (9)) <2003TL4099>.



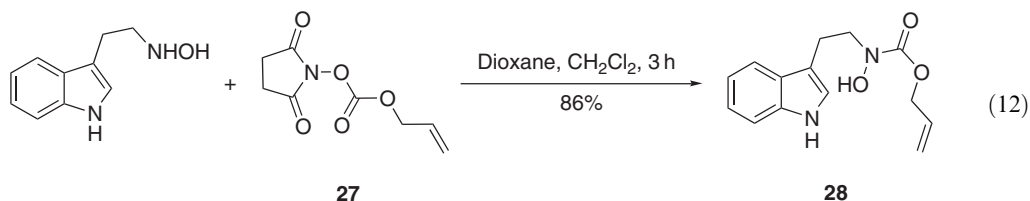
The treatment of nonanedioic acid **22** with *N,N'*-carbonyldiimidazole initially leads to the formation of the corresponding imidazolide **23**, which reacts with *N*-methylhydroxylamine to provide the hydroxamic acid **24** (Equation (10)) <1996JCS(P2)2673>.



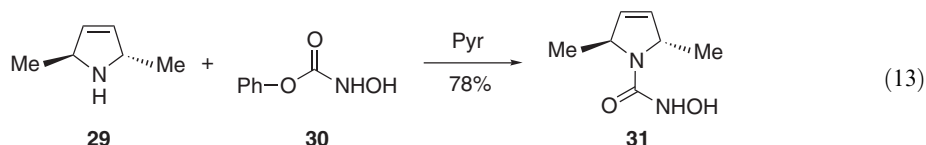
In a similar manner 2-cyclohexenol has been converted into hydroxamic acid **26** via an imidazolide species **25** (Equation (11)) <1995T6517>.



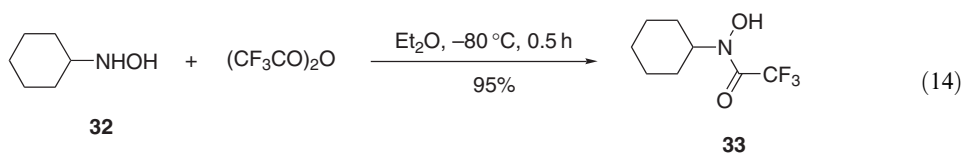
Hydroxylamines react with 2,5-dioxopyrrolidin-1-yl esters **27** under mild conditions to provide the corresponding *N*-acylhydroxylamines **28** (Equation (12)) <1995RTC27>.



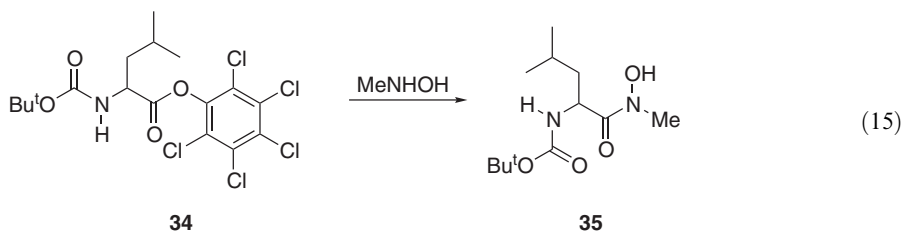
The treatment of 2,5-dimethyl-2,5-dihydro-1*H*-pyrrole **29** with hydroxycarbamic acid phenyl ester **30** leads to the formation of the hydroxyamide **31** (Equation (13)) <1995TL5449>.



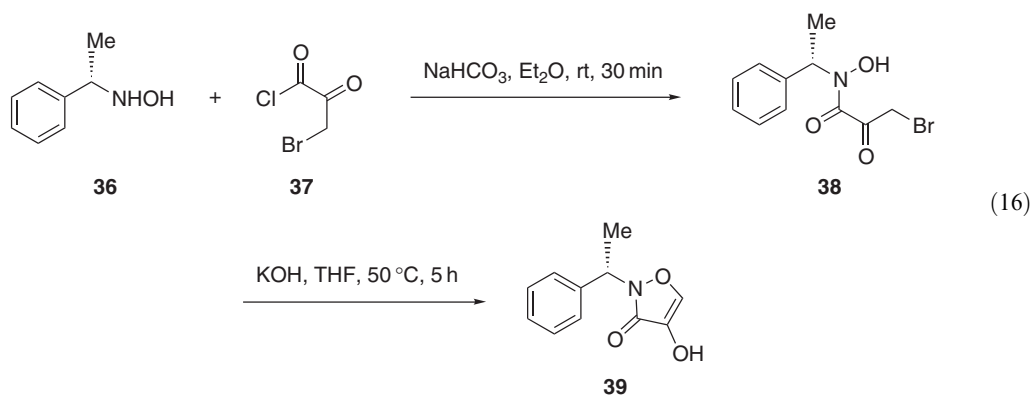
N-Trifluoroacetoxyhydroxamic acids **33** are prepared by the treatment of hydroxylamines **32** with trifluoroacetic anhydride at low temperature. The reaction is rapid and very high yielding (Equation (14)) <1995SC3509>.



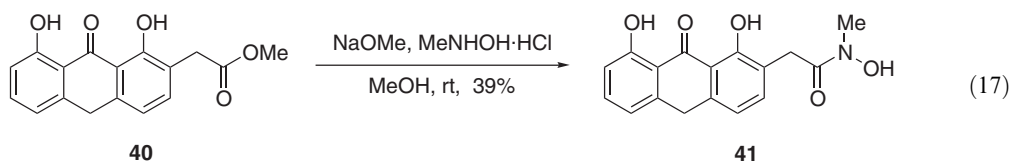
Pentachlorophenyl esters **34** have been shown to react with *N*-methylhydroxylamine to provide the *N*-methylhydroxamic acid **35** (Equation (15)) <1996MI759>.



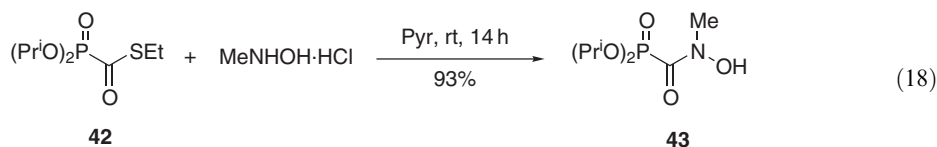
The reaction of *N*-(1-phenylethyl)hydroxylamine **36** with bromopyruvic acid chloride **37** leads to the formation of *N*-substituted bromopyruvohydroxamic acid **38**, which upon treatment with potassium hydroxide undergoes a cyclization reaction providing isoxazolone **39** (Equation (16)) <1996MI377>.



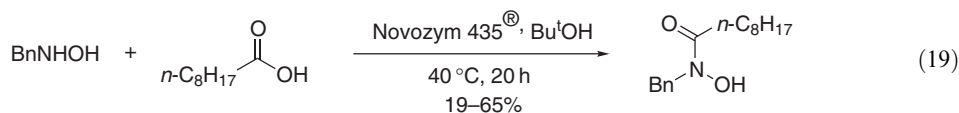
The addition of a freshly prepared solution of the sodium salt of *N*-methylhydroxylamine to ester **40** provides hydroxamic acid **41** (Equation (17)) <1997JMC2780>.



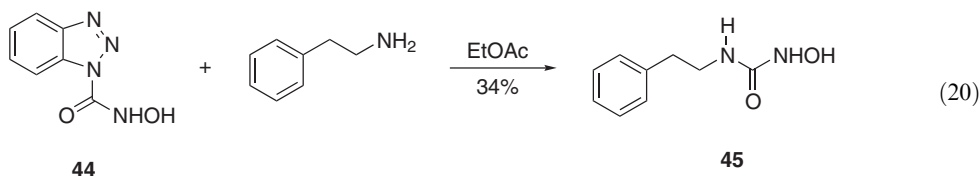
(Diisopropylphosphono)thiolformate **42** reacts with *N*-methylhydroxylamine hydrochloride to provide *N*-methyl[(diisopropoxyphosphinyl)formyl]hydroxamic acid **43** (Equation (18)) <1997JOC3858>. It is important to note that only C—S bond cleavage is observed during the reaction, and no C—P bond cleavage takes place.



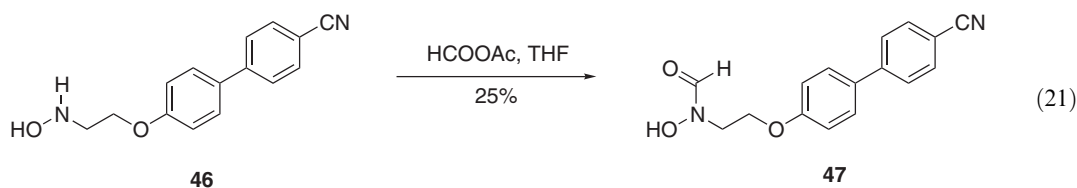
The lipase Novozym 435[®] (*Candida antarctica* lipase *B* on Lewatit *E*) catalyzes the reaction between carboxylic acids and hydroxylamines to provide the corresponding hydroxamic acid products (Equation (19)) <2000M549>.



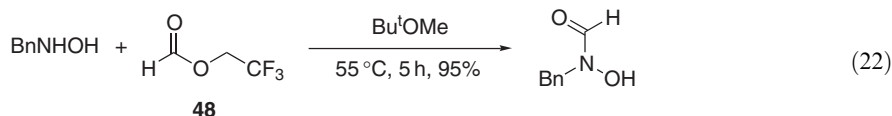
1-(*N*-Hydroxycarbamoyl)benzotriazole **44**, a “solid HONCO donor,” undergoes reactions with primary amines to provide *N*-hydroxyureas such as **45** (Equation (20)) <2000MI569>.



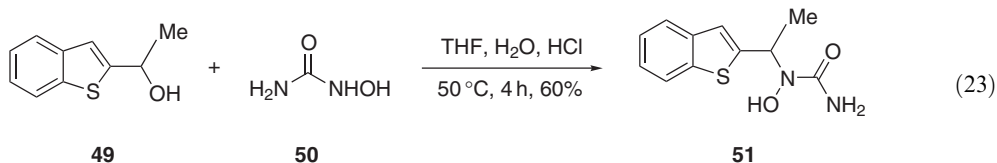
The conversion of hydroxylamine **46** into *N*-hydroxyformamide **47** via an *N*-formylation reaction using formic acetic anhydride has been reported (Equation (21)) <2001BMCL1553>.



An alternative method for the *N*-formylation of hydroxylamines has been reported <2002OL111>. 2,2,2-Trifluoroethylformate **48** is a highly effective formylating reagent for the conversion of hydroxylamines into *N*-hydroxyformamides (Equation (22)).

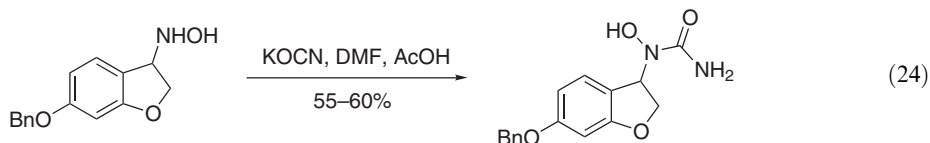


The acid-catalyzed coupling of *N*-hydroxyurea **50** with a number of 1-aryl alcohols, for example **49**, to provide an *N*-substituted-*N*-hydroxyurea **51** has been reported (Equation (23)) <2001SC3081>. The reaction is simple, highly efficient, and can be carried out on a multi-kilogram scale.

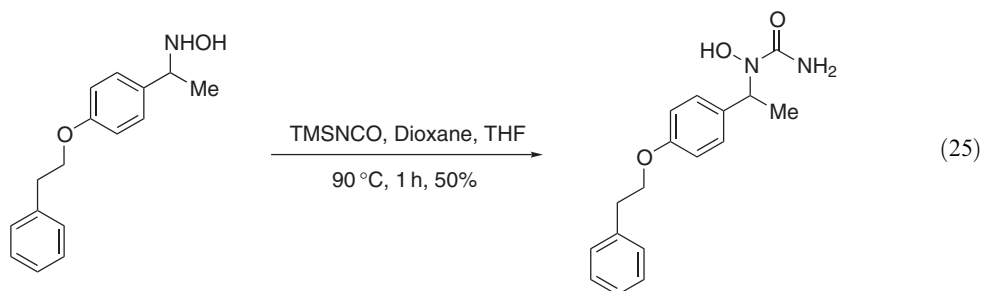


5.07.2.1.2 From the addition of isocyanates to hydroxylamines

The treatment of hydroxylamines with potassium cyanate (KOCN) has been shown to provide the corresponding *N*-hydroxyureas (Equation (24)) <1996TL4639, 1997JOC5385, 1998SL1217>.

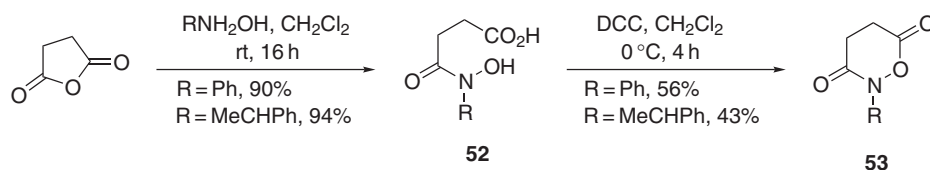


Trimethylsilyl isocyanate (TMSNCO) also brings about the conversion of hydroxylamines into the corresponding *N*-hydroxyurea (Equation (25)). Trimethylsilyl isocyanate was found to be adequate for research scale; however, potassium cyanate was found to be more practical for larger-scale reactions <1997JMC1955>.



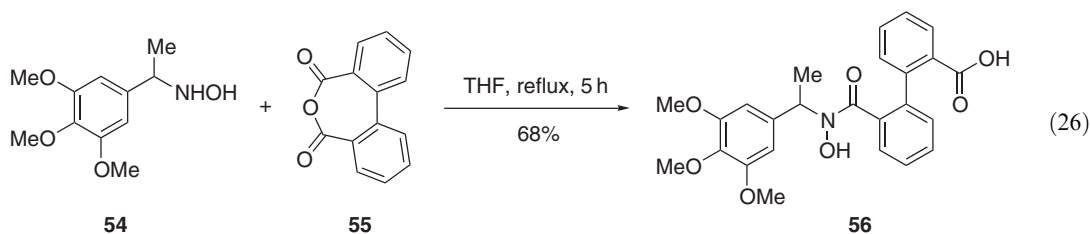
5.07.2.1.3 From the ring opening of cyclic acid anhydrides

The reaction of *N*-substituted hydroxylamines with maleic anhydride readily yields the corresponding *N*-hydroxysuccinamic acids **52**. Upon treatment with dicyclohexylcarbodiimide (DCC), the *N*-hydroxysuccinamic acids ring-close to provide the tetrahydro-1,2-oxazine-3,6-diones **53** (Scheme 5) <1995T12837>.



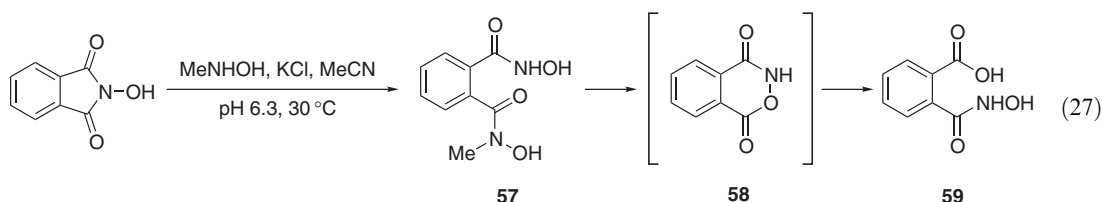
Scheme 5

The attack of hydroxylamine **54** on diphenic anhydride **55** provides hydroxamic acid **56** in good yield (Equation (26)) <1997JMC3292>.



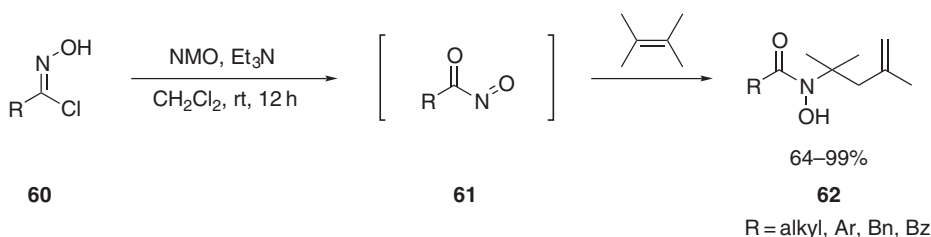
5.07.2.1.4 From N-substituted phthalimides

The cleavage of *N*-hydroxyphthalimide using *N*-methylhydroxylamine provides *N,N'*-dihydroxy-*N*-methylphthalamide **57**. Upon ring closure, the *O*-cyclized intermediate benzo[α][1,2]oxazine-1,4-dione **58** is obtained, which can ring-open to provide *N*-hydroxyphthalamic acid **59** (Equation (27)) <1996IJC(B)1275>.



5.07.2.1.5 From nitrile oxides

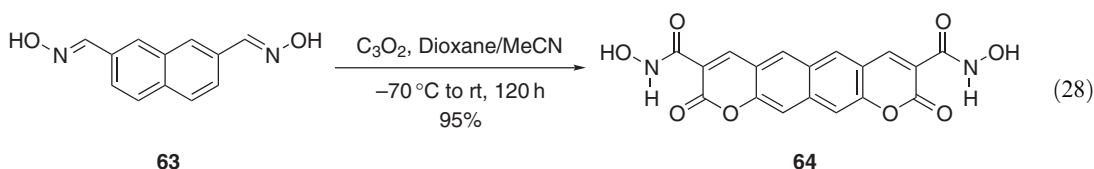
The mild oxidation of nitrile oxides **60** using *N*-methylmorpholine-*N*-oxide (NMO) in the presence of triethylamine generates nitrosocarbonyl intermediates **61** that undergo ene reactions with a range of different alkenes, forming a C—N bond to furnish the corresponding ene products **62** in good yields (Scheme 6) <1998TL3233>.



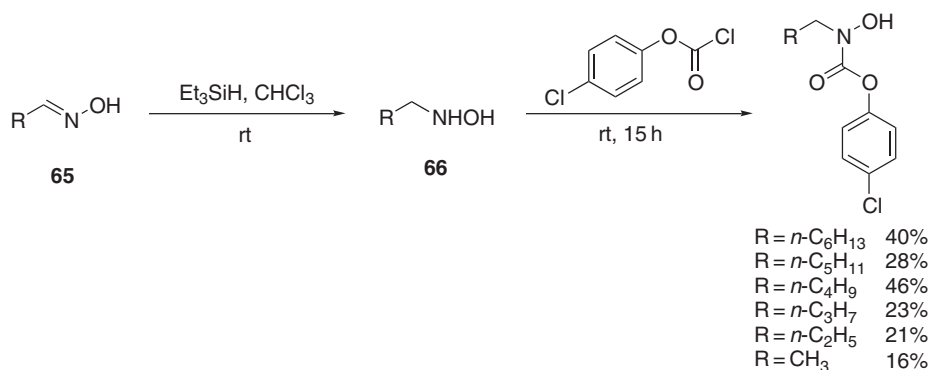
Scheme 6

5.07.2.1.6 From oximes

The treatment of dioxime **63** with carbon suboxide at low temperature provides the tetracyclic bis(hydroxy)amide derivative **64** in excellent yield (Equation (28)) <1998MI675>.



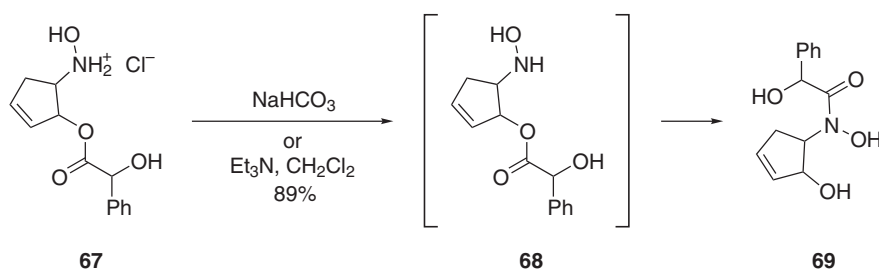
A one-pot synthesis of hydroxamic acids from alkyloximes has been developed <2000JMC3981>. The reduction of alkyloximes **65** using triethylsilane (Et_3SiH) provides the corresponding hydroxylamines **66**, which were then reacted with 4-chlorophenyl chloroformate to form the *N*-alkyl-*N*-hydroxycarbamates (Scheme 7).



Scheme 7

5.07.2.1.7 From O-acyl to N-acyl transfer

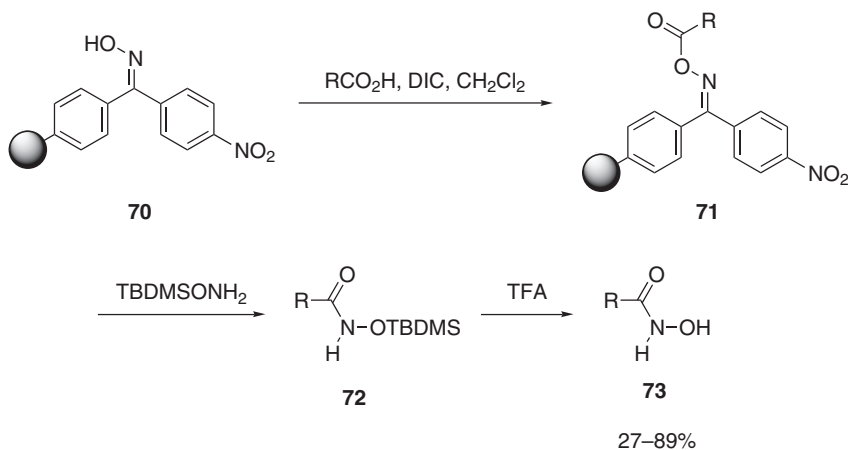
Neutralization of hydrochloride salt **67** by treatment with either aqueous sodium hydrogen carbonate (NaHCO_3) or triethylamine (Et_3N) provides intermediate **68**, which undergoes an acyl-transfer reaction to give hydroxamic acid **69** in high yield (Scheme 8) <1995TL7535>.



Scheme 8

5.07.2.1.8 From solid-phase synthesis

A solid-supported synthesis of hydroxamic acids has been developed (Equation (29)) <1998TL3397>. Kaiser oxime resin **70** is coupled to a range of aliphatic and aromatic carboxylic acids in the presence of the coupling reagent N,N' -diisopropylcarbodiimide (DIC) to form the *O*-acylated oxime resin **71**. Cleavage from the resin is achieved using *t*-butyldimethylsilylhydroxylamine (TBDMSOH₂) yielding *O*-protected hydroxamic acid **72**, which can be deprotected using trifluoroacetic acid at room temperature to give hydroxamic acid **73**.



(29)

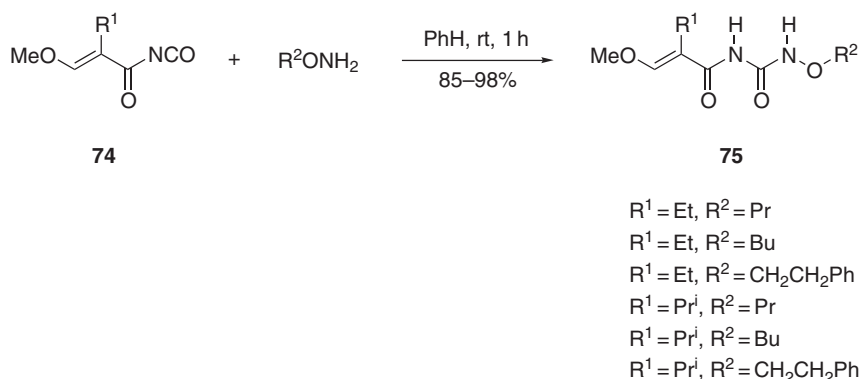
5.07.2.2 Hydroxamates

5.07.2.2.1 From acylation of alkoxyamines

The acylation of alkoxyamines to form the corresponding hydroxamates can be successfully carried out using a number of traditional and nontraditional acylating reagents: acid chlorides <1996BMCL1055>, acid fluorides <2000TL2453>, acid bromides <1995JOC376, 2001SL1272>, acid anhydrides <2001JCS(P1)2850>, succinic anhydrides <1995JOC109, 1999BMC3025, 2000JOC4833>, pentafluorophenyl esters <1999BMCL1365>, and the employment of peptide-coupling conditions <2002BMCL2553, 2003OL971>.

5.07.2.2.2 From addition of hydroxylamines to isocyanates

The preparation of isocyanate **74** *in situ* from the treatment of the corresponding acid chloride with silver cyanate in benzene at reflux followed by the subsequent reaction with a range of *O*-substituted hydroxylamines at room temperature yielded a range of ureas **75** in excellent yields (Scheme 9) <1995JHC1625>.



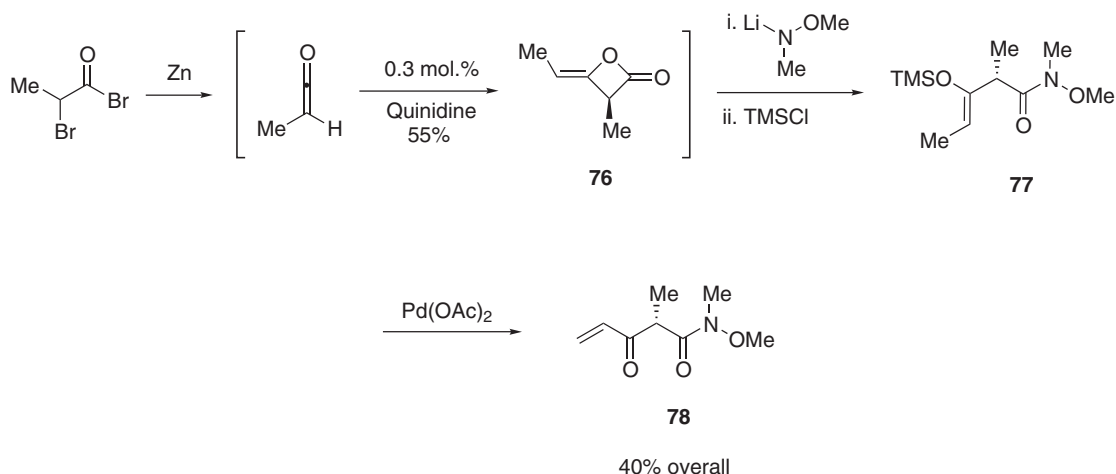
Scheme 9

5.07.2.2.3 From methylketenes

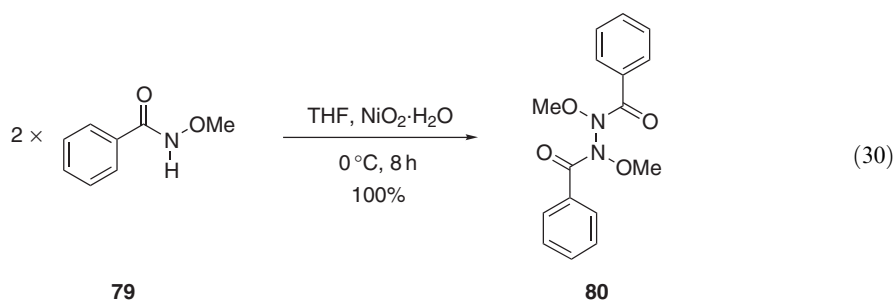
Treatment of bromopropionyl bromide with zinc yields methylketene, which in the presence of quinidine forms methylketene dimer **76** in 55% yield with 98% ee. Dimer **76** reacts with the lithium salt of *N,O*-dimethylhydroxylamine to form the corresponding enolate which is trapped using trimethylsilyl chloride (TMSCl) yielding trimethylsilyl enol ether **77**. Oxidation of **77** with a stoichiometric amount of palladium(II) acetate resulted in the formation of the α,β -unsaturated ketone **78** (Scheme 10) <2000OL1529, 2001OL1499>.

5.07.2.2.4 From oxidation of *O*-alkylhydroxamates

A series of *O*-alkylhydroxamates **79** were oxidized with either ceric ammonium nitrate (CAN) or nickel peroxide ($\text{NiO}_2 \cdot \text{H}_2\text{O}$) yielding the corresponding hydrazines **80** in quantitative yields in most instances (Equation (30)) <1995JA4870>. Nickel peroxide was found to be a superior oxidizing agent with respect to CAN due to its ability to oxidize the majority of the *O*-alkylhydroxamates, whilst the hydrazines with bulky groups (e.g., Bu^t , adamantyl) decomposed under the reaction conditions where CAN was employed. Lead(IV) acetate has also been shown to oxidize *O*-alkylhydroxamates to the corresponding hydrazines <1999T3413>.

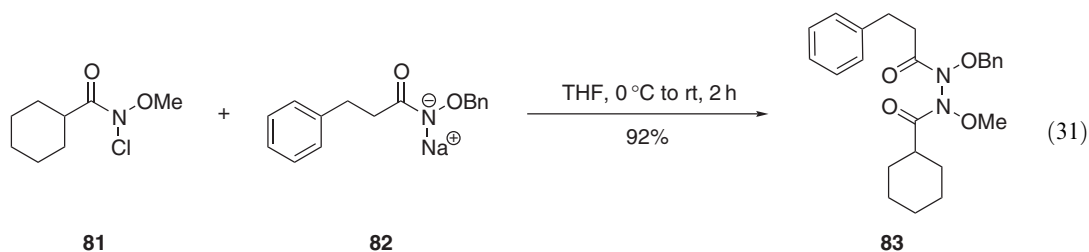


Scheme 10



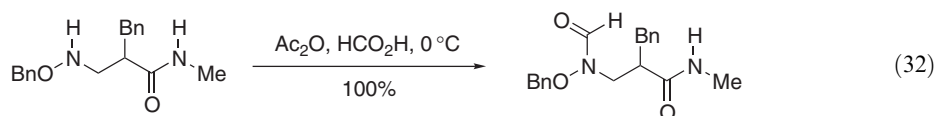
5.07.2.2.5 From N-chloro-O-alkylhydroxamates

The reaction of *N*-chloro-*O*-methylcyclohexanohydroxamic acid **81** with the sodium salt of *N*-benzyloxy-3-phenylpropionamide **82** gives the unsymmetrical hydrazine **83** in excellent yield (Equation (31)) <1995JA4870>.



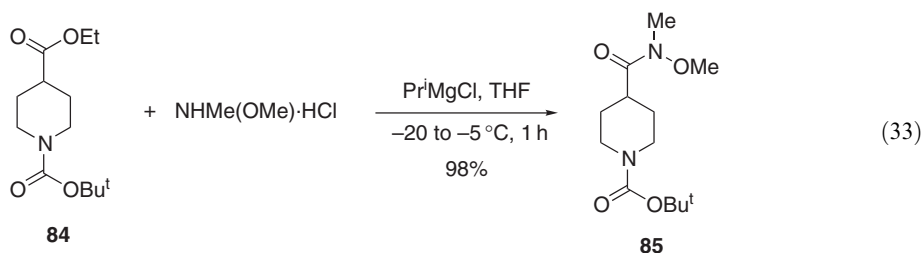
5.07.2.2.6 From the formylation of hydroxylamines

Formylation of hydroxylamines is achieved in quantitative yield using a combination of formic acid and acetic anhydride to generate the mixed acetic formic anhydride *in situ*, which carries out the formylation reaction (Equation (32)) <1998BMCL3515, 1999BMCL691>. Formylation of hydroxylamines also takes place when a combination of *N,N'*-carbonyldiimidazole (CDI) and formic acid is used <2003BMCL2709>.



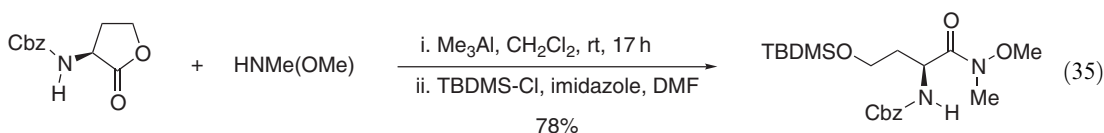
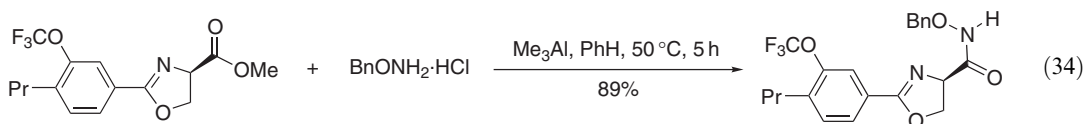
5.07.2.2.7 From the addition of hydroxylamines to esters

The reaction of ethyl *N*-*t*-butoxycarbonylisonipecotate **84** with *N,O*-dimethylhydroxylamine hydrochloride in the presence of Grignard reagent furnishes the desired hydroxamate **85** in high yield (Equation (33)) <2000JMC3895>.

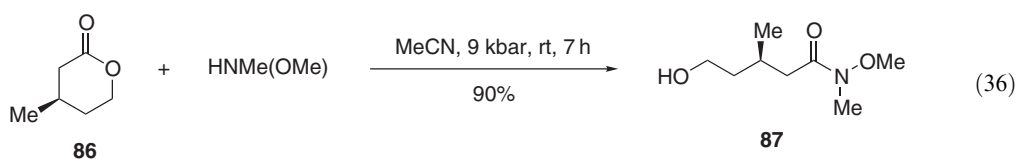


5.07.2.2.8 Formation of Weinreb amides

The reaction of esters (Equation (34)) <1996TL3519, 1999JOC4528, 2002JMC3112> or the ring opening of lactones (Equation (35)) <1996TL3165, 1997TL5119, 1997BSB665, 1999TL2973, 1999TL2887, 2000JA2995, 2001JOC4369, 2002BMCL69, 2002BMC1659> with hydroxylamines leads to the formation of Weinreb amides in generally high yields.

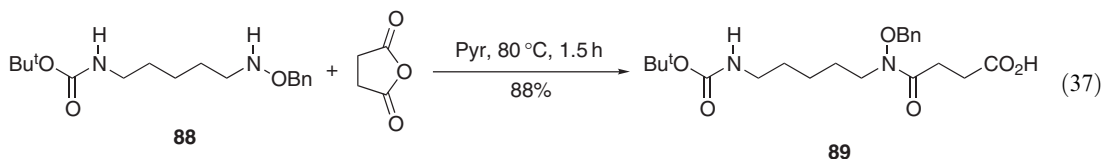


High-pressure aminolysis has been shown to be a useful, viable alternative to using Weinreb's aluminum reagent for the synthesis of Weinreb's amides. It is highly efficient, uses mild neutral conditions and has a relatively easy work-up procedure. A mixture of lactone **86** and *N,O*-dimethylhydroxylamine in acetonitrile was subjected to high pressure, and upon work-up, the desired amide **87** was obtained in excellent yield (Equation (36)) <1997JOC5299>.



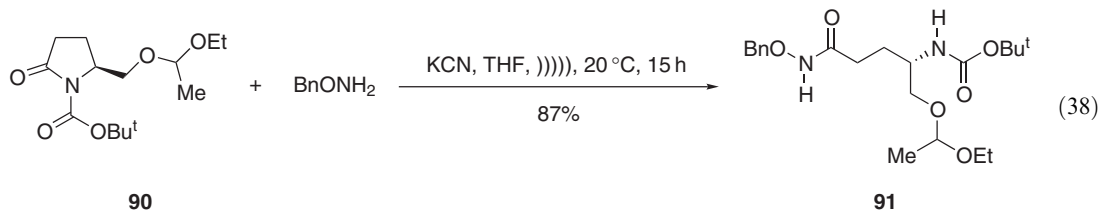
5.07.2.2.9 From the reaction of hydroxylamines with succinic anhydride

Heating *O*-benzylhydroxylamine **88** with succinic anhydride in pyridine results in the formation of carboxylic acid **89** in excellent yield (Equation (37)) <1995JOC109>.



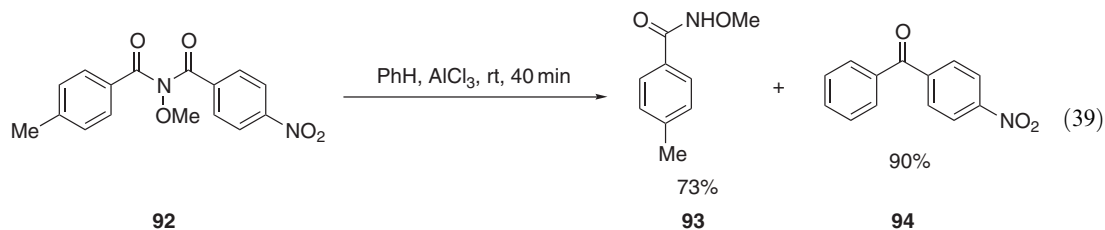
5.07.2.2.10 From the ring opening of pyrrolidinones

When a mixture of *N*-*t*-butoxycarbonylpyrrolidinone **90** and *O*-benzylhydroxylamine is subjected to sonication in the presence of potassium cyanide, hydroxamate **91** is furnished in excellent yield (Equation (38)) <1999EJO3483>. Formation of **91** also takes place when pyrrolidinone **90** is stirred with *O*-benzylhydroxylamine in aqueous sodium carbonate solution; however, the yield is slightly reduced (81%).



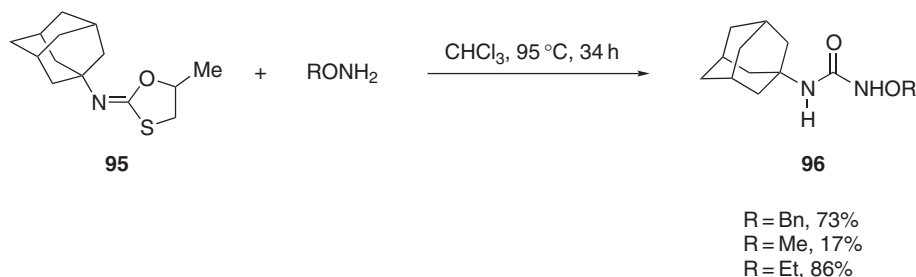
5.07.2.2.11 From fragmentation of imides

The attack of benzene upon a carbonyl group of imide **92** in the presence of aluminum chloride (AlCl_3) results in the formation of hydroxamate **93** and benzophenone **94** in high yields (Equation (39)) <1996H633>.



5.07.2.2.12 From 2-imino-1,3-oxathiolanes

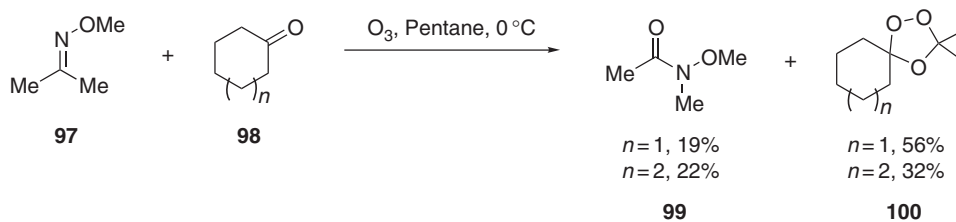
The treatment of 2-(1-adamantylimino)-5-methyl-1,3-oxathiolane **95** with *O*-alkylhydroxylamines furnishes adamantylalkoxyureas **96** in a range of yields (Scheme 11) <1997S38>. The reaction is thought to proceed by initial attack of hydroxylamine on the imine function resulting in ring opening. Subsequent intramolecular cyclization with the elimination of 2-methylthiirane yields the adamantylalkoxyurea.



Scheme 11

5.07.2.2.13 From ozonolysis of O-alkyloximes

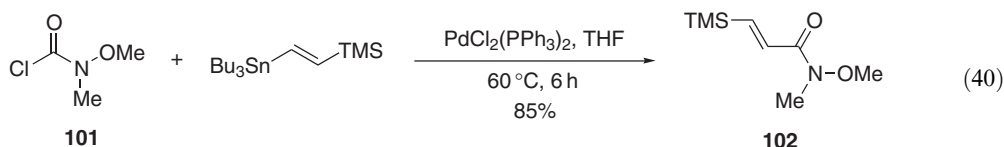
Ozonolysis of a mixture of *O*-methyloxime **97** and cyclic ketone **98** results in the formation of *N*-methoxy-*N*-methylacetamide **99** in low yields with the major product being a trioxaspiro compound **100** (Scheme 12) <1997MI1381>.



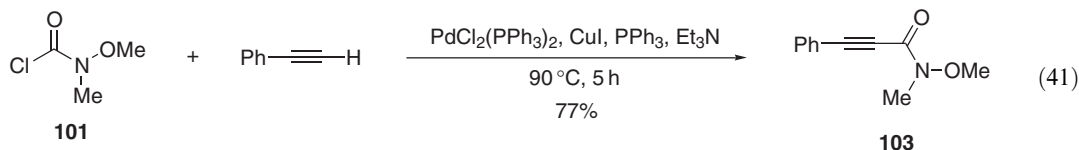
Scheme 12

5.07.2.2.14 From palladium-catalyzed reactions of *N*-methoxy-*N*-methylcarbamoylchloride

Treatment of a wide range of organostannanes, where the tin is appended to either a *sp*- or *sp*²-atom, with *N*-methoxy-*N*-methylcarbamoyl chloride **101** employing bis(triphenylphosphine)palladium(II) chloride ($\text{PdCl}_2(\text{PPh}_3)_2$) as a catalyst results in C—C bond formation yielding *N*-methoxy-*N*-methylamides **102** in moderate-to-good yields (Equation (40)) <1998CL163>.

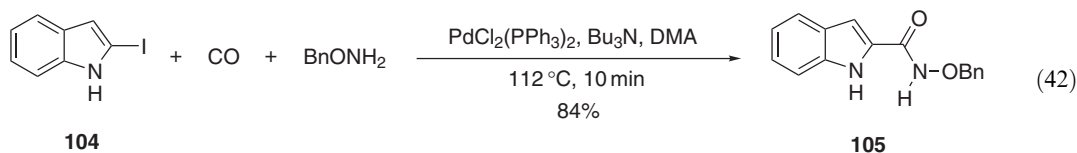


Using Sonogashira conditions, aliphatic and aromatic terminal alkynes were demonstrated to undergo palladium-catalyzed reactions with *N*-methoxy-*N*-methylcarbamoyl chloride **101** furnishing alkynylamides **103** (Equation (41)) in yields similar to those displayed from the alkenylstannanes in Equation (40).



5.07.2.2.15 From palladium-catalyzed carbonylation reactions

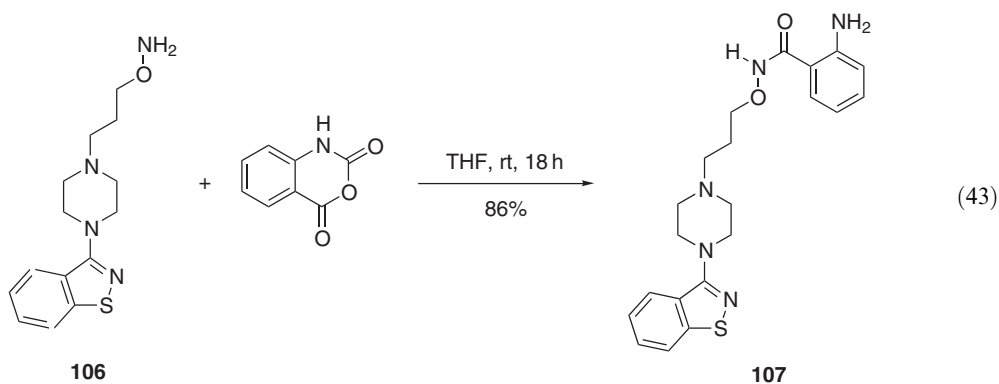
The palladium-catalyzed reaction of 2-iodoindole **104** and carbon monoxide in the presence of *O*-benzylhydroxylamine resulted in hydroxamate **105** (Equation (42)). This reaction was found to be very rapid, clean and highly efficient <1998TL2421>.



Palladium(II) acetate has also been used to catalyze the carbonylation of alkenyl iodides <2000T5253> and alkenyl triflates <2000T10275, 2001JA9455>.

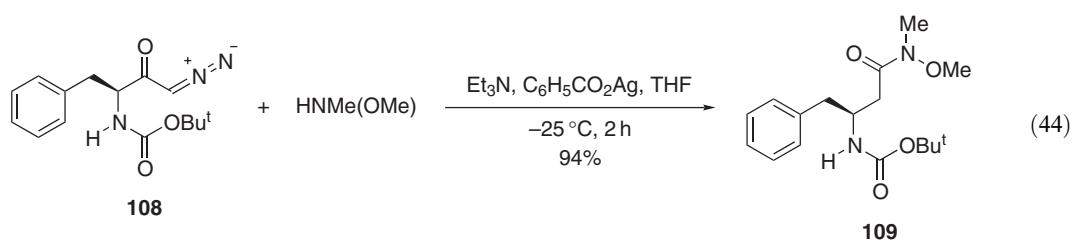
5.07.2.2.16 From reactions with isatoic anhydride

Treatment of isatoic anhydride with hydroxylamine **106** results in ring-opening affording hydroxamate **107** in high yield with the elimination of carbon dioxide (Equation (43)) <1998BMC811>.



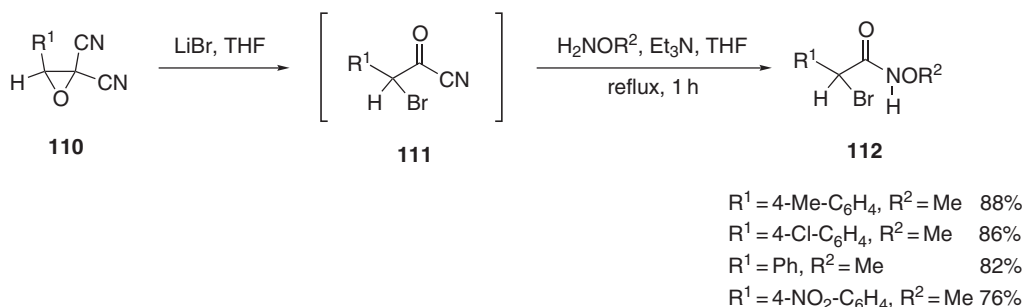
5.07.2.2.17 From rearrangement of N-protected diazo ketones

N-*t*-Butoxycarbonyl diazoketone **108** undergoes a Wolff rearrangement in the presence of *N,O*-dimethylhydroxylamine which acts as the nucleophile. This leads to the formation of the corresponding *N*-*t*-butoxycarbonyl- β -aminodimethylhydroxamate **109** in excellent yield (Equation (44)) <1998TL4239>.



5.07.2.2.18 From ring opening of gem-dicyano epoxides

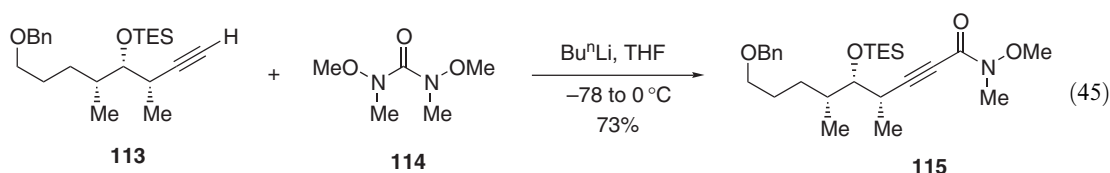
The regioselective ring opening of epoxide **110** using Br^- as the nucleophile by attack at the β -carbon to the two nitrile groups results in the formation of intermediate **111** with loss of lithium cyanide. Acylcyanide **111** then reacts *in situ* with *O*-protected hydroxylamines yielding α -bromo-hydroxamic acids **112** in good yield (Scheme 13) <2000TL2559>.



Scheme 13

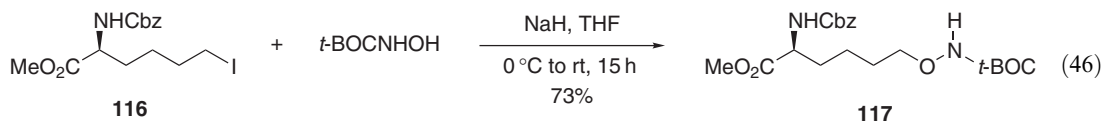
5.07.2.2.19 From N-methoxy-N-methylurea

Lithiation of alkyne **113** using *n*-butyllithium yields the corresponding lithio-acetylide, which undergoes an addition reaction with *N*-methoxy-*N*-methylurea **114** to form hydroxamate **115** in good yield (Equation (45)) <2001JOC1373>.



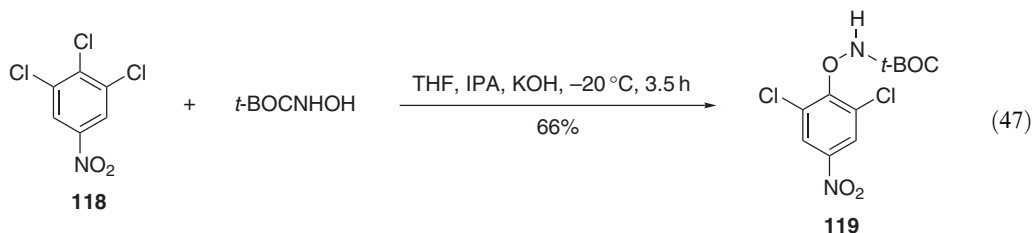
5.07.2.2.20 From alkyl halides

Alkylation of *t*-butyl-*N*-hydroxycarbamate occurs after initial treatment with sodium hydride followed by addition of iodo ester **116** to furnish *t*-butoxycarbonylaminoxy ester **117** in reasonable yield (Equation (46)) <2001SC579>.



5.07.2.2.21 From aryl halides

The addition of 3,4,5-trichloronitrobenzene **118** to *t*-butyl *N*-hydroxycarbamate in the presence of potassium hydroxide (KOH) results in the formation of *N*-*t*-BOC-*O*-phenylhydroxylamine **119** in moderate yield (Equation (47)) <2002TL6735>. It was observed that the treatment of hydroxylamine **119** with sodium hydrogen carbonate resulted in a rearrangement, affording the corresponding *N*-*t*-BOC-*N*-hydroxyaniline.



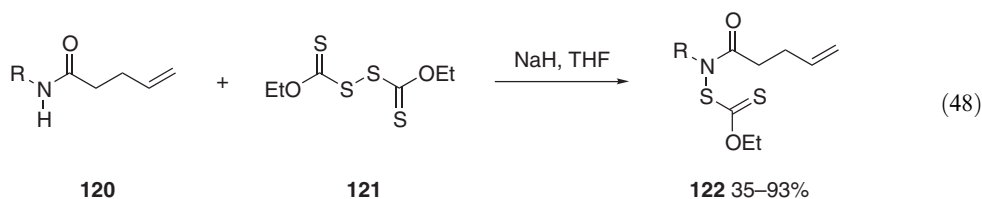
5.07.3 AMIDES SUBSTITUTED BY SULFUR, SELENIUM, OR TELLURIUM

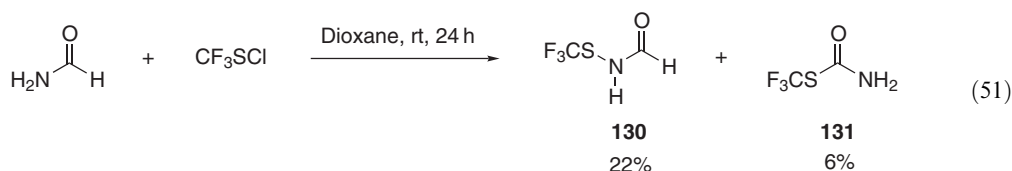
The synthesis of *N*-sulfur amides, *N*-selenium amides, and *N*-tellurium amides has been reviewed in COFGT (1995). There have been no significant developments in the chemistry of *N*-selenium amides and *N*-tellurium amides.

5.07.3.1 Amide Derivatives: Oxidation State +2, Dicoordinate

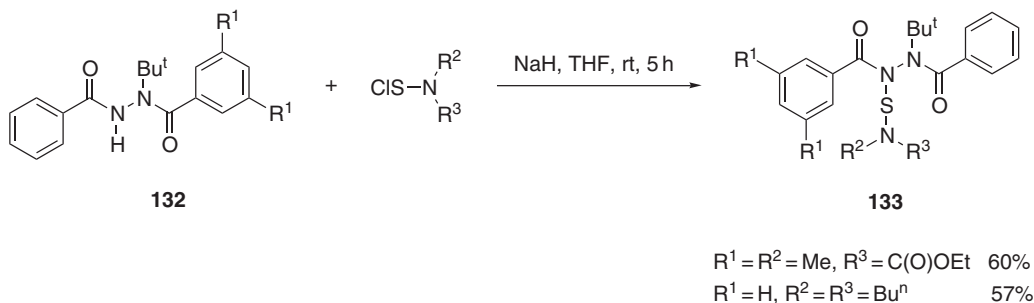
5.07.3.1.1 From amides

A wide range of amides have been transformed into the corresponding *N*-(*O*-ethylthiocarbonylsulfanyl)amides **122** in varying yields <2002OL2707>. Deprotonation of amide **120** with sodium hydride (NaH), followed by treatment with bis(ethoxythiocarbonyl)disulfane **121** affords the corresponding xanthates **122** (Equation (48)).





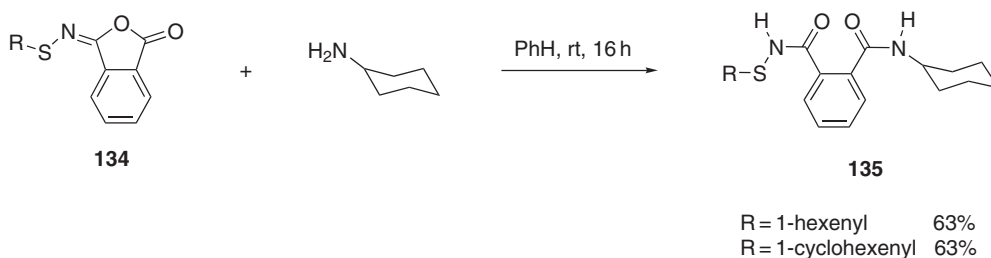
Diacylhydrazines **132** react with aminosulfonyl chlorides in the presence of sodium hydride (NaH) affording the corresponding *N*-sulfonylated diacylhydrazine derivatives **133** in moderate yields (Scheme 15) <2001JCR(S)342, 2002MI1250>.



Scheme 15

5.07.3.1.5 From ring opening of imino-phthalides

The reaction of phthalide derivatives **134** with cyclohexylamine results in the formation of *N*-(1-alkenylthio)-*N'*-cyclohexylphthalimides **135** in moderate yield (Scheme 16) <1996JOC4232>. Stable products are only obtained with the use of cyclohexylamine; other primary amines do not effect the same reaction.

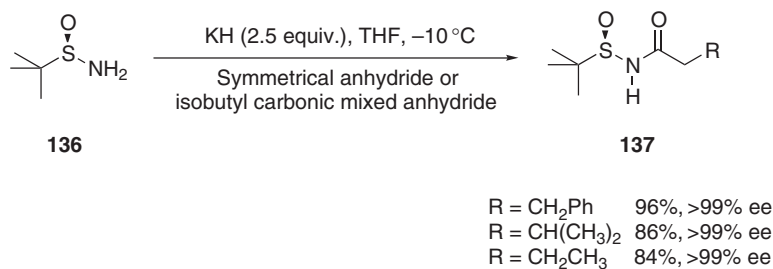


Scheme 16

5.07.3.2 Amide Derivatives: Oxidation State +4, Tricoordinate

5.07.3.2.1 From sulfinamides

The synthesis of enantiomerically pure *N*-acylsulfinamides **137** is achieved in high yield by treatment of (*R*)-sulfinamide **136** with a base, followed by the addition of a symmetrical anhydride or an isobutyl carbonic mixed anhydride (Scheme 17) <1999JOC5472>. It was observed that addition of the sulfinamide to the anhydride resulted in slight racemization.



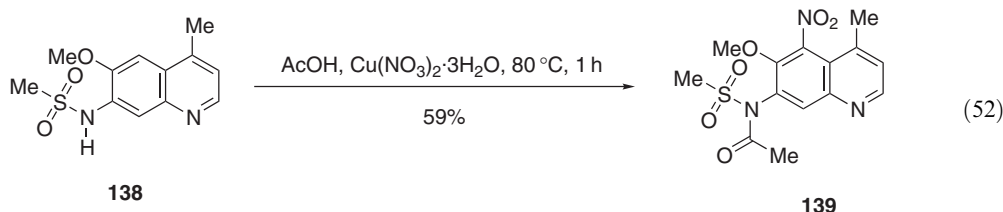
Scheme 17

5.07.3.3 Amide Derivatives: Oxidation State +6, Tetracoordinate

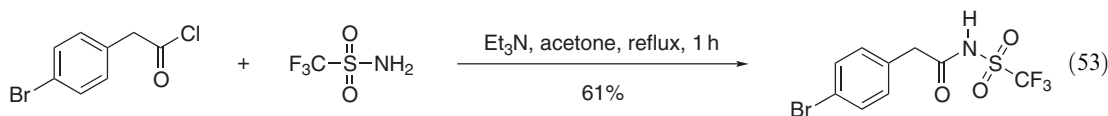
5.07.3.3.1 From acylation of sulfonamides

Sulfonamides react with activated carboxylic acids to provide an easy route into *N*-acylsulfonamides. Activation can be achieved using *N,N'*-carbonyldiimidazole (CDI), *N*-hydroxysuccinimide, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide either as the hydrochloride salt (EDCI) or supported on Merrifield's resin (P-EDC) (Table 2).

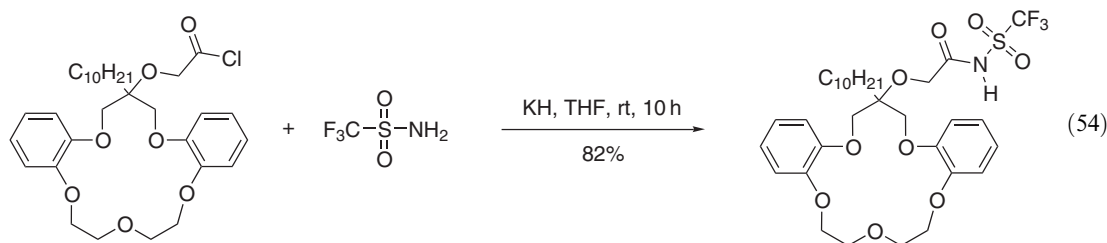
Treatment of quinoline **138** with copper(II) nitrate in the presence of acetic acid results in *N*-acylation and also nitration at the C-5 position of the quinoline ring yielding the acylated quinoline **139** in moderate yield (Equation (52)) <1997JOC568>.



The reaction of trifluoromethanesulfonamide with acid chlorides in the presence of triethylamine affords the corresponding *N*-acyltrifluoromethanesulfonamides (Equation (53)) <1996JMC1509>.

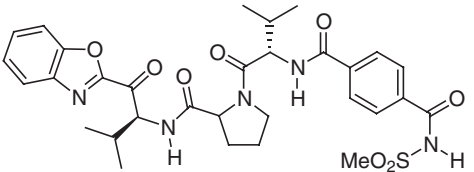
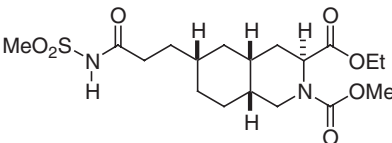
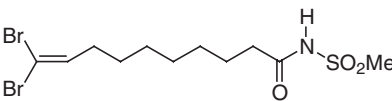
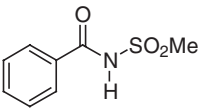
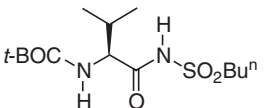


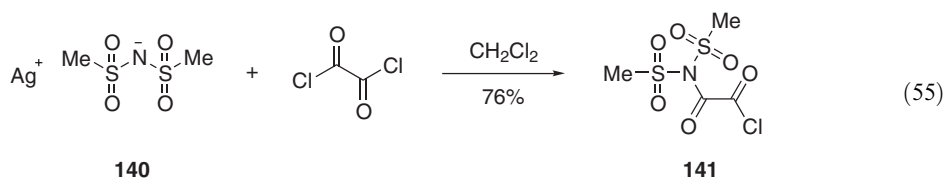
N-Acyltrifluoromethanesulfonamides can also be prepared in high yields by the addition of an acid chloride to a mixture of trifluoromethanesulfonamide and potassium hydride (KH) (Equation (54)) <1997CC1499>.



Treatment of silver bis(methanesulfonyl)imide **140** with oxalyl chloride results in the formation of oxalyl chloride dimesylamide **141** in good yield (Equation (55)) <1997AX(C)781>.

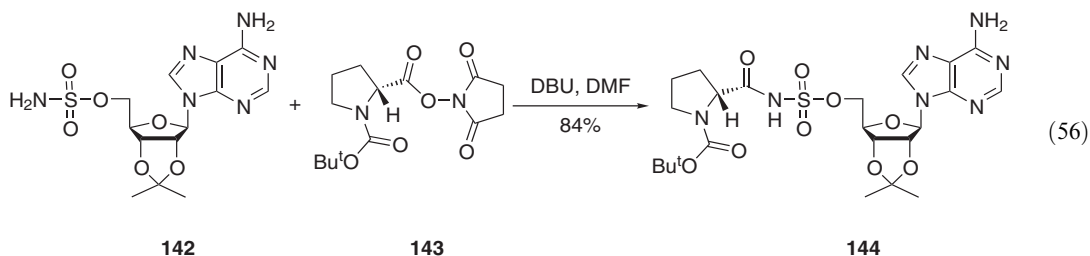
Table 2 Acylation of sulfonamides

<i>Sulfonamide</i>	<i>Reagents</i>	<i>N-Acylsulfonamide</i>	<i>Yield (%)</i>	<i>References</i>
MeSO ₂ NH ₂	EDCI, DMAP, CH ₂ Cl ₂		33	<1995JMC3972>
MeSO ₂ NH ₂	CDI, DBU, THF		89	<1996JMC2232>
MeSO ₂ NH ₂	NHS/DCC, THF, DMAP, HMPA		67	<1997BMCL3053>
MeSO ₂ NH ₂	DMAP, ClCH ₂ CH ₂ Cl, Bu ^t OH, Amberlyst-15, EtOAc		66	<1998TL5891>
<i>n</i> -BuSO ₂ N(SiMe ₃) ₂	Et ₃ N, BOP, CH ₂ Cl ₂ , rt, 15 h		59	<1998BMCL2241>

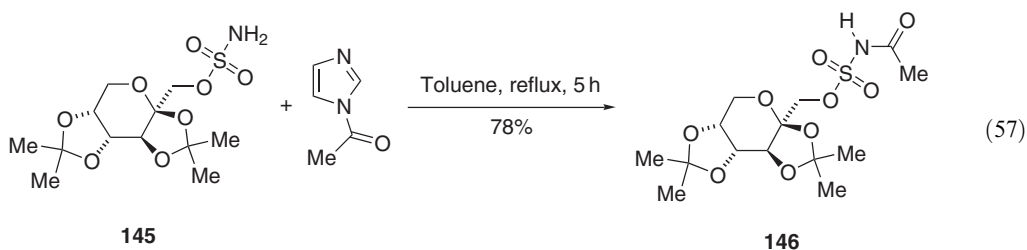


Similarly, the sodium salt of trifluoromethanesulfonamide reacts with oxalyl chloride furnishing *N,N'*-bis(trifluoromethanesulfonyl)oxamide <2001JGU993>.

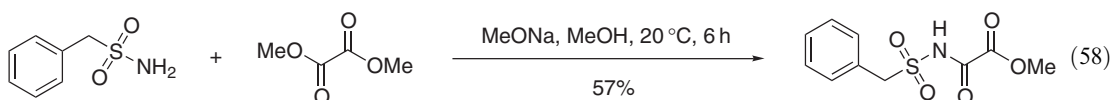
O-Sulfamoyladenine derivative **142** reacts with *N*-hydroxysuccinimide esters **143** in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) to afford *O*-(*N*-*t*-BOC-*D*-prolylsulfamoyl)adenine **144** in high yield (Equation (56)) <1996BOC273>.



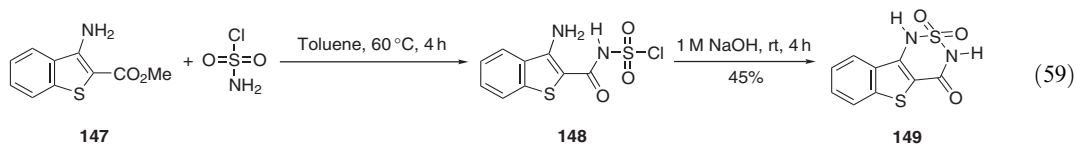
The reaction of 1-acetylimidazole with topiramate **145** in toluene at reflux furnishes the imidazole salt of *N*-acetylsulfamate **146** in good yield (Equation (57)) <1998JMC1315>.



Sulfonamides react with esters to afford *N*-acylsulfonamides. Treatment of dimethyl oxalate with phenylmethylsulfonamide in the presence of sodium methoxide results in monoacylation, furnishing methyl *N*-(benzylsulfonyl)oxamate in moderate yield (Equation (58)) <1999IZV396>.



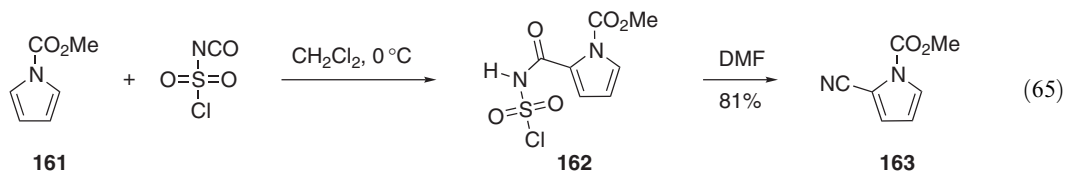
Condensation of esters with sulfamoyl chloride ($\text{H}_2\text{NSO}_2\text{Cl}$) provides another route to *N*-acylsulfonamides. Methyl benzo[*b*]thiophene-2-carboxylate **147** is first converted into the sulfonamide **148**, which under basic conditions undergoes cyclization yielding thiadiazine **149** (Equation (59)) <2000JMC683>.



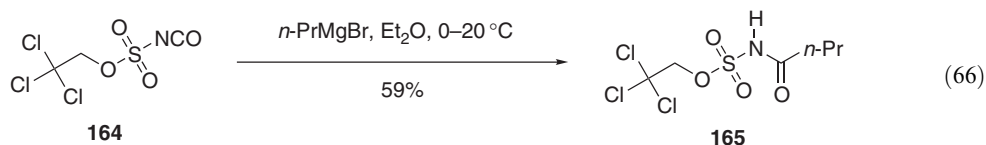
The reaction between sulfonamide **150** and succinic anhydride in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) affords *N*-acylsulfonamide carboxylic acid **151** (Equation (60)) <2002MI1791>.

5.07.3.3.3 From sulfonyl isocyanates

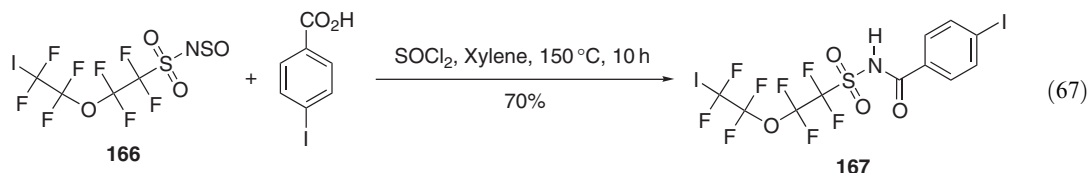
The reaction of chlorosulfonyl isocyanate (CSI) with *N*-methoxycarbonylpyrrole **161** yields methyl 2-chlorosulfonylcarbamoylpyrrole-1-carboxylate **162**. Treatment of **162** with DMF results in the formation of methyl 2-cyanopyrrole-1-carboxylate **163** in high yield (Equation (65)) <1996H2361>.



The reaction of sulfonyl isocyanates with Grignard reagents allows access to a wide range of *N*-acylsulfamates. Treatment of β,β,β -trichloroethoxysulfonyl isocyanate **164** with propylmagnesium bromide affords the corresponding *N*-butyrylsulfamate **165** in moderate yield (Equation (66)) <2003MI83>.

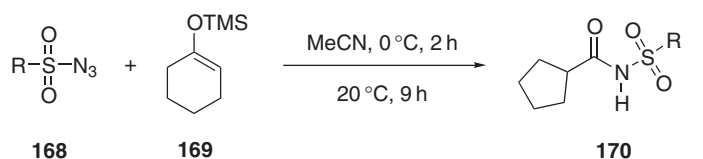


N-Perfluoroalkanesulfonylamides are produced from the reaction between *N*-sulfinylperfluoroalkane sulfonylamides and carboxylic acids. Heating *N*-sulfinylperfluoroalkanesulfonylamide **166** with 4-iodobenzoic acid with a catalytic amount of thionylchloride affords the analogous sulfonylamide **167** in high yield (Equation (67)) <1995JFC203>.



5.07.3.3.4 From sulfonyl azides

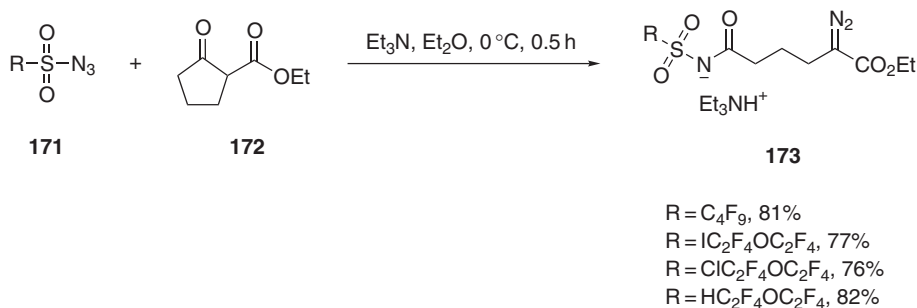
The reaction of perfluoroalkanesulfonyl azides **168** with 1-cyclohexenyl trimethylsilyl enol ether **169** results in the formation *N*-(perfluoroalkanesulfonyl)cyclopentanecarboxamide **170** in high yields (Scheme 18) <1999JFC(96)79>. It is notable that α -(*N*-perfluoroalkanesulfonyl)aminocyclohexanone is not obtained from the reaction suggesting the rearrangement that occurs thermodynamically favors the five-membered ring over the six-membered ring. When the reaction conditions are applied to 1-cyclooctenyl trimethylsilyl enol ether, α -(*N*-perfluoroalkanesulfonyl)aminocyclooctanone is the main product with only small quantities of *N*-(perfluoroalkanesulfonyl)cycloheptanecarboxamide formed.



R = CF₃, 75%
 R = C₈F₁₇, 97%
 R = IC₂F₄OC₂F₄, 96%
 R = ClC₂F₄OC₂F₄, 87%
 R = HC₂F₄OC₂F₄, 94%

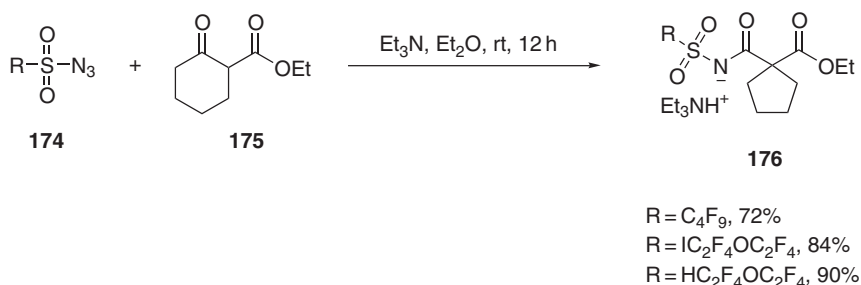
Scheme 18

The reaction of perfluoroalkanesulfonyl azides **171** with ethyl 2-oxocyclopentanecarboxylate **172** results in the formation of the corresponding *N*-perfluoroalkanesulfonylcarbamoyl substituted α -diazo esters as their triethylamine salts **173** in good yields (Scheme 19) <2000JFC25>.



Scheme 19

Treatment of ethyl 2-oxocyclohexanecarboxylate **175** with perfluoroalkanesulfonyl azides **174** results in a ring-contraction reaction affording the cyclopentane derivative **176** in high yields (Scheme 20) <2000JFC25>. It is presumed the pathway for this ring contraction proceeds via a cyclic triazoline intermediate.

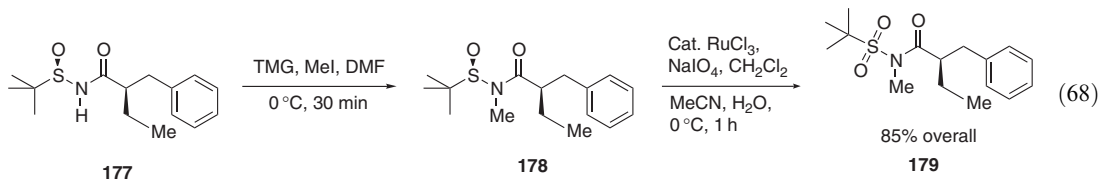


Scheme 20

Similar reactions of sulfonyl azides have been reported <1999JOC5132>.

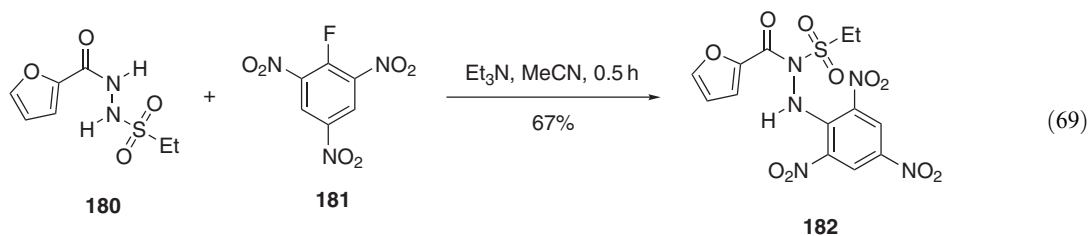
5.07.3.3.5 From oxidation of *N*-acylsulfonamides

N-Acylsulfonamide **177** is converted into *N*-methyl-*N*-acylsulfonamide **179** in two steps. First alkylation utilizing methyl iodide (MeI) and 1,1,3,3-tetramethylguanidine (TMG) affords *N*-methyl-*N*-acylsulfonamide **178**. Oxidation of **178** employing ruthenium(III) chloride (RuCl₃) and sodium (meta)periodate (NaIO₄) furnishes sulfonamide **179** in an excellent overall yield (Equation (68)) <1999JOC5472>.



5.07.3.3.6 From 1-acyl-2-(alkylsulfonyl)hydrazines

The reaction of *N*-furoyl-*N'*-(ethylsulfonyl)hydrazine **180** with picryl fluoride **181** in the presence of triethylamine furnishes *N*-furoyl-*N*-(ethylsulfonyl)-*N'*-picrylhydrazine **182** in moderate yield, formed from the rearrangement of the initial product (Equation (69)) <2000JOU1634>. Under similar conditions *N*-[(benzothio)acetyl]-*N'*-(alkylsulfonyl)hydrazines afford *N*-(alkylsulfonyl)-*N*-picryl-*N'*-[(benzothio)acetyl]hydrazines.

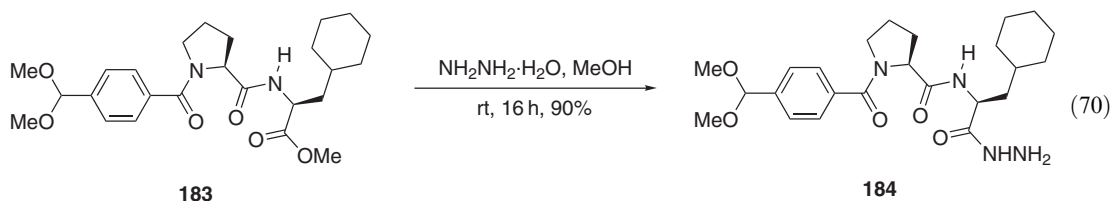


5.07.4 AMIDES SUBSTITUTED BY NITROGEN

5.07.4.1 Acylhydrazine Derivatives

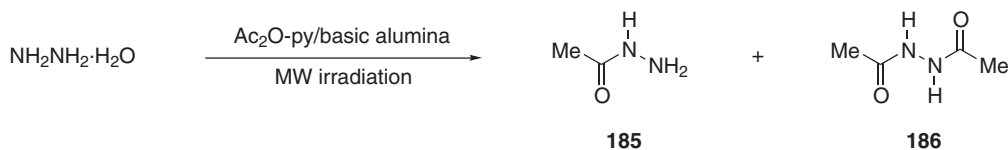
5.07.4.1.1 From acylation of hydrazine and its derivatives

Easy access to *N*-monoacylhydrazines is achieved by the reaction of esters or lactones with hydrazine hydrate or hydrazine derivatives. There are many different examples of this type of transformation within the literature. A recent and typical example involves the treatment of a methanolic solution of methyl ester **183** with 10 equiv. of hydrazine monohydrate resulting in the formation of the corresponding acylhydrazine **184** in excellent yield (Equation (70)) <2003OBC1625>.



The conversion of alkyl esters into acylhydrazines has also been carried out in a methanol/ethanol mixture <2003BMC1701>.

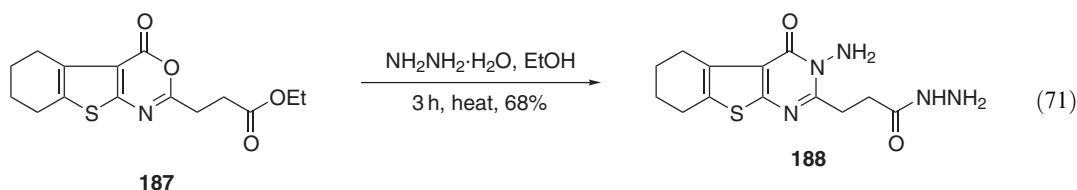
The acylation of hydrazine has also been achieved in quantitative yield in solvent-free conditions by irradiating an acetic anhydride–pyridine mixture in the presence of hydrazine hydrate over basic alumina to yield selectively either the mono- **185** or diacetate **186** derivative depending on the time the mixture is subjected to irradiation (Scheme 21) <2002TL4261>.



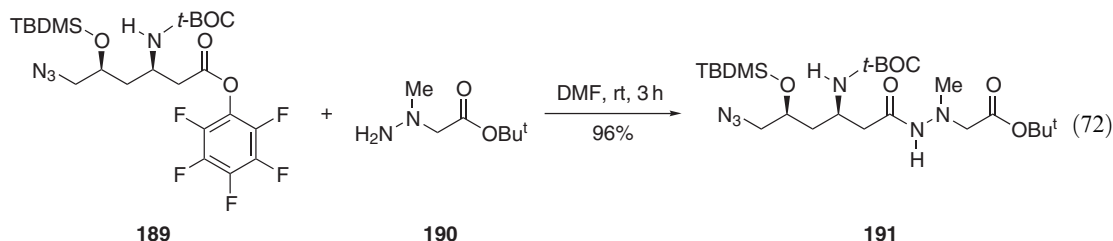
Time (min)	Yield (%)	
	185	186
1	100	0
5	0	100

Scheme 21

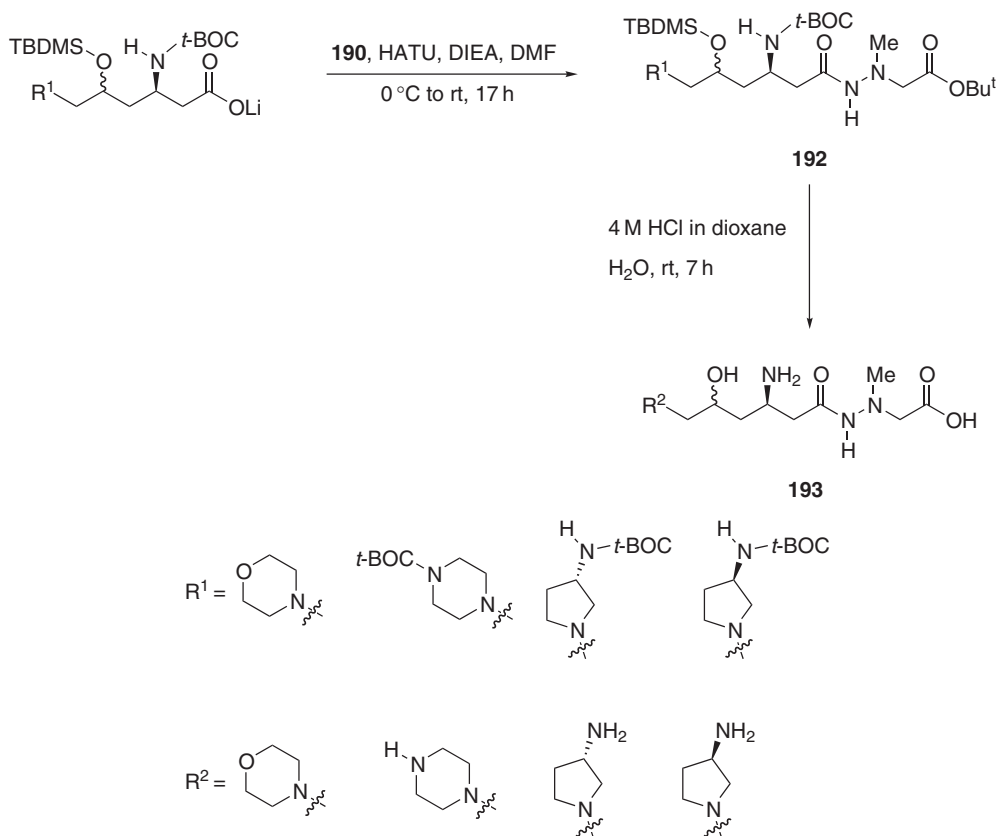
Treatment of oxazinone derivative **187** with hydrazine hydrate results in reaction on both the ester and lactone functions yielding the amino pyrimidinone derivative **188** in good yield (Equation (71)) <2003MI245>.



A number of different activated esters have been used toward the synthesis of acylhydrazines. Condensation of pentafluorophenyl- β -amino acid ester **189** with hydrazine derivative **190** affords the corresponding acylhydrazine **191** in excellent yield (Equation (72)) <2003BMCL2413>. An approach using solid-supported reagents is also described.

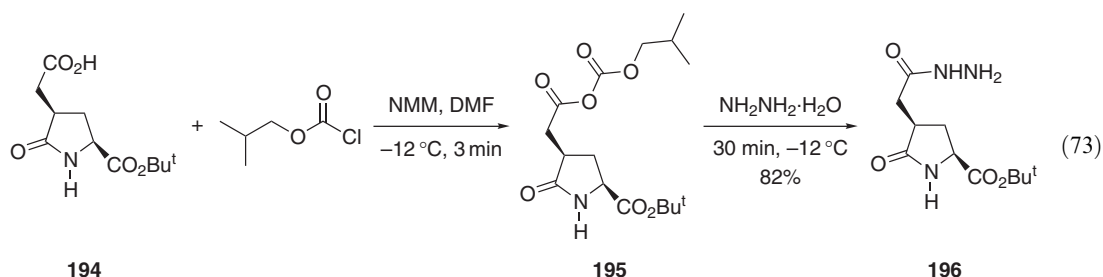


Hydrazine **190** has also been coupled with lithium salts of carboxylic acids using *N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU) as the coupling reagent to yield the corresponding hydrazides **192**, which upon treatment with acid afford the deprotected compounds **193** (Scheme 22).

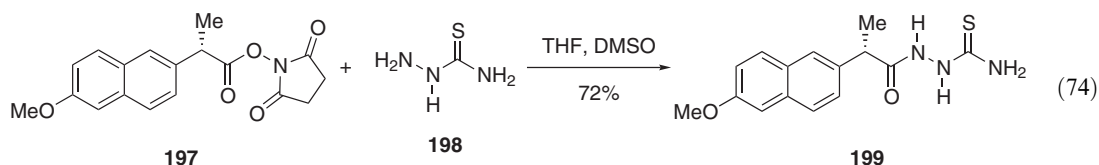


Scheme 22

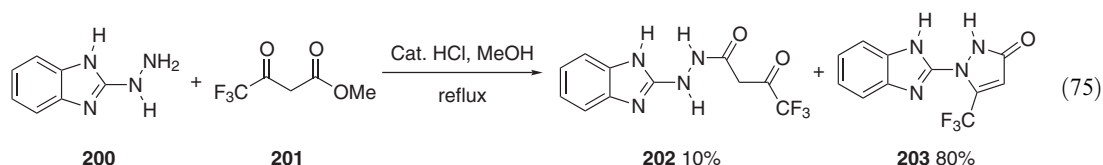
Carboxylic acid **194** is activated with *i*-butyl chloroformate yielding intermediate **195**, which is treated with hydrazine hydrate to afford the corresponding acylhydrazine **196** in good yield (Equation (73)) <2002JCS(P1)613>. Similarly, ethyl chloroformate has been used to activate carboxylic acids which have then been taken through to acylhydrazines <2001JMC2069, 2003JMC512>.



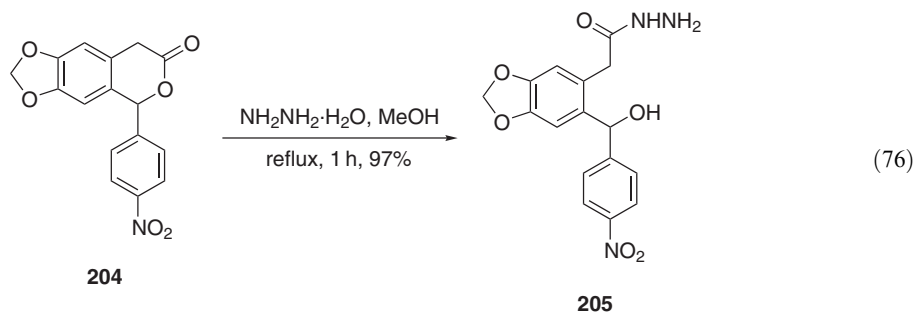
N-Hydroxysuccinimide has also been used to activate carboxylic acids. Heating *N*-hydroxysuccinimide ester **197** with thiosemicarbazide **198** affords the corresponding 1-acylthiosemicarbazide **199** in good yield (Equation (74)) <2001PHA613>.



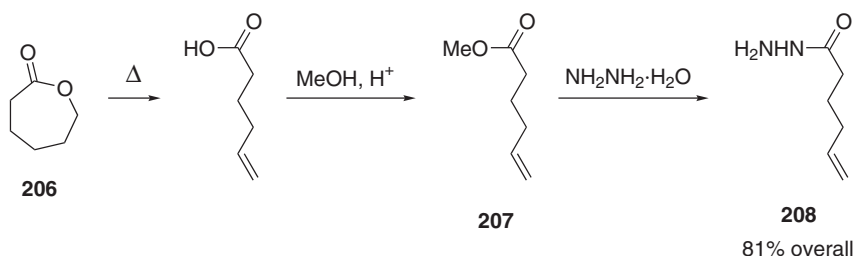
Heating 2-hydrazino-1*H*-benzimidazole **200** with trifluoroacetoacetic acid ester **201** under acidic conditions results in a mixture of two compounds: the linear product **202** and the subsequent isomeric-cyclized pyrazole-derived product **203** (Equation (75)) <2001CHE120>.



Treatment of pyran-2-one derivatives with hydrazine hydrate results in ring cleavage affording the corresponding hydrazide <2000BMCL1913>. This chemistry also works well with isochromanones. The reaction of isochromanone derivative **204** with hydrazine results in the rapid formation of hydrazide **205** in near quantitative yield (Equation (76)) <2003MI351>.

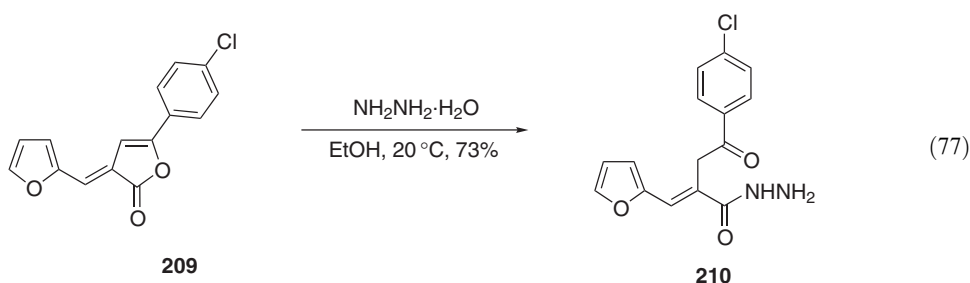


Oxepan-2-one **206** can be transformed to hex-5-enoic acid hydrazide **208** in a three-step process <2002TL6127>. Heating oxepan-2-one **206** results in the formation of hex-5-enoic acid, which is converted into its methyl ester **207** using methanol in the presence of acid. Finally treatment of **207** with hydrazine affords hydrazide **208** in good overall yield (Scheme 23).

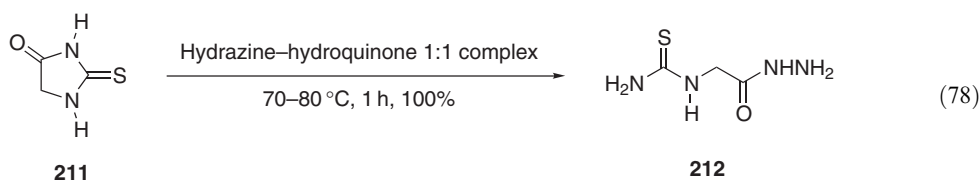


Scheme 23

Treatment of 3*H*-furan-2-one derivatives with hydrazine yields the ring-opened hydrazide <2000MI895>. The reaction of 3*H*-furan-2-one **209** with hydrazine hydrate in ethanolic conditions yields product **210** in good yield (Equation (77)).



The reaction of hydrazine–hydroquinone 1:1 complex with 2-thiohydantoin **211** in the solid state affords the ring-opened hydantoic acid hydrazide **212** in quantitative yield (Equation (78)) <2000JPO388>.

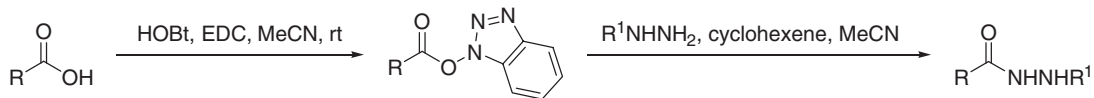








A highly efficient method for the preparation of a wide range of carboxylic acid hydrazides has been developed <2002JOC9471>. The treatment of a carboxylic acid with 1-hydroxybenzotriazole (HOBt) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) yields the activated 1-hydroxybenzotriazole ester which upon treatment with a hydrazine derivative furnishes the desired hydrazide in high yield (Scheme 24). This method also proceeds successfully if *N,N'*-dicyclohexylcarbodiimide (DCC) is substituted for EDC.

A similar method for the preparation of acylhydrazines from carboxylic acids via an activated 1-hydroxybenzotriazole ester in the presence of *N*-methylmorpholine (NMM) results in the formation of anthraquinonoylhydrazide **213** in excellent yield (Equation (79)) <2003JMC1603>.

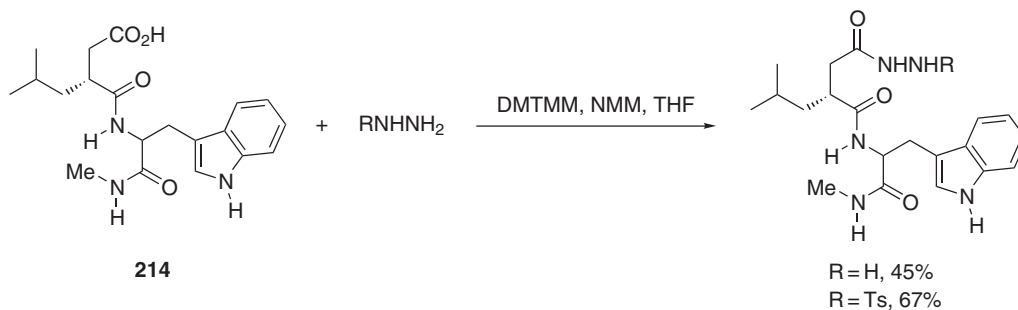
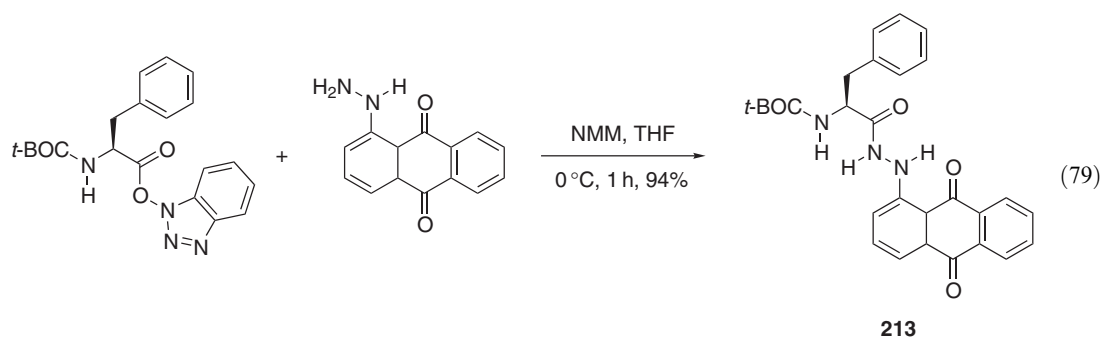
Synthesis of hydrazides from carboxylic acid **214** with hydrazines under classical DCC–HOBt coupling conditions only resulted in low yields or messy reactions. However, treatment of **214** with a mixture of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)methylmorpholinium chloride (DMTMM) and *N*-methylmorpholine (NMM) with the appropriate hydrazine resulted in improved yields of the corresponding hydrazides (Scheme 25) <2003BMCL1783>.

The reaction of triazin-5-one **215** with boiling glacial acetic acid results in diacetylation occurring to yield hydrazide **216** in high yield (Equation (80)) <2002JOU1686>. It was observed that heating **215** in acetic anhydride and benzene at reflux resulted in only monoacetylation.

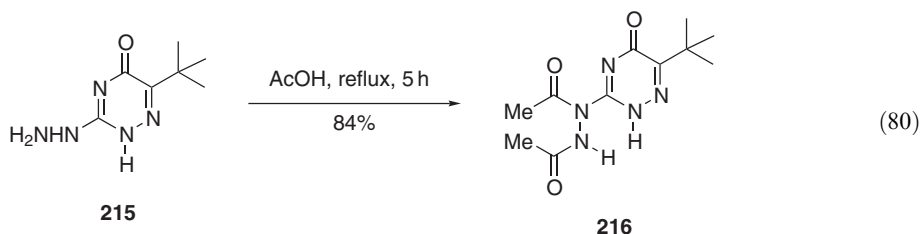


Product	Yield (%)
	98
	97
	96
	96
	98
	98

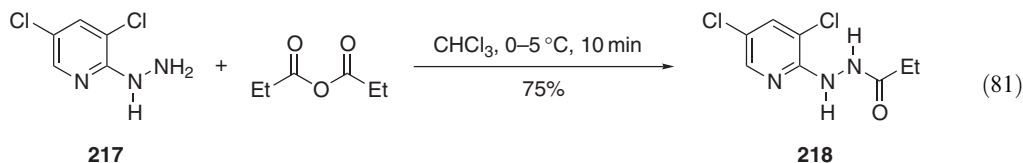
Scheme 24



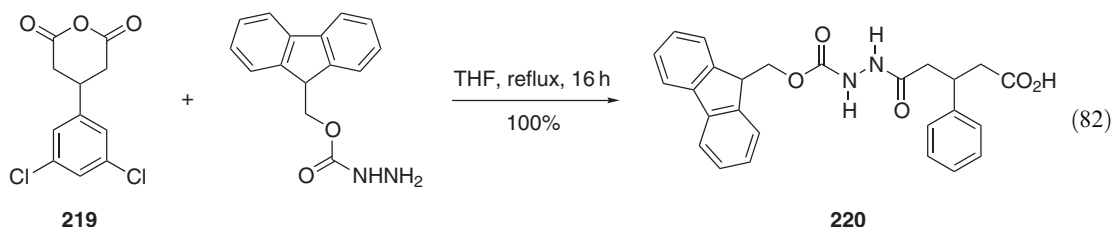
Scheme 25



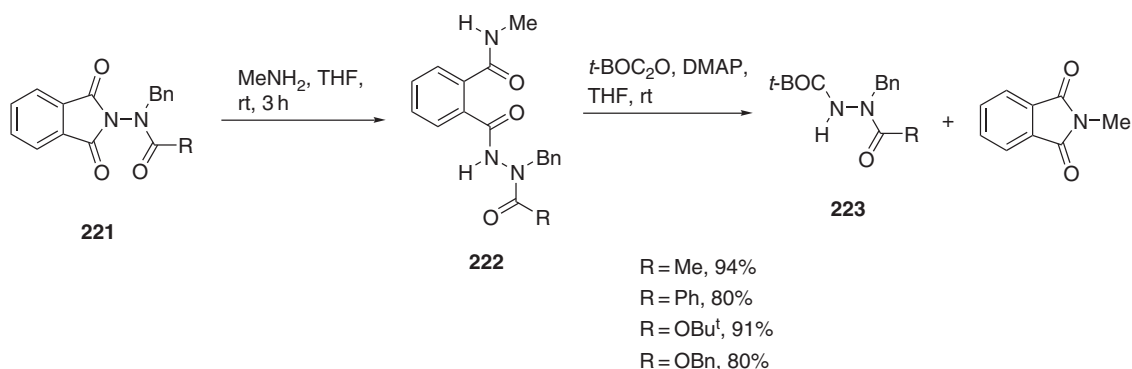
Treatment of (3,5-dichloropyridin-2-yl)hydrazine **217** with propionic acid anhydride results in the rapid formation of the corresponding hydrazide **218** in good yield (Equation (81)) <2000CHE941>.



Cyclic anhydride **219** is prepared by heating the corresponding 3-phenylglutaric acid in acetic anhydride at reflux. The reaction of anhydride **219** with *N*-(9-fluorenylmethoxycarbonyl)hydrazine results in quantitative formation of hydrazide **220** (Equation (82)) <2001JMC1938>. Succinic anhydride reacts in a similar manner <1999KFZ22>.



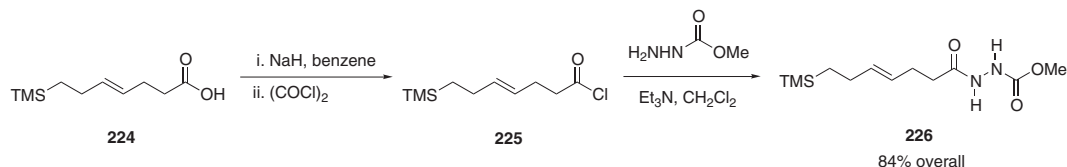
The reaction of *N*-benzyl-*N*-acylaminophthalimides **221** with methylamine results in the opening of the phthaloyl ring affording the corresponding product **222**. Treatment of **222** with di-*t*-butyl dicarbonate *t*-BOC₂O in the presence of catalytic 4-dimethylaminopyridine (DMAP) yields the mono-*t*-butoxycarbonylhydrazine derivatives **223** with elimination of methyl phthalimide in good yields (Scheme 26) <2002TL249>.



Scheme 26

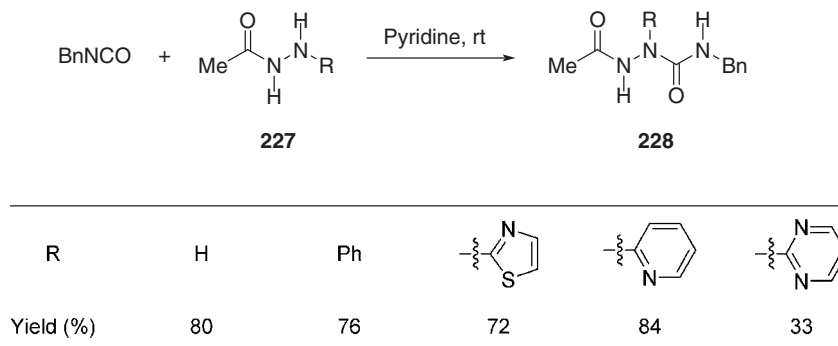
Acid chlorides have been used for the preparation of acylhydrazines <1997SC2433, 2000BMC381, 2002MI601, 2002IJC(B)2642>. Carboxylic acid **224** was converted into the corresponding acid chloride **225** by firstly forming the sodium salt and then treatment with oxalyl

chloride. Acid chloride **225** was then reacted with methyl carbazate under basic conditions affording *N,N'*-diacylhydrazine **226** in high yield (Scheme 27) <1999TL395>. Acid bromides have also been used for the synthesis of *N*-acylhydrazines <1999JOC2924>.



Scheme 27

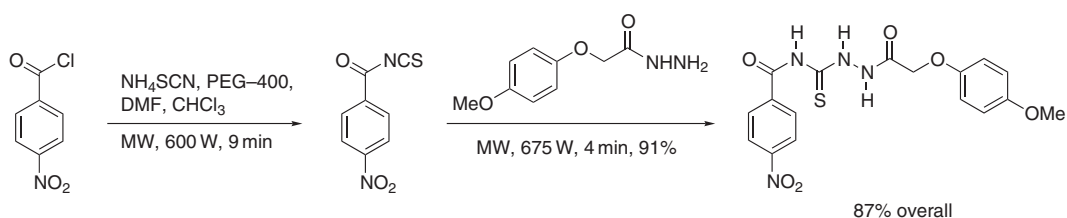
The reaction of tosyl isocyanates <2002JHC1325> or alkyl isocyanates <1998AP352, 2001JMC1475, 2003CCC792> with *N*-acylhydrazine derivatives results in the formation of semicarbazides. Benzyl isocyanate reacts with *N*-acetylhydrazines **227** to form the corresponding semicarbazides **228** in generally good yields (Scheme 28) <2001JMC1475>.



Scheme 28

In a similar method, isothiocyanates react with *N*-acylhydrazine derivatives to furnish thiosemicarbazides. Aryl isothiocyanates <1999JHC1183, 1999MI207, 2000MI153, 2003BMC1701>, alkyl isothiocyanates <2003AP95, 2003MI263>, trimethylsilyl isothiocyanates <1998JMC1344>, and ammonium thiocyanate for the *in situ* preparation of isothiocyanates <2002SC1097, 2002SC1121> have all been used toward the synthesis of thiosemicarbazides.

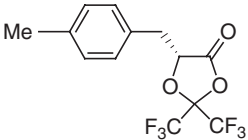
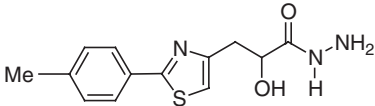
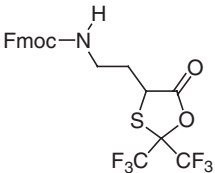
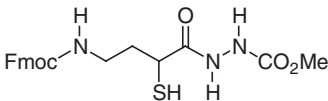
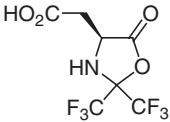
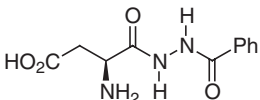
The synthesis of thiosemicarbazides can be achieved in high yields by irradiation in a microwave <2002SC3087>. First, the preparation of isothiocyanate is achieved by irradiating 4-nitrobenzoyl chloride and ammonium thiocyanate in a microwave. Addition of an aryloxyacetic acid hydrazide followed by further irradiation results in the corresponding thiosemicarbazide in excellent yield (Scheme 29).



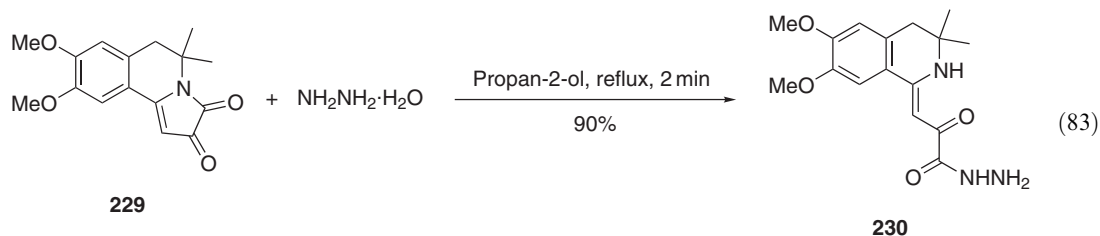
Scheme 29

Hydrazides attack the carbonyl group of oxazolidinone, oxathiolanone, and dioxolanone derivatives to give the ring-opened species with elimination of hexafluoroacetone (Table 3).

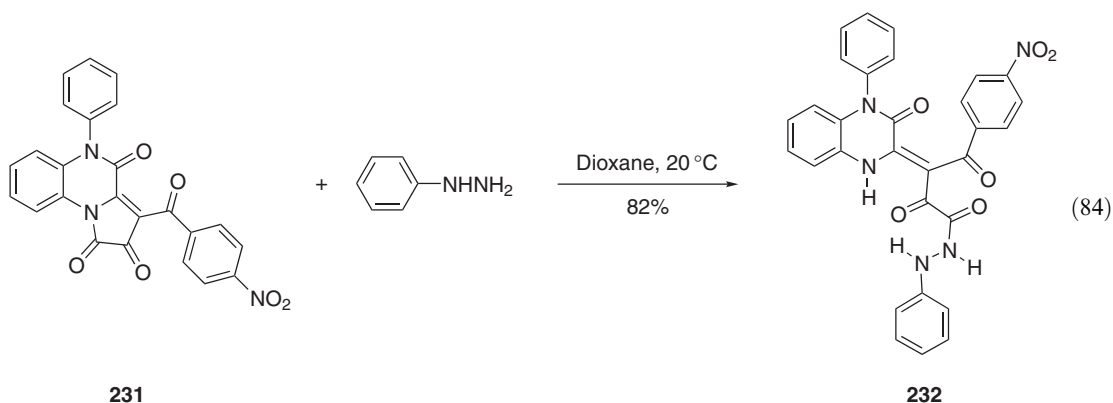
Table 3 Acylhydrazines from oxazolidinone, oxathiolanone, and dioxolanone derivatives

Starting material	Conditions	Product	Yield (%)	References
	$\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$, Diethyl ether, 20 °C		91	<2002M41>
	$\text{H}_2\text{NNHCO}_2\text{Me}$, DMF, 12 h		Not stated	<2003TL1059>
	$\text{H}_2\text{NNHCOPh}$, EtOAc, 20 °C, 16 h		98	<2003H189>

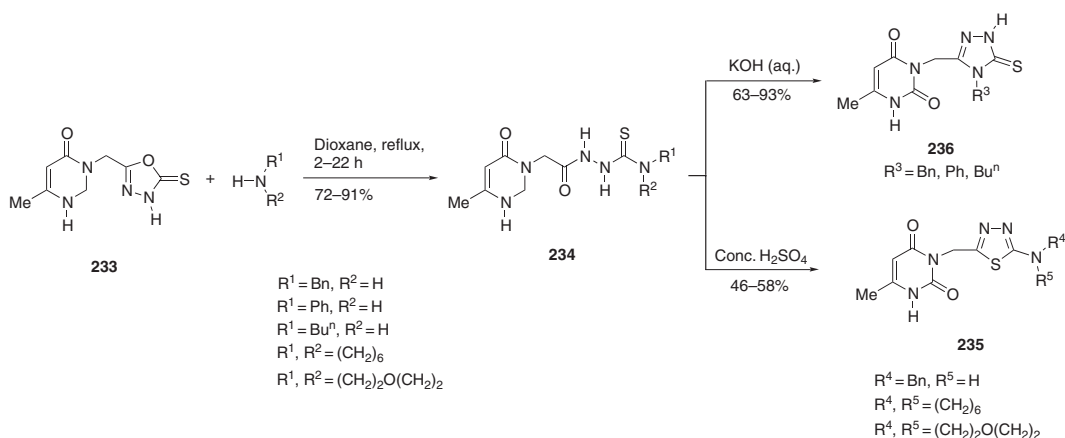
Treatment of dihydropyrroloisoquinolinedione **229** with hydrazine hydrate results in ring cleavage and the formation of hydrazide **230** almost instantaneously in excellent yield (Equation (83)) <1998CHE957>.



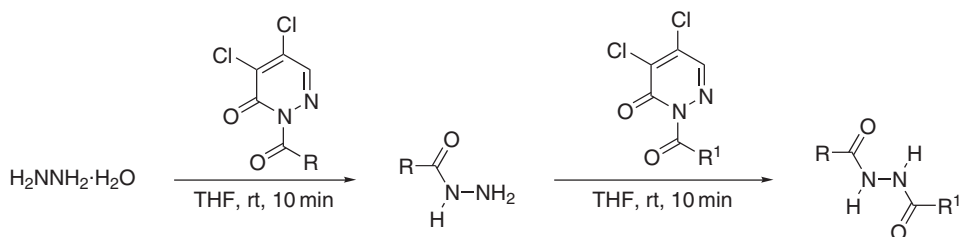
In a similar type of reaction, pyrroloquinoxalinetrione **231** reacts with phenylhydrazine to form the corresponding phenylhydrazide **232** in good yield (Equation (84)) <2001KFZ11>.



Oxadiazolethione derivative **233** reacts with a range of amines to form the corresponding thiosemicarbazides **234** in high yields. Treatment of thiosemicarbazide derivatives **234** with acid or base results in cyclization occurring to thiadiazoles **235** or triazolethiones **236** respectively (Scheme 30) <2002JCR(S)170>.



allows a wide range of symmetric and unsymmetric 1,2-diacylhydrazines to be synthesized (Scheme 31) <2003S560>.



$R = R^1 = \text{C}_6\text{H}_5$, 4-Me- C_6H_4 , 4-Cl- C_6H_4 , 2,4-Cl₂- C_6H_3 , 4- C_6H_5 - C_6H_4 , 4-MeO- C_6H_4 , 2-furyl, Et

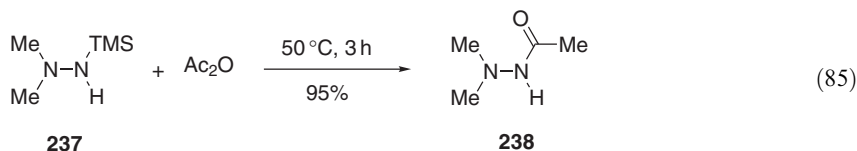
$R = \text{C}_6\text{H}_5$, $R^1 = \text{Et}$; $R = \text{C}_6\text{H}_5$, $R^1 = 4\text{-Me-C}_6\text{H}_4$; $R = \text{C}_6\text{H}_5$, $R^1 = 4\text{-Cl-C}_6\text{H}_4$; $R = \text{C}_6\text{H}_5$, $R^1 = 2,4\text{-Cl}_2\text{-C}_6\text{H}_3$;

$R = \text{C}_6\text{H}_5$, $R^1 = 2\text{-furyl}$; $R = 2,4\text{-Cl}_2\text{-C}_6\text{H}_3$, $R^1 = 2\text{-furyl}$; $R = 4\text{-MeO-C}_6\text{H}_4$, $R^1 = 2\text{-furyl}$; $R = 2\text{-furyl}$, $R^1 = \text{Et}$

Scheme 31

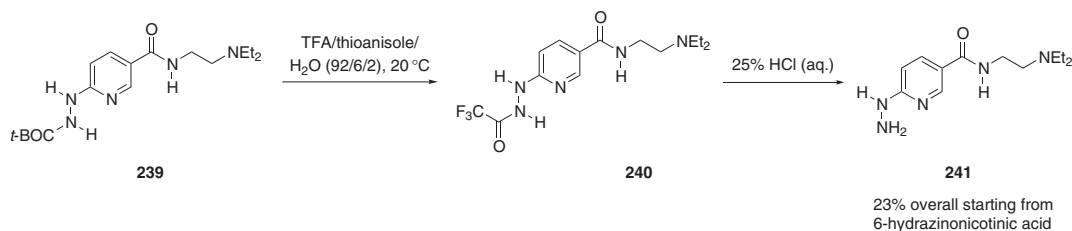
5.07.4.1.2 From acylation of N-silylhydrazines

The reaction of (*N*',*N*'-dimethylhydrazino)trimethylsilane **237** with acetic anhydride results in the removal of the silyl protecting group followed by acylation at the same nitrogen atom to furnish *N*',*N*'-dimethylacetohydrazide **238** in excellent yield (Equation (85)) <1999IZV169>.



5.07.4.1.3 From acylation of *t*-butoxycarbonylhydrazines

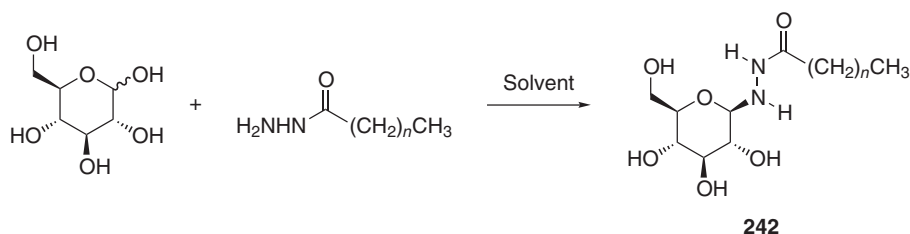
The attempted *t*-BOC-protection of *N*-*t*-BOC-hydrazine **239** with trifluoroacetic acid (TFA) in the presence of thioanisole yielded the trifluoroacetylhydrazine **240** and not the desired free hydrazine **241**. Treatment of **240** with acid resulted in cleavage of the trifluoroacetyl group furnishing hydrazine **241** (Scheme 32) <2002JMC5802>.



Scheme 32

5.07.4.1.4 From reaction of alcohols, ethers, and thioethers

The condensation of D-glucose with a range of hydrazides in either DMF or methanol results in the formation of glycosylhydrazides **242**, i.e., 1-glycosyl-2-acylhydrazines (Scheme 33) <2000MI378>.

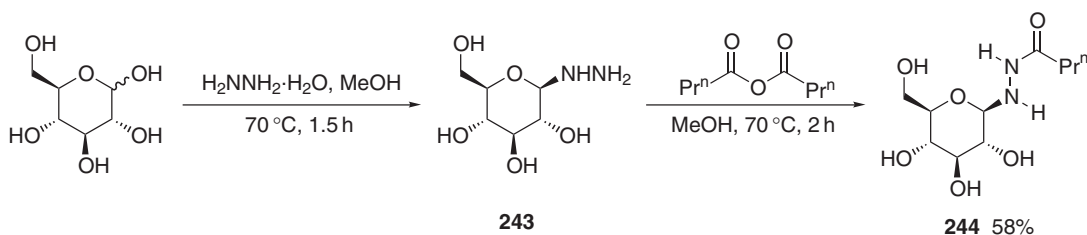


$n=2$, Solvent = MeOH, 70 °C, 1 d, 91%

$n=10$, Solvent = DMF, 70 °C, 3 d, 92%

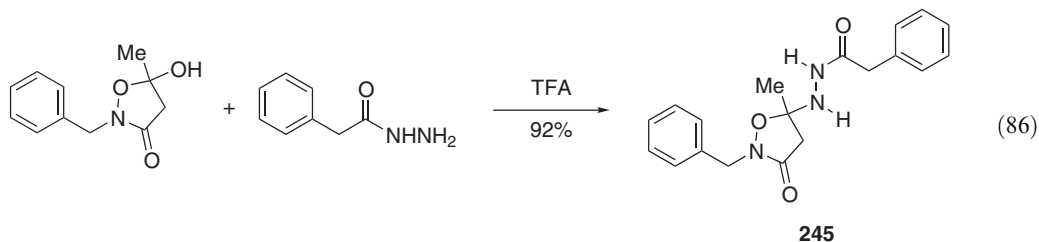
Scheme 33

The same transformation can be carried out by treating D-glucose with hydrazine monohydrate to form the glycosylhydrazine **243**, followed by acylation using an acid anhydride to yield glycosylhydrazide **244** (Scheme 34) <2000MI378>.

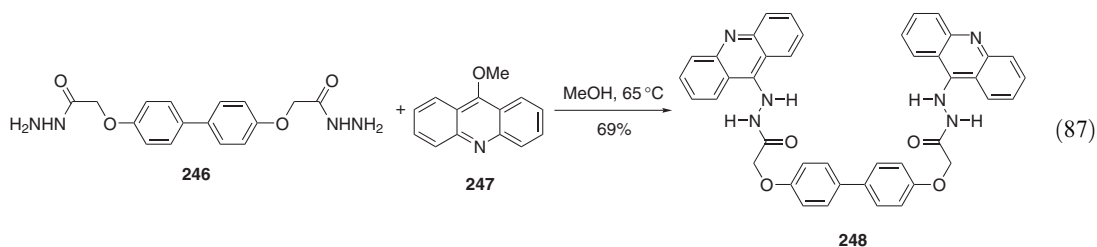


Scheme 34

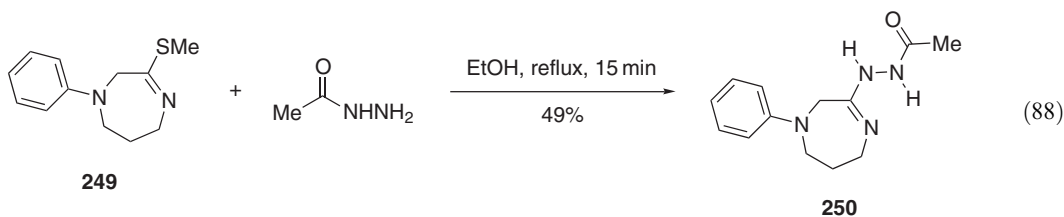
The condensation of alcohols with hydrazides occurs in the presence of trifluoroacetic acid (TFA) to form the acylhydrazino product **245** (Equation (86)) <2000JGU1887, 2002EJO2046>.



Heating (4'-hydrazinocarbonylmethoxy-biphenyl-4-yloxy)acetic acid hydrazide **246** with 9-methoxyacridine **247** in methanol results in dicondensation, producing the diacridinylhydrazide **248** in good yield (Equation (87)) <2001KFZ10>.

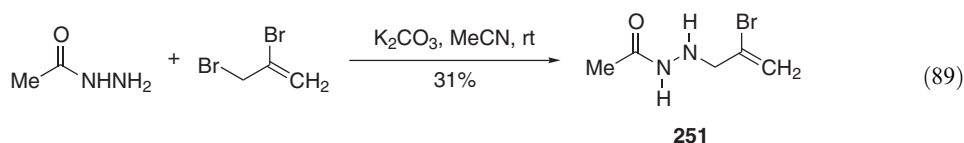


Thioethers undergo condensation reactions with hydrazides to form acylhydrazines. The reaction of methyl thioether **249** with acetic acid hydrazide takes place rapidly to yield hydrazide **250** in moderate yield (Equation (88)) <2001MI53>.

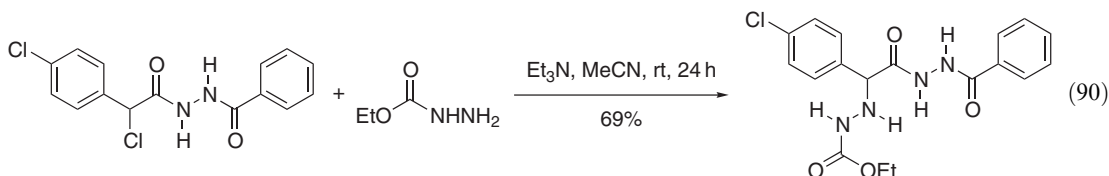


5.07.4.1.5 From alkyl and aryl halide compounds

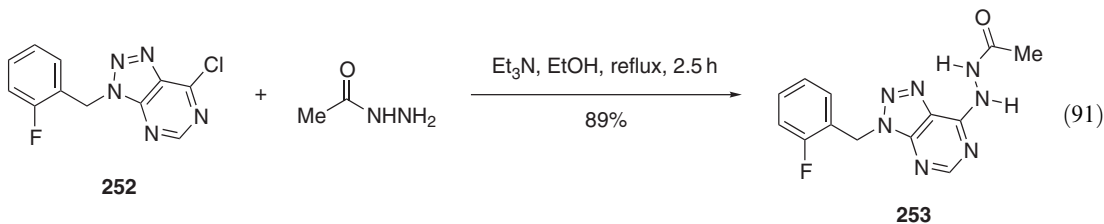
Alkylation of hydrazides is achieved by reaction with an alkyl halide under basic conditions. A mixture of acetic acid hydrazide, 2,3-dibromopropene, and potassium carbonate in acetonitrile at ambient temperature results in the formation of *N*-(2-bromo)prop-2-en-1-yl-*N'*-acetylhydrazine **251** in low yield (Equation (89)) <2003T4451>.



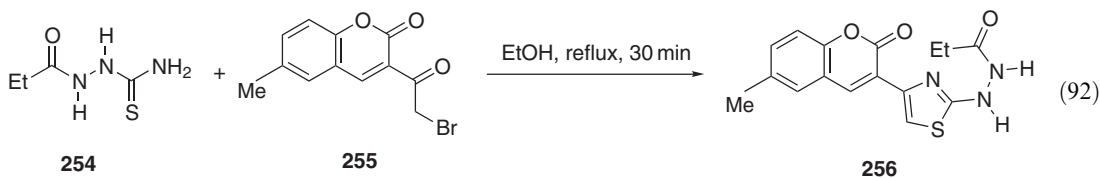
Alkylation of hydrazides can also be carried out using alkyl chlorides in the presence of an organic base (Equation (90)) <1999CJC263>.



Similarly, heating a mixture of chlorotriazolopyrimidine derivative **252**, acetic acid hydrazide, and triethylamine in ethanol results in the introduction of the hydrazide function onto the pyrimidine ring furnishing compound **253** in high yield (Equation (91)) <2002JHC885>.

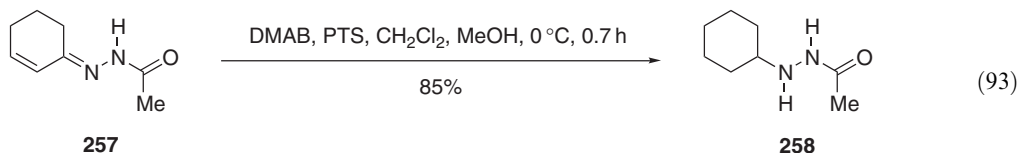


Bromoacetyl derivatives undergo condensation reactions with 1-acylthiosemicarbazides to form thiazole-derived compounds. 1-Propionylthiosemicarbazide **254** rapidly reacts with 3-bromoacetylchromen-2-one derivative **255** to yield thiazolylhydrazide **256** (Equation (92)) <1999IJC(B)18>.

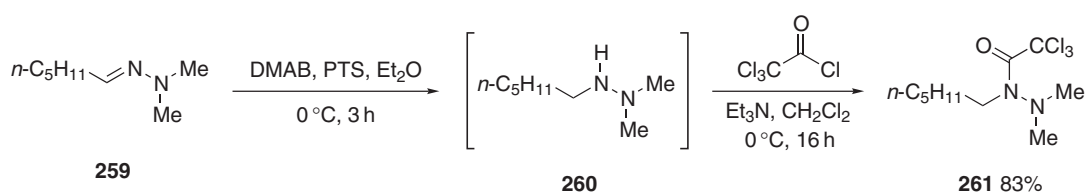


5.07.4.1.6 From reduction of hydrazones

The 1,2-reduction of a range of α,β -unsaturated hydrazones is readily achieved by treatment with a mixture of dimethylamine–borane (DMAB) and *p*-toluenesulfonic acid (PTS). Reduction of 2-cyclohexenone acetohydrazone **257** under these conditions proceeds rapidly to furnish acetic acid *N'*-cyclohexylhydrazide **258** in high yield (Equation (93)) <2002T7925>.

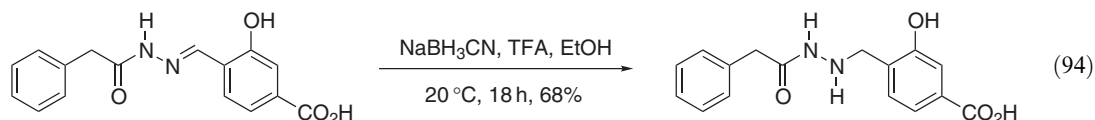


Hydrazone **259** is reduced under similar conditions to afford the intermediate hydrazine **260**, which upon treatment with trichloroacetyl chloride furnishes the corresponding hydrazide **261** in good yield (Scheme 35) <2002T7925>.

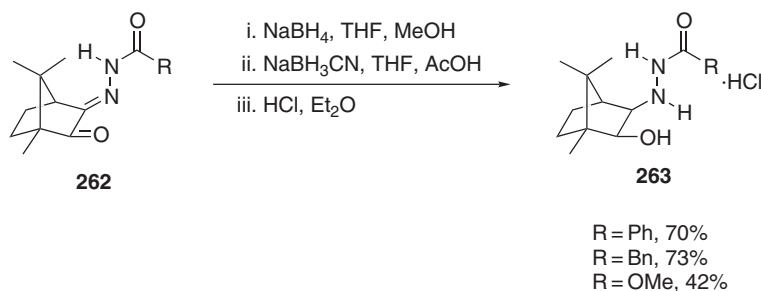


Scheme 35

Reduction of hydrazones can also be achieved using a combination of sodium cyanoborohydride and trifluoroacetic acid (Equation (94)) <2001EJO141>.



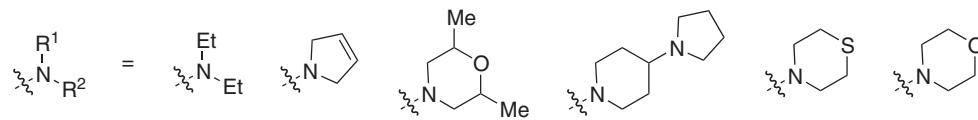
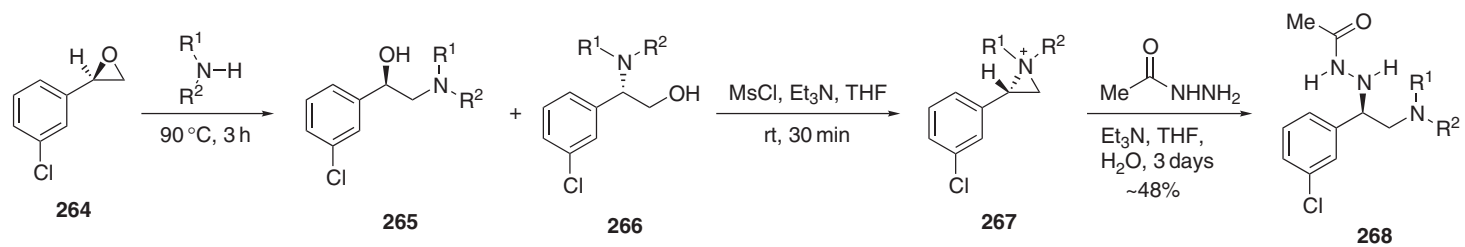
Sequential treatment of acylhydrazones **262** with sodium borohydride in the presence of methanol followed by sodium cyanoborohydride under acidic conditions results in the reduction of both the ketone function and the hydrazone function affording in good yield hydrazino derivatives **263**, which are isolated as their hydrochloride salts (Scheme 36) <2002TL607>.



Scheme 36

5.07.4.1.7 From ring opening of aziridinium ion species

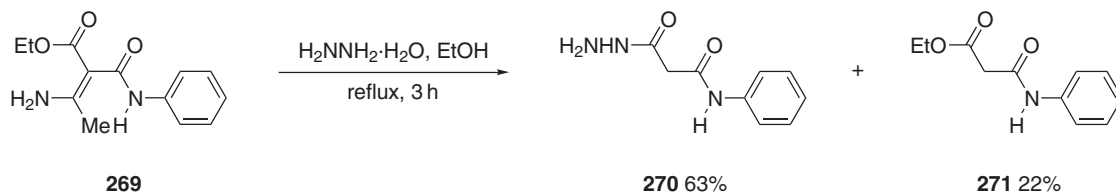
Treatment of chiral epoxide **264** with a secondary amine results in the formation of amino alcohol regioisomers **265** and **266**. Treatment of these regioisomers with methanesulfonyl chloride (MsCl) furnishes the mesylate intermediate, which undergoes a ring closure with displacement of the mesylate group to afford the aziridinium species **267**. Regiospecific ring opening with acetic acid hydrazide at the benzylic carbon atom yields hydrazide **268** (Scheme 37) <2002TL979>.



Scheme 37

5.07.4.1.8 From malonamic acid derivatives

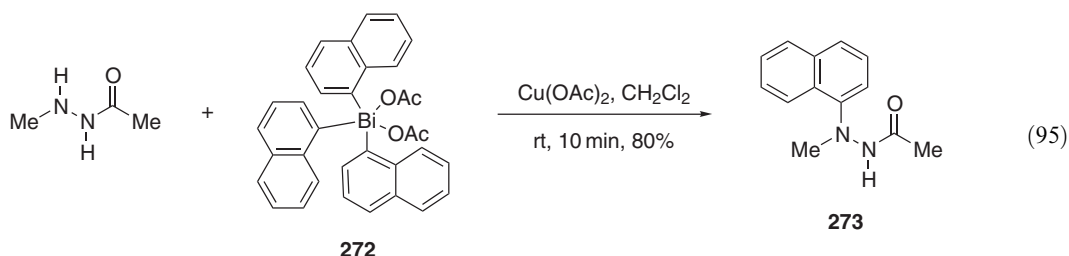
Treatment of malonamic acid derivative **269** with hydrazine hydrate results in β -carbon cleavage affording phenylmalonamic acid hydrazide **270** in moderate yield with a small quantity of *N*-phenylmalonamic acid ethyl ester **271** produced (Scheme 38) <2002SC3767>. The reaction between diethyl acetylmalonate and hydrazine hydrate to furnish a mixture of malonyldihydrazide and diethyl malonate is also reported.



Scheme 38

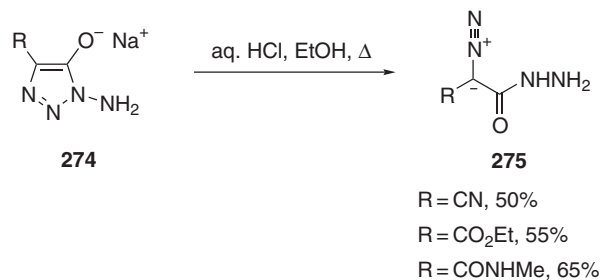
5.07.4.1.9 From arylation of hydrazides

The reaction of monoacylated 1,2-disubstituted hydrazines with pentavalent bismuth compounds of the type $\text{Ar}_3\text{Bi}(\text{OAc})_2$ results in arylation of the nonacylated nitrogen atom. 1-Acetyl-2-methylhydrazine reacts rapidly with 1 equiv. of trinaphthylbismuth diacetate **272** in the presence of a catalytic amount of copper(II) acetate to furnish hydrazide **273** in good yield (Equation (95)) <2002TL6213>.



5.07.4.1.10 From 1-amino-5-hydroxytriazole derivatives

The treatment of triazole derivatives **274** with aqueous hydrochloric acid in ethanol heated at reflux provides diazoacetohydrazides **275** in moderate yields (Scheme 39) <2001CHE294>.

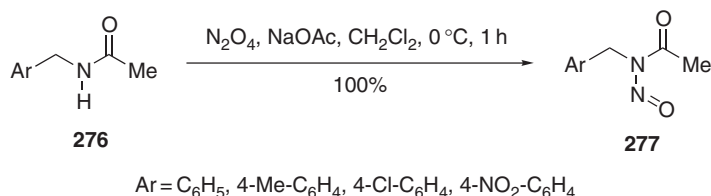


Scheme 39

5.07.4.2 N-Nitrosoamides

5.07.4.2.1 From amides

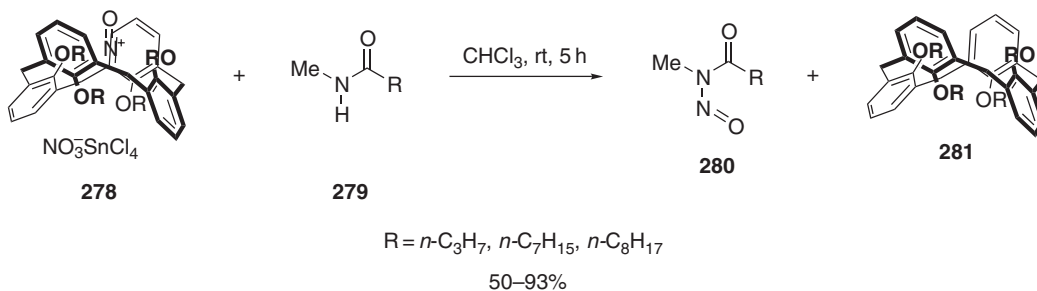
N-Nitrosoamides are easily prepared in excellent yields from the corresponding amides. Treatment of amides **276** with dinitrogen tetroxide (N_2O_4) in the presence of sodium acetate results in the rapid formation of N-nitrosoamides **277** in quantitative yield (Scheme 40) <1999JOC5966>. Similar transformations also using dinitrogen tetroxide have been reported <2001JOC1115, 2001JOC2681, 2002JOC2942, 2002TL4711>.



Scheme 40

Sodium nitrite has also been used for the synthesis of N-nitrosoamides, either in the presence of aqueous hydrochloric acid <2002CHE543> or acetic anhydride and acetic acid <2002OL2349>.

Nitrosation of amides has also been achieved using calix[4]arene-nitrosonium complexes <2003JA2997, 2003OL1253>. The reaction of (*O*-*n*-hexyloxy)calix[4]arene-nitrosonium complex **278** with secondary amide **279** results in the formation of the corresponding N-nitrosoamide **280** in moderate yield with calix[4]arene **281** as the elimination product (Scheme 41).

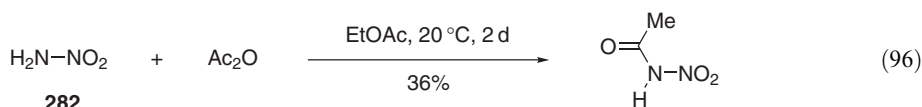


Scheme 41

5.07.4.3 N-Nitroamides

5.07.4.3.1 From amides

The reaction of nitramide **282** with acetic anhydride at ambient temperature results in the slow formation of N-nitroacetamide (Equation (96)) <2002JOU1>.

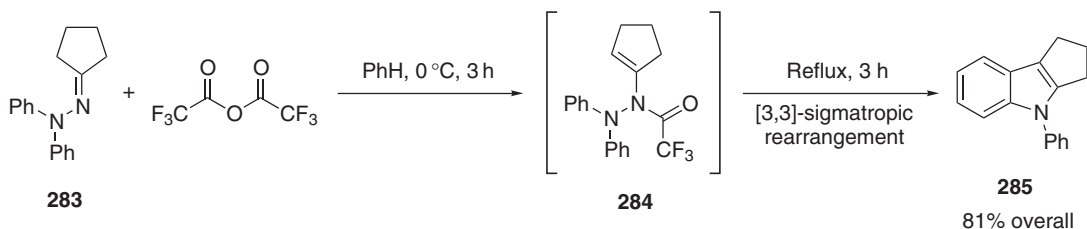


5.07.4.4 Acylhydrazones

5.07.4.4.1 From acylation of hydrazones

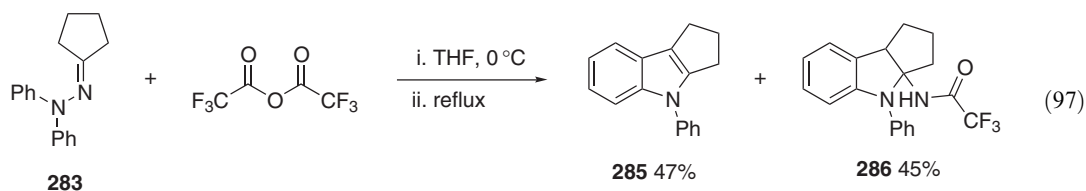
The acylation of hydrazones can be achieved using standard acylating conditions/reagents; DCC coupling of acids <1998MI931>, acid chlorides <2002PHA796>, and acid anhydrides <1999JCS(P1)1333>.

Treatment of hydrazone **283** with trifluoroacetic anhydride in benzene results in acylation affording intermediate **284**. After acylation is complete, the mixture is heated at reflux resulting in a [3,3]-sigmatropic rearrangement furnishing indole **285** in good overall yield (Scheme 42) <2001S1635>.

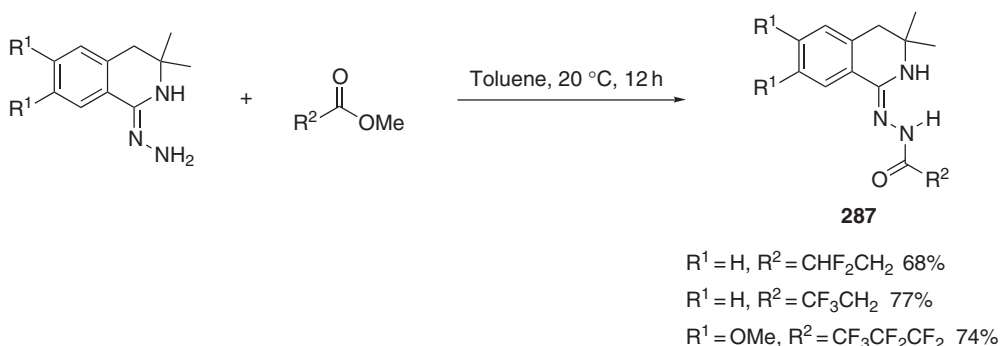


Scheme 42

The selection of solvent was particularly important to the synthesis of indoles. When benzene was substituted for THF, a mixture of the corresponding indole **285** and indoline **286** was observed (Equation (97)).



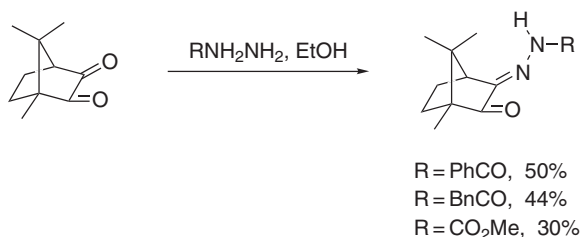
The reaction of hydrazones with perfluorocarboxylic esters proceeds at ambient temperature providing perfluoroacylhydrazones **287** in good yields (Scheme 43) <2000CHE319>.



Scheme 43

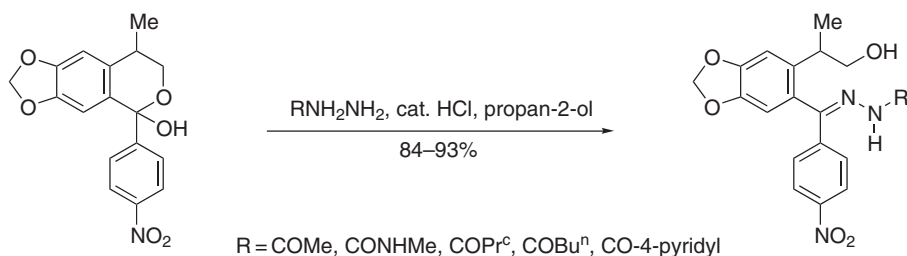
5.07.4.4.2 From acylhydrazines

The condensation of acylhydrazines with aldehydes and ketones furnishes the analogous acylhydrazones in varying yields (Scheme 44) <2002IJC(B)1937, 2002TL607, 2003MI351, 2003MI213, 2003RRC119>.



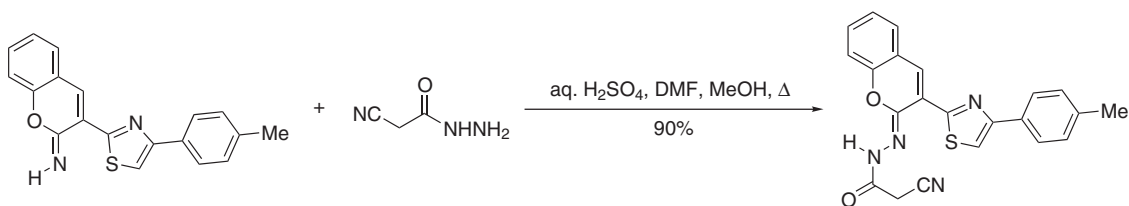
Scheme 44

Hemiacetals have been shown to react with a range of acylhydrazines resulting in the formation of a mixture of the (*E*)/(*Z*) isomers of the corresponding acylhydrazones in high yields (Scheme 45) <2000BMCL899>.



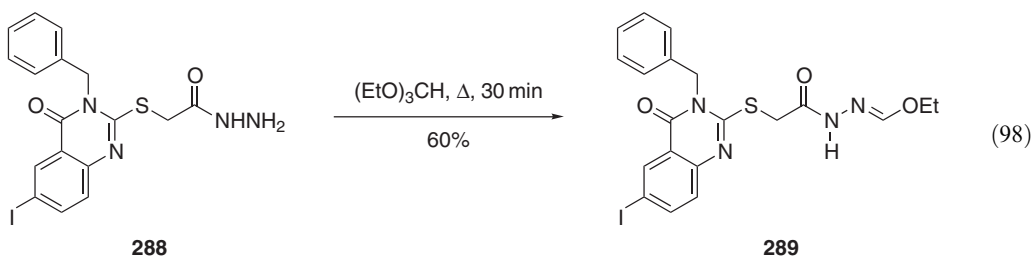
Scheme 45

Imines also undergo the same condensation reaction with acylhydrazines to afford the acylhydrazones in high yield (Scheme 46) <2002CHE1389>.



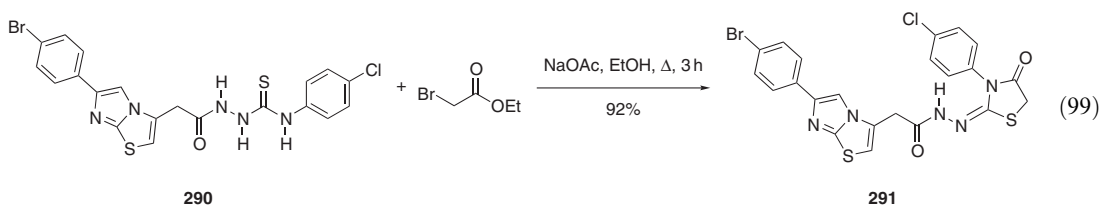
Scheme 46

The reaction of acylhydrazine **288** with triethyl orthoformate results in the rapid formation of acylhydrazone **289** in moderate yield (Equation (98)) <2003AP95>.



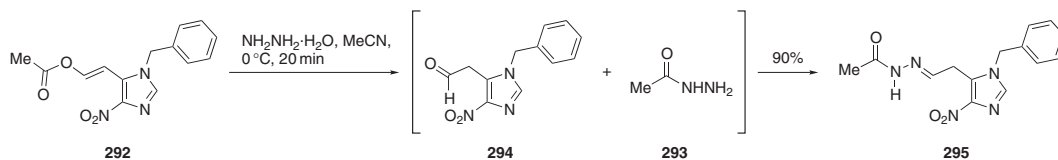
5.07.4.4.3 From thiosemicarbazides

The reaction of ethyl bromoacetate with thiosemicarbazide **290** takes place in the presence of sodium acetate to provide oxo-thiazolidinylidene hydrazide derivative **291** in excellent yield (Equation (99)) <2002M1305, 2000PHA900>.



5.07.4.4 From vinyl esters

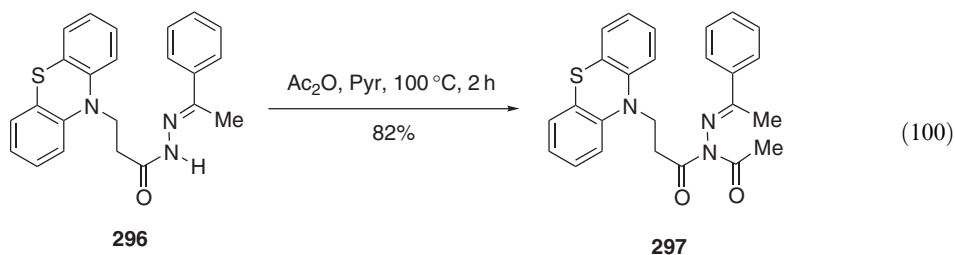
Treatment of vinyl ester **292** with hydrazine monohydrate results in the initial deacylation of **292** to form the intermediate acetohydrazide **293** and aldehyde **294**. The condensation reaction between these intermediates furnishes acetylhydrazone **295** in high overall yield (Scheme 47) <2002T9567>.



Scheme 47

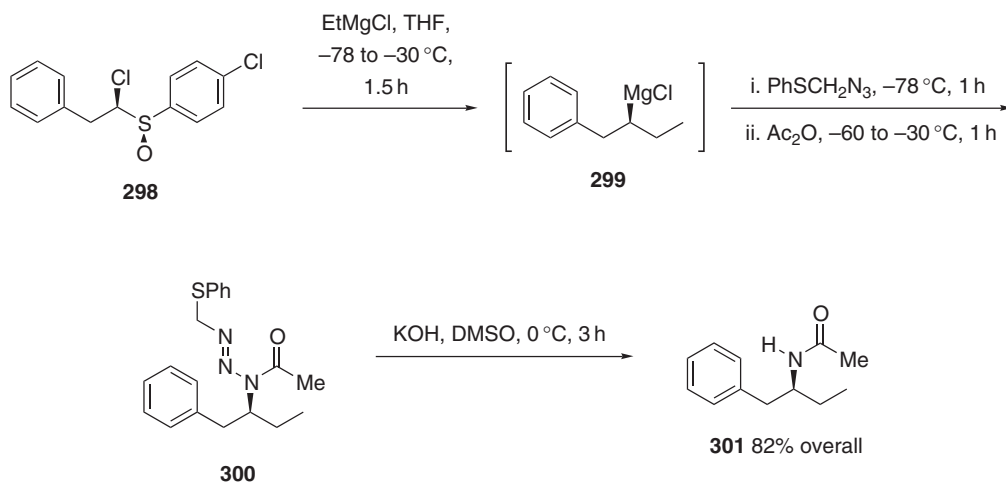
5.07.4.5 N,N-Diacylhydrazones

The treatment of acylhydrazone **296** with acetic anhydride in the presence of pyridine furnishes the mixed N,N-diacylhydrazone **297** in good yield (Equation (100)) <2003SC143>.



5.07.4.6 N-Acyl Triazenes

The reaction of enantiomerically pure α -chloro sulfoxide **298** with ethylmagnesium chloride produces Grignard reagent **299** *in situ*. Treatment of **299** with azidomethyl phenyl sulfide followed by acetic anhydride provides N-acetyl triazene **300**. Cleavage employing potassium hydroxide furnishes acetamide **301** in good overall yield with a high enantiomeric excess (Scheme 48) <2001OL1945>. For a similar reaction, albeit in low yield (15%) <1996MI466>.

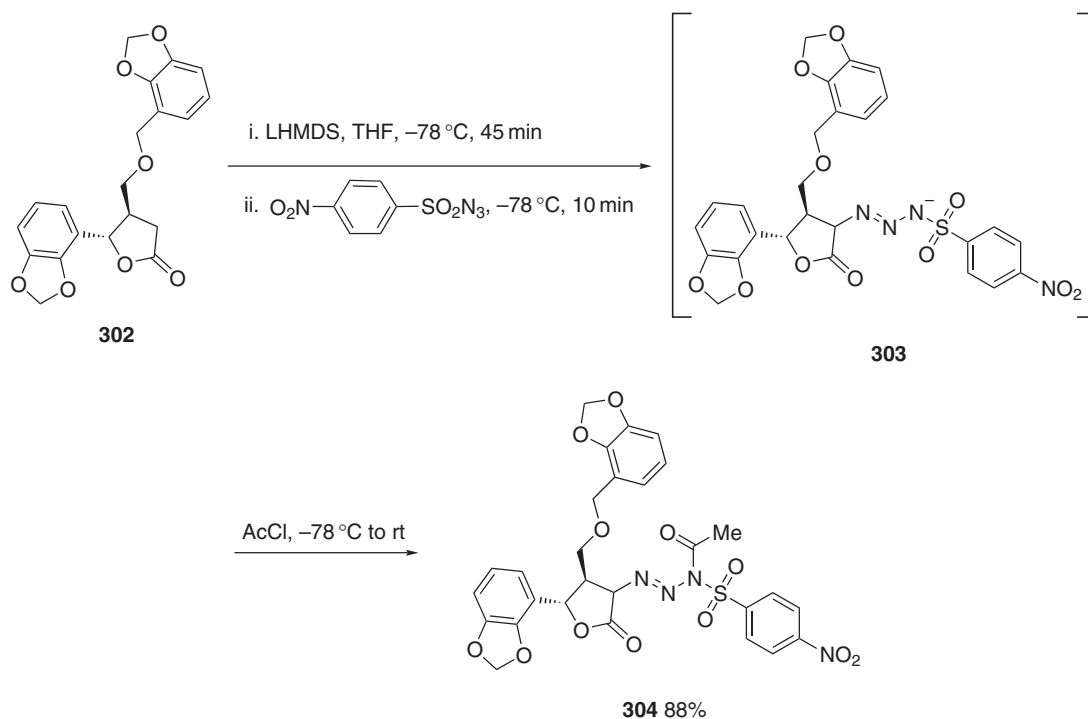


Scheme 48

5.07.4.7 N-Acyl-N-(4-nitrobenzenesulfonyl) Triazenes

5.07.4.7.1 From diazo-transfer to lactones

Treatment of lactone **302** with a base followed by the addition of 4-nitrobenzenesulfonyl azide provides the intermediate triazene anion **303**, which is trapped with acetyl chloride to furnish N-acetyl-N-(4-nitrobenzenesulfonyl)triazene derivative **304** in high yield (Scheme 49) <2001JOC6719>.



Scheme 49

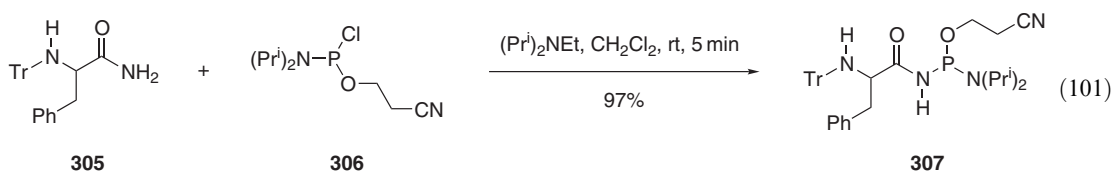
5.07.5 AMIDES SUBSTITUTED BY PHOSPHORUS, ANTIMONY, ARSENIC, OR BISMUTH

The synthesis of *N*-phosphorus amides, *N*-antimony amides, *N*-arsenic amides, and *N*-bismuth amides has been reviewed in COFGT (1995). There have been no new developments in the chemistry of *N*-antimony amides, *N*-arsenic amides, and *N*-bismuth amides.

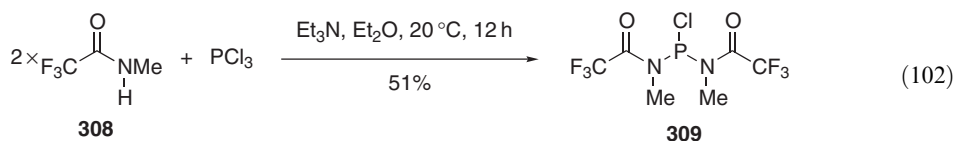
5.07.5.1 Amide Derivatives: Oxidation State +3, Tricoordinate

5.07.5.1.1 From amides

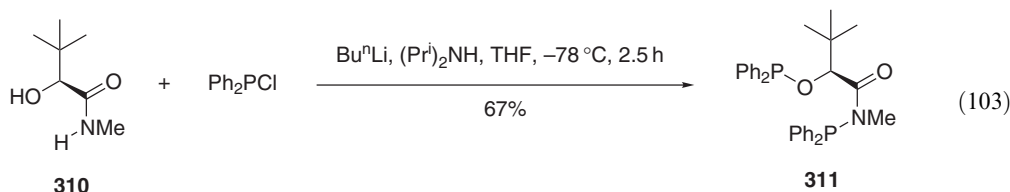
2-Cyanoethyl-*N,N*-diisopropylaminophosphorochloridite **306** has been employed to phosphitylate amides yielding the corresponding phosphorodiamidite <1995JOC4856, 1998TL3725, 1998TL4891, 2000JOC8229>. These reactions are usually rapid, are chemoselective (i.e., only the nitrogen, and not the oxygen atom is phosphitylated) and proceed in yields ranging from 40% to 97%. Treatment of *N*-trityl-L-phenylalanamide **305** with 2-cyanoethyl *N,N*-diisopropylaminophosphorochloridite **306** in the presence of Hünig's base furnishes *N*-acylphosphorodiamidite **307** in excellent yield (Equation (101)).



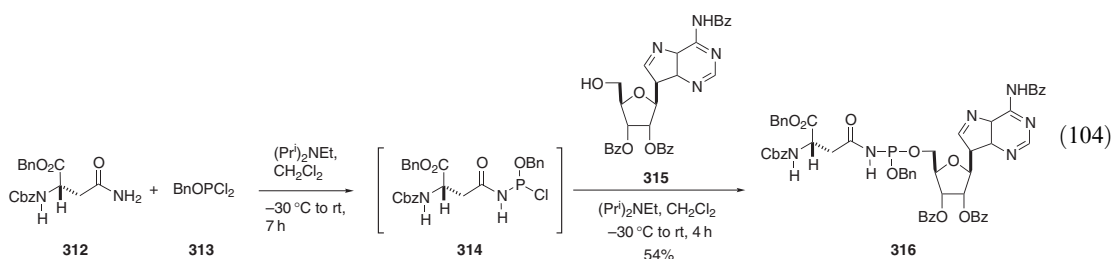
The reaction between 2,2,2-trifluoro-*N*-methylacetamide **308** and phosphorus trichloride in the presence of triethylamine results in the formation of bis(*N*-methyltrifluoromethylacetamido)chlorophosphine **309** in moderate yield (Equation (102)) <1995JGU232>.



Treatment of hydroxyamide **310** with 2 equiv. of *n*-butyllithium in the presence of a catalytic amount of diisopropylamine followed by the addition of chlorodiphenylphosphine resulted in the formation of amidophosphine-phosphinite **311** in moderate yield (Equation (103)) <1998TA4043>.

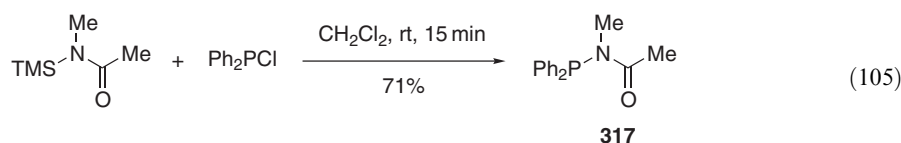


A “one-pot” procedure has been developed for the synthesis of *N*-acylphosphoramidites. L-Asparagine derivative **312** was treated with benzyloxydichlorophosphine **313** in the presence of Hünig’s base to form monochlorophosphine **314**. Addition of *N*-benzoyl-2',3'-di-*O*-benzoyladenine **315** and further Hünig’s base furnished *N*-acylphosphoramidite **316** (Equation (104)) <2002JOC4372>.



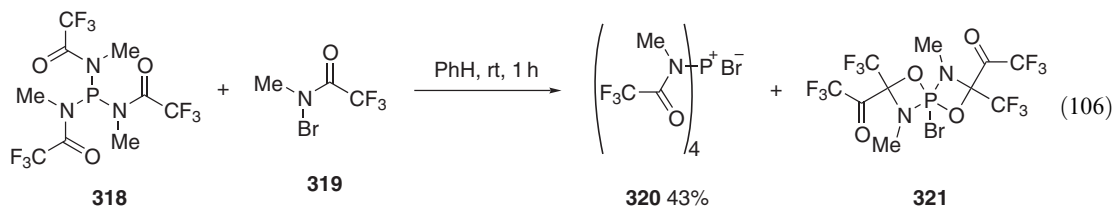
5.07.5.1.2 From silylamides

The reaction between *N*-methyl-*N*-trimethylsilylacetamide and chlorodiphenylphosphine proceeds cleanly and rapidly at room temperature in dichloromethane affording *N*-methylacetamido phosphine **317** in good yield (Equation (105)) <2000JCS(D)2205>. When the reaction was attempted in toluene, heating was required for the reaction to proceed. This led to unwanted by-products being formed such as $\text{Ph}_2\text{PP}(\text{O})\text{Ph}_2$.



5.07.5.2 Amide Derivatives: Oxidation State +3, Tetracoordinate

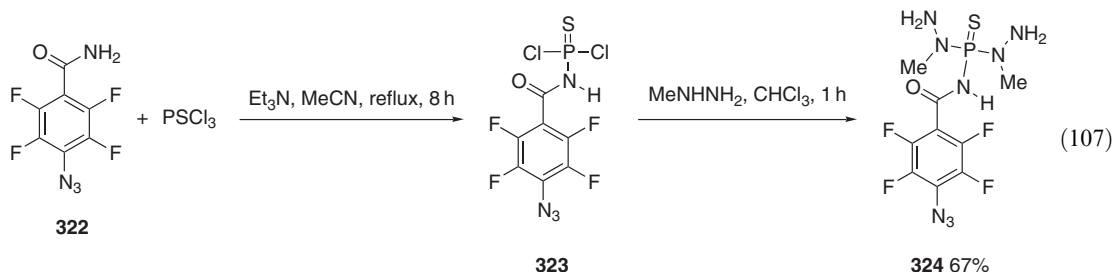
The reaction of phosphorus tris(*N*-methyl-*N*-trifluoroacetamide) **318** with *N*-bromo-*N*-methyltrifluoroacetamide **319** at ambient temperature yields tetrakis(*N*-methyltrifluoroacetamido)-phosphorus bromide **320** with spiro compound **321** formed as a by-product (Equation (106)) <1997JGU151>.



5.07.5.3 Amide Derivatives: Oxidation State +5, Tetracoordinate

5.07.5.3.1 From amides

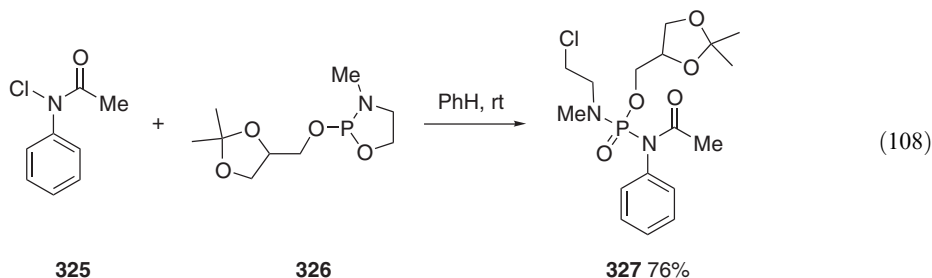
The reaction of 4-azido-2,3,5,6-tetrafluorobenzamide **322** with PSCl_3 in the presence of excess triethylamine results in the formation of the monosubstituted compound **323**. The addition of methylhydrazine *in situ* furnishes **324** in moderate yield (Equation (107)) <1998JOC9019>.



The phosphorylation of primary and secondary amides and thioamides using phosphoric anhydride (P_4H_{10}) has been reported <1996MI465>.

5.07.5.3.2 From N-chloroamides

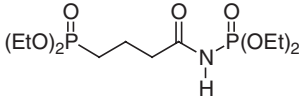
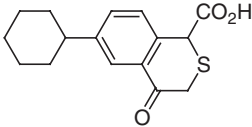
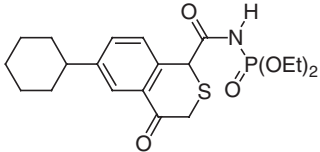
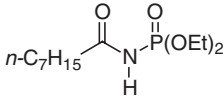
N-Chloroacetanilide **325** reacts with a range of phosphoric acid esters **326** to yield the corresponding phosphoramidic acid esters **327** in good yields (Equation (108)) <1999JGU383>.



5.07.5.3.3 From acylation of phosphoramines

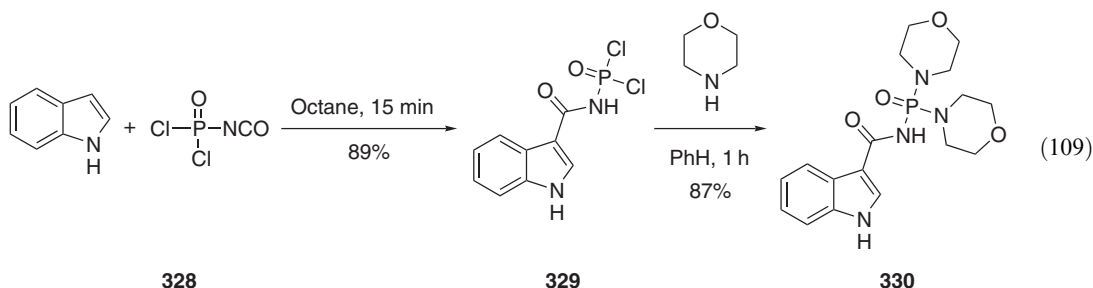
The synthesis of phosphoramides can be achieved by the acylation of phosphoramidates employing acid chlorides <1998BMCL289, 2001BMC773>, carboxylic acids <1999JMC751>, and acetylcarbonic acid alkyl esters <2002CC2004> (Table 4).

Table 4 Acylation of phosphoramidates

<i>Acyating agent</i>	<i>Conditions</i>	<i>Product</i>	<i>Yield (%)</i>
$(\text{EtO})_2\text{P}(\text{O})(\text{CH}_2)\text{COCl}$	$(\text{EtO})_2\text{P}(\text{O})\text{NH}_2$, Et_3N , Et_2O , Δ , 4 days		25
	$(\text{EtO})_2\text{P}(\text{O})\text{NH}_2$, DMF, 0°C , 1.5 h		36
$n\text{-C}_7\text{H}_{15}\text{C}(\text{O})\text{OCO}_2\text{Et}$	$(\text{EtO})_2\text{P}(\text{O})\text{NH}_2$, BuLi, CH_2Cl_2 , -78 to 18°C		n/a

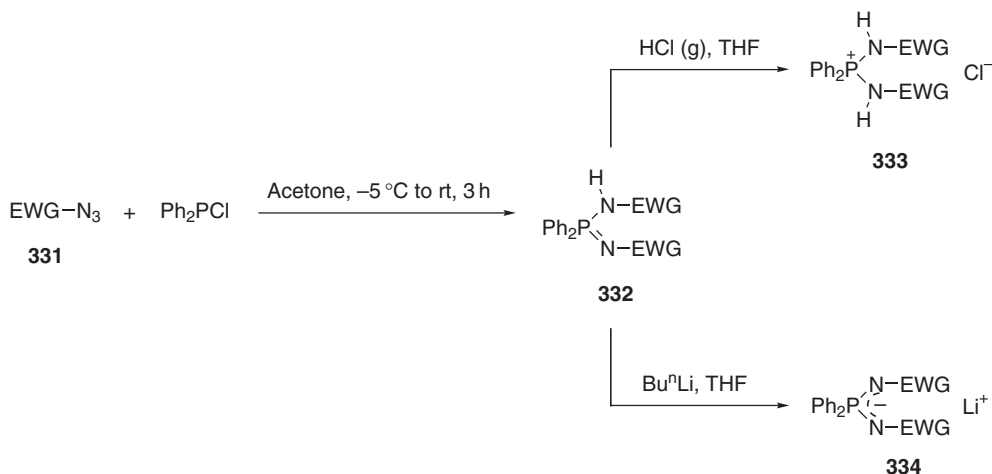
5.07.5.3.4 From isocyanates

Electron-rich heterocycles have been treated with Kirsanov's isocyanate (phosphorisocyanatidic dichloride), **328** resulting in C-acylation and the introduction of phosphoramidate groups into the molecule. Indole reacts with isocyanate **328** affording *N*-(indolyl-3-carboxy)amidophosphoric dichloride **329** in high yield. Compound **329** can then undergo a substitution reaction with morpholine to furnish indole-3-carboxylic acid *N*-(dimorpholylphosphato)amide **330** in good yield (Equation (109)) <1998CHE380>.



5.07.5.3.5 From acyl azides

Acyl azides with suitable electron-withdrawing groups **331** undergo a double Staudinger reaction when treated with diphenylphosphine yielding the corresponding diaminodiphenylphosphonium monoazaylides **332**. Stable diaminodiphenylphosphonium chlorides **333** can be formed in quantitative yields from monoazaylide **332** by treatment with gaseous HCl. Lithium diaminodiphenylphosphonium diaza-ylides **334** can be prepared in good-to-excellent yields by adding one stoichiometric equivalent of *n*-BuLi to monoazaylide **332** (Scheme 50) <2001S69>.



EWG = PhC(O), **332** 100%, **333** 90%, **334** 100%

EWG = *p*-MeC₆H₄C(O), **332** 100%, **333** 72%, **334** 100%

EWG = *p*-MeOC₆H₄C(O), **332** 100%, **333** 70%, **334** 90%

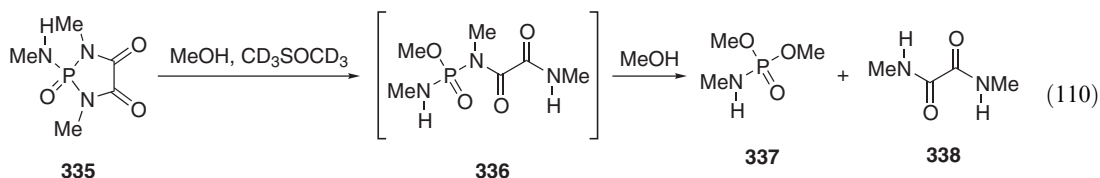
EWG = *p*-ClC₆H₄C(O), **332** 100%, **333** 71%, **334** 90%

EWG = , **332** 100%, **333** 70%, **334** 90%

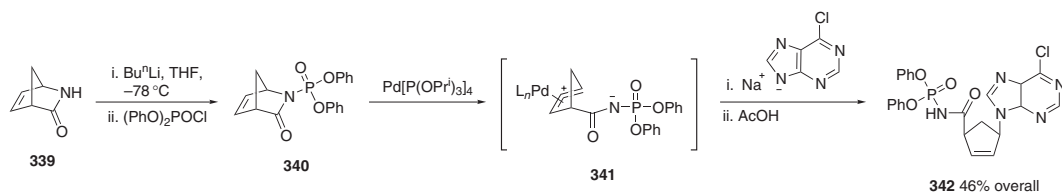
Scheme 50

5.07.5.3.6 From ring-opening reactions

The reaction of phospholidine **335** with methanol in deuterated dimethyl sulfoxide was monitored using NMR studies. It was observed that after 4 d 70% methanolysis to methylamino derivative **336** had taken place. If the reaction is not stopped at this point or the reaction is carried out without the presence of dimethyl sulfoxide then **336** is no longer observed and only methylphosphoramidic acid **337** and *N,N'*-dimethyloxalamide **338** are present in the reaction mixture due to the second methanolysis occurring (Equation (110)) <1995JCS(P2)1809>.



Treatment of azabicycloheptenone **339** with diphenyl chlorophosphate introduces a diphenylphosphoryl group onto the nitrogen atom affording **340** in almost quantitative yield. The coupling reaction of **340** with the sodium salt of 6-chloropurine was carried out in the presence of $\text{Pd}[\text{P}(\text{OPr}^i)_3]_4$ and goes via intermediate **341** to furnish **342** in moderate yield (Scheme 51) <1997JOC1580>.



Scheme 51

5.07.6 AMIDES SUBSTITUTED BY SILICON

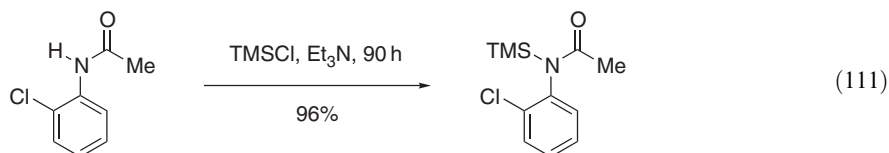
The chemistry of organosilyl nitrogen-containing compounds has been reviewed in COFGT (1995).

5.07.6.1 N-Silylamide Derivatives

5.07.6.1.1 From silylation of amides

A range of different silylating agents can be used to carry out the silylation of amides. This route is frequently used to provide easy access to *N*-silylamides. TMSCl, trimethylsilyl trifluoromethanesulfonate (TMSOTf), *N,O*-bis(trimethylsilyl)acetamide (BSA), and *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) are all commercially available silylation reagents that introduce TMS groups into a variety of compounds.

Treatment of simple *N*-substituted acetamides with TMSCl results in the formation of *N*-TMS amides. Heating *N*-(2-chlorophenyl)acetamide in the presence of TMSCl and triethylamine yields the corresponding *N*-TMS, *N*-(2-chlorophenyl)acetamide in almost quantitative yield (Equation (111)) <1998JHC555>.



Heating *N*-formylglycine in benzene in the presence of triethylamine and TMSCl results in the formation of *N*-formyl-*N,O*-bis(trimethylsilyl)glycine **343** in high yield <1996JCS(P1)883>.

Similarly, heating bis-*N,N*-(hydroxyethyl)glycineamide in chloroform with triethylamine and TMSCl affords *N,N*-bis(2-methylsiloxyethyl)glycine trimethylsilamide **344** in good yield (Figure 1) <1998JGU44>.

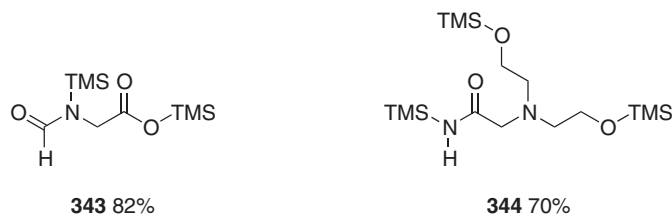
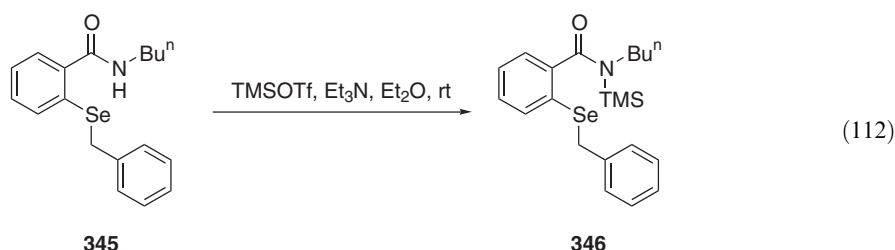


Figure 1 *N*-TMS amides from *N*-formylglycine and bis-*N,N*-(hydroxyethyl)glycineamide.

Treatment of benzamide derivative **345** with TMSOTf in the presence of triethylamine yields the corresponding *N*-TMS benzamide derivative **346** (Equation (112)) <1995AJC1221>.



Heating 2-acetyl-amino-6-hydroxypurine with BSA in acetonitrile affords the bis(trimethylsilyl) derivative **347** <1997TL3195>. The tris(trimethylsilyl) derivative of D-pantothenic acid **348** is prepared by heating D-pantothenic acid with BSTFA in pyridine (Figure 2) <2000MI1175>. BSTFA is often preferred to BSA due to the advantage that both BSTFA and its by-product, trifluoroacetamide, are more volatile than the corresponding nonfluorinated compounds.

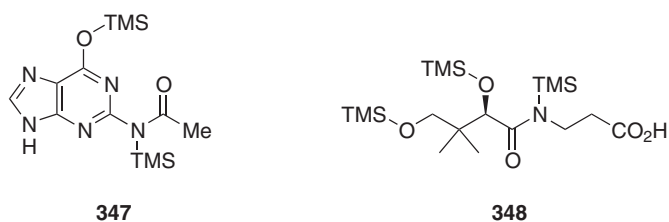
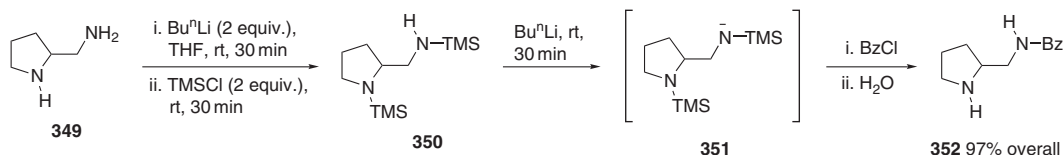


Figure 2 *N*-TMS amides from *N,O*-bis(trimethylsilyl)acetamide.

Heating amides in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of ammonium sulfate results in the formation of the corresponding *N*-TMS amides <1997TL1411, 2000JMC3906, 2001CAR83, 2002JCS(P1)1800>.

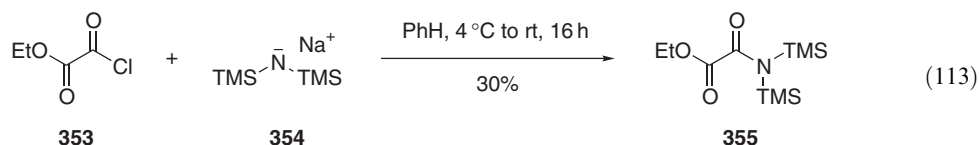
5.07.6.1.2 From acylation of *N*-silylamines

The benzylation of primary amines over secondary amines within the same molecule can be achieved by introducing a temporary protecting TMS group to each nitrogen atom of the molecule. Treatment of diamine **349** with 2 equiv. of a base and 2 equiv. of TMSCl affords intermediate **350**. Deprotonation of the remaining acidic proton results in the formation of anion **351** which undergoes a benzylation reaction when treated with benzoyl chloride. Removal of the TMS protecting groups occurs with aqueous work-up yielding monobenzoylated diamine **352** in excellent yield (Scheme 52) <1999TL6745>.

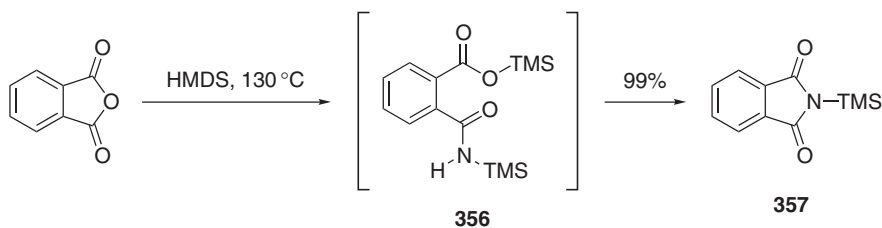


Scheme 52

Treatment of ethyl oxalyl chloride **353** with sodium hexamethyldisilylamide **354** prepared *in situ* from sodium amide and HMDS resulted in the addition of the disilylamide group yielding ethyl *N,N*-bis(trimethylsilyl)oxamate **355** (Equation (113)) <1996JCS(P1)883>.

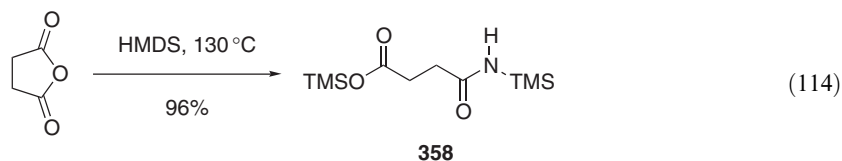


Heating phthalic anhydride in HMDS results in the formation of the ring-opened intermediate **356** which then cyclizes with the elimination of trimethylsiloxide anion to form *N*-(trimethylsilyl)-phthalimide **357** in virtually quantitative yield (Scheme 53) <2003DOK55>.



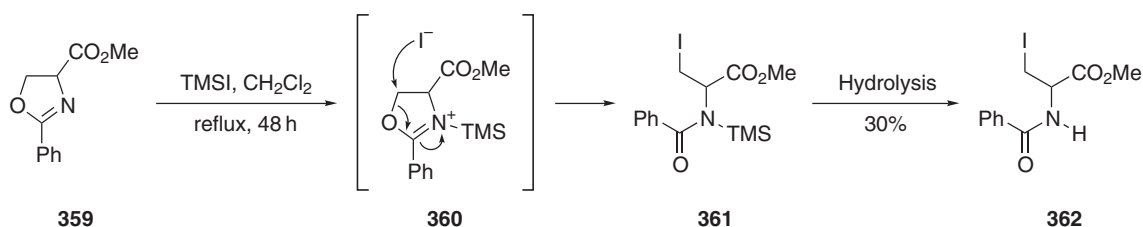
Scheme 53

Under the same conditions succinic anhydride forms *N*-silylamide **358** in excellent yield (Equation (114)).



5.07.6.1.3 From ring opening of oxazolines

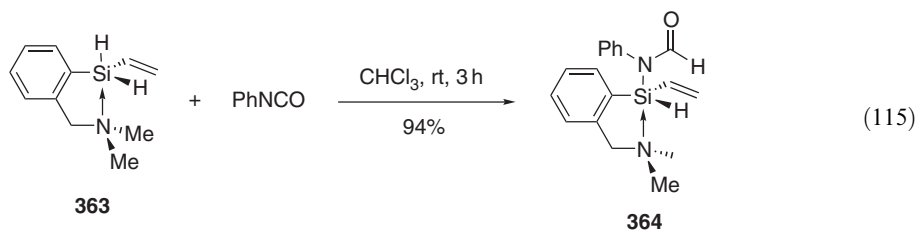
The reaction of oxazoline **359** with trimethylsilyl iodide (TMSI) results in the formation of the *N*-TMS oxazolinium salt **360** which leads to *N*-TMS amino ester **361**. Hydrolysis of **361** affords (\pm)-methyl [2-(*N*-benzoyl)amino-3-iodo]propanoate **362** in 30% overall yield (Scheme 54) <1998TA437>.



Scheme 54

5.07.6.1.4 From hydrosilylation reactions

The hydrosilylation-type reaction between silane **363** and phenyl isocyanate takes place under mild conditions resulting in the formation of *N*-silylformamide **364** in excellent yield (Equation (115)) <1998JOM131>.



5.07.7 AMIDES SUBSTITUTED BY BORON OR ALUMINUM

The chemistry of organoboron or organoaluminum nitrogen-containing compounds has been reviewed in COFGT (1995). There have been no significant advances with regard to the synthesis of amides substituted by boron or aluminum.

5.07.8 AMIDES SUBSTITUTED BY METALS

The chemistry of organometallic amides has been reviewed in COFGT (1995). There have been no major advances with regard to the synthesis of amides substituted by metals.

REFERENCES

- 1975M611 W. Gottardi, *Monatsh. Chem.* **1975**, 106, 611–623.
 1995AJC1221 M. C. Fong, M. J. Laws, C. H. Schiesser, *Aust. J. Chem.* **1995**, 48, 1221–1226.
 1995COFGT(5)309 R. D. Connell, *N*-Heterosubstituted amides, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 309–392.
 1995JA4870 M. V. De Almeida, D. H. R. Barton, I. Bytheway, J. A. Ferreira, M. B. Hall, W. Liu, D. K. Taylor, L. Thomson, *J. Am. Chem. Soc.* **1995**, 117, 4870–4874.
 1995JCS(P2)1809 J.-M. Grévy, M. Mulliez, *J. Chem. Soc., Perkin Trans. 2* **1995**, 1809–1816.
 1995JFC203 S. Zhu, B. Xu, J. Zhang, *J. Fluorine Chem.* **1995**, 74, 203–206.
 1995JGU232 A. D. Sinitsa, L. I. Nesterova, D. M. Malenko, V. V. Pirozhenko, E. B. Rusanov, A. N. Chernega, *J. Gen. Chem. USSR (Engl. Trans.)* **1995**, 65, 232–239.
 1995JHC1625 D.-K. Kim, G. Kim, J. Lim, K. H. Kim, *J. Heterocycl. Chem.* **1995**, 32, 1625–1629.
 1995JMC3972 P. D. Edwards, M. A. Zottola, M. Davis, J. Williams, P. A. Tuthill, *J. Med. Chem.* **1995**, 38, 3972–3982.
 1995JOC109 R. J. Bergeron, J. S. McManis, O. Phanstiel IV, J. R. T. Vinson, *J. Org. Chem.* **1995**, 60, 109–114.
 1995JOC376 P. A. Jacobi, J. I. Kravitz, W. Zheng, *J. Org. Chem.* **1995**, 60, 376–385.
 1995JOC4856 J. Robles, E. Pedroso, A. Grandas, *J. Org. Chem.* **1995**, 60, 4856–4861.
 1995RTC27 J. H. van Maarseveen, E. H. H. Obery, M. B. Bolster, H. W. Scheeren, C. G. Kruse, *Recl. Trav. Chim. Pays-Bas* **1995**, 114, 27–34.
 1995SC3509 P. F. Santos, A. M. Lobo, S. Prabhakar, *Synth. Commun.* **1995**, 25, 3509–3518.
 1995T6517 J. Boivin, A.-C. Callier-Dublanchet, B. Quiclet-Sire, A.-M. Schiano, S. Z. Zard, *Tetrahedron* **1995**, 51, 6517–6528.
 1995T12837 G. Proctor, J. Nally, N. H. R. Ordsmith, *Tetrahedron* **1995**, 51, 12837–12842.
 1995TL5449 G. V. Shustov, A. Rauk, *Tetrahedron Lett.* **1995**, 36, 5449–5452.
 1995TL7535 J. P. Muxworthy, J. A. Wilkinson, G. Proctor, *Tetrahedron Lett.* **1995**, 36, 7535–7538.
 1996BMCL1055 M. Sakurai, P. Wirsching, K. D. Janda, *Biorg. Med. Chem. Lett.* **1996**, 6, 1055–1060.
 1996BOC273 D. Heacock, C. J. Forsyth, K. Shiba, K. MusierForsyth, *Bioorg. Chem.* **1996**, 24, 273–289.
 1996H633 K. Uto, T. Sakamoto, K. Matsumoto, Y. Kikugawa, *Heterocycles* **1996**, 43, 633–640.
 1996H2361 K. Satake, K. Yano, M. Fujiwara, M. Kimura, *Heterocycles* **1996**, 43, 2361–2365.
 1996IJC(B)1275 M. N. Khan, *Indian J. Chem., Sect. B* **1996**, 35, 1275–1281.
 1996JCS(P1)883 A. P. Johnson, R. W. A. Luke, R. W. Steele, A. N. Boa, *J. Chem. Soc., Perkin Trans. 1* **1996**, 883–893.
 1996JCS(P2)2673 D. A. Brown, R. A. Coogan, N. J. Fitzpatrick, W. K. Glass, D. E. Abukshima, L. Shiels, M. Ahlgren, K. Smolander, T. T. Pakkanen, T. A. Pakkanen, M. Perakyla, *J. Chem. Soc., Perkin Trans. 2* **1996**, 2673–2679.
 1996JFC1 A. R. Ritter, C. F. Hammer, *J. Fluorine Chem.* **1996**, 77(1), 1–7.
 1996JMC1509 P. T. Flaherty, T. D. Greenwood, A. L. Manheim, J. F. Wolfe, *J. Med. Chem.* **1996**, 39, 1509–1513.

- 1996JMC2232 P. L. Ornstein, M. B. Arnold, N. K. Allen, T. Bleisch, P. S. Borromeo, C. W. Lugar, J. D. Leander, D. Lodge, D. D. Schoepp, *J. Med. Chem.* **1996**, *39*, 2232–2244.
- 1996JOC4232 M. D. Refvik, A. L. Schwan, *J. Org. Chem.* **1996**, *61*, 4232–4239.
- 1996MI377 D. Geffken, S. van Brandis, *Sci. Pharm.* **1996**, *64*, 377–382.
- 1996MI465 D. A. Efremov, J. C. Tebby, P. M. Zavlin, *Phosphorus, Sulfur, Silicon Relat. Elem.* **1996**, *110*, 465–468.
- 1996MI466 M. B. K. Smith, B. F. Schmidt, G. Czerwinski, L. A. Taneyhill, E. J. Snyder, A. M. Kline, C. J. Michejda, R. H. Smith, *Chem. Res. Toxicol.* **1996**, *9*, 466–475.
- 1996MI759 Y. Gafni, H. Weizman, J. Libman, A. Shanzer, I. Rubinstein, *Chem. Europ. J.* **1996**, *2*, 759–766.
- 1996TL3165 M. Seki, K. Matsumoto, *Tetrahedron Lett.* **1996**, *37*, 3165–3168.
- 1996TL3519 S. L. Less, P. F. Leadlay, C. J. Dutton, J. Staunton, *Tetrahedron Lett.* **1996**, *37*, 3519–3520.
- 1996TL4639 J. R. Flisak, I. Lantos, L. Liu, R. T. Matsuoka, W. L. Mendelson, L. M. Tucker, A. J. Villani, W.-Y. Zhang, *Tetrahedron Lett.* **1996**, *37*, 4639–4642.
- 1997AX(C)781 J. Dalluhn, D. Henschel, A. Blaschette, P. G. Jones, *Acta Crystallogr., Part C* **1997**, *53*, 781–783.
- 1997BMC779 S. A. Beers, E. A. Malloy, W. Wu, M. Wachter, J. Ansell, M. Singer, M. Steber, A. Barbone, T. Kirchner, D. Ritchie, D. Argentieri, *Biorg. Med. Chem.* **1997**, *5*, 779–786.
- 1997BMCL3053 J. R. Falck, Y. Y. Belosludtsev, K. K. Reddy, K. M. Reddy, M. F. Shortt, K. Chauhan, J. H. Capdevila, S. Wei, *Biorg. Med. Chem. Lett.* **1997**, *7*, 3053–3056.
- 1997BSB665 J. De Brabander, B. A. Kulkarni, R. Garcia-Lopez, M. Vandewalle, *Bull. Soc. Chim. Belg.* **1997**, *106*, 665–669.
- 1997CC1499 V. J. Huber, S. N. Ivy, J. Lu, R. A. Bartsch, *J. Chem. Soc., Chem. Commun.* **1997**, *16*, 1499–1500.
- 1997JGU151 L. I. Nesterova, D. M. Malenko, V. V. Pirozhenko, A. D. Sinita, *J. Gen. Chem. USSR (Engl. Trans.)* **1997**, *67*, 151–153.
- 1997JMC1955 A. O. Stewart, P. A. Bhatia, J. G. Martin, J. B. Summers, K. E. Rodriques, M. B. Martin, J. H. Holms, J. L. Moore, R. A. Craig, T. Kolasa, J. D. Ratajczyk, H. Mazdiyasni, F. A. J. Kerdesky, S. L. DeNinno, R. G. Maki, J. B. Bouska, P. R. Young, C. Lanni, R. L. Bell, G. W. Carter, C. D. W. Brooks, *J. Med. Chem.* **1997**, *40*, 1955–1968.
- 1997JMC2780 K. Miller, H. Prinz, *J. Med. Chem.* **1997**, *40*, 2780–2787.
- 1997JMC3292 K. A. Ohemeng, B. L. Podlogar, V. N. Nguyen, J. I. Bernstein, H. M. Krause, J. J. Hilliard, J. F. Barrett, *J. Med. Chem.* **1997**, *40*, 3292–3296.
- 1997JOC568 D. Roberts, J. A. Joule, *J. Org. Chem.* **1997**, *62*, 568–577.
- 1997JOC1580 N. Katagiri, M. Takebayashi, H. Kokufuda, C. Kaneko, K. Kanehira, M. Torihara, *J. Org. Chem.* **1997**, *62*, 1580–1581.
- 1997JOC3858 C. J. Salomon, E. Breuer, *J. Org. Chem.* **1997**, *62*, 3858–3861.
- 1997JOC5299 Y. Araki, T. Konoike, *J. Org. Chem.* **1997**, *62*, 5299–5309.
- 1997JOC5385 I. Lantos, J. Flisak, L. Liu, R. Matsuoka, W. Mendelson, D. Stevenson, K. Tubman, L. Tucker, W.-Y. Zhang, J. Adams, M. Sorenson, R. Garigipati, K. Erhardt, S. Ross, *J. Org. Chem.* **1997**, *62*, 5385–5391.
- 1997MI1381 K. Griesbaum, X. Liu, A. Kassiaris, M. Scherer, *Liebigs Ann. Recl.* **1997**, 1381–1390.
- 1997S38 A. Shirayev, P. K. T. Lin, I. K. Moiseev, *Synthesis* **1997**, 38–41.
- 1997SC2433 A. M. M. ElSaghier, A. A. Maihub, H. A. AlShirayda, *Synth. Commun.* **1997**, *27*, 2433–2444.
- 1997TL1411 L. A. Agrofoglio, J.-C. Jacquinet, G. Lancelot, *Tetrahedron Lett.* **1997**, *38*, 1411–1412.
- 1997TL3195 R. A. Goodnow Jr., A.-R. Richou, S. Tam, *Tetrahedron Lett.* **1997**, *38*, 3195–3198.
- 1997TL5119 L. A. Paquette, A. Braun, *Tetrahedron Lett.* **1997**, *38*, 5119–5122.
- 1998AP352 A. H. Abadi, *Arch. Pharm. (Weinheim, Ger.)* **1998**, *331*, 352–358.
- 1998BMC811 F. Navas III, F. L. M. Tang, L. T. Schaller, M. H. Norman, *Biorg. Med. Chem.* **1998**, *6*, 811–823.
- 1998BMCL289 H. T. Lee, W. H. Roark, J. A. Picard, D. R. Sliskovic, B. D. Roth, R. L. Stanfield, K. L. Hamelehle, R. F. Bousley, B. R. Krause, *Biorg. Med. Chem. Lett.* **1998**, *8*, 289–294.
- 1998BMCL2241 J. Sakaki, T. Murata, Y. Yuamoto, I. Nakamura, T. Frueh, T. Pitterna, G. Iwasaki, K. Oda, T. Yamamura, K. Hayakawa, *Biorg. Med. Chem. Lett.* **1998**, *8*, 2241–2246.
- 1998BMCL3515 Y. Jin, D. H. Kim, *Biorg. Med. Chem. Lett.* **1998**, *8*, 3515–3518.
- 1998CHE380 A. A. Tolmachev, A. A. Chaikovskaya, R. V. Smalii, T. N. Kudrya, *Chem. Heterocycl. Compd. (Engl. Transl.)* **1998**, *34*, 380–381.
- 1998CHE957 A. G. Mikhailovskii, M. O. Dekaprilevich, *Chem. Heterocycl. Compd. (Engl. Transl.)* **1998**, *34*, 957–963.
- 1998CL163 M. Murakami, Y. Hoshino, H. Ito, Y. Ito, *Chem. Lett.* **1998**, 163–164.
- 1998JFC105 M. Lieb, M. Peach, V. Popov, *J. Fluorine Chem.* **1998**, *88*, 105–106.
- 1998JGU44 V. A. Pestunovich, N. F. Lasareva, O. B. Kozyreva, L. V. Klyba, G. A. Gavrilova, M. G. Voronkov, *J. Gen. Chem. USSR (Engl. Trans.)* **1998**, *68*, 44–45.
- 1998JHC555 S. El Ghammarti, B. Rigo, H. Mejdi, J. P. Henichart, D. Couturier, *J. Heterocycl. Chem.* **1998**, *35*, 555–565.
- 1998JMC1315 B. E. Maryanoff, M. J. Costanzo, S. O. Nortey, M. N. Greco, R. P. Shank, J. J. Schupsky, M. P. Ortegon, J. L. Vaught, *J. Med. Chem.* **1998**, *41*, 1315–1343.
- 1998JMC1344 R. Xing, R. P. Hanzlik, *J. Med. Chem.* **1998**, *41*, 1344–1351.
- 1998JOC4878 M. Makosza, M. Bialecki, *J. Org. Chem.* **1998**, *63*, 4878–4888.
- 1998JOC9019 R. S. Pandurangi, P. Lusiak, R. R. Kuntz, W. A. Volkert, J. Rogowski, M. S. Platz, *J. Org. Chem.* **1998**, *63*, 9019–9030.
- 1998JOM131 M. Weinmann, O. Walter, G. Huttner, H. Lang, *J. Organomet. Chem.* **1998**, *561*, 131–141.
- 1998MI675 G. Zagotto, M. Palumbo, E. Uriarte, L. Bonsignore, G. Delogu, G. Podda, *Farmaco* **1998**, *53*, 675–679.
- 1998MI931 E. Carvalho, J. Iley, M. D. Perry, E. Rosa, *Pharmaceut. Res.* **1998**, *15*, 931–935.
- 1998SL1217 K. Zong, S. I. Shin, H. R. Kim, E. K. Ryu, *Synlett* **1998**, 1217–1218.

- 1998TA437
1998TA4043
1998TL2421
1998TL3233
1998TL3397
1998TL3725
1998TL4239
1998TL4891
1998TL5891
1998TL6227
1999BMC3025
1999BMCL1365
1999BMCL691
1999BMCL3137
1999CJC263
1999EJO3483
1999IJC(B)18
1999IZV169
1999IZV396
1999JCS(P1)1333
1999JFC(96)79
1999JGU383
1999JHC1183
1999JMC751
1999JOC2924
1999JOC4528
1999JOC5132
1999JOC5472
1999JOC5966
1999KFZ22
1999MI207
1999SC1779
1999T3413
1999TA713
1999TL395
1999TL2887
1999TL2973
1999TL6745
2000BMC381
2000BMCL899
2000BMCL1913
2000CHE319
2000CHE931
2000CL944
2000JA2995
2000JCS(D)2205
2000JFC25
2000JGU1887
2000JMC683
2000JMC3895
A. Laaziri, J. Uziel, S. Jugé, *Tetrahedron Asymm.* **1998**, *9*, 437–447.
E. A. Broger, W. Burkart, M. Hennig, M. Scalone, R. Schmid, *Tetrahedron Asymmetry* **1998**, *9*, 4043–4054.
J. M. Herbert, A. H. McNeill, *Tetrahedron Lett.* **1998**, *39*, 2421–2424.
P. Quadrelli, M. Mella, P. Caramella, *Tetrahedron Lett.* **1998**, *39*, 3233–3236.
A. Golebiowski, S. Klopfenstein, *Tetrahedron Lett.* **1998**, *39*, 3397–3400.
T. Moriguchi, T. Yanagi, T. Wada, M. Sekine, *Tetrahedron Lett.* **1998**, *39*, 3725–3728.
D. Limal, A. Quesnel, J.-P. Briand, *Tetrahedron Lett.* **1998**, *39*, 4239–4242.
D. Filippov, C. M. Timmers, A. R. Roerdink, G. A. van der Marel, J. H. van Boom, *Tetrahedron Lett.* **1998**, *39*, 4891–4894.
C. F. Sturino, M. Labelle, *Tetrahedron Lett.* **1998**, *39*, 5891–5894.
K. Zong, S. I. Shin, E. K. Ryu, *Tetrahedron Lett.* **1998**, *39*, 6227–6228.
Y. Lu, M. J. Miller, *Biorg. Med. Chem.* **1999**, *7*, 3025–3038.
J. Lee, S. U. Kang, M. K. Kang, M. W. Chun, Y. J. Jo, J. H. Kwak, S. Kim, *Biorg. Med. Chem. Lett.* **1999**, *9*, 1365–1370.
D. H. Kim, Y. Jin, *Biorg. Med. Chem. Lett.* **1999**, *9*, 691–696.
D. G. Smith, A. D. Gribble, D. Haigh, R. J. Iff, P. Lavery, P. Skett, B. P. Slingsby, R. Stacey, R. W. Ward, A. West, *Biorg. Med. Chem. Lett.* **1999**, *9*, 3137–3142.
C. Barre, S. Carret, M. Guerro, P. Le Grel, M. Baudy-Floc'h, *Can. J. Chem.* **1999**, *77*, 263–270.
N. Langlois, A. Moro, *Eur. J. Org. Chem.* **1999**, 3483–3488.
V. A. Vardhan, V. R. Kumar, V. R. Rao, *Indian J. Chem., Sect. B* **1999**, *38*, 18–23.
A. D. Kirilin, A. A. Dokuchayev, M. B. Sokova, E. A. Chernyshev, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1999**, 169–173.
S. G. Zlotin, A. I. Gerasuto, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1999**, 396–398.
D. Loakes, D. M. Brown, S. A. Salisbury, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1333–1338.
Y. Xu, G. Xu, S. Zhu, G. Zhu, Y. Jia, Q. Huang, *J. Fluorine Chem.* **1999**, *96*, 79–86.
E. E. Nifant'ev, D. A. Predvoditelev, S. V. Suvorkin, M. A. Malenkovskaya, V. K. Bel'skii, *J. Gen. Chem. USSR (Engl. Trans.)* **1999**, *69*, 383–389.
M. T. Cocco, C. Congiu, V. Onnis, A. M. Bernard, P. P. Piras, *J. Heterocycl. Chem.* **1999**, *36*, 1183–1188.
T. Oda, K. Notoya, M. Gotoh, S. Taketomi, Y. Fujisawa, H. Makino, T. Sohda, *J. Med. Chem.* **1999**, *42*, 751–760.
A. Cheguillaume, F. Lehardy, K. Bouget, M. Baudy-Floc'h, P. Le Grel, *J. Org. Chem.* **1999**, *64*, 2924–2927.
D. Compère, C. Marazano, B. C. Das, *J. Org. Chem.* **1999**, *64*, 4528–4532.
L. Benati, D. Nanni, P. Spagnolo, *J. Org. Chem.* **1999**, *64*, 5132–5138.
B. J. Backes, D. R. Dragoli, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 5472–5478.
R. W. Darbeau, E. H. White, F. Song, N. R. Darbeau, J. Chou, *J. Org. Chem.* **1999**, *64*, 5966–5978.
N. V. Kolotova, E. N. Koz'minykh, V. E. Kolla, B. Y. Syropyatov, E. V. Voronina, V. O. Koz'minykh, *Khim. Farm. Zh.* **1999**, *33(5)*, 22–28.
E. Bacu, M. Petrovanu, A. Couture, P. Grandclaude, *Phosphorus, Sulfur, Silicon Relat. Elem.* **1999**, *149*, 207–220.
B. Zajc, *Synth. Commun.* **1999**, *29*, 1779–1784.
S. A. Glover, G. Mo, A. Rauk, *Tetrahedron* **1999**, *55*, 3413–3426.
D. Ma, K. Cheng, *Tetrahedron Asymmetry* **1999**, *10*, 713–719.
T. K. Sarkar, P. Gangopadhyay, T. K. Satapathi, *Tetrahedron Lett.* **1999**, *40*, 395–396.
S. F. Martin, R. K. Hom, *Tetrahedron Lett.* **1999**, *40*, 2887–2890.
H. Sato, Y. S. Kim, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 2973–2976.
T. Wang, Z. Zhang, N. A. Meanwell, *Tetrahedron Lett.* **1999**, *40*, 6745–6747.
N. Amishiro, S. Nagamura, C. Murakata, A. Okamoto, E. Kobayashi, M. Asada, K. Gomi, T. Tamaoki, M. Okabe, N. Yamaguchi, K. Yamaguchi, H. Saito, *Biorg. Med. Chem.* **2000**, *8*, 381–391.
T. Hámori, S. Sólyom, P. Berzsenyi, F. András, I. Tarnawa, *Biorg. Med. Chem. Lett.* **2000**, *10*, 899–902.
T. A. Miller, J. Ghosh, C. E. Myers, T. L. Macdonald, *Biorg. Med. Chem. Lett.* **2000**, *10*, 1913–1916.
V. A. Glushkov, Y. V. Shklyayev, O. A. Maiorova, G. A. Postanogova, E. V. Feshina, *Chem. Heterocycl. Compd. (Engl. Transl.)* **2000**, *36*, 319–325.
K. I. Kobrakov, V. K. Korolev, I. I. Rybina, V. I. Kelarev, *Chem. Heterocycl. Compd. (Engl. Transl.)* **2000**, *36*, 931–943.
K. Sogabe, Y. Hasegawa, Y. Wada, T. Kitamura, S. Yanagida, *Chem. Lett.* **2000**, 944–945.
H. Takahashi, Y. Hitomi, Y. Iwai, S. Ikegami, *J. Am. Chem. Soc.* **2000**, *122*, 2995–3000.
P. Braunstein, C. Frison, X. Morise, R. D. Adams, *J. Chem. Soc., Dalton Trans.* **2000**, 2205–2214.
Y. Xu, Y. L. Wang, S. Z. Zhu, *J. Fluorine Chem.* **2000**, *105*, 25–30.
K. N. Zelenin, I. V. Lagoda, *J. Gen. Chem. USSR (Engl. Transl.)* **2000**, *70*, 1887–1889.
A. Martínez, A. Castro, C. Gil, M. Miralpeix, V. Segarra, T. Doménech, J. Beleta, J. M. Palacios, H. Ryder, X. Miró, C. Bonet, J. M. Casacuberta, F. Azorín, B. Piña, P. Puigdoménech, *J. Med. Chem.* **2000**, *43*, 683–689.
Z.-Y. Wei, W. Brown, B. Takasaki, N. Plobeck, D. Delorme, F. Zhou, H. Yang, P. Jones, L. Gawell, H. Gagnon, R. Schmidt, S.-Y. Yue, C. Walpole, K. Payza, S. St-Onge, M. Labarre, C. Godbout, A. Jakob, J. Butterworth, A. Kamassah, P.-E. Morin, D. Projean, J. Ducharme, E. Roberts, *J. Med. Chem.* **2000**, *43*, 3895–3905.

- 2000JMC3906 C. K. Chu, L. Ma, S. Olgen, C. Pierra, J. Du, G. Gumina, E. Gullen, Y.-C. Cheng, R. F. Schinazi, *J. Med. Chem.* **2000**, *43*, 3906–3912.
- 2000JMC3981 A. Kalsi, M. J. Kavarana, T. Lu, D. L. Whalen, D. S. Hamilton, D. J. Creighton, *J. Med. Chem.* **2000**, *43*, 3981–3986.
- 2000JOC4833 J. M. Roosenberg II, M. J. Miller, *J. Org. Chem.* **2000**, *65*, 4833–4838.
- 2000JOC8229 T. Moriguchi, T. Yanagi, M. Kunimori, T. Wada, M. Sekine, *J. Org. Chem.* **2000**, *65*, 8229–8238.
- 2000JOU1634 V. N. Knyazev, O. Y. Borbulevich, O. V. Shishkin, *J. Org. Chem. USSR (Engl. Transl.)* **2000**, *36*, 1634–1641.
- 2000JPO388 G. Kaupp, J. Schmeyers, *J. Phys. Org. Chem.* **2000**, *13*, 388–394.
- 2000M549 F. van Rantwijk, M. A. P. J. Hacking, R. A. Sheldon, *Monatsh. Chem.* **2000**, *131*, 549–569.
- 2000MI153 L. Ben Gaied, H. Zantour, *Phosphorus, Sulfur, Silicon Relat. Elem.* **2000**, *157*, 153–164.
- 2000MI378 J. Auge, N. Lubin-Germain, *J. Carbohydr. Chem.* **2000**, *19*, 378–392.
- 2000MI569 I. Butula, M. J. M. Takac, *Croat. Chem. Acta.* **2000**, *73*, 569–574.
- 2000MI895 A. S. S. Hamad, A. I. Hashem, *Molecules* **2000**, *5*, 895–907.
- 2000MI1175 M. Rychlik, *J. Agric. Food Chem.* **2000**, *48*, 1175–1181.
- 2000OL1529 M. A. Calter, F. C. Bi, *Org. Lett.* **2000**, *2*, 1529–1531.
- 2000OL2221 Z. P. Demko, M. Bartsch, K. B. Sharpless, *Org. Lett.* **2000**, *2*, 2221–2223.
- 2000PHA900 N. S. Habib, S. Fahmy, S. M. El-Khawass, T. A. Aziem, *Pharmazie* **2000**, *55*, 900–906.
- 2000SL813 M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati, A. Tsadjout, *Synlett* **2000**, 813–815.
- 2000T5253 Z. Szarka, R. Skoda-Földes, L. Kollár, Z. Berente, J. Horváth, Z. Tuba, *Tetrahedron* **2000**, *56*, 5253–5257.
- 2000T5667 B. G. Jackson, S. W. Pedersen, J. W. Fisher, J. W. Misner, J. P. Gardner, M. A. Staszak, C. Doecke, J. Rizzo, J. Aikins, E. Farkas, K. L. Trinkle, J. Vicenzi, M. Reinhard, E. P. Kroeff, C. A. Higginbotham, R. J. Gazak, T. Y. Zhang, *Tetrahedron*, **2000**, *56*, 5667–5677.
- 2000T10275 S. P. Fearnley, R. L. Funk, R. J. Gregg, *Tetrahedron*, **2000**, *56*, 10275–10281.
- 2000TL2453 M. Kanai, J. M. Percy, *Tetrahedron Lett.* **2000**, *41*, 2453–2455.
- 2000TL2559 S. Boukhris, A. Souizi, *Tetrahedron Lett.* **2000**, *41*, 2559–2562.
- 2001BMC773 S. Ladame, M. Bardet, J. Périé, M. Willson, *Biorg. Med. Chem.* **2001**, *9*, 773–783.
- 2001BMCL1553 M. R. Michaelides, J. F. Dellaria, J. Gong, J. H. Holms, J. J. Bouska, J. Stacey, C. K. Wada, H. R. Heyman, M. L. Curtin, Y. Guo, C. L. Goodfellow, I. B. Elmore, D. H. Albert, T. J. Magoc, P. A. Marcotte, D. W. Morgan, S. K. Davidsen, *Biorg. Med. Chem. Lett.* **2001**, *11*, 1553–1556.
- 2001CAR83 Y. Saito, A. Nyilas, L. A. Agrofoglio, *Carbohydr. Res.* **2001**, *331*, 83–90.
- 2001CHE120 M. V. Povstyanov, V. P. Kruglenko, V. M. Povstyanov, *Chem. Heterocycl. Compd. (Engl. Transl.)* **2001**, *37*, 120–121.
- 2001CHE294 Y. A. Rozin, E. A. Vorob'ova, Y. Y. Morzherin, V. A. Bakulev, *Chem. Heterocycl. Compd. (Engl. Transl.)* **2001**, *37*, 294–304.
- 2001EJO141 D. Cabaret, M. G. Gonzalez, M. Wakselman, S. A. Adediran, R. F. Pratt, *Eur. J. Org. Chem.* **2001**, 141–149.
- 2001JA9455 R. A. Augst Jr., R. L. Funk, *J. Am. Chem. Soc.* **2001**, *123*, 9455–9456.
- 2001JCR(S)342 Q. M. Wang, R. Q. Huang, F. C. Bi, Z. G. Li, *J. Chem. Res. (S)* **2001**, 342–343.
- 2001JCS(P1)2850 M. R. G. da Costa, M. J. M. Curto, S. G. Davies, J. Sanders, F. C. Teixeira, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2850–2855.
- 2001JGU993 B. A. Shainyan, A. A. Grigor'eva, *J. Gen. Chem. USSR (Engl. Transl.)* **2001**, *71*, 993–993.
- 2001JMC1475 S. V. Andurkar, C. Béguin, J. P. Stables, H. Kohn, *J. Med. Chem.* **2001**, *44*, 1475–1478.
- 2001JMC1938 G. A. G. Sulyok, C. Gibson, S. L. Goodman, G. Hölzemann, M. Wiesner, H. Kessler, *J. Med. Chem.* **2001**, *44*, 1938–1950.
- 2001JMC2069 S. Massa, A. Mai, G. Sbardella, M. Esposito, R. Ragno, P. Loid, G. Brosch, *J. Med. Chem.* **2001**, *44*, 2069–2072.
- 2001JOC1115 X. Creary, M. A. Butchko, *J. Org. Chem.* **2001**, *66*, 1115–1121.
- 2001JOC1373 J. A. Marshall, M. M. Yanik, *J. Org. Chem.* **2001**, *66*, 1373–1379.
- 2001JOC2681 R. W. Darbeau, D. J. Heurtin, L. M. Siso, R. S. Pease, R. E. Gible, D. E. Bridges, D. L. Davis, D. G. Gbenekama, N. R. Darbeau, *J. Org. Chem.* **2001**, *66*, 2681–2685.
- 2001JOC4369 S. J. Stachel, C. B. Lee, M. Spassova, M. D. Chappell, W. G. Bornmann, S. J. Danishefsky, T.-C. Chou, Y. Guan, *J. Org. Chem.* **2001**, *66*, 4369–4378.
- 2001JOC6719 R. C. D. Brown, C. J. R. Bataille, G. Bruton, J. D. Hinks, N. A. Swain, *J. Org. Chem.* **2001**, *66*, 6719–6728.
- 2001KFZ10 S. A. Lyakhov, E. A. Lyakhova, N. N. Panchenko, L. A. Litvinova, S. A. Andronati, *Khim. Farm. Zh.* **2001**, *35*(12), 10–13.
- 2001KFZ11 I. V. Mashevskaya, R. R. Makhmudov, G. A. Aleksandrova, A. V. Duvalov, A. N. Maslivets, *Khim. Farm. Zh.* **2001**, *35*(2), 11–13.
- 2001MI53 R. Gurny, W. Pakulska, E. Brzezinska, *Acta Pol. Pharm.* **2001**, *58*, 53–60.
- 2001OL1499 M. A. Calter, X. Guo, W. Liao, *Org. Lett.* **2001**, *3*, 1499–1501.
- 2001OL1945 R. W. Hoffmann, B. Hölzer, O. Knopff, *Org. Lett.* **2001**, *3*, 1945–1948.
- 2001PHA613 B. Berk, G. Aktay, E. Yesilada, M. Ertan, *Pharmazie* **2001**, *56*, 613–616.
- 2001S69 H. J. Cristau, M. Taillefer, I. Jouanin, *Synthesis* **2001**, 69–74.
- 2001S1635 O. Miyata, Y. Kimura, T. Naito, *Synthesis* **2001**, 1635–1638.
- 2001SC579 M. Adamezyk, R. E. Reddy, *Synth. Commun.* **2001**, *31*, 579–586.
- 2001SC3081 R. R. Copp, B. T. Fohey, G. Lannoye, *Synth. Commun.* **2001**, *31*, 3081–3086.
- 2001SL1272 K. Ando, *Synlett* **2001**, 1272–1274.
- 2001TL4539 A. Klepacz, A. Zwierzak, *Tetrahedron Lett.* **2001**, *42*, 4539–4540.
- 2002BMC1659 S. Wittmann, M. Schnabelrauch, I. Scherlitz-Hofmann, U. Möllmann, D. Ankel-Fuchs, L. Heinisch, *Biorg. Med. Chem.* **2002**, *10*, 1659–1670.

- 2002BMCL69 N. Murakami, M. Kawanishi, S. Itagaki, T. Horii, M. Kobayashi, *Biorg. Med. Chem. Lett.* **2002**, *12*, 69–72.
- 2002BMCL2553 K. Amsoms, S. L. Oza, E. Ravaschino, A. Yamani, A.-M. Lambeir, P. Rajan, G. Bal, J. B. Rodriguez, A. H. Fairlamb, K. Augutyns, A. Haermers, *Biorg. Med. Chem. Lett.* **2002**, *12*, 2553–2556.
- 2002CC2004 L. A. Adams, R. J. Cox, J. S. Gibson, M. B. Mayo-Martin, M. Walter, W. Whittingham, *J. Chem. Soc., Chem. Commun.* **2002**, 2004–2005.
- 2002CHE543 A. E. Shchekotikhin, D. A. Silaev, E. P. Baberkina, I. G. Makarov, V. N. Buyanov, N. N. Suvorov, *Chem. Heterocycl. Compd. (Engl. Transl.)* **2002**, *38*, 543–546.
- 2002CHE1389 N. Y. Gorobets, A. V. Borisov, A. V. Silin, V. M. Nikitchenko, S. N. Kovalenko, *Chem. Heterocycl. Compd. (Engl. Transl.)* **2002**, *38*, 1389–1396.
- 2002EJO2046 J. Sinkkonen, V. Ovcharenko, K. N. Zelenin, I. P. Bezhan, B. A. Chakchir, F. Al-Assar, K. Pihlaja, *Eur. J. Org. Chem.* **2002**, 2046–2053.
- 2002IJC(B)1937 S. K. Srivastava, S. Srivastava, S. D. Srivastava, *Indian J. Chem., Sect. B* **2002**, *41*, 1937–1945.
- 2002IJC(B)2642 P. Rani, S. V. K. Archana, A. Kumar, *Indian J. Chem., Sect. B* **2002**, *41*, 2642–2646.
- 2002JCR(S)170 R. Smicius, V. Jakubkiene, M. M. Burbuliene, A. Mikalainyte, P. Vainilavicius, *J. Chem. Res. (S)* **2002**, 170–172.
- 2002JCS(P1)613 A. Dinsmore, P. M. Doyle, M. Steger, D. W. Young, *J. Chem. Soc., Perkin Trans. 1* **2002**, 613–621.
- 2002JCS(P1)1800 H. R. Moon, H. O. Kim, L. S. Jeong, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1800–1804.
- 2002JHC885 G. Biagi, I. Giorgi, O. Livi, F. Pacchini, V. Scartoni, *J. Heterocycl. Chem.* **2002**, *39*, 885–888.
- 2002JHC1325 A. S. S. Hamad, A. Hashem, *J. Heterocycl. Chem.* **2002**, *39*, 1325–1328.
- 2002JMC3112 T. Kline, N. H. Andersen, E. A. Harwood, J. Bowman, A. Malanda, S. Endsley, A. L. Erwin, M. Doyle, S. Fong, A. L. Harris, B. Mendelsohn, K. Mdululi, C. R. H. Raetz, C. K. Stover, P. R. Witte, A. Yabannavar, S. Zhu, *J. Med. Chem.* **2002**, *45*, 3112–3129.
- 2002JMC5802 M. Eisenhut, A. Mohammed, W. Mier, F. Schönsiegel, M. Friebe, A. Mahmood, A. G. Jones, U. Haberkorn, *J. Med. Chem.* **2002**, *45*, 5802–5805.
- 2002JOC2942 R. W. Darbeau, R. S. Pease, E. V. Perez, *J. Org. Chem.* **2002**, *67*, 2942–2947.
- 2002JOC4372 Y. Ding, J. Wang, S. M. Schuster, N. G. J. Richards, *J. Org. Chem.* **2002**, *67*, 4372–4375.
- 2002JOC9471 X. Zhang, M. Breslav, J. Grimm, K. Guan, A. Huang, F. Liu, C. A. Maryanoff, D. Palmer, M. Patel, Y. Qian, C. Shaw, K. Sorgi, S. Stefanick, D. Xu, *J. Org. Chem.* **2002**, *67*, 9471–9474.
- 2002JOU1 A. A. Lobanova, S. G. Il'yasov, N. I. Popov, R. R. Sataev, *J. Org. Chem. USSR (Engl. Transl.)* **2002**, *38*, 1–6.
- 2002JOU1686 L. M. Mironovich, *J. Org. Chem. USSR (Engl. Transl.)* **2002**, *38*, 1686–1688.
- 2002M41 K. Burger, E. Windeisen, E. Heistracher, T. Lange, A. A. H. Abdel-Aleem, *Monatsh. Chem.* **2002**, *133*, 41–58.
- 2002M1305 N. Ulusoy, M. Kiraz, O. Kucukbasmaci, *Monatsh. Chem.* **2002**, *133*, 1305–1315.
- 2002MI601 B. Chai, S. Cao, H. D. Liua, G. H. Songa, X. H. Qian, *Heterocycl. Commun.* **2002**, *8*, 601–606.
- 2002MI1250 Q. Wang, J. Cheng, R. Huang, *Pest Manage. Sci.* **2002**, *58*, 1250–1253.
- 2002MI1791 J. K. Lee, K. C. Ahn, O. S. Park, Y. K. Ko, D.-W. Kim, *J. Agric. Food Chem.* **2002**, *50*, 1791–1803.
- 2002OL111 D. R. Hill, C.-N. Hsiao, R. Kurukulasuriya, S. J. Wittenberger, *Org. Lett.* **2002**, *4*, 111–113.
- 2002OL2349 D. T. Glatzhofer, R. R. Roy, K. N. Cossey, *Org. Lett.* **2002**, *4*, 2349–2352.
- 2002OL2549 S. Caddick, J. D. Wilden, H. D. Bush, S. N. Wadman, D. B. Judd, *Org. Lett.* **2002**, *4*, 2549–2551.
- 2002OL2707 F. Gagosz, C. Moutrille, S. Z. Zard, *Org. Lett.* **2002**, *4*, 2707–2709.
- 2002PHA796 M. Ajitha, K. Rajnarayana, M. Sarangapani, *Pharmazie* **2002**, *57*, 796–799.
- 2002S733 Y. J. Kang, H. A. Chung, J. J. Kim, Y. J. Yoon, *Synthesis* **2002**, 733–738.
- 2002SC1097 X. C. Wang, Z. Li, B. G. Wei, J. Y. Yang, *Synth. Commun.* **2002**, *32*, 1097–1103.
- 2002SC1121 X. C. Wang, Z. Li, Y. X. Da, Y. J. Ma, *Synth. Commun.* **2002**, *32*, 1121–1127.
- 2002SC3087 Z. Li, X. C. Wang, *Synth. Commun.* **2002**, *32*, 3087–3092.
- 2002SC3767 C. J. Jung, E. B. Watkins, M. A. Avery, *Synth. Commun.* **2002**, *32*, 3767–3778.
- 2002T2085 V. Benin, P. Kaszynski, J. G. Radziszewski, *Tetrahedron* **2002**, *58*, 2085–2090.
- 2002T7925 M. E. Casarini, F. Ghelfi, E. Libertini, U. M. Pagnoni, A. F. Parsons, *Tetrahedron* **2002**, *58*, 7925–7932.
- 2002T9567 F. N. Burnett, R. S. Hosmane, *Tetrahedron* **2002**, *58*, 9567–9578.
- 2002TL249 N. Brosse, B. Jamart-Grégoire, *Tetrahedron Lett.* **2002**, *43*, 249–251.
- 2002TL607 O. Bedel, D. Urban, Y. Langlois, *Tetrahedron Lett.* **2002**, *43*, 607–609.
- 2002TL979 C. T. Lowden, J. S. Mendoza, *Tetrahedron Lett.* **2002**, *43*, 979–982.
- 2002TL4261 S. Paul, P. Nanda, R. Gupta, A. Loupy, *Tetrahedron Lett.* **2002**, *43*, 4261–4265.
- 2002TL4711 L. Chen, X. Zhang, A. Schultz, *Tetrahedron Lett.* **2002**, *43*, 4711–4715.
- 2002TL6213 O. Tubrik, U. Mäeorg, U. Ragnarsson, *Tetrahedron Lett.* **2002**, *43*, 6213–6215.
- 2002TL6127 H.-G. Bretinger, *Tetrahedron Lett.* **2002**, *43*, 6127–6131.
- 2002TL6735 D. C. Boyles, T. T. Curran, D. Greene, D. Macikenas, R. V. Parlett IV, *Tetrahedron Lett.* **2002**, *43*, 6735–6737.
- 2003AP95 A. A. Khalil, S. G. A. Hamide, A. M. Al-Obaid, H. I. El-Subbagh, *Arch. Pharm. (Weinheim, Ger.)* **2003**, *336*, 95–103.
- 2003BMC1701 Y. A. Al-Soud, N. A. Al-Masoudi, A. E. S. Ferwanah, *Biorg. Med. Chem.* **2003**, *11*, 1701–1708.
- 2003BMCL1783 F. Augé, W. Hornebeck, M. Decarme, J.-Y. Laronze, *Biorg. Med. Chem. Lett.* **2003**, *13*, 1783–1786.
- 2003BMCL2413 B. Raju, K. Mortell, S. Anandan, H. O'Dowd, H. Gao, M. Gomez, C. Hackbarth, C. Wu, W. Wang, Z. Yuan, R. White, J. Trias, D. V. Patel, *Biorg. Med. Chem. Lett.* **2003**, *13*, 2413–2418.
- 2003BMCL2709 S. J. Davies, A. P. Ayscough, R. P. Beckett, R. A. Bragg, J. M. Clements, S. Doel, C. Grew, S. B. Launchbury, G. M. Perkins, L. M. Pratt, H. K. Smith, Z. M. Spavold, S. W. Thomas, R. S. Todd, M. Whittaker, *Biorg. Med. Chem. Lett.* **2003**, *13*, 2709–2713.
- 2003CCC792 M. Dobosz, M. Pitucha, I. Dybala, A. E. Koziol, *Collect. Czech. Chem. Commun.* **2003**, *68*, 792–800.
- 2003DOK55 S. V. Basenko, M. G. Voronkov, *Dokl. Akad. Nauk SSSR* **2003**, 55–57.

- 2003H189 K. Burger, T. Lange, M. Rudolph, *Heterocycles* **2003**, 59, 189–198.
2003JA2997 G. V. Zyryanov, Y. Kang, D. M. Rudkevich, *J. Am. Chem. Soc.* **2003**, 125, 2997–3007.
2003JMC512 A. Mai, S. Massa, R. Ragno, I. Cerbara, F. Jesacher, P. Loid, G. Brosch, *J. Med. Chem.* **2003**, 46, 512–524.
2003JMC1603 M. Kim, Q. Mao, B. L. Davidson, D. F. Wiemer, *J. Med. Chem.* **2003**, 46, 1603–1608.
2003MI83 A. Akrmı, M. Beji, A. Baklouti, *Phosphorus, Sulfur, Silicon Relat. Elem.* **2003**, 178, 83–88.
2003MI213 P. Marakos, N. Pouli, S. Papakonstantinou-Garoufalias, E. Mikros, *J. Mol. Struct.* **2003**, 650, 213–221.
2003MI245 A. A. S. El-Ahl, M. A. Ismail, F. A. Amer, *Phosphorus, Sulfur, Silicon Relat. Elem.* **2003**, 178, 245–259.
2003MI263 W. Karpyak, M. D. Obushak, M. I. Ganushchak, *Molecules* **2003**, 8, 263–268.
2003MI351 N. Micale, M. Zappala, S. Grasso, *Farmaco* **2003**, 58, 351–356.
2003OBC1625 S. L. Roberts, R. L. E. Furlan, S. Otto, J. K. M. Sanders, *Organic and Biomolecular Chemistry* **2003**, 1, 1625–1633.
2003OL971 B. Baek, M. Lee, K.-Y. Kim, U.-I. Cho, D. W. Boo, I. Shin, *Org. Lett.* **2003**, 5, 971–974.
2003OL1253 G. V. Zyryanov, D. M. Rudkevich, *Org. Lett.* **2003**, 5, 1253–1256.
2003RRC119 E. Bacu, D. Samson-Belei, A. Couture, P. Grandclaudeon, *Rev. Roum. Chim.* **2003**, 48, 119–124.
2003S560 Y. D. Park, J. J. Kim, H. A. Chung, D. H. Kweon, S. D. Cho, S. G. Lee, Y. J. Yoon, *Synthesis* **2003**, 560–564.
2003SC143 E. Bacu, A. Couture, P. Grandclaudeon, *Synth. Commun.* **2003**, 33, 143–152.
2003SC935 S. P. L. de Souza, J. F. M. da Silva, M. C. S. de Mattos, *Synth. Commun.* **2003**, 33, 935–939.
2003T4451 C. W. G. Fishwick, R. Grigg, V. Sridharan, J. Virica, *Tetrahedron* **2003**, 59, 4451–4468.
2003TL1059 G. Radics, R. Pires, B. Kokschi, S. M. El-Kousy, K. Burger, *Tetrahedron Lett.* **2003**, 44, 1059–1062.
2003TL4099 G.-R. Vasanthakumar, V. V. S. Babu, *Tetrahedron Lett.* **2003**, 44, 4099–4101.

Biographical sketch

Martin A. Wilson was born in Poole in Dorset, England. He received his MChem degree from the University of East Anglia in 2001. Martin is currently engaged in Ph.D. research under the supervision of Sean P. Bew at the University of East Anglia. Martin's research is concerned with the development of novel synthetic strategies towards the synthesis of chiral non-racemic aziridines. Away from the laboratory, Martin enjoys music, reading and is a keen follower of football and rugby.

5.08

Acylphosphorus, -arsenic, -antimony, and -bismuth Functions

K. AFARINKIA

King's College London, London, UK

5.08.1	INTRODUCTION	357
5.08.2	DICOORDINATED PHOSPHORUS FUNCTIONS	358
5.08.2.1	Functions with a P=C Bond	358
5.08.3	TRICOORDINATED PHOSPHORUS FUNCTIONS	358
5.08.3.1	Functions with P-H or P-C Bond Only	358
5.08.3.2	Functions with One P-Heteroatom Bond Only	361
5.08.3.2.1	P-O-, -S-, and -N-bonded systems	361
5.08.3.2.2	P-other heteroatom-bonded systems	361
5.08.3.3	Functions with Two P-Heteroatom Bonds	363
5.08.4	TETRACOORDINATED PHOSPHORUS FUNCTIONS	364
5.08.4.1	Functions with Single P-C Bonds	364
5.08.4.2	Functions with Single P-Heteroatom or P-Metal Bonds Only	365
5.08.4.3	Functions with Double P-Heteroatom Bonds	366
5.08.4.3.1	P=O bonded systems	366
5.08.4.3.2	P-other heteroatom bonded systems	370
5.08.5	HIGHER-COORDINATED SPECIES	371

5.08.1 INTRODUCTION

Since the 1990s, preparation and synthetic applications of acylphosphorus species (more commonly known as α -ketophosphorus species) have continued to be an important and productive area of investigation. Because of their application to the synthesis of other phosphorus-containing molecules, acylphosphorus species have always been amongst the most important functional groups in organophosphorus chemistry. However, as the application of these species to the synthesis of nonphosphorus-containing molecules continues to grow, they have also become of interest to the wider chemistry community.

As a result, along with modification to the traditional preparative routes to this class of compounds, a number of newer methods have also been developed. These include two methods that in COFGT (1995) were identified as possible areas for future development <1995COFGT(5)393>. One is the oxidation of α -hydroxyphosphonates and the other is the use of masked carbonyl functions. However, undoubtedly the most exciting new development in this field is the synthesis and application of acylphosphorus species, which are asymmetric at the phosphorus atom. Related to this, an important and potentially useful area of research has been in the field of higher-coordinated acylphosphorus species, in particular acylphosphoranes. Such transient species are observed as intermediates in amidation reactions when asymmetric phosphines are employed as nucleophilic catalysts.

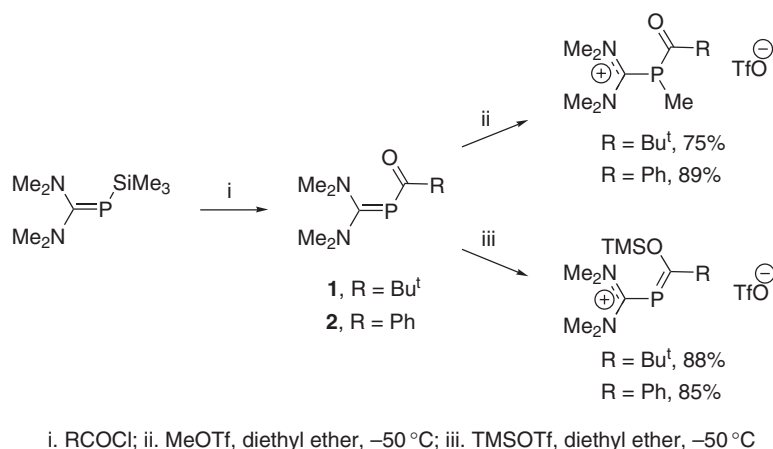
Therefore, in this review some of the important synthetic applications of these species are discussed along with the preparation of acylphosphorus compounds and those of other group V elements.

Along with the progress in the preparation and chemistry of acylphosphorus compounds, the range and chemistry of acylarsine and acylantimony compounds also continues to grow. As yet no acylbismuth compounds have been isolated.

5.08.2 DICOORDINATED PHOSPHORUS FUNCTIONS

5.08.2.1 Functions with a P=C Bond

The only report on this class of compounds since <1995COFGT(5)393> is on the preparation and reactivity of **1** and **2** (Scheme 1) <1999EJI2369>. These molecules appear to have a versatile chemistry and in particular react with a wide range of Lewis acids (see Section 5.08.3.2.2 and Scheme 16). More importantly, they react with alkylating reagents at the phosphorus atom and with silylating agents through the oxygen atom (Scheme 1) <1999EJI2369>. There are also reports of preparation and reactions of a bis(acyl)phosphine anion (see Section 5.08.3.1 and Scheme 9).

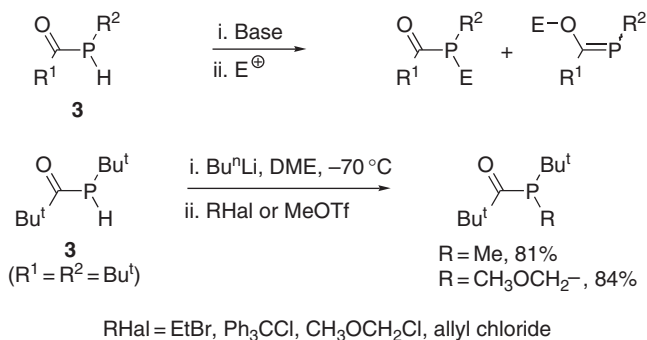


Scheme 1

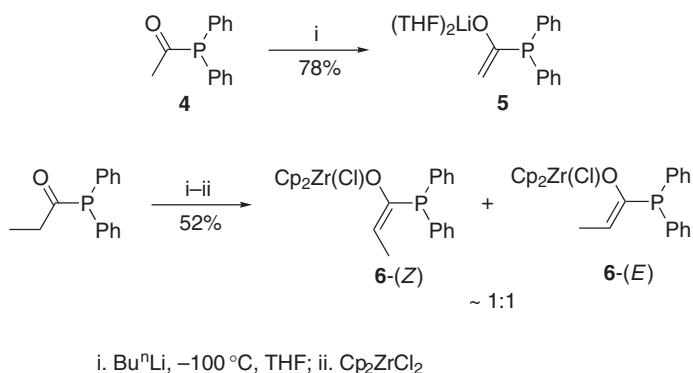
5.08.3 TRICOORDINATED PHOSPHORUS FUNCTIONS

5.08.3.1 Functions with P—H or P—C Bond Only

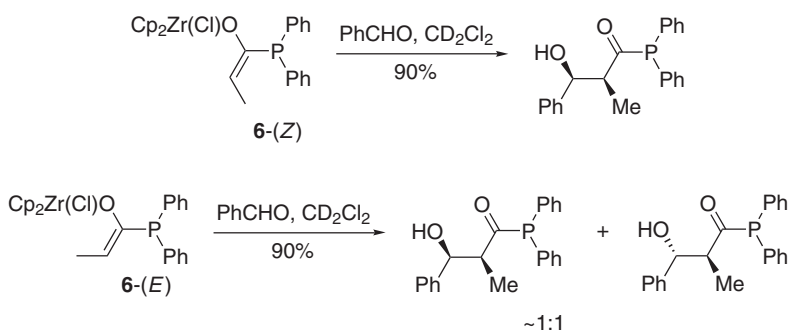
Tricoordinated acylphosphorus, -arsenic, -antimony, and -bismuth functions are analogs of amides and as such have a similar chemical behavior. No further studies on primary acylphosphines are reported. However, secondary and tertiary acylphosphines continue to provide rich and interesting chemistry. For example, it has been shown that secondary acylphosphines such as **3** can be easily deprotonated and the resulting delocalized anion can be trapped with a range of electrophiles, reacting either through the oxygen atom or the phosphorus atom depending on the nature of the electrophiles (Scheme 2). For alkylation however, reaction through the oxygen atom or the phosphorus atom depends on the coordinating properties of the solvent. In solvents such as dimethoxyethane or in the presence of crown ethers, anions of acylphosphines react with even sterically demanding alkylating agents through phosphorus (Scheme 2) <1996RJOC1520>. Furthermore, tertiary acylphosphines such as **4** can also be deprotonated affording an “enolate” (Scheme 3) <1994OM208>. The lithium enolate anion **5** is only characterized spectroscopically but an X-ray structure of the zirconate analog **6-(Z)** has been obtained to complement its spectroscopic characterization <1994OM208>. Both **6-(Z)** and **6-(E)** undergo aldol reaction with benzaldehyde (Scheme 4).



Scheme 2



Scheme 3

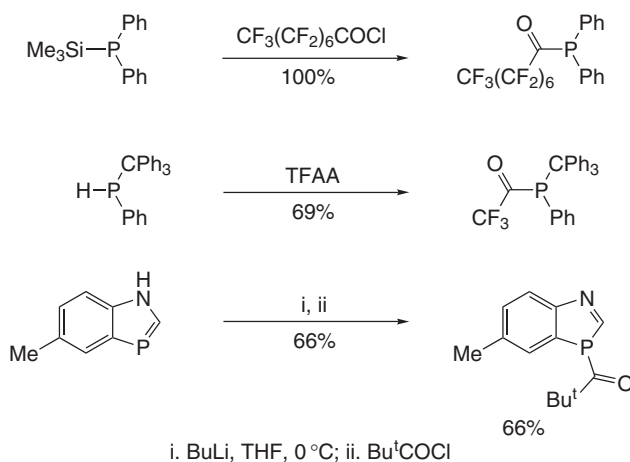


Scheme 4

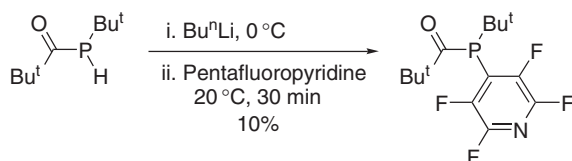
Treatment of an acid chloride (or anhydride) with either a primary (or trimethylsilylphosphine) or secondary phosphine (or bistrimethylsilylphosphine) still remains the main synthetic routes to secondary and tertiary acylphosphines, respectively (Scheme 5) <2002JOM(646)113, 2003JOM(667)112, 1996JFC29>.

However, there are a couple of newer synthetic methods. One is the transformation of secondary acylphosphines into tertiary acylphosphines. This can be achieved by deprotonation of the secondary acylphosphine and treatment of the resultant anion with a carbon electrophile (Schemes 2 and 6) <2000RJOC750, 1996RJOC1520>, or by treatment of the secondary acylphosphine with an aryl bromide under palladium catalysis (Scheme 7) <1996RJOC1520>. Another reported route is the hydrozirconation of phospholene **7** followed by ring opening and trapping of the resulting phosphorus anion with an acid chloride (Scheme 8) <1994OM5166>.

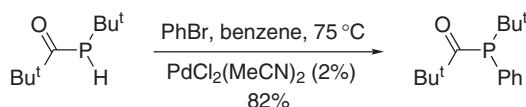
Finally, as already seen, the phosphorus atom in **1** and **2** is nucleophilic enough to react with alkylating reagents at the phosphorus atom (Scheme 1) <1999EJI2369>.



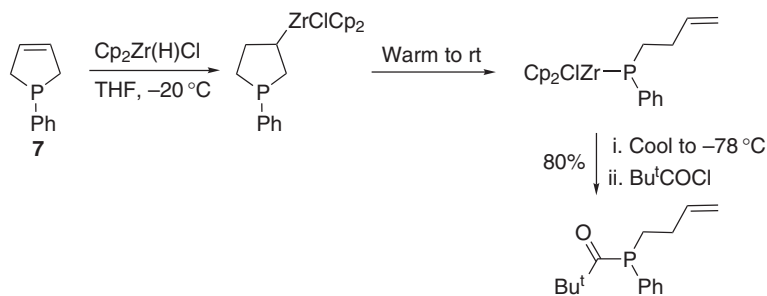
Scheme 5



Scheme 6

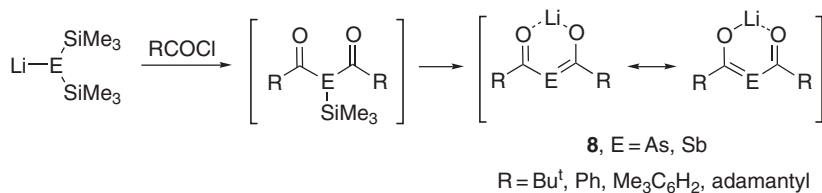


Scheme 7



Scheme 8

There are now reports of the preparation of bis(acyl)antimony compounds [<2000ZAAC\(626\)421>](#) to add to preparations of bis(acyl)arsines [<2003NJC466, 1998OM5924, 2001JCS\(D\)3219>](#), although they all remain poorly characterized and are mostly found as enolized forms, e.g., **8** (Scheme 9).

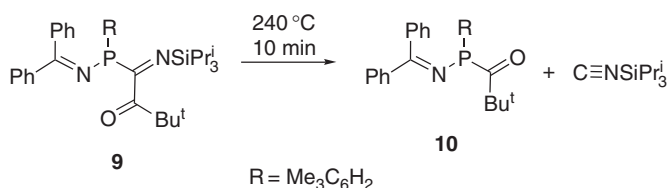


Scheme 9

5.08.3.2 Functions with One P—Heteroatom Bond Only

5.08.3.2.1 P—O-, —S-, and —N-bonded systems

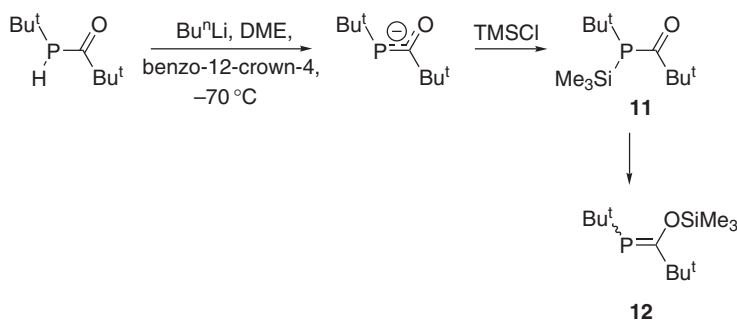
Compound **10** was obtained as a by-product during the attempted distillation of **9** (Scheme 10) <1998CEJ903>.



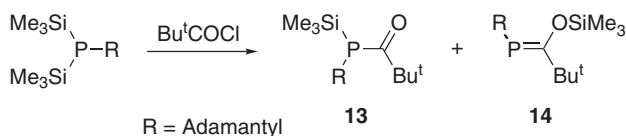
Scheme 10

5.08.3.2.2 P—other heteroatom-bonded systems

As was mentioned earlier, *P*-silyl derivatives such as **11** are obtained from the deprotonation of *t*-butylpivaloylphosphine with BuLi in the presence of a crown ether, and trapping of the resulting anion with a chlorosilane (Scheme 11) <1996RJOC1520>. These species are thermodynamically unstable and readily rearrange to the corresponding *O*-silyl isomer in what is the equivalent of the Chapman rearrangement in amides. As a result, species such as **12** are the ones which are usually obtained in similar reactions (e.g., see Scheme 12).

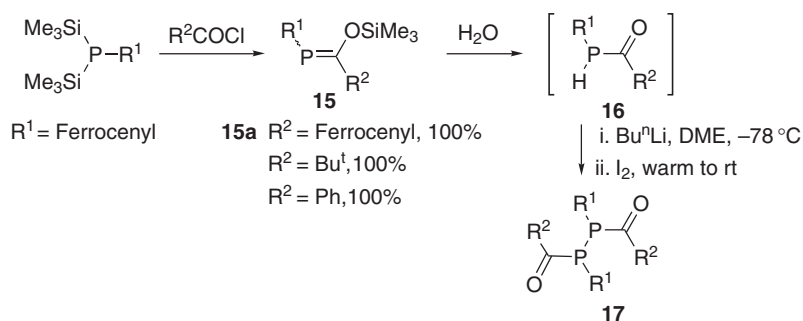


Scheme 11

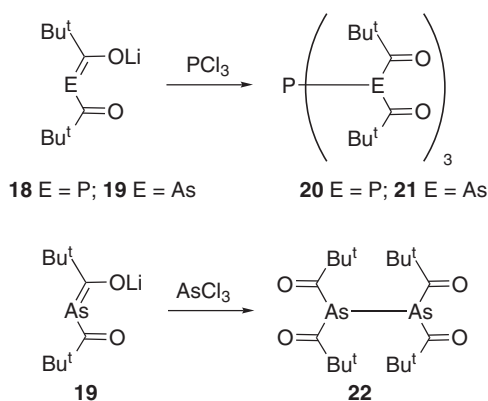


Scheme 12

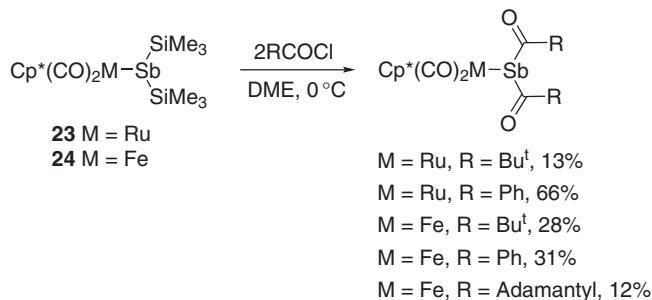
This method can be applied to a range of other *P*-derivatives of acylphosphines. However, there are now two new methods for the synthesis of these species. It has been shown that bis(trimethylsilyl)adamantylphosphine reacts with pivaloyl chloride to give *P*-silylacylphosphine **13** with the corresponding **14** (presumably obtained from the rearrangement of **13** to the thermodynamically more stable isomer) as a major by-product (Scheme 12) <1995PS(101)245>. Furthermore, oxidation of the anion from **16** (obtained from hydrolysis of **15**) afforded the corresponding dimers **17**, the structure of one of which was confirmed by X-ray crystallography (Scheme 13) <1997JOM(529)127>. An interesting variation on this theme was reported recently. The lithium anions **18** and **19** of a bis(acyl)phosphine and bis(acyl)arsine analogs react with PCl_3 to afford the expected products **20** and **21**, respectively. In contrast, when **19** is reacted with AsCl_3 or SbCl_3 , an oxidative coupling led to **22** (Scheme 14) <2002JCS(D)2417>.



Scheme 13

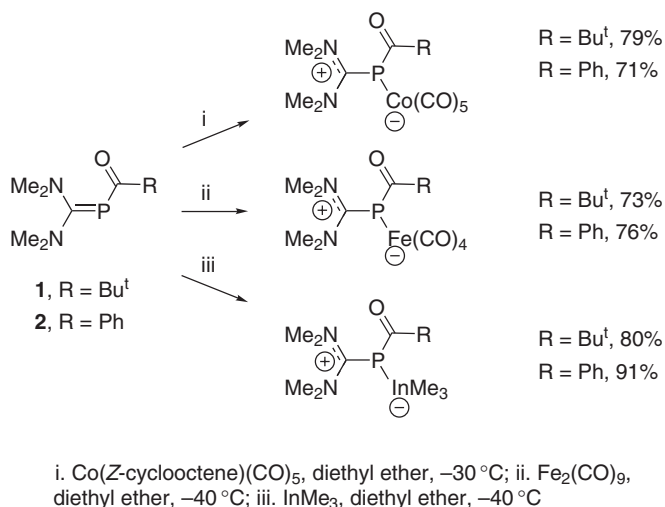


Scheme 14



Scheme 15

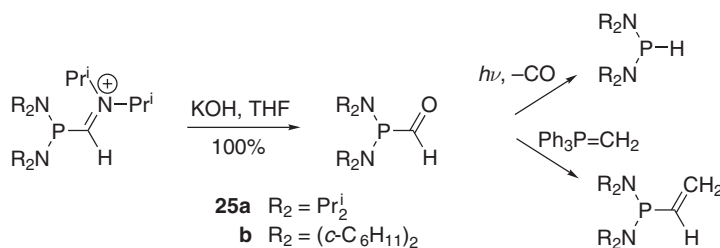
Antimony analogs have been prepared by a different route where **23** and **24** are bis-acylated (Scheme 15) <2000ZAAC(626)421>. Metal derivatives are prepared by reaction of **1** and **2** with a range of Lewis acids (Scheme 16). The presence of a phosphorus–metal bond in these compounds is confirmed by X-ray crystallography. Organoaluminum and organoboron Lewis acid derivatives, as well as silylating agents (Scheme 1), are believed to react through oxygen, although these species have only been characterized spectroscopically.



Scheme 16

5.08.3.3 Functions with Two P–Heteroatom Bonds

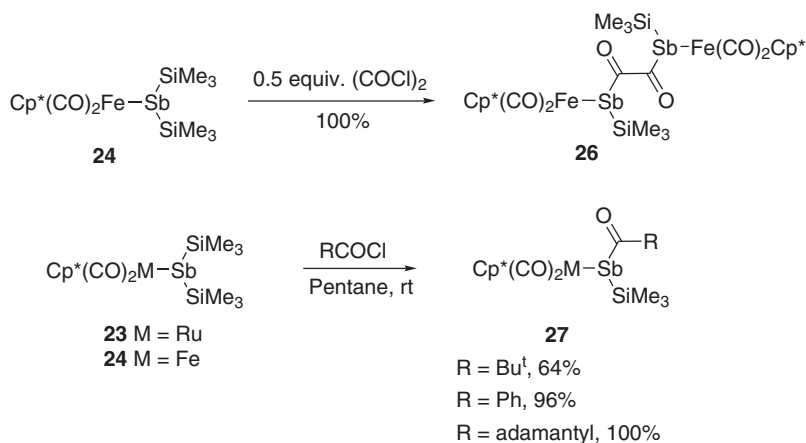
There are still very few reports of this type of acylphosphine. The only example reported since <1995COFGT(5)393> appears to be **25**, which shows interesting chemistry (Scheme 17) <1999AG(E)2201>.



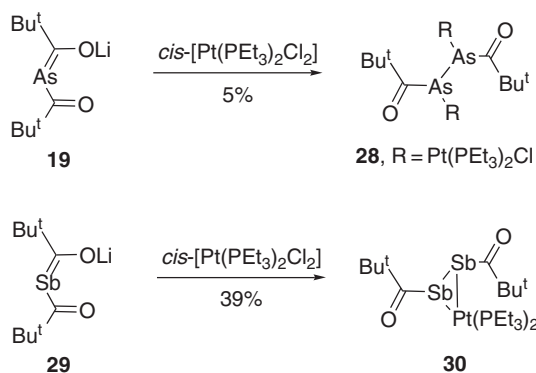
Scheme 17

In contrast, there has been considerable information on the other elements of this group. Treatment of iron complex **24** with 0.5 equiv. of oxalyl chloride affords **26**, whereas treatment of **24** or the analogous ruthenium complex **23** with 1 equiv. of acid chloride affords compounds **27**; the structures of the pivaloyl derivatives were confirmed by X-ray crystallography (Scheme 18) <2000ZAAC(626)421>.

Treatment of lithiated bis(acyl)arsine **19** with *cis*-[PtCl₂(PEt₃)₂] affords **28**, whereas the reaction of bis(acyl)antimony compound **29** affords **30** (Scheme 19) <1998CC2199>.



Scheme 18



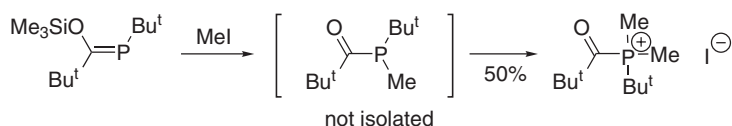
Scheme 19

5.08.4 TETRACOORDINATED PHOSPHORUS FUNCTIONS

The most common access to these classes of compounds remains the addition of a tricoordinated nucleophilic phosphorus species (phosphorous acid or ester) to an acylating agent, typically an acid chloride (Arbuzov reaction). However, there are now a number of alternative syntheses in the literature allowing for a more diverse approach to their preparation. These methods do not appear to be restricted in the range of phosphorus substituents, although they are discussed according to the substitution criteria used elsewhere in this review.

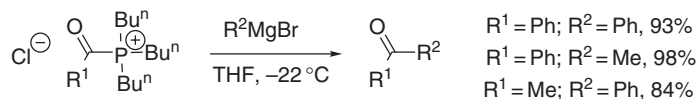
5.08.4.1 Functions with Single P—C Bonds

Due to insignificant delocalization of the phosphorus lone pair into the adjacent carbonyl group <2003JOM(667)112>, the phosphorus atom in acylphosphines is quite nucleophilic and can be quaternized under mild conditions with iodomethane (Scheme 20) <1996RJOC1520>. Treatment of tributylphosphine with acid chloride also affords quaternary salts <2000CC2307, 1998T12233>.

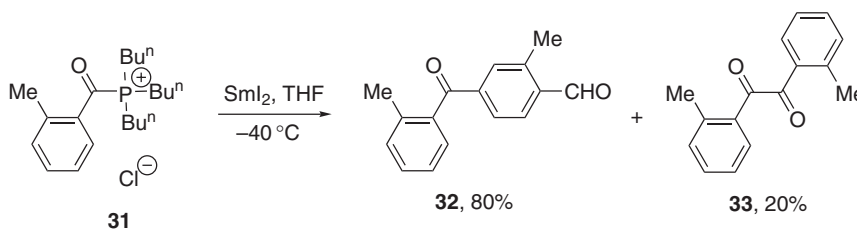


Scheme 20

These quaternary salts have interesting chemistry and in particular react with Grignard reagents to afford ketones (Scheme 21) <1998T12233>. Interestingly, phosphonium salt **31** reacts with samarium diiodide to afford the 4-benzoyl benzaldehyde **32** as the major product and diketone **33** as a minor product (Scheme 22) <2000CC2307>.

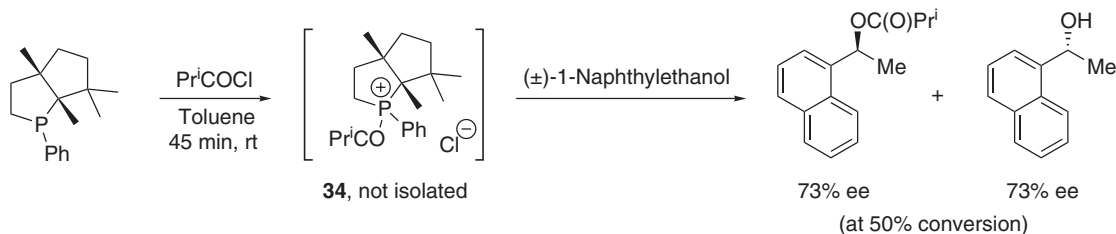


Scheme 21



Scheme 22

It should be noted here that acylphosphonium species, such as **34**, are the postulated intermediates formed during nucleophilic catalysis of the esterification of an alcohol by acid chlorides in the presence of phosphines. This has recently culminated in the development of asymmetric nucleophilic catalysis, which has been used to resolve alcohols such as 1-naphthylethanol (Scheme 23) <2003JOC5020, 2003JACS4166>.

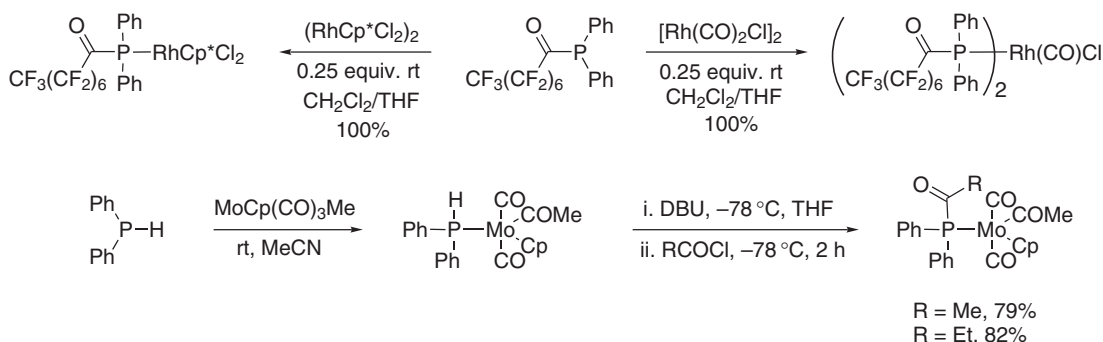


Scheme 23

5.08.4.2 Functions with Single P—Heteroatom or P—Metal Bonds Only

As already mentioned, the phosphorus atom of acylphosphines is strongly nucleophilic and can therefore bind to a number of metals. There have been quite a few reports of such compounds in the literature since <1995COFGT(5)393>. A good number are characterized by spectroscopy and X-ray crystallography where a phosphorus–metal bond has been confirmed <1999PS(144–146)717, 1998CEJ1917, 1994OM4179, 2000JOM(601)271, 2003JOM(667)112, 2000JCS(D)3074, 1997JCS(D)3589> (Scheme 24), although there are examples where the binding to the metal appears to be through the carbonyl π -bond <1995OM1525, 2000JOM(607)156>.

A similar chelation/bonding of bis(acyl)arsine has also been reported <1998OM5924, 2001JCS(D)3219>.



DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene

Scheme 24

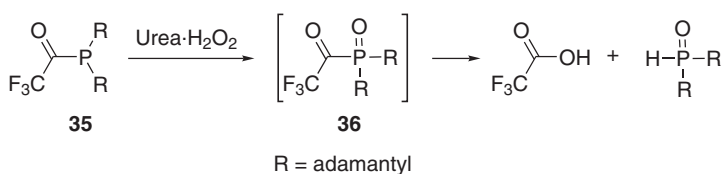
5.08.4.3 Functions with Double P—Heteroatom Bonds

5.08.4.3.1 P=O bonded systems

There are numerous examples of the preparation of this class of compounds since the last review of the subject <1995COFGT(5)393>. Two recent reviews also cover the key recent developments in this field <B2003MI319, 2002TCC(220)201>.

(i) With no other heteroatom substituent

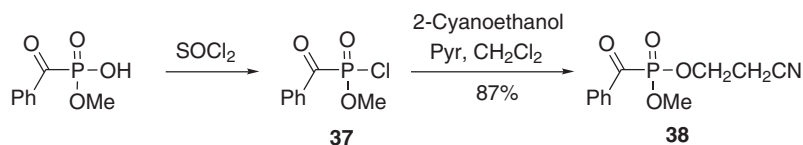
Attempted oxidation of acylphosphines **35** afforded **36** as transient species that could only be characterized by spectroscopy (Scheme 25) <1996JFC29>.



Scheme 25

(ii) With at least one halogen substituent

Treatment of an acylphosphonic monoester with thionyl chloride afforded the monochloride **37**, which was then transformed to the asymmetric acylphosphonate **38** (Scheme 26) <1994JSC(P1)1847>.

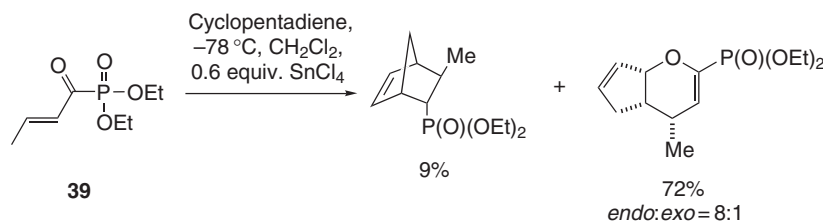


Scheme 26

(iii) With at least one oxygen substituent (but no halogen substituent)

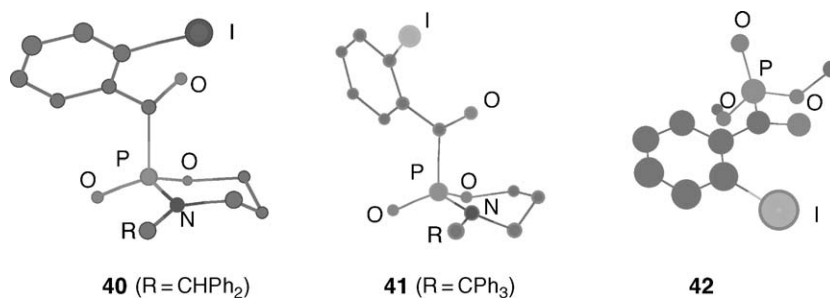
This is by far the largest class of compounds within the acylphosphorus functions. Arbuzov reaction is the main route for the synthesis of these compounds (see, e.g., references <2001TL743, 2000HAC232, 2000HAC470, 2000JOC9331, 1996PS(113)179>). One of the main developments of

this route has been the use of α,β -unsaturated acid chlorides. For example, trimethyl phosphite adds to 2-butenoyl chloride to afford **39** with only a trace of cyclic phosphorane as by-product <1994NJC1183, 1996JOC7455>. These β,γ -unsaturated α -ketophosphonates have interesting and varied chemistry both as heterodienes <2000JACS1635, 1996JOC7455, 2002T6521> and as dienophiles <2002T6521> in Diels–Alder cycloadditions (Scheme 27).



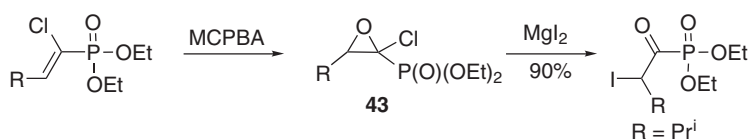
Scheme 27

The investigation on the configuration and structure of α -ketophosphonates has continued. X-Ray crystallography has confirmed that at least in solid state, the $\text{P}=\text{O}$ and $\text{C}=\text{O}$ bonds adopt an almost *anti*-conformation in 1,2,3-oxazaphosphorinanes **40**, **41** (dihedral angles 132° and 157° , respectively) <2001TL743>, and an orthogonal arrangement in noncyclic ketophosphonates **42** (dihedral angle 95°) (Scheme 28) <1997AX1462>.



Scheme 28

In addition to the traditional Arbuzov method, a number of alternative syntheses of α -ketophosphonates are now reported in the literature. The first of these is the rearrangement of 1-halo-1,2-epoxyphosphonates such as **43** (Scheme 29) <1998PS(133)167>.

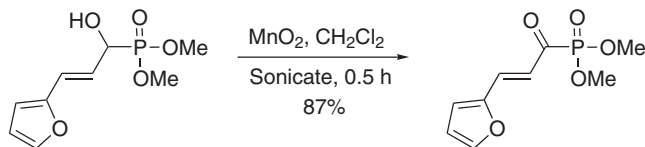


Scheme 29

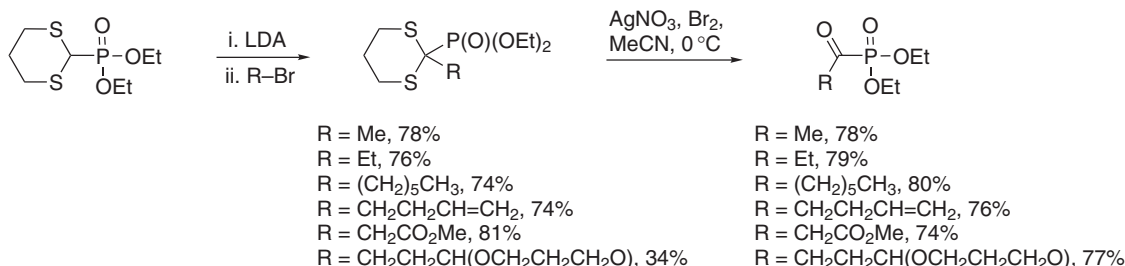
Another new approach to the synthesis of α -ketophosphonates is by oxidation of α -hydroxyphosphonates. Alumina-supported CrO_3 <2000TL3169, 2001SC2245>, alumina-supported and solution-phase KMnO_4 <2001TL4369>, zinc dichromate <2002TL477>, and (particularly mild) CrO_2 and MnO_2 <1998TL8389> have all been used (Scheme 30). This is a promising method as α -hydroxyphosphonates are synthetically more accessible and are documented in the literature with a wide range of substituents. However, to date the compounds that have been prepared by this method remain very limited in their range of phosphorus substituents.

Finally, the use of masked ketones has become a very useful method for the synthesis of α -ketophosphonates. The main advantage of this route is that a potentially wider range of α -ketophosphonates can be prepared by this method. However, there is also a disadvantage in that only very mild methods for unmasking of the $\text{C}=\text{O}$ function can be employed, or the resulting

α -ketophosphonates may decompose as they are formed. Nitrosation of a carbanion at the position α - to a phosphonate <1995PS(102)45>, oxidation of α -diazophosphonates <1999PS(144-146)313>, and hydrolysis of a dithiane (Scheme 31) <2003S357> have all been used.

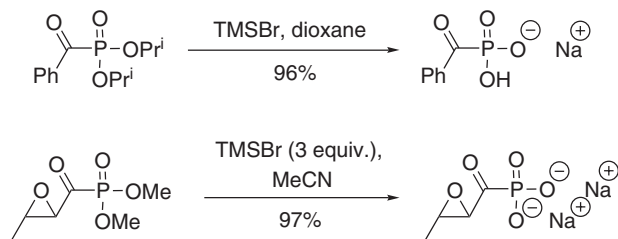


Scheme 30



Scheme 31

The sensitivity of α -ketophosphonates to hydrolysis is well documented, but there are new methods for the cleavage of α -ketophosphonates to α -ketophosphonic acids without further side reactions (Scheme 32) <1996JOC7212, 1995TL6759>.



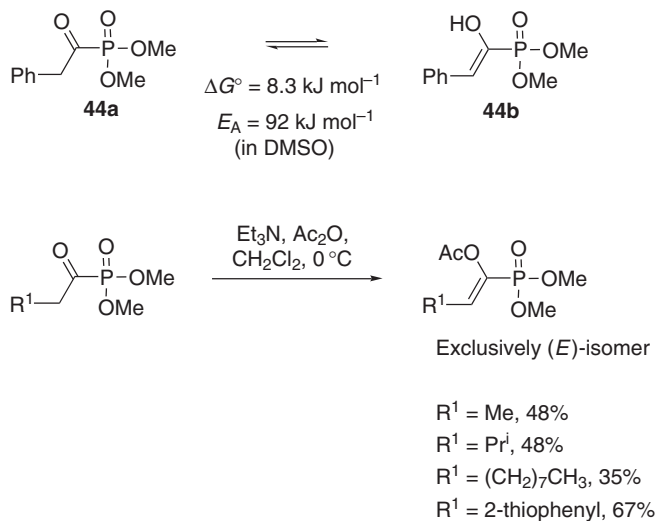
Scheme 32

α -Ketophosphonates have been shown to be synthetically versatile molecules and have been used for the synthesis of a number of phosphorus-containing and nonphosphorus-containing molecules. In particular, it has been demonstrated that α -ketophosphonates are readily enolized and even β -aryl- α -ketophosphonates such as **44** exist in both solution and solid state in enol forms (Scheme 32) <1997TL1663, 2000HAC232>. The enol forms of α -ketophosphonates can be trapped as silyl ethers and acetates (Scheme 33) <1997TL1663>, as well as nonaflates and triflates <1999TL5337> with the latter two being useful intermediates for the synthesis of α -substituted vinylphosphonates.

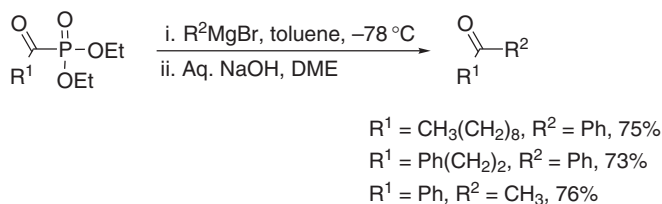
α -Ketophosphonates have also been shown to be excellent precursors of difluoromethylenephosphonic acids, isosteres of phosphoric acids in which the electron-withdrawing fluoro-substituents help to increase the pK_a of the phosphonic acid moiety <1996JOC1537, 1994TL551, 2001JFC127>.

Asymmetric reduction of racemic α -ketophosphonates with an enantiopure reagent is another new area of development in recent years <1999TL7705, 1995LA1963, 1996T589, 1996TA89, 1994TA1965>. This is complemented by investigation of the nucleophilic addition of Grignard reagents <1998T12233> and alkylindiums <2003TL2803> to α -ketophosphonates to afford ketones (Scheme 34). The formal reduction of α -ketophosphonates with lanthanoid metals has also been investigated <1995JOM(491)173, 2000JOC475> and shown to be synthetically useful (Scheme 35). The further investigation of the reactions of carbenes generated from deoxygenation of

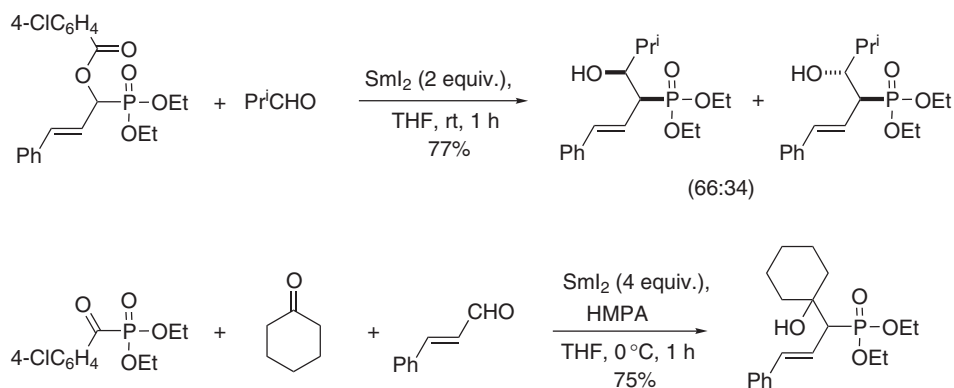
α -ketophosphonates has also been reported <1993RJGC2245, 1996JCR(S)176, 1996JCS(P1)555, 2000MI304>. The ketonic character of the C=O bond of an α -ketophosphonate functionality is further demonstrated through a number of other reactions including their reaction toward Vilsmeier–Haack reagent and the use of the product in heterocyclic synthesis <1999SC4025, 2000PS(158)179>, reductive amination <1996T10685>, and olefination <1997S162>.



Scheme 33

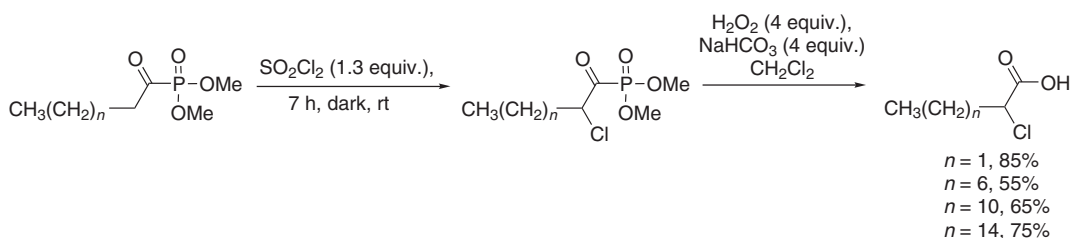


Scheme 34



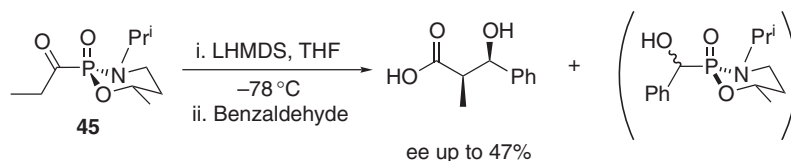
Scheme 35

Introduction of substituents at the position α - to a ketophosphonate has remained elusive even though it potentially has a role in asymmetric synthesis. α -Chlorination of a ketophosphonate using sulfonyl chloride has been reported and used for the synthesis of α -chlorocarboxylic acids (Scheme 36) <2001T4793, 1998TL8739>.

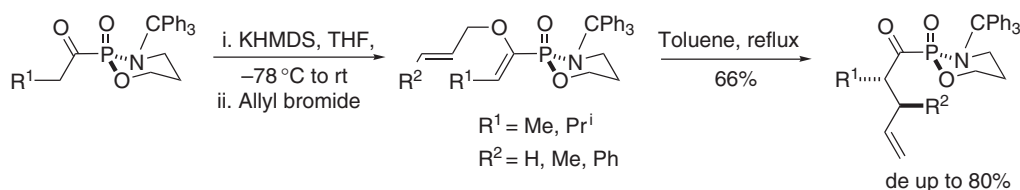


Scheme 36

Although the mechanism of chlorination of α -ketophosphonates using sulfonyl chloride has not been investigated, it is most likely a radical reaction. Anionic reactions of α -ketophosphonates have been more elusive. Evans has reported an inefficient aldol reaction between the enolate of **45** and benzaldehyde (Scheme 37) <1993JOC5293>. However, recently it has been shown that introduction of carbon substituents at the position α - to a ketophosphonate can be achieved through a [3,3]-sigmatropic shift of the corresponding enol ether (Scheme 38) <2004JOC6500>.



Scheme 37



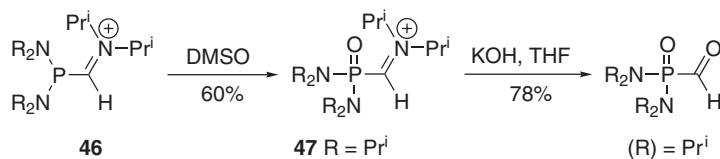
Scheme 38

(iv) *With at least one sulfur substituent (but no halogen or oxygen substituent)*

There appear to be no examples of this class of compounds reported since <1995COFGT(5)393>.

(v) *With at least one nitrogen substituent (but no halogen or chalcogen substituent)*

Oxidation of compound **46** and subsequent hydrolysis is reported to afford **47** (Scheme 39) <1999AG(E)2201>.



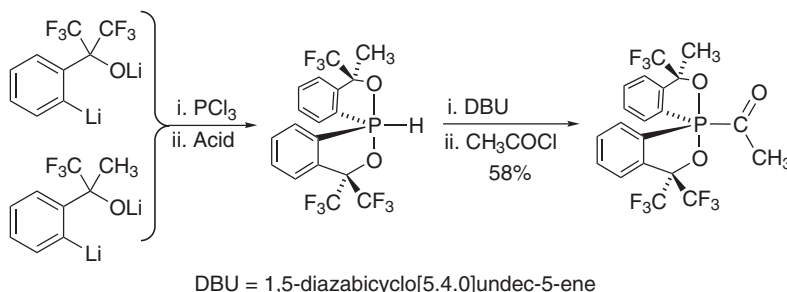
Scheme 39

5.08.4.3.2 *P=other heteroatom bonded systems*

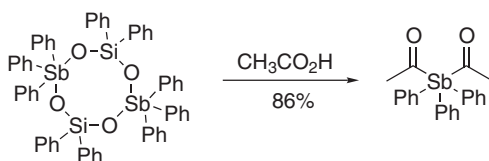
There appear to be no examples of this class of compounds reported since <1995COFGT(5)393>.

5.08.5 HIGHER-COORDINATED SPECIES

Five-coordinated acylphosphorus species continue to be rarely encountered and only one example has been reported since <1995COFGT(5)393> (Scheme 40) <2002JOM(643–644)441>. The first example of a pentacoordinated antimony compound has now been reported (Scheme 41) <1999RJGC82>.



Scheme 40



Scheme 41

REFERENCES

- 1993RJGC2245 D. V. Griffiths, P. A. Griffiths, H. Karim, B. J. Whitehead, *Russ. J. Gen. Chem.* **1993**, 63, 2245–2251.
- 1993JOC5293 N. J. Gordon, S. A. Evans Jr., *J. Org. Chem.* **1993**, 58, 5293–5294.
- 1994OM4179 N. Carleton, J. F. Corrigan, S. Doherty, R. Pixner, Y. Sun, N. J. Taylor, A. J. Carty, *Organometallics* **1994**, 13, 4179–4182.
- 1994TA1965 T. Gajda, *Tetrahedron Asymm.* **1994**, 5, 1965–1972.
- 1994TL551 M. S. Smyth, T. R. Burke Jr., *Tetrahedron Lett.* **1994**, 35, 551–554.
- 1994JSC(P1)1847 M. Mahajna, E. Breuer, *J. Chem. Soc., Perkin Trans. 1* **1994**, 1847–1849.
- 1994OM208 P. Veya, C. Floriani, A. Chiesi-Villa, C. Guastini, *Organometallics* **1994**, 13, 208–213.
- 1994NJC1183 N. Lauth De Viguerie, M. Willson, J. Périé, *New J. Chem.* **1994**, 18, 1183–1195.
- 1994OM5166 N. Cenac, M. Zablocka, A. Igau, J.-P. Majoral, M. Pietrusiewicz, *Organometallics* **1994**, 13, 5166–5168.
- 1995COFGT(5)393 K. Afarinkia, M. V. Vinader, Acylphosphorus, -arsenic, -antimony, and -bismuth functions, in *Comprehensive Organic Functional Group Transformations*, C. J. Moody, Ed., Elsevier, Oxford, **1995**, Vol. 5, pp. 393–407.
- 1995LA1963 C. Meier, W. H. G. Laux, J. W. Bats, *Liebigs Ann. Chem.* **1995**, 1963–1979.
- 1995OM1525 W. Tikkanen, A. L. Kim, K. B. Lam, K. Ruekert, *Organometallics* **1995**, 14, 1525–1528.
- 1995PS(102)45 M. P. Kaushik, R. Vaidyanathaswamy, *Phosphorus Sulfur Silicon* **1995**, 102, 45–50.
- 1995JOM(491)173 Y. Taniguchi, N. Fujii, K. Takaki, Y. Fujiwara, *J. Organometal. Chem.* **1995**, 491, 173–179.
- 1995TL6759 C. J. Salomon, E. Breuer, *Tetrahedron Lett.* **1995**, 36, 6759–6760.
- 1995PS(101)245 J. R. Goerlich, R. Schmutzler, *Phosphorus Sulfur Silicon* **1995**, 101, 245–251.
- 1996JOC7212 A. R. Glabe, K. L. Sturgeon, S. B. Ghizzoni, W. K. Musker, J. N. Takahashi, *J. Org. Chem.* **1996**, 61, 7212–7216.
- 1996JOC1537 D. Solas, R. L. Hale, D. V. Patel, *J. Org. Chem.* **1996**, 61, 1537–1539.
- 1996T589 C. Meier, W. H. G. Laux, *Tetrahedron* **1996**, 52, 589–598.
- 1996JCR(S)176 D. V. Griffiths, P. A. Griffiths, K. Karim, B. J. Whitehead, *J. Chem. Res. (S)* **1996**, 176–177.
- 1996JCS(P1)555 D. V. Griffiths, P. A. Griffiths, K. Karim, B. J. Whitehead, *J. Chem. Soc., Perkin Trans. 1* **1996**, 555–561.
- 1996JOC7455 L. A. Telan, C.-D. Poon, S. A. Evans Jr., *J. Org. Chem.* **1996**, 61, 7455–7462.
- 1996PS(113)179 D. St. C. Green, U. Gruss, G. Haegle, H. R. Hudson, L. Lindblom, M. Pianka, *Phosphorus Sulfur Silicon* **1996**, 113, 179–207.
- 1996TA89 C. Meier, W. H. G. Laux, *Tetrahedron Asymm.* **1996**, 7, 89–94.
- 1996JFC29 J. R. Goerlich, V. Plack, R. Schmutzler, *J. Fluorine Chem.* **1996**, 76, 29–35.
- 1996T10685 A. Ryglowski, P. Kafarski, *Tetrahedron* **1996**, 52, 10685–10692.

- 1996RJOC1520 Yu. A. Veits, E. G. Neganova, I. P. Beletskaya, *Russ. J. Org. Chem.* **1996**, 32, 1520–1522.
- 1997S162 W. Huang, Y. Zhang, C. Yuan, *Synthesis* **1997**, 162–164.
- 1997AX1462 D. V. Griffith, J. E. Harris, J. R. Miller, *Acta Crystallogr.* **1997**, C53, 1462–1464.
- 1997JCS(D)3589 H. Adams, N. A. Bailey, P. Blenkiron, M. J. Morris, *J. Chem. Soc., Dalton Trans.* **1997**, 3589–3598.
- 1997TL1663 K. Afarinkia, J. Echenique, S. C. Nyburg, *Tetrahedron Lett.* **1997**, 38, 1663–1666.
- 1997JOM(529)127 R. Pietschnig, E. Niecke, M. Nieger, K. Airola, *J. Organomet. Chem.* **1997**, 529, 127–133.
- 1998TL8389 Y. Liao, H. Shabany, C. D. Spilling, *Tetrahedron Lett.* **1998**, 39, 8389–8392.
- 1998PS(133)167 P. Coutrot, C. Grison, M. Lecouvey, A. Kribii, A. El Gadi, *Phosphorus Sulfur Silicon* **1998**, 133, 167–193.
- 1998CEJ1917 M. Scheer, E. Leiner, P. Kramkowski, M. Schiffer, G. Baum, *Chem. -Eur. J.* **1998**, 4, 1917–1923.
- 1998CC2199 S. J. Black, D. E. Hibbs, M. B. Hursthouse, C. Jones, J. W. Steed, *J. Chem. Soc., Chem. Commun.* **1998**, 2199–2200.
- 1998CEJ903 B. Manz, J. Kerth, G. Maas, *Chem. -Eur. J.* **1998**, 4, 903–913.
- 1998OM5924 C. Jones, S. J. Black, J. W. Steed, *Organometallics* **1998**, 17, 5924–5926.
- 1998TL8739 C. Stevens, L. De Buyck, N. De Kimpe, *Tetrahedron Lett.* **1998**, 39, 8739–8742.
- 1998T12233 H. Maeda, K. Takahashi, H. Ohmori, *Tetrahedron* **1998**, 54, 12233–12242.
- 1999PS(144–146)313 C. E. McKenna, B. A. Kashemirov, Z.-M. Li, *Phosphorus, Sulfur and Silicon and Rel. Elem.* **1999**, 144–146, 313–316.
- 1999TL5337 T. Okauchi, T. Yano, T. Fukamachi, J. Ichikawa, T. Minami, *Tetrahedron Lett.* **1999**, 40, 5337–5340.
- 1999PS(144–146)717 M. Scheer, P. Kramkowski, M. Schiffer, J. Muller, *Phosphorus, Sulfur and Silicon and Rel. Elem.* **1999**, 144–146, 717–720.
- 1999SC4025 H. Chen, D.-Q. Qian, G.-X. Xu, Y.-X. Liu, X.-D. Chen, X.-D. Shi, R.-Z. Cao, L.-Z. Liu, *Synth. Commun.* **1999**, 29, 4025–4033.
- 1999RJGC82 S. N. Zaburdaeva, L. S. Korchemnaya, A. Yu. Fedorov, V. A. Dodonov, *Russ. J. Gen. Chem.* **1999**, 69, 82–84.
- 1999TL7705 A. Barco, S. Benetti, P. Bergamini, C. De Risi, P. Marchetti, G. P. Pollini, V. Zanirato, *Tetrahedron Lett.* **1999**, 40, 7705–7708.
- 1999EJ12369 L. Weber, S. Uthmann, H.-G. Stammer, B. Neumann, W. W. Schoeller, R. Boese, D. Bläser, *Eur. J. Inorg. Chem.* **1999**, 2369–2381.
- 1999AG(E)2201 D. Amsallem, H. Gornitzka, A. Baceiredo, G. Bertrand, *Angew. Chem., Int. Ed. Engl.* **1999**, 38, 2201–2203.
- 2000PS(158)179 D.-Q. Qian, Y.-X. Liu, R.-Z. Cao, L.-Z. Liu, *Phosphorus Sulfur Silicon* **2000**, 158, 179–186.
- 2000ACS1635 D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, 122, 1635–1649.
- 2000JOM(607)156 R. S. Dickson, G. D. Fallon, W. R. Jackson, A. Polas, *J. Organomet. Chem.* **2000**, 607, 156–163.
- 2000JOM(601)271 J. D. King, M. J. Mays, C.-Y. Mo, P. R. Raithby, M. A. Rennie, G. A. Solan, T. Adatia, G. Conole, *J. Organomet. Chem.* **2000**, 601, 271–283.
- 2000JOC475 K. Takaki, Y. Itono, A. Nagafuji, Y. Naito, T. Shishido, K. Takehira, Y. Makioka, Y. Taniguchi, Y. Fujiwara, *J. Org. Chem.* **2000**, 65, 475–481.
- 2000TL3169 B. Kaboudin, *Tetrahedron Lett.* **2000**, 41, 3169–3171.
- 2000RJOC750 Yu. A. Veits, N. B. Karlstedt, A. V. Chuchuryukin, I. P. Beletskaya, *Russ. J. Org. Chem.* **2000**, 36, 750–756.
- 2000ZAAC(626)421 L. Weber, C. A. Mast, M. H. Scheffer, H. Schumann, S. Uthmann, R. Boese, D. Blaser, H.-G. Stammer, A. Stammer, *Z. Anorg. Allg. Chemie* **2000**, 626, 421–429.
- 2000CC2307 H. Maeda, Y. Huang, N. Hino, Y. Yamauchi, H. Ohmori, *J. Chem. Soc., Chem. Commun.* **2000**, 23, 2307–2308.
- 2000JCS(D)3074 H. Adams, N. A. Bailey, P. Blenkiron, M. J. Morris, *J. Chem. Soc., Dalton Trans.* **2000**, 3074–3081.
- 2000HAC232 Z. Ziora, A. Maly, B. Lejczak, P. Kafarski, J. Holband, G. Wojcik, *Heteroatom Chem.* **2000**, 11, 232–239.
- 2000HAC470 R. Chen, A. Schlossman, E. Breuer, G. Hagele, C. Tillmann, J. M. Van Gelder, G. Golomb, *Heteroatom Chem.* **2000**, 11, 470–479.
- 2000JOC9331 X. Chen, A. J. Wiemer, R. J. Hohl, D. F. Wiemer, *J. Org. Chem.* **2000**, 67, 9331–9339.
- 2000MI304 D. V. Griffiths, J. E. Harris, K. Karim, B. J. Whitehead, *Arkivoc* **2000**, 1, 304.
- 2001TL4369 H. Firouzabadi, N. Iranpoor, S. Sobhani, A.-R. Sardarian, *Tetrahedron Lett.* **2001**, 42, 4369–4371.
- 2001JCS(D)3219 C. Jones, P. C. Junk, J. W. Steed, R. C. Thomas, T. C. Williams, *J. Chem. Soc., Dalton Trans.* **2001**, 21, 3219–3226.
- 2001SC2245 B. Kaboudin, R. Nazari, *Synth. Commun.* **2001**, 31, 2245–2250.
- 2001JFC127 Z. Wang, Y. Gu, A. J. Zapata, G. B. Hammond, *J. Fluorine Chem.* **2001**, 107, 127–132.
- 2001TL743 K. Afarinkia, R. Angell, C. L. Jones, J. Lowman, *Tetrahedron Lett.* **2001**, 42, 743–746.
- 2001T4793 C. V. Stevens, B. Vanderhoydonck, *Tetrahedron* **2001**, 57, 4793–4800.
- 2002JOM(646)113 A. Surana, S. Singh, R. K. Bansal, N. Peulecke, A. Spannenberg, J. Heinicke, *J. Organomet. Chem.* **2002**, 646, 113–124.
- 2002JCS(D)2417 C. Jones, P. C. Junk, T. C. Williams, *J. Chem. Soc., Dalton Trans.* **2002**, 2417–2418.
- 2002JOM(643–644)441 M. Nakamoto, S. Kojima, S. Matsukawa, Y. Yamamoto, K.-Y. Akiba, *J. Organomet. Chem.* **2002**, 643, 441–452.
- 2002T6521 S. Hanessian, P. Compain, *Tetrahedron* **2002**, 58, 6521–6529.
- 2002TL477 H. Firouzabadi, N. Iranpoor, S. Sobhani, *Tetrahedron Lett.* **2002**, 43, 477–480.
- 2003JOM(667)112 A. R. Baber, M. L. Clarke, A. G. Orpen, D. A. Ratcliffe, *J. Organomet. Chem.* **2003**, 667, 112–119.
- 2003JOC5020 E. Vedejs, O. Daugulis, L. A. Harper, J. A. MacKay, D. R. Powell, *J. Org. Chem.* **2003**, 68, 5020–5027.

- 2003JACS4166 E. Vedejs, O. Daugulis, *J. Am. Chem. Soc.* **2003**, 125, 4166–4173.
 2003TL2803 D. Y. Kim, D. F. Wiemer, *Tetrahedron Lett.* **2003**, 44, 2803–2805.
 2002TCC(220)201 C. E. McKenna, B. A. Kashemirov, *Top. Curr. Chem.* **2002**, 220, 201–238.
 2003S357 K. Afarinkia, A. Faller, A. J. Twist, *Synthesis* **2003**, 357–360.
 2003NJC466 S. Bruce, D. E. Hibbs, C. Jones, J. W. Steed, R. C. Thomas, T. C. Williams, *Nouv. J. Chem.* **2003**, 27, 466–474.
 B2003MI319 P. Savignac, B. Igora, Ketophosphonates. *Modern Phosphonate Chemistry*, CRC Press, New York, **2003**, pp. 319–379.
 2004JOC6500 K. Afarinkia, A. J. Twist, H.-w. Yu, *J. Org. Chem.* **2004**, 69, 6500–6504.

Biographical sketch

Dr. Kamyar Afarinkia was born in Tehran, Iran in 1963. After graduating from Imperial College, University of London, UK in 1987, he studied for a Ph.D. under the supervision of Prof. Charles Rees, CBE FRS and Prof. Sir John Cadogan, CBE FRS at the same institution. In 1990, he took up a postdoctoral position at Johns Hopkins University, Baltimore, USA, under supervision of Prof Gary H. Posner, working on the synthesis of vitamin D₃ analogs. In 1992, he returned to the UK and was appointed as a Senior Scientist at Glaxo R&D in Ware, Hertfordshire where he worked as a medicinal chemist in projects on hypertension and diabetes. In 1995, he was appointed to his current position at King's College, University of London. His area of research includes application of asymmetric organophosphorus reagent in synthesis, chemistry of α -amino and α -hydroxy phosphonic acids, total synthesis of natural products and the Diels-Alder cycloaddition of 2(H)-pyran-2-ones, 2(H)-pyridin-2-ones and 2(H)-1,4-oxazin-2-ones.

5.09

Acylsilicon, -germanium, or -boron Functions

P. J. STEVENSON
Queens University, Belfast, UK

5.09.1	ACYLSILICON DERIVATIVES, $R^1\text{COSiR}_3^2$	375
5.09.1.1	Simple Aroyl and Alkanoyl Silanes	376
5.09.1.1.1	Hydrolysis of dithianes and <i>N,O</i> -acetals	376
5.09.1.1.2	Oxidation of α -silyl alcohols	376
5.09.1.1.3	Silyl- and acyl-metallic species	380
5.09.1.1.4	Transition metal-catalyzed synthesis	382
5.09.1.1.5	Silyl oxirane rearrangement	383
5.09.1.1.6	<i>gem</i> -bis(Trialkylsilyl) compounds	384
5.09.1.2	Functionalized Acyl Silanes	386
5.09.1.2.1	α -Haloacyl silanes	386
5.09.1.2.2	α,β -Unsaturated acyl silanes	386
5.09.1.2.3	Cyclopropylacylsilanes	390
5.09.1.3	Chemistry of Acyl Silanes	390
5.09.1.3.1	Asymmetric reduction of acyl silanes	390
5.09.1.3.2	Annulation reactions of alkenoyl silanes	390
5.09.1.3.3	Acyl silanes as precursors to alkenes and alkynes	393
5.09.1.3.4	Oxygen heterocycles from acyl silanes	393
5.09.2	ACYLGERMANIUM DERIVATIVES, $R^1\text{COGeR}_3^2$	393
5.09.2.1	Oxidation of α -Germyl Alcohols	394
5.09.2.2	Coupling of Germyl Metallic Species and Carboxylic Acid Derivatives	394
5.09.2.3	Hydrogermylcarbonylation of Alkynes	395
5.09.2.4	Chemistry of Acyl Germanes	395
5.09.3	ACYLBORON DERIVATIVES	396

5.09.1 ACYLSILICON DERIVATIVES, $R^1\text{COSiR}_3^2$

The sections used in this review are similar to those used in chapter 5.09 of COFGT (1995). However, developments in reductive silylation have been incorporated into [Section 5.09.1.1.2](#) for organizational reasons. In the areas of enol ether metallation/hydrolysis, silylation of acyl metallic species, rearrangement of silyloxycarbenes, Claisen rearrangement, formylsilanes, α -ketoacylsilanes, and other functionalized acyl silanes, no further advances have occurred in these areas since the publication of chapters 5.09.1.1.3, 5.09.1.1.5, 5.09.1.1.8, 5.09.1.1.9, 5.09.1.2, 5.09.1.3.2, and 5.09.1.3.5 in COFGT (1995), so these topics have been omitted in this survey. New sections on silyloxirane rearrangement, and *gem*-bis(trialkylsilyl) compounds as versatile precursors to acyl silanes are included. Finally, a new section on the chemistry of acyl silanes is included.

Ricci [<1997G619, 1998JOM\(567\)181>](#) and Patrocínio [<2001MI7>](#) reviewed the synthesis, chemistry, and properties of acyl silanes, and Moser [<2001T2065>](#) reviewed the Brook rearrangement as a lynchpin in domino processes. Material taken from these reviews is presented to

provide the most direct and synthetically useful routes to acyl silanes and to highlight the most important aspects of their chemistry. The material in this survey covers mainly the period 1994 to mid-2003, though some important chemistry from beyond this period is also included for the sake of completeness.

Many different types of acyl silanes have been synthesized containing a wide variety of additional function groups. Acylphenyldimethylsilanes have become very popular in the review period, probably reflecting the fact that phenyldimethylsilyllithium is easy to prepare and is the starting point for making other phenyldimethylsilyl metallic species, which participate in a wide variety of preparative reactions. The most popular methods for preparing simple acyl silanes are displacement reactions from suitable carbonyl functional groups. Silyl-substituted oxiranes have emerged as very versatile intermediates for acyl silane formation and can be easily modified to give chiral acyl silanes. Conceptually new methods have emerged for making acyl silanes which start from bis(diphenylmethyl)silanes and give rise to highly functionalized products. Tandem processes incorporating Brook rearrangement are an exciting new area, which give rise to complex products from simple starting materials.

New methods are presented for the preparation of acylgermanium compounds, the most noteworthy of which is the base-catalyzed addition of trifurylgermane to aldehydes followed by oxidation.

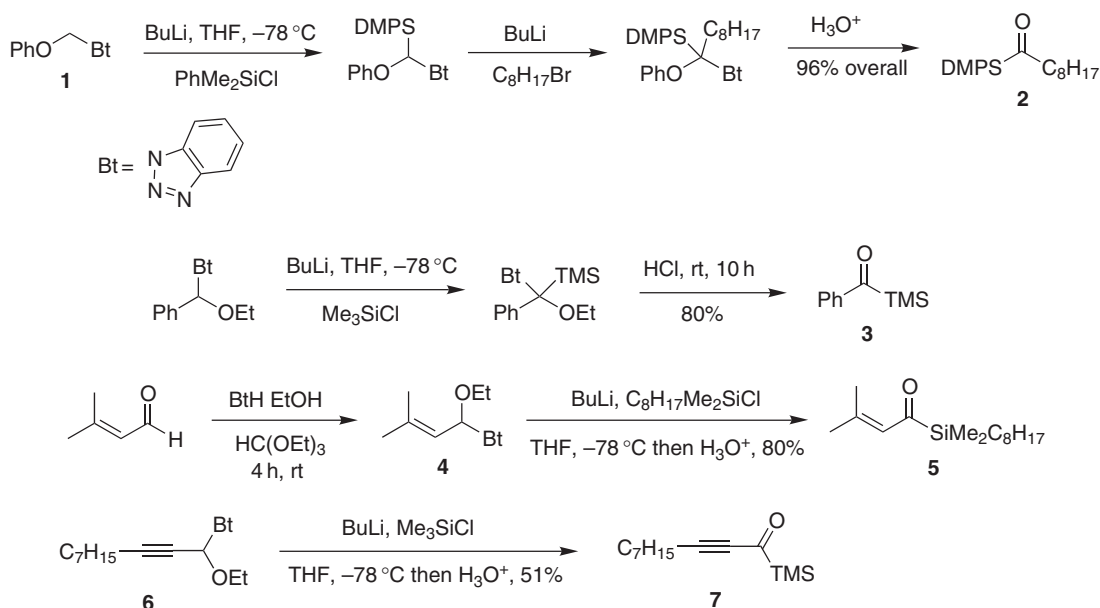
5.09.1.1 Simple Aroyl and Alkanoyl Silanes

5.09.1.1.1 Hydrolysis of dithianes and *N,O*-acetals

Reaction of acyl anion equivalents with electrophilic silylating agents, followed by regeneration of the carbonyl group, is a well-established method for preparing alkanoyl silanes. This methodology was developed by Corey and Brook in the 1960s using 1,3-dithianes as acyl anion equivalents, and was extensively covered in chapter 5.09.1.1.1 in COFGT (1995). The methodology continues to be employed, reflecting its reliability <1996JOC1794, 1999EJO1571, 1997TL6595>. However, one potential drawback with the approach is that it can be difficult to regenerate the carbonyl functionality from the dithiane in sensitive substrates. *N,O*-Acetals derived from benzotriazole have been employed as acyl anion equivalents <1996OM486, 1996JOC7551>. The advantages of this approach are threefold. First, the *N,O*-acetals are easily prepared by treating the required aldehyde with benzotriazole and the alcohol of choice along with a dehydrating agent. Second, the organolithium reagents derived from the *N,O*-acetals are relatively stable and are readily silylated with electrophilic silylating agents. Third, and perhaps most important, the silylated *N,O*-acetals are easily hydrolyzed to the carbonyl functionality when treated with dilute acid. Hence, the *N,O*-acetal **1** can be deprotonated with butyllithium and reacted with alkyl bromide and silylating agent in any order to give, on hydrolysis, the acyl silane **2** (Scheme 1). The chemistry can be readily extended to *N,O*-acetals derived from aromatic aldehydes. Again, deprotonation followed by silylation and subsequent mild regeneration of the carbonyl group gave **3** in excellent yield. Attempts have been made to extend the chemistry to α,β -unsaturated aldehydes, where the *N,O*-acetals **4** are readily formed. However, the subsequent deprotonation gave rise to an ambident allylic anion which can react at two sites, either C-1 or C-3. When there are two substituents at C-3 as in **4**, silylation occurs exclusively at C-1. On mild acid hydrolysis the required acyl silane **5** was isolated. The corresponding *N,O*-acetal derived from acrolein gave a 3:1 mixture of C-1 and C-3 regioisomeric adducts, respectively. *N,O*-Acetals **6** derived from conjugated acetylenic aldehydes can also be employed and gave alkynoyltrimethylsilanes **7** after hydrolysis.

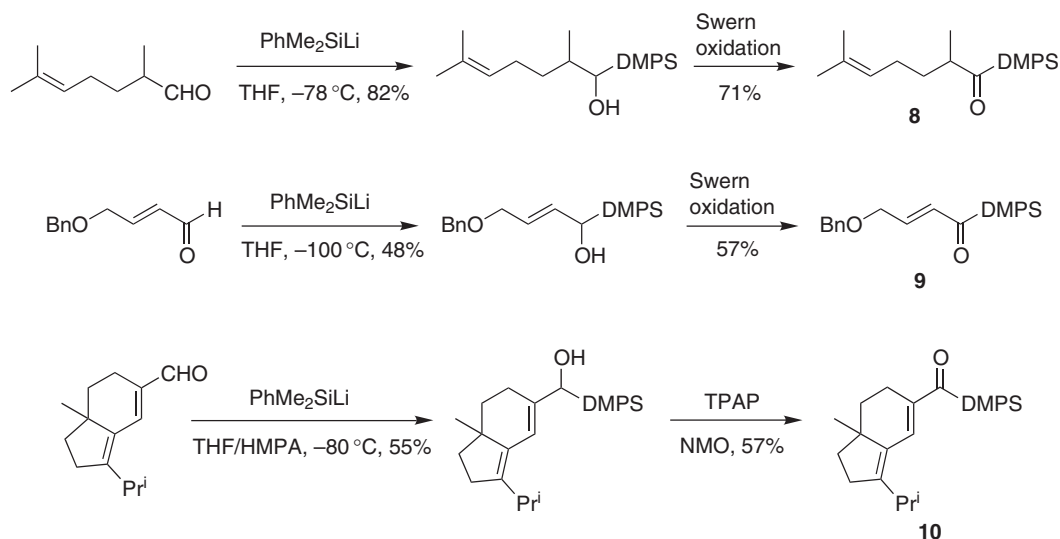
5.09.1.1.2 Oxidation of α -silyl alcohols

As previously noted in chapter 5.09.1.1.2 in COFGT (1995), oxidation of α -silyl alcohols to acyl silanes is not straightforward as there are two competing pathways, one giving the desired α -acylsilyl compound and the other giving aldehyde with loss of silicon. Originally, Jones' reagent was used to perform this oxidation, but this has the disadvantage that large amounts of unwanted aldehyde are also produced. Use of lead tetraacetate as oxidant gave the aldehyde exclusively <2000JOC2292>. However, the Swern oxidation or its variants appears to have become the method of choice for performing this difficult oxidation, as illustrated by the formation of **8**



Scheme 1

<2000JOC2292> and **9** <1994JOC3055> (Scheme 2). Interestingly, the first example of tetrapropylammonium perruthenate (TPAP) for this oxidation is reported for the synthesis of **10** <2000OL1903>. Other reagents that have been used to oxidize α-silyl alcohols to acyl silanes include potassium permanganate on alumina <2001SC2457> and the Dess–Martin periodinane <1994TL8999>.



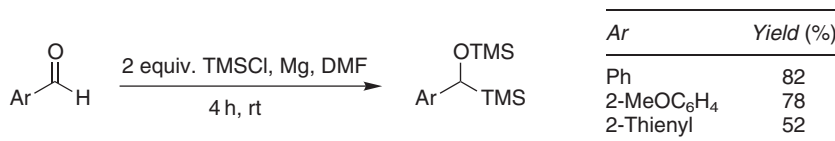
Scheme 2

(i) α-Silyl alcohols by silyl addition to aldehydes

There was statement in chapter 5.09.1.1.2 in COFGT (1995) that “methods for the direct preparation of (α-hydroxyalkyl)silanes are limited.” Evidence has now accumulated to suggest that this statement may need to be amended. Addition of trialkylsilyl organometallic reagents to aldehydes followed by oxidation is a reliable method for preparing acyl silanes as long as the corresponding silyllithium is available. Dimethylphenylsilyllithium can be easily prepared from

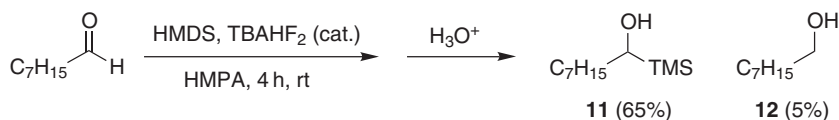
dimethylphenylsilyl chloride and has emerged as the reagent of choice for reaction with aldehydes. There are sporadic examples of this chemistry outside this review period <1992JOC386, 1987JOC5583> and Scheme 2 highlights some recent examples <2000JOC2292, 1994JOC3055, 2000OL1903>. α -Dimethylphenylsilyl alcohols are much less prone to undergo Brook rearrangement than the corresponding α -trimethylsilyl alcohols, making this chemistry very direct and attractive for preparing bulky acyl silanes.

However, in general the procedure is not without problems. First, the simplest member in the series requires access to trimethylsilyllithium. Unfortunately, this reagent cannot be directly prepared in high yield by reaction of trimethylsilyl chloride with lithium metal. Therefore, alternative procedures are required. Aromatic aldehydes react with trimethylsilyl chloride and magnesium to give α -trimethylsilyl trimethylsilyl ethers in moderate to excellent yields (Scheme 3) <1995CL829>. However, it is highly unlikely that this reaction involves trimethylsilylmagnesium intermediates. It is believed that this reaction proceeds via radical anions with magnesium acting merely as an electron source. Additional examples of this type of chemistry appeared in chapter 5.09.1.1.7 in COFGT (1995) under the heading Reductive Silylation where esters derived from aromatic carboxylic acids, imidoyl chlorides, and cyanohydrins were converted to acyl silanes by reaction with trimethylsilyl chloride and a group 1 or 2 metal. The major drawback with this approach is that the metal can also reduce the carbonyl compounds leading to by-products.



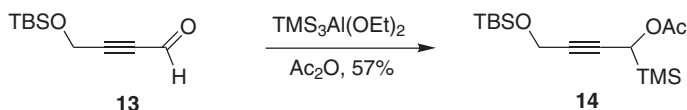
Scheme 3

Another approach to the trimethylsilyl anion involves the reaction of hexamethyldisilane with tetrabutylammonium fluoride (TBAF) in HMPA as solvent <1994PAC1471>. Fluoride ion has a high affinity for silicon and this results in cleavage of the silicon–silicon bond to give trimethylsilyl fluoride and the trimethylsilyl anion, which can subsequently react with an aldehyde. However, the original procedure is very moisture sensitive, and commercially available TBAF is sold as the trihydrate, which is difficult to dry. The use of the nonhygroscopic fluoride reagent, tetrabutylammonium hydrogen fluoride (TBAHF₂), to mediate this reaction has been introduced (Scheme 4) <1997SL693>. This salt was easily prepared by reaction of tetrabutylammonium hydroxide with 48% hydrofluoric acid followed by azeotropic removal of water with toluene. Reaction of octanal with hexamethyldisilane in the presence of a catalytic quantity of TBAHF₂ gave, after hydrolysis of the silyl ether, alcohols **11** and **12** in 65% and 5% yields, respectively. Another general problem with this chemistry is the inherent instability of α -trimethylsilyl alcohols which show a strong tendency to undergo Brook rearrangement, giving rise to alcohol **12**. Using this new fluoride-containing catalyst, the amount of Brook rearrangement product appears to be diminished. In general, this chemistry fails with aromatic aldehydes, with pinacol dimers being the major reaction products, suggesting radical anion formation under the reaction conditions.



Scheme 4

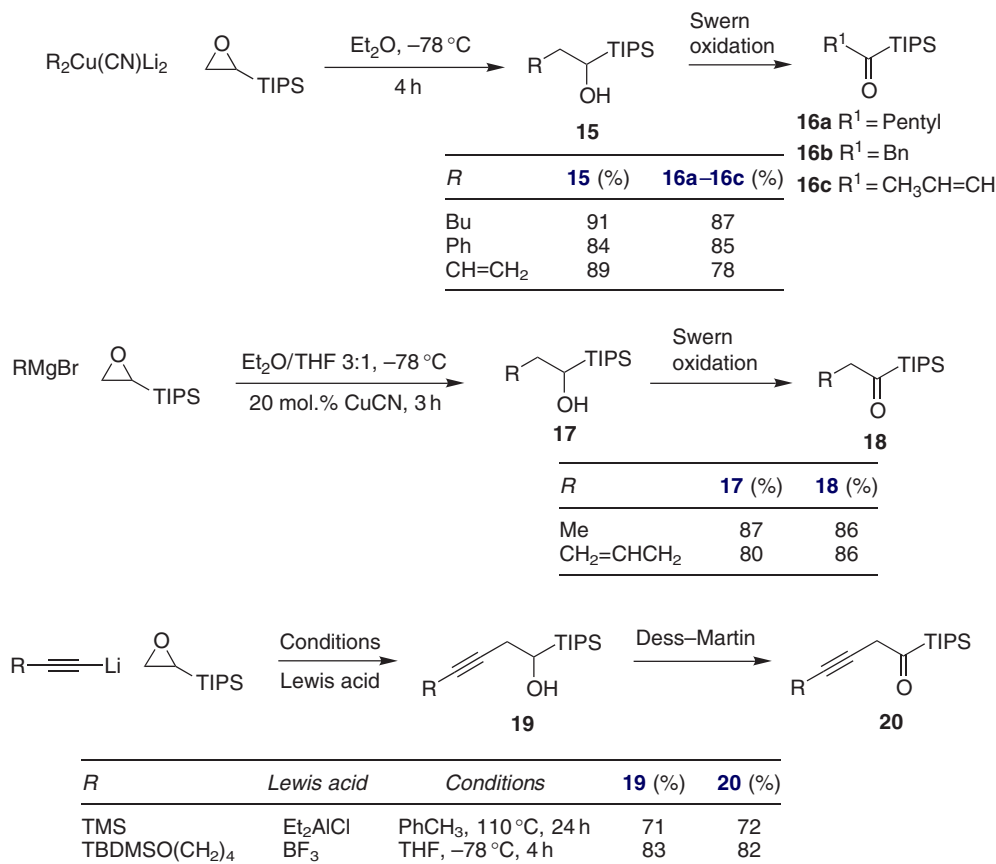
Tris(trimethylsilyl)aluminum etherate was readily prepared in one step, in 40% yield, by reaction of lithium, aluminum, and trimethylsilyl chloride in diethyl ether <1980JOM(195)47>. This reagent was employed as a trimethylsilyl-transfer reagent with conjugated acetylenic aldehyde **13** to give α -trimethylsilylacetylenic acetates **14** on work-up, with no 1,4-addition products being observed (Scheme 5) <2000CEJ655>. This reagent also reacts with α,β -unsaturated aldehydes to give α -trimethylsilylallylic alcohols in reasonable yield <1994JOC332>.



Scheme 5

(ii) α -Silyl alcohols by regioselective ring-opening reactions of silyl oxiranes

Triisopropylsilyl oxiranes are easy to prepare and it has recently been demonstrated that these are effective substrates for the synthesis of triisopropylacylsilanes (Scheme 6) <1994TL8999>. The key to the success of this chemistry is the regioselective nucleophilic ring-opening reaction at the carbon β to the silyl group. It appears that the bulk of the substituents on the silicon atom imparts stability toward Lewis-acid-mediated oxirane rearrangement and directs nucleophiles to the carbon β to silicon. A variety of organometallic nucleophiles was employed ranging from higher-order cuprates, and Grignard reagent plus copper(I) cyanide, to lithium acetylides. In each case, the yield of α -triisopropylsilyl alkanols **15**, **17**, and **19** was excellent. In the case of lithium acetylides, a Lewis acid was also required to promote the ring-opening reaction which proceeded without oxirane rearrangement. With α -triisopropylsilyl alkanols to hand, oxidation gave the acyltriisopropylsilyl derivatives **16**, **18**, and **20** in high yield. For the less functionalized substrates, the acyl silane was obtained with a Swern oxidation. In the case of the allylacylsilane, the double bond rapidly moved into conjugation with the carbonyl group under the reaction conditions. Oxidation of the homopropargyl alcohols **19** proved problematic using Swern oxidation but gave good yields of products **20** using the Dess–Martin periodinane.



Scheme 6

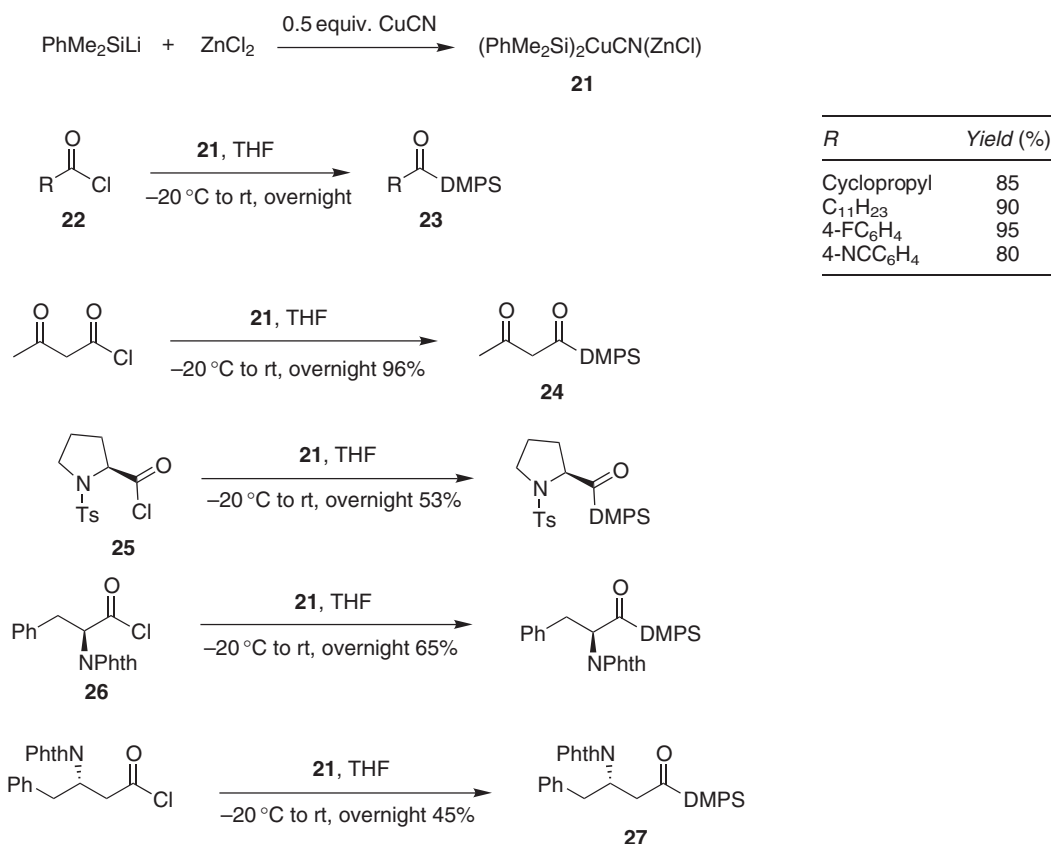
However, it should be noted that this chemistry cannot be applied to bulky triphenylsilyl oxiranes, as these species undergo rapid rearrangement to α -triphenylsilyl aldehydes (and products derived therefrom) when treated with Grignard reagents <1996JOC4395>.

5.09.1.1.3 Silyl- and acyl-metallic species

Synthesis of acyl silanes by a direct coupling of an activated acyl compound with a silyl metallic species is conceptually the most direct route to acyl silanes. In chapter 5.09.1.1.4 in COFGT (1995), the chemistry of acid chlorides and *S*-2-pyridyl esters with a range of silyl metallic reagents including cuprates was presented, and this is an excellent method for preparing acyl silanes. A major development in the intervening period has been the emergence of phenyldimethylsilyllithium and organometallic reagents derived from this, and their reactions with a much wider range of acyl compounds including acylimidazoles, esters, and amides.

(i) Reactions with acid chlorides

Phenyldimethylsilyllithium, readily prepared from phenyldimethylsilyl chloride and lithium shot, is the starting point for making the mixed copper zinc phenyldimethylsilyl reagent **21**, which reacts with acid chlorides **22** at $-20\text{ }^{\circ}\text{C}$ to give acylphenyldimethylsilanes **23** in excellent yield (Scheme 7) <1995S92>. Although the exact nature of reagent **21** remains unknown, it can be easily prepared by adding dimethylphenylsilyllithium to anhydrous zinc chloride at low temperature, followed by transmetalation with copper(I) cyanide. The only disadvantage of this procedure is that 2 mol of valuable silylating agent is required per mole of acid chloride. A very wide range of aliphatic and aromatic acid chlorides reacts with this reagent, and in all cases reported the yields were excellent. The reagent reacts chemoselectively with acid chlorides in the presence

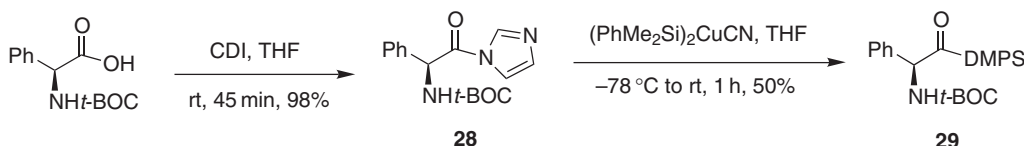


Scheme 7

of aryl fluoride, cyanide, ester, alkyl chloride, and imide functionalities. Of particular note is the use of 3-oxobutyryl chloride where potential enolization of the substrate, or of product **24**, and the basicity of the silylating reagent could have, in principle, presented problems. Acid chlorides (**25**, **26**) derived from chiral α -amino acids were also employed, and again the yields of acyl silane products were excellent. However, no mention was made of the potential epimerization of the acid chlorides or the configurational stability of the products. This chemistry was extended to give protected β -aminoacylphenyldimethylsilanes **27**. The main drawback with this chemistry is that the protecting group for the amino function must be compatible with the conditions employed for preparing the acid chloride, and was therefore limited to tosyl and phthalimido [\[1996JOC7242, 1999EJO437\]](#). Other common *N*-protecting groups tend to be incompatible with acid chloride functionality, particularly with respect to racemization of the α -chiral center, and this does somewhat restrict the application of the methodology.

(ii) Reactions with acylimidazoles

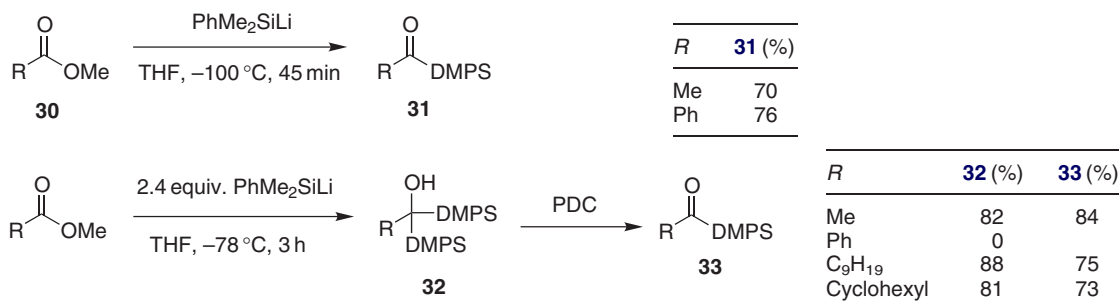
Acylimidazoles **28** are readily generated *in situ* from the corresponding *N*-*t*-BOC protected amino acids. These species react with higher-order phenyldimethylsilyl cuprates to give the highly functionalized acyl silane **29** (Scheme 8) [\[2000POL529\]](#). Interestingly, no zinc chloride was required with this variation of the methodology (cf. Scheme 7). Homochiral α -aminoacylsilanes can be used as stable synthetic equivalents to α -amino aldehydes [\[1999EJO437\]](#) and the incorporation of the easily removable *t*-BOC protecting group is a major advantage of this approach.



Scheme 8

(iii) Reactions with carboxylic acid esters

Methyl esters **30** react with dimethylphenylsilyllithium at very low temperature to give acylphenyldimethylsilanes **31** directly in excellent yield (Scheme 9) [\[1994JCS\(P1\)257\]](#). Using dimethylphenylsilyllithium, preformed prior to addition of the ester, had the major advantage that no acyloin condensation products were formed as was previously observed when trimethylsilyl chloride was reacted with lithium in the presence of ester [\[1975JOM\(93\)51\]](#). However, it was noted that the reaction was not general due to the perennial problem of the phenyldimethylsilyllithium reacting further with the acyl silane product in preference to the ester. The chemistry failed completely for α,β -unsaturated esters and for esters derived from aromatic carboxylic acids. A more general approach was to trap the acyl silane product with another equivalent of dimethylphenylsilyllithium to give the α,α -disilyl alcohols **32**. However, this modification was not without

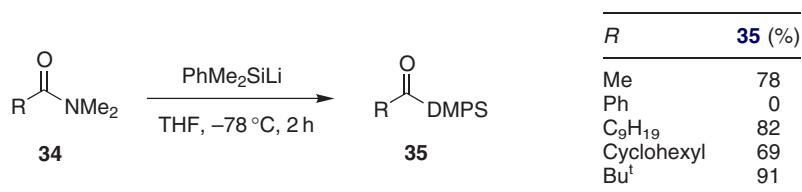


Scheme 9

problems, and when there was α -branching on the ester, methoxide-induced 1,2-phenyl shifts of the acylphenyldimethylsilane **31** led to substantial amounts of by-products with the accompanying reduction in yield. Once isolated, the α,α -disilyl alcohols **32** were oxidized to the required alkanoylphenyldimethylsilanes **33** in good yield using pyridinium dichromate as oxidant. The one-step procedure, when successful, gave better overall yields than the two-step process and was less wasteful of the valuable silylating agent.

(iv) *Reactions with carboxylic acid amides*

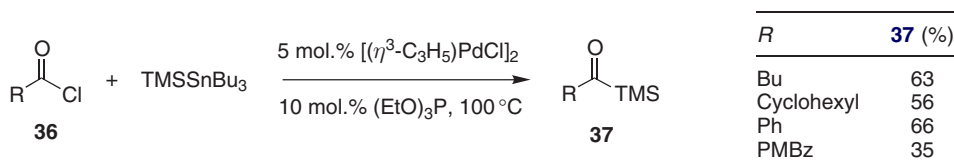
N,N-Dimethylamides **34** also react with dimethylphenylsilyllithium at low temperature in THF to give the corresponding acyldimethylphenylsilanes **35** normally in good-to-excellent yields (Scheme 10) <1994JCS(P1)257>. It was essential to quench the reaction at low temperature, otherwise a different pathway was followed on work-up. This chemistry appears to be fairly general for aliphatic amides, and is tolerant of steric hindrance at the α -carbon with *t*-butyl- and cyclohexylacylsilanes formed in excellent and good yields, respectively. In the case of (**34**; R = phenyl), the reaction took a different course and only α -dimethylaminobenzylidimethyl(phenyl)silane was isolated.



Scheme 10

5.09.1.1.4 *Transition metal-catalyzed synthesis*

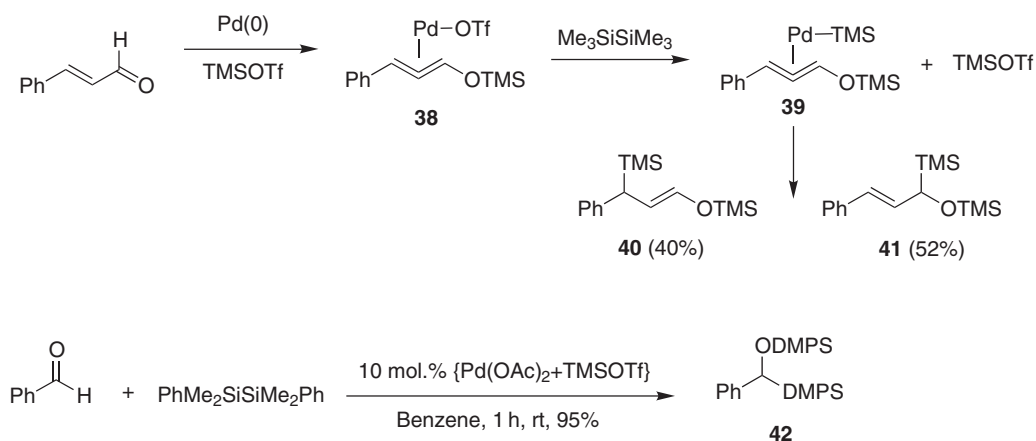
Transition metal approaches to acyl silanes reported in chapter 5.09.1.1.6 in COFGT (1995) included addition of hexamethyl silane to acid chlorides, and double bond isomerization of α -silyloxyallylsilanes followed by hydrolysis of the resulting enol ether. The former reaction is not without problems and only proceeded for aroyl chlorides, somewhat limiting its general applicability. A general method for palladium-catalyzed trimethylsilylation of acid chlorides **36** was achieved using commercially available trimethyl(tributylstannyl)silane (Scheme 11) <1999TL3113>. The procedure involves simply heating the neat reagents with 5 mol.% of a palladium catalyst and triethyl phosphite ligand.



Scheme 11

The new procedure was convenient and the yields of acyltrimethylsilanes **37** were moderate for both aromatic and aliphatic acid chlorides. On introduction of branching at the α -carbon the reaction times increased enormously along with a small decrease in yield. Unfortunately, substituents were not tolerated on the aromatic ring and the yield dropped to 35% when *p*-methoxybenzoyl chloride was employed. In all cases small amounts of acyltributylstannyl derivatives were formed as minor by-products.

A palladium(0) trimethylsilyl triflate-catalyzed addition of hexaalkyldisilanes to cinnamaldehyde and aromatic aldehydes has been reported (Scheme 12) <2002JA11598>. The role of the trimethylsilyl triflate was to trimethylsilylate the carbonyl oxygen, which results in attack of palladium to form an η^3 -siloxyallylpalladium intermediate **38**. This reacts with hexaalkyldisilane

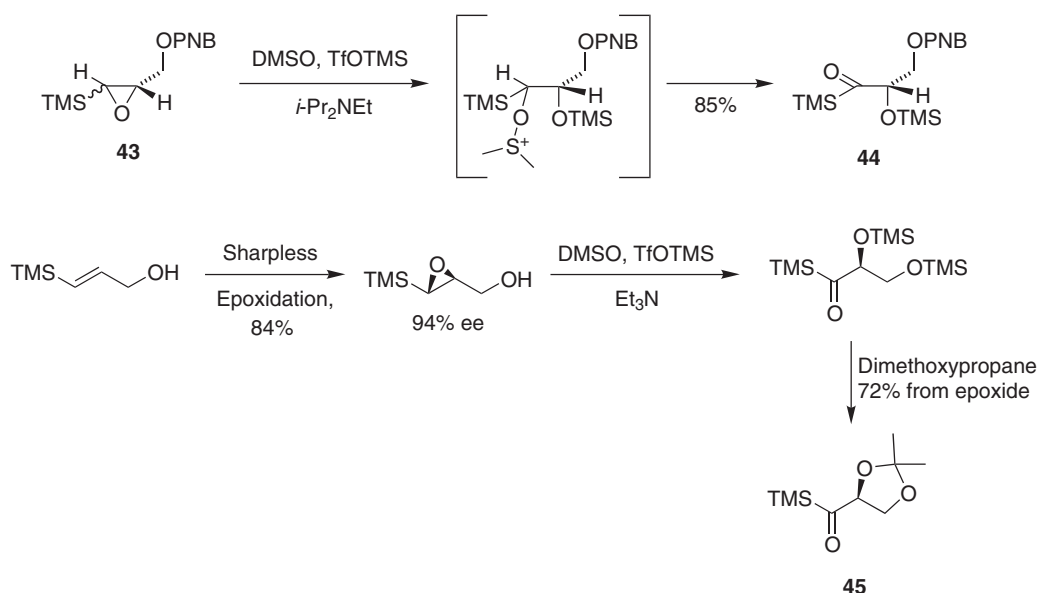


Scheme 12

to place a trimethylsilyl group onto the palladium, giving rise to **39** and regenerating the trimethylsilyl triflate catalyst. In the case of cinnamaldehyde, there are two positions for reductive elimination giving rise to two products **40** and **41**, with low regioselectivity for formation of α -silyl alcohol **41**. However, when benzaldehyde was employed, α -silyl ether **42** was formed exclusively in order to regain aromaticity. The catalytic nature of this reaction, together with the mildness of the reaction conditions, makes it an attractive synthetic procedure.

5.09.1.1.5 Silyl oxirane rearrangement

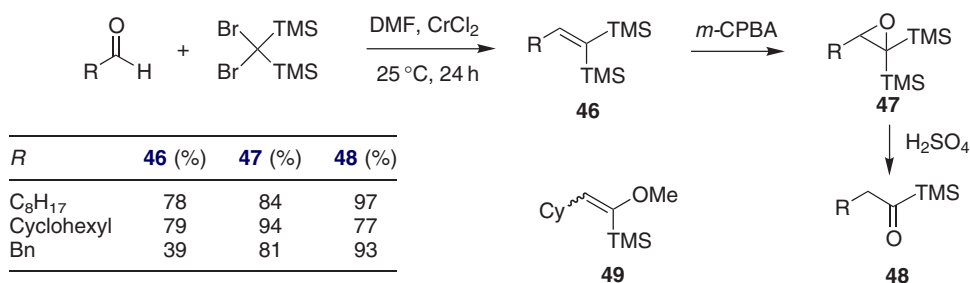
Chiral trimethylsilyl oxirane **43**, readily available by Sharpless epoxidation of the corresponding allylic alcohol, was efficiently converted into chiral acyl silane **44** under oxidizing conditions (Scheme 13) <1994JOC4355, 1995TA577>. The mechanism appears to involve a trimethylsilyl triflate-catalyzed regioselective ring-opening reaction of the oxirane with dimethyl sulfoxide followed by loss of dimethyl sulfide to give the chiral acyltrimethylsilane. This chemistry was modified to give acyl silane **45**, a stable synthetic equivalent of the unstable 2,3-*O*-isopropylidene glyceraldehyde.



Scheme 13

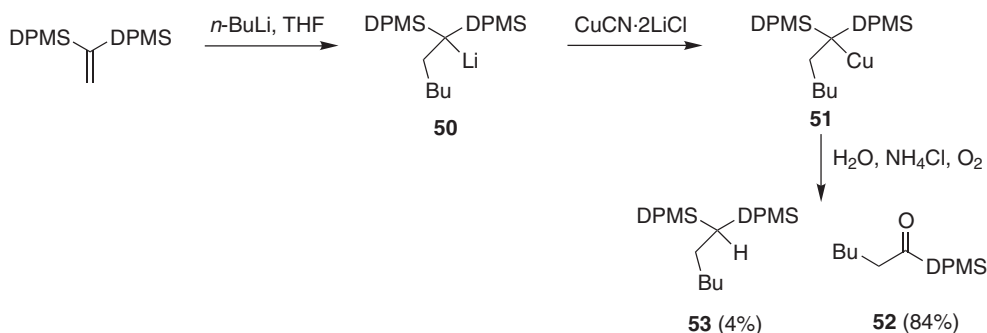
5.09.1.1.6 *gem*-bis(Trialkylsilyl) compounds

Dibromobis(trimethylsilyl)methane is readily available in multigram quantities by silylation of dibromomethane, using lithium diisopropylamide as base. This reacts with aldehydes in the presence of chromium(II) chloride to give homologated bis(trimethylsilyl) alkenes **46** in high yield (Scheme 14) <1997JCS(P1)2279>. The conditions are extremely mild and the reaction also proceeds with enolisable aldehydes, although the yield for phenylacetaldehyde was poor. It was necessary to use DMF as solvent, with only starting dibromide being recovered when THF was employed. The intermediates in this reaction are believed to be geminal chromium derivatives. This methodology was compatible with ester, nitrile, and alkyne functionalities. Bis(trimethylsilyl) alkenes **46** were converted into the corresponding oxiranes **47** on treatment with MCPBA at room temperature in excellent yields. On treatment with sulfuric acid in methanol at room temperature, bis(disilyl) oxiranes **47** were converted into the acyltrimethylsilanes **48** in high yield. On monitoring the reaction by NMR spectroscopy, enol ether **49** could be detected suggesting that the first step in the process was an acid-catalyzed regioselective ring opening of the epoxide followed by the loss of trimethylsilanol. Subsequent hydrolysis of the enol ether gave the acyltrimethylsilane **48**. One drawback of the procedure is that it is not particularly atom efficient with respect to silicon, and 8 equiv. of expensive chromium(II) chloride is required per mole of silyl alkene **46** produced.



Scheme 14

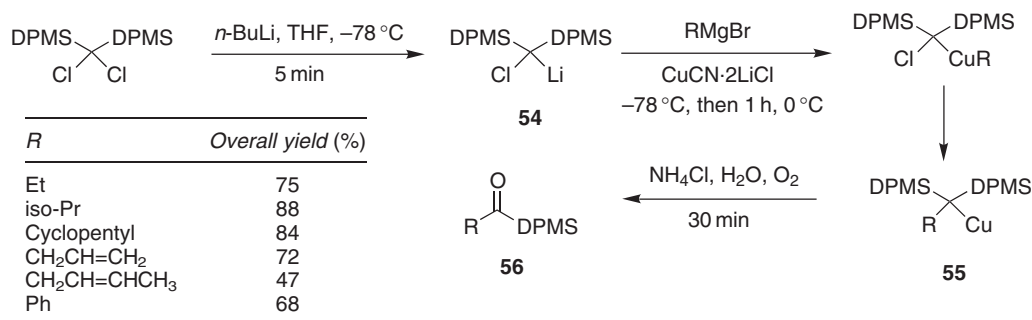
n-Butyllithium reacts with 1,1-di(methyldiphenylsilyl)ethene to give 1,1-bis(methyldiphenylsilyl)hexyllithium **50** which transmetalates on treatment with copper(I) salts to give organocuprate **51** (Scheme 15). Amazingly, this organocuprate is water stable, and on aqueous work-up it is rapidly oxidized by atmospheric oxygen to give the acylmethyldiphenylsilane **52**. Small amounts of protonated species **53** are always formed as a by-product but this was minimized when a copper(I) cyanide–lithium chloride complex was employed as the copper source <2001JA11109>.



Scheme 15

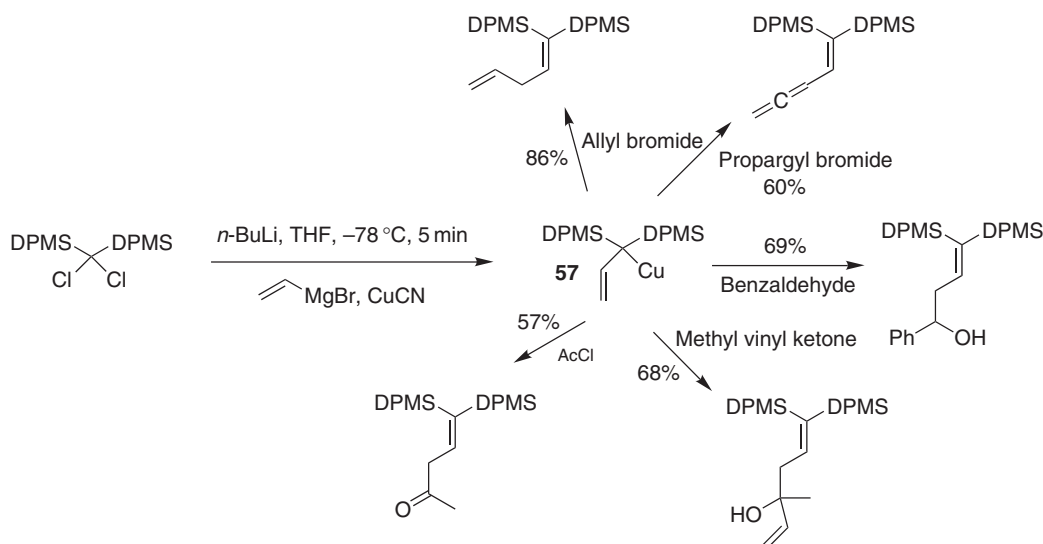
The ease with which the *gem*-disilylalkyl cuprate furnishes acylmethyldiphenylsilanes has prompted the search for new methods for making these versatile organometallic species, avoiding the use of bis(methyldiphenylsilyl)ethene, and the outcome of those studies is truly spectacular

(Scheme 16) <2001JA11109>. Treatment of dichlorobis(methyldiphenylsilyl)methane with *n*-butyllithium gave chlorobis(methyldiphenylsilyl)methylolithium **54** which reacted with an organolithium or Grignard reagent in the presence of copper(I) cyanide–lithium chloride complex to give the desired organocuprate intermediate **55**. The mechanism is believed to involve the formation of an α -silylorganolithium species followed by lithium–copper transmetalation. Subsequent internal displacement of chloride by the alkyl group on copper gives the desired organometallic species, which was oxidized to the acylmethyldiphenylsilanes **56** on work-up. This methodology is truly versatile as judged by the diversity of the groups that can be easily introduced. With Grignard reagents derived from secondary alkyl halides, the yields remained high. In the case where allylmagnesium bromide was employed the yield was excellent, but there was a tendency for the double bond to move into conjugation with the carbonyl group on purification. In the case of a 2-butenyl Grignard reagent, the reaction proceeded without allylic rearrangement although the yield was only moderate.



Scheme 16

The methodology can be extended to vinylmagnesium bromide which gave the allylcopper intermediate **57** (Scheme 17) <2002TL2399>. This species is an ambident nucleophile, which reacted with a very wide range of electrophiles at the carbon γ to silicon giving a range of highly functionalized bis(methyldiphenylsilyl) alkenes in moderate-to-excellent yield. The regioselectivity is probably explained by the bulk of the silicon substituents, and reactivity at the α -position was observed only when acid was used to quench the reaction. When propargyl bromide was used as electrophile, the substitution proceeded with allylic rearrangement to give the corresponding allene. With α,β -unsaturated aldehydes and ketones, exclusive 1,2-addition was observed. This chemistry is a very interesting development as it was previously noted that bis(silyl) alkenes are key intermediates in the synthesis of acyl silanes.

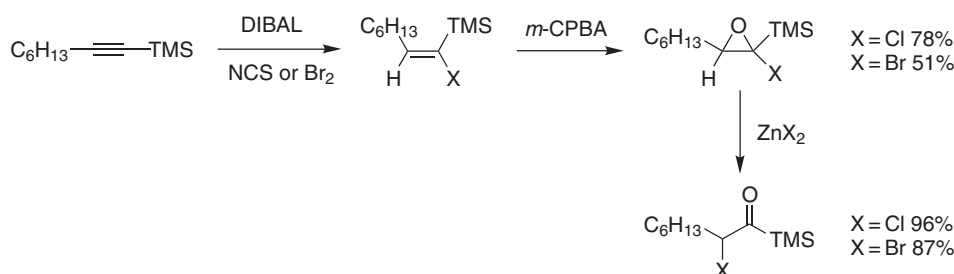


Scheme 17

5.09.1.2 Functionalized Acyl Silanes

5.09.1.2.1 α -Haloacyl silanes

α -Halogenation of acyl silanes and halogenation of silyl enol ethers derived from acyl silanes have previously been reported in chapter 5.09.1.3.1 in COFGT (1995) as robust methods for making α -haloacyl silanes. However, in general, there are few good methods for generating α -haloacyl silanes and new procedures are welcome. One attractive new method is Lewis acid-catalyzed rearrangement of 2-halo-2-trimethylsilyl oxiranes in which the halogen undergoes a 1,2-shift to an electron-deficient carbon (Scheme 18) <1995TL5353>. The starting materials are readily available from terminal alkynes. Both α -bromo- and α -chloroacyl silanes can be prepared in high yield using this methodology.



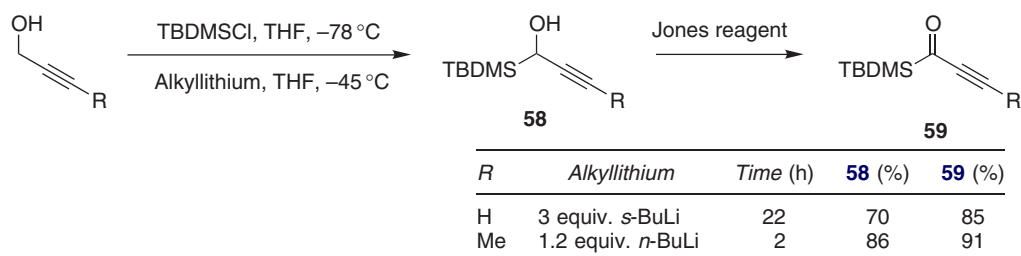
Scheme 18

5.09.1.2.2 α,β -Unsaturated acyl silanes

From the various functionalized acyl silanes discussed in COFGT (1995), the α,β -unsaturated family has seen significant development and application. Previous good synthetic methods for preparing α,β -unsaturated acyl silanes covered in chapter 5.09.1.3.3. of COFGT (1995) include the hydroboration–oxidation of silyl-substituted enynes, metallation–silylation and hydrolysis of unsaturated enol ethers, and aldol reactions of acyl silanes. Many of the methods described in the previous section can be directly applied to the synthesis of α,β -unsaturated acyl silanes. However, the methodology described in this section is restricted to methods that rely on the unsaturation to effect the desired chemistry, or methods which introduce the unsaturation. Methodology based on the reverse Brook rearrangement can also be employed to prepare α -silyl alkanols. In order to make the thermodynamics of the reverse Brook rearrangement favorable, an excess of base is required and the driving force is transfer of negative charge from carbon to oxygen. Typically the substrates which undergo reverse Brook rearrangement are silyl ethers in which it is relatively easy to generate an α -alkoxyorganolithium derivative.

(i) Acetylenic acyl silanes from reverse Brook rearrangement then oxidation

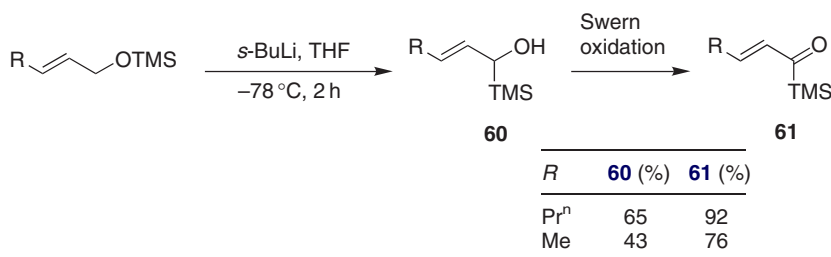
This is normally achieved by having additional activation such as allyl, propargyl, or benzyl groups. The reverse Brook rearrangement was used as a key step in the preparation of alkynoyl silane **59** (Scheme 19) <2000TL6589>. Conditions were reported for the one-pot *O*-silylation reverse Brook rearrangement. Surprisingly, the one-pot procedure gave a better yield of **58** than when preformed silyl ether was subjected to the reaction conditions (which gave **58** in only 16% yield). Terminal alkynes participate in this chemistry though an extra equivalent of base and very much longer reaction times are required. The α -silyl alcohols **58** were oxidized to the alkynoyldimethyl(*t*-butyl)silanes **59** in high yield using Jones oxidation. Similar chemistry can be used to prepare alkynoyltrimethylsilanes. However, in this case a Swern oxidation is required to convert the α -silyl alcohol to the ketone in high yield.



Scheme 19

(ii) α,β -Unsaturated acyl silanes from reverse Brook rearrangement then oxidation

Trialkylsilyl ethers derived from allylic alcohols are sufficiently acidic to be deprotonated by alkylolithiums. The corresponding α -alkoxyorganolithium derivatives undergo reverse Brook rearrangement to give α -silylallylic alcohols **60** in acceptable yield [<2002T9613>](#). These substrates are oxidized to the alkenoyltrimethylsilanes in excellent yield using Swern oxidation (Scheme 20).

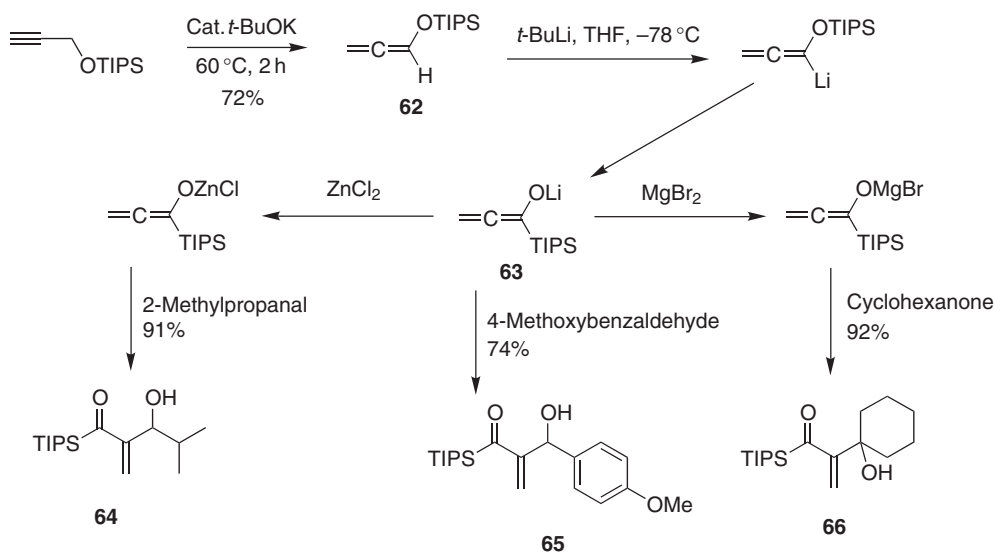


Scheme 20

Reverse Brook rearrangement on silyl ethers derived from methallyl alcohol has recently been reported but unfortunately no yields were given for the transformation [<2001OL453>](#).

(iii) α,β -Unsaturated acyl silanes via reverse Brook rearrangement of allenes

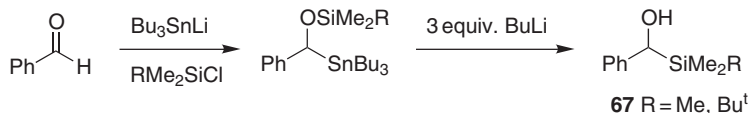
It is well known that in enol ethers the proton geminal to oxygen is fairly acidic and readily lithiated. Allene silyl enol ethers **62** were readily prepared by the base-catalyzed isomerization of the corresponding silyl propargyl ethers for which the silyl groups were TBDMS, TIPS, and TBDPS (Scheme 21). The procedure failed for the less robust TES and DMPS groups. The organolithium derivative derived from these allenes underwent a reverse Brook rearrangement to give the unusual cumulene enolate **63** which was trapped with aldehydes and ketones to give the highly functionalized alkenoylsilane aldol products **64–66** [<1998TL5937, 1999JOC7547>](#). Attempting to quench the organolithium derivative with deuteriated water showed no deuterium incorporation into the recovered allene, suggesting that deprotonation was slow relative to the reverse Brook rearrangement. When the aldehyde was nonenolizable, excellent yields of product were directly obtained from the lithium enolate **63**. In order to get efficient addition reactions with enolizable aldehydes, it was necessary to convert the lithium enolate into the zinc enolate, which was readily accomplished by addition of zinc chloride prior to addition of the aldehyde. For addition to ketones, the most effective additive was magnesium bromide. Direct formation of the magnesium enolate by reaction of allene with isopropylmagnesium chloride failed. Similar chemistry can be carried out on the TBDPS and TBDMS silyl enol ethers with comparable yields of product, although the correct choice of organolithium reagent is crucial and it seems to vary with the nature of the silyl group.



Scheme 21

(iv) Phenylacetylsilanes from reverse Brook rearrangement then oxidation

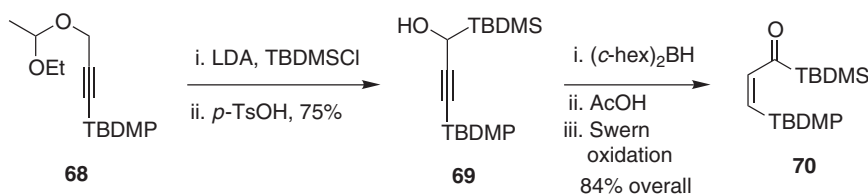
For the reverse Brook rearrangement to be a general method for the preparation of α -silyl alcohols, it is necessary to be able to generate α -alkoxyorganolithiums with no additional activating groups. Linderman and Ghannam [<1990JA2392>](#) demonstrated first that α -alkoxyorganolithiums generated from organotin reagents and *n*-butyllithium readily undergo reverse Brook rearrangement. The major advantage of this approach is that the required starting materials are easy to prepare. Readily available tributylstannyl lithium adds to aldehydes to give the addition products in high yields, and these can be readily *O*-silylated. This methodology has recently been used to prepare TMS, TBDPS, and TBDMS silyl alcohols **67** from benzaldehyde, although no yields or conditions were given (Scheme [22](#)) [<2001OL1261>](#). As previously noted in [Section 5.09.1.1.2](#), α -silyl alcohols are readily oxidized to acyl silanes.



Scheme 22

(v) Acetylenic acyl silanes from silylation of propargylic ethers then oxidation

Protected α -silyl propargylic alcohols can be made simply by generating the propargylic lithium derivative and trapping with an electrophilic silylating agent (Scheme [23](#)) [<2002JOC1786>](#). The organolithium derived from propargyl ether **68** was silylated and gave, after, removal of the

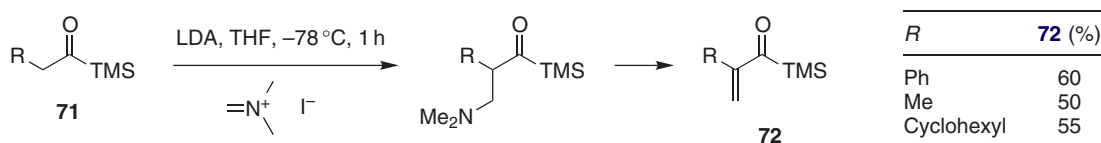


Scheme 23

acetal protecting group, the α -silyl alcohol **69**. Selective *cis*-reduction of the alkyne by hydroboration–protonolysis followed by Swern oxidation gave the highly functionalized alkenoyl silane **70**. Reverse Brook methodology has a slight advantage over this procedure in that the *O*-protecting group is incorporated into the substrate making it more atom efficient.

(vi) α,β -Unsaturated acyl silanes from Mannich reactions on acyl silanes

Alkanoyl silanes bearing hydrogens α to the carbonyl group behave in many respects as ketones. Lithium enolates generated from the acyl silanes **71** react at low temperatures with Eschenmoser's salt to give β -amino ketones which spontaneously eliminate dimethylamine on work-up to provide alkenoyl silanes **72** in moderate-to-good yields (Scheme 24) <1995S261>.

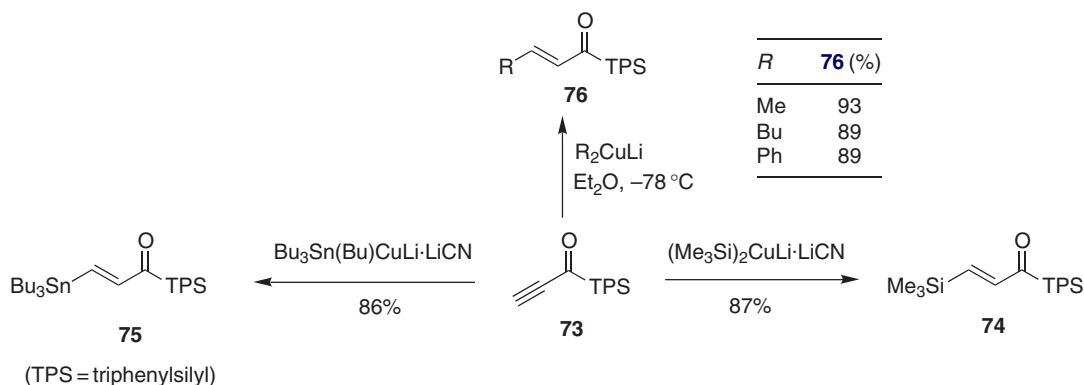


Scheme 24

In general, more complex acyl silanes can be made in good yield by Mukaiyama-type aldol reaction of acyl silane silyl enol ethers with acetals <2003T8203>.

(vii) α,β -Unsaturated acyl silanes via 1,4-addition

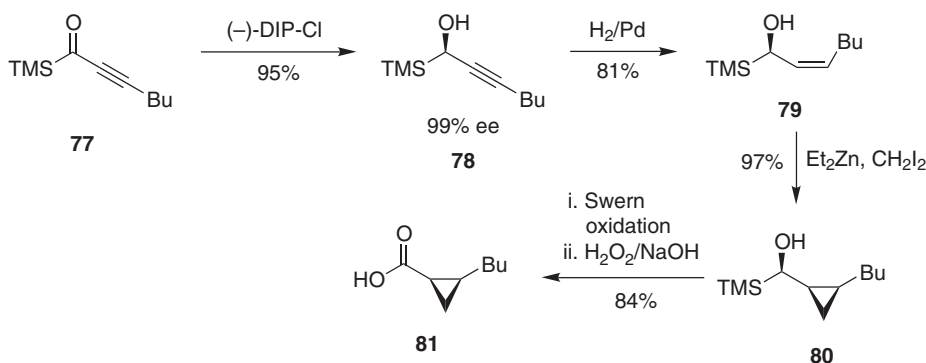
1,4-Addition of organometallic reagents to acetylenic acyl silanes was reported in chapter 5.09.1.3.4 in COFGT (1995) as a versatile method for preparing α,β -unsaturated acyl silanes. Full experimental conditions for these procedures are now available and the conditions have been optimized. Alkynoyltriphenylsilane **73** reacts with silyl and stannyl cuprates to give β -functionalized propenoyltriphenylsilanes **74** and **75**, respectively (Scheme 25) <2001T6267>. These substrates are versatile intermediates for further carbon–carbon bond-forming reactions giving rise to highly functionalized derivatives. In particular, the β -stannylpropenoylsilanes participate in Stille coupling reactions with vinyl iodides to give dienoylsilanes in excellent yields. Addition of alkyl cuprates to alkynoyltriphenylsilane **73** results in high yields of 3-alkylpropenoyltriphenylsilanes **76**. These compounds are very versatile intermediates and can be desilylated using TBAF to give α,β -unsaturated aldehydes or can undergo Wittig reaction followed by desilylation to give stereochemically pure 1,3-(*E*),(*E*)-dienes.



Scheme 25

5.09.1.2.3 Cyclopropylacysilanes

Methods for forming cyclopropylacysilanes in chapter 5.09.1.3.4 of COFGT (1995) included carbene addition to α -silylallylic alcohols followed by oxidation, reaction of enolates derived from α -haloacyl silanes with α,β -unsaturated carbonyl compounds, and reaction of sulfur ylides derived from α -haloacyl silanes with acrolein. Optically active α -silyl alcohols are masked chiral aldehydes or carboxylic acids. This chirality can be used to induce additional chirality into the substrate. The chiral α -silyl alcohol can then be converted back into acyl silane and the silicon efficiently removed. Hence, asymmetric reduction of acyl silane **77** using (–)-*B*-chlorodiisopinocampheylborane gave the α -trimethylsilyl alcohol **78** in both high yield and ee (Scheme 26) <1998TL4311>. Reduction of the alkyne gave the *cis*-alkene **79**. α -Silylallylic alcohols are interesting substrates in that the hydroxyl group can direct face-selective reactions onto the alkene. Hence, substrate **79** underwent face-selective cyclopropanation to give the depicted isomer **80** as the sole reaction product. Swern oxidation regenerated the acyl silane which was oxidized to the optically pure carboxylic acid **81** in good yield over the two steps.



Scheme 26

5.09.1.3 Chemistry of Acyl Silanes

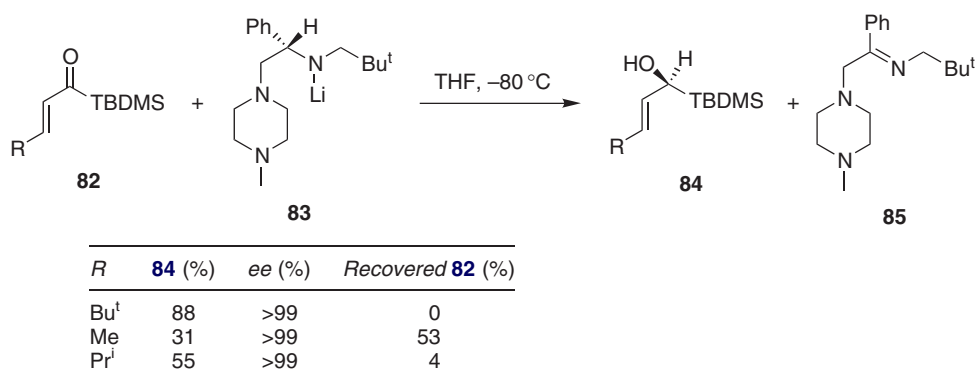
In a departure to the format of chapter 5.09 in COFGT (1995), a short section on the chemistry of acyl silanes is included. By far the most impressive advance in this chemistry has been the development of new annulation procedures.

5.09.1.3.1 Asymmetric reduction of acyl silanes

Alkenoyl(*t*-butyldimethyl)silanes **82** are reduced by LDA at low temperature to give α -silyl alcohols **84** (Scheme 27) <1999OL237>. The mechanism is believed to involve a hydride transfer in a Meerwein–Ponndorf–Verley-type reduction, with LDA being oxidized to the corresponding imine. This chemistry can be extended to chiral lithium amide bases **83** to give optically pure α -silyl alcohols. After extensive screening, it was found that reduction of **82** proceeded at low temperature to give **84** in good yield and ee. A major drawback with this chemistry is that allylic protons can be removed with base, competing with the reduction. On aqueous work-up starting material was recovered and this accounts for the moderate yield for reduction when R = methyl. However, in all cases investigated, the ee values were greater than 99%.

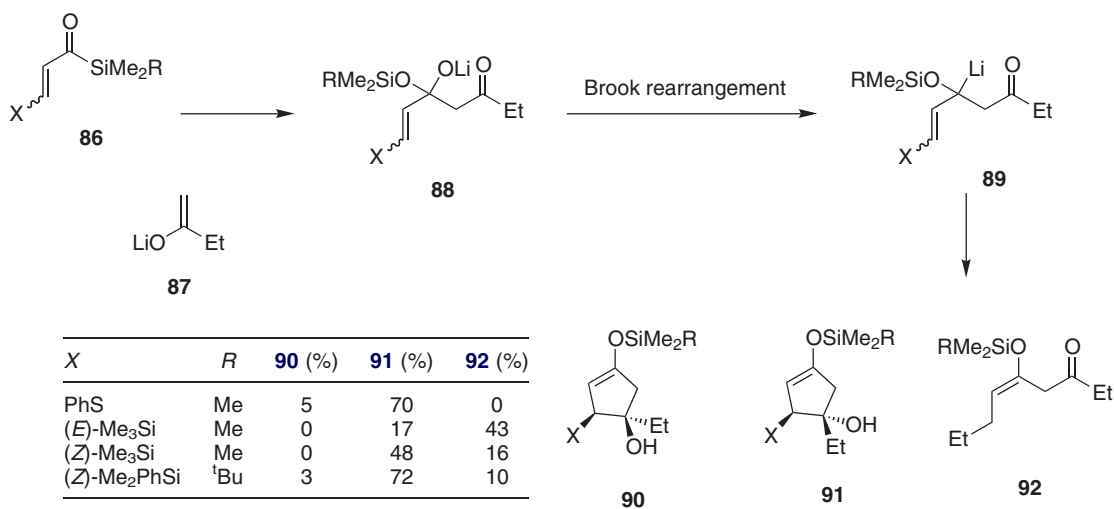
5.09.1.3.2 Annulation reactions of alkenoyl silanes

The potential of incorporating Brook rearrangement reactions into tandem processes has been recognized and the subject has recently been reviewed <2001T2065>. Of particular note is the emergence of new efficient annulation procedures based on this strategy. Annulation of β -silyl- or β -thiophenyl-substituted alkenoyl silanes **86** with lithium enolates **87** derived from ketones has



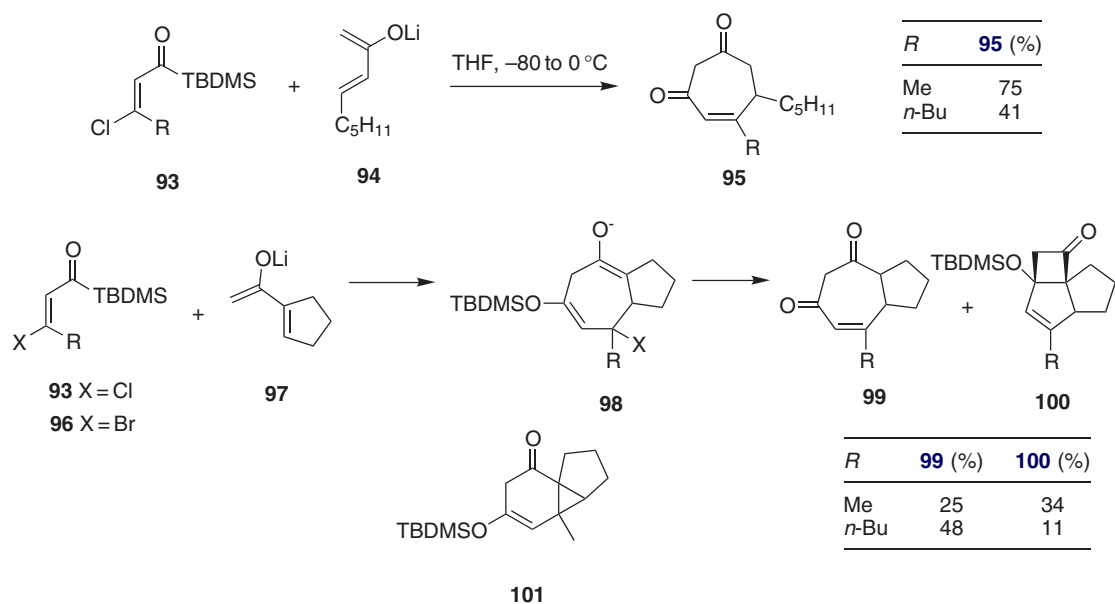
Scheme 27

emerged as a powerful procedure for the formation of five-membered rings (Scheme 28) <2002JOC1786>. The initial stages of the mechanism almost certainly proceed by a nucleophilic addition of the enolate to the acyl silane giving rise to alkoxide **88**, which undergoes a Brook rearrangement to give a resonance stabilized allyl anion **89**. The latter stages are less clear-cut mechanistically, but the diastereoisomeric cyclic products **90** and **91** can be viewed as arising from allyl anion addition to the ketone. However, it should be noted that the actual sequence may be much more subtle, possibly involving cyclopropane intermediates. For the chemistry to proceed efficiently, the substituent X must be capable of stabilizing negative charge, hence the choice of thiophenyl and trialkylsilyl groups. When X was thiophenyl, the product ratio was independent of the stereochemistry of the acyl silane **86**, and mixtures of **90** and **91** resulted with the latter predominating. In contrast, the stereochemistry of acyl silane **86** with X = trialkylsilyl was important, with the (Z)-isomer undergoing cyclization while the (E)-isomer resulted in predominant formation of acyclic product **92**. Employing (Z)- β -dimethylphenylsilylacylsilanes with a more bulky acylsilane resulted in predominant formation of the diastereoisomers **91** in which the silicon and tertiary alcohol were *trans*.



Scheme 28

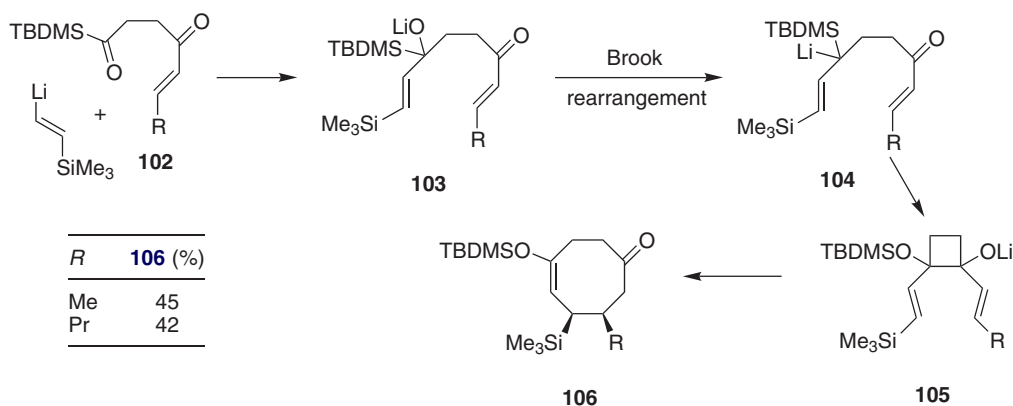
This chemistry has been developed further using lithium enolates derived from α,β -unsaturated ketones **94** reacting with β -halo- α,β -unsaturated acyl silanes **93** to give seven-membered ring products **95** (Scheme 29) <1999OL677>. Again, the first two steps in the pathway are clear-cut, i.e., addition of the lithium enolate to the acyl silane followed by Brook rearrangement to give an *O*-silylated allyl anion. The product can be “visualized” as arising from an intramolecular 1,4-addition of the allyl anion to the ketone followed by elimination of chloride, although again it should be noted that the actual sequence of events may be more complex than this simplistic view.



Scheme 29

When the enolate **97**, derived from acetylcyclopentene, was reacted with **93**, the reaction took a different course and substantial amounts of tricyclo[5.3.0.0]decenone derivatives **100** were formed as well as the expected product **99**. The formation of **100** can be rationalized as an intramolecular $\text{S}_{\text{N}}2'$ -substitution of the allylic chloride by the enolate **98**. When a low-temperature quench experiment was carried out, an additional tricyclic compound **101** was isolated. This could have arisen by an intramolecular $\text{S}_{\text{N}}2$ reaction of enolate **98** with the allylic chloride. When quenching was carried out at higher temperatures, the amount of **101** increased at the expense of **99**, suggesting that **99** may be derived from cyclopropane **101**. When the substituent at the β -carbon of **93** was changed from chloride to bromide, i.e., **96**, then the tricyclic product **100** became the sole reaction product. This chemistry allows extremely rapid entry to this complex carbocyclic framework. However, when the lithium enolate derived from acetylcyclohexene was employed, a mixture of annulated and tricyclic products was obtained in the ratio 8:5, demonstrating how finely balanced is the system. Detailed, checked experimental procedures for the [4 + 3]-annulations have been published [\[1999OS199\]](#). The seven-membered ring annulation chemistry was extended to enolates derived from cycloheptenone to give rapid excess to bicyclo[3.3.2]decenones [\[2002OL1031\]](#).

Eight-membered rings are difficult to form by direct cyclization. A tandem process involving additions of β -trimethylsilylvinyllithium to highly functionalized acyl silanes **102** has been developed as a new route to eight-membered ring compounds **106** (Scheme 30) [\[2003OL3705\]](#).

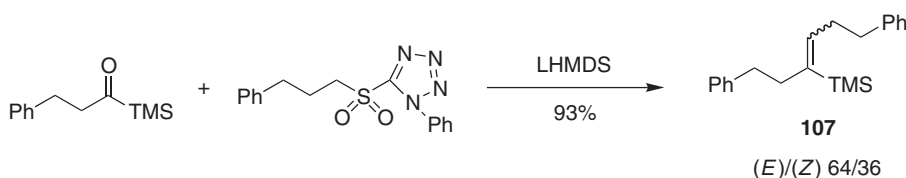


Scheme 30

The mechanism is believed to involve chemoselective addition of β -trimethylsilylvinyl lithium to the acyl silane **102** to give **103** followed by a Brook rearrangement to produce allyllithium intermediate **104**. Cyclization onto the ketone carbonyl group to give cyclobutane **105**, followed by an anion-accelerated Cope rearrangement, will give **106**.

5.09.1.3.3 Acyl silanes as precursors to alkenes and alkynes

All reactions of nucleophilic reagents with acyl silanes are complicated by the fact that the initially formed intermediate, with negative charge on oxygen, can undergo a Brook rearrangement. Therefore, acyl silanes are potential precursors of either vinyl silanes or silyl enol ethers in Julia olefinations. Normally, in the Julia reaction with phenyl sulfones, the Brook rearrangement is dominant and silyl enol ethers are produced in good yield. This chemistry has recently been employed in an elegant synthesis of serratenediol <2001OL3215>. However, when 1-phenyl-1*H*-tetrazol-5-yl sulfones are employed, the so-called modified Julia reaction was observed and vinyl silane **107** was produced in high yield with moderate (*E*)-selectivity (Scheme 31) <2003OL2789>. The origin of the chemoselectivity is that the heterocyclic portion of the sulfone transfers to oxygen faster than the silyl group.

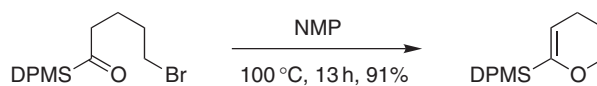


Scheme 31

Butanoyldimethylphenylsilane was converted into 1-(dimethylphenylsilyl)butyne in 85% yield when treated with triflic anhydride and pyridine <1998JCS(P1)1237>.

5.09.1.3.4 Oxygen heterocycles from acyl silanes

Appropriately substituted ω -haloacyl silanes undergo cyclization to give the five- and six-membered ring α -silyl enol ethers when heated in polar solvents (Scheme 32) <1999T14587>. The corresponding aldehydes and ketones do not participate in this chemistry; the difference in reactivity was attributed to the enhanced nucleophilicity of the carbonyl oxygen of acyl silanes. The use of dipolar aprotic solvents such as *N*-methylpyrrolidinone (NMP) or *N,N*-dimethylformamide was crucial in obtaining high yields. The products were robust enough to survive the hydrogen halide by-product, but reaction times could be halved by the addition of triethylamine.



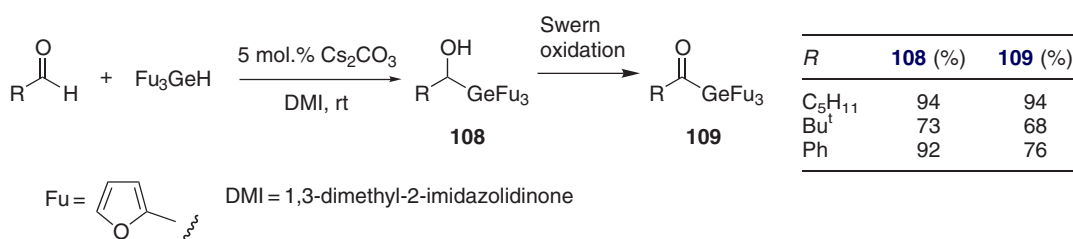
Scheme 32

5.09.2 ACYLGERMANIUM DERIVATIVES, $R^1\text{COGeR}_3^2$

Acylgermanes have been much less widely synthesized and studied than their acyl silane counterparts. The methods reported for preparing acylgermanes in chapter 5.09.2 of COFGT (1995) were very similar to those for making acyl silanes and that trend has continued. Addition of trialkylgermyl organometallic species to carbonyl compounds is the most common method employed. Only one conceptually new method for making acylgermanes was found in the review period.

5.09.2.1 Oxidation of α -Germyl Alcohols

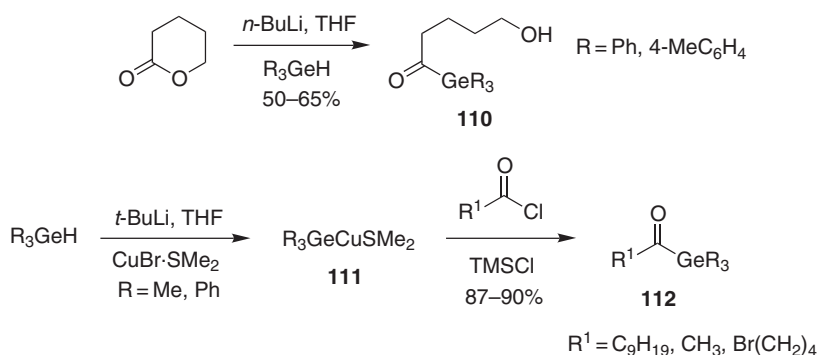
It was reported in chapter 5.09.2.1 of COFGT (1995) that trialkylgermyllithiums add to aldehydes and the corresponding α -germyl alcohols can be oxidized to the acylgermanes with either Swern oxidation or with diisopropyl azodicarboxylate. Recently, it was discovered that tris(2-furyl)germane adds to aldehydes using catalytic quantities of the relatively weak bases potassium *t*-butoxide or caesium carbonate to give tris(2-furyl)germyl alkanols **108** in high yields (Scheme 33) <2001T9827>. This result is unusual in that the bases employed were previously deemed insufficiently strong to generate the tris(2-furyl)germyl anion from tris(2-furyl)germane, and the initially formed α -germyl alkoxide was not deemed sufficiently basic to extract hydrogen from tris(2-furyl)germane to complete the catalytic cycle. A wide range of solvents could be employed, including alcohols, although the preferred solvent was 1,3-dimethyl-2-imidazolidinone (DMI). The reactions could be run at room temperature or slightly below and were extremely rapid (complete in minutes). The chemistry was chemoselective for aldehydes in the presence of ketones, esters, and nitriles. Swern oxidation gave the corresponding acylgermanes **109** in good yields, whereas the Dess–Martin periodinane led to complex mixtures from which the acylgermanes could be isolated in only low yield.



Scheme 33

5.09.2.2 Coupling of Germyl Metallic Species and Carboxylic Acid Derivatives

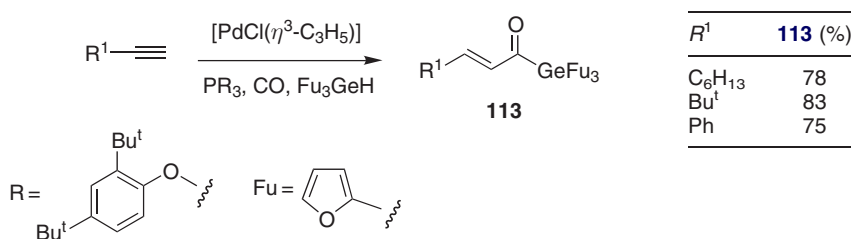
It was previously reported in chapter 5.09.2.2 of COFGT (1995) that lithiated organogermanes add to esters, lactones, and tertiary amides to directly give acylgermanes. This chemistry continues to find application for the synthesis of acyl silanes. Hence, addition of lithiated organogermanes to δ -valerolactone was used to prepare functionalized acylgermanes **110** (Scheme 34) <1997JA4797>. Trimethylgermyllithium was generated in essentially quantitative yield by reaction of trimethylgermanium hydride with *t*-butyllithium. Transmetalation with copper(I) bromide–dimethyl sulfide complex gave a copper(I) reagent **111** which reacted with acid chlorides at low temperature to give acyltrimethylgermanes **112** in excellent yield <1995OM5011>. In order to achieve a high yield of **112**, it was necessary to add trimethylsilyl chloride to the reaction mixture. No explanation was offered for the role of this additive, but yields were poor without it. This chemistry has been extended for preparing acyltriphenylgermanes from functionalized acid chlorides, and again the yields are excellent <1998JOC4711>. The germylcopper reagent was highly chemoselective for the acid chloride and tolerant to alkyl bromide, chloride, and phenyl selenide functionality.



Scheme 34

5.09.2.3 Hydrogermylcarbonylation of Alkynes

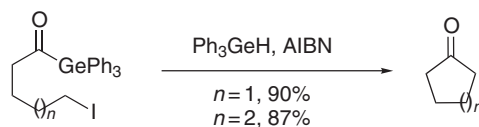
α,β -Unsaturated acyltrifurylgermanes **113** can be prepared in one step by reaction of terminal alkynes with carbon monoxide and tris(2-furyl)germane in the presence of a palladium catalyst and phosphite ligand (Scheme 35) <2002JA4220>. The reaction proceeds at room temperature under 1 atm of carbon monoxide with a low catalyst loading of 2.5 mol.%, making this procedure synthetically very useful. One example of a substrate bearing a free tertiary alcohol was presented, although with a secondary alcohol protection was required. The reaction was completely regio-selective, with the carbonyl group attaching to the terminal carbon of the alkyne, and was *trans*-stereoselective. The acyltris(2-furyl)germanes reacted with diethylamine to afford the tertiary amides in high yield and regenerating the valuable tris(2-furyl)germane. If secondary amine was added to the reaction with the alkyne, it then became catalytic in tris(2-furyl)germane.



Scheme 35

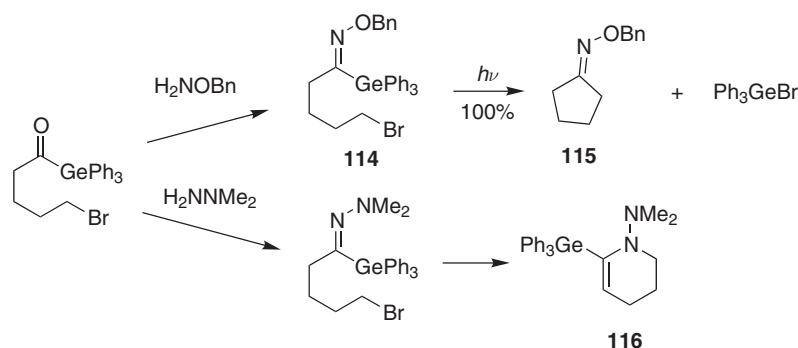
5.09.2.4 Chemistry of Acyl Germanes

Acyltriarylgermanes have emerged as the best radical acceptors yet identified in intramolecular 5-*exo*- and 6-*exo-trig* cyclization reactions, giving cyclic products in excellent yield <1997JA4797, 1995JA6603, 1995JCS(P2)3049>. Alkyl radical addition to an acyltriarylgermane generates an oxygen-centered radical that fragments to form a ketone and produce a triphenylgermyl radical, which re-enters the radical chain reaction. The overall transformation only requires an initiator and a catalytic amount of triarylgermanium hydride. Acyltriarylgermanes are approximately one order of magnitude more reactive than alkenes and 10^4 – 10^5 times more reactive than a methyl ketone in radical cyclization reactions. The only disadvantage seems to be susceptibility to steric hindrance, with tertiary radicals failing to cyclize. The reactivity can be tuned by appropriate choice of substituent on germanium, with phenyl compounds reacting approximately two orders of magnitude faster than the ethyl analogs. Acylgermanes behave quite differently to acylsilanes in radical cyclization reactions, in that the intermediate oxygen radical is not prone to undergo Brook rearrangement, ensuring that the products are ketones and not silyl-protected secondary alcohols (Scheme 36).



Scheme 36

Acyltriphenylgermanes are robust-enough substrates to form the corresponding *O*-benzyl oximes and *N,N*-dimethylhydrazones in high yield when treated with the corresponding amines and hydrazines (Scheme 37) <1998JOC4711>. The products are relatively stable and can be handled with no special precautions. However, the *N,N*-dimethylhydrazone required for radical cyclization could not be isolated as it underwent a subsequent ionic cyclization to **116**. Irradiation of a benzene solution of *O*-benzyl oxime **114** at 25 °C results in cyclization to **115** in quantitative yield.



Scheme 37

5.09.3 ACYLBORON DERIVATIVES

It was reported in chapter 5.09.3 of COFGT (1995) that no verified examples of acylboron derivatives had ever been isolated and that theoretical calculations suggested that acylboranes were highly reactive species and prone to rearrangement. No preparations of acylboranes have been identified in the review period.

REFERENCES

- 1975JOM(93)51 J. P. Picard, A. Ekouya, J. Dunogues, N. Duffaut, R. Calas, *J. Organomet. Chem.* **1975**, 93, 51–70.
 1980JOM(195)47 L. Rosch, G. Altnau, *J. Organomet. Chem.* **1980**, 195, 47–53.
 1987JOC5583 M. Suzuki, H. Koyano, R. Noyori, *J. Org. Chem.* **1987**, 52, 5583–5588.
 1990JA2392 R. J. Linderman, A. Ghannam, *J. Am. Chem. Soc.* **1990**, 112, 2392–2398.
 1992JOC386 A. G. M. Barrett, J. M. Hill, E. M. Wallace, *J. Org. Chem.* **1992**, 57, 386–389.
 1994JCS(P1)257 I. Fleming, U. Ghosh, *J. Chem. Soc., Perkin Trans. 1* **1994**, 257–262.
 1994JOC332 S. D. Burke, A. D. Piscopio, M. E. Kort, M. A. Matulenko, M. H. Parker, D. M. Armistead, K. Shankara, *J. Org. Chem.* **1994**, 59, 332–347.
 1994JOC3055 P. F. Cirillo, J. S. Panek, *J. Org. Chem.* **1994**, 59, 3055–3063.
 1994JOC4355 P. Raubo, J. Wicha, *J. Org. Chem.* **1994**, 59, 4355–4356.
 1994PAC1471 T. Hiyama, Y. Hatanaka, *Pure Appl. Chem.* **1994**, 66, 1471–1478.
 1994TL8999 B. H. Lipshutz, C. Lindsley, R. Susfalk, T. Gross, *Tetrahedron Lett.* **1994**, 35, 8999–9002.
 1995CL829 Y. Ishino, H. Maekawa, H. Takeuchi, K. Sukata, I. Nishiguchi, *Chem. Lett.* **1995**, 829–830.
 1995JA6603 D. P. Curran, J. Xu, E. Lazzarini, *J. Am. Chem. Soc.* **1995**, 117, 6603–6604.
 1995JCS(P2)3049 D. P. Curran, J. Xu, E. Lazzarini, *J. Chem. Soc., Perkin Trans. 2* **1995**, 3049–3059.
 1995OM5011 E. Piers, R. Lemieux, *Organometallics* **1995**, 14, 5011–5012.
 1995S92 B. F. Bonini, M. Comesfranchini, G. Mazzanti, U. Passamonti, A. Ricci, P. Zani, *Synthesis* **1995**, 92–96.
 1995S261 B. F. Bonini, M. Comesfranchini, A. Mazzanti, G. Mazzanti, A. Ricci, P. Zani, *Synthesis* **1995**, 261–264.
 1995TA577 P. Raubo, J. Wicha, *Tetrahedron Asymm.* **1995**, 6, 577–586.
 1995TL5353 Y. Horiuchi, M. Taniguchi, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1995**, 36, 5353–5356.
 1996JOC1794 T. H. Chuang, J. M. Fang, W. T. Jiaang, Y. M. Tsai, *J. Org. Chem.* **1996**, 61, 1794–1805.
 1996JOC4395 P. F. Hudrlik, M. E. Ahmed, R. R. Roberts, A. M. Hudrlik, *J. Org. Chem.* **1996**, 61, 4395–4399.
 1996JOC7242 B. F. Bonini, M. Comesfranchini, G. Mazzanti, A. Ricci, M. Sala, *J. Org. Chem.* **1996**, 61, 7242–7243.
 1996JOC7551 A. R. Katritzky, H. Lang, Z. Wang, Z. Lie, *J. Org. Chem.* **1996**, 61, 7551–7557.
 1996OM486 A. R. Katritzky, Z. Q. Wang, H. Y. Lang, *Organometallics* **1996**, 15, 486–490.
 1997G619 B. F. Bonini, M. C. Franchini, M. Fochi, G. Mazzanti, A. Ricci, *Gazz. Chim. Ital.* **1997**, 127, 619–628.
 1997JA4797 D. P. Curran, U. Diederichsen, M. Palovich, *J. Am. Chem. Soc.* **1997**, 119, 4797–4804.
 1997JCS(P1)2279 D. M. Hodgson, P. J. Comina, M. G. B. Drew, *J. Chem. Soc., Perkin Trans. 1* **1997**, 2279–2289.
 1997SL693 A. Mori, A. Fujita, K. Ikegashira, Y. Nishihara, T. Hiyama, *Synlett* **1997**, 693–694.
 1997TL6595 J. P. Bouillon, C. Portella, *Tetrahedron Lett.* **1997**, 38, 6595–6598.
 1998JCS(P1)1237 I. Fleming, J. M. Mwaniki, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1237–1247.
 1998JOC4711 U. Iserloh, D. P. Curran, *J. Org. Chem.* **1998**, 63, 4711–4716.
 1998JOM(567)181 B. F. Bonini, M. Comesfranchini, M. Fochi, G. Mazzanti, A. Ricci, *J. Organomet. Chem.* **1998**, 567, 181–189.
 1998TL4311 K. Sakaguchi, H. Mano, Y. Ohfune, *Tetrahedron Lett.* **1998**, 39, 4311–4312.
 1998TL5937 M. A. Tius, H. P. Hu, *Tetrahedron Lett.* **1998**, 39, 5937–5940.
 1999EJO437 B. F. Bonini, M. Comesfranchini, M. Fochi, J. Gawronski, G. Mazzanti, A. Ricci, G. Varchi, *Eur. J. Org. Chem.* **1999**, 437–445.
 1999EJO1571 J. P. Bouillon, C. Portella, *Eur. J. Org. Chem.* **1999**, 1571–1580.

- 1999JOC7547 I. A. Stergiades, M. A. Tius, *J. Org. Chem.* **1999**, *64*, 7547–7551.
1999OL237 K. Takeda, Y. Ohnishi, T. Koizumi, *Org. Lett.* **1999**, *1*, 237–239.
1999OL677 K. Takeda, Y. Ohtani, *Org. Lett.* **1999**, *1*, 677–679.
1999OS199 K. Takeda, A. Nakajima, M. Takeda, E. Yoshii, *Org. Synth.* **1999**, *76*, 199–213.
1999T14587 Y. M. Tsai, C. D. Cherng, H. C. Nieh, J. A. Sieh, *Tetrahedron* **1999**, *55*, 14587–14598.
1999TL3113 F. Geng, R. E. Maleczka, *Tetrahedron Lett.* **1999**, *40*, 3113–3114.
2000CEJ655 D. Sole, J. Bonjoch, S. Garcia-Rubio, E. Peidro, J. Bosch, *Chem. Eur. J.* **2000**, *6*, 655–665.
2000JOC2292 M. D. Paredes, R. Alonso, *J. Org. Chem.* **2000**, *65*, 2292–2304.
2000OL1903 K. Takeda, D. Nakane, M. Takeda, *Org. Lett.* **2000**, *2*, 1903–1905.
2000POL529 B. F. Bonini, M. Comesfranchini, M. Foichi, A. Mazzanti, G. Mazzanti, A. Ricci, G. Varchi, *Polyhedron* **2000**, *19*, 529–531.
2000TL6589 K. Sakaguchi, M. Fujita, H. Suzuki, M. Higashino, Y. Ohfune, *Tetrahedron Lett.* **2000**, *41*, 6589–6592.
2001JA11109 A. Inoue, J. Kondo, H. Shinokubo, K. Oshima, *J. Am. Chem. Soc.* **2001**, *123*, 11109–11110.
2001MI7 A. F. Patrocínio, P. J. S. Moran, *J. Braz. Chem. Soc.* **2001**, *12*, 7–31.
2001OL453 N. A. Powell, W. R. Roush, *Org. Lett.* **2001**, *3*, 453–456.
2001OL1261 P. Wipf, J. L. Methot, *Org. Lett.* **2001**, *3*, 1261–1264.
2001OL3215 J. Zhang, E. J. Corey, *Org. Lett.* **2001**, *3*, 3215–3216.
2001SC2457 A. F. Patrocínio, P. J. S. Moran, *Synth. Commun.* **2001**, *31*, 2457–2461.
2001T2065 W. H. Moser, *Tetrahedron* **2001**, *57*, 2065–2084.
2001T6267 A. Capperucci, A. Degl'Innocenti, P. Dondoli, T. Nocentini, G. Reginato, A. Ricci, *Tetrahedron* **2001**, *57*, 6267–6276.
2001T9827 T. Nakamura, H. Yorimitsu, H. Shinokubo, K. Oshima, *Tetrahedron* **2001**, *57*, 9827–9836.
2002JA4220 H. Kinoshita, H. Shinokubo, K. Oshima, *J. Am. Chem. Soc.* **2002**, *124*, 4220–4221.
2002JA11598 S. Ogoshi, S. Tomiyasu, M. Morita, H. Kurosawa, *J. Am. Chem. Soc.* **2002**, *124*, 11598–11599.
2002JOC1786 K. Takeda, K. Yamawaki, N. Hatakeyama, *J. Org. Chem.* **2002**, *67*, 1786–1794.
2002OL1031 K. Takeda, Y. Sawada, K. Sumi, *Org. Lett.* **2002**, *4*, 1031–1033.
2002TL2399 A. Inoue, J. Kondo, H. Shinokubo, K. Oshima, *Tetrahedron Lett.* **2002**, *43*, 2399–2402.
2002T9613 A. Kamimura, Y. Kaneko, A. Ohta, K. Matsuura, Y. Fujimoto, A. Kakehi, S. Kanemasa, *Tetrahedron* **2002**, *58*, 9613–9620.
2003OL3705 K. Takeda, H. Haraguchi, Y. Okamoto, *Org. Lett.* **2003**, *5*, 3705–3707.
2003OL2789 P. Jankowski, K. Plesniak, J. Wicha, *Org. Lett.* **2003**, *5*, 2789–2792.
2003T8203 M. Honda, N. Ohkura, S. Saisyo, M. Segi, T. Nakajima, *Tetrahedron* **2003**, *59*, 8203–8212.

Biographical sketch

Paul Stevenson was born in Londonderry, studied at Sheffield University, where he obtained a B.Sc. in 1980. He moved to Queens University, Belfast and in 1984 obtained a Ph.D. under the direction of Professor R. Grigg. He took up present post in 1984 and spent 4 months each at SERC NMR Centre at Warwick University and the MRC Biomedical NMR research laboratories at Mill Hill. His scientific interests include heterocyclic chemistry, alkaloid synthesis, and transition-metal-catalyzed cyclization reactions.

5.10

Acyl Metal Functions

G. J. TANOURY

Vertex Pharmaceuticals Inc., Cambridge, MA, USA

5.10.1	GENERAL INTRODUCTION	399
5.10.2	GROUP 1 DERIVATIVES	400
5.10.3	GROUP 2 DERIVATIVES	400
5.10.4	LANTHANIDE DERIVATIVES	400
5.10.5	TRANSITION METAL DERIVATIVES	400
5.10.5.1	Introduction	400
5.10.5.2	Acyltitanium Compounds	401
5.10.5.3	Acylzirconium Compounds	401
5.10.5.4	Acylhafnium Compounds	403
5.10.5.5	Acylvanadium Compounds	403
5.10.5.6	Acyltantalum Compounds	403
5.10.5.7	Acylchromium Compounds	403
5.10.5.8	Acylmolybdenum Compounds	404
5.10.5.9	Acyltungsten Compounds	405
5.10.5.10	Acylmanganese Compounds	405
5.10.5.11	Acylrhenium Compounds	407
5.10.5.12	Acyliron Compounds	408
5.10.5.13	Acylruthenium Compounds	412
5.10.5.14	Acylosmium Compounds	413
5.10.5.15	Acylcobalt Compounds	414
5.10.5.16	Acylrhodium Compounds	416
5.10.5.17	Acyliridium Compounds	419
5.10.5.18	Acylnickel Compounds	420
5.10.5.19	Acylpalladium Compounds	422
5.10.5.20	Acylplatinum Compounds	428
5.10.5.21	Acylzinc Compounds	429
5.10.5.22	Acylniobium Compounds	429
5.10.5.23	Acyltechnetium Compounds	429
5.10.5.24	Acylgold Compounds	429
5.10.6	GROUP 3 DERIVATIVES	430
5.10.6.1	Acylaluminum Compounds	430
5.10.7	GROUP 4 DERIVATIVES	430
5.10.7.1	Acyltin Compounds	430
5.10.8	ACTINIDE DERIVATIVES	431
5.10.8.1	Acylthorium Compounds	431
5.10.8.2	Acyluranium Compounds	431

5.10.1 GENERAL INTRODUCTION

Acyl metal chemistry has enjoyed tremendous growth and synthetic application since the publication of COFGT (1995) <[1995COFGT\(5\)435](#)>. Main group acyl metal chemistry has seen modest advances, with acylstannanes being the largest. Transition-metal acyl compounds, however, have

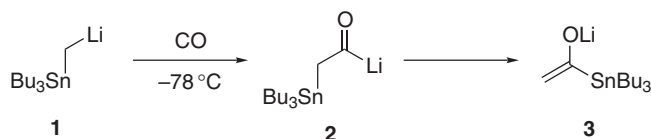
experienced remarkable development. Numerous compounds having a host of ligands, in a variety of oxidation states, and as neutral, cationic, and anionic complexes, have been isolated and characterized. Additionally, these complexes have been applied to organic synthesis.

The acyl metal compounds described herein relate to those compounds and complexes that have been prepared *in situ* and/or isolated and characterized. The literature covering acyl metal complexes generated as intermediates in catalytic reactions (hydroformylation and carboalkoxylation of alkenes and alkynes, for example) has not been covered.

5.10.2 GROUP 1 DERIVATIVES

In chapter 5.10.2 in <1995COFGT(5)435>, group 1 compounds focused on acyllithiums. The acyllithiums were generated by five methods: (i) addition of RLi to CO; (ii) deprotonation of the formyl group of aldehydes; (iii) Li—Te exchange of acytellurides; (iv) desilylation of acyl silanes; and (v) intramolecular trapping reactions. Since that publication, acyllithiums have received limited attention.

Iwamoto and co-workers <1999JOM(574)171> have reported an anionic 1,2-stannyl rearrangement of acyllithium **2**, generated by addition of CO to **1** (Scheme 1). Compound **3**, formed by rearrangement of **2**, was subsequently converted to the triethylsilyl ether in 88% yield from **1**.



Scheme 1

For the first time, the acyllithium compounds generated by the addition of alkyl- and aryllithium compounds to CO were characterized by low-temperature IR spectroscopy in liquid Xe <1995CB1051>.

5.10.3 GROUP 2 DERIVATIVES

In chapter 5.10.3 in <1995COFGT(5)435>, acylmagnesium compounds were the only group 2 derivatives discussed in any detail, being generated by reaction of RMgX with CO. No further advances have occurred in the area of group 2 derivatives since the publication of COFGT (1995).

5.10.4 LANTHANIDE DERIVATIVES

In chapter 5.10.4 in <1995COFGT(5)435>, acylsamarium compounds were the most important lanthanide derivatives discussed. The acylsamarium compounds were generated by the addition of CO to alkenylsamarium intermediates. No further advances have occurred in the area of lanthanide derivatives since the publication of COFGT (1995).

5.10.5 TRANSITION METAL DERIVATIVES

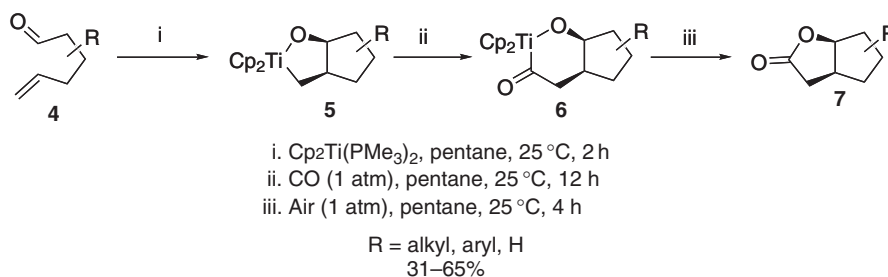
5.10.5.1 Introduction

Acyl transition metal derivatives continue to dominate the field of acyl metal chemistry. The major methods for generating the η^1 -acyl compounds are the insertion of CO into a metal carbon bond, or the insertion of a metal into anhydrides or acyl chlorides. Nearly 60% of the work in this field has focused on four metals in the order: $\text{Pd} > > > \text{Fe} > \text{Rh} > \text{Pt}$. Several other transition metals, however, have also enjoyed further development.

5.10.5.2 Acyltitanium Compounds

Chapter 5.10.5.2 in <1995COFGT(5)435> discussed the preparation of acyltitanium compounds from $\text{Cp}_2\text{Ti}(\text{CO})_2$ and acyl halides or alkyl iodides. Additional examples included the reactions of a titanacyclopentane and a titanacyclobutene with CO. Developments in this field since that publication are described below.

The synthesis of γ -butyrolactones from enals **4** was reported via formation of acyltitanium species **6** (Scheme 2) <1996JA1557>. Insertion of CO into titanacycle **5** gave **6**, which underwent subsequent reductive elimination to give γ -butyrolactone **7**.

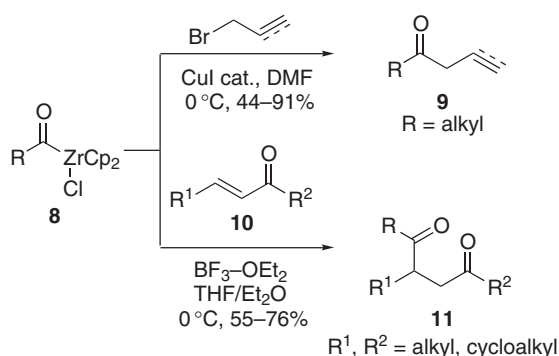


Scheme 2

5.10.5.3 Acylzirconium Compounds

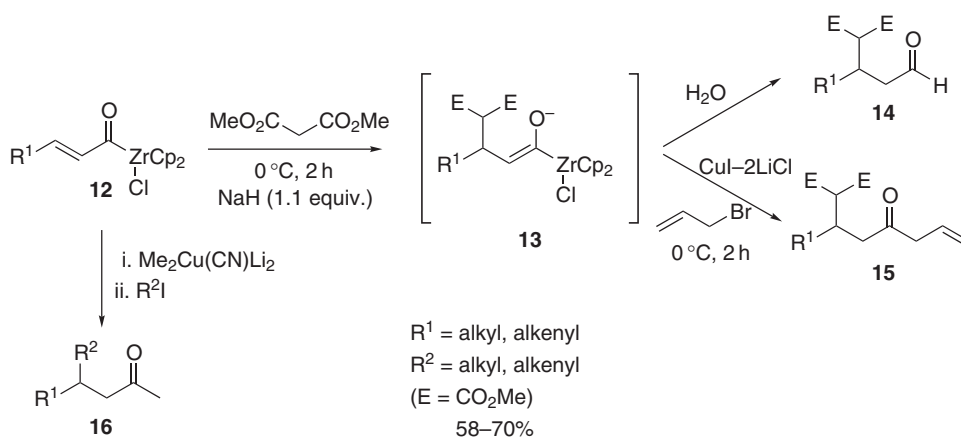
Chapter 5.10.5.3 in <1995COFGT(5)435> described the formation of acylzirconium compounds by the insertion of CO into Zr—C alkyl bonds. The acylzirconium species were shown to be precursors for aldehydes, esters, and carboxylic acids. Developments in this field since the publication of COFGT (1995) are described below.

Acylzirconium complexes are isolable materials and have been shown in many examples to be excellent acyl anion equivalents. The acylzirconium species **8** can be coupled to propargylic and allylic halides using Cu(I) catalysis to give the corresponding cross-coupled adduct **9**, or to enones **10** to give 1,4-diones **11** (Scheme 3) <2002T10429, 2000TL109>.



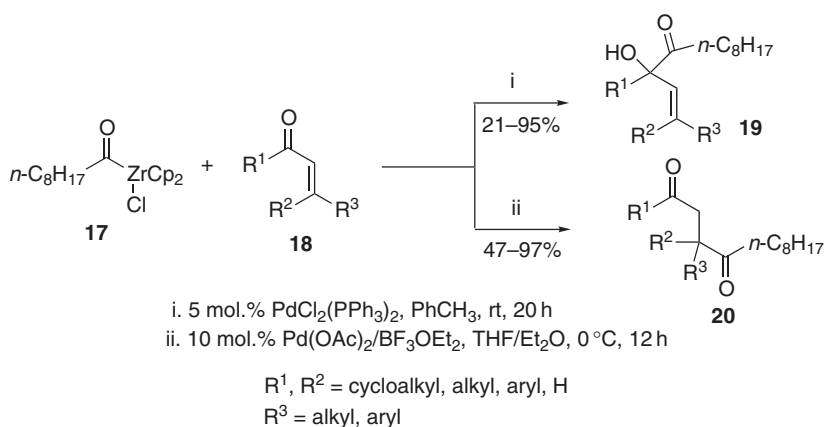
Scheme 3

α,β -Unsaturated acylzirconocenes possess bimodal reactivity. Enacylzirconocene **12** underwent conjugate addition of stabilized malonate nucleophiles followed by aqueous quench to give **14** or by addition to allyl bromide catalyzed by CuCl—2LiCl to give **15** (Scheme 4). Intermediate **13** was proposed in the formation of these adducts. Also, addition of a higher-order cuprate **12** followed by quenching with an alkyl iodide provided **16** <2000TL7525>.



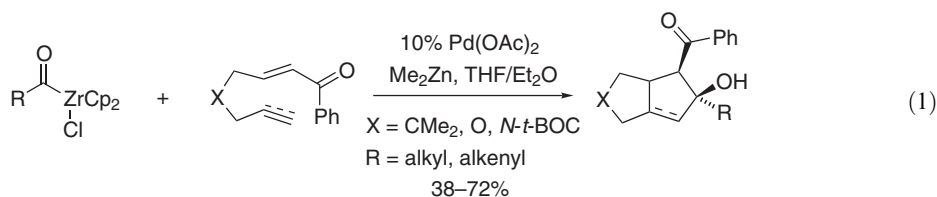
Scheme 4

Acylzirconium species can also be coupled to α,β -unsaturated enones using Pd(0) catalysis. The addition can be directed in a 1,2-fashion or a 1,4-fashion depending on the palladium source and whether a Lewis acid is added (Scheme 5) <1998TL8141, 2002T7559>. Reaction of **17** and **18** in the presence of a palladium(II) salt resulted in 1,2-addition to give **19**. If $BF_3 \cdot OEt_2$ was added, and the solvent was changed to THF:Et₂O, 1,4-addition ensued to give **20**. An enantioselective variant of the 1,2-addition reaction has also been reported <1999AG(E)2395>.



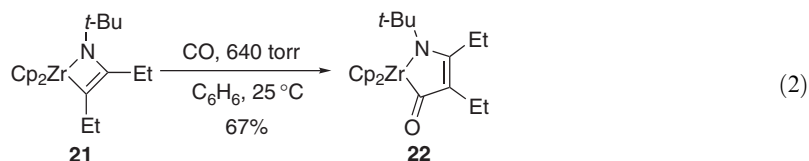
Scheme 5

Further examples of this chemistry involve additions to ynones to give enediones and cyclopentenones <2001TL1737> and additions to dienones/enynones to give bicyclo[3.3.0] compounds (Equation (1)) <2002OL4061>.



(1)

Insertion of CO into azazirconacyclobutene **21** resulted in formation of acyl complex **22** (Equation (2)) <1996JOC4532>.



5.10.5.4 Acylhafnium Compounds

No further advances have occurred in this area since the publication of chapter 5.10.5.4 in <1995COFGT(5)435>. In that publication, two examples were noted. In both cases, the acylhafnium compound was generated by insertion of CO into an Hf-aryl or Hf-benzylic bond.

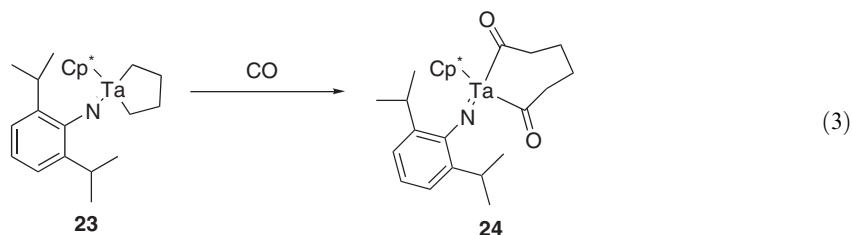
5.10.5.5 Acylvanadium Compounds

No further advances have occurred in this area since the publication of chapter 5.10.5.5 in <1995COFGT(5)435>. In that publication, one example was noted for the preparation of Cp₂V(COR)CO compounds.

5.10.5.6 Acyltantalum Compounds

Chapter 5.10.5.6 in <1995COFGT(5)435> gave one example of an acyltantalum compound, generated by the insertion of CO into a Ta-C alkyl bond. The acyl ligand is η²-coordinated to tantalum. Developments in this field since that publication are described below.

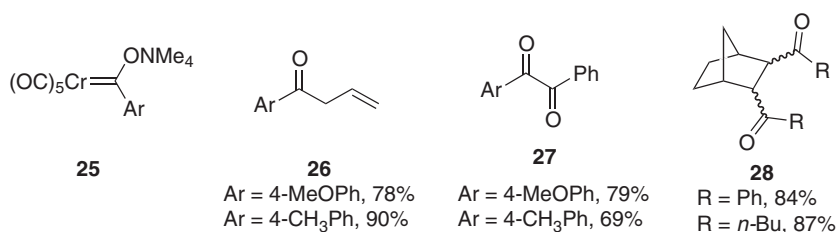
Half-sandwich imidotantalacyclopentane complexes **23** react with excess CO to give the diacyl complex **24**, for which no yield was given (Equation (3)) <1995CC2261>.



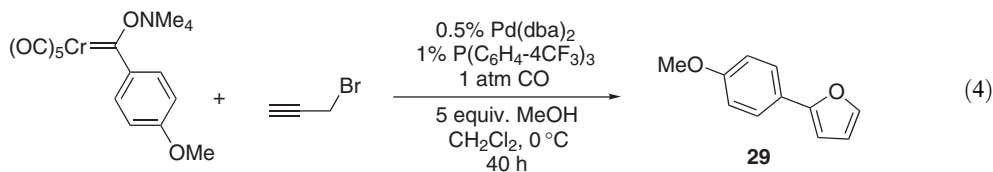
5.10.5.7 Acylchromium Compounds

Chapter 5.10.5.7 in <1995COFGT(5)435> described the formation of acylchromium species by two methods: addition of organolithium compounds to chromium carbonyls, and the insertion of CO into Cr-aryl bonds. Developments in this field since that publication are described below.

Tetralkylammonium acyl chromates **25** undergo a variety of reactions with alkenes and allylic and aryl halides under palladium catalysis. Ketones were prepared by reaction with allyl bromide in the presence of Pd(PPh₃)₄ and CO to give ketone **26** <1999CL309>. α-Diketones **27** have been prepared by reaction of **25** with iodobenzene <2000CL168>, and double acylation of norbornene (and other alkenes) was observed with **25** in the presence of Pd(OAc)₂, giving **28**.



Reaction of the 4-methoxyphenyl analog of **25** with propargyl bromide gave furan **29** (Equation (4)) <2003H333>.

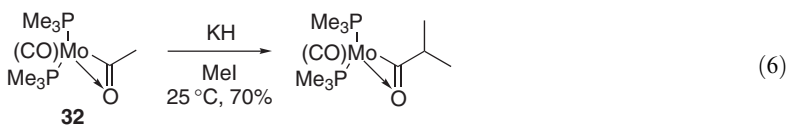
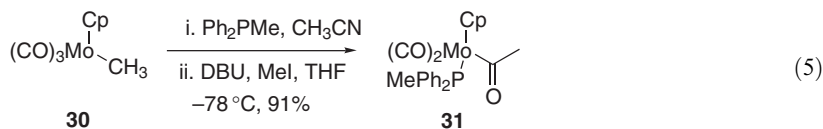


Acyl chromates such as the above have also been categorized as Fischer-type chromium carbenes. Further discussions of these species can be found in Chapter 5.25 on metal carbenes.

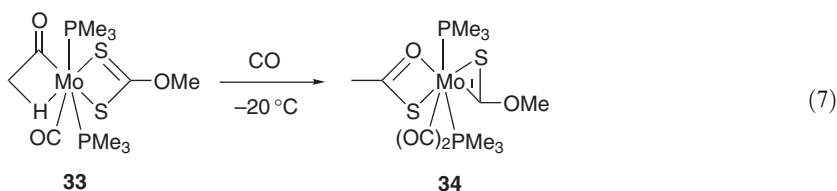
5.10.5.8 Acylmolybdenum Compounds

Chapter 5.10.5.8 in <1995COFGT(5)435> described the generation of acylmolybdenum compounds in a manner similar to their acylchromium counterparts. The two major methods of formation were addition of alkylmolybdenum compounds to molybdenum carbonyls and the insertion of CO into Mo—C benzylic bonds. Developments in this field since that publication are described below.

Reaction of alkylmolybdenum complex **30** with Ph₂PMe provided acyl complex **31** (Equation (5)). The phosphine ligand of complex **31** can be further elaborated by deprotonation followed by alkylation or acylation <1997JCS(D)3589>. The reaction of **31** with Ph₃P has shown to effect transformation to the corresponding Ph₃P analog of **31** <2003OM2284>. η^2 -Acylmolybdenum complex **32** can be alkylated by deprotonation with KH and subsequent addition of MeI (Equation (6)) <1999JOM(582)3>.



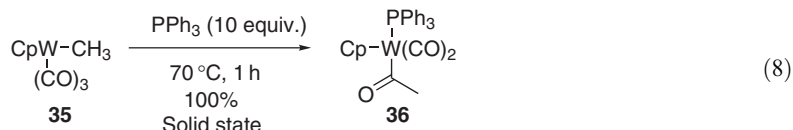
The acetyl xanthate complex **33** underwent partial desulfurization/rearrangement to generate the alkoxythiocarbonyl monothioacetate Mo complex **34** (Equation (7)) <1995OM589>. Compound **34** was fully characterized but no yield was reported.



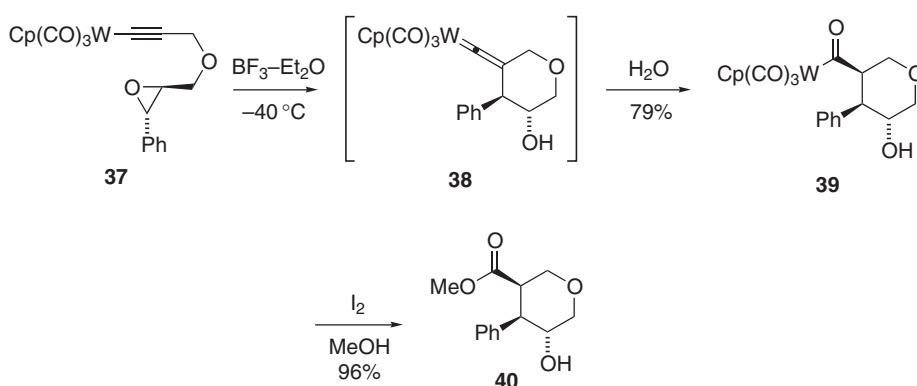
5.10.5.9 Acyltungsten Compounds

Chapter 5.10.5.9 in <1995COFGT(5)435> described the formation of acyltungsten compounds by the addition of organolithiums to tungsten carbonyls and by migration of an alkyl group from tungsten to a CO ligand. Developments in this field since that publication are described below.

In a manner identical to the corresponding molybdenum complex, tungsten complex **35** reacted with PPh_3 to give the acyl complex **36** (Equation (8)) <2003OM2284>.



Tungsten complex **37** bearing the *trans*-epoxide was converted into the six-membered ring acyl metal compound **39** via intermediate **38** and subsequent hydrolysis. Reaction of **39** with MeOH and I_2 provided the methyl ester **40** (Scheme 6) <2003JOC1872>.

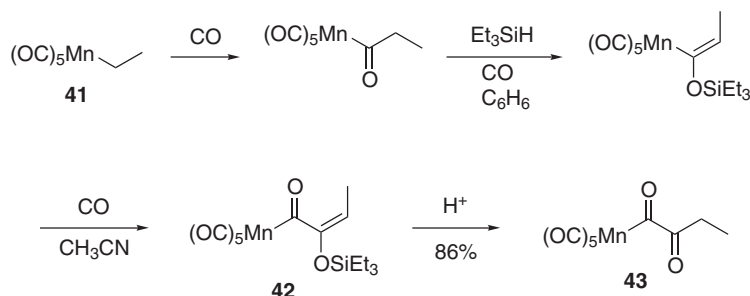


Scheme 6

5.10.5.10 Acylmanganese Compounds

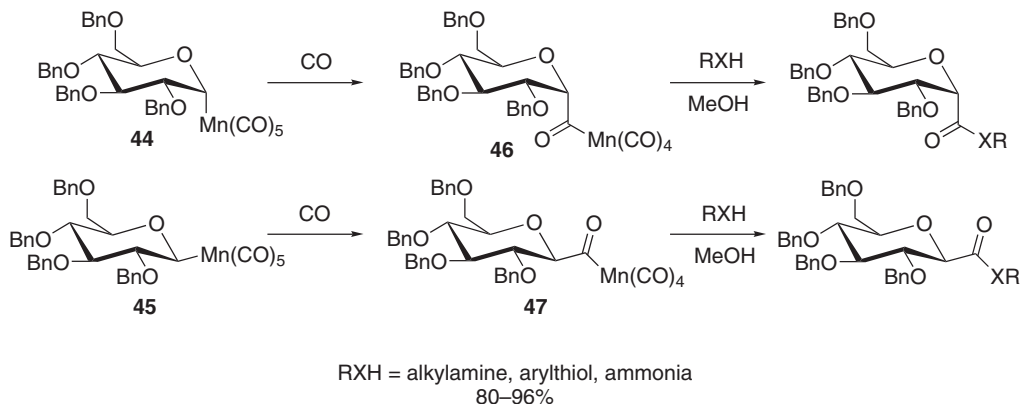
Chapter 5.10.5.10 in <1995COFGT(5)435> discussed the formation of acylmanganese compounds by the addition of anionic manganese carbonyls to acyl and alkyl halides. Other methods discussed involved an AlBr_3 -mediated insertion of CO into an Mn-C alkyl bond, and addition of lithium dialkyl cuprates to a manganese carbonyl complex. Developments in this field since that publication are described below.

Manganese alkyl complexes have been bis-carbonylated to generate acyl complexes (Scheme 7) <1998OM4169>. Insertion of CO into the alkyl complex **41**, followed by silylation and a second CO insertion, gave the adduct **42**. Acid hydrolysis of **42** gave α -ketoacyl metal complex **43**.



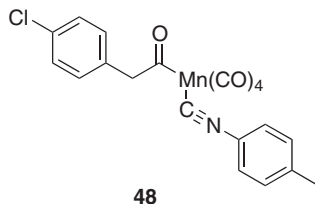
Scheme 7

Anomerically pure pyranosylmanganese pentacarbonyl complexes **44** and **45** underwent migratory insertion of CO to generate the corresponding acylmanganese derivatives **46** and **47** (Scheme 8) <2000JOM(593)49>. The chemistry was applied to the formation of C-glycosyl and C-aryl glycosidic systems. The analogous furanosylmanganese pentacarbonyl complexes performed the same chemistry.

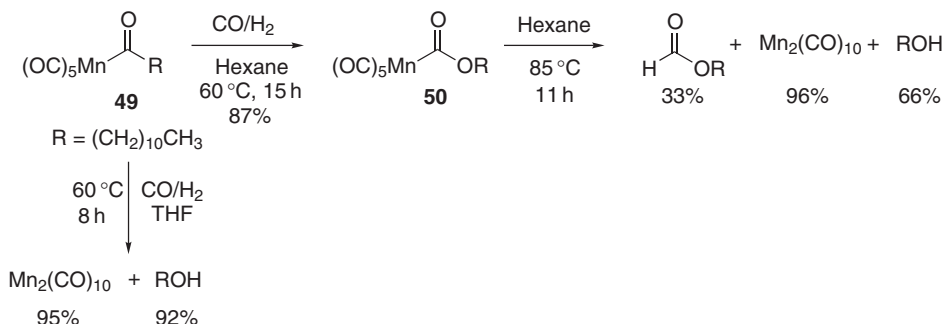


Scheme 8

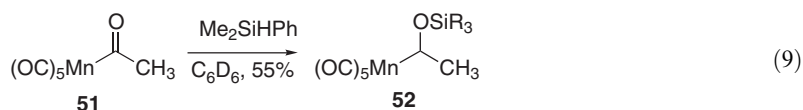
Transformations of readily available acylmanganese complexes have been further developed by several workers. The coupling of isocyanide acyl complexes **48** to alkynes provided several azaheterocycles <2002ICA419>.

**48**

The reaction of complexes **49** with syngas (CO/H₂) in hexane resulted in the formation of [Mn(CO)₅{C(O)OR}] complexes **50**, while reaction in tetrahydrofuran (THF) gave Mn₂(CO)₁₀ and ROH. Further reaction of **50** in hexane at 85 °C gave the formate HC(O)OR in addition to ROH and Mn₂(CO)₁₀ (Scheme 9) <1998JOM(564)267>. Treatment of **51** with monohydrosilanes furnished **52** (Equation (9)) <1996JA10069>.



Scheme 9

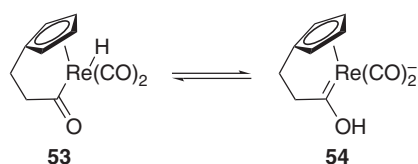


5.10.5.11 Acylrhenium Compounds

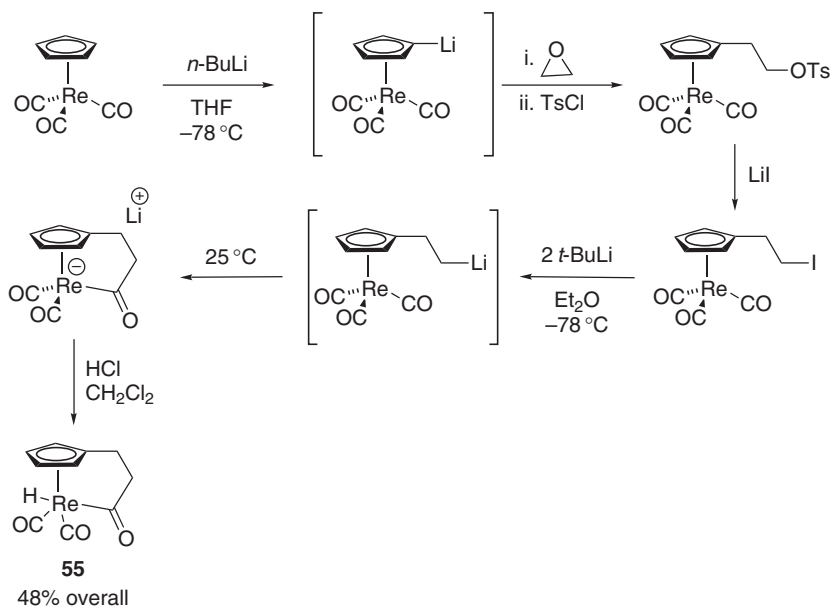
Chapter 5.10.5.11 in <1995COFGT(5)435> described the formation of acylrhenium compounds by methods similar to their acylmanganese counterparts. Specifically, reaction of anionic acylrhenium compounds with acyl halides, and the addition of organolithiums to rhenium carbonyl complexes encompassed the major methods of formation. Developments in this field since that publication are described below.

Acylrhenium compounds possess several unique properties. Specifically, Re(I), Re(III), and dirhenium acyl complexes are known. Numerous pentacarbonylacylrhenium(I) compounds have been prepared and fully characterized <1995JOM(494)105>. Reaction of $(\text{CO})_5\text{Re}^-\text{Na}^+$ with $\text{F}_5\text{C}_6\text{X}$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) readily provided $\text{F}_5\text{C}_6(\text{CO})\text{Re}(\text{CO})_4\text{X}^-\text{Na}^+$ <1999JOU1640>.

Studies on ring-strained rhenium complexes have shown that an equilibrium exists between acylrhenium hydrides **53** and the corresponding hydroxycarbenes **54** (Scheme 10). Acyl complex **55** was prepared from $\text{CpRe}(\text{CO})_3$ by insertion into a C—Li bond (Scheme 11) <1995JA4189, 1997JA3971>.

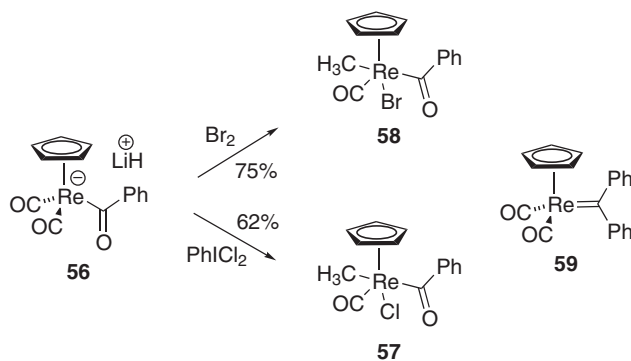


Scheme 10



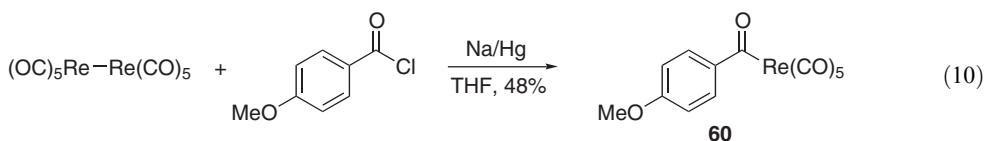
Scheme 11

Oxidation of $\text{Li}[\text{CpRe}(\text{CO})_2(\text{COPh})]$ **56** with PhICl_2 or Br_2 gave $\text{CpRe}(\text{CO})_2(\text{COPh})\text{Cl}$ **57** and $\text{CpRe}(\text{CO})_2(\text{COPh})\text{Br}$ **58**, respectively (Scheme 12) <1996JOM(524)133>. Carbene **59** was also formed in 12% yield.



Scheme 12

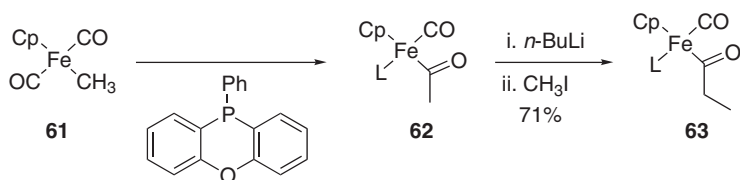
Dirhenium complexes have been shown to be useful precursors to acylrhenium compounds. As shown in Equation (10), for example, decacarbonyldirhenium was converted into the acyl complex **60** by reaction with 4-methoxybenzoyl chloride in the presence of sodium amalgam <1998OM1946>.



5.10.5.12 Acyliron Compounds

Chapter 5.10.5.12 in <1995COFGT(5)435> discussed several methods for formation of acyliron compounds. Collman's reagent, $\text{Na}[\text{Fe}(\text{CO})_4]$, is a versatile reagent for formation of acyliron complexes by reaction with alkyl halides and tosylates. Migratory insertion of CO into Fe—C bonds and carbonylation of acyliron complexes were two other methods described in COFGT (1995). Acyliron compounds have been studied and developed to a great extent since the publication of <1995COFGT(5)453>. A large number of applications relating to transformations of the acyl ligand and to their uses in organic synthesis have been reported.

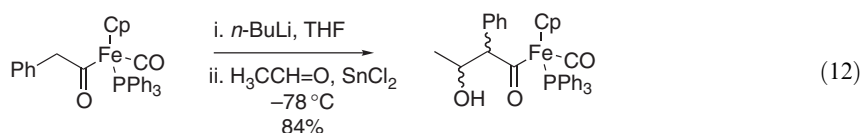
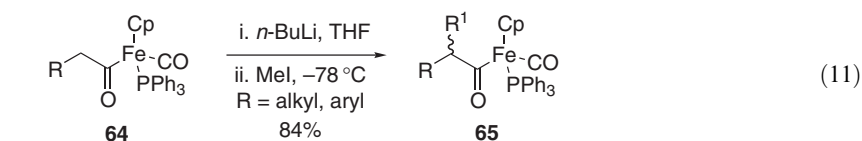
The transformation of the acyl ligand has mostly dealt with deprotonation of an acetyliron compound followed by alkylation or aldol reaction. $\text{CpFe}(\text{CO})_2\text{CH}_3$ **61** was converted into the acyl complex by reaction with 10-phenylphenoxaphosphine as shown in Scheme 13 <1996PJC603>. The acyl ligand in **62** was further elaborated by deprotonation with *n*-BuLi and alkylation with MeI to give **63**. Attempts to convert **61** into the corresponding acyliron complex with simple phosphines failed.



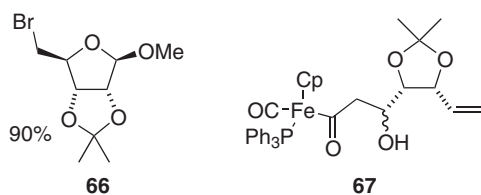
Scheme 13

The alkylation of (2-, 3-, and 4-methylphenylacetyl)iron complexes **64** with various alkyl halides was studied to determine the diastereoselectivity of the reaction (Equation (11)). For $\text{R} = 2\text{-methylphenyl}$, the highest selectivity was observed <1996PJC446>. The deprotonations were performed with *n*-BuLi and lithium diisopropylamide (LDA), each base giving a different result. In the case of **64**, where $\text{R} = \text{Et}$, deprotonation with *n*-BuLi in THF followed by alkylation with MeI gave the product **65** ($\text{R} = \text{Et}$, $\text{R}^1 = \text{Me}$) in 87.5% diastereoselectivity favoring the

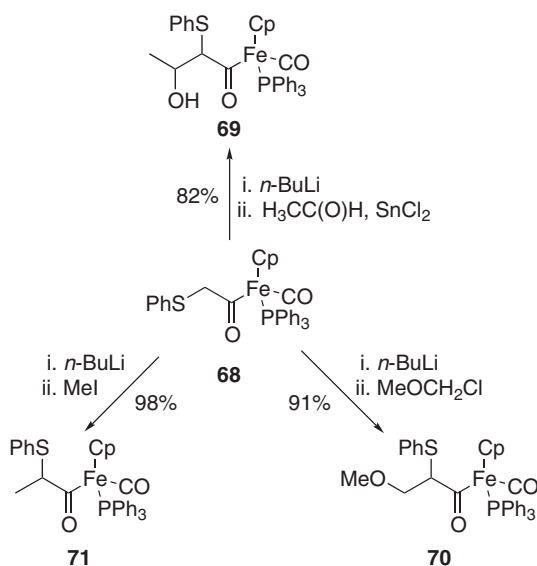
((*R*)(*S*)/(*S*)(*R*)) adduct, and for $R = \text{Me}$, deprotonation and alkylation with EtI gave **65** ($R = \text{Me}$, $R^1 = \text{Et}$) in 89% diastereoselectivity favoring the ((*R*)(*S*)/(*S*)(*S*)) adduct <1997PJC1108>. The phenyl analog was also used in aldol condensations with acetaldehyde (Equation (12)). The aldol reactions were practically non-stereoselective, although the use of SnCl_2 or Et_2AlCl as an additive allowed some selectivity to be observed <1996T12553>.



Compound **64** ($R = \text{H}$) was deprotonated and reacted with furanoside **66** to form a mixture of stereoisomeric complexes **67** <1998PJC688>. The adduct was formed by a Grob-type fragmentation of the furanoside to the open-chain aldehyde which reacted with the acetyliron anion. Decomplexation yielded the corresponding heptenoic esters.

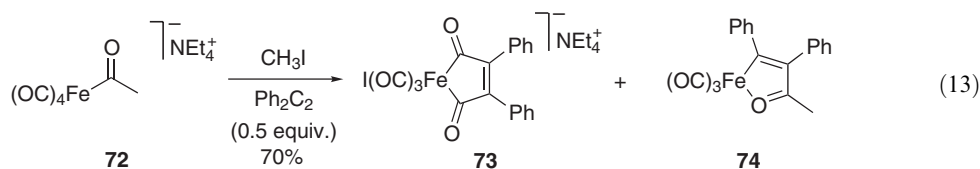


The thioacetyliron complex **68** was prepared by reaction of the acetyl complex with PhSSPh . Compound **68** was alkylated and reacted with aldehydes and ketones in a manner similar to **63** to give compounds **69–71** (Scheme 14) <1998T14201, 1996JOM(523)1>.

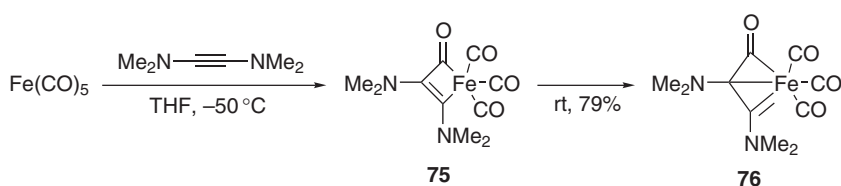


Scheme 14

Collman's reagent **72** was reacted with excess MeI and diphenyl acetylene to give **73** and **74**, as seen in Equation (13) <2002JOM(642)107>.

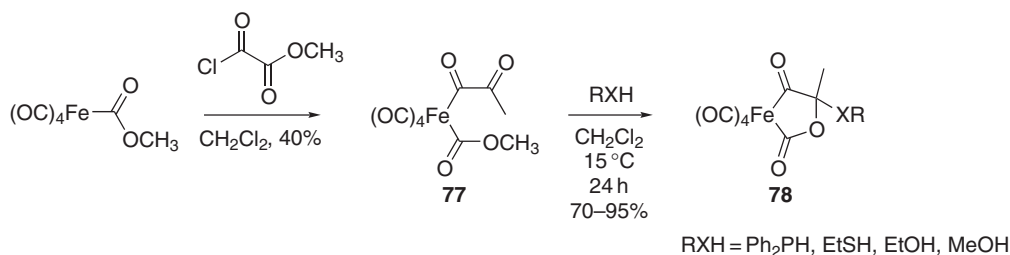


Pentacarbonyliron reacted with bis(dimethylamino)ethyne via an associative pathway to give ferrabicyclobutenone **76** via the intermediate ferracyclobutenone **75**, as shown in Scheme 15 <2002AG(E)2393>. Compound **76** underwent C—C coupling and C—C bond-cleavage reactions to generate various organoiron compounds.



Scheme 15

Acyliron compound **77** was shown to undergo thermal rearrangement to the metallalactone **78** ($XR = OMe$) (Scheme 16). Nucleophilic reagents were also shown to effect the same rearrangement <2002OM2196>.

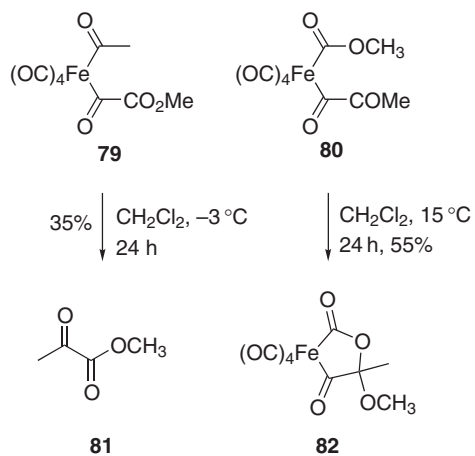


Scheme 16

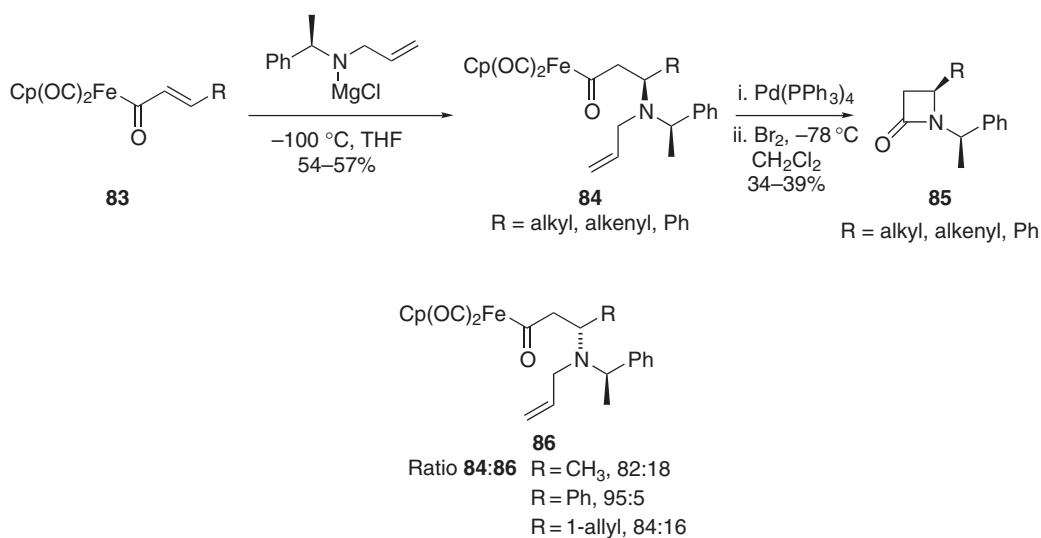
In a similar manner, acyliron complexes **79** and **80** have been shown to react thermally to generate the coupled α -keto ester **81** and the ferraoxacycle **82**, respectively (Scheme 17) <1996CC857>.

Conjugate addition of the magnesium salt of (α -methylbenzyl)allylamine to α,β -unsaturated acyliron complex **83** afforded diastereomer **84** as shown in Scheme 18 <1999JCS(P1)3105>. Pd-Catalyzed deallylation provided the corresponding secondary amines, which upon oxidative decomplexation (Br_2 or NBS) gave the β -lactams **85**. Addition of (α -methylbenzyl)allylamine as the free amine gave a mixture of **84** and diastereomer **86**.

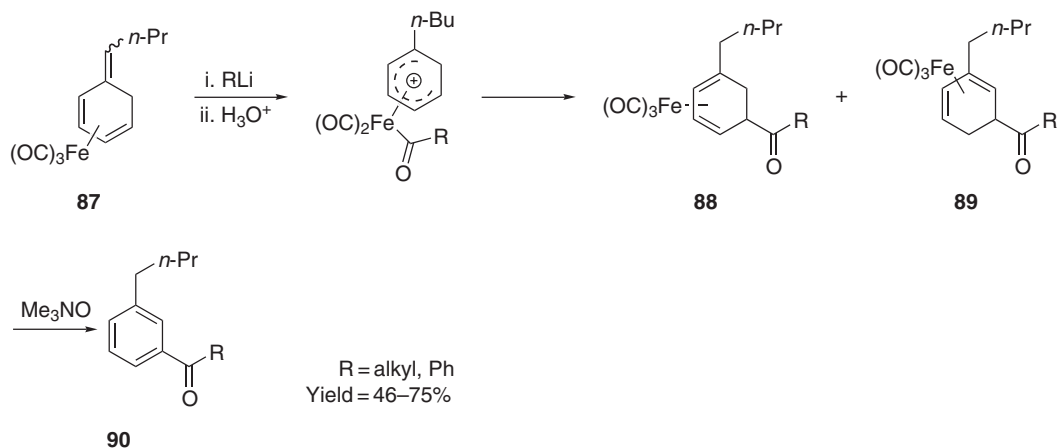
Cyclohexadienetricarbonyliron complex **87**, upon reaction with organometallic reagents, generated the tricarbonyliron complexes **88** and **89** as depicted in Scheme 19 <1998CL395>. Compounds **88** and **89** were further transformed to 3-alkylphenyl ketones **90** by treatment with trimethylamine *N*-oxide. In a similar manner, iron complexes **91** were reacted with organocuprate reagents, followed by treatment with acetic anhydride and CO, then K_2CO_3 , giving 3-acylanilines **92** and **93** (Scheme 20) <1998CL393>.



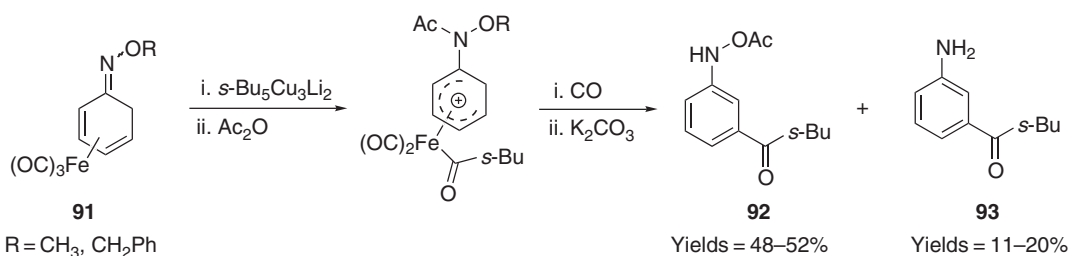
Scheme 17



Scheme 18

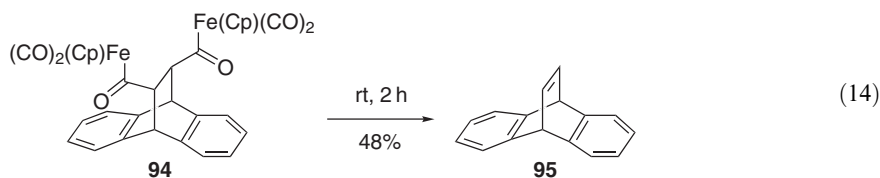


Scheme 19



Scheme 20

Preparation of the bis(acyliron) complex **94** was performed by reaction of the corresponding ethanoanthracene acid dichloride with $\text{Na}[\text{Fe}(\text{CO})_2\text{Cp}]$. Thermolysis of **94** provided 9,10-ethenoanthracene **95** (Equation (14)) <1996JOM(515)173>.

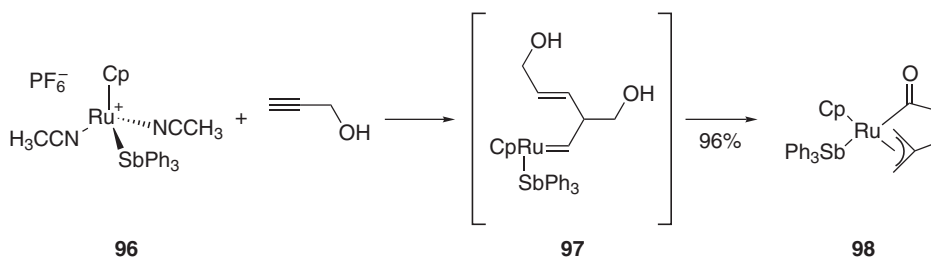


A number of alkynyl-, alkenyl-, and alkadienyl acyliron complexes were generated by reaction of the corresponding aliphatic acid chloride with the potassium or sodium salt of anionic $\text{Cp}(\text{CO})_2\text{Fe}$, generated by reduction of $[\text{Cp}(\text{CO})_2\text{Fe}]_2$ with K-selectride or 2% Na/Hg <1995SL1194>.

5.10.5.13 Acylruthenium Compounds

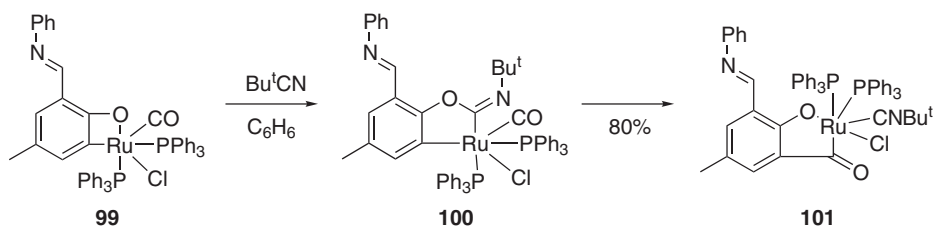
Chapter 5.10.5.13 in <1995COFGT(5)435> described the formation of acylruthenium compounds by the reaction of anionic ruthenium carbonyls with alkyl iodides and acyl chlorides, and the insertion of CO into $\text{Ru}-\text{C}$ alkenyl bonds. Developments in this field since that publication are described below.

Reaction of the cationic half-sandwich complex **96** with alkynes bearing α -alkyl substituents resulted in a 1,2-hydrogen migration leading to butadienylcarbene complexes **97**. In the case of propargyl alcohol, **97** rearranges to the η^3 -allyl-acyl complex **98** as shown in Scheme 21 <2003OM2124>.



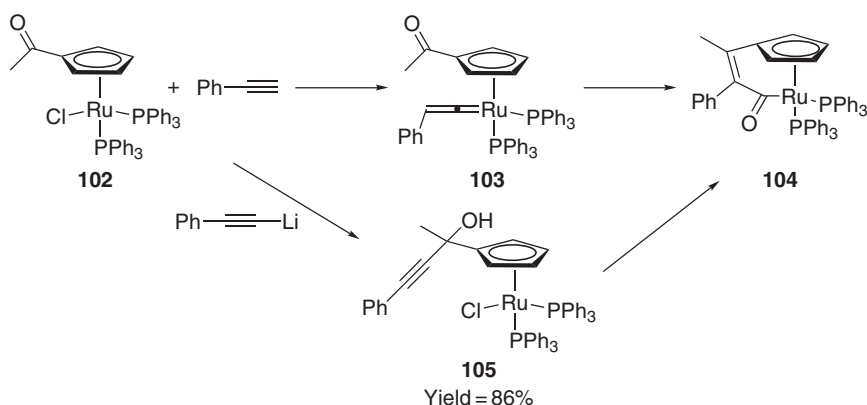
Scheme 21

Ruthenium complexes of the type **99** react with *t*-butyl isocyanate to generate the imidic ester **100** (Scheme 22). Complex **100** reacts further in solution to give the acyl ruthenacycle **101**.



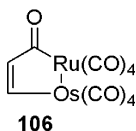
Scheme 22

The formation of acylruthenium compound **104** from the reaction of acetylcyclopentadienyl complex **102** with phenyl acetylene proceeded through the vinylidene intermediate **103** (Scheme 23) <2002OM1355>. In this reaction, the oxygen atom of the acetyl group is transferred to the α -carbon atom of the acetylene unit. Reaction of **102** with lithium phenylacetylide generated alcohol **105**, which was also transformed into **104**.

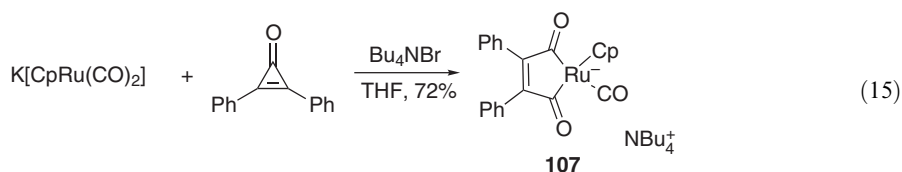


Scheme 23

The reaction of $\text{Ru}(\text{CO})_5$ with $\text{Os}(\text{CO})_4(\eta^2-\text{C}_2\text{H}_2)$ afforded the dimetallacyclic acylruthenium compound **106** <2000OM2766>. Kinetic studies showed that the reaction was slowed by the addition of CO, in accord with the initial step being dissociation of CO from $\text{Os}(\text{CO})_4(\eta^2-\text{C}_2\text{H}_2)$.



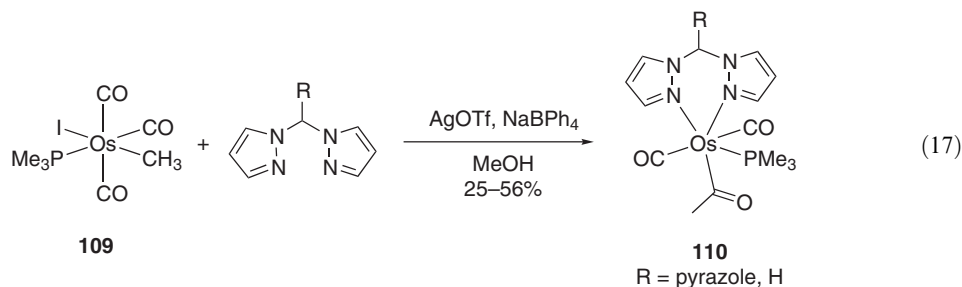
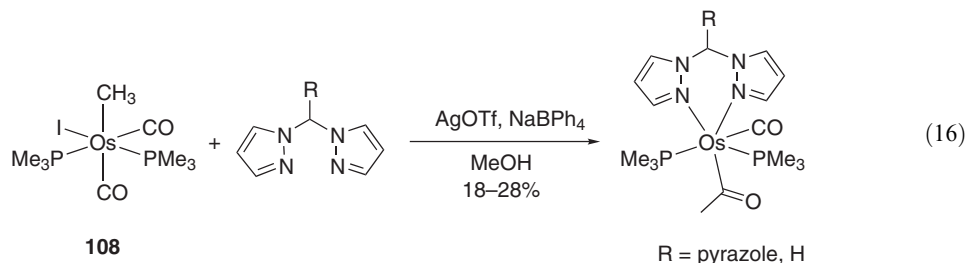
In an interesting transformation, $\text{K}[\text{CpRu}(\text{CO})_2]$ reacts with diphenylcyclopropene to generate the diacylruthenacycle **107** shown in Equation (15) <2000CEJ692>.



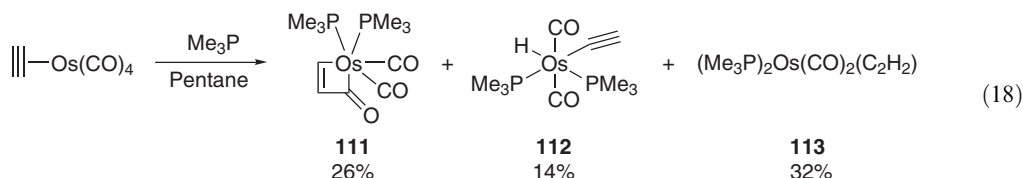
5.10.5.14 Acylosmium Compounds

Chapter 5.10.5.14 in <1995COFGT(5)435> described the formation of acylosmium compounds from anionic osmium carbonyls. Reaction of the carbonyl complexes with alkyl iodides, followed by reaction with CO, provides the acyl complexes. Developments in this field since that publication are described below.

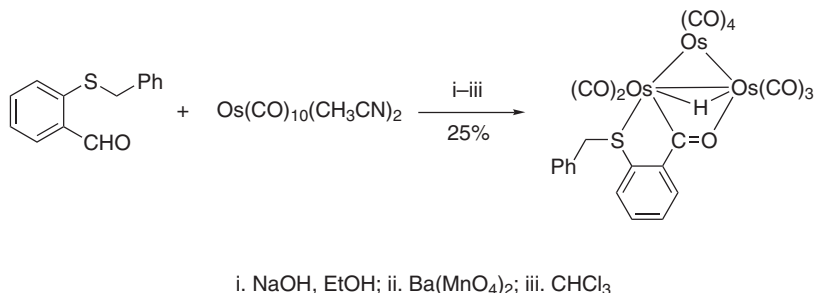
The reaction of osmium carbonyl complexes **108** and **109** with silver salts in the presence of bis- and tris(pyrazol-1-yl)methane, respectively, resulted in the formation of the acylosmium compounds shown in Equations (16) and (17) <2000OM4320>. The solvento complex, formed by the displacement of one CO ligand by a solvent molecule in **110** was also observed. Formation of the solvento complex can be minimized by adjusting the reaction conditions. An intermediate Os—Ag complex was isolated in one case and studied by NMR spectroscopy.



In the presence of excess Me_3P , $\text{Os}(\text{CO})_4(\text{C}_2\text{H}_2)$ was converted into the acyl osmacycle **111** (Equation (18)) <1999OM2331>. Compounds **112** and **113** were also formed.



The triosmium cluster $\text{Os}_3(\text{CO})_{10}(\text{CH}_3\text{CN})_2$ reacted with 2-(benzylthio)benzaldehyde to give the acyl complexes shown in Scheme 24 <1995JOM(2)273>.

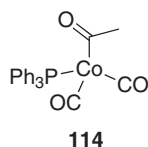


Scheme 24

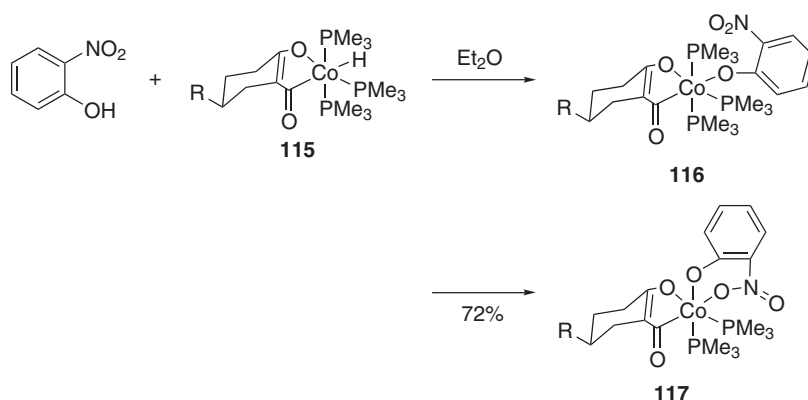
5.10.5.15 Acylcobalt Compounds

Chapter 5.10.5.15 in <1995COFGT(5)435> described the formation of acylcobalt compounds by the reaction of $\text{NaCo}(\text{CO})_4$ with acyl chlorides, or alkyl halides and CO. Further examples included the hydrometallation of alkenes with $(\text{CO})_4\text{CoH}$ in the presence of CO, or the addition of $(\text{CO})_4\text{CoH}$ to ketenes. Developments in this field since that publication are described below.

Cobalt-catalyzed carbonylations proceed through reactive acyl intermediates. Within the context of alkene hydroformylations, **114** was detected and characterized as the reactive intermediate by time-resolved IR spectroscopy <2000IC3098>.

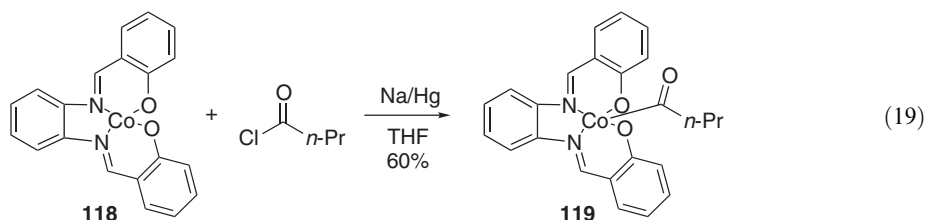


The reaction of 2-nitrophenols with acylhydridocobalt complex **115** resulted in the formation of the phenolato complex **116** (Scheme 25) <2003ICA179>. Upon further reaction in solution, one of the oxygen atoms of the nitro group displaced one phosphine ligand to give compound **117**.

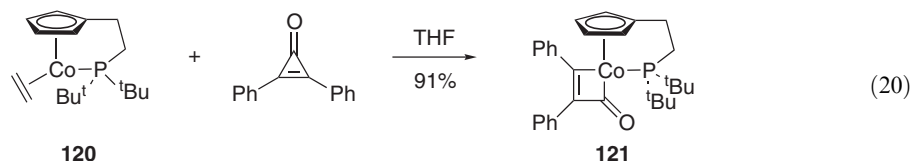


Scheme 25

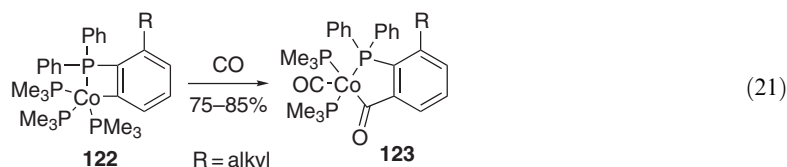
The pentacoordinated salophencobalt(III) complex **119** was synthesized by reaction of complex **118** with butanoyl chloride in the presence of sodium amalgam (Equation (19)) <2002MI213>. Compound **119** was fully characterized including X-ray analysis, collision-induced dissociation, and high-resolution MS.



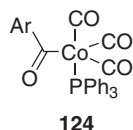
Reaction of ethene complex **120** with diphenylcyclopropene gave the acylcobaltacyclobutene compound **121**, which was characterized by X-ray crystallography (Equation (20)) <2000OM2108>. Reaction of **120** with dimethoxycyclopropene did not give the Co-inserted product, but resulted in displacement of the ethene ligand and formation of the corresponding cyclopropene olefin complex.



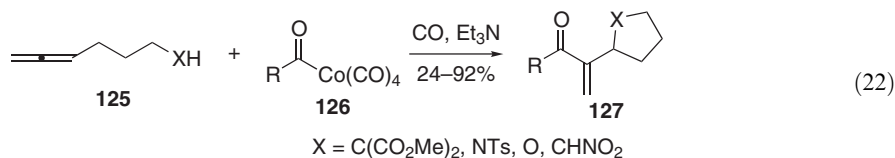
Insertion of CO into cobaltaphosphabenzocyclobutanes **122** gave the ring-expanded products **123** (Equation (21)) <2003EJI853, 2002EJI3305>.



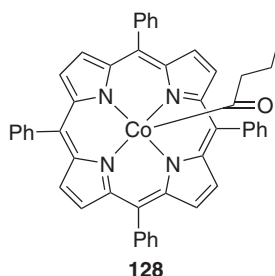
Palladium catalysis has been used to generate aroylcobalt complexes. Thus, reaction of $\text{K}[\text{Co}(\text{CO})_4]$, ArI , and PPh_3 in the presence of $\text{Pd}(\text{PPh}_3)_4$ gave aroyl complexes **124** <1995JCS(D)3489>.



Allenes **125** underwent acylation–cyclization by treatment with the acylcobalt complexes **126** in the presence of $\text{CO}/\text{Et}_3\text{N}$ in THF to generate the adducts **127** (Equation (22)) <1995TL509>. The methodology provides access to a range of five-membered ring systems.



$\text{Co}(\text{II})$ porphyrins reacted with propanal to give the corresponding acyl $\text{Co}(\text{III})$ porphyrins such as **128** <1999JOM(575)21>. In the presence of $t\text{-BuOOH}$, the acyl radical of the aldehyde is generated and couples to the $\text{Co}(\text{II})$ porphyrin. The reaction was applied to 2-allyl- and 2-allyloxyaryl aldehydes to give the corresponding $\text{Co}(\text{III})$ adduct following intramolecular cyclization of the acyl radical.



5.10.5.16 Acylrhodium Compounds

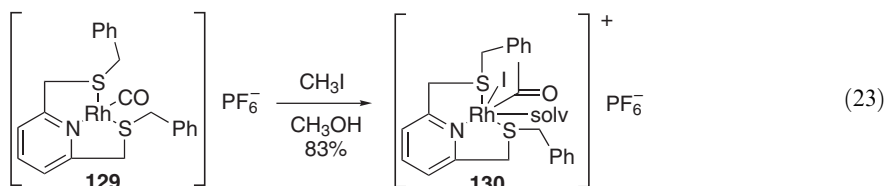
Chapter 5.10.5.16 in <1995COFGT(5)435> described the formation of acylrhodium compounds by the reaction of rhodium complexes with acid chlorides, addition of rhodium carbonyls to alkyl iodides, and direct insertion of $\text{Rh}(\text{CO})_4\text{Cl}_2$ into $\text{C}-\text{C}$ bonds of strained alkanes. Developments in this field since that publication are described below.

Acylrhodium compounds are a cornerstone of the hydroformylation process, playing a vital role as key intermediates in the reactions. A large majority of the work on acylrhodium compounds centers around these reactions, but only to the extent of commenting on them as intermediates. Because of this trend, portions of this work will not be covered in this subsection, except where the acylrhodium species has been isolated.

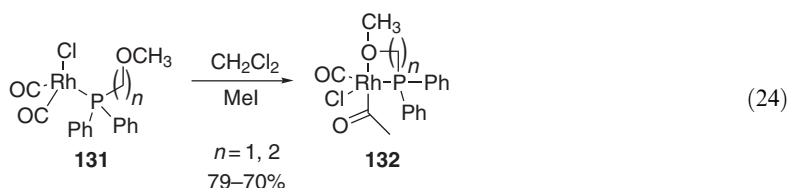
One of the most widely utilized methods for the generation of acylrhodium complexes has been oxidative insertion of an $\text{Rh}(\text{I})$ species into an aryl or alkyl halide followed by CO migration to

form the corresponding acylrhodium complex. Advances in this area have centered around the formation of novel complexes, and continuing mechanistic investigations.

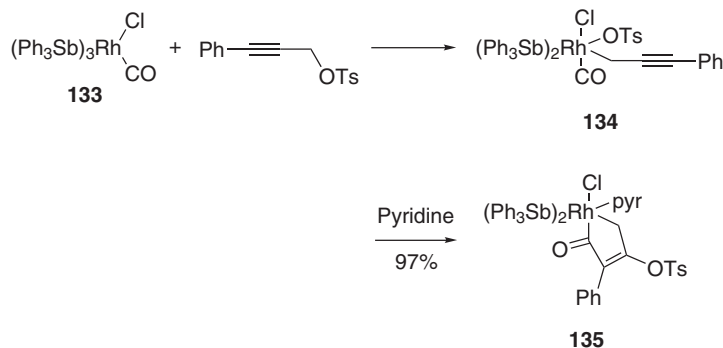
The cationic Rh complex **129**, for example, reacted with MeI to give the corresponding acetylrhodium compound **130**, shown in Equation (23) <2003OM2535>. Rate constants and activation parameters were obtained.



Reaction of Rh(I) complexes **131**, bearing a pendant ether moiety, with MeI produced the acylrhodium compounds **132** possessing intramolecular coordination of the ether oxygen atom (Equation (24)) <2002APOC302>. The compounds were fully characterized.



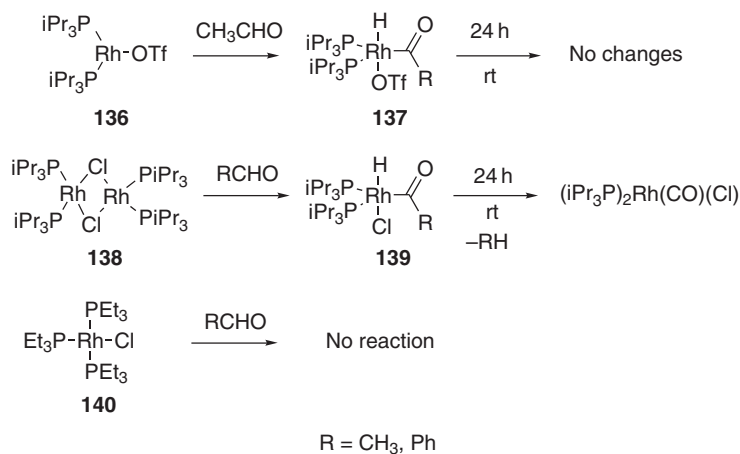
Reaction of rhodium complex **133** with phenylpropargyl tosylate, as shown in Scheme 26, gave compound **134**. Upon reaction with pyridine, the acyl rhodacycle **135** was formed <2001ICA187>.



Scheme 26

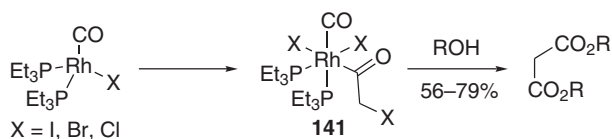
A remarkable ligand effect was observed in the oxidative addition of rhodium phosphine complexes to aldehydes <2001AG(E)1119>. As seen in Scheme 27, the rhodium triflate complex **136** readily inserted into acetaldehyde to generate the stable acylrhodium complex **137**. The rhodium chloride dimer **138** underwent the same reaction. However, after 24 h at room temperature, **139** decomposed to yield RH and $(i\text{-Pr}_3\text{P})_2\text{Rh}(\text{CO})(\text{Cl})$. Finally, complex **140** gave no reaction under the same conditions. The bridged chloro complex **138** had been previously studied in more depth in oxidative additions to aldehydes and acid chlorides <1995OM4929>. The structure of **137** was determined by single-crystal X-ray analysis, although the isolated yield of **137** was not given.

An investigation into the role of steric effects on the migratory insertion of CO into Rh—C bonds revealed a very enlightening result. The ligand dppms ($\text{Ph}_2\text{PCH}_2\text{P}(\text{S})\text{Ph}_2$), the monophosphine sulfide of dppe, promoted the insertion of CO into Rh—C bonds at a rate 3000 times faster than the analogous Rh complex bearing the dppe ligand <1999JA11233>.



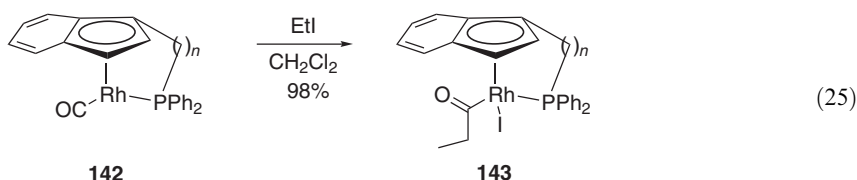
Scheme 27

Rhodium complexes have been shown to catalyze the carbonylation of diiodomethane to give the corresponding dialkyl malonates, as shown in [Scheme 28](#) <1998ICA(280)99>. The active catalyst is RhX(CO)(PEt₃)₂. Although the diiodoacylrhodium intermediate **141** (X = I) was not isolated, the corresponding dichloro (X = Cl) and dibromo (X = Br) complexes were prepared and fully characterized.

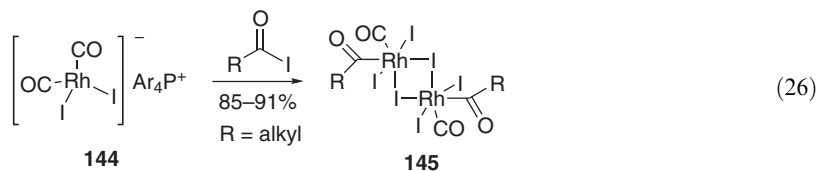


Scheme 28

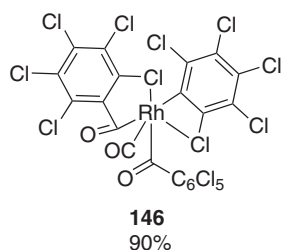
Oxidative addition of alkyl halides to indenylrhodium complex **142** was achieved, which upon subsequent CO migration provided the acylrhodium complex **143** in very high diastereoselectivities ([Equation \(25\)](#)) <1998OM4338>. The diastereoselectivity depended on the length of the spacer. For $n = 2$, the ((*R**),(*R**)) isomer was generated with 92% de, and for $n = 4$, the ((*R**),(*S**)) diastereomer predominated with a 96% de. Evidence has been reported for the migration of an alkyl group in the CO insertion and decomplexation steps in this transformation ($n = 3$) <2001OM2431>.



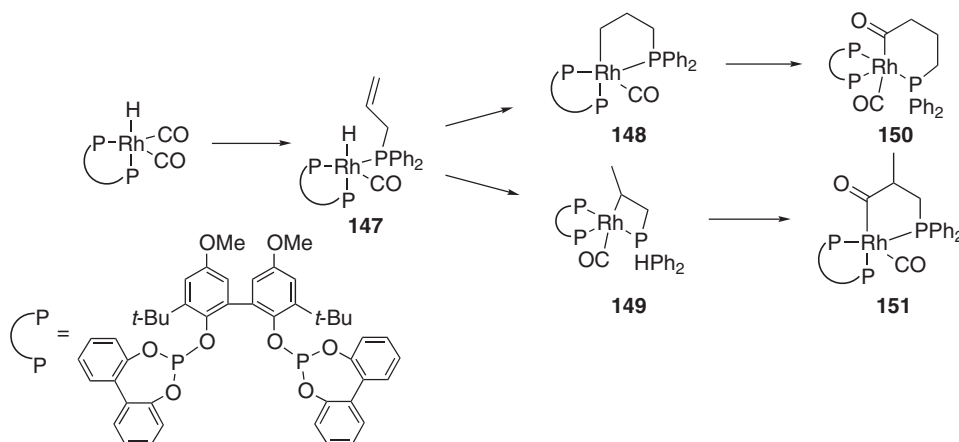
The novel anionic acylrhodium complex **145** was prepared by reaction of acyl iodides with complex **144** as shown in [Equation \(26\)](#) <1995POL167>.



Reaction of octahedral tris(pentachlorophenyl)rhodium(III) with CO resulted in the insertion of 2 equiv. of CO to generate the bis(acyl)rhodium complex **146** <2000ICA(308)51>.



Scheme 29 outlines the results from a study aimed at exploring the hydroformylation of allyldiphenylphosphine [<1997JOM\(535\)201>](#). Compound **147** was formed by the reaction of allyldiphenylphosphine as shown. Thermal reaction of **140** resulted in migration of hydride to give rhodacycles **148** and **149** that underwent subsequent CO insertion to give the corresponding acyl rhodacycles **150** and **151**. Formation of compound **150** was reversible, while **151** formed irreversibly. Formation of the intermediates was followed by ^1H and ^{31}P -NMR spectroscopy. Yields were not given.

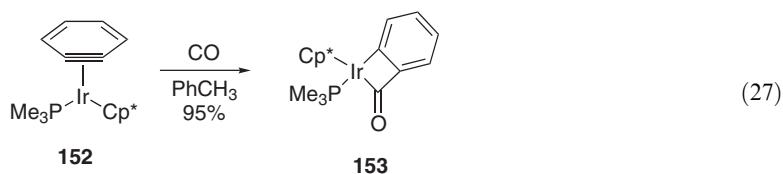


Scheme 29

5.10.5.17 Acyliridium Compounds

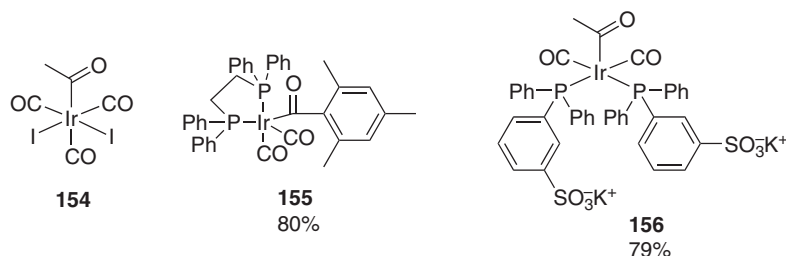
Chapter 5.10.5.17 in [<1995COFGT\(5\)435>](#) described the formation of acyliridium compounds by the addition of alkylolithiums to iridium chloride complexes, followed by CO insertion. Additionally, alkylation of iridate carbonyl complexes with alkyl halides, or insertion of iridium complexes into acyl bromides, were described as methods for the formation of acyliridium compounds. Developments in this field since that publication are described below.

Treatment of iridium benzyne complex **152** with CO in toluene gave the CO-insertion product **153** in very high yield (Equation (27)) [<2003OM2134>](#). The tetrafluorobenzyne analog was unreactive toward CO.



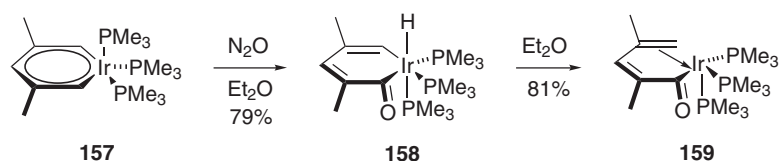
Acyliridium complexes are readily formed by insertion of CO into Ir–alkyl and –aryl bonds. Compound **154** was generated from the precursor five-coordinate methyl analog (yield not given) [<1998CC1023>](#), and **155** was formed from the precursor four-coordinate (dppe)Ir(CO)(mesitylene) complex [<1995JA3510>](#). In the case of **154**, CO pressures as high as 400 psi were necessary.

Insertion of CO into iridium complex $\text{trans-Ir}(\text{CH}_3)(\text{CO})_2(\text{TPPMSK})_2$, bearing the water-soluble phosphine ligand 4- $\text{KO}_3\text{SC}_6\text{H}_4\text{PPh}_2$ (TPPMSK), gave **156** in DMSO. The reaction could be conducted in water when excess ligand was present, suppressing hydrolysis of the Ir—CH₃ bond <1998POL1177>.



Lithium iridate $\text{Cp}^*(\text{PMe}_3)\text{IrHLi}$, generated by treatment of $\text{Cp}^*(\text{PMe}_3)\text{IrH}_2$ with *t*-BuLi, reacted with acyl chlorides and anhydrides to give $\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{COR})\text{H}$ complexes. The lithium iridate was aggregated in benzene, but was converted into a single symmetrical species in THF, and was a dimer in dimethoxyethane (DME) <1999OM2005>.

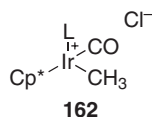
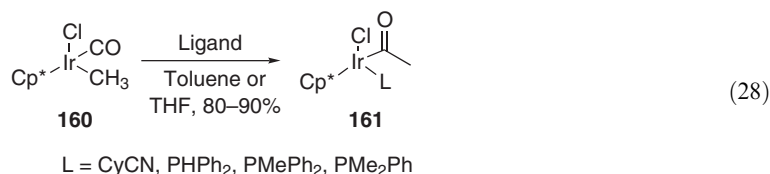
Iridacyclohexadienones such as **157** have been made by the reaction of iridabenzene with water (Scheme 30) <1997JA8503>. The iridacycle underwent isomerization at ambient temperature to give the 2,4-dimethylpentadienoyl iridium species **159**.



Scheme 30

Iridium dihydride complexes $\text{Cp}^*(\text{PMe}_3)\text{IrH}_2$ reacted with aromatic and hindered aliphatic acid chlorides in the presence of an amine to give Ir-acyl hydride complexes $\text{Cp}^*(\text{PMe}_3)\text{Ir}(\text{C}(\text{O})\text{R})\text{H}$ <2000OM2073>. Kinetic studies showed the reaction to be first order in $\text{Cp}^*(\text{PMe}_3)\text{IrH}_2$ and acid chloride, and zero order in amine.

The reaction of Ir complex **160** with the ligands shown in Equation (28) in toluene or THF provided the methyl migration products **161**. The phenyl analog or the iodide complexes did not react under the same conditions. Additionally, if the reaction of **160** was performed in acetonitrile, the cationic complex **162** was formed <1995ICA485>.

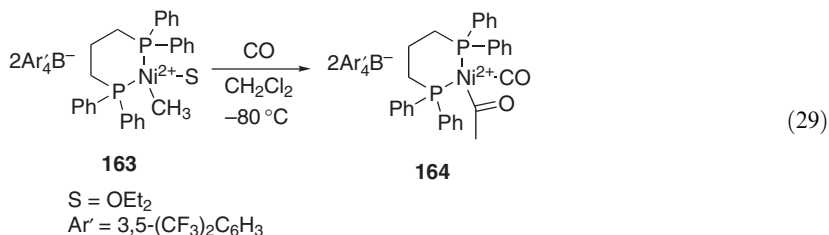


5.10.5.18 Acylnickel Compounds

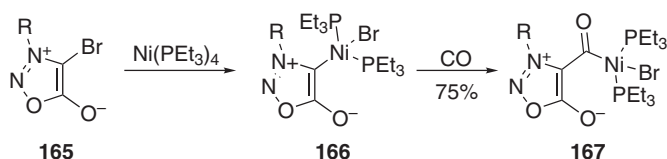
Chapter 5.10.5.18 in <1995COFGT(5)435> described the formation of acylnickel compounds by insertion of CO into the Ni—C bond of alkylnickel complexes. Besides this method, one example

of the oxidative addition of benzoyl chloride to $\text{Ni}(t\text{-BuNC})_4$ was discussed. Developments in this field since that publication are described below.

Carbonylation of dppp-derived Ni(II) cationic complex **163** afforded several four- and five-coordinate complexes such as **164** (Equation (29)), which were characterized by NMR spectroscopy and are relevant to intermediates formed during the copolymerization of ethylene with CO <2001OM16, 2001JA9172>.

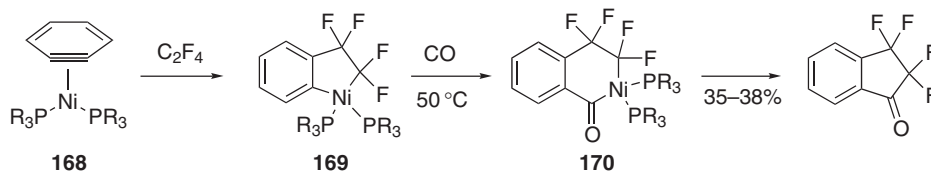


Oxidative insertion of $\text{Ni}(\text{PEt}_3)_4$ into the C—Br bond of bromosydnone **165** gave the Ni(II) bromide **166**, which upon carbonylation gave the acylnickel complex **167** (Scheme 31) <2001IZV525>. Similar results were also obtained for the corresponding Pd(0) and Pt(0) complexes.



Scheme 31

Aryne Ni complexes **168** reacted with tetrafluoroethene to give the corresponding five-membered nickelacycle **169**. Further reaction with CO gave the nickelacyclohexanone compound **170**, which underwent reductive elimination to give the corresponding tetrafluoroindanone (Scheme 32) <1997JCS(D)3105>.

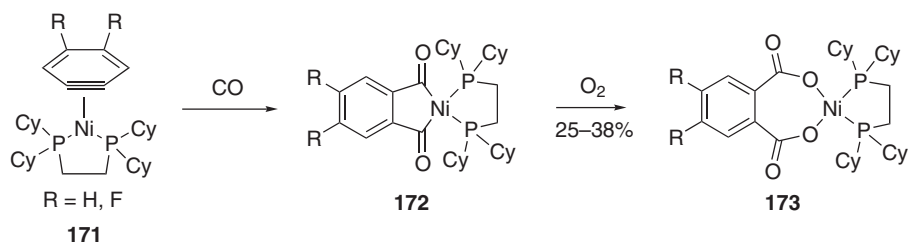


Scheme 32

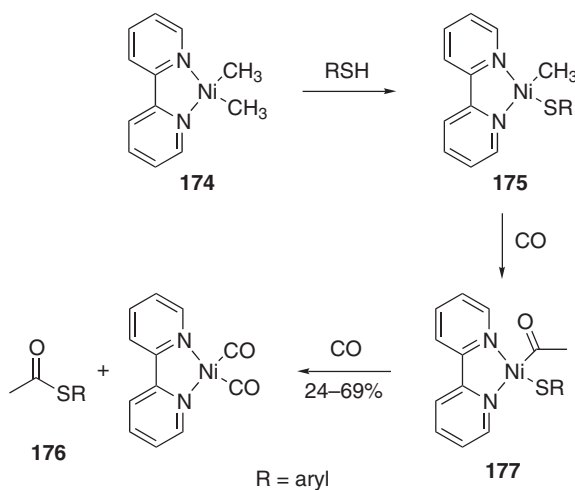
As shown in Scheme 33, reaction of nickel benzyne complexes **171** with CO gave the bis(acyl) nickelacycles **172** <1996OM928>. Reaction of **172** with oxygen gave the stable (phthalato)nickel complexes **173**. Subsequent reaction with I_2 provided the corresponding phthalic anhydrides.

In studies to further understand the mechanism of the acetyl-CoA synthase function of CO dehydrogenase, the acylnickel complex **177** was generated from **174** by reaction with thiols to give **175**, followed by CO insertion (Scheme 34) <1995JA6489>. Further reaction of **175** with CO liberated thioacetate **176** and $(\text{bipy})\text{Ni}(\text{CO})_2$.

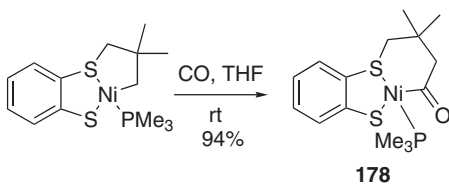
In similar studies by Sellmann and co-workers <1996JA5368>, the nickel complex **178** was prepared by CO insertion as shown in Equation (30).



Scheme 33



Scheme 34



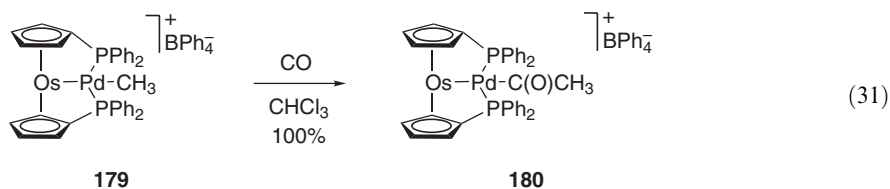
(30)

5.10.5.19 Acylpalladium Compounds

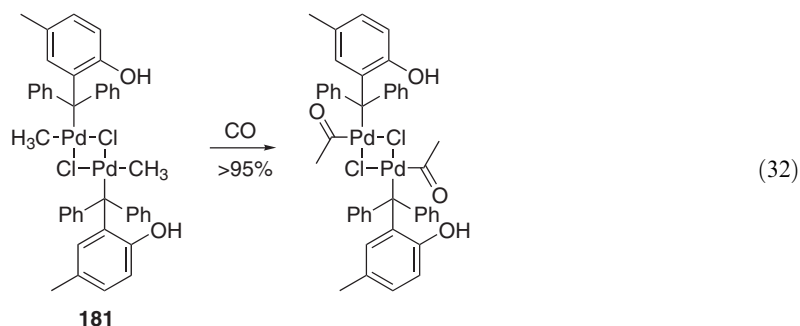
Chapter 5.10.5.19 in <1995COFGT(5)435> described the formation of acylpalladium compounds by two methods: oxidative addition of allylic or benzylic bromides followed by CO insertion, and insertion of CO into the Pd—C bond of arylpalladium complexes. Developments in this field since that publication are described below.

Palladium-catalyzed alkoxy carbonylations of alkenes and CO/olefin copolymerizations are two of the major areas where acylpalladium compounds play a vital role as key intermediates in the reaction process. A vast majority of the work on acylpalladium compounds centers around these reactions, but only to the extent of noting the acyl metal as an intermediate. Because of this trend, a large portion of this work will not be covered in this section, except where the acylpalladium species has been isolated.

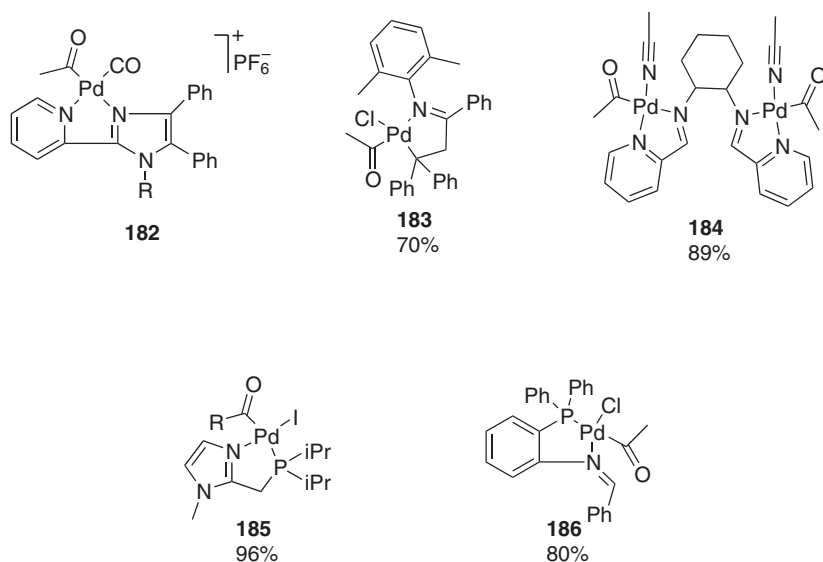
Acylpalladium complex **179** was formed by the reaction of cationic alkylpalladium complex **180** with CO (Equation (31)) <2003OM913>. Compound **180** was also an effective catalyst for the methoxycarboxylation of ethylene and styrene.



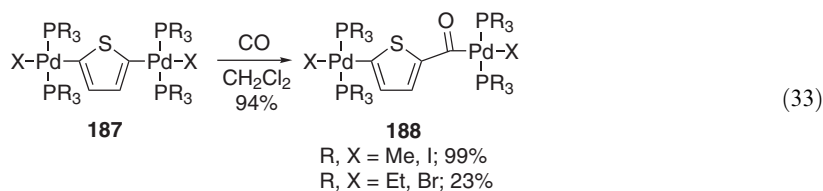
The dimeric complex **181** was converted into the dimeric acylpalladium compound by insertion of CO into the Pd—C bond (Equation (32)) <2002JCS(D)4726>.



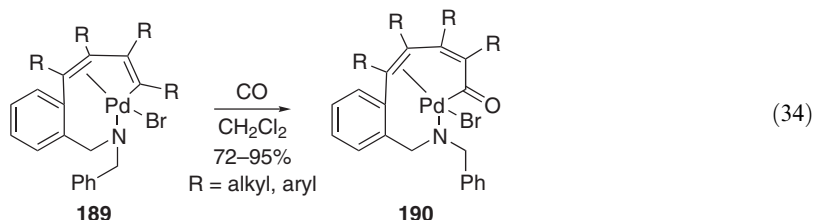
The monocationic acyl complex **182** was prepared in a similar fashion, by CO insertion <2002OM5820>. A new iminophosphine ligand was prepared and shown to be an effective ligand for the generation of stable, isolable acylpalladium complexes such as **183** by insertion of CO into the Pd—C bond of the corresponding methyl complex <2001JCS(D)3384>. A novel diacyldipalladium complex was generated using the racemic bis(bidentate) ligand shown in complex **184** <2001OM3459>. Again, complex **184** was prepared by CO insertion into the Pd—methyl bond of the corresponding alkyl complex. Acylpalladium complexes **185** were prepared by oxidative addition of aryl and alkyl iodides to Pd(dba)₂ in the presence of the appropriate imidazolylphosphine, with subsequent insertion of CO <2001JCS(D)1091>. Complex **186** was simply generated by insertion of CO into the Pd—C bond of the methyl complex <2001OM1292>. Unfortunately, **186** did not catalyze the copolymerization of CO and ethylene.



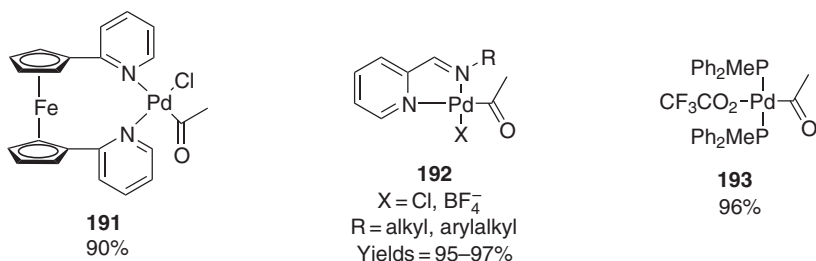
The interesting thienyl dipalladium complexes **187** underwent CO insertion to form the mono-acyl complexes **188** (Equation (33)) <1999JOM(588)268>.



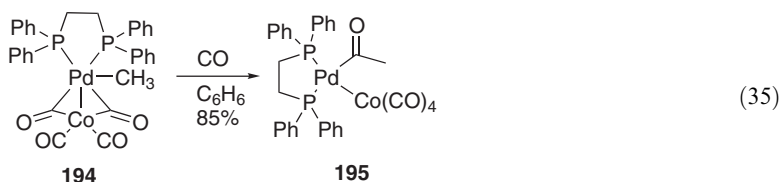
Complex **190** was generated by a very interesting series of reactions starting with $\text{Pd}(\text{OAc})_2$ trimer reacting with dibenzylamine, followed by metathesis with NaBr , and insertion of 2 equiv. of acetylene compound R_2C_2 <1999OM2683>. Insertion of CO into **189** resulted in formation of the dienoylpalladium complex **190** (Equation (34)).



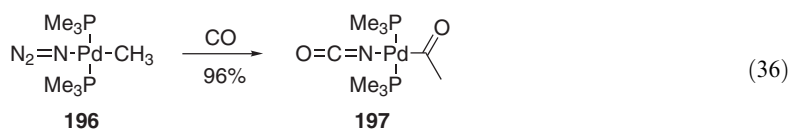
The coordination chemistry of 1,1'-bis(2-pyridyl)ferrocene (BPF) toward palladium has been studied <1996JOM(514)125>. The methyl complex $(\text{BPF})\text{Pd}(\text{Me})\text{Cl}$ was prepared and shown to be stable. Reaction with CO provided the acyl complex **191**. The intriguing [(alkylcarbaldimino)-pyridine] acylpalladium complexes **192** were prepared by CO insertion into the $\text{Pd}-\text{CH}_3$ bond <1996JOM(508)109>. The R substituent had an unprecedented influence on the half-life for the CO insertion. Reaction of trifluoroacetic acid with $\text{Me}_2(\text{Ph}_2\text{MeP})_2\text{Pd}$ generated the corresponding monomethyl trifluoroacetate complex and methane gas <1995MI558>. Subsequent reaction with CO provided complex **193** via CO insertion.



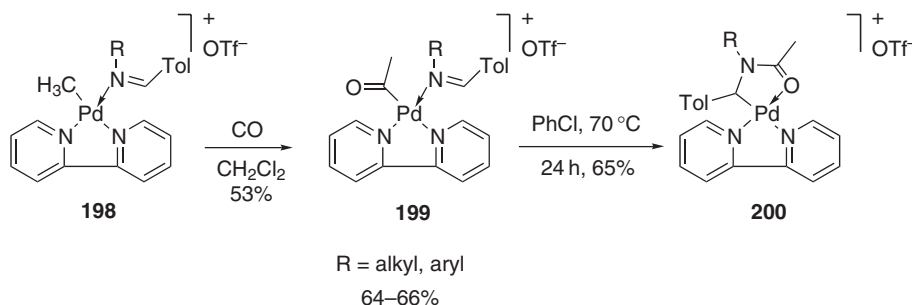
The Pd–Co heterodinuclear complex **194** was reacted with CO to generate the monoacyl complex **195** (Equation (35)) <1997CL377, 2001OM2065>. The insertion of CO into the $\text{Co}(\text{CO})_4$ moiety is less favorable.



The azido complex **196** underwent reaction with CO to give the acetyl palladium isocyanate **197** (Equation (36)) <2000JOM(603)152>. Reaction occurred both at the palladium center and at the azido ligand.

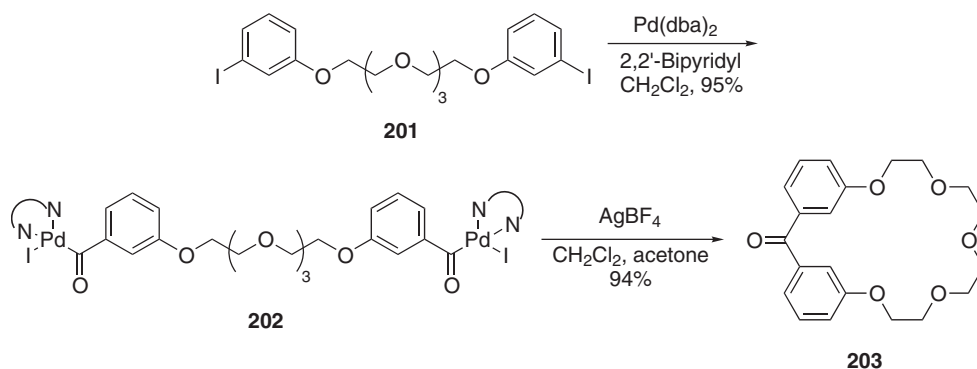


The cationic bipyridyl palladium complex **198** underwent classical CO insertion to give **199**. Upon further reaction at 70 °C, imine insertion occurred to give complex **200** (Scheme 35) <1998OM04>. This sequence was a unique combination of CO insertion, amide bond formation, and carbonyl chelation.



Scheme 35

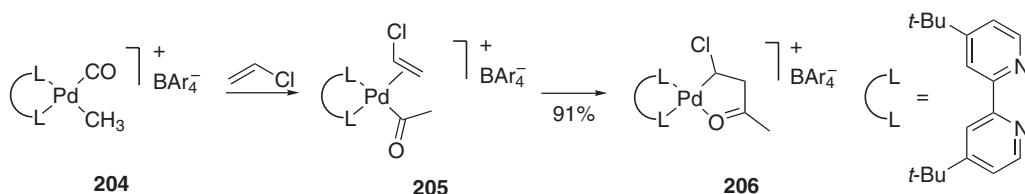
The reaction of diiodide **201** with Pd(dba)₂ gave dinuclear complex **202**. Subsequent reaction with AgBF₄ effected a macrocyclization to give diaryl ketone **203** (Scheme 36) <2003OM2193>.



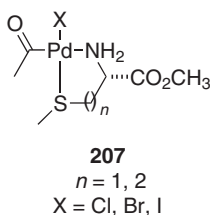
Scheme 36

The reaction of cationic complex **204** with vinyl chloride resulted in migratory insertion of CO into the Pd–methyl bond to give **205** (Scheme 37) <2003OM1878>. Further reaction resulted in the 1,2-insertion product **206**.

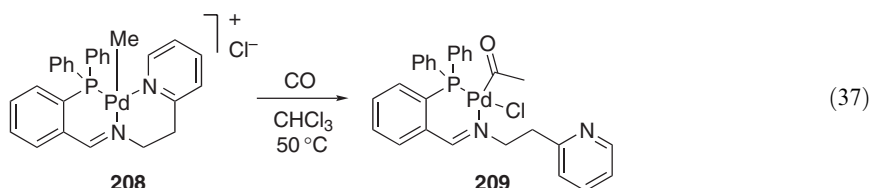
Synthesis of the palladium complexes **207**, bearing the bidentate methioninyl or *S*-methyleysteinylligand, was completed by CO insertion into the Pd–methyl bond <1996ICA(252)203>.



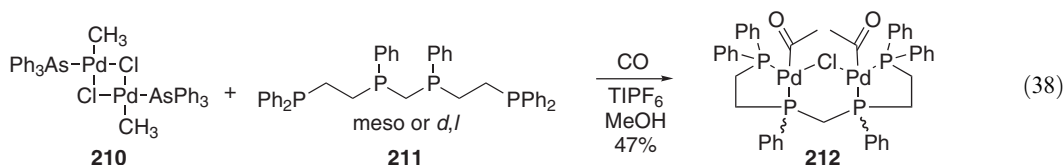
Scheme 37



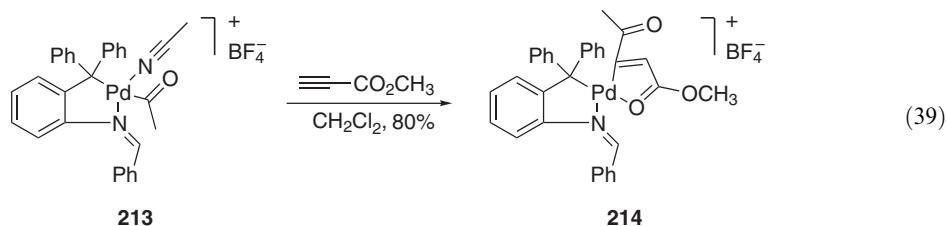
A new, multifunctional, semilabile P-bis-nitrogen ligand was used to generate complex **209** (Equation (37)) <1995CC331>. Reaction of the precursor cationic compound **208** with CO resulted in insertion into the Pd–methyl bond, de-ligation of the pyridine moiety, and coordination of chloride ion. The isolated yield of **209** was not given.



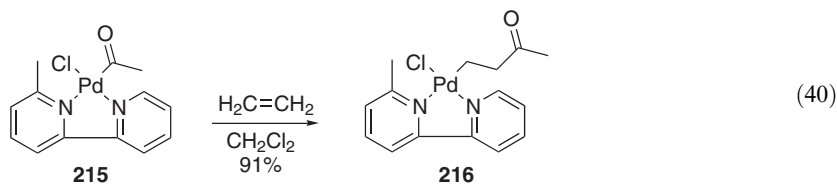
The linear meso or *d,l*-tetraphosphine **211** was reacted with the palladium dimer **210** in the presence of CO to give the chloride-bridged acyl complex **212** (Equation (38)) <2003OM1494>.



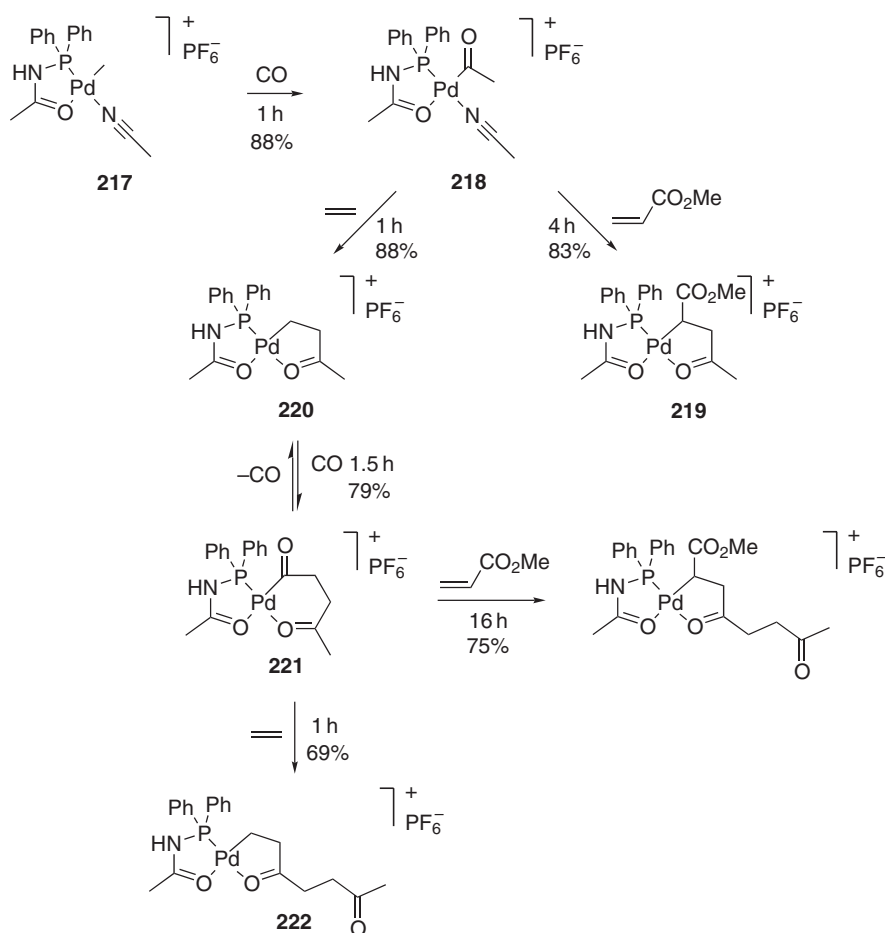
Reaction of acylpalladium complex **213** with methyl propiolate resulted in insertion of the alkyne into the palladium–acyl bond followed by carbonyl coordination to give **214** (Equation (39)) <2001OM5557>.



Insertion of ethene into the palladium–acyl bond during the copolymerization of CO and ethene has been shown to be a key mechanistic step. Formation of **216** by insertion of ethene into the Pd–acyl bond of **215** (Equation (40)) provided an isolable intermediate reflective of the intermediates formed during the copolymerization <2001OM4111>.

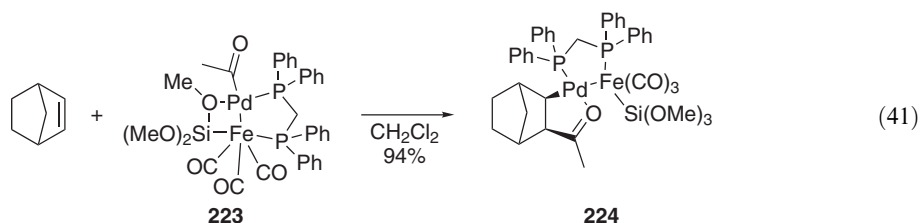


Upon reaction with CO, palladium complex **217** gave the inserted product **218** (Scheme 38). Subsequent insertion of methyl acrylate gave complex **219**, while insertion of ethene gave **220**. Reaction of **220** with another equivalent of CO gave the inserted product **221**, which underwent a second ethene insertion to give the methyl ketone adduct **222** <2000AG(E)2867>. Throughout this sequence, carbonyl coordination from the amidophosphine remained intact.



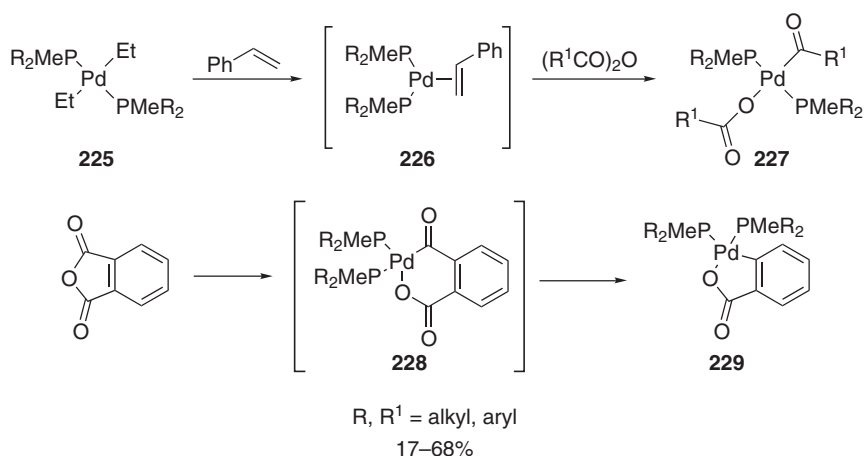
Scheme 38

Norbornene and norbornadiene inserted across the *exo*-face of their double bonds into the Pd–acyl bond of **223** to give the adduct **224** bearing carbonyl coordination, as illustrated in Equation (41) <1999NJC(23)1215>. The chemistry was extended to chiral olefins.

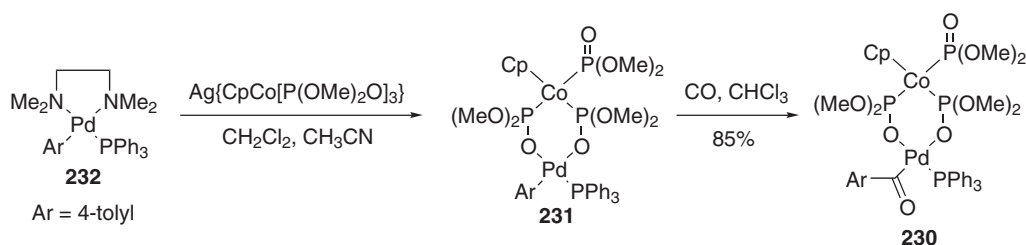


Acyclic anhydrides undergo oxidative addition to palladium–styrene complex **226**, formed from dialkyl complex **225**, to generate the acyl(carboxylato)palladium(II) complex **222** (Scheme 39) <1999BCJ573>. Similarly, reaction of **225** with phthalic anhydride gave acylpalladium complex **228**, which upon loss of CO gave the palladacycle **229**. Subsequent treatment of **227** ($\text{R}^1 = \text{Me}$) with formic acid yielded acetaldehyde, acetic acid, and CO_2 , while subsequent reaction with dihydrogen gave acetaldehyde, acetic acid, and ethanol <1995CL367>.

The intriguing acyl complex **230** was prepared by CO insertion into the Pd–aryl bond of **231** (Scheme 40). Complex **231** was formed by reaction of the TMEDA complex **232** with $\text{Ag}\{\text{CpCo}[\text{P}(\text{OMe})_2\text{O}]\}$ as shown in <1997AJC(50)1047>.

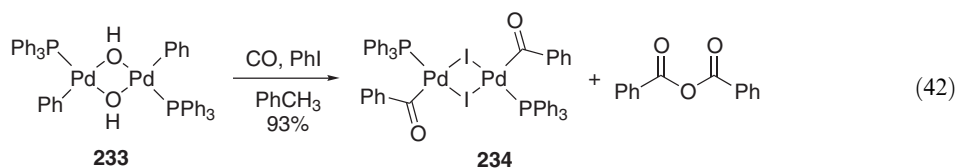


Scheme 39



Scheme 40

The carbonylation of **233** in the presence of PhI resulted in formation of acylpalladium complex **234** and benzoic anhydride (Equation (42)) <1995JA4305>. This reaction corresponds, to some extent, to the generation of benzoic acid from haloarenes, CO, and alkali, catalyzed by (Ph₃P)₂PdCl₂.

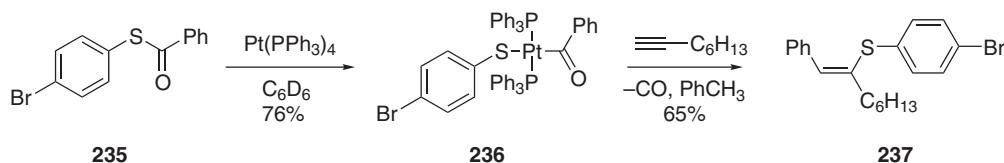


5.10.5.20 Acylplatinum Compounds

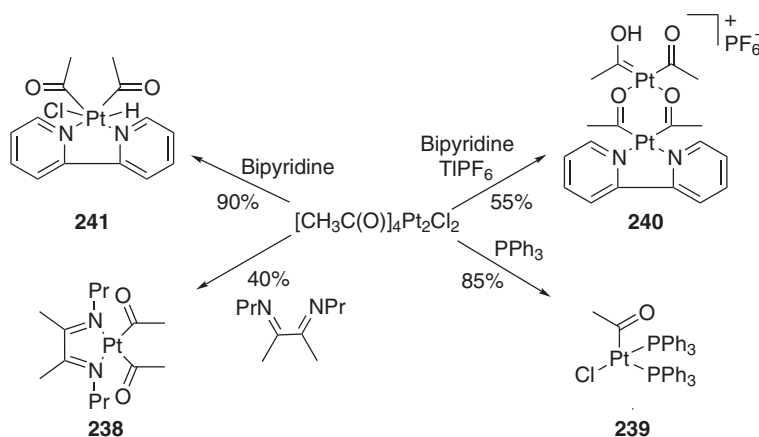
Chapter 5.10.5.20 in <1995COFGT(5)435> provided several examples of methods for formation of acylplatinum compounds. The methods involved the oxidative addition of Pt(0) complexes to cyclopropanones, 1,2-cyclobutandiones, anhydrides, and aldehydes. Developments in this field since that publication are described below.

Reaction of tetrakis(triphenylphosphine)platinum(0) with thioesters **235** resulted in insertion into the C—S bond to generate acylplatinum(II) complexes **236**. Reaction of these intermediates with terminal alkynes gave the addition products **237** regio- and stereoselectively (Scheme 41) <2001JA5108>.

The platinum acyl complexes [RC(O)]₄Pt₂Cl₂ have been shown to be useful intermediates for the preparation of various acylplatinum complexes (Scheme 42). Starting with this complex, mono- and bis(acyl)platinum complexes **238** <2002OM4369>, **239** <2000ZAAC661, 1999OM564>, **240** <1999POL1953>, and **241** <1998OM3101> have been prepared.



Scheme 41



Scheme 42

5.10.5.21 Acylzinc Compounds

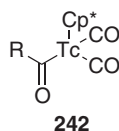
No further advances have occurred in this area since the publication of chapter 5.10.3 in [<1995COFGT\(5\)435>](#). In that publication, the acylzinc species was an intermediate (not isolated) in the preparation of acyloin compounds from dialkylzincs, potassium *t*-butoxide, and CO.

5.10.5.22 Acylniobium Compounds

Acyl niobocene complexes have been prepared by the reaction of olefin hydride complexes with CO under appropriate conditions [<1997OM4161>](#). Acyl niobocenes have been used for the preparation of oxoacylniobocenes [<2000JOM\(598\)167>](#).

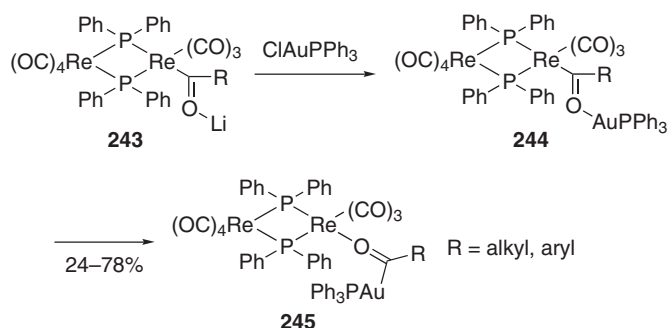
5.10.5.23 Acyltechnetium Compounds

A review has been written on the various methods for the synthesis of different types of technetium complexes. Among those presented are acyltechnetium compounds of the general structure [242](#) [<2003MI91>](#).



5.10.5.24 Acylgold Compounds

The first example of an acylgold complex has been reported [<1998JOM\(553\)497>](#). Reaction of the lithium salts [243](#) with ClAuPPh_3 resulted in an exchange to give gold compound [244](#) (Scheme 43). Upon further reaction, [244](#) underwent a rearrangement to give acylgold compounds [245](#) [<1998JOM\(553\)497>](#).



Scheme 43

5.10.6 GROUP 3 DERIVATIVES

5.10.6.1 Acylaluminum Compounds

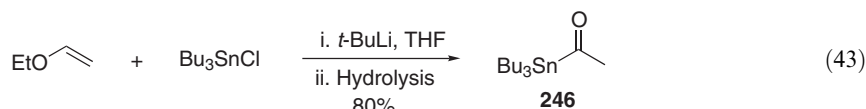
In chapter 5.10.6.1 in <1995COFGT(5)435>, the discussion of group 3 derivatives focused on acylaluminum compounds. One example was given showing the formation of the acylaluminum compound by transmetalation of an acylzirconium species with $AlCl_3$. No further advances have occurred in this area since the publication of COFGT (1995).

5.10.7 GROUP 4 DERIVATIVES

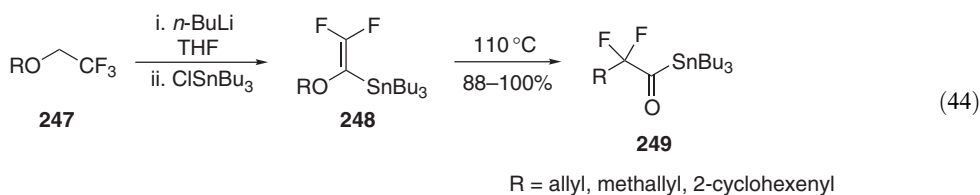
5.10.7.1 Acyltin Compounds

In chapter 5.10.7.1 in <1995COFGT(5)435>, the discussion of group 4 derivatives focused on acyltin compounds. The methods for formation of the acyltin species involved the addition of anionic trialkyltin compounds to acyl chlorides, esters, or aldehydes (followed by oxidation), or the addition of acyl anion equivalents to electrophilic trialkyltin compounds. Developments in this field since that publication are described below.

Metallation of vinyl ethyl ether with t -BuLi followed by quenching with Bu_3SnCl and hydrolysis gave the acetylstannane **246** (Equation (43)) <1995JA10889>.



A very nice method to prepare fluoroalkyl acylstannanes is shown in Equation (44). Metallation of allyl ethers **247** followed by quenching with tributyltin chloride gave stannanes **248**. Thermal sigmatropic rearrangement gave the acyltin compounds **249** <2001TL6377>.

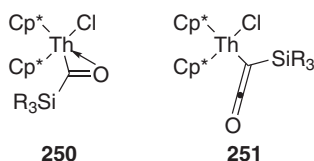


5.10.8 ACTINIDE DERIVATIVES

5.10.8.1 Acylthorium Compounds

Chapter 5.10.8.1 in <1995COFGT(5)435> gave two examples of acylthorium compounds, formed by insertion of CO into thorium—alkyl bonds. The acylthorium compounds are η^2 -acyl complexes. Developments in this field since that publication are described below.

Thorium complex $\text{Cp}^*\text{Th}(\text{Cl})(\text{SiR}_3)$ underwent insertion of CO to generate **250** <1995JA3621>. Compound **250** inserted another molecule of CO to give the metalloxy ketene intermediate **251** in 41% yield.



5.10.8.2 Acyluranium Compounds

No further advances have occurred in this area since the publication of chapter 5.10.8.2 in <1995COFGT(5)435>. In that publication, one example of an acyluranium species was given, being generated by the reaction of uranium tricyclopentadienyl with acetyl chloride.

REFERENCES

- 1995MI558 Y.-J. Kim, J.-Y. Lee, *Bull. Korean Chem. Soc.* **1995**, 16, 558–561.
 1995CB1051 M. Tacke, *Chem. Ber.* **1995**, 128, 1051–1053.
 1995CC331 P. Wehman, R. E. Ruelke, V. E. Kaasjager, P. C. J. Kamer, H. Kooijman, A. L. Spek, C. J. Elsevier, K. Vrieze, P. W. N. M. van Leeuwen, *J. Chem. Soc., Chem. Commun.* **1995**, 331–332.
 1995CC2261 V. C. Gibson, A. D. Poole, *J. Chem. Soc., Chem. Commun.* **1995**, 2261–2262.
 1995CL367 K. Nagayama, F. Kawataka, M. Sakamoto, I. Shimizu, A. Yamamoto, *Chem. Lett.* **1995**, 367–368.
 1995COFGT(5)435 P. Warner, Acyl metal functions, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 435–470.
 1995ICA485 D. Monti, G. Frachey, M. Bassetti, A. Haynes, G. J. Sunley, P. M. Maitlis, A. Cantoni, G. Bocelli, *Inorg. Chim. Acta* **1995**, 240, 485–493.
 1995JA3510 B. P. Cleary, R. Eisenberg, *J. Am. Chem. Soc.* **1995**, 117, 3510–3512.
 1995JA3621 N. S. Radu, M. P. Engeler, C. P. Gerlach, T. D. Tilley, *J. Am. Chem. Soc.* **1995**, 117, 3621–3622.
 1995JA4305 V. V. Grushin, H. Alper, *J. Am. Chem. Soc.* **1995**, 117, 4305–4315.
 1995JA4189 C. P. Casey, C. J. Czerwinski, R. K. Hayashi, *J. Am. Chem. Soc.* **1995**, 117, 4189–4190.
 1995JA6489 G. C. Tucci, R. H. Holm, *J. Am. Chem. Soc.* **1995**, 117, 6489–6496.
 1995JA10889 R. Coleman, E. Grant, *J. Am. Chem. Soc.* **1995**, 117, 10889–10904.
 1995JCS(D)3489 Y. Misumi, Y. Ishii, M. Hidai, *J. Chem. Soc., Dalton Trans.* **1995**, 3489–3496.
 1995JOM273 S.-M. Lee, K.-K. Cheung, W.-T. Wong, *J. Organomet. Chem.* **1995**, 494, 273–278.
 1995JOM(494)105 J.-A. M. Andersen, J. R. Moss, *J. Organomet. Chem.* **1995**, 494, 105–113.
 1995OM589 L. Contreras, A. Pizzano, L. Sanchez, E. Carmona, A. Monge, C. Ruiz, *Organometallics* **1995**, 14, 589–591.
 1995OM4929 K. Wang, T. J. Emge, A. S. Goldman, C. Li, S. P. Nolan, *Organometallics* **1995**, 14, 4929–4936.
 1995POL167 L. Howe, E. E. Bunel, *Polyhedron* **1995**, 14, 167–173.
 1995SL1194 K. Rueck-Braun, J. Kuehn, *Synlett* **1995**, 1194–1196.
 1995TL509 R. W. Bates, T. R. Devi, *Tetrahedron Lett.* **1995**, 36, 509–512.
 1996CC857 M. Sellin, D. Luart, J.-Y. Salaun, P. Laurent, L. Toupet, H. des Abbayes, *J. Chem. Soc., Chem. Commun.* **1996**, 857–858.
 1996ICA(252)203 H. A. Ankersmit, N. Veldman, A. L. Spek, K. Eriksen, K. Goubitz, K. Vrieze, G. van Koten, *Inorg. Chim. Acta* **1996**, 252, 203–219.
 1996JA1557 W. E. Crowe, A. T. Vu, *J. Am. Chem. Soc.* **1996**, 118, 1557–1558.
 1996JA5368 D. Sellmann, D. Haussinger, F. Knoch, M. Moll, *J. Am. Chem. Soc.* **1996**, 118, 5368–5374.
 1996JA10069 B. T. Gregg, A. R. Cutler, *J. Am. Chem. Soc.* **1996**, 118, 10069–10084.
 1996JOC4532 T. A. Hanna, A. M. Baranger, R. G. Bergman, *J. Org. Chem.* **1996**, 61, 4532–4541.
 1996JOM(508)109 R. E. Ruelke, J. G. P. Delis, A. M. Groot, C. J. Elsevier, P. W. N. M. van Leeuwen, K. Vrieze, K. Goubitz, H. Schenk, *J. Organomet. Chem.* **1996**, 508, 109–120.
 1996JOM(514)125 J. G. P. Delis, P. W. N. M. van Leeuwen, K. Vrieze, N. Veldman, A. L. Spek, J. Fraanje, K. Goubitz, *J. Organomet. Chem.* **1996**, 514, 125–136.
 1996JOM(515)173 V. Weinrich, A. Geisbauer, K. Suenkel, W. Beck, *J. Organomet. Chem.* **1996**, 515, 173–181.

- 1996JOM(523)1 K. Wisniewski, Z. Pakulski, A. Zamojski, W. S. Sheldrick, *J. Organomet. Chem.* **1996**, 523, 1–7.
- 1996JOM(524)133 A. C. Filippou, B. Lungwitz, G. Kociok-Koehn, I. Hinz, *J. Organomet. Chem.* **1996**, 524, 133–146.
- 1996OM928 M. A. Bennett, D. C. R. Hockless, M. G. Humphrey, M. Schultz, E. Wenger, *Organometallics* **1996**, 15, 928–933.
- 1996PJC446 K. Wisniewski, A. Zamojski, Z. W. Guo, Z. Ciunik, *Pol. J. Chem.* **1996**, 70, 446–457.
- 1996PJC603 H. Stepowska, Z. Zamojski, *Pol. J. Chem.* **1996**, 70, 603–606.
- 1996T12553 Z.-W. Guo, A. Zamojski, *Tetrahedron* **1996**, 52, 12553–12570.
- 1997AJC(50)1047 M. Glaum, W. Klau, B. W. Skelton, A. H. White, *Aust. J. Chem.* **1997**, 50, 1047–1052.
- 1997CL377 A. Fukuoka, S. Fukagawa, M. Hirano, S. Komiya, *Chem. Lett.* **1997**, 377–378.
- 1997JA3971 C. P. Casey, C. J. Czerwinski, K. A. Fusie, R. K. Hayashi, *J. Am. Chem. Soc.* **1997**, 119, 3971–3978.
- 1997JA8503 J. R. Blecke, R. Behm, *J. Am. Chem. Soc.* **1997**, 123, 8503–8511.
- 1997JCS(D)3105 M. A. Bennett, M. Glewis, D. C. R. Hockless, E. Wenger, *J. Chem. Soc., Dalton Trans.* **1997**, 3105–3114.
- 1997JCS(D)3589 H. Adams, N. A. Bailey, P. Blenkinsop, M. J. Morris, *J. Chem. Soc., Dalton Trans.* **1997**, 3589–3598.
- 1997JOM(535)201 A. van Rooy, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Organomet. Chem.* **1997**, 535, 201–207.
- 1997OM4161 A. Antinolo, F. Carrillo-Hermosilla, I. del Hierro, A. Otero, M. Fajardo, Y. Mugnier, *Organometallics* **1997**, 16, 4161–4166.
- 1997PJC1108 E. Bartnicka, A. Zamojski, *Pol. J. Chem.* **1997**, 71, 1108–1112.
- 1998CC1023 T. Ghaffar, H. Adams, P. M. Maitlis, A. Haynes, G. J. Sunley, M. J. Baker, *J. Chem. Soc., Chem. Commun.* **1998**, 1023–1024.
- 1998CL393 S. H. Ban, Y. Hayashi, K. Narasaka, *Chem. Lett.* **1998**, 393–394.
- 1998CL395 M. Iwakoshi, S. H. Ban, Y. Hayashi, K. Narasaka, *Chem. Lett.* **1998**, 395–396.
- 1998ICA(280)99 W. S. Weston, D. J. Cole-Hamilton, *Inorg. Chim. Acta* **1998**, 280, 99–117.
- 1998OM4338 Y. Kataoka, A. Shibahara, Y. Saito, T. Yamagata, K. Tani, *Organometallics* **1998**, 17, 4338–4340.
- 1998POL1177 D. P. Paterniti, J. D. Atwood, *Polyhedron* **1998**, 17, 1177–1181.
- 1998JOM(553)497 H.-J. Haupt, D. Petters, U. Florke, *J. Organomet. Chem.* **1998**, 553, 497–501.
- 1998JOM(564)267 X. Yin, J.-A. M. Andersen, A. Cotton, J. R. Moss, *J. Organomet. Chem.* **1998**, 564, 267–276.
- 1998OM04 R. D. Dghaym, K. J. Yaccato, B. A. Arndtsen, *Organometallics* **1998**, 17, 4–6.
- 1998OM1946 W.-M. Xue, Y. Wang, M. C.-W. Chan, Z.-M. Su, K.-K. Cheung, C.-M. Che, *Organometallics* **1998**, 17, 1946–1955.
- 1998OM3101 M. Gerisch, C. Bruhn, A. Vyater, J. A. Davies, D. Steinborn, *Organometallics* **1998**, 17, 3101–3104.
- 1998OM4169 B. T. Gregg, A. R. Cutler, *Organometallics* **1998**, 17, 4169–4175.
- 1998PJC688 E. Bartnicka, Zamojski, *Pol. J. Chem.* **1998**, 72, 688–693.
- 1998T14201 K. Wisniewski, A. Zamojski, R. D. Rogers, *Tetrahedron* **1998**, 54, 14201–14212.
- 1998TL8141 Y. Hanzawa, N. Tabuchi, T. Taguchi, *Tetrahedron Lett.* **1998**, 39, 8141–8144.
- 1999AG(E)2395 Y. Hanzawa, N. Tabuchi, K. Saito, S. Noguchi, T. Taguchi, *Angew. Chem., Int. Ed. Engl.* **1999**, 38, 2395–2398.
- 1999BCJ573 K. Nagayama, F. Kawataka, M. Sakamoto, I. Shimizu, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **1999**, 72, 573–580.
- 1999CL309 H. Sakurai, K. Tanabe, K. Narasaka, *Chem. Lett.* **1999**, 309–310.
- 1999JA11233 L. Gonsalvi, H. Adams, G. J. Sunley, E. Ditzel, A. Haynes, *J. Am. Chem. Soc.* **1999**, 123, 11233–11234.
- 1999JCS(P1)3105 S. G. Davies, N. M. Garrido, P. A. McGee, J. P. Shilcock, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3105–3110.
- 1999JOM(574)171 K. Iwamoto, N. Chatani, S. Murai, *J. Organomet. Chem.* **1999**, 574, 171–175.
- 1999JOM(575)21 J.-Y. Watanabe, J.-I. Setsune, *J. Organomet. Chem.* **1999**, 575, 21–32.
- 1999JOM(582)3 L. Contreras, A. Pizzano, L. Sanchez, E. Carmona, *J. Organomet. Chem.* **1999**, 582, 3–8.
- 1999JOM(588)268 Y.-J. Kim, S.-C. Lee, M. H. Cho, S.-W. Lee, *J. Organomet. Chem.* **1999**, 588, 268–277.
- 1999JOU1640 V. A. Ivushkin, P. K. Sazonov, G. A. Artamkina, I. P. Beletskaya, *J. Org. Chem. USSR (Engl. Transl.)* **1999**, 35, 1640–1652.
- 1999NJC(23)1215 P. Braunstein, J. Cossy, M. Knorr, C. Strohmann, P. Vogel, *Nouv. J. Chim.* **1999**, 23, 1215–1222.
- 1999OM2005 T. H. Peterson, J. T. Golden, R. G. Bergman, *Organometallics* **1999**, 18, 2005–2020.
- 1999OM2331 T. Mao, Z. Zhang, J. Washington, J. Takats, R. B. Jordan, *Organometallics* **1999**, 18, 2331–2341.
- 1999OM2683 J. Vicente, I. Saura-Llamas, J. Turpin, M. C. Ramirez de Arellano, P. G. Jones, *Organometallics* **1999**, 18, 2683–2693.
- 1999OM564 M. Gerisch, F. W. Heinemann, C. Bruhn, J. Scholz, D. Steinborn, *Organometallics* **1999**, 18, 564–572.
- 1999POL1953 M. Gerisch, C. Bruhn, D. Steinborn, *Polyhedron* **1999**, 18, 1953–1956.
- 2000AG(E)2867 P. Braunstein, C. Frison, X. Morise, *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 2867–2870.
- 2000CL168 H. Sakurai, K. Tanabe, K. Narasaka, *Chem. Lett.* **2000**, 168–169.
- 2000IC3098 S. M. Massick, J. G. Rabor, S. Elbers, J. Marhenke, S. Bernhard, J. R. Schoonover, P. C. Ford, *Inorg. Chem.* **2000**, 39, 3098–3106.
- 2000ICA(308)51 M. P. Garcia, A. P. Martinez, M. V. Jimenez, C. Siurana, L. A. Oro, F. J. Lahoz, A. Tiripicchio, *Inorg. Chim. Acta* **2000**, 308, 51–58.
- 2000JOM(593)49 P. DeShong, E. D. Soli, G. A. Slough, D. R. Sidler, V. Elango, P. J. Rybczynski, L. J. S. Vosejka, T. A. Lessen, T. X. Le, G. B. Anderson, W. Von Philipsborn, M. Vohler, D. Rentsch, O. Zerbe, *J. Organomet. Chem.* **2000**, 593, 49–62.
- 2000JOM(598)167 A. Antinolo, I. del Hierro, I. Lopez-Solera, S. Garcia-Yuste, A. Otero, M. Fajardo, A. Rodriguez, *J. Organomet. Chem.* **2000**, 598, 167–173.
- 2000JOM(603)152 Y.-J. Kim, Y.-S. Kwak, S.-W. Lee, *J. Organomet. Chem.* **2000**, 603, 152–160.
- 2000OM2073 S. N. Paisner, P. Burger, R. G. Bergman, *Organometallics* **2000**, 19, 2073–2083.
- 2000OM2108 J. Foerstner, A. Kakoschke, R. Wartchow, H. Butenschoen, *Organometallics* **2000**, 19, 2108–2113.
- 2000OM2766 G.-Y. Kiel, Z. Zhang, J. Takats, R. B. Jordan, *Organometallics* **2000**, 19, 2766–2776.

- 2000OM4320 G. Bellachioma, G. Cardaci, A. Macchioni, F. Valentini, C. Zuccaccia, E. Foresti, P. Sabatino, *Organometallics* **2000**, *19*, 4320–4326.
- 2000TL109 Y. Hanzawa, K. Narita, T. Taguchi, *Tetrahedron Lett.* **2000**, *41*, 109–112.
- 2000TL7525 Y. Hanzawa, K. Narita, A. Kakuuchi, T. Taguchi, *Tetrahedron Lett.* **2000**, *41*, 7525–7528.
- 2000CEJ692 L. H. Gade, H. Memmler, U. Kauper, A. Schneider, S. Fabre, I. Bezougli, M. Lutz, C. Galka, I. J. Scowen, M. McPartlin, *Chem. -Eur. J.* **2000**, *6*, 692–708.
- 2000ZAAC661 D. Steinborn, T. Hoffmann, M. Gerisch, C. Bruhn, H. Schmidt, K. Nordhoff, J. A. Davies, K. Kirschbaum, I. Jolk, *Z. Anorg. Allg. Chem.* **2000**, *626*, 661–666.
- 2001AG(E)1119 R. Goikhman, D. Milstein, *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1119–1122.
- 2001ICA187 A. Kayan, A. Wojcicki, *Inorg. Chim. Acta* **2001**, *319*, 187–193.
- 2001JA5108 K. Sugoh, H. Kuniyasu, T. Sugae, A. Ohtaka, Y. Takai, A. Tanaka, C. Machino, N. Kambe, H. Kurosawa, *J. Am. Chem. Soc.* **2001**, *123*, 5108–5109.
- 2001JA9172 C. S. Shultz, J. M. DeSimone, M. Brookhart, *J. Am. Chem. Soc.* **2001**, *123*, 9172–9173.
- 2001JCS(D)1091 M. A. Jalil, S. Fujinami, H. Nishikawa, *J. Chem. Soc., Dalton Trans.* **2001**, 1091–1098.
- 2001JCS(D)3384 K. S. Coleman, M. L. H. Green, S. I. Pascu, N. H. Rees, A. R. Cowley, L. H. Rees, *J. Chem. Soc., Dalton Trans.* **2001**, 3384–3395.
- 2001OM16 C. S. Shultz, J. M. DeSimone, M. Brookhart, *Organometallics* **2001**, *20*, 16–18.
- 2001OM1292 K. R. Reddy, K. Surekha, G.-H. Lee, S.-M. Peng, J.-T. Chen, S.-T. Liu, *Organometallics* **2001**, *20*, 1292–1299.
- 2001OM3459 C. R. Baar, M. C. Jennings, R. J. Puddephatt, *Organometallics* **2001**, *20*, 3459–3465.
- 2001OM5557 K. R. Reddy, K. Surekha, G.-H. Lee, S.-M. Peng, S.-T. Liu, *Organometallics* **2001**, *20*, 5557–5563.
- 2001OM2065 A. Fukuoka, S. Fukagawa, M. Hirano, N. Koga, S. Komiya, *Organometallics* **2001**, *20*, 2065–2075.
- 2001OM2431 Y. Kataoka, A. Shibahara, T. Yamagata, K. Tani, *Organometallics* **2001**, *20*, 2431–2433.
- 2001OM4111 S. Stoccoro, G. Minghetti, M. A. Cinelli, A. Zucca, M. Manassero, *Organometallics* **2001**, *20*, 4111–4113.
- 2001IZV525 V. N. Kalinin, F. M. She, V. N. Khandozhko, P. V. Petrovskii, *Russian Chem. Bull. (Translation of Izvestiya Akademii Nauk, Seriya Khimicheskaya)* **2001**, *50*, 525–530.
- 2001TL1737 Y. Hanzawa, A. Kakuuchi, M. Yabe, K. Narita, N. Tabuchi, T. Taguchi, *Tetrahedron Lett.* **2001**, *42*, 1737–1739.
- 2001TL6377 M. R. Garayt, J. M. Percy, *Tetrahedron Lett.* **2001**, *42*, 6377–6380.
- 2002AG(E)2393 A. C. Filippou, T. Rosenauer, *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2393–2396.
- 2002APOC302 P. Das, M. Sharma, N. Kumari, D. Konwar, D. K. Dutta, *Appl. Organomet. Chem.* **2002**, *16*, 302–306.
- 2002EJ13305 H.-F. Klein, R. Beck, U. Florke, H.-J. Haupt, *Eur. J. Inorg. Chem.* **2002**, 3305–3312.
- 2002ICA419 C. L. Homrighausen, J. J. Alexander, J. A. Krause Bauer, *Inorg. Chim. Acta* **2002**, *334*, 419–436.
- 2002JCS(D)4726 J. S. Kim, A. Sen, I. A. Guzei, L. M. Liable-Sands, A. L. Rheingold, *J. Chem. Soc., Dalton Trans.* **2002**, 4726–4731.
- 2002OM1355 J.-F. Liu, S.-L. Huang, Y.-C. Lin, Y.-H. Liu, Y. Wang, *Organometallics* **2002**, *21*, 1355–1361.
- 2002OM4369 A. Vyater, C. Wagner, K. Merzweiler, D. Steinborn, *Organometallics* **2002**, *21*, 4369–4376.
- 2002OM5820 A. Bastero, A. Ruiz, C. Claver, B. Milani, E. Zangrando, *Organometallics* **2002**, *21*, 5820–5829.
- 2002JOM(642)107 A. Elarraoui, J. Ros, R. Yanez, X. Solans, M. Font-Bardia, *J. Organomet. Chem.* **2002**, *642*, 107–112.
- 2002OM2196 P. Cabon, M. Sellin, J.-Y. Salauen, V. Patinec, H. des Abbayes, M. M. Kubicki, *Organometallics* **2002**, *21*, 2196–2202.
- 2002OL4061 Y. Hanzawa, M. Yabe, Y. Oka, T. Taguchi, *Org. Lett.* **2002**, *4*, 4061–4064.
- 2002T7559 Y. Hanzawa, N. Tabuchi, K. Narita, A. Kakuuchi, M. Yabe, T. Taguchi, *Tetrahedron* **2002**, *58*, 7559–7571.
- 2002T10429 Y. Hanzawa, K. Narita, M. Yabe, T. Taguchi, *Tetrahedron* **2002**, *58*, 10429–10435.
- 2002MI213 R. Alvarez, A. Cabrera, G. Espinosa-Perez, S. Hernandez-Ortega, L. Velasco, B. Esquivel, *Transition Metal Chemistry (Dordrecht, Netherlands)* **2002**, *27*, 213–217.
- 2003EJ1853 H.-F. Klein, R. Beck, U. Florke, H.-J. Haupt, *Eur. J. Inorg. Chem.* **2003**, 853–862.
- 2003H333 M. Nakamura, M. Yamane, H. Sakurai, K. Narasaka, *Heterocycles* **2003**, *59*, 333–345.
- 2003ICA179 H.-F. Klein, X. Li, U. Florke, H.-J. Haupt, *Inorg. Chim. Acta* **2003**, *342*, 179–184.
- 2003JOC1872 R. J. Madhushaw, C.-L. Li, H.-L. Su, C.-C. Hu, S.-F. Lush, R.-S. Liu, *J. Org. Chem.* **2003**, *68*, 1872–1877.
- 2003OM913 O. V. Gusev, A. M. Kalsin, P. V. Petrovskii, K. A. Lyssenko, Y. F. Oprunenko, C. Bianchini, A. Meli, W. Oberhauser, *Organometallics* **2003**, *22*, 913–915.
- 2003OM1494 P. Nair, G. K. Anderson, N. P. Rath, *Organometallics* **2003**, *22*, 1494–1502.
- 2003OM1878 H. Shen, R. F. Jordan, *Organometallics* **2003**, *22*, 1878–1887.
- 2003OM2124 E. Becker, K. Mereiter, M. Puchberger, R. Schmid, K. Kirchner, *Organometallics* **2003**, *22*, 2124–2133.
- 2003OM2134 R. P. Hughes, R. B. Laritchev, A. Williamson, C. D. Incarvito, L. N. Zakharov, A. L. Rheingold, *Organometallics* **2003**, *22*, 2134–2141.
- 2003OM2193 Y. Suzuki, K. Osakada, *Organometallics* **2003**, *22*, 2193–2195.
- 2003OM2284 O. G. Adeyemi, N. J. Coville, *Organometallics* **2003**, *22*, 2284–2290.
- 2003OM2535 M. Bassetti, A. Capone, L. Mastrofrancesco, M. Salamone, *Organometallics* **2003**, *22*, 2535–2536.
- 2003MI91 I. D. Gridnev, T. Imamoto, *Science of Synthesis* **2003**, *2*, 91–110.

Biographical sketch

Gerald J. Tanoury was born in Detroit, MI. He studied at Wayne State University, where he received a B.S. with honors in Chemistry in 1982. After a short time at the Dow Chemical Company, he started his graduate studies in 1984 under the direction of Professor Barry M. Trost at Stanford University, obtaining his Ph.D. in 1989. He spent the next 2 years as an NIH Postdoctoral Fellow in the laboratories of Professor E. J. Corey at Harvard University, completing his postdoctoral work in 1992. After beginning his industrial career as a Medicinal Chemist at the Burroughs-Wellcome Company, he joined Sepracor Inc. in 1995 as a process chemist. He moved to Vertex Pharmaceuticals, Inc. in 2001 where he is currently a Senior Staff Investigator in the Process Chemistry division. His scientific interests include organic process research and development, metal-catalyzed organic reactions, computational studies of organic reactions, and the application of automated robotic technology and statistical analysis to process R&D.

5.11

Thio-, Seleno-, and Telluroacyl Halides

M. F. HEANEY

*National University of Ireland, Maynooth,
Republic of Ireland*

5.11.1	INTRODUCTION	436
5.11.2	GENERAL METHODS	436
5.11.3	THIOACYL FLUORIDES	436
5.11.3.1	Thioacyl Fluorides via Dechlorination of 1-Chlorosulphenyl Chlorides	436
5.11.3.2	Miscellaneous Reactions	437
5.11.4	THIOACYL CHLORIDES	437
5.11.4.1	Thioacyl Chlorides from Dithiocarboxylic Acids	437
5.11.4.2	Thioacyl Chlorides from 1,1-Dichlorosulphenyl Chlorides	438
5.11.4.3	Thioacyl Chlorides via Sulfurization of Polyhaloalkenes, -alkanes, and -alkyl Derivatives	438
5.11.4.4	Thioacyl Chlorides via Thioketenes, Ketenes, and Alkenes	439
5.11.4.5	Thioacyl Chlorides via <i>S</i> -Benzyl Thioethers	439
5.11.4.6	Thioacyl Chlorides via the Reaction between Thiophosgene and Diazoketones	439
5.11.4.7	Thioacyl Chlorides via <i>S</i> -Acetyl 1,1-Dichloroalkyl Disulfides	439
5.11.4.8	Thioacyl Chlorides via Acyl Chlorides	439
5.11.4.9	Thioacyl Chlorides via Dehydrofluorination of Thiols	439
5.11.4.10	Thioacyl Chlorides from Thiocarboxylic Acids	439
5.11.4.11	Thioacyl Chlorides from Reaction between Thiophosgene and Aryllithium Salts	439
5.11.4.12	Miscellaneous Reactions	440
5.11.5	THIOACYL BROMIDES	441
5.11.6	THIOACYL IODIDES	441
5.11.7	HIGHER OXIDATION STATES OF SULFUR	441
5.11.7.1	Sulfur(IV) Derivatives: Halosulfines	441
5.11.7.1.1	<i>Halosulfines via dehydrohalogenation of sulfonyl halides</i>	441
5.11.7.1.2	<i>Halosulfines via oxidation of thioacyl halides</i>	443
5.11.7.1.3	<i>Halosulfines via dichlorosulphenyl chlorides</i>	443
5.11.7.1.4	<i>Preparation of perhalogenated aliphatic halosulfines</i>	444
5.11.7.1.5	<i>Halogenation of stabilized sulfur ylides</i>	444
5.11.7.2	Sulfur(VI) Derivatives	444
5.11.7.2.1	<i>Halosulfenes by dehydrohalogenation of α-halosulfonyl halides</i>	444
5.11.7.2.2	<i>Halosulfinimides by dehydrohalogenation of 1,2-dihalosulfenamides</i>	444
5.11.8	SELENOACYL HALIDES	448
5.11.9	SELENOACYL FLUORIDES	448
5.11.9.1	Selenoacyl Fluorides from Mercuric Perfluoroalkylselenols	448
5.11.10	SELENOACYL CHLORIDES	450
5.11.11	SELENOACYL BROMIDES	450
5.11.12	SELENOACYL IODIDES	450
5.11.13	HIGHER OXIDATION STATES OF SELENIUM	451
5.11.14	TELLUROACYL HALIDES	451
5.11.15	TELLUROACYL FLUORIDES	452
5.11.15.1	Telluroacyl Fluorides via Pyrolysis of Perfluoroalkyltrimethylstannyl Tellurides	452
5.11.16	TELLUROACYL CHLORIDES	455
5.11.17	TELLUROACYL BROMIDES	456
5.11.18	TELLUROACYL IODIDES	456
5.11.19	HIGHER OXIDATION STATES OF TELLURIUM	456

5.11.1 INTRODUCTION

This chapter describes developments in the preparation of chalcogenoacyl halides that have appeared since the publication of chapter 5.11 in COFGT (1995) <1995COFGT(5)471>. In the period 1995–2003 a number of new examples of thioacyl halides (largely chlorides), halosulfines, halosulfinimides, and halosulfenes have appeared; however, none of the new synthetic approaches could be considered as truly general methods for the synthesis of thioacyl halides. Further, a review on the preparation of perfluoroalkanethiocarboxylic acid derivatives, including thioacyl chlorides <1999UKZ10>, would appear to be the only review article on the synthesis of thioacyl halides since the publication of COFGT (1995) <1995COFGT(5)471>.

5.11.2 GENERAL METHODS

The most common subclasses of thioacyl halides to be prepared continued to be aromatic thioacyl chlorides and aliphatic examples substituted with electron-withdrawing groups (predominantly highly halogenated alkyl groups) or with groups bearing no α -protons. There were no advances in the synthesis of thioacyl bromides or iodides and just a few new thioacyl fluorides were described. The approach adopted for the synthesis of chlorosulfines, chlorosulfenes, and halosulfinimides was dehydrohalogenation of sulfonyl halides, α -halosulfonyl halides, and of 1,2-dihalosulfenamides, respectively.

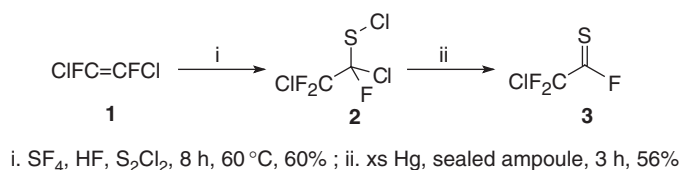
Perhaps the single most significant development in the preparation of the chalcogenoacyl halides since the publication of chapter 5.11 in COFGT (1995) <1995COFGT(5)471> was the synthesis and characterization of the first ever examples of seleno- and telluroacyl fluorides. The inherent instability of the C=Se and C=Te double bonds is responsible for the paucity of examples of compounds with a seleno- or telluroacyl halide functional group. To date, seleno- and telluroacyl fluorides carrying a perfluoroalkyl group capable of stabilizing the C=Se/Te double bond represent the only examples of this subclass of chalcogenoacyl halide. The preparative route of choice to selenoacyl fluorides was from mercury(II) selenols, whereas telluroacyl fluorides were best prepared from trimethylstannyltellurols. As of April 2004, the preparation of seleno- or telluroacyl chlorides, bromides, or iodides as well as seleno/telluroacyl halides containing higher oxidation states of these chalcogens remains a challenge for the future.

5.11.3 THIOACYL FLUORIDES

There have been very few new preparations of thioacyl fluorides reported in the literature since the publication of chapter 5.11.3 in COFGT (1995) <1995COFGT(5)471>. At that time a limited number of examples of thioacyl fluorides had been prepared by the following routes: sulfurization of polyhaloalkenes and related species, dehydrofluorination of 1,1-difluorothiols, acidic cleavage of *S*-benzyl thioethers and by pyrolysis of thioesters. No new examples of thioacyl fluorides prepared by any of these approaches have appeared in the intervening period.

5.11.3.1 Thioacyl Fluorides via Dechlorination of 1-Chlorosulphenyl Chlorides

1,2-Dichloro-1,2,2-trifluoroethanesulphenyl chloride **2**, itself prepared from 1,2-dichloro-1,2-difluoroethene **1**, underwent dechlorination following treatment with mercury and yielded chlorodifluoroethanethioyl fluoride **3** (Scheme 1) <1992ZOR892>.



Scheme 1

5.11.3.2 Miscellaneous Reactions

A synthesis of difluorothioacetyl fluoride **4** was reported in a Russian patent <1994MI2021261> and 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-octadecafluoroundecanthioyl fluoride **5** was claimed in a Japanese patent which also claimed the seleno- and telluroacyl analogs **62** and **73** (see Sections 5.11.9.1 and 5.11.15.1) <1997JAP(K)09235582>.

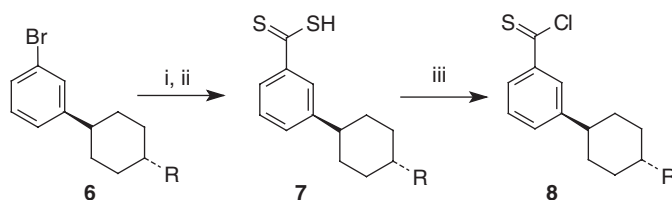


5.11.4 THIOACYL CHLORIDES

The synthesis of thioacyl chlorides has attracted more attention than any of the other chalcogenoacyl halides since the publication of chapter 5.11 of COFGT (1995) <1995COFGT(5)471>. Several examples of aromatic thioacyl chlorides have been described whilst examples of aliphatic analogs remain scarce.

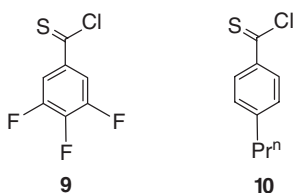
5.11.4.1 Thioacyl Chlorides from Dithiocarboxylic Acids

Access to arylthioacyl chlorides by treatment of the corresponding dithiocarboxylic acid with thionyl chloride has continued to be demonstrated <1997WOP9736847, 2001USP6190576>. The dithiocarboxylic acids 7,4-(*trans*-4-propylcyclohexyl)phenyldithiocarboxylic acid and 4-(*trans*-4-pentylcyclohexyl)phenyldithiocarboxylic acid, themselves prepared from a Grignard reaction between the bromo precursor **6** and carbon disulfide, were reacted with thionyl chloride in boiling diethyl ether to furnish the thioacyl halides **8** (Scheme 2). Crude yields of 4-(*trans*-4-propylcyclohexyl)phenyldithiocarboxylic acid and its pentyl analog were high, 80% and 96% yield, respectively. Both acids converted in quantitative yield to murex (deep purple) colored acid chlorides, the former was an oily substance, whereas the latter was a paste. The authors used the products without further purification <1997WOP9736847, 2001USP6190576>. 3,4,5-Trifluorophenylthionyl chloride **9**, also a deep murex oil <1997WOP9737960>, and 4-*n*-propylthiobenzoyl chloride **10**, a dark purplish red oily material <1998WOP9812166, 2001USP6177154>, were similarly prepared in crude yields of 89% and 100%, respectively.

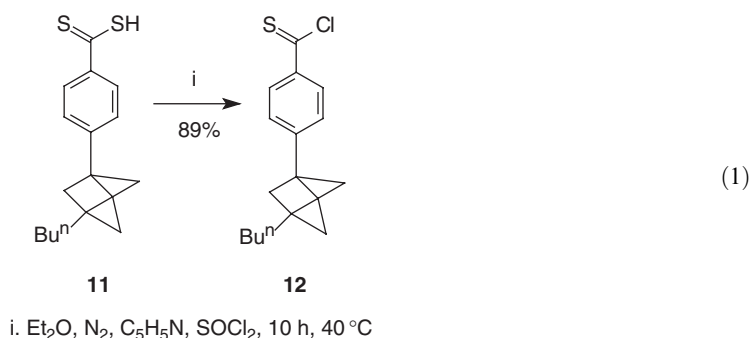


i. THF, N₂, Mg; ii. CS₂; iii. Et₂O, SOCl₂, reflux, 8 h

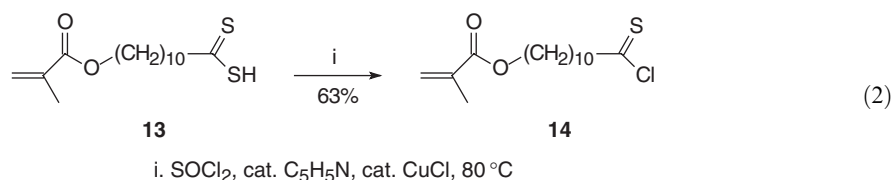
Scheme 2



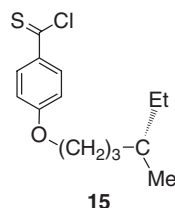
The preparation of 4-(3-butylbicyclo[1.1.1]pent-1-yl)benzenethioyl chloride **12** was claimed in a recent patent concerned with new liquid crystal compounds having a bicyclo[1.1.1]pentane structure. The thioacyl chloride, a dark purplish red oil, was prepared from its parent dithioic acid **11** by a procedure that differed from that described for related arylthioacyl chlorides **8–10** in that the reaction of the dithioic acid with thionyl chloride was catalyzed by pyridine (Equation (1)) <1998WOP9835924>.



11-Chloro-11-thioxoundecyl 2-methyl-2-propenoate **14** has been prepared by reaction of dithioic acid **13** with thionyl chloride. In this preparation pyridine and copper(I) chloride were both added as catalysts for the reaction which was conducted in the absence of solvent. The reaction mixture was heated at reflux until the evolution of gases subsided. Following removal of the excess thionyl chloride by vacuum distillation, the product was purified by chromatography to afford the thioacyl chloride (Equation (2)) <1989EUP348166, 1993USP5254198>.



The (*S*)-enantiomer of 4-[(4-methylhexyl)oxy]benzenecarbothioyl chloride **15** has been claimed in a Japanese patent as an intermediate *en route* to cyclohexylthiodiazyl derivatives which are of potential interest as liquid crystal compositions. The corresponding dithioacid was registered as a reactant in the same patent <1992JAP(K)04159270>.



5.11.4.2 Thioacyl Chlorides from 1,1-Dichlorosulfonyl Chlorides

There have been no developments in this area since the work reported in chapter 5.11.4.2 of COFGT (1995) <1995COFGT(5)471>. Thus, to date there have only been a limited number of examples of α -carbamoyl and of arylthioacyl chlorides prepared by triphenylphosphine-initiated dechlorination of 1,1-dichlorosulfonyl chlorides.

5.11.4.3 Thioacyl Chlorides via Sulfurization of Polyhaloalkenes, -alkanes, and -alkyl Derivatives

There have been no new examples of preparation of thioacyl chlorides from the treatment of polyhaloalkenes, -alkanes, or -alkyl derivatives with sulfur since those reported in the 1960s and summarized in chapter 5.11.4.3 of COFGT (1995) <1995COFGT(5)471>.

5.11.4.4 Thioacyl Chlorides via Thioketenes, Ketenes, and Alkenes

The most recent examples of thioacyl chlorides prepared by way of reaction between thioketenes and HCl, or from reaction of ketenes or alkenes with thiophosgene are those which date from the mid-1970s to the early 1980s and were recorded in chapter 5.11.4.4 of COFGT (1995) <1995COFGT(5)471>.

5.11.4.5 Thioacyl Chlorides via *S*-Benzyl Thioethers

The preparation of thioacyl chlorides by the action of Lewis or Brønsted acids on *S*-benzyl thioethers reported in 1987 and recorded in chapter 5.11.4.5 of COFGT (1995) <1995COFGT(5)471> remains the only example of this preparative route to thioacyl chlorides.

5.11.4.6 Thioacyl Chlorides via the Reaction between Thiophosgene and Diazoketones

There have been no developments in this area since the preparation of two examples of α -chlorothioacyl chlorides from the reaction of aryl diazoketones with thiophosgene in ether which were recorded in COFGT (1995) <1995COFGT(5)471>.

5.11.4.7 Thioacyl Chlorides via *S*-Acetyl 1,1-Dichloroalkyl Disulfides

The generation and trapping of thioacyl chlorides upon treatment of *S*-acetyl 1,1-dichloroalkyl disulfides with morpholine remains the only example of thioacyl chloride preparation by this method; this work was recorded in COFGT (1995) <1995COFGT(5)471>.

5.11.4.8 Thioacyl Chlorides via Acyl Chlorides

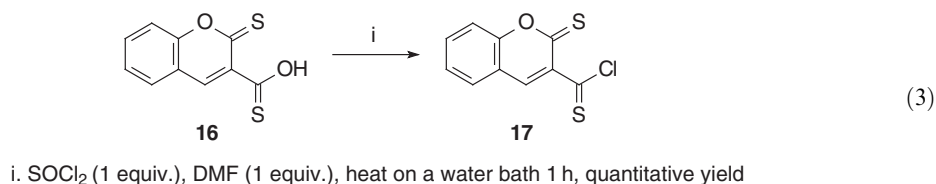
There remains only the one successful example of the seemingly obvious functional group interconversion between acyl and thioacyl halides which was recorded in COFGT (1995) <1995COFGT(5)471>.

5.11.4.9 Thioacyl Chlorides via Dehydrofluorination of Thiols

The generation of thioacyl chlorides by dehydrofluorination of 1-chloro-1-fluorothiols remains a rare reaction with only a single reported example, dating from 1967, recorded in COFGT (1995) <1995COFGT(5)471>.

5.11.4.10 Thioacyl Chlorides from Thiocarboxylic Acids

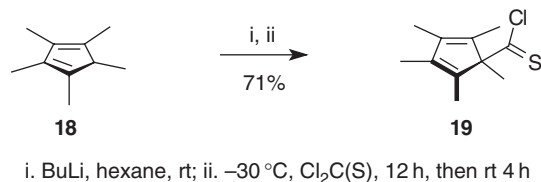
2-Thioxo-2*H*-1-benzopyran-3-carbothieryl chloride **17** was prepared from the monothiocarboxylic acid **16** following treatment with thionyl chloride (Equation (3)) <1996KGS909>.



5.11.4.11 Thioacyl Chlorides from Reaction between Thiophosgene and Aryllithium Salts

There have only been two reports on the use of thiophosgene in the formation of thioacyl chlorides. The first one, the reaction of Cl₂CS with aryl diazoketones, is referred to above. The second one involved the reaction of pentamethylcyclopentadienyllithium, generated *in situ* from

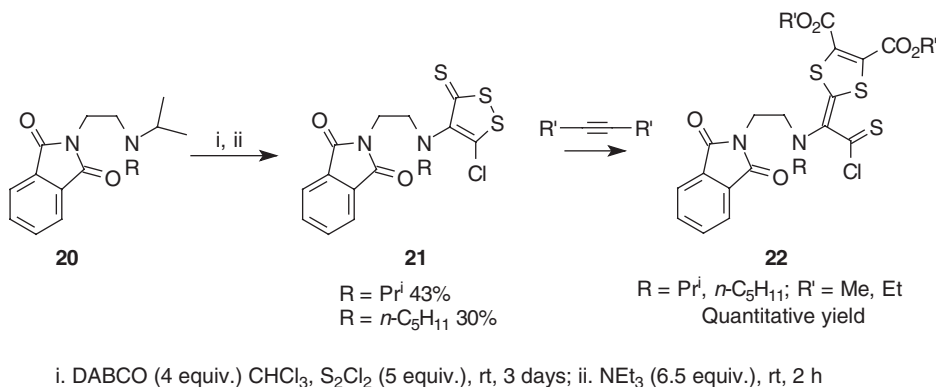
the cyclopentadiene **18**, with thiophosgene to form 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene-5-thiocarbonyl chloride **19** as a reddish oil that was purified by fractional distillation under vacuum (Scheme 3). The cyclopentadiene-5-thiocarbonyl chloride **19** was an air- and moisture-stable compound which was fully characterized by ^1H and ^{13}C NMR spectroscopy. The steric bulk of the pentamethylcyclopentadienyl moiety was believed to account for the stability of **19** toward nucleophiles <1993CB415>.



Scheme 3

5.11.4.12 Miscellaneous Reactions


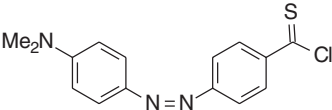
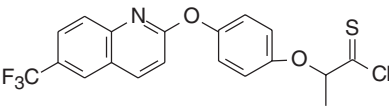
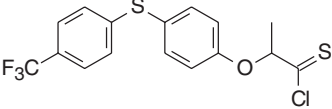
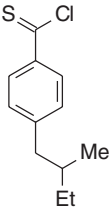
A novel class of stable thioacid chlorides, the 2-{[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-amino}-2-(1,3-dithiol-2-ylidene)ethanethiyl chlorides **22**, has been prepared following cycloaddition of dialkyl acetylenedicarboxylates to the 5-chloro-1,2-dithiole-3-thiones **21**, themselves prepared as potential antitumor agents. The reaction sequence began with treatment of *N*-(2-phthalimidoethyl)-*N*-alkylisopropylamines **20** in CHCl_3 with S_2Cl_2 and DABCO; subsequent treatment with Et_3N afforded the 5-chloro-1,2-dithiole-3-thiones **21**. The thiocarbonyl chloride was unmasked following cycloaddition to the activated alkyne (Scheme 4). The thioacyl chlorides **22**, obtained in quantitative yield, were stable solids which were fully characterized by spectroscopy <2003OL929>.



Scheme 4

Further interesting and unique examples of thioacyl chlorides have been found within the patent literature (Table 1). In the main, the patents describe these compounds as reactants within synthetic schemes and unfortunately no information was found on preparation of the thioacyl halides themselves. However, the reader may be interested in the structural diversity within the selection of structures shown in Table 1. In the quest for new materials, trimethylthioacetyl chloride **23** was employed as a reactant without reference to its synthesis or commercial availability <2000USP6099903>. 4-Dimethylaminophenylazo-4'-thioacyl chloride **24** was employed as a reactant in the synthesis of labeled phosphoramidite compositions. The patent claims to have purchased **24**, but no preparative information for **24** can be found in the chemical literature <2000USP6114518>. Amongst the other thioacyl chlorides found in the literature were 2-[4-[(6-trifluoromethyl)-2-quinolinyl]oxo]phenoxy]propanethiyl chloride **25** and 2-[4-[(4-trifluoromethyl)phenyl]thio]phenoxy]propanethiyl chloride **26**, which were employed as reactants

Table 1 Miscellaneous thioacyl chlorides

Thioacyl chloride	Compound number	References
	23	<2000USP6099903>
	24	<2000USP6114518>
	25	<1994JAP(K)06128213>
	26	<1994JAP(K)06128213>
	27	<1995JAP(K)07070049>

in the preparation of new herbicidal compounds <1994JAP(K)06128213>. Finally, 4-(2-methylbutyl)benzenecarbothioyl chloride **27** was claimed in a Japanese patent describing new materials for optically active liquid crystals <1995JAP(K)07070049>.

5.11.5 THIOACYL BROMIDES

No further advances have occurred in this area since the publication of chapter 5.11.5 in COFGT (1995) <1995COFGT(5)471>. The inherent instability and high reactivity of the thioacyl bromides is the likely reason why no new examples of these compounds have been reported.

5.11.6 THIOACYL IODIDES

No references to these compounds were found in the literature up to the publication of chapter 5.11.6 in COFGT (1995) <1995COFGT(5)471> and the preparation of the first examples of thioacyl iodides remains a synthetic challenge even up to the end of April 2004.

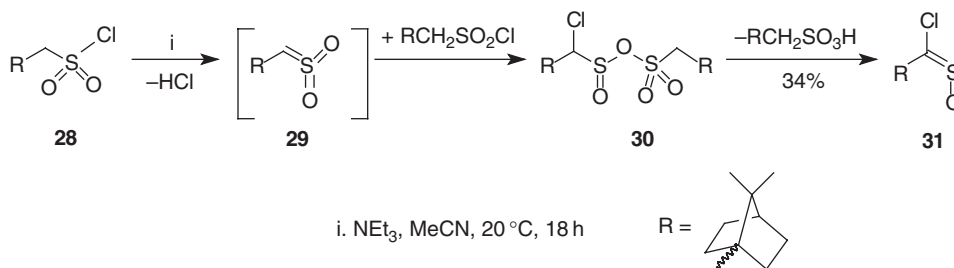
5.11.7 HIGHER OXIDATION STATES OF SULFUR

5.11.7.1 Sulfur(IV) Derivatives: Halosulfines

5.11.7.1.1 Halosulfines via dehydrohalogenation of sulfonyl halides

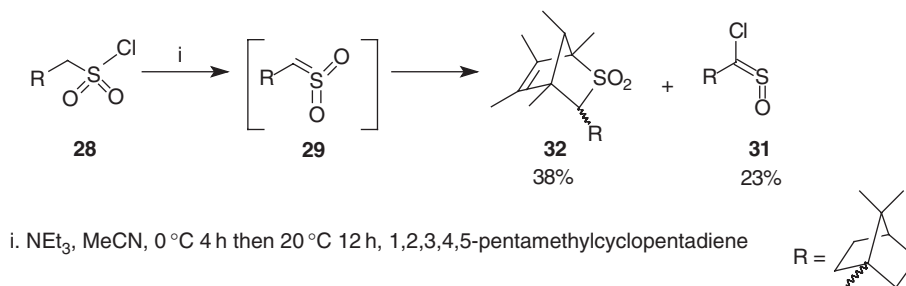
Dehydrohalogenation of sulfonyl halides leads to halosulfines. The reaction is known to be sensitive to experimental conditions such as the choice of reaction solvent as well as temperature, base and the presence of any additives. The reaction mechanism, somewhat complex, is discussed in chapter 5.11.7.1.1 of COFGT (1995) <1995COFGT(5)471>.

The formation of chloro(7,7-dimethylbicyclo[2.2.1]hept-1-yl)sulfine **31** which was isolated from reaction of 10-camphanesulfonyl chloride **28** with NEt_3 in MeCN at 20°C is the only new example of a chlorosulfine prepared from reaction of a sulfonyl halide with a tertiary amine. Initial base-induced HCl elimination from **28** generated the transient sulfene **29**, which was captured by a second sulfonyl halide to generate the mixed sulfinic-sulfonic anhydride **30**, and subsequent sulfonate elimination generated the chlorosulfine **31** which was stable to purification by chromatography (Scheme 5) <1995LA2137>.



Scheme 5

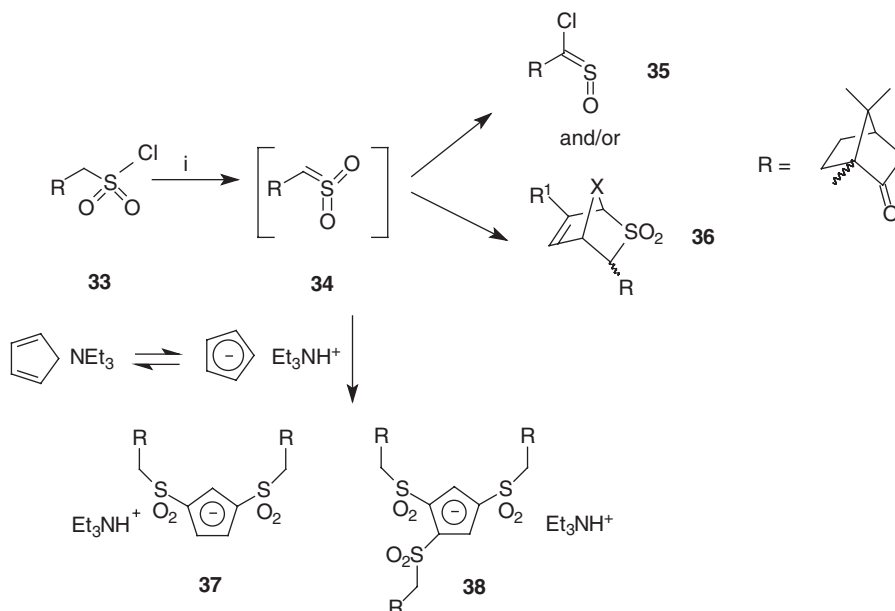
The same sulfine was isolated as a by-product during a reaction designed to trap the transient sulfene **29** in a [4 + 2]-cycloaddition reaction with 1,2,3,4,5-pentamethylcyclopentadiene in MeCN in the presence of NEt_3 at 0°C . Under the competitive reaction conditions the chlorosulfine **31** was formed together with the *exo*- and *endo*-isomers of cycloaddition product **32** (Scheme 6). Interestingly, in non-nitrilic solvents, e.g., THF, formation of the chlorosulfine did not compete with sulfene trapping and the Diels-Alder adducts were the only products of reaction. However, despite the observed chemospecificity the isolated yield of the cycloadducts **32** was only 26% <1995LA2151>.



Scheme 6

The preparation of chloro[(1*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]sulfine **35** (camphor-chlorosulfine) from (+)-10-camphorsulfonyl chloride **33** employing triethylamine or pyridine as base with yields ranging 24–75% was discussed in chapter 5.11.7.1.1 of COFGT (1995) <1995COFGT(5)471>. Ironically, **35** was isolated in even higher yield (93%) from a reaction between the sulfonyl chloride **33** and 1,3-cyclohexadiene which was designed to trap the intermediate sulfene **34** in a [4 + 2]-cycloaddition (Scheme 7 and Table 2) <1995LA2137>. Significantly, when the diene was changed from 1,3-cyclohexadiene to cyclopentadiene, no chlorosulfine was detected and the [4 + 2]-cycloadduct **36** was isolated in just 12% yield. In this case, triethylammonium cyclopentadienide, which exists in equilibrium with NEt_3 and cyclopentadiene, trapped the sulfene **34** and the di- and trisulfonylated products **37** and **38** were the major reaction products. When cyclopentadiene was kept as the 4π -component and the nitrilic reaction solvent changed to THF, a 79% yield of the Diels-Alder adduct **36** was observed and no chlorosulfine or sulfonylated cyclopentadienides were detected. A further dramatic shift in chemoreactivity accompanied a change in base from NEt_3 to *N*-ethyl-diisopropylamine (THF, 0°C), whereupon the Diels-Alder adduct **36** represented only 7% of the reaction products and the chlorosulfine **35** was formed in 80% yield. The slow generation of sulfene **34** induced by EtNPr_2 was believed to be responsible for promoting chlorosulfine formation over the [4 + 2]-cycloaddition reaction with cyclopentadiene. However, even with EtNPr_2 as base, in the

presence of more reactive dienes, e.g., methylcyclopentadiene, neither halosulfine formation nor sulfonation competed with the hetero-Diels–Alder reaction and the [4 + 2]-adduct was isolated in 69% yield as the only product of reaction [<1995LA2137>](#). These observations serve to illustrate the sensitivity of the reaction between sulfonyl halides and base to experimental conditions with the relative distribution of products, chlorosulfine, sulfonylated products or [4 + 2]-cycloadducts, varying with choice of base, reaction solvent or diene component.



i. Base, diene and reaction conditions - as per Table 2

Scheme 7

Table 2 Chlorosulfine **35** prepared according to [Scheme 7](#)

Base	Reaction conditions	Diene	Yield	
			Sulfine 35	[4 + 2]-adduct 36
NEt ₃	MeCN, 0 °C, 1 h	1,3-cyclohexadiene	93%	-
NEt ₃	MeCN, 0 °C, 1.5 h	Cyclopentadiene	-	12% ^a X = CH ₂ , R = H
NEt ₃	THF, 0 °C, 2 h	Cyclopentadiene	-	79% X = CH ₂ , R = H
NEtPr ₂ ⁱ	THF, 0 °C, 3 h	Cyclopentadiene	80%	7% X = CH ₂ , R = H
NEtPr ₂ ⁱ	THF, 0 °C, 5 h; 20 °C 16 h	1- and 2-methyl cyclopentadiene ^b	-	69% X = CH ₂ , R = Me

^a Di- and trisulfones **37** and **38** comprised the major products. ^b Mixture of 1- and 2-methylcyclopentadiene.

5.11.7.1.2 Halosulfines via oxidation of thioacyl halides

No further examples of peracid-induced oxidation of thioacyl halides to furnish aryl chlorosulfines or *N,N*-disubstituted α -carbamoyl chlorosulfines have appeared since the demonstration of this preparative route to halosulfines in the 1970s. The original reactions were discussed in chapter 5.11.7.1.2 of COFGT (1995) [<1995COFGT\(5\)471>](#).

5.11.7.1.3 Halosulfines via dichlorosulfonyl chlorides

There have been no new examples of halosulfene generation by way of mild basic hydrolysis of α -dichlorosulfonyl chlorides since the first examples reported in the 1970s which were summarized in chapter 5.11.7.1.3 of COFGT (1995) [<1995COFGT\(5\)471>](#).

5.11.7.1.4 Preparation of perhalogenated aliphatic halosulfines

No further advances have occurred in this area since the publication of chapter 5.11.7.1.4 of COFGT (1995) <1995COFGT(5)471>.

5.11.7.1.5 Halogenation of stabilized sulfur ylides

No new examples of formation of halosulfines from stabilized sulfur ylides were reported since the publication of chapter 5.11.7.1.5 in COFGT (1995) <1995COFGT(5)471>.

5.11.7.2 Sulfur(VI) Derivatives

The treatment of sulfonyl chlorides with base is a well-known method for the generation of sulfenes, although their high reactivity has continued to prevent the isolation of sulfenes as free stable species. Consequently, the evidence in support of sulfene existence continues to lie with their characterization as amine complexes, and [2 + 2]- or [4 + 2]-cycloaddition products as was described in chapter 5.11.7.2 of COFGT (1995) <1995COFGT(5)471>. In the early examples, enammones were employed as dienes for sulfene trapping by Diels–Alder cycloaddition reactions, and recent progress in this area lies with the application of cyclopentadiene as an effective trap for sulfenes bearing either bulky or electron-attracting substituents, and its 1,2,3,4,5-pentamethyl derivative as a trap for simple sulfenes <1995LA2137, 1995LA2151>.

5.11.7.2.1 Halosulfenes by dehydrohalogenation of α -halosulfonyl halides

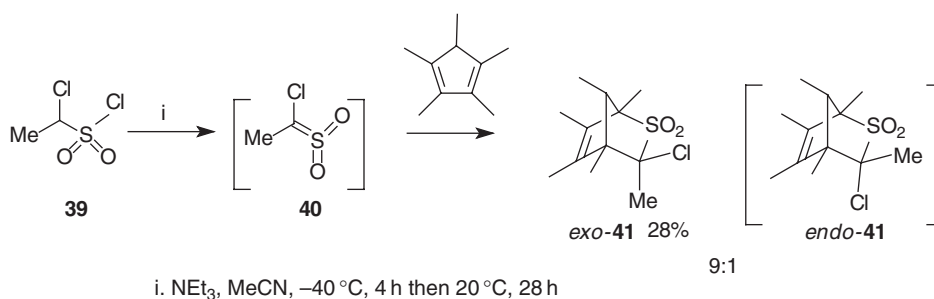
The intermediacy of sulfenes in the generation of halosulfines by dehydrohalogenation of sulfonyl halides was discussed in Section 5.11.7.1.1. That such halosulfines may persist under reaction conditions designed to trap the sulfene in a Diels–Alder reaction with cyclopentadiene (or its substituted analogs) was also discussed in the same section. Critical factors in determining the nature of the reaction products—namely halosulfene, [4 + 2]-cycloadduct, or sulfonylated cyclopentadienide—have been shown to be choice of solvent and base as well as diene structure <1995LA2137, 1995LA2151>. The characteristics of 1,2,3,4,5-pentamethylcyclopentadiene which make it a suitable diene trap for simple sulfenes are its high reactivity (100 times more reactive as a diene than cyclopentadiene) and low acidity (pK_a 26.1 as opposed to pK_a 18 for cyclopentadiene), permitting experimentation with bases stronger than Et_3N without risking products arising from sulfonylation reaction. The ready availability of the pentamethylcyclopentadiene is also attractive <1995LA2151>.

Treatment of 1-chloroethylsulfonyl chloride **39** with Et_3N generated unstable chloro(methyl)sulfene **40** which was trapped *in situ* by way of a hetero-Diels–Alder reaction with 1,2,3,4,5-pentamethylcyclopentadiene. The reaction occurred in MeCN at $-40^\circ C$ to form the [4 + 2]-adduct **41** (Scheme 8). The diastereoselectivity of the reaction in generation of the *endo*- and *exo*-adducts in 1:9 ratio, as judged from the 1H NMR spectrum of the crude reaction mixture, was explained on the basis of the relative size of the C-2 substituents with the larger methyl group occupying the *endo*-position. Following separation of the crude reaction products by flash column chromatography the *exo*-adduct was isolated in 28% yield, an isolated sample of the *endo*-adduct was not reported. The structure of the major diastereoisomer of **41** as the *exo*-adduct was confirmed by single-crystal X-ray structure determination <1995LA2151>.

5.11.7.2.2 Halosulfinimides by dehydrohalogenation of 1,2-dihalosulfenamides

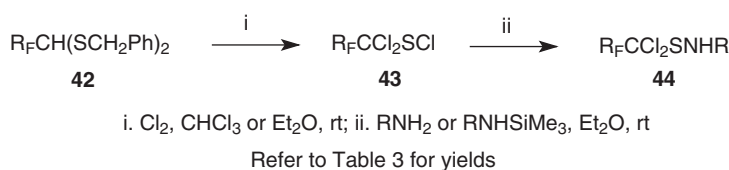
Sulfinimides represent a relatively rare class of organic heterocumulene, and indeed at the time of publication of chapter 5.11 in COFGT (1995) <1995COFGT(5)471> there were no reported examples of α -halosulfinimides. It has since been shown that lithium hexamethyldisilazane-induced dehydrochlorination of 1,2-dihalosulfenamides is a viable synthetic route to α -halosulfinimides and both α -chloro **45** and α -fluoro **53** derivatives have been prepared.

The dichlorosulfenamide substrates **44** required for formation of the α -chlorosulfinimides **45** were prepared in two steps from the *S,S*-dibenzyl dithioacetals of polyfluorinated aliphatic aldehydes **42**. Initial chlorination led to the 1,1-dichloropolyfluoroalkylsulfonyl chlorides **43**, and subsequent



Scheme 8

reaction with the appropriate amine afforded the sulfenamides **44** (Scheme 9 and Table 3). The preparation of the precursors was documented in the same papers <1992ZOR14, 1992ZOR427, 1995HAC9>. Addition of lithium hexamethyldisilazane to a solution of the appropriate sulfenamide **44** in either diethyl ether or hexane yielded the α -chlorosulfinimides **45** in good yield and as single geometrical isomers (Equation (4) and Table 4) <1992ZOR427, 1995HAC9>.

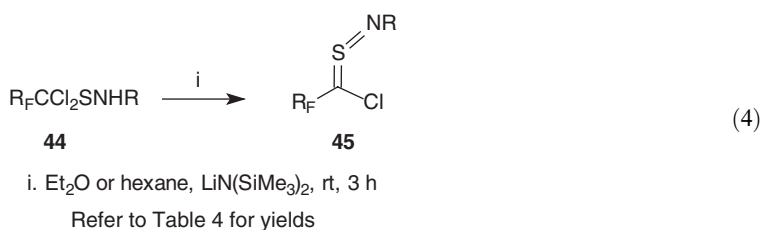


Scheme 9

Table 3 1,1-Dichlorosulfenamides **44** prepared from **43** according to Scheme 9

R_F	R	Sulfenamide, yield	References
H(CF ₂) ₄	Bu ^t	44a , 90%	<1992ZOR427>
H(CF ₂) ₄	C ₆ H ₄ Me	44b ^a	<1992ZOR427>
H(CF ₂) ₄	1-Ad	44c , 70%	<1995HAC9>
H(CF ₂) ₄	CH ₃	44d , 64%	<1995HAC9>
<i>n</i> -C ₃ F ₇	Bu ^t	44e , 72%	<1995HAC9>
H(CF ₂) ₄	1-Ad	44f , 70%	<1995HAC9>
CF ₃	1-Ad	44g , 71%	<1995HAC9>

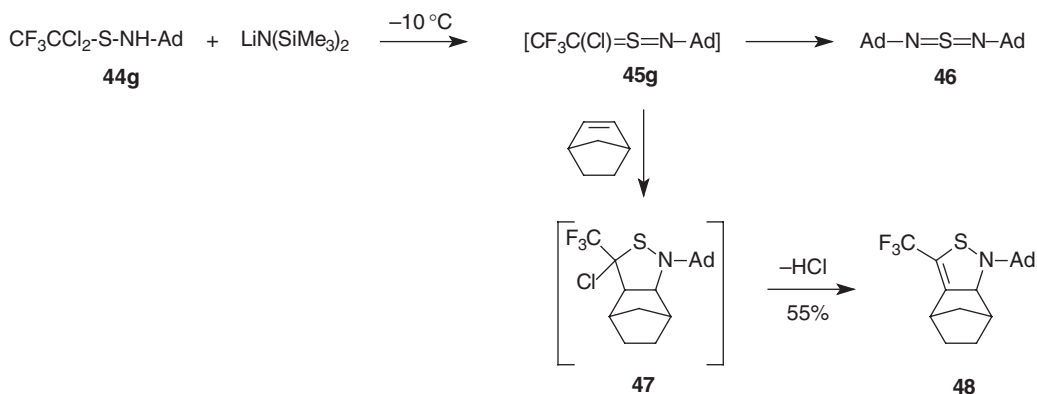
^a Thermally unstable, obtained in quantitative yield as a viscous yellow oil and used without further purification.

**Table 4** α -Chlorosulfinimides **45** prepared according to Equation (4)

R_F	R	Sulfinimide, yield	References
H(CF ₂) ₄	Bu ^t	45a , 74%	<1992ZOR427>
H(CF ₂) ₄	C ₆ H ₄ Me	45b , 66%	<1992ZOR427>
H(CF ₂) ₄	1-Ad	45c , 40%	<1995HAC9>
H(CF ₂) ₄	CH ₃	45d , 47%	<1995HAC9>
<i>n</i> -C ₃ F ₇	Bu ^t	45e , 70%	<1995HAC9>
<i>n</i> -C ₃ F ₇	1-Ad	45f , 50%	<1995HAC9>
CF ₃	1-Ad	45g , 0%	<1995HAC9>

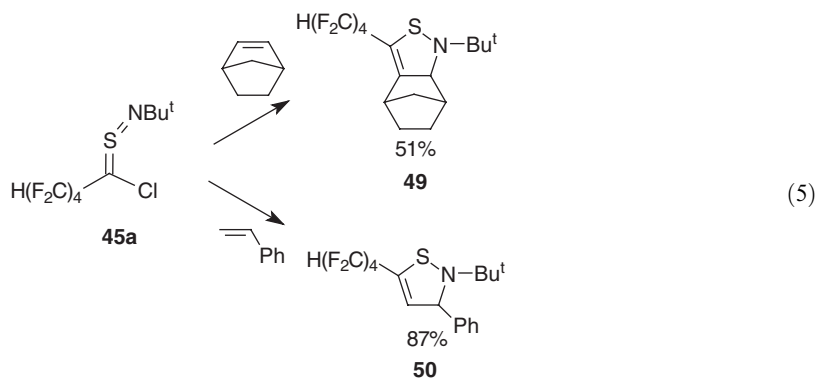
In contrast to related sulfur-containing heterocumulenes, alkyl-N=S=X (X = O, NR), which lack thermal stability, the examples $R_F\text{CCl}=\text{S}=\text{NR}$ (**45a–45f**) were thermally stable up to 100 °C and were stable to purification by vacuum distillation. Thus, it was surprising that efforts to prepare the *C*-trifluoromethyl *N*-1-adamantyl analog, **45g**, $R_F = \text{CF}_3$, failed under experimental conditions analogous to those employed in the synthesis of **45a–45f** [$R_F = \text{H}(\text{CF}_2)_4$ or C_3F_7]. On the basis of these observations it was believed that the *C*-perfluoroalkyl substituent was critical for thermal stability of the halosulfonimides and that the *N*-substituent played no role in influencing the stability. Reaction of the sulfenamide **44g** with lithium hexamethyldisilazane in hexane at 20 °C failed to yield the expected sulfinimide **45g** but instead the *N,N'*-bis(adamantyl)sulfur diimide **46** was isolated in 80% yield <1995HAC9>.

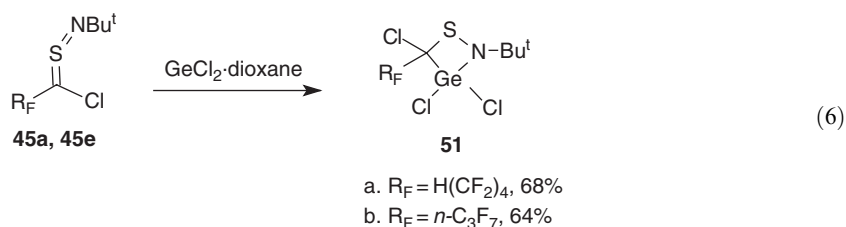
If, however, the reaction between **44g** and lithium hexamethyldisilazane was conducted at low temperature (−10 °C), in the presence of norbornene, the 4-thia-3-azatricyclo[5.2.1.0]decan-5-ene **48** accompanied the sulfur diimide **46**. The formation of the azatricyclodecanane **48** was indirect evidence for the existence of **45g**. The tricycle probably arose via a [3 + 2]-cycloaddition of the transient sulfinimide **45g** to norbornene. Elimination of HCl from the primary cycloadduct **47** afforded **48**, the yield of which was maximized at 55% when NEt_3 was added to the reaction mixture to trap the eliminated HCl (Scheme 10) <1995HAC9>.



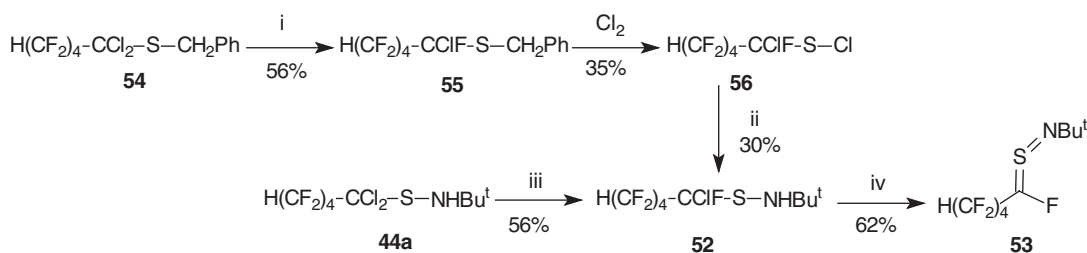
Scheme 10

Isolated α -halosulfonimides have also been trapped in [3 + 2]-cycloadditions; the reaction of **45a** with norbornene generated **49**, whereas reaction with styrene afforded **50**, in each case the isolated product arises as a result of HCl elimination from the primary cycloadduct (Equation (5)). The sulfonimides were also trapped in [3 + 1]-cycloadditions and 1,2,3-thiazagermetidines **51** resulted, in good yield, from addition of **45** to germanium dichloride dioxane (Equation (6)) <1995HAC9>.





N-t-Butyl-1,1,2,2,3,3,4,4-octafluorobutyl-*C*-fluorosulfenimide **53** represents the first example of an α -fluorosulfenimide. Attempts to prepare this compound by direct fluorination (SbF_3) of the corresponding α -chlorosulfenimide **45a** failed and a complex mixture of products resulted which was analyzed by ^{19}F NMR spectroscopy but provided no evidence for the presence of any of the fluorosulfenimide **53** <1998RJOC960>. However, a successful preparation of **53** was achieved starting from *N-t*-butyl-1-chloro-1,2,2,3,3,4,4,5,5-nonafluoro-1-chloropentylsulfenamide **52**. Preparation of the starting material is noteworthy. Two approaches to the preparation of **52** were illustrated (Scheme 11).



i. SbF_3 , CH_3CN , 1 h, 83°C ; ii. Bu^tNH_2 , Et_2O , 1 h, rt; iii. SbF_3 , CH_3CN , 1 h, 83°C ; iv. $\text{LiN}(\text{SiMe}_3)_2$, Et_2O , rt, 4 h

Scheme 11

In the first, antimony trifluoride-induced fluorination of the dichloropolyfluoroalkylbenzyl sulfide **54** afforded the 1-chloro-1-fluorosulfide **55**. Chlorination of this sulfide yielded the sulfonyl chloride **56**. Finally, reaction with *t*-butylamine gave the desired sulfenamide **52**. A significant drawback to this approach was the difficulty of product purification, since benzyl chloride, the by-product from the chlorination reaction, has a similar boiling point to both the chlorofluorosulfonyl chloride **56** and the final sulfenamide **52**. A more attractive route to the sulfenamide **52** began with the α -chloroalkylsulfenamide **44a**. In the first example of direct fluorination of an α -chloroalkylsulfenamide, it was shown that **52** could be prepared from **44a**, in 56% yield, by treatment with SbF_3 <1998RJOC960>.

Lithium hexamethyldisilazane-induced dehydrochlorination of *N-t*-butyl-1,1,2,2,3,3,4,4,5,5-nonafluoro-1-chloropentylsulfenamide **52** afforded the *C*-fluorosulfenimide **53** in 62% yield as a thermally stable yellow liquid which was distilled in *vacuo* <1998RJOC960>. That the product, like the corresponding α -chlorosulfenimides **45**, presented as a single geometrical isomer was known from the presence of only one set of signals in its ^1H , ^{13}C , and ^{19}F NMR spectra. Indeed, even upon cooling to -70°C the ^1H NMR spectra of **53** and its chlorine analogs **45** did not change, thereby indicating their existence as single isomers. It is significant that the α -fluorosulfenimide **53**, unlike the analogous α -chloro compounds **45**, did not partake in [3+2]- or [3+1]-cycloadditions. Following from *ab initio* calculations performed with use of the 6-31G* basis set and complete geometry optimization on *N*-methyl-*C*-pentafluoroethyl-*C*-fluorosulfenimide and on its *C*-chloro analog as test cases, the observed difference in reactivity was attributed to two factors: (i) the greater LUMO energy of the *C*-fluorosulfenimide and (ii) a pronounced electrostatic effect of the F versus Cl atom on the carbon atom of the $\text{C}=\text{S}=\text{N}$ triad <1998RJOC960>.

5.11.8 SELENOACYL HALIDES

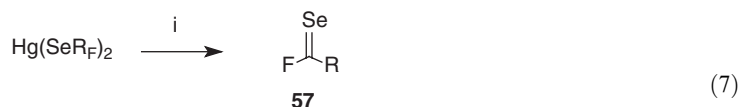
The limited stability of selenoacyl halides is largely responsible for the dearth of examples of compounds in this class and, despite the preponderance of selenocarbonyl amides and esters, the first selenoacyl halides have only recently appeared in the literature. It is significant that in all of the characterized examples, the selenoacyl halides carry a perfluoroalkyl substituent <1991CB51, 1988C265>. Selenocarbonyl difluoride, $\text{F}_2\text{C}(\text{Se})$, whilst not strictly a member of the family of selenoacyl halides, is of interest as it is the first selenocarbonyl halide to have been prepared. Its synthesis is briefly outlined here as the experimental procedure employed has subsequently been adopted to provide access to selenoacyl halides.

Selenocarbonyl difluoride was first prepared from $\text{Hg}(\text{SeCF}_3)_2$ following reaction with AlI_3 in octamethylcyclotetrasiloxane (OMCTS); the thallium or caesium salts of trifluoromethylselenol were also shown to be suitable starting materials <1980ZN(B)526>. Selenocarbonyl difluoride is a reactive species and added metal fluorides, MF ($\text{M} = \text{Cs}, \text{Tl}, \text{Ag}, \text{NMe}_4$), to give F_3CSeM . Upon photochemical activation $\text{F}_2\text{C}(\text{Se})$ dissolved in CFCl_3 and dimerized. The resultant 2,2,4,4-tetrafluoro-1,3-diselenate pyrolyzed to the monomer above 360°C <1980ZN(B)526>. Preparation of selenocarbonyl difluoride from $\text{CF}_3\text{SeSnMe}_3$ and its ready participation in $[4+2]$ -cycloaddition chemistry with a range of dienes (e.g., isoprene, cyclopentadiene, and 1,3-cyclohexadiene) have been documented <1986JFC415, 1988JOM153>.

5.11.9 SELENOACYL FLUORIDES

5.11.9.1 Selenoacyl Fluorides from Mercuric Perfluoroalkylselenols

The mercury(II) perfluoroalkaneselenol approach to selenocarbonyl difluoride may provide general access to selenoacyl fluorides. Thus, the perfluoroalkylselenoacyl fluorides **57** were prepared from reaction between $\text{Hg}(\text{SeC}_2\text{F}_5)_2$ or $\text{Hg}(\text{SeC}_3\text{F}_7)_2$ and either AlI_3 or Et_2AlI in OMCTS at 5×10^{-3} torr (Equation (7) and Table 5).



i. Et_2AlI , or AlI_3 , 5×10^{-3} Torr, OMCTS, trap product at -196°C

Table 5 Selenoacyl fluorides **57** prepared according to Equation (7)

R_F	R	Yield	References
C_2F_5	CF_3	44%	<1988C265, 1991CB51>
$n\text{-C}_3\text{F}_7$	C_2F_5	39%	<1991CB51>

The experimental procedure involved addition of an OMCTS solution of the mercury(II) salt to a flask containing the aluminum halide. The reaction was exothermic and the solvent, as well as the reaction products, were volatile under the conditions of the experiment. Accordingly, a glass trap cooled to -65°C was employed to condense the solvent and another cooled to -196°C , trapped the products. It was necessary to control the rate of addition of the mercury salt since, if the reaction became too vigorous, contamination of the products resulted. Both $\text{CF}_3\text{C}(\text{Se})\text{F}$ and $\text{C}_2\text{F}_5\text{C}(\text{Se})\text{F}$ were deep purple in color and had limited thermal stability. At low temperatures polymerization to rubber-like compounds was rapid. Pyrolytic cleavage of $[\text{RC}(\text{Se})\text{F}]_n$ **58** proceeded almost quantitatively to afford the monomers $\text{RC}(\text{Se})\text{F}$ **57** together with the *cis*- and *trans*-1,3-diselenates **59** (Equation (8)). The makeup of the pyrolysis products varied with the perfluoroalkyl substituent (Table 6). $\text{RC}(\text{Se})\text{F}$ **57** were also unstable in sunlight. The deep purple color of the monomer faded to yellow within 30 min at room temperature in CFCl_3 as dimerization to the corresponding 1,3-diselenates **59** occurred (Equation (9)) <1988C265, 1991CB51>.

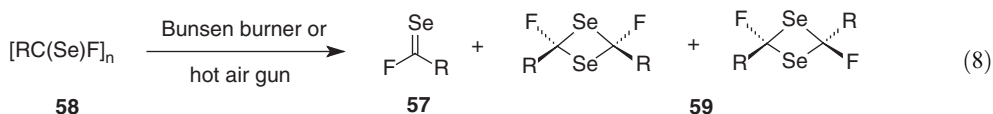
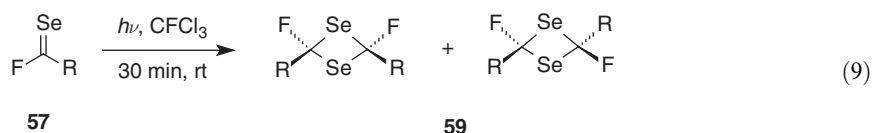


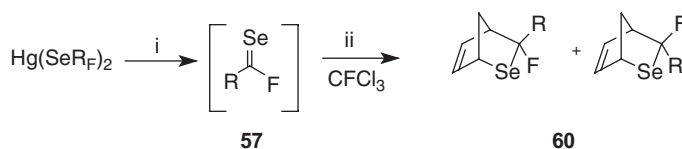
Table 6 Selenoacyl fluorides **57** and 1,3-diselenates **59** prepared as pyrolysis products of **58** according to Equation (8)

R	Monomer 57 :mixed dimers 59	References
CF ₃	15:85	<1991CB51>
C ₂ F ₅	33:77	<1991CB51>



¹⁹F and ⁷⁷Se NMR spectroscopic data (−50 °C, *d*₈-toluene) were presented in support of the structure of **57**. Two fluorine resonance signals were observed in the ¹⁹F NMR spectrum of **57**: R = CF₃; 60.2 ppm (q, CF, ³*J*_{F,F} 16.9 Hz, ²*J*_{F,Se} 314.7 Hz) and −71.3 ppm (d, CF₃, ³*J*_{F,F} 16.9 Hz). A single peak at 1560 ppm in the ⁷⁷Se NMR spectrum of the same compound was characteristic of the selenocarbonyl moiety. Three fluorine resonances −73.6 ppm (m, CF), −87.7 ppm (m, CF₃), and −113.3 ppm (m, CF₂) in the ¹⁹F NMR spectrum support the structure of **57**, R = C₂F₅ <1988C265, 1991CB51>.

Chemical proof of the existence of selenoacyl fluorides **57** was gleaned from the *in situ* trapping, by cyclopentadiene in a [4+2]-cycloaddition reaction which resulted in the formation of the isomeric 3-fluoro-3-perfluoroalkyl-2-selenabicyclo[2.2.1]hept-5-enes **60** (Scheme 12). In each case the dominant stereoisomer had the 3-fluoro substituent in the *exo*-orientation. The low yields of the cycloadducts were attributable to a degree of polymerization of the intermediate selenoacyl fluorides which could not be prevented in spite of the speed of addition of the diene component (Table 7) <1988C265, 1991CB51>. Further indirect evidence for the existence of **57** was demonstrated by the *in situ* trapping with a second selenoacyl fluoride in a [2+2]-cycloaddition (Scheme 13 and Table 8). The reaction procedure involved generation of the perfluoroselenocarbonyl components **57** according to Equation (7) and the ratio of the starting mercury(II) perfluoroselenols was chosen so as to generate an excess of the less reactive transient selenocarbonyl component **57**. The monomers were condensed in CFCl₃ following warming with a heat gun. The solutions were then placed in sunlight and the fading color indicated the onset of [2+2]-cycloaddition. In order to increase the yield of the cycloaddition products any polymeric material in the reaction vessel was repeatedly depolymerized by heating. The unsymmetrical diselenates **61**, fully characterized by spectroscopic methods, were accompanied by the corresponding symmetrical dimers **59** and 2,2,4,4-tetrafluoro-1,3-diselenate, as appropriate. The relative yields of the hetero- and homodimers are related to the ratio of the starting perfluoroalkylselenoacyl fluorides <1991CB51>.



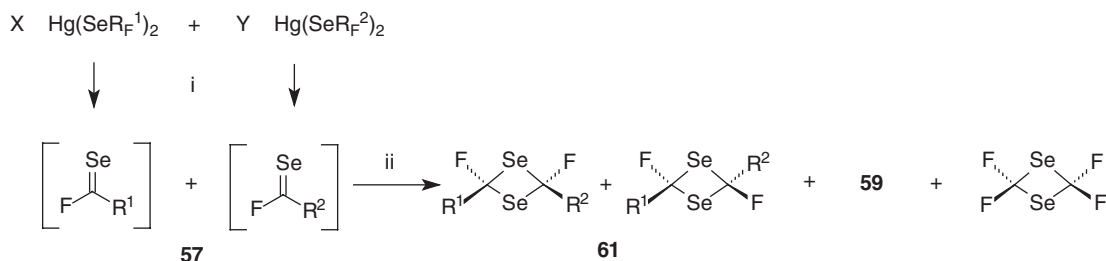
i. Et₂AlI, 5 × 10^{−3} torr, OMCTS, trap product at −196 °C

ii. cyclopentadiene, warm from −196 to 20 °C as rapidly as possible

Scheme 12

Table 7 [4 + 2]-Cycloaddition products **60** prepared from selenoacyl fluorides **57** according to Scheme 12

R_F	R	Yield	References
C_2F_5	CF_3	5.7%	<1988C265, 1991CB51>
C_3F_7	C_2F_5	4.3%	<1991CB51>



- i. Et_2All or All_3 , 5×10^{-3} torr, OMCTS, trap at -196°C
 ii. Condense in CFCl_3 with warming, sunlight, repeated heating to depolymerize any $[\text{R}^1\text{C}(\text{SeF})_n]$ or $[\text{R}^2\text{C}(\text{SeF})_n]$

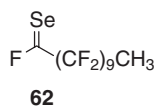
For starting ratios X and Y of mercuric perfluoroselenols and product ratios, see Table 8

Scheme 13**Table 8** Unsymmetrical diselenates **61** prepared by [2 + 2]-cycloaddition of selenoacyl fluorides **57** generated *in situ* according to Scheme 13

$\text{Hg}(\text{SeR}_F^1):\text{Hg}(\text{SeR}_F^2) \text{ X:Y}$	R_F^1	R_F^2	R^1	R^2	Yield	References
2:1	CF_3	C_2F_5	F	CF_3	4.2% ^a	<1991CB51>
1:1	CF_3	$n\text{-C}_3\text{F}_7$	F	C_2F_5	10% ^b	<1991CB51>
1:6	C_2F_5	$n\text{-C}_3\text{F}_7$	CF_3	C_2F_5	25% ^c	<1991CB51>

^a Accompanied by **59** $R = CF_3$ and 2,2,4,4-tetrafluoro-1,3-diselenate. ^b Accompanied by **59** $R = C_2F_5$ and 2,2,4,4-tetrafluoro-1,3-diselenate. ^c Accompanied by **59** $R = C_2F_5$.

The only other selenoacyl halide found in the literature up to April 2004 was 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-octadecylfluoroundecaneselenoyl fluoride **62**, which was claimed in a Japanese patent <1997JAP(K)09235582>.



5.11.10 SELENOACYL CHLORIDES

There have been no synthetic routes to selenoacyl chlorides published up to the end of April 2004.

5.11.11 SELENOACYL BROMIDES

There have been no reports on the preparation of selenoacyl bromides up to the end of April 2004.

5.11.12 SELENOACYL IODIDES

No reports on the preparation of selenoacyl iodides have been found up to the end of April 2004.

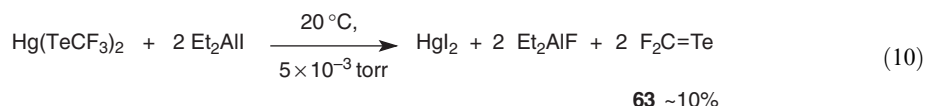
5.11.13 HIGHER OXIDATION STATES OF SELENIUM

As of April 2004, there have been no reports on the preparation of selenoacyl halides where the selenium atom is in the higher oxidation (IV) or (VI) state.

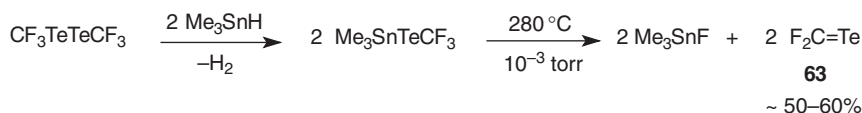
5.11.14 TELLUROACYL HALIDES

The inherent instability of the carbon to tellurium double bond accounts for the dearth of tellurocarbonyl compounds in the literature. Substituents capable of functioning as π -donors can contribute to stabilizing the carbon-to-heteroatom multiple bond and so when COFGT (1995) went to press, a few telluroesters <1979CC645, 1980JCS(P1)2191, 1987CC820> and telluroamides <1979CC1102, 1991SL105> stabilized by resonance had been prepared. No free telluroaldehydes or ketones have been isolated, those which have been generated being trapped *in situ* in a Diels–Alder cycloaddition <1989AG(E)179, 1989JA8749>. In the intervening period the first telluroacyl halides have been reported, all of which owe their existence to the electronegative effect of their perfluoroalkyl substituents which serve to effect a strengthening of the skeletal σ -bonding <1991CC1378, 1993JCS(D)2547, 1996JCS(D)4463, 1997PS413, 2000JCS(D)11>.

Tellurocarbonyl difluoride, $\text{F}_2\text{C}(\text{Te})$ **63**, was the first tellurocarbonyl compound to have been isolated and whilst, strictly, this structure does not fall under the remit of this chapter the author has included its synthesis since the route developed for its preparation has subsequently been shown to be applicable to synthesis of higher homologs. Two approaches to $\text{F}_2\text{C}(\text{Te})$ have been demonstrated, the first starting from $\text{Hg}(\text{TeCF}_3)_2$ <1991CC1378, 1993JCS(D)2547> and the second starting from $\text{Me}_3\text{SnTeCF}_3$ <1993JCS(D)2547>. Both parallel approaches previously developed for the corresponding selenium compound <1980ZN(B)526, 1986JFC415, 1988JOM153>. Following a highly exothermic reaction between $\text{Hg}(\text{TeCF}_3)_2$ and Et_2AlI at 20°C , 5×10^{-3} torr, in the absence of solvent $\text{F}_2\text{C}(\text{Te})$ **63** was isolated in low yield (Equation (10)) <1991CC1378, 1993JCS(D)2547>. Due to its very limited thermal stability, tellurocarbonyl difluoride, $\text{F}_2\text{C}(\text{Te})$ **63**, a deep violet, transient, amorphous solid, was condensed in a cold trap at -196°C immediately upon formation. The mercury(II) trifluoromethyltellurol route was not especially reliable, since it was technically difficult with the product yield being sensitive to small deviations in experimental conditions, and was suited only to the preparation of very small quantities of material.



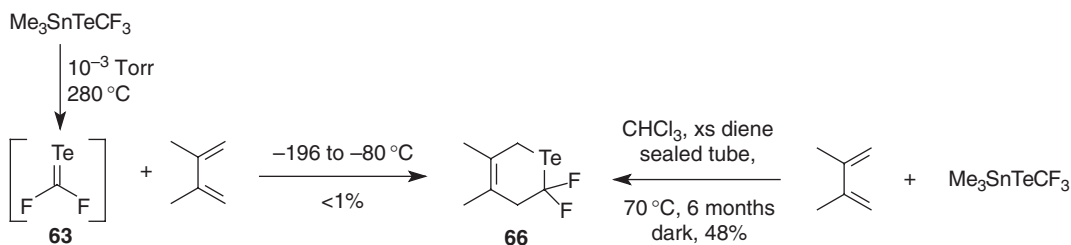
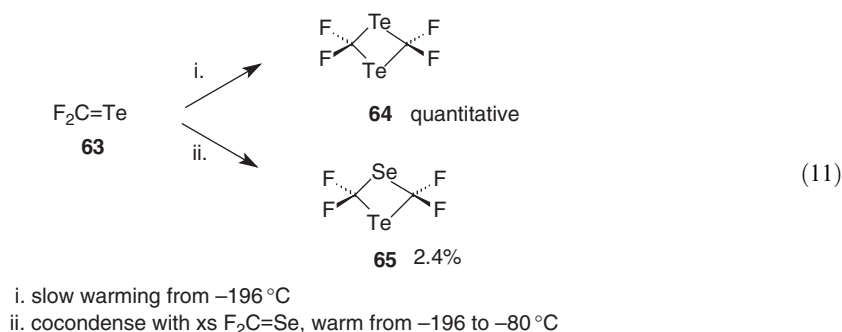
The more synthetically useful approach to $\text{F}_2\text{C}(\text{Te})$ **63** involved pyrolysis of $\text{Me}_3\text{SnTeCF}_3$ <1993JCS(D)2547>. The starting stannyltelluride, itself a novel compound, was prepared on a 10 g scale from reaction between $(\text{CF}_3\text{Te})_2$ and Me_3SnH <1993JCS(D)2547>. Passing the stannyltelluride at 10^{-3} torr and 280°C through a pyrolysis tube (30 cm \times 2.5 cm) packed with glass wool generated $\text{F}_2\text{C}(\text{Te})$ **63** which was trapped at -195°C . The yield of $\text{F}_2\text{C}(\text{Te})$ **63** varied with the packing density of glass wool in the tube (Scheme 14) <1993JCS(D)2547>.



Scheme 14

Due to the limited thermal stability of $\text{F}_2\text{C}(\text{Te})$ **63** characterization was problematic; however, adaptation of the pyrolysis apparatus permitted a recording of its IR spectrum in the gas phase (77 K) and in an argon matrix at 13 K <1993JCS(D)2547>. Further modification of the pyrolysis apparatus allowed connection to the inlet of a mass spectrometer and thus characterization of the molecule by mass spectrometry <1993JCS(D)2547>.

Chemical support for the structure of tellurocarbonyl difluoride **63** rests with the characterization of the products of [2 + 2]- and [4 + 2]-cycloaddition reactions. Quantitative dimerization of **63** upon slow warming above -196°C gave the 1,3-ditellurethane **64** as a dark red solid which, whilst sensitive to both air and light, has been unambiguously characterized by an X-ray crystal structure determination <1991CC1378, 1993JCS(D)2547>. The unsymmetrical [2 + 2]-cycloadduct **65** was obtained as the component trapped at -55°C following fractionation of the products of cocondensation of $\text{F}_2\text{C}(\text{Te})$ with excess $\text{F}_2\text{C}(\text{Se})$ on warming from -196°C to -80°C . Cycloadduct **65** is extremely sensitive to light but may be stored for indefinite periods at -80°C (Equation (11)) <1991CC1378, 1993JCS(D)2547>. Both the cycloadducts have limited stability at room temperature <1991CC1378, 1993JCS(D)2547>. Further chemical evidence in support of $\text{F}_2\text{C}(\text{Te}) **63** lay with the formation of a [4 + 2]-cycloaddition product with 2,3-dimethyl-1,3-butadiene <1993JCS(D)2547>. Yields following direct cocondensation of the reactants were small (<1%) as the bulk of $\text{F}_2\text{C}(\text{Te})$ had dimerized before its partner had reached its melting point; however, yields significantly improved when the reaction was conducted directly from the stannyltelluride without isolation of $\text{F}_2\text{C}(\text{Te}) **63**. Under the latter conditions, 6,6-difluoro-3,4-dimethyl-1-telluracyclohex-3-ene **66** was isolated in 48% yield after 6 months reaction at 70°C in CHCl_3 in a sealed tube in the dark (Scheme 15) <1993JCS(D)2547>.$$



Scheme 15

5.11.15 TELLUROACYL FLUORIDES

5.11.15.1 Telluroacyl Fluorides via Pyrolysis of Perfluoroalkyltrimethylstannyl Tellurides

Hass and co-workers have demonstrated that the pyrolytic approach to telluroacyl fluorides may have some generality and have prepared trifluoromethyltelluroacyl fluoride <1996JCS(D)4463>, pentafluoroethyltelluroacyl fluoride <1997PS413, 2000JCS(D)11>, and heptafluoropropyltelluroacyl fluoride <1997PS413, 2000JCS(D)11> by pyrolysis of $\text{Me}_3\text{SnTeC}_2\text{F}_5$, $\text{Me}_3\text{SnTe}(n\text{-C}_3\text{F}_7)$ and $\text{Me}_3\text{Sn}(n\text{-C}_4\text{F}_9)$, respectively.

The required starting perfluoroalkylstannyl telluride **69** was prepared in each case from reaction of trimethylstannane with the corresponding bis(perfluoroalkyl)mono- **67** or ditelluride **68** <1996JCS(D)4463, 1997PS413, 2000JCS(D)11>. The starting materials of choice for synthesis of the tellurides are the corresponding, commercially available, perfluoroiodoalkanes; reaction between R_fI , tellurium (3 equiv.), and copper (3 equiv.) (Equation (12)) occurred upon heating the reactants at 180°C in a sealed ampoule, either *in vacuo* (10^{-3} torr) or at atmospheric pressure under argon. The role of the copper was twofold; it functioned as a catalyst and as an iodide scavenger. Upon

completion of the reaction the crude mixtures were separated by fractional condensation (Table 9). Significantly, the composition of the product mixture varied with reaction duration such that the ditellurides became an important by-product as the reaction progressed. Thus, the ditelluride **68** ($R_F = C_2F_5$), whilst absent after 36 h reaction, was obtained as 16% of the product mixture after a further 24 h heating (Table 9) <1996JCS(D)4463, 1997PS413>.

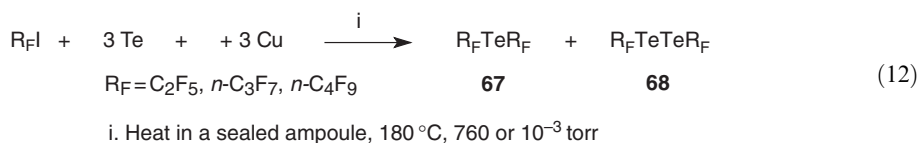
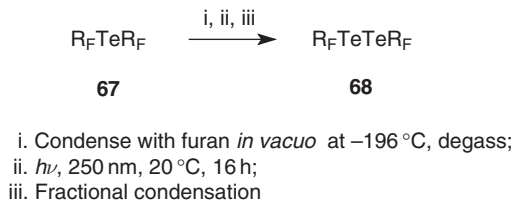


Table 9 Bis(perfluoroalkyl) mono- **67**, and ditellurides **68**, prepared according to Equation (12)

R_F	Conditions	Yield [condensation temperature]		References
		Monotelluride 67	Ditelluride 68	
C_2F_5	36 h, 10^{-3} Torr	68% [-78°C]	-	<1996JCS(D)4463>
C_2F_5	60 h, 10^{-3} Torr	58% [-78°C]	16% [-40°C]	<1996JCS(D)4463>
$n\text{-}C_3F_7$	18 h, 10^{-3} Torr	43% [-63°C]	-	<1996JCS(D)4463, 1997MI413>
$n\text{-}C_4F_9$	18 h, 760 Torr	33% [-30°C]	-	<1996JCS(D)4463, 1997MI413>

Ditellurides **68** were also obtained when the monotellurides were heated at 200 °C with an excess of tellurium in the presence of a catalytic amount of copper <1996JCS(D)4463>. However, the most effective conversion of bis(perfluoroalkyl) monotellurides **67** into ditellurides **68** was achieved by photochemical activation of a condensed mixture of furan and the monotellurides (Scheme 16). The product mixture was separated by fractional condensation (Table 10) <1997PS413, 2000JCS(D)11>.



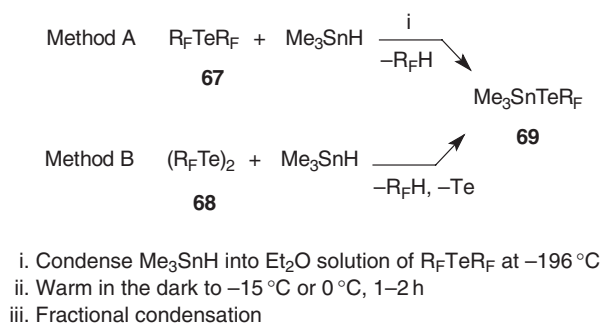
Scheme 16

Table 10 Bis(perfluoroalkyl) ditellurides **68** prepared according to Scheme 16

R_F	Yield [condensation temperature]	References
$n\text{-}C_3F_7$	73% [-40°C]	<1997MI413, 2000JCS(D)11>
$n\text{-}C_4F_9$	45% [-5°C]	<1997MI413, 2000JCS(D)11>

The stannyl tellurides **69** resulted from reaction of trimethylstannane with the corresponding bis(perfluoroalkyl) mono- **67** or bistellurides **68** <1996JCS(D)4463, 1997PS413, 2000JCS(D)11>. The reaction involved condensation of trimethylstannane into an ether solution of the monotelluride **67** cooled to -196°C (Scheme 17, method A). After warming to between -15°C to 0°C and stirring in the dark for 1–2 h, reaction was complete and the products were separated by fractional condensation (Table 11). Treatment of trimethylstannane with the bistellurides **68** under comparable conditions also furnished stannyl tellurides **69** in reasonable yield (Scheme 17, method B and Table 11) <1996JCS(D)4463, 1997PS413, 2000JCS(D)11>.

With sufficient quantities of perfluoroalkyltrimethylstannyl tellurides **69** available from the reaction sequence starting from the perfluoroiodoalkanes, preparation of telluroacyl fluorides **70** by pyrolysis was possible (Equation (13) and Table 12). The experimental setup involved passing the perfluoroalkyltrimethylstannyl telluride **69** through a quartz-glass pyrolysis tube at 500°C and 10^{-3} torr. The pyrolysis tube was connected to two U-tubes. The first was cooled to

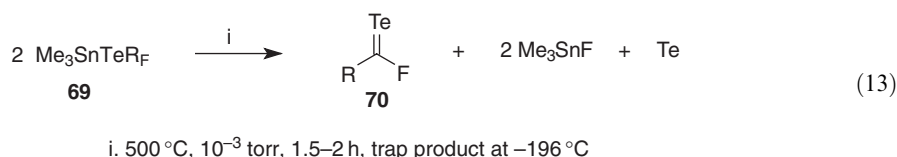


Scheme 17

Table 11 Perfluoroalkyltrimethylstannyl tellurides **69** prepared according to Scheme 17

R_F	Method	Yield [in vacuo trap to trap condensation temperature]	References
C_2F_5	A	66% [-40 to -196°C]	<1996JCS(D)4463>
$n\text{-C}_3\text{F}_7$	A	65% [-40 to -196°C]	<1997MI413, 2000JCS(D)11>
$n\text{-C}_4\text{F}_9$	A	52% [-15 to -196°C]	<1997MI413, 2000JCS(D)11>
C_2F_5	B	60%	<1996JCS(D)4463>
$n\text{-C}_3\text{F}_7$	B	75%	<2000JCS(D)11>
$n\text{-C}_4\text{F}_9$	B	41%	<2000JCS(D)11>

$-30/-45^\circ\text{C}$, and functioned to collect unreacted starting material as well as the by-product trimethylstannyl fluoride, whilst the second was cooled to -196°C and collected the product. By continuously raising the level of the liquid nitrogen the whole wall of the product trap was covered in a film of the product. The telluroacyl fluorides **70** were all glassy green solids of limited thermal stability, and thus it was important that the level of coolant was not allowed to fall below the product level, otherwise dimerization was problematic <1996JCS(D)4463, 1997PS413, 2000JCS(D)11>. The yield of trifluoromethyltelluroacyl fluoride **70** varied with the packing density of glass wool in the tube; too high a density caused some decomposition to tellurium as well as other unidentified products and too low a density resulted in inefficient pyrolysis <1996JCS(D)4463>.

Table 12 Perfluoroalkyltellurocarbonyl fluorides **70** prepared from the stannyl tellurides **69** according to Equation (13)

69 , R_F	70 , R	Yield	References
C_2F_5	CF_3	47%	<1996JCS(D)4463>
$n\text{-C}_3\text{F}_7$	C_2F_5	^a	<1997MI413, 2000JCS(D)11>
$n\text{-C}_4\text{F}_9$	$n\text{-C}_3\text{F}_7$	^a	<1997MI413, 2000JCS(D)11>

^a Yield not reported.

Each of the perfluoroalkyltellurocarbonyl fluorides **70** had sufficient stability at low concentration in the gas phase to permit direct characterization by spectroscopic methods if the pyrolysis apparatus was connected to the gas inlet of a mass spectrometer or an IR flow cell. Three strong absorption bands at 1248, 1224, and 1166cm^{-1} could be considered to represent $\text{C}=\text{Te}$, $\text{C}-\text{F}$ (symmetric) and $\text{C}-\text{F}$ (asymmetric) stretches; however, assignments remain speculative and have thus been avoided. Diagnostic peaks in the mass spectrum included m/z 230 (M^+), 211 ($\text{M}-\text{F}$), 161 (TeCF^+), 130 (Te^+), and 69 (CF_3^+) <1996JCS(D)4463>. IR and MS data were also available for $(\text{C}_2\text{F}_5)\text{C}(\text{Te})\text{F}$ <1997PS413, 2000JCS(D)11> and its $\text{He}(1)$ photoelectron spectrum

was assigned by *ab initio* calculations, and radical cation state comparison based on resolved vibrational fine structures <1999ZAAC1726>. Direct evidence for $(n\text{-C}_3\text{F}_7)\text{C}(\text{Te})\text{F}$ rests with its MS alone <2000JCS(D)11>.

In view of the limited spectroscopic data supporting the structure of the perfluoroalkyltelluroacyl fluorides **70**, chemical evidence of their existence was most valuable. Support for $(\text{CF}_3)\text{C}(\text{Te})\text{F}$, and its homologs $(\text{C}_2\text{F}_5)\text{C}(\text{Te})\text{F}$ and $(n\text{-C}_3\text{F}_7)\text{C}(\text{Te})\text{F}$ came from their dimerization products, and [2+2]-cycloadditions occurred upon warming above -196°C (Equation (14) and Table 13) <1996JCS(D)4463, 1997PS413, 2000JCS(D)11>. The 2,4-difluoro-2,4-bis(trifluoromethyl)telluretane **71** ($\text{R} = \text{CF}_3$) was a volatile, red, air-stable solid, which was the subject of an X-ray crystallographic study <1996JCS(D)4463>. The homologs **71** ($\text{R} = \text{C}_2\text{F}_5$, $n\text{-C}_3\text{H}_7$) were air-sensitive violet liquids, stable at room temperature for a few days if stored under air-free conditions <2000JCS(D)11>. In all cases the 1,2-ditelluretanes **71** existed as an inseparable mixture of *cis*- and *trans*-isomers <1996JCS(D)4463, 2000JCS(D)11>.

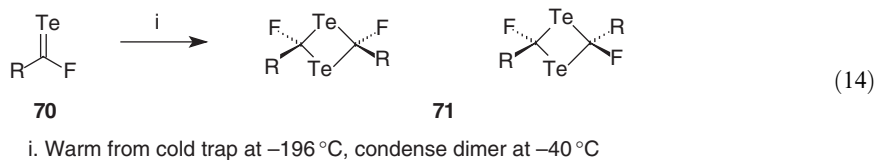


Table 13 *cis*-/*trans*-2,4-Difluoro-2,4-bis(perfluoroalkyl)-1,3-ditelluretanes **71** prepared according to Equation (14)

<i>R</i>	Yield	References
CF_3	100% ^a	<1996JCS(D)4463>
C_2F_5	64% ^b	<1997MI413, 2000JCS(D)11>
$n\text{-C}_3\text{F}_7$	49% ^b	<1997MI413, 2000JCS(D)11>

^a Crude yield; ^b Isolated yield.

Further evidence for $(\text{CF}_3)\text{C}(\text{Te})\text{F}$ and $(\text{C}_2\text{F}_5)\text{C}(\text{Te})\text{F}$ as intermediates via their chemical reactivity rests with the isolation of [4+2]-cycloaddition products with 2,3-dimethylbutadiene <1996JCS(D)4463, 2000JCS(D)11>. The reaction was conducted *in situ*; thus, 2-fluoro-3,6-dihydro-4,5-dimethyl-2-perfluoroalkyltellurins **72** resulted when a CHCl_3 solution of the appropriate perfluoroalkylstannyl telluride **69** was heated with a large excess of the diene (Equation (15) and Table 14). The tellurin **72**, $\text{R} = \text{CF}_3$, was an extremely air-sensitive yellow oil <1996JCS(D)4463>, whereas the 2-pentafluoroethyl analog **72** ($\text{R} = \text{C}_2\text{F}_5$) was a bright yellow, moisture-sensitive liquid <2000JCS(D)11>.

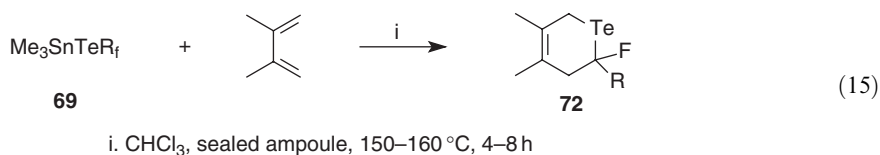


Table 14 2-Fluoro-2-perfluoroalkyltellurins **72** prepared according to Equation (15)

R_F	<i>R</i>	Reaction conditions	Yield [condensation temperature]	References
C_2F_5	CF_3	CHCl_3 , 150°C , 4 h	86% [-10°C]	<1996JCS(D)4463>
$n\text{-C}_3\text{F}_7$	C_2F_5	CHCl_3 , 160°C , 15 h	75% [-30°C]	<2000JCS(D)11>

2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-Octadecylfluoroundecanetelluroyl fluoride **73**, claimed in a Japanese patent, is the only other telluroacyl halide found in the literature up to April 2004 <1997JAP(K)09235582>.

5.11.16 TELLUROACYL CHLORIDES

No references to telluroacyl chlorides have been found up to the end of April 2004.

5.11.17 TELLUROACYL BROMIDES

No references to these compounds have been found up to the end of April 2004.

5.11.18 TELLUROACYL IODIDES

No reports on the synthesis of telluroacyl iodides have appeared up to the end of April 2004.

5.11.19 HIGHER OXIDATION STATES OF TELLURIUM

There have been no reports on the preparation of telluroacyl halides where the tellurium atom is in the higher oxidation (IV) or (VI) state up to the end of April 2004.

REFERENCES

- 1979CC645 A. G. M. Barrett, D. H. R. Barton, R. W. J. Read, *J. Chem. Soc., Chem. Commun.* **1979**, 645–647.
 1979CC1102 K. A. Lerstrup, L. Henriksen, *J. Chem. Soc., Chem. Commun.* **1979**, 1102–1103.
 1980JCS(P1)2191 A. G. M. Barrett, D. H. R. Barton, R. W. J. Read, *J. Chem. Soc., Perkin Trans. 1* **1980**, 2191–2195.
 1980ZN(B)526 A. Darmadi, A. Haas, B. Koch, *Z. Naturforsch., Teil B* **1980**, 35B, 526–529.
 1986JFC415 A. Haas, *J. Fluorine Chem.* **1986**, 32, 415–439.
 1987CC820 T. Severengiz, W. W. du Mont, *J. Chem. Soc., Chem. Commun.* **1987**, 820–821.
 1988C265 A. Haas, M. Spehr, *Chimia* **1988**, 42, 265–267.
 1988JOM153 J. Grobe, D. Le Van, J. Welzel, *J. Organomet. Chem.* **1988**, 340, 153–160.
 1989AG(E)179 G. Erker, R. Hock, *Angew. Chem., Int. Ed. Engl.* **1989**, 101, 179–181.
 1989EUP348166 Kawashima, M.; Omura, I. European Patent 348 166 (**1989**) (*Chem. Abstr.* **1991**, 114, 30120).
 1989JA8749 M. Segi, T. Koyama, Y. Takata, T. Nakajima, S. Suga, *J. Am. Chem. Soc.* **1989**, 111, 8749–8751.
 1991CB51 R. Boese, A. Haas, M. Spehr, *Chem. Ber.* **1991**, 124, 51–61.
 1991CC1378 R. Boese, A. Haas, C. Limberg, *J. Chem. Soc., Chem. Commun.* **1991**, 1378–1379.
 1991SL105 M. Segi, A. Kojima, T. Nakajima, S. Suga, *Synlett* **1991**, 105–106.
 1992JAP(K)04159270 Murayama, A.; Ishikawa, M.; Matsumoto, S.; Sugita, S.; Toda, S.; Yamashita, T.; Yoshiyasu, T. Jpn. Kokai 04 159 270 (**1992**) (*Chem. Abstr.* **1993**, 118, 49877).
 1992ZOR14 L. N. Markovskii, E. I. Slyusarenko, V. M. Timoshenko, E. I. Kaminskaya, A. G. Kirilenko, Yu. G. Shermolovich, *Zh. Org. Khim.* **1992**, 28, 14–22.
 1992ZOR427 Y. G. Shermolovich, V. M. Timoshenko, A. B. Rozhenko, L. N. Markovskii, *Zh. Org. Khim.* **1992**, 28, 427–428.
 1992ZOR892 B. V. Kunshenko, V. O. Omarov, N. N. Muratov, L. M. Yagupol'skii, *Zh. Org. Khim.* **1992**, 28, 892–900.
 1993CB415 P. Jutzi, K.-H. Schwartz, A. Mix, H.-G. Stammer, B. Neumann, *Chem. Ber.* **1993**, 126, 415–420.
 1993JCS(D)2547 R. Boese, A. Haas, C. Limberg, *J. Chem. Soc., Dalton Trans.* **1993**, 2547–2556.
 1993USP5254198 Kawashima, M.; Omura, I. US Patent 5 254 198 (**1993**) (*Chem. Abstr.* **1991**, 114, 30120).
 1994JAP(K)06128213 Ishizaki, M.; Osada, S. Jpn. Kokai 06 128 213 (**1994**) (*Chem. Abstr.* **1994**, 121, 205215).
 1994MI2021261 Porosyatnikov, V. A.; Novikova, L. L.; Ermolov, A. F. Russia Patent. 2 021 261 (**1994**) (*Chem. Abstr.* **1995**, 123, 285248).
 1995COFGT(5)471 A. C. Williams, in *Thio-, seleno-, and telluroacyl halides in Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 471–504.
 1995HAC9 J.-T. Ahlemann, H. W. Roesky, L. N. Markovsky, V. M. Timoshenko, Y. G. Shermolovich, *Heteroatom Chem.* **1995**, 6, 9–13.
 1995JAP(K)07070049 Katagiri, K.; Shinjo, K.; Yoshinaga, K. Jpn. Kokai 07 070 049 (**1995**) (*Chem. Abstr.*, **1995**, 123 70530).
 1995LA2137 G. Opitz, M. Deissler, T. Ehli, K. Rieth, H. Irngartinger, M. L. Ziegler, B. Nuber, *Liebigs Ann. Chem.* **1995**, 2137–2149.
 1995LA2151 G. Opitz, M. Deissler, K. Rieth, R. Wegner, H. Irngartinger, B. Nuber, *Liebigs Ann. Chem.* **1995**, 2151–2163.
 1996JCS(D)4463 J. Beck, A. Haas, W. Herrendorf, H. Heuduk, *J. Chem. Soc., Dalton Trans.* **1996**, 4463–4470.
 1996KGS909 A. A. Avetisyan, I. L. Aleksanyan, A. G. Alvandzhyan, *Khim. Geterotsikl. Soedin.* **1996**, 909–912.
 1997JAP(K)09235582 Fukuchi, T. Jpn. Kokai 09 335 582 (**1997**) (*Chem. Abstr.* **1997**, 127, 295968).
 1997PS413 M. Baum, H. Bock, A. Haas, Z. Havlas, C. Monse, B. Solouki, *Phosphorus Sulfur Silicon* **1997**, 124 & 125, 413–417.
 1997WOP9736847 Ando, T.; Matsui, S.; Miyazawa, K.; Takeuchi, H.; Koizumi, Y.; Sekiguchi, Y.; Nakagawa, E.; Takeshita, F. *PCT Int. Appl. WO* (World Intellectual Property Organisation Pat. Appl.) 9 736 847 (**1997**) (*Chem. Abstr.* **1997**, 127, 301549).
 1997WOP9737960 Matsui, S.; Koizumi, Y.; Miyazawa, K.; Sekiguchi, Y.; Nakagawa, E. *PCT Int. Appl. WO* (World Intellectual Property Organisation Pat. Appl.) 9 737 960 (**1997**) (*Chem. Abstr.* **1997**, 127, 313406).
 1998RJOC960 Yu. G. Shermolovich, V. M. Timoshenko, V. V. Listvan, N. N. Il'chenko, L. N. Markovskii, *Russ. J. Org. Chem. (Engl. Transl.)* **1998**, 34, 960–963.

- 1998WOP9812166 Matsui, S.; Ando, T.; Miyazawa, K.; Takeuchi, H.; Hisatsune, Y.; Takeshita, F.; Nakagawa, E. *PCT Int. Appl. WO* (World Intellectual Property Organisation Pat. Appl.) 9 812 166 (**1998**) (*Chem. Abstr.* **1998**, 128, 237548).
- 1998WOP9835924 De Meijere, A.; Messner, M.; Kazhushkov, S.; Demus, D.; Kobayashi, K.; Miyazawa, K.; Matsui, S.; Takeuchi, H. *PCT Int. Appl. WO* (World Intellectual Property Organisation Pat. Appl.) 9 835 924 (**1998**) (*Chem. Abstr.* **1998**, 129, 223634).
- 1999UKZ10 V. M. Timoshenko, Yu. G. Shermolovich, *Ukr. Khim. Zh. (Russ. Ed.)* **1999**, 65, 10–16.
- 1999ZAAC1726 B. Solouki, H. Bock, A. Haas, M. Baum, C. Monse, Z. Havlas, *Z. Anorg. Allg. Chem.* **1999**, 625, 1726–1731.
- 2000JCS(D)11 M. Baum, J. Beck, A. Haas, W. Herrendorf, C. Monse, *J. Chem. Soc., Dalton Trans.* **2000**, 11–15.
- 2000USP6099903 Kaloyeros, A. E.; Welch, J. T.; Toscano, P. J.; Claessen, R.; Kornilov, A.; Banger, K. K.; US Patent 6 099 903 (**2000**) (*Chem. Abstr.* **2001**, 133, 142859).
- 2000USP6114518 Pitner, J. B.; Linn, C. P. US Patent 6 114 518 (**2000**) (*Chem. Abstr.* **2001**, 133, 177415).
- 2001USP6177154 Matsui, S.; Ando, T.; Miyazawa, K.; Takeuchi, H.; Hisatsune, Y.; Takeshita, F.; Nakagawa, E. US Patent 6 177 154 (**2001**) (*Chem. Abstr.* **1998**, 128, 237548).
- 2001USP6190576 Ando, T.; Matsui, S.; Miyazawa, K.; Takeuchi, H.; Koizumi, Y.; Sekiguchi, Y.; Nakagawa, E.; Takeshita, F. US Patent 6 190 576 (**2001**) (*Chem. Abstr.* **1997**, 127, 301549).
- 2003OL929 M. Garcia-Valverde, R. Pascual, T. Torroba, *Org. Lett.* **2003**, 5, 929–932.

Biographical sketch

Frances Heaney was born in Northern Ireland and studied at Queen's University, Belfast, where she obtained a B.Sc. in 1986 and a Ph.D. in 1990 under the direction of Professor R. Grigg. After spending two years as a Postdoctoral Research Fellow in the laboratories of Dr. Peter Boyle at Trinity College, Dublin, she took up her first academic position in the Chemistry Department at the National University of Ireland, Galway. In 1999 she took up her present position as Chemistry Lecturer at the National University of Ireland, Maynooth. Her scientific interests include synthetic chemistry, heterocyclic chemistry, rearrangement reactions, and reaction mechanisms.

5.12

Thio-, Seleno-, and Telluroacyloxy Functions, $R^1C(S)OR^2$, $R^1C(Se)OR^2$, $R^1C(Te)OR^2$, etc.

A. ISHII and J. NAKAYAMA

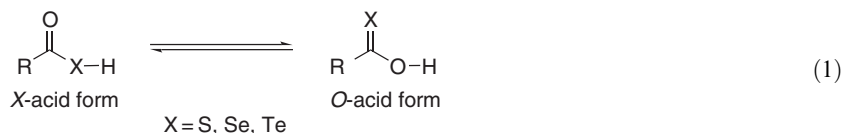
Saitama University, Saitama, Japan

5.12.1 CARBOXYLIC ACID ANALOGS, $RC(Y)OH$	460
5.12.1.1 General Aspects	460
5.12.1.2 Carbothioic <i>O</i> -Acids	460
5.12.1.2.1 Spectroscopic methods	460
5.12.1.2.2 Theoretical methods	461
5.12.1.3 Carboselenoic <i>O</i> -Acids	462
5.12.1.3.1 Spectroscopic methods	462
5.12.1.3.2 Theoretical methods	463
5.12.1.4 Carbotelluroic <i>O</i> -Acids	463
5.12.1.5 Higher Oxidation States of the Chalcogen	464
5.12.2 CARBOXYLIC ACID ESTER ANALOGS, $R^1C(Y)OR^2$	465
5.12.2.1 General Methods	465
5.12.2.2 Carbothioic Acid <i>O</i> -Esters, $R^1C(S)OR^2$	465
5.12.2.2.1 Synthesis	465
5.12.2.2.2 Properties and reactions	469
5.12.2.3 Carboselenoic Acid <i>O</i> -Esters, $R^1C(Se)OR^2$	473
5.12.2.3.1 Synthesis	473
5.12.2.3.2 Spectroscopy	476
5.12.2.3.3 Reactions	476
5.12.2.4 Carbotelluroic Acid <i>O</i> -Esters, $R^1C(Te)OR^2$	478
5.12.2.5 Higher Oxidation States of the Chalcogen	478
5.12.3 CARBOXYLIC ANHYDRIDE ANALOGS, $R^1C(Y)OCOR^2$ AND $R^1C(Y)OC(Y')R^2$	479
5.12.3.1 Introduction	479
5.12.3.2 Carbothioic Anhydrides	480
5.12.3.3 Carboselenoic Anhydrides	481
5.12.3.4 Carbotelluroic Anhydrides	481
5.12.4 THIO-, SELENO-, AND TELLUROACYLOXY HETEROATOM FUNCTIONS, $R^1C(Y)OXR_n^2$	481
5.12.4.1 X = Group 13 Elements	481
5.12.4.1.1 <i>B</i> -Thioacyloxy compounds	481
5.12.4.2 X = Group 14 Elements (Except Carbon)	482
5.12.4.2.1 <i>Si</i> -Thioacyloxy compounds	482
5.12.4.2.2 <i>Si</i> -Selenoacyloxy compounds	483
5.12.4.2.3 <i>Si</i> -Telluroacyloxy compounds	484
5.12.4.3 X = Group 15 Elements	484
5.12.4.3.1 <i>O</i> -(Thioacyl)hydroxylamines and -oximes	485
5.12.4.3.2 <i>O</i> -(Selenoacyl)- and <i>O</i> -(telluroacyl)hydroxylamines and -oximes	486
5.12.4.3.3 <i>P</i> -Thioacyloxy compounds and their selenium analogs	486
5.12.4.4 X = Group 16 Elements	487
5.12.4.5 X = Group 17 Elements	488

5.12.1 CARBOXYLIC ACID ANALOGS, RC(Y)OH

5.12.1.1 General Aspects

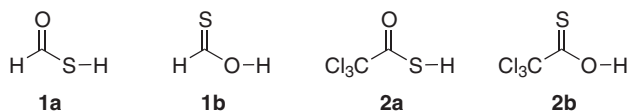
Carbothioic (thiocarboxylic), carboselenoic (selenocarboxylic), and carbotelluroic (tellurocarboxylic) acids can exist as a tautomeric mixture of *X*-acid ($X = \text{S, Se, Te}$) and *O*-acid forms (Equation (1)). The equilibrium generally lies exclusively to the left (see section 5.05.1), and the presence of small amounts of *O*-acid forms of thioformic and trichlorothioacetic acids was detected spectroscopically in the equilibrium mixture <1972ZAAC78, 1974JST123>. Kato and co-workers <1994JA2195, 1996JA1262, 1998PS(136-138)295> revealed that a range of chalcogeno acids exist as the *O*-acid form in polar solvents.



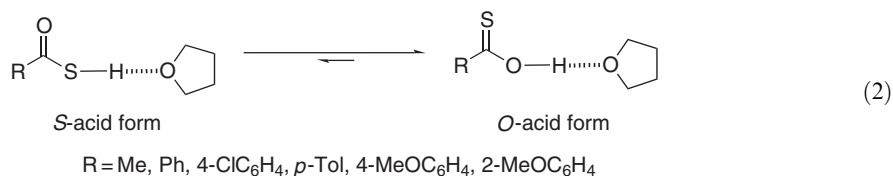
5.12.1.2 Carbothioic *O*-Acids

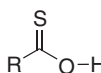
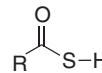
5.12.1.2.1 Spectroscopic methods

The IR spectrum of thioformic acid exhibited absorptions at 1,402, 1,235, and 1,160 cm^{-1} , suggesting the presence of both *S*-acid **1a** and *O*-acid **1b** forms in the tautomeric equilibrium at room temperature <1972ZAAC78, 1974JST123>. Similarly, IR and ^1H NMR spectroscopic studies on trichlorothioacetic acid **2** showed the presence of the *S*-acid/*O*-acid equilibrium <1977JST25>. In the ^1H NMR spectrum of **2** determined in the temperature range of 75–93 $^{\circ}\text{C}$, a very weak signal was observed at δ 2.36 assigned to the OH proton of **2b**. The percentage of **2b** calculated by integral values was only ~1%.



Kato and co-workers <1996JA1262> disclosed that thioacetic acid and arenecarbothioic acid exist in the *O*-acid form in polar solvents, based on observations of the UV, IR, and NMR spectra measured in THF (Equation (2)). For example, a solution of 4-methoxythiobenzoic acid **3** in THF, colored deep yellow, exhibited an absorption maximum at 413 nm, which was not observed in a hexane or dichloromethane solution (light yellow). The IR spectrum of **3** in THF did not show bands due to S—H and C=O stretching vibrations, whereas in the solid state, strong bands appeared at 2,512 and 1,670 cm^{-1} that correspond to the above vibrations. In ^1H and ^{13}C NMR spectra measured at -90°C in THF- d_8 , the OH proton and the C=S carbon of **3** appeared at δ_{H} 14.52 and δ_{C} 212.3, respectively. A close similarity of ^1H and ^{13}C NMR spectra was observed for acetone and methanol solutions. These observations indicate that carbothioic acid **3** exists as the *O*-acid form in a polar solvent. The ratio of *O*-acid form/*S*-acid form of **3** determined by the ^1H NMR integral ratio was 60/40 at -30°C , 87/13 at -70°C , and >99/<1 at -90°C . Table 1 summarizes relevant ^1H and ^{13}C NMR data of **3** and other carbothioic acids measured in THF- d_8 at -90°C . In the case of 2-methoxythiobenzoic acid **4** and thioacetic acid **5**, the two forms were observed in comparable amounts. The solvent effect on the *S*-acid/*O*-acid equilibrium was explained as follows <1996JA1262>: in a polar solvent, the hydrogen-bonding interaction with the solvent enables more delocalization of the electrons on the thiocarboxy group. A stronger hydrogen-bonding interaction is feasible when the hydrogen on the thiocarboxy group localizes on the more negative oxygen atom rather than the sulfur atom. The above observation suggests that this stabilization effect compensates the formation of the energetically less favorable C—S double bond.

**Table 1** Relevant ^1H and ^{13}C NMR data of carbothioic acids in $\text{THF-}d_8$ at -90°C

<i>R</i>				
	$\delta_{\text{H}}(\text{O-H})$	$\delta_{\text{C}}(\text{C=S})$	$\delta_{\text{H}}(\text{S-H})$	$\delta_{\text{C}}(\text{C=O})$
4-MeOC ₆ H ₄ 3	14.52	212.3		
Ph	14.28	213.5		
4-ClC ₆ H ₄	14.90	212.0		
<i>p</i> -Tol	14.62	210.8		
2-MeOC ₆ H ₄ 4	14.68	217.8	5.86	188.0
Me 5	14.38	221.2	6.44	195.5

Source: <1996JA1262>.

A study was carried out to examine whether Lewis acids affect the *S*-acid/*O*-acid equilibrium of thioacetic acid <2003EJO1784>. The ^{13}C NMR spectrum of thioacetic acid, which shows a peak at δ 194.09 in CDCl_3 at room temperature, was not affected by the addition of a catalytic amount of $\text{Rh}_2(\text{OAc})_4$ or $\text{BF}_3\cdot\text{OEt}_2$.

5.12.1.2.2 Theoretical methods

Ab initio SCF-MO calculations on *s-cis* and *s-trans* conformers of *S*-acid **1a** and *O*-acid **1b** forms of thioformic acid **1** have been reported (Figure 1) <1989JCS(F2)1945>. The order of stability is *s-cis S*-acid (*cis-1a*) > *s-trans S*-acid (*trans-1a*) > *s-cis O*-acid (*cis-1b*) > *s-trans O*-acid (*trans-1b*). The effects that make *s-cis* forms more stable than *s-trans* forms have been interpreted in terms of the extended *s-cis* π -electron delocalization and the occurrence of intramolecular hydrogen bonding in the *s-cis* forms. A similar result was reported for thioacetic acid **5** (Figure 1) <1990JST67>.

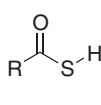
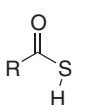
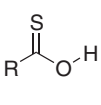
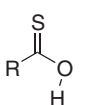
					
R = H 1	<i>cis-1a</i>	<i>trans-1a</i>	<i>cis-1b</i>	<i>trans-1b</i>	
	0.0	6.3	13.0	40.2	kJ mol^{-1}
R = Me 5	<i>cis-5a</i>	<i>trans-5a</i>	<i>cis-5b</i>	<i>trans-5b</i>	
	0.0	10.10	12.05	47.22	kJ mol^{-1}

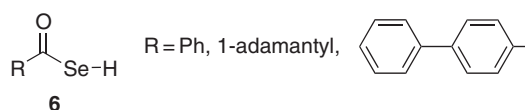
Figure 1 Relative energies (kJ mol^{-1}) among *s-cis* and *s-trans* conformers of *S*-acid and *O*-acid forms of thioformic acid **1** <1989JCS(F2)1945> and thioacetic acid **5** <1990JST67> by *ab initio* SCF-MO calculations at the 6-31G* **1** or 4-31G* **5** level.

Calculations of vibrational frequencies on thioformic *O*-acids **1** showed that absorptions at 1,235 and $1,160\text{ cm}^{-1}$, previously assigned to COH in-plane bending and C=S stretching modes, respectively <1972ZAAC78, 1974JST123>, are due to C—O stretching and COH bending modes, respectively <1989JCS(F2)1945>. The calculated C=S stretching frequency of *s-cis* thioformic *O*-acid (*cis-1b*) is 935 cm^{-1} .

The effect of the substituents (F, Cl, NH₂, OH, and Me) on the gas-phase acidities of formic acid and its silicon and sulfur derivatives R–M(Y)XH (M = C, Si; X, Y = O, S; R = F, Cl, OH, NH₂, and Me) was studied at the CBS-Q level of theory <2000MP709>. The orders of the calculated acidities for relevant compounds are HC(S)SH > HC(S)OH > HC(O)SH > HC(O)OH and ClC(S)OH > FC(S)OH > HOC(S)OH > HC(S)OH > MeC(S)OH > H₂NC(S)OH. The calculations showed that the chloro derivatives are stronger acids than the fluoro derivatives, which was explained in terms of the greater polarizability or softness of the chlorine atom compared to that of the fluorine atom.

5.12.1.3 Carboselenenic O-Acids

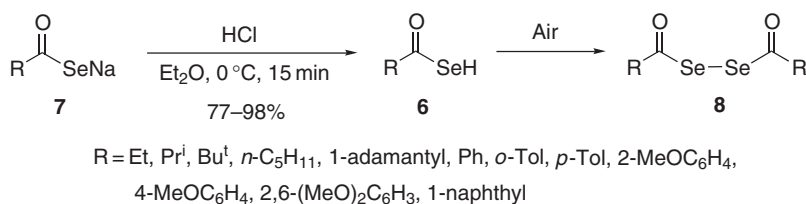
In general, carboselenenic acids are extremely air-sensitive materials. The IR and ¹H NMR spectra of acids **6** (R = Ph, 1-adamantyl, 4-biphenyl) only showed absorptions characteristic of carboselenenic *Se*-acids <1972ACSI465, 1987NKK1430, 1995COFGT(5)505>.



Carboselenenic acids, however, were revealed to exist predominantly in the *O*-acid form in polar solvents at low temperatures <1994JA2195, 1996JA1262, 1998PS(136-138)295>.

5.12.1.3.1 Spectroscopic methods

Kato and co-workers <1994JA2195> prepared carboselenenic acids **6** by acidification of the corresponding sodium salts **7** in high yields. The carboselenenic acids were stable in the solid state at 0 °C under argon, whereas they were oxidized immediately to the diselenides **8** upon exposure to air (Scheme 1).



Scheme 1

The ¹H, ¹³C, and ⁷⁷Se NMR spectra of 4-methoxyselenobenzoic acid (**6**, R = 4-MeOC₆H₄), measured at –90 °C in THF-*d*₈, showed signals at δ_H 15.3 (O–H), δ_C 222.2 (C=Se), and δ_{Se} 753.9 (C=Se), respectively. In addition, the UV–Vis spectrum of **6** (R = 4-MeOC₆H₄) in THF showed an absorption maximum at 502 nm due to the *n*–π* transition of the C=Se moiety, and the IR spectrum exhibited weakened absorption of the C=O stretching vibration. The data summarized in Figure 2 indicate that the *O*-acid form, 4-MeOC₆H₄C(Se)OH, is dominant in a polar solvent such as THF at low temperatures (Equation (3)) <1994JA2195, 1996JA1262, 1998PS(136-138)295>. This solvent effect is explained in terms of the energetically more favorable hydrogen-bonding interaction between the *O*-acid form and the solvent than that between the *Se*-acid form and the solvent (see Section 5.12.1.2.1).

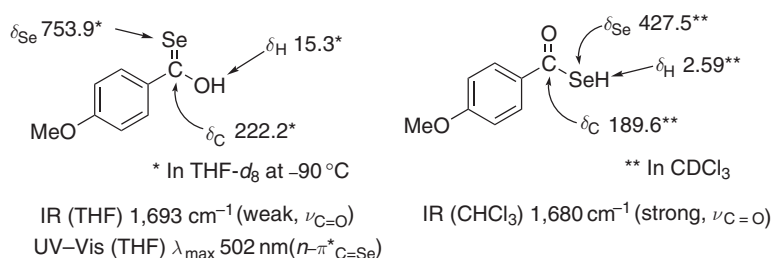
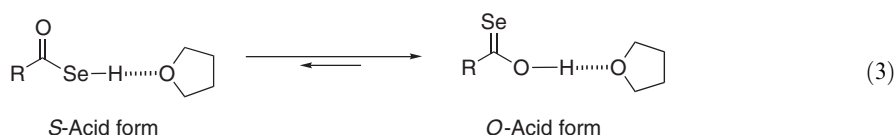


Figure 2 Relevant spectroscopic data of two forms of 4-methoxyselenobenzoic acid (**6**, $\text{R} = 4\text{-MeOC}_6\text{H}_4$) <1994JA2195>.



5.12.1.3.2 Theoretical methods

The structures, gas-phase acidities, and vibrational spectra of RC(Se)OH and RC(O)SeH ($\text{R} = \text{H}, \text{F}, \text{Cl}, \text{NH}_2, \text{Me}$) were studied at the B3LYP level of theory with the 6-311+G(d,p) basis set <1999JPC(A)431>. For all 10 acids studied, the *s-cis* conformers were predicted to have lower energies than the corresponding *s-trans* conformers (Figure 3). The *s-cis*/*s-trans* enthalpy difference varies between 0.3 and 9.9 kcal mol^{-1} . Optimized geometries of *s-cis* RC(Se)OH are summarized in Table 2. Vibrational frequencies of the Se—H group in RC(O)SeH were calculated to be $2,404$ ($\text{R} = \text{F}$)– $2,382$ ($\text{R} = \text{Cl}$) cm^{-1} , while those of the O—H group in RC(Se)OH to be $3,769$ ($\text{R} = \text{F}$)– $3,684$ ($\text{R} = \text{H}$) cm^{-1} . The calculated acidities increase in the order $\text{ClC(=O)SeH} > \text{FC(=O)SeH} > \text{HC(=O)SeH} > \text{H}_2\text{NC(=O)SeH} > \text{MeC(=O)SeH}$ for *Se*-acid forms and $\text{ClC(=Se)OH} > \text{FC(=Se)OH} > \text{HC(=Se)OH} > \text{H}_2\text{NC(=Se)OH} > \text{MeC(=Se)OH}$ for *O*-acid forms, where RC(=Se)OH is always stronger in acidity than the corresponding RC(=O)SeH . The decreased acidity of FC(=Y)XH compared with ClC(=Y)XH was explained by a much smaller polarizability, charge capacity, or softness of fluorine.

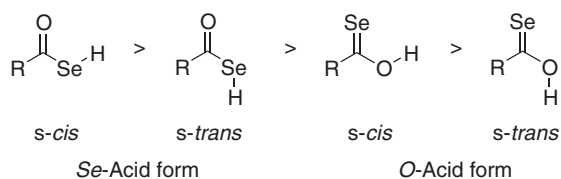
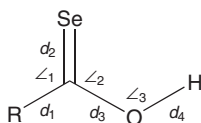


Figure 3 Calculated relative stability among *s-cis* and *s-trans* conformers of RC(Y)XH ($\text{X}, \text{Y} = \text{O}, \text{Se}$; $\text{R} = \text{H}, \text{F}, \text{Cl}, \text{NH}_2, \text{Me}$) at the B3LYP/6-311+G(d,p) level <1999JPC(A)431>.

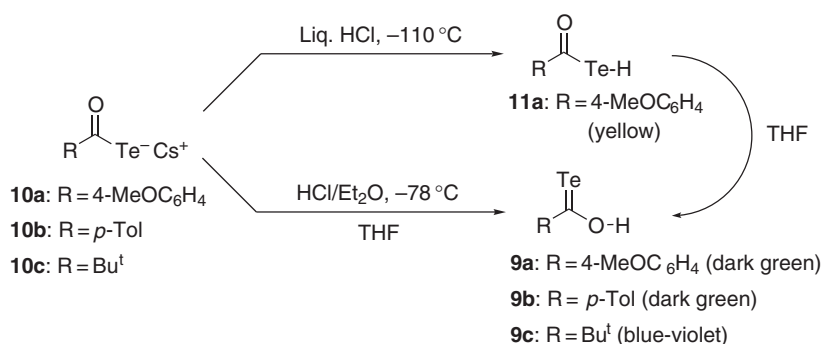
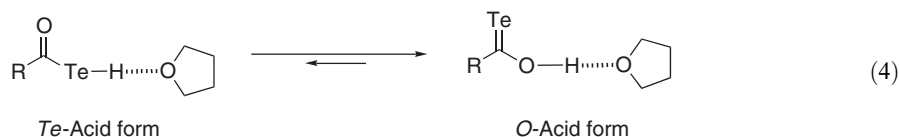
5.12.1.4 Carbotelluroic O-Acids

Carbotelluroic *O*-acids **9**, synthesized by acidification of the caesium salts **10** (Scheme 2), were revealed, by a manner similar to those for carbothioic and carboselenoic acids described in Sections 5.12.1.2.1 and 5.12.1.3.1, to exist predominantly in the *O*-acid form in THF at low temperatures (Equation (4)) <1996JA1262>.

Table 2 Optimized geometries^{a,b} of *s-cis* RC(Se)OH <1999JPC(A)431>


<i>R</i>	<i>d</i> ₁	<i>d</i> ₂	<i>d</i> ₃	<i>d</i> ₄	∠ ₁	∠ ₂	∠ ₃
H	1.087	1.775	1.328	0.972	123.1	126.4	108.6
F	1.321	1.778	1.320	0.969	123.6	128.4	107.9
Cl	1.739	1.780	1.327	0.971	124.9	125.8	107.5
Me	1.495	1.793	1.337	0.971	126.3	122.3	108.2
H ₂ N	1.338	1.818	1.324	0.968	125.7	123.0	107.1

^a B3LYP/6-311+G(d,p). ^b Bond lengths (*d*) in Å and bond angles (∠) in degrees.

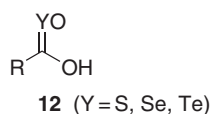
**Scheme 2**

Thus, dark green (**9a** and **9b**) or blue-violet **9c** THF solutions of **9** were obtained by the treatment of caesium salts **10** with dry hydrogen chloride at -78°C . The colored THF solutions showed an absorption maximum at 652 nm, **9a**, 672 nm, **9b**, or 594 nm, **9c**, at -90°C due to the $n-\pi^*$ transition of the C=Te group. The ^1H , ^{13}C , and ^{125}Te NMR spectra of **9a** in THF-*d*₈ measured at -90°C showed characteristic signals at δ_{H} 16.02 (O—H), δ_{C} 222.9 (C=Te), and δ_{Te} 952 (C=Te), respectively. Interestingly, the reaction of the salt **10a** with liquid HCl at -110°C yielded a yellow solid (Scheme 2). A yellow solution of the solid in toluene showed a characteristic ^{125}Te signal at δ 535 (-90°C) due to Te-acid **11a**, and addition of THF to the solution resulted in an instant color change to dark green due to O-acid **9a**. This solvent effect is interpreted in terms of the energetically favorable hydrogen-bonding interaction between the O-acid form and the solvent (see Section 5.12.1.2.1).

Carbotelluroic acids **9** are extremely sensitive toward oxygen and temperature <1996JA1262>. Exposure of a THF solution of **9a** to air at -90°C led to the immediate decomposition to black tellurium and a yellow oil containing [4-MeOC₆H₄C(O)]₂Te. Under argon conditions, no appreciable change in the solution took place at -78°C for at least 1 min.

5.12.1.5 Higher Oxidation States of the Chalcogen

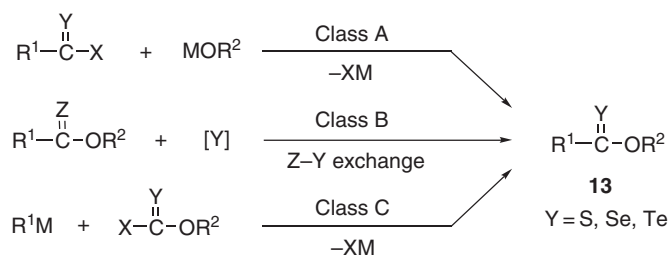
No reports have appeared on compounds of type **12** bearing higher oxidation states of the chalcogen atoms of carbothioic, carboselenoic, and carbotelluroic O-acids.



5.12.2 CARBOXYLIC ACID ESTER ANALOGS, $\text{R}^1\text{C}(\text{Y})\text{OR}^2$

5.12.2.1 General Methods

The preparation of *O*-alkyl or *O*-aryl carbothioates (thiocarboxylates, thionoesters), carboselenoates (selenocarboxylates), and carbotelluroates (tellurocarboxylates) **13** can be roughly divided into three classes on the basis of the final step of bond formation (Scheme 3) <1995COFGT(5)509>. Since the publication of chapter 5.12.2 in <1995COFGT(5)509>, some new papers have appeared on the synthesis of *O*-alkyl and *O*-aryl carbothioates and carboselenoates **13** (Y = S, Se), while no further advances have occurred on the synthesis of *O*-alkyl and *O*-aryl carbotelluroates **13** (Y = Te).



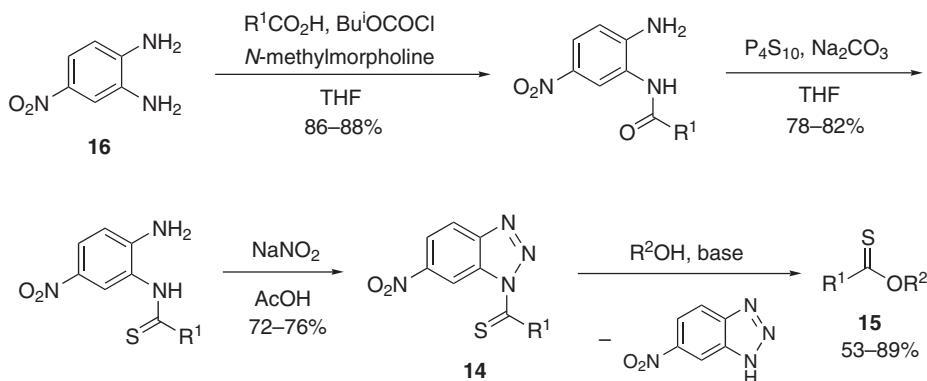
Scheme 3

5.12.2.2 Carbothioic Acid *O*-Esters, $\text{R}^1\text{C}(\text{S})\text{OR}^2$

5.12.2.2.1 Synthesis

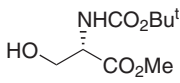
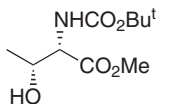
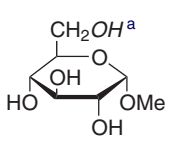
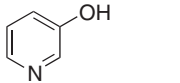
(i) Class A: from $\text{RC}(\text{S})\text{X}$

A new method using 1-thioacyl-6-nitrobenzotriazoles **14** as a thioacylating agent has been developed by Shalaby and Rapoport (Scheme 4) <1999JOC1065>. Several thionoesters **15** bearing other functional groups were synthesized in moderate-to-good yields. The thioacyl compounds **14** were prepared from 4-nitro-1,2-phenylenediamine **16** by a three-step route. The reaction of **14** with alcohols was carried out either in pyridine or in the presence of imidazole or DBU in dichloromethane, THF, or DMF. Table 3 shows the yields and ^{13}C NMR chemical shifts of thionoester carbons of **15** prepared in these ways.



Scheme 4

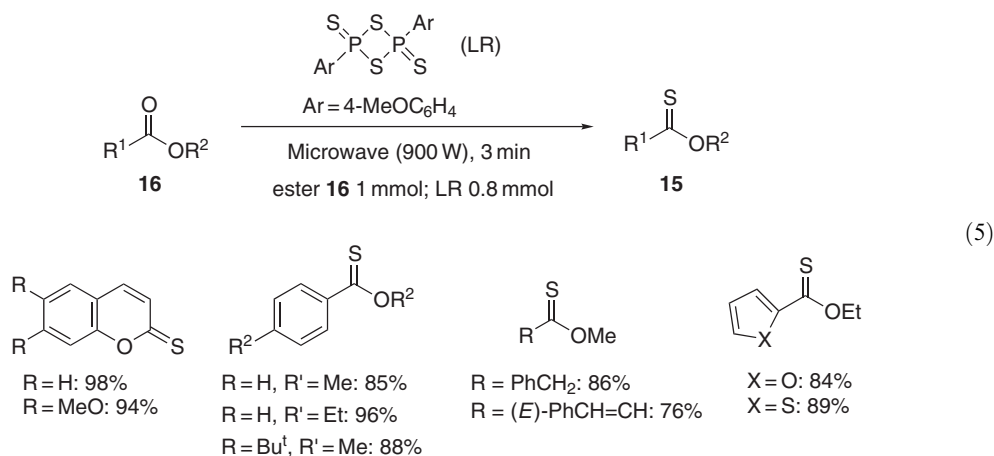
Table 3 Yields and ^{13}C NMR chemical shifts of thionoester carbons of **15**

R^1	$R^2\text{OH}$	Yield (%)	$\delta_{\text{C}} (\text{C}=\text{S})$
Me	PhCH_2OH	81	219.6
Et	PhCH_2OH	83	225.1
Bu^t	PhCH_2OH	79	231.0
Ph	PhCH_2OH	89	211.0
Ph	Cyclohexanol	74	210.6
Ph	Menthol	69	210.7
Ph		74	210.5
Ph		66	210.0
Ph		79 ^b	211.0
Ph		67	210.5
Cyclopropyl	PhCH_2OH	83	224.7
$(\text{CH}_2)_2\text{CO}_2\text{Me}$	PhCH_2OH	63	221.0
$\text{CH}(\text{OAc})\text{CH}_2\text{CO}_2\text{Me}$	PhCH_2OH	53	221.0
$\text{CH}(\text{OAc})\text{Ph}$	PhCH_2OH	64	215.5

Source: <1999JOC1065>.

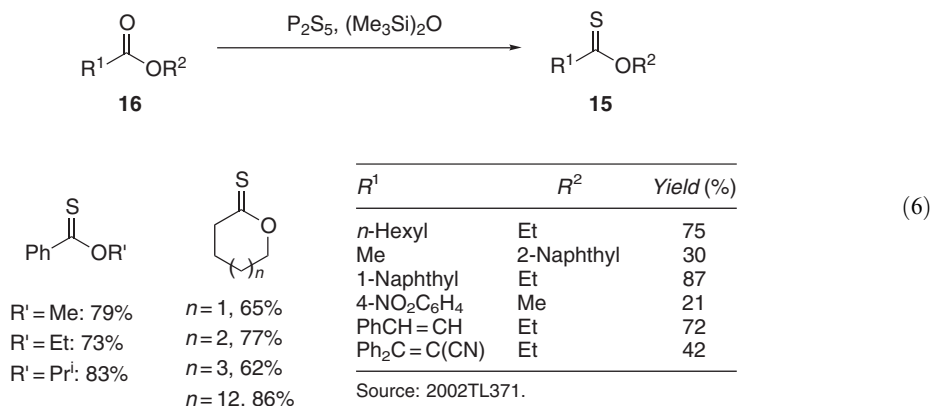
^a The reactive OH is italicized. ^b Isolated as 2,3,4-tri-*O*-acetyl-6-thiobenzoyloxy derivative.(ii) Class B: from $\text{RC}(\text{Z})\text{OR}$

Direct thionation of esters to the thionoesters with Lawesson's reagent (LR) usually requires high reaction temperatures, long reaction times, and an excess amount of the reagent, and the yields are moderate <1990JA3029, 1990JA3040, 1990JA6263, 1995COFGT(5)509>. Varma and Kumar reported an expeditious, solvent-free conversion of esters into thionoesters with LR by exposure to microwave irradiation (Equation (5)) <1999OL697>. This procedure converts ketones, flavones, isoflavones, and amides into thioanalogs in high yields.



The combination of P_2S_5 with $(\text{Me}_3\text{Si})_2\text{O}$ converts esters **16** into the thionoesters **15** (Equation (6)) in yields comparable to or superior to those obtained with LR <2002TL371>. An additional advantage is that reagent-derived by-products may be readily

removed by a mild hydrolytic work-up or by filtration through silica gel. Typically, the reaction is carried out by treating an ester **16** with 0.25–0.33 equiv. of P_2S_5 and 1.7 equiv. of $(Me_3Si)_2O$ in refluxing xylene, ethylbenzene, toluene, or acetonitrile.

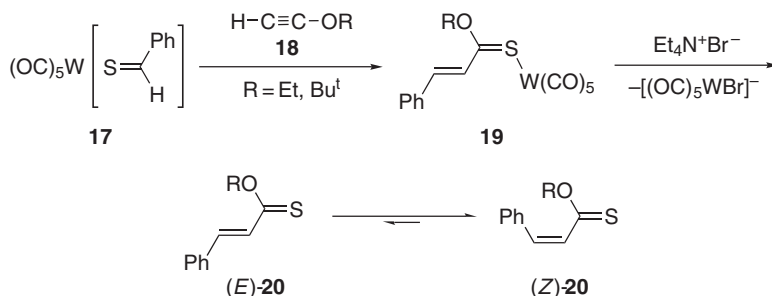


(iii) Class C: from $XC(S)OR$

No further advances have occurred in this area since the publication of chapter 5.12.2.3 in <1995COFGT(5)509>.

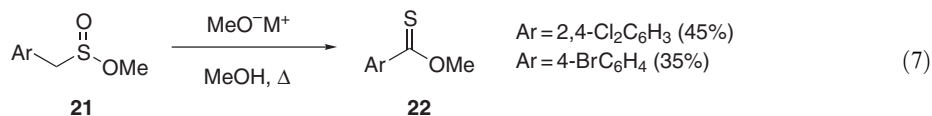
(iv) Miscellaneous

Pentacarbonyltungsten-coordinated thiobenzaldehyde **17** reacted with alkoxyethynes **18** to form the (*E*)- α,β -unsaturated thionoester complexes **19** in a highly regio- and stereoselective manner (Scheme 5) <1995CB883>. The structure of the complex ($R = \text{Et}$) was determined by X-ray crystallography. The thionoester ligands were cleaved intact from the metal by treatment with $\text{Et}_4\text{N}^+\text{Br}^-$ to yield a mixture of (*E*)- and (*Z*)-thionoesters **20**. The 10:1 *E/Z* ratio of the initial reaction mixture changed to 2.6:1 after chromatographic purification.

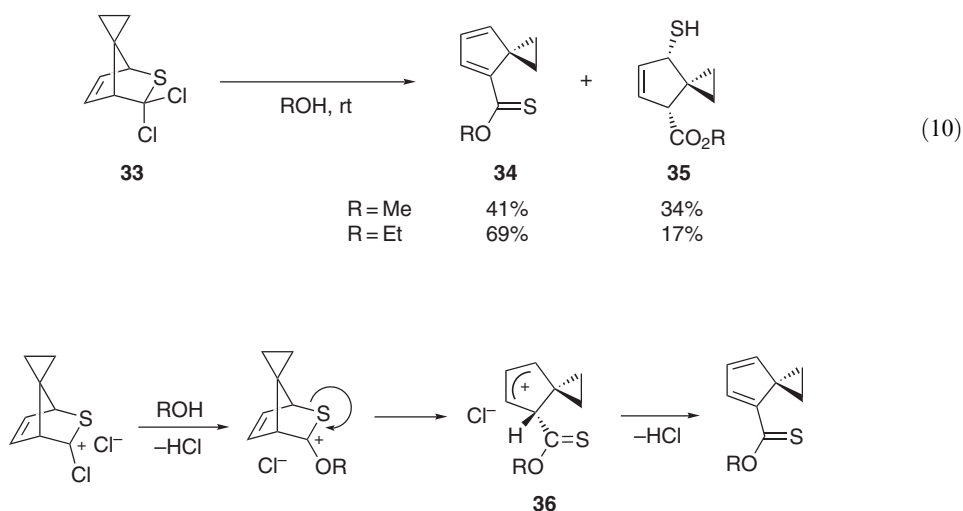


Scheme 5

Treatment of methyl sulfinates **21** with MeOLi or MeONa in refluxing methanol yielded *O*-methyl arenecarbothioates **22**, albeit in low yields (Equation (7)) <1996BSF1127>. Thioaldehyde *S*-oxides **23** and thiosulfinates **24** were considered to be key intermediates for the thionoesters **22** (Scheme 6).



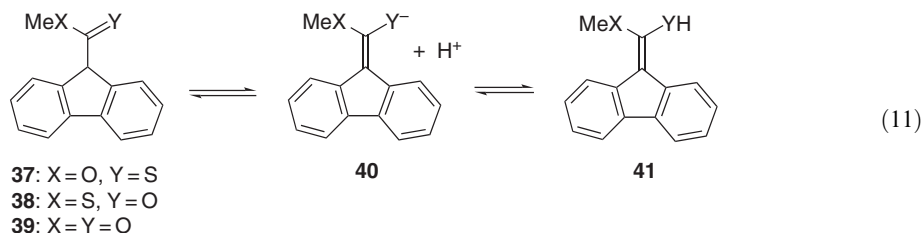
Alcoholysis of dichlorothiatriccycle **33**, obtained by a cycloaddition of spiro[2.4]hepta-4,6-diene and thiophosgene, formed *O*-alkyl spiro[2.4]hepta-4,6-diene-4-carbothioates **34** in moderate yields along with the esters **35** (Equation (10)) <2002JOC3682>. A mechanism involving the cyclopentenylum ion intermediate **36** was proposed (Scheme 7).



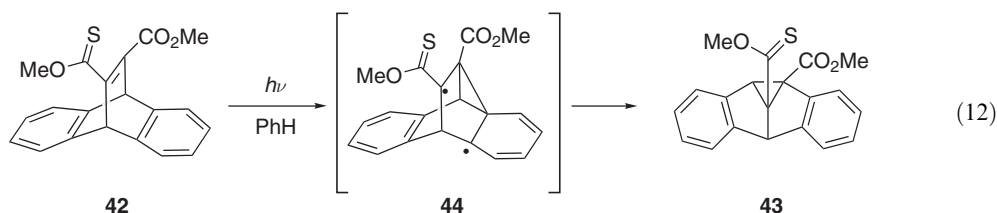
Scheme 7

5.12.2.2.2 Properties and reactions

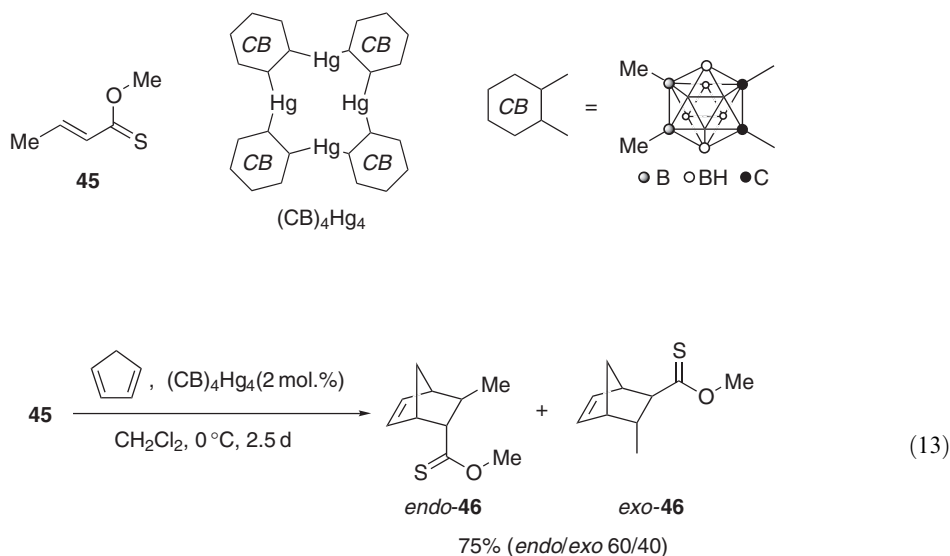
Carbon-acid dissociation constants (concentration quotients applicable at ionic strength = 0.10 M), pQ_a^K , determined for *O*-methyl 9*H*-fluorene-9-carbothioate **37**, *S*-methyl 9*H*-fluorene-9-carbothioate **38**, and methyl 9*H*-fluorene-9-carboxylate **39** were 7.40, 10.51, and 11.52, respectively, by monitoring UV spectral changes of these substances (Equation (11)) <1994JA8358>. These values indicate that the thiono group in **37** exerts an acid-strengthening effect, and **37** is 4 pK units more acidic than its oxygen analog **39**. Rates of acid-catalyzed ketonization of their enolate ions **40** are directly proportional to the acid concentration at low acidities, but the proportionality drops off in more concentrated acids, and acid catalysis becomes saturated. This saturation is caused by conversion of **40** to its less reactive enol form **41**. From a break in the rate profile for **37**, the acidity constant (pQ_a^E) of the enol **41** (X = O; Y = S) was determined to be 1.60; combination of this value with the carbon-acid acidity constant gave the keto–enol equilibrium constant (pK_E) of **37** to be 5.80.



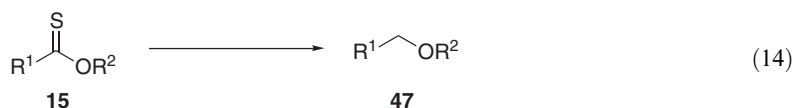
The radical-stabilizing effect of a thionoester group was shown in the di- π -methane rearrangement of dibenzobarrelenecarbothioate **42** yielding **43** as the sole product (Equation (12)) <1995AX(C)2691>. The structure of the photoproduct **43**, another thionoester, was determined by X-ray crystallography, and the C=S bond length was shown to be 1.630(3) Å. In this rearrangement, the initial vinyl-benzo bond formation takes place exclusively at the vinyl carbon atom carrying the CO₂Me group to give biradical intermediate **44**, where the biradical is stabilized by resonance interaction with the thionoester group.



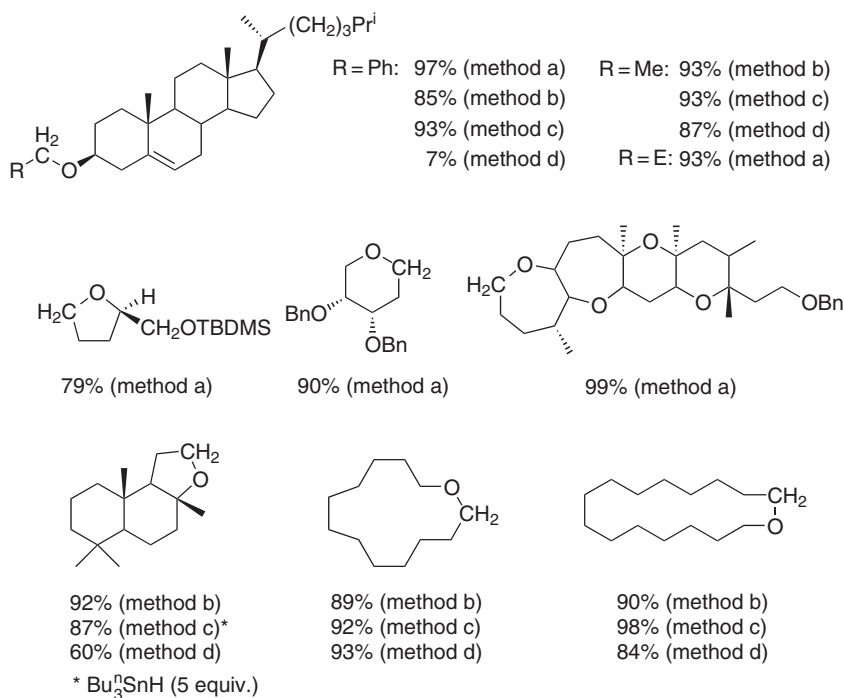
Complexation of *O*-methyl (*E*)-2-butenethioate **45** with *B*-octamethyl [12]-mercuracarborand-4 [(CB)₄Hg₄] was observed by ¹⁹⁹Hg NMR spectroscopy <1999TL7651>. The original signal due to (CB)₄Hg₄ at δ −1,204 in dichloromethane shifted to δ −997 by addition of an equimolar amount of the thionoester **45**. This observation indicates the coordination of the sulfur atom to the mercury atoms, which leads to the activation of **45**. Thus, a Diels–Alder reaction of **45** with cyclopentadiene in the presence of (CB)₄Hg₄ as a Lewis acid catalyst yielded a 60:40 mixture of the *endo*- and *exo*-adducts **46** in 75% yield (Equation (13)). No adducts were obtained with HgI₂ or Hg(OAc)₂.



Thionoesters **15** are transformed to the corresponding ethers **47** by desulfurization (Equation (14)). The synthetic utility of this transformation using Raney nickel was illustrated in the preparation of macrocyclic ethers <1983JOC2635, 1995COFGT(5)509>. The conversion of acyclic and cyclic thionoesters into ethers has also been accomplished by treatment with Ph₃SnH–AIBN <1995CC1583>, Ph₃SnH–Et₃B <1999T3479>, Buⁿ₃SnH–Et₃B–AIBN <1999T3479>, and Ph₂SiH₂–Ph₃SnH–Et₃B–AIBN <2000SL811> as summarized in Figure 4. These reactions proceed by a radical mechanism and the sulfur atom is eliminated as (R₂R'M)₂S (M = Sn, Si).

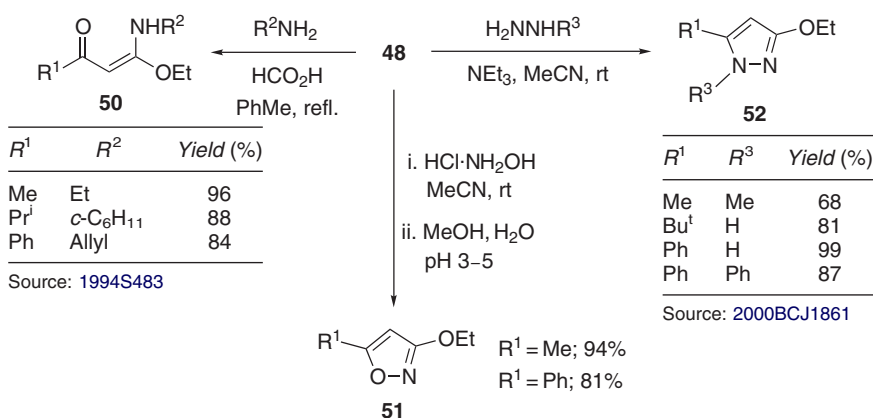
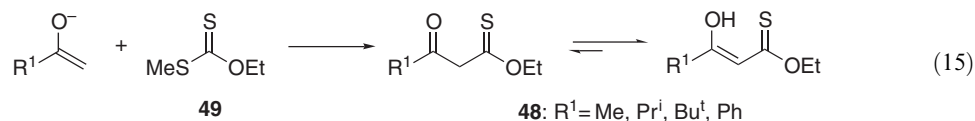


Highly enolized β -oxo thionoesters **48**, prepared by reaction of an enolate with *O*-ethyl *S*-methyl dithiocarbonate **49** (Equation (15)), reacted with primary amines <1994S483, 1999SC599>, hydroxylamine <2000BCJ1861>, or hydrazines <2000BCJ1861> to give α -oxo-ketene *O,N*-acetals **50**, isoxazoles **51**, or 1*H*-pyrazoles **52**, respectively (Scheme 8).



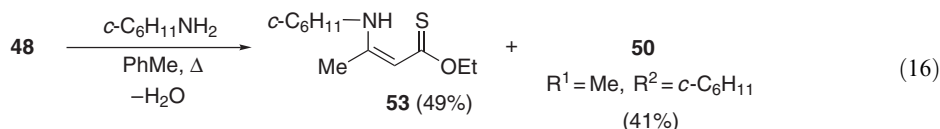
Method	Reagents and conditions	References
a	Ph ₃ SnH (5 equiv.), AIBN (0.15 equiv.), PhMe, refl.	<1995CC1583>
b	Ph ₃ SnH (2.2 equiv.), Et ₃ B (0.5 equiv.), PhMe, rt	<1999T3479>
c	i. Bu ⁿ SnH (2.2 equiv.), Et ₃ B (0.5 equiv.), PhMe, rt; ii. AIBN (0.25 equiv.), 85 °C	<1999T3479>
d	i. Ph ₂ SiH ₂ (3 equiv.), Ph ₃ SnH (0.5 equiv.), Et ₃ B (0.5 equiv.), PhMe, rt; ii. AIBN (0.2–0.4 equiv.), 110 °C	<2000SL811>

Figure 4 Transformation of R¹C(S)OR² to R¹CH₂OR² by methods a–d.

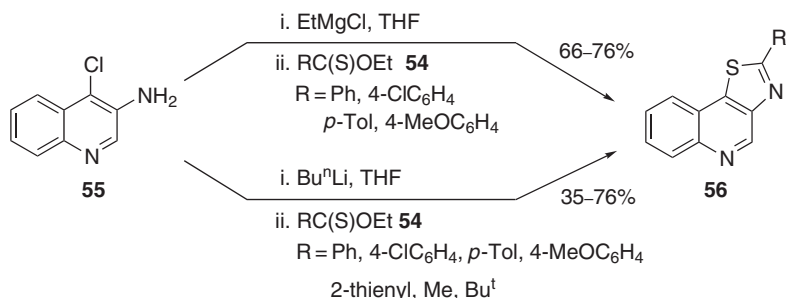


Scheme 8

Condensation of **48** with cyclohexylamine with azeotropic elimination of water yielded *O*-ethyl 3-*N*-cyclohexylamino-2-butenethioate **53** (49%) and the corresponding *O,N*-acetal **50** (41%) (Equation (16)) <1994S483>.

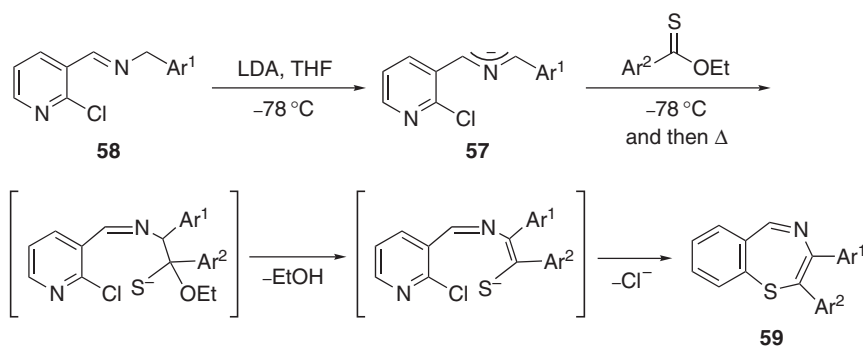


O-Ethyl carbothioates **54** react with a metal amide derived from 3-amino-4-chloroquinoline **55** to yield 2-substituted thiazolo[4,5-*c*]quinolines **56** in 35–76% yields (Scheme 9) <1995PS(101)173>.



Scheme 9

O-Ethyl carbothioates were also employed as a building block for the synthesis of another heterocycle. Thus, anions **57**, prepared from methyldene amines **58**, were allowed to react with thionoesters to give pyrido[3,2-*f*][1,4]thiazepines **59** in moderate yields (Scheme 10) <1996S986>.



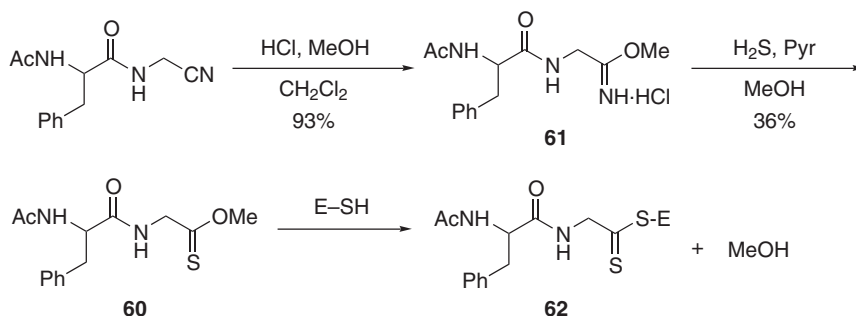
Ar^1	Ar^2	Yield (%)	Ar^1	Ar^2	Yield (%)
Ph	Ph	65	Ph	2-Thienyl	55
<i>p</i> -Tol	Ph	68	<i>p</i> -Tol	2-Thienyl	60
4-MeOC ₆ H ₄	Ph	63	4-MeOC ₆ H ₄	2-Thienyl	57
Ph	4-MeOC ₆ H ₄	59	Ph	3,4-(OCH ₂ O)C ₆ H ₃	71
4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	58			

Source: <1996S986>.

Scheme 10

A kinetic study on the cysteine proteinase catalytic mechanism was carried out using the thionoester of a dipeptide <2001BJ343, 1998MI173>. The dipeptide thionoester **60** was prepared by reaction of the imidate **61** with H₂S in the final step. The reaction of thionoester **60** with the thiol group of a cysteine residue in four natural enzymes (E—SH) (papain, caricain, actinidin, and

ficin) was monitored by stopped-flow spectral analysis to observe the increase and decay of the absorption at 315 nm due to the carbodithioate intermediates **62** (Scheme 11). The absorption appeared within 1 s, and gradually decayed over 100 s.



Scheme 11

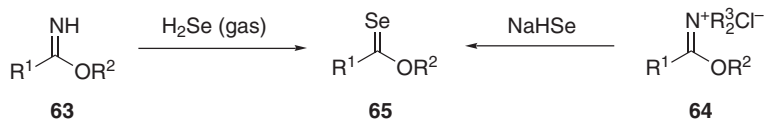
5.12.2.3 Carboselenoic Acid *O*-Esters, $\text{R}^1\text{C}(\text{Se})\text{OR}^2$

5.12.2.3.1 Synthesis

Most of the synthetic methods for *O*-alkyl and *O*-aryl carboselenoates belong to class B. A few reports have been added to Sections 5.12.2.3.1.(iv) and (v) since the publication of chapter 5.12.2.3.1 in <1995COFGT(5)509>.

(i) Reaction of alkyl or aryl imidates or their salts with H_2Se or NaHSe

The reaction of imidates **63** with gaseous H_2Se or, alternatively, that of the salts **64** with NaHSe yields the *O*-alkyl and *O*-aryl carboselenoates **65** (Scheme 12) <1995COFGT(5)509>. Imidates **63** are prepared by the reaction of nitriles with alcohols in the presence of hydrogen chloride <1962BSB563, 1977JOC2645>. The salts **64** are obtained by condensation of alcohols with (chloroalkylidene)ammonium chlorides $[\text{R}^1\text{C}(=\text{N}^+\text{R}_2)\text{Cl}\cdot\text{Cl}^-]$, prepared from *N,N*-disubstituted amides and phosgene <1975JCS(P1)1574, 1977JCS(P1)1723>. The latter method has more generality. Using the two methods, several kinds of *O*-alkyl and *O*-aryl carboselenoates **65**, involving *O*-alkyl selenoformates, were synthesized in low-to-high yields <1995COFGT(5)509>.

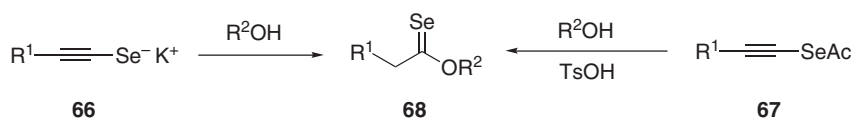


Scheme 12

No further advances have occurred in this area since the publication of chapter 5.12.2.3.1.(i) in <1995COFGT(5)509>.

(ii) Reaction of alkyneselenolate salts or alkyneselenols with alcohols

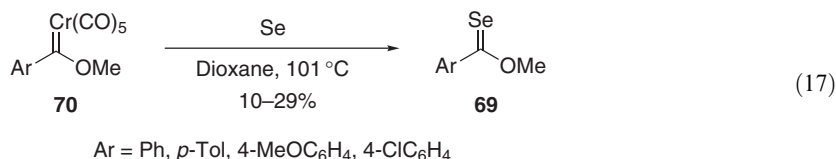
The reaction of alkyneselenolate salts **66** or alkyneselenols, generated *in situ* from (acetylseleno)-alkynes **67**, with alcohols yields *O*-alkyl carboselenoates of the type of **68** in moderate-to-high yields (Scheme 13) <1976JOC729, 1990BCJ835>. No further advances have occurred in this area since the publication of chapter 5.12.2.3.1.(ii) in <1995COFGT(5)509>.



Scheme 13

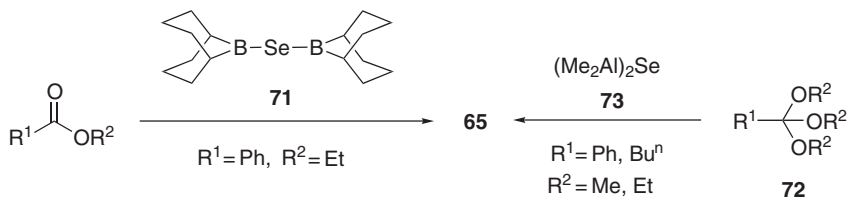
(iii) Reaction of alkoxy-carbene chromium complexes with elemental selenium

O-Methyl arenecarbosenoates **69** were formed by the reaction of alkoxy-carbene chromium complexes **70** with elemental selenium albeit in low yields (Equation (17)) <1974CB915, 1975GEP(O)2410157>. No further reports have appeared on this reaction since the publication of chapter 5.12.2.3.1.(iii) in <1995COFGT(5)509>.



(iv) Reaction of esters or orthoesters with selenation reagents

Direct selenation of ethyl benzoate to *O*-ethyl selenobenzoate with bis(1,5-cyclooctanediyl)boryl selenide **71** <1992CL1843, 1997BCJ197> and conversion of orthoesters **72** into *O*-alkyl carbosenoates **65** with bis(dimethylaluminum) selenide **73** have been reported (Scheme 14) <1992TL7865>.



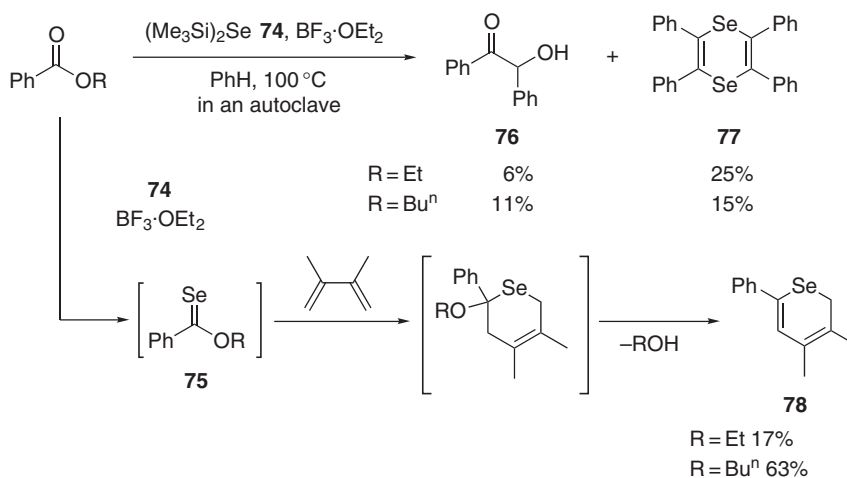
Scheme 14

Direct selenation of esters with a combination of bis(trimethylsilyl) selenide **74** and BF₃·OEt₂ was examined by Takikawa and co-workers <1994BCJ876>. The reaction, however, required drastic reaction conditions (at 100–150 °C in an autoclave), so that *O*-ethyl and *O*-butyl selenobenzoates **75** were not isolated, but benzoin **76** and 1,4-diselenins **77** were obtained in low yields. The intermediary formation of **75** was proposed based on the result that 2*H*-selenin **78** was formed when the reaction was carried out in the presence of 2,3-dimethyl-1,3-butadiene (Scheme 15).

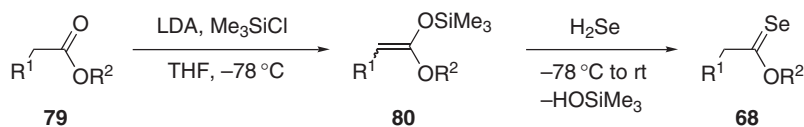
Wright reported that esters bearing α-hydrogens **79** were converted into *O*-alkyl carbosenoates of the type of **68** in high yields by the reaction of the formed ketene trimethylsilyl acetal intermediates **80** with hydrogen selenide (Scheme 16) <1994TL1331>. The reaction of **80** with hydrogen selenide proceeds quickly at –78 °C. This method is applicable to prepare *O*-*t*-butyl and *O*-benzyl carbosenoates and oxepane-2-selenone (ε-selenolactone) **81**.

(v) Miscellaneous

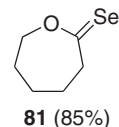
Pentacarbonyltungsten-coordinated selenobenzaldehyde **82** reacts with *t*-butoxyethyne **83** to give the 3,4-dihydro-1,2-diselenin–ditungsten complex **84** in 36% yield (Scheme 17) <1995CB1149>. The formation of the ditungsten complex **84** was explained in terms of a [4 + 2]-cycloaddition of



Scheme 15

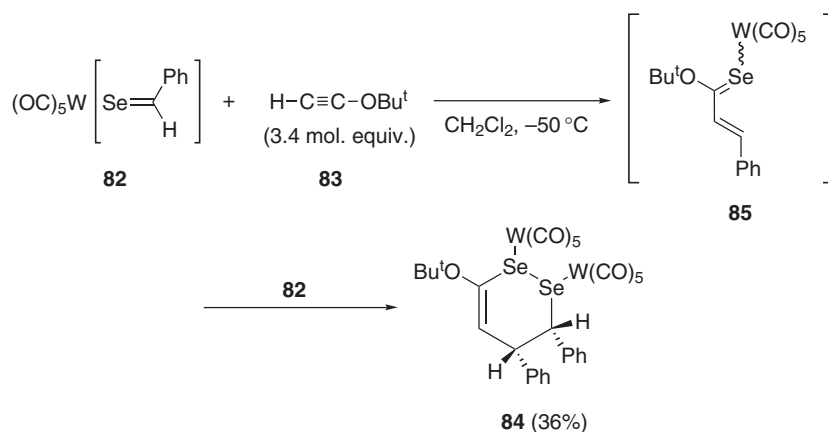


R^1CH_2	R^2	Yield (%)
(Z)-Me(CH ₂) ₇ CH=CH(CH ₂) ₇	Me	90
PhCH ₂	Me	74
Et	Cholesteryl	62
Br(CH ₂) ₄	Et	87
MeSCH ₂ CH ₂	Me	83
Et	PhCH ₂	80
α -C ₆ H ₁₁ CH ₂ CH ₂	Bu ^t	72



Source: 1994TL1331.

Scheme 16



Scheme 17

the initially formed α,β -unsaturated carboselenoate–tungsten complexes **85** with **82**. Unlike the case of the sulfur analog <1995CB883> (see Scheme 4), the tungsten complex **85** could not be isolated.

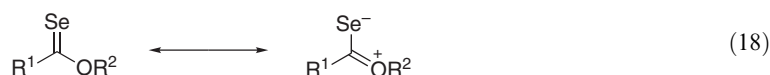
5.12.2.3.2 Spectroscopy

(i) UV–Vis spectra

The absorption due to the lowest electronic transition ($n-\pi^*$) of the selenocarbonyl group in $R^1C(Se)OR^2$ ($R^1 = H$ or alkyl; $R^2 =$ alkyl or aryl) appears in the range of 435–469 nm with molar extinction coefficients (ϵ) 43–98, while that of $R^1C(Se)OR^2$ ($R^1 = Ph$; $R^2 =$ alkyl or aryl) is observed in the range of 489–523 nm with ϵ 130–200 <1995COFGT(5)509>. These absorptions cause the yellow to red color of *O*-alkyl and *O*-aryl carboselenoates.

(ii) NMR spectra

Reported ^{13}C and ^{77}Se NMR chemical shifts of the selenocarbonyl groups in *O*-alkyl and *O*-aryl carboselenoates fall within the range of δ_C 215–238 and δ_{Se} 915–1,052, respectively <1995COFGT(5)521>. These nuclei resonate at higher fields than those of selenoketones which appear at ca. δ_C 290 and δ_{Se} 1,613–2,135. This observation can be explained by considering the resonance shown in Equation (18). The ^{17}O NMR chemical shift (δ 160.6) of *O*-ethyl selenobenzoate was reported <1983JCS(P2)1471>.

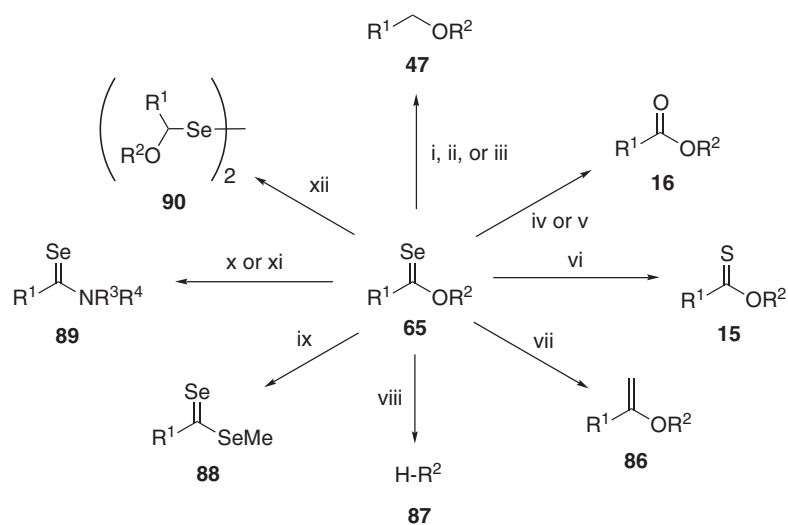


5.12.2.3.3 Reactions

Representative transformations and reaction products of *O*-alkyl and *O*-aryl carboselenoates **65** are summarized in Scheme 18 and Figure 5 <1995COFGT(5)521>. The $R^1C(Se)O$ group of **65** can be transformed into R^1CH_2O- , **47** <1977JCS(P1)1723>, $R^1C(O)O-$, **16** <1978CC393, 1980JCS(P1)1650, 1979CC755, 1981T(S)213>, $R^1C(S)O-$, **15** <1977AG(E)725, 1979JCR(S)160>, and $R^1C(=CH_2)O-$, **86** <1977JCS(P1)1723> groups, and hydrogen **87** <1975JCS(P1)1574>. Carboselenoates **65** are also converted into methyl carbodiselenoates **88** and selenoamides **89** by treatment with dimethylaluminum methaneselenolate <1993JA5823> and primary alkylamide, magnesium bromide, or secondary amines <1977JOC2645>, respectively. Reduction of **65** with $NaBH_4$ followed by exposure to air gives diselenides **90** <1977JCS(P1)1723>.

Treatment of **65** ($R^1 = CH_3$, $R^2 =$ alkyl) with potassium bis(trimethylsilyl)amide gives condensation products **91** <1977JCS(P1)1723>. The reaction of **65** with hydrazine hydrate yields bishydrazones **92** <1979JHC365>. *O*-Ethyl carboselenoates are employed as a building block to synthesize selenium-containing and other selenium-free heterocycles. Two reports describe the condensation leading to selenazole derivatives **93** and **94** <1987S363, 1985JOC1741>. Condensation reactions of **65** ($R^2 = Et$) with *o*-phenylenediamines, *o*-aminophenols, and *o*-aminothiophenols giving **95** <1977JHC1321>, with 4-substituted semi- and thiosemicarbazides giving **96** <1978JHC237>, and with *o*-aminobenzamide and *o*-aminothiobenzamide giving **97** <1978JHC1415> have been reported (Figure 5).

The reaction of *O*-methyl arenecarboselenoates **98** with dimethylaluminum alkanethiolates **99** yielded the *S*-alkyl arenecarboselenothioates **100** in moderate-to-good yields (Equation (19)) <1995JOC2942>.



i. NaBH_4 and then PET_3 ($\text{R}^1 = \text{H}$); ii. NaBH_4 – PET_3 ($\text{R}^1 = \text{Me}$); iii. W-2 Raney Ni ($\text{R}^1 = \text{Ph}$); iv. $[\text{PhSe}(\text{O})]_2\text{O}$; v. $(4\text{-MeOC}_6\text{H}_4)_2\text{Te}=\text{O}$; vi. S_8 , heat; vii. $\text{CH}_2=\text{PPh}_3$; viii. Bu_3SnH ($\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{cholesteryl}$); ix. Me_2AlSeMe ; x. R^3NHMgBr ; xi. $\text{R}^3\text{R}^4\text{NH}$; xii. NaBH_4 and then air.

Scheme 18

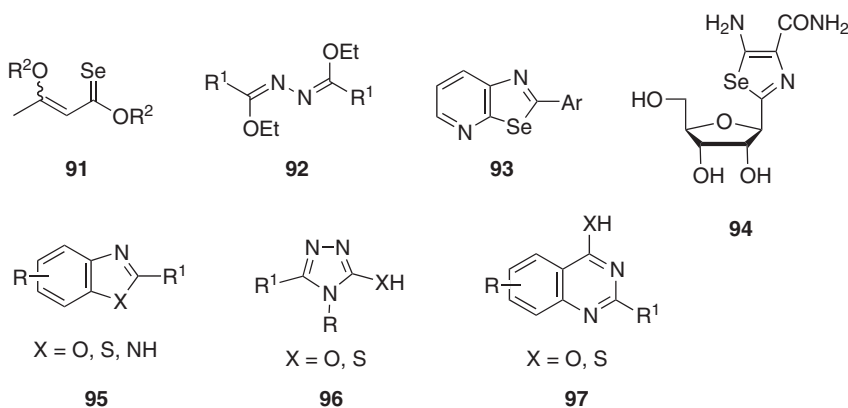
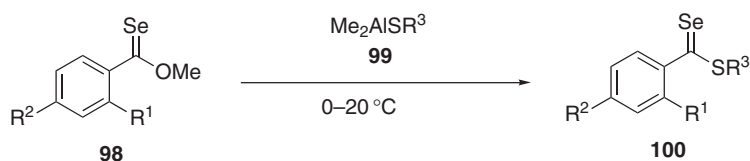


Figure 5

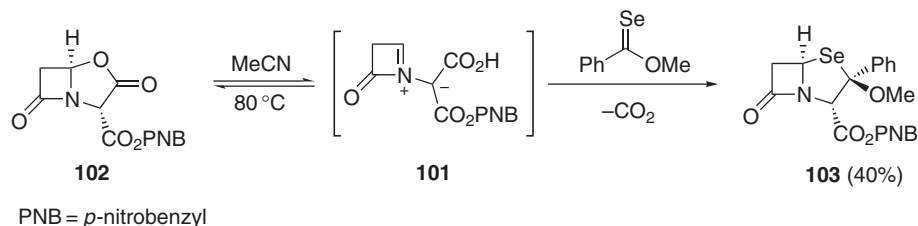


R^1	R^2	R^3	Yield (%)
H	H	Bu^n	75
H	H	Bu^s	42
H	H	Et	40
H	Me	Bu^t	81

R^1	R^2	R^3	Yield (%)
H	MeO	Me	54
Me	H	Me	92
Me	H	Bu^n	80

Source: <1995JA2942>.

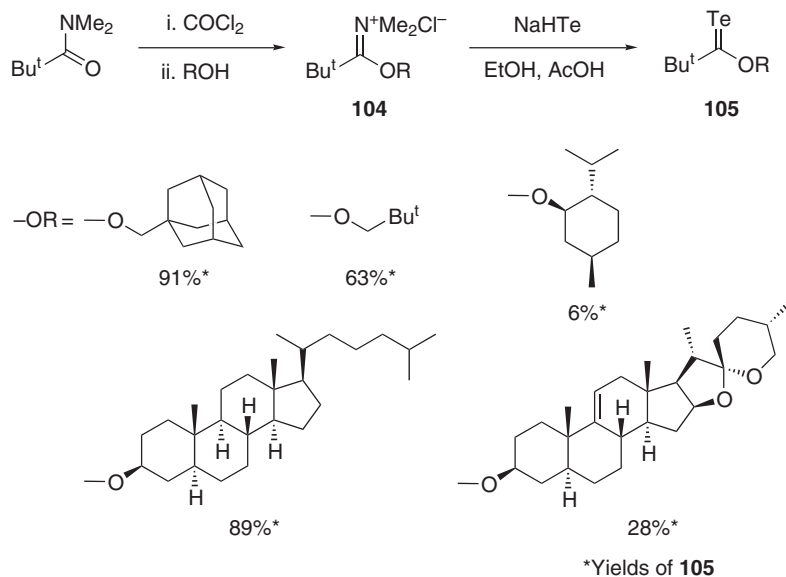
O-Methyl selenobenzoate functions as a dipolarophile and reacts with azomethine ylide **101**, which is generated thermally from oxazolidinone **102**, to give rise to the cycloadduct **103** (Scheme 19) <2000T5579>.



Scheme 19

5.12.2.4 Carbotelluroic Acid *O*-Esters, R¹C(Te)OR²

The only successful method for the synthesis of *O*-alkyl carbotelluroates is the reaction of (alkoxymethylene)ammonium chloride **104** with neutral ethanolic NaHTe to give five *O*-alkyl telluropivalates **105** (Scheme 20) <1979CC645, 1980JCS(P1)2191>. These telluropivalates **105** have a characteristic purple color (λ_{\max} 584–596 nm) and are unaffected by water, oxygen in the dark, and anaerobic photolysis (>500 nm) in benzene solution.

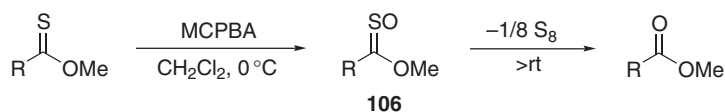


Scheme 20

No further advances have occurred in this area since the publication of chapter 5.12.2.4 in <1995COFGT(5)509>. The reaction of ketene trimethylsilyl acetals **80** with hydrogen telluride at -78°C was examined as an analogous reaction to that with hydrogen selenide for the synthesis of carboselenoates (Scheme 15) <1994TL1331>. This reaction afforded a purple solution characteristic of an *O*-alkyl carbotelluroate, but the putative carbotelluroate could not be isolated.

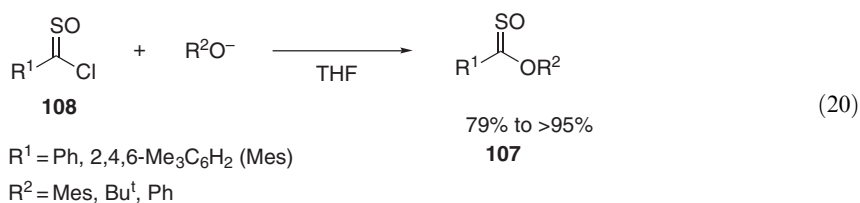
5.12.2.5 Higher Oxidation States of the Chalcogen

This is a rare class of compounds, and *O*-methyl carbothioate *S*-oxide **106** (Scheme 21) <1991TL7411> was the only example at the publication of <1995COFGT(5)509>. The compounds **106** are thermally unstable and decompose to the corresponding esters at room temperature.



Scheme 21

In 1996, Bonini and co-workers reported the preparation of thionoester *S*-oxides **107** by the reaction of chlorosulfines **108** with sterically demanding phenoxide and *t*-alkoxide ions (Equation (20)) <1996PS(108)289>. In the substitution reaction, the geometrical configuration of a starting chlorosulfine is predominantly retained. For example, the (*Z*)- and (*E*)-isomers of phenyl(chloro)sulfine with mesitol gave the (*Z*)- and (*E*)-oxides in a ratio 7:1 and 1:9, respectively (Table 4, runs 1 and 2). In the IR spectra of **107**, absorptions due to the S=O stretching vibration appear in the region of 1,060–1,140 cm⁻¹.

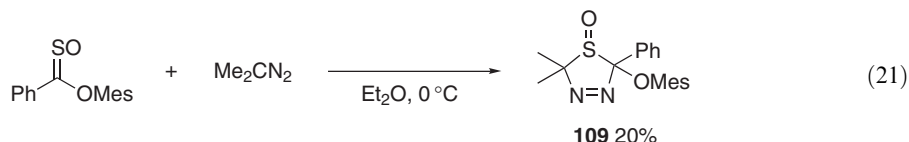
Table 4 Preparation of thionoester *S*-oxides **107** by reaction of chlorosulfines **108** with alkoxides

Run	Configuration of 108	R ¹	R ²	Yield (%)	Z/E	ν (S=O) ^a
1	<i>Z</i>	Ph	Mes ^b	>95	7/1	1060 ^c
2	<i>E</i>	Ph	Mes ^b	>95	1/9	
3	<i>Z</i>	Ph	Bu ^t	83	3/1	1140 ^d
4	<i>E</i>	Ph	Bu ^t	83	1/3	
5	<i>Z/E</i> = 4/1	Mes ^b	Bu ^t	>95	ND ^e	1070
6	<i>Z/E</i> = 4/1	Mes ^b	Ph	79	ND ^e	1070

Source: <1996PS(108)289>

^a In CCl₄. ^b 2,4,6-trimethylphenyl. ^c *Z*-isomer. ^d *Z* and *E* mixture. ^e Not determined.

These thionoester *S*-oxides **107** undergo partial decomposition to the corresponding esters by exposure to the light of a normal lamp for 3 days at room temperature. The reaction of *O*-mesityl thiobenzoate *S*-oxide with 2-diazopropane gave the thiadiazoline *S*-oxide **109** in 20% yield (Equation (21)) <1996PS(108)289>.

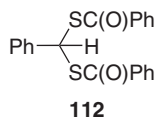
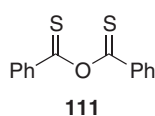


O-Alkyl(aryl) carboselenoate and carbotelluroate analogs remain unknown.

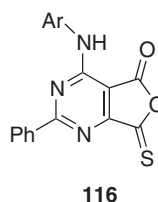
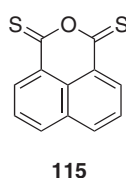
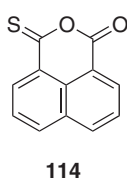
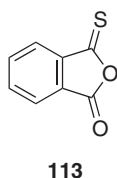
5.12.3 CARBOXYLIC ANHYDRIDE ANALOGS, R¹C(Y)OCOR² AND R¹C(Y)OC(Y')R²

5.12.3.1 Introduction

No acyclic carbothioic anhydride (thionoanhydride) are known to date. Bis(thiobenzoic) anhydride **111** supposedly reported in 1940 <1940JCS831> was revealed not to be the compound but a mixture of bis(benzoylthio) compound **112** and benzoic acid <1978ACS(B)780>.



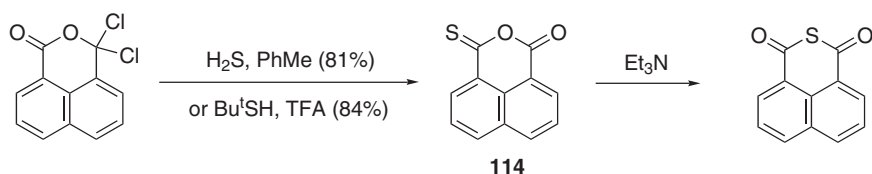
A few cyclic anhydrides **113–116** are known, but this class of compounds is still rare. One report appeared on the reaction of **115** <1999S1109> after the publication of chapter 5.12.3 in <1995COFGT(5)509>. No reports have appeared on carboselenoic and carbottelluroic anhydrides.



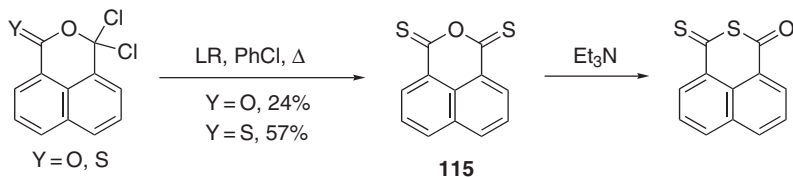
5.12.3.2 Carbothioic Anhydrides

Phthalic monothioanhydride **113** is obtained by the reaction of phthaloyl chloride with hydrogen disulfide <1967JOC3709>. It is quite unstable thermally and isomerizes readily to the corresponding thioanhydride (thioanhydride).

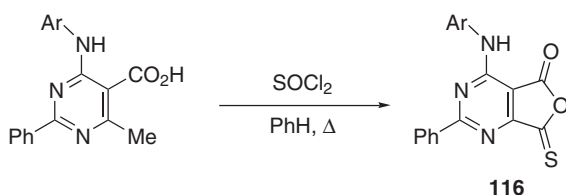
1,8-Naphthalic monothioanhydride **114** <1989JA4746>, 1,8-naphthalic dithioanhydride **115** <1984JA6084, 1989JA4746>, and 4-anilino-5-oxo-2-phenyl-7-thioxo-5,7-dihydrofuro[3,4-*d*]pyrimidines **116** <1986S142> were synthesized by reactions shown in Schemes 22 and 23 and Equation (22). Treatment of **114** and **115** with triethylamine leads to isomerization to the corresponding thioanhydride.



Scheme 22

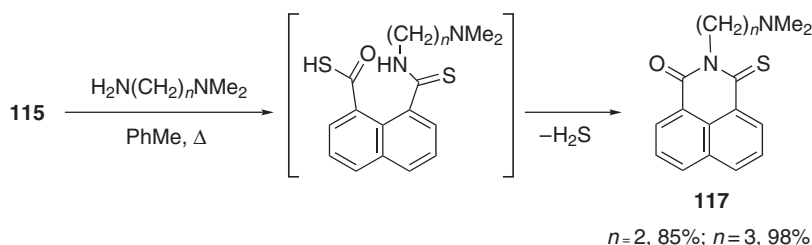


Scheme 23



(22)

Huang *et al.* reported reactions of **115** with *N,N*-dimethylethylenediamine and *N,N*-dimethylpropane-1,3-diamine to yield **117** in high yields <1999S1109> (Scheme 24).



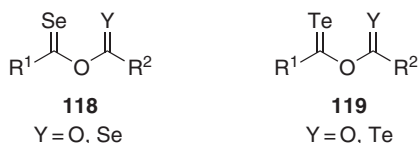
Scheme 24

5.12.3.3 Carboselenoic Anhydrides

No example of the carboselenoic anhydrides **118** has been reported. It was reported that *O*-silyl carboselenoates $[\text{RC}(\text{Se})\text{OSiR}^1\text{R}^2]$ reacted with acid chlorides to give the carboxylic selenoanhydrides $[\text{RC}(\text{O})_2\text{Se}]$ <1994JCS(P1)1083>.

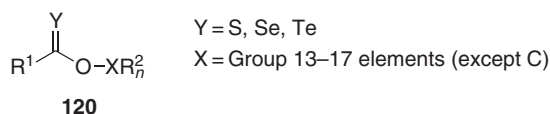
5.12.3.4 Carbotelluroic Anhydrides

There are no reports of carbotelluroic anhydrides **119**.



5.12.4 THIO-, SELENO-, AND TELLUROACYLOXY HETEROATOM FUNCTIONS, $\text{R}^1\text{C}(\text{Y})\text{OXR}_n^2$

This section concerns a type of compound, $\text{R}^1\text{C}(\text{Y})\text{OXR}_n^2$ **120** (Y = S, Se, and Te, and X = Group 13–17 elements except carbon), which have 1-thioxoalkoxy (thioacyloxy), 1-selenoxoalkoxy (selenoacyloxy), and 1-telluroxoalkoxy (telluroacyloxy) functional groups.

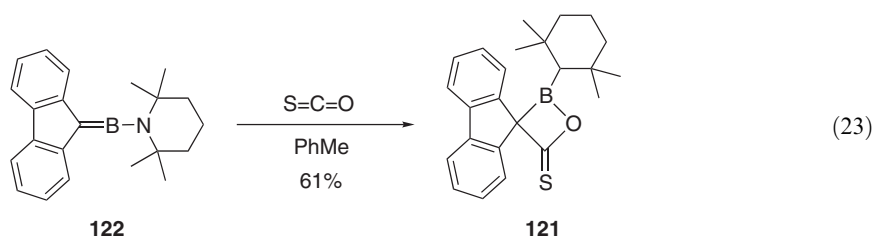


5.12.4.1 X = Group 13 Elements

A compound having a $-\text{C}(\text{S})-\text{O}-\text{B}-$ linkage was reported in 1993 <1993CB1119>. No further advances have occurred in this area since the publication of chapter 5.12.4.5.1 in <1995COFGT(5)509>.

5.12.4.1.1 B-Thioacyloxy compounds

1,2-Oxaboretane-4-thione **121** was obtained by a cycloaddition of 9-fluorenylidene(tetramethylpiperidino)borane **122** with $\text{S}=\text{C}=\text{O}$ in toluene at 0°C in 61% yield (Equation (23)) <1993CB1119>.



5.12.4.2 X = Group 14 Elements (Except Carbon)

The chemistry of *Si*-thioacyloxy, *Si*-selenoacyloxy, and *Si*-telluroacyloxy compounds (*O*-silyl carbochalcogenoates) was reviewed in chapter 5.12.4.5.3 in <1995COFGT(5)509>.

It was reported that reactions of thioacetic and thiobenzoic acids with Me_2SnCl_2 in water under basic conditions yielded bis(thioacetoxo)- **123** and bis(thiobenzoyloxy)stannanes **124**, respectively, in high yields <1979NKK1224>. Compound **123** was reported to be colorless plates (m.p. 56.5–57.0 °C) and to show $\text{C}=\text{S}$ stretching at $1,195\text{ cm}^{-1}$.



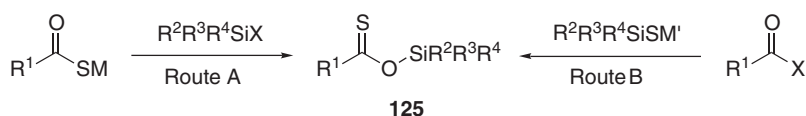
123: R = Me

124: R = Ph

As to other elements, Ge and Pb, the corresponding compounds have not been reported. Reactions of *O*-silyl carboselenoates and sodium carbotelluroates with Ph_3MCl (M = Ge, Sn, Pb) gave the corresponding *Se*-substituted $[\text{RC}(\text{O})\text{SeMPh}_3]$ <1994JCS(P1)1083> and *Te*-substituted $[\text{RC}(\text{O})\text{TeMPh}_3]$ compounds <2002OM1487>, respectively.

5.12.4.2.1 *Si*-Thioacyloxy compounds

General synthetic methods for preparing *Si*-thioacyloxy compounds **125** are shown in Scheme 25.



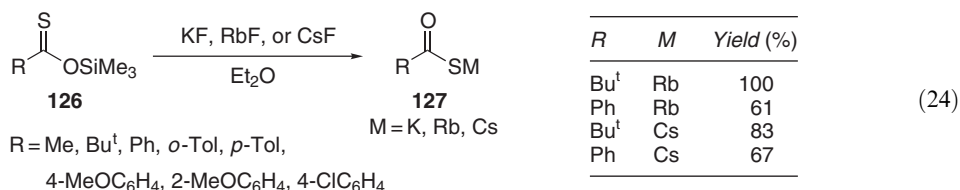
Scheme 25

Route A involves (i) the reaction of carbothioic acids with disilazanes <1966JOC3439, 1982JOC3966>, silyl chlorides in the presence of a tertiary amine <1966MI74, 1966JOC3439>, or disilylcarbodiimide <1976MI563>, (ii) that of potassium or ammonium salts of carbothioic acids with TMSCl <1973BCJ244, 1972IJS(A)279>, (iii) that of mixed thioanhydrides, $\text{R}^1\text{C}(\text{O})\text{SC}(\text{Y})\text{NHR}^2$ (Y = O, S), with TMSCl and triethylamine <1971S435, 1973MI47>, or (iv) that of *S*-tributylstannyl thioacetate with bromosilane <1980M193>. Route B involves the reaction of acyl chlorides or carboxylic anhydrides with bis(trimethylsilyl) sulfide <1972MI223, 1979JGU940>, lithium silanethiolate <1976JCS(D)1661>, or $\text{MeC}(=\text{N-TMS})\text{S}^-$ <1980JCS(P2)1557>.

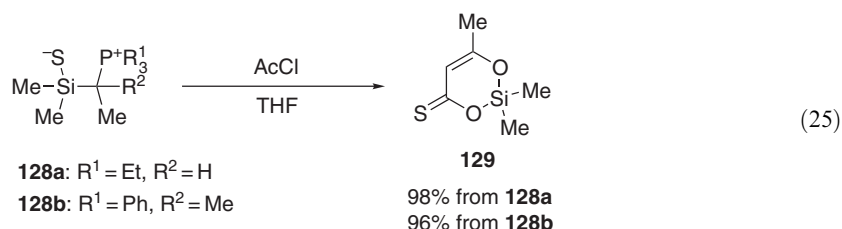
The color of *O*-silyl carbothioates **125** is generally yellow and the longest absorption maxima, assigned to the $n-\pi^*$ transition of the $\text{C}=\text{S}$ groups, are observed $\sim 430\text{ nm}$ in their UV-Vis spectra <1973BCJ244>. The predominance of the *O*-silyl form and not the *S*-silyl form has been interpreted in terms of bond energies of the isomers <1966JOC3439>.

O-Silyl carbothioates **125** are extremely sensitive to moisture and readily hydrolyzed even by moisture in air to give the corresponding carbothioic acids and hexamethyldisiloxane <1966JOC3439, 1973BCJ244>. The reaction with electrophilic species such as halonium ions <1986TL4593>, acyl chlorides <1972MI223, 1976JCS(P1)564>, alkyl halides <1972MI223>, and triethylethoxystannane <1975JGU2421> takes place at the sulfur atom.

Kato and co-workers <1999IC507> reported that *O*-trimethylsilyl carbothioates **126** reacted with KF, RbF, and CsF in ether to give the corresponding K, Rb, and Cs salts **127** in moderate-to-high yields (Equation (24)). The structures of $\text{ArC(O)S}^-\text{K}^+$ (Ar = Ph, 2-MeOC₆H₄, 4-MeOC₆H₄) and 2-MeOC₆H₄C(O)S⁻Rb⁺ were characterized by X-ray crystallography.

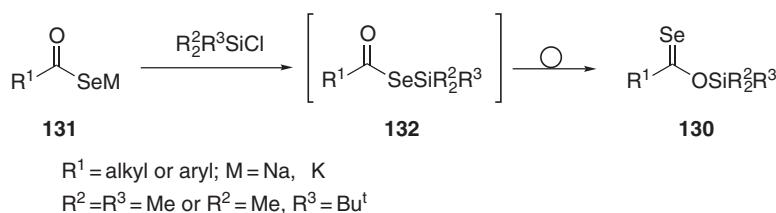


In 2000, the preparation of cyclic compounds bearing a $-\text{C}(\text{S})\text{OSi}-$ linkage was reported <2000IZV933>. Thus, the reaction of betaines **128** with acetyl chloride in THF yielded 1,3-dioxa-2-silacyclohex-5-ene-4-thiones **129** in high yields (Equation (25)).



5.12.4.2.2 Si-Selenoacyloxy compounds

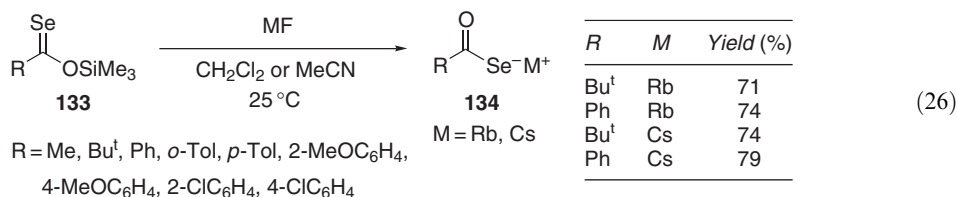
Silyl selenoacetate exists as an equilibrium mixture of MeC(O)SeSiH₃ (major) and MeC(Se)OSiH₃ (minor) <1972JCS(D)359, 1976JCS(D)1661>. In contrast, triorganosilyl carboselenoates **130** exist exclusively in *O*-triorganosilyl forms. The reaction of sodium or potassium carboselenoates **131** with chlorosilanes gives *Se*-triorganosilyl carboselenoates **132** initially, which quickly rearrange to **130** (Scheme 26) <1992CB417>.



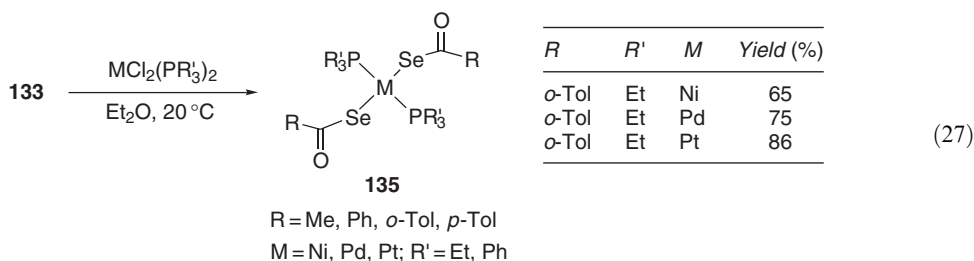
Scheme 26

O-Triorganosilyl carboselenoates **130** are thermally stable but very sensitive to water to be quickly hydrolyzed affording diselenide [$\text{R}^1\text{C}(\text{O})\text{SeSeC}(\text{O})\text{R}^1$] and disiloxane as the final products <1992CB417>.

O-Trimethylsilyl carboselenoates **133** are readily converted into the rubidium and caesium salts **134** by treatment with RbF and CsF, respectively (Equation (26)) <1993CC277, 1994BCJ1881>. The salts are white (R = alkyl) or yellow (R = aryl) crystals and decompose at room temperature with liberation of red selenium upon exposure to air.



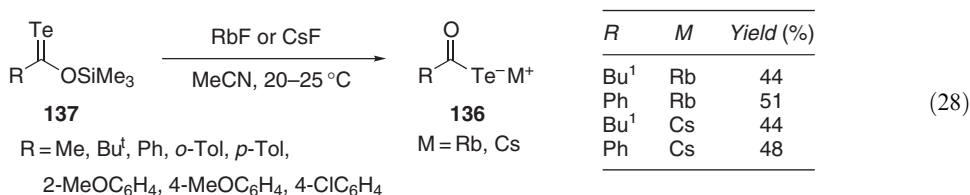
The reaction of **133** with $\text{MCl}_2(\text{PR}'_3)_2$ ($\text{M} = \text{Ni}, \text{Pd}, \text{Pt}$) yielded bis(carboselenoato)bis(triorgano-phosphine)-Ni(II), -Pd(II), and -Pt(II) complexes **135** in good yields (Equation (27)) <1996JCS(D)79>. X-Ray crystallography showed that the carbonyl oxygen atoms do not coordinate to the metal in the solid state.



5.12.4.2.3 Si-Telluroacyloxy compounds

The reaction of bis(trimethylsilyl) telluride $[(\text{TMS})_2\text{Te}]$ with pivaloyl chloride or dipivaloyl telluride gave a 65:35 equilibrium mixture of $\text{Bu}^t\text{C}(\text{Te})\text{O}-\text{TMS}$ and $\text{Bu}^t\text{C}(\text{O})\text{Te}-\text{TMS}$ <1987CC820>. The predominant existence of the *O*-silyl form was attributed to the strong affinity of silicon for oxygen though it is not sufficient to result in the quantitative formation of a $\text{C}=\text{Te}$ double bond. *O*-Trimethylsilyl telluropivalate has a characteristic blue color and exhibits the longest absorption maximum at 624 nm in the UV-Vis spectrum. The reaction of $(\text{TMS})_2\text{Te}$ with acetyl chloride or diacetyl telluride gave a blue solution suggesting the formation of *O*-trimethylsilyl telluroacetate <1985AG(E)1041>. Rearrangement of *o*-TolC(O)Te-TBDMS to *o*-TolC(Te)O-TBDMS was observed in a ^{13}C NMR study <1990TL3587>, a rearrangement similar to that shown in Scheme 26.

Kato and co-workers reported the preparation of rubidium and caesium salts **136** by treatment of *O*-trimethylsilyl carbotelluroates **137** with RbF and CsF in MeCN at room temperature (Equation (28)) <1995BCJ3507>.



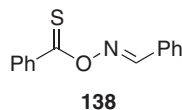
5.12.4.3 X = Group 15 Elements

Acyclic and cyclic *O*-(thioacyl)hydroxylamines and -oximes and thioacyloxy phosphorus compounds are known, though being still a rare class of compounds <1995COFGT(5)509>.

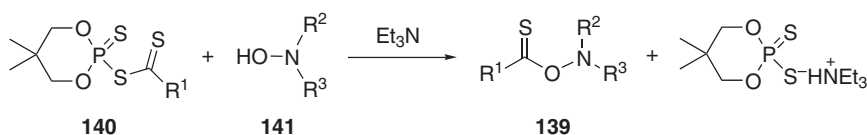
The corresponding compounds consisting of heavier elements (As, Sb, Bi) are unknown. The reaction of potassium carbothioates with Ph_3AsCl gave the *S*-arsinyl compounds <2001JCS(D)518>. The reaction of *O*-silyl carboselenoates with Ph_2MCl ($\text{M} = \text{P}, \text{As}$) gave the corresponding *Se*-substituted compounds $[\text{RC}(\text{O})\text{SeMPh}_2]$ <1994JCS(P1)1083>.

5.12.4.3.1 *O*-(Thioacyl)hydroxylamines and -oximes

O-(Thiobenzoyl)oxime **138** was obtained by the reaction of thiobenzoyl chloride with $\text{PhCH}=\text{NONa}$ in 30% yield as a yellow solid <1978JCS(P2)1167>. Compound **138** is thermally unstable and decomposes to biphenyl, dibenzoyl disulfide, and benzonitrile when heated in boiling chloroform <1978JCS(P2)1167>.



In 2002, the synthesis of *O*-(thioacyl)hydroxylamines **139** by the reaction of *S*-thioacyl dithiophosphates **140** with hydroxylamines **141** was reported (Equation (29)) <2002S1047, 2002PS(177)1851>. The steric effects of the substituents of **140** and **141** are crucial for successful synthesis. When R^1 of **140** is sterically less demanding (Pr^n or $(\text{CH}_2)_4\text{CO}_2\text{Me}$), the reaction with monosubstituted hydroxylamines **141** ($\text{R}^3 = \text{H}$) gave the thiohydroxamic acids $[\text{R}^1\text{C}(\text{S})\text{N}(\text{OH})\text{R}^2]$ and not **139**. In the case of $\text{R}^1 = \text{Ph}$, **139** was obtained only when *t*-butylhydroxylamine (**141**, $\text{R}^2 = \text{Bu}^t$, $\text{R}^3 = \text{H}$) was employed.

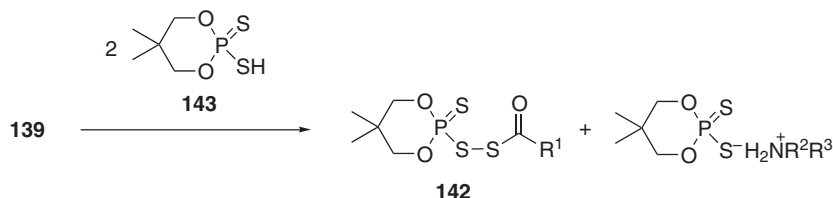


R^1	R^2	R^3	Yield (%)
Bu^t	Pr^i	H	73 ^a
Bu^t	Bu^t	H	96
Bu^t	$\text{CH}(\text{Me})\text{Ph}$	H	95
Bu^t	$\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$	H	71
Bu^t	Pr^i	PhCO	95 ^b
Ph	Bu^t	H	74

(29)

^a Not isolated.^b DBU was used as the base.

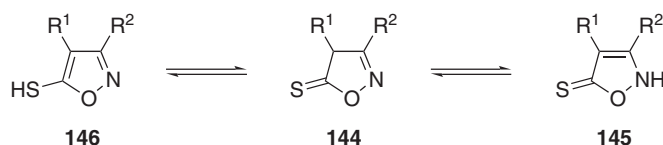
O-(Thioacyl)hydroxylamines **139** yielded disulfides **142** by treatment with dithiophosphoric acid **143** (Equation (30)). For this reaction, a radical chain mechanism was proposed, initiated by single electron transfer from the anion of **143** to the protonated form of **139**, rather than a straightforward thiophilic attack of the dithiophosphate ion <2002JCS(P2)1747, 2002S1047, 2002PS(177)1851>.



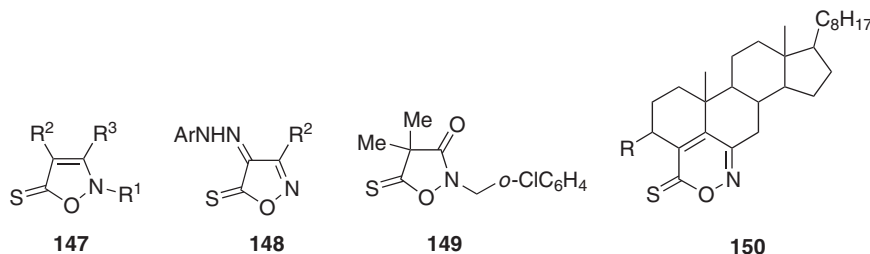
(30)

For cyclic thioacyloxy nitrogen compounds, no further advances have occurred since the publication of chapters 5.12.4.4.1(i)–(iii) in reference <1995COFGT(5)509>.

Although 2-isoxazoline-5-thiones **144** and 3-isoxazoline-5-thiones **145** exist as possible tautomeric forms of isoxazole-5-thiols **146** (Scheme 27), the compound was concluded to exist exclusively as **146** <1967JHC54>. However, introduction of substituent(s) to the 2- and 4-positions enabled the preparation of thioacyloxy compounds such as **147**, **148**, and **149** <1995COFGT(5)509>. Fused 6*H*-1,2-oxazine-6-thiones **150** are also known.



Scheme 27

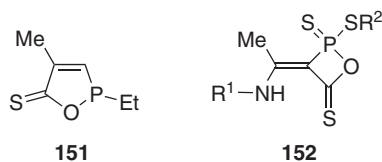


5.12.4.3.2 *O*-(Selenoacyl)- and *O*-(telluroacyl)hydroxylamines and -oximes

O-Selenoacyl and *O*-telluroacyl analogs are unknown in either cyclic or acyclic forms.

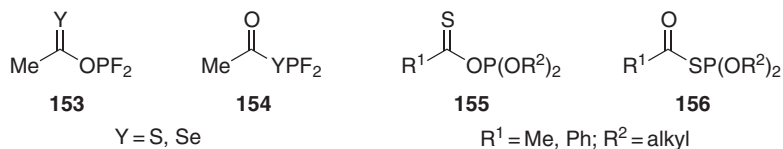
5.12.4.3.3 *P*-Thioacyloxy compounds and their selenium analogs

Cyclic *P*-thioacyloxy compounds, 1,2-oxaphosphol-3-ene-5-thione **151** <1973JGU2635> and 1,2-oxaphosphetane-4-thiones **152**, are known <1976CB1779>. These compounds are formed by isomerization of the respective *P*-acylthio compounds.

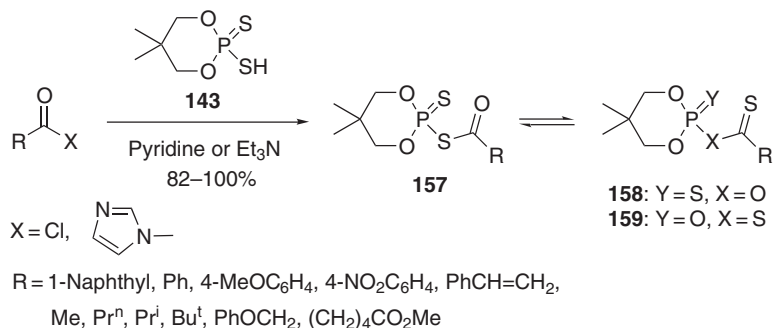


Isomerization between *P*-thioacyloxy and *P*-acylthio forms was studied on *O*-difluorophosphino thioacetate (**153**, Y = S) and *S*-difluorophosphino thioacetate (**154**, Y = S), which were prepared by treatment of *S*-tributylstannyl thioacetate and *O*-silyl thioacetate, respectively, with PBrF₂ at 193 K <1984JCS(D)2301>. Isomers **153** (Y = S) and **154** (Y = S) begin to isomerize to each other at 243 and 228 K, respectively, and the ratio of **153** (Y = S):**154** (Y = S) reached 4.3:1 at 243 K. Alternatively, treatment of an equilibrium mixture of *O*- and *Se*-silyl selenoacetates with PBrF₂ gave first *Se*-bonded isomer **154** (Y = Se) at 193 K, and then *O*-bonded isomer **153** (Y = Se) at 263 K though in less than ~10% yield.

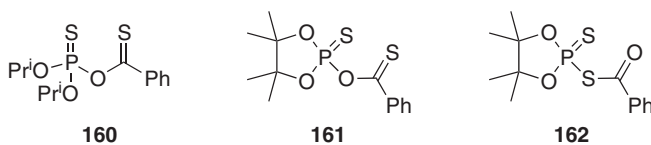
Phosphorylation of *O*-trimethylsilyl thioacetate with (R²O)₂PCl gave a mixture of thioacetyl phosphite **155** (R¹ = Me) and *S*-acetyl phosphorothioite **156** (R¹ = Me) in the ratio 5:95 <1989JGU1548>. Interestingly, the phenyl-stabilized thiocarbonyl structure leads to an increase of the proportion of the *O*-phosphorylated isomer; the reaction of *O*-trimethylsilyl thiobenzoate with (PrⁱO)₂PCl gave a 1:1 mixture of *O*- (**155**, R¹ = Ph, R² = Prⁱ) and *S*-phosphorylation (**156**, R¹ = Ph, R² = Prⁱ) products (44%).



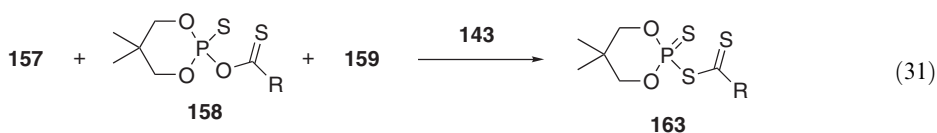
In 2000 and 2002, Doszczak and co-workers <2000CC2093, 2002JCS(P1)1271> reported the synthesis of mixed thioanhydrides **157** by the reaction of dithiophosphoric acid **143** with acyl chlorides or *N*-acylimidazoles (Scheme 28). The thioanhydrides **157** isomerize in solution to *O*-thioacyl monothiophosphates **158** and *S*-thioacyl monothiophosphates **159**. For example, the proportion of **158** (R = Ph) reaches 62% after heating for 2 h in refluxing benzene (**157** (R = Ph), 33%; **159** (R = Ph), 5%), from which **158** (R = Ph) is isolated. In a similar manner, *O*-thiobenzoyl monothiophosphate **160** was isolated in 37% yield, whereas monothiophosphate **161** was obtained as an inseparable mixture with *S*-benzoyl dithiophosphate **162** <2002JCS(P1)1271>.



Scheme 28

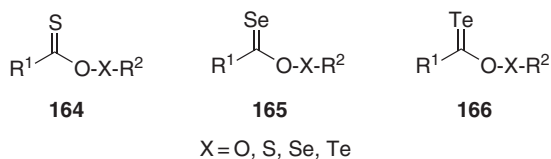


Treatment of an equilibrium mixture of **157–159** with dithiophosphoric acid **143** gives *S*-thioacyl dithiophosphates **163** (Equation (31)), which serve as a thioacylating agent toward nitrogen and sulfur nucleophiles to furnish thioamides and carbodithioates, respectively <2000CC2093, 2003SC1797>.



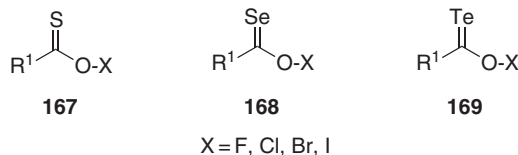
5.12.4.4 X = Group 16 Elements

No further advances have occurred in this area since the publication of chapters 5.12.4.2 and 5.12.4.3 in <1995COFGT(5)509>. A paper has reported the activation energy of the homolytic decomposition of some peroxides including the MeC(S)OOBu^t <1982MI52>. The reaction of *O*-silyl carboselenoates with RSI, RSeBr, RTel gave the corresponding *Se*-substituted compounds [RC(O)SeMR; M = S, Se, Te] <1994JCS(P1)1083>. Thus, compounds of types **164–166**, except **164** (X = O), have not been reported.



5.12.4.5 X = Group 17 Elements

No advances have occurred in this area since the publication of chapter 5.12.4.1 in reference <1995COFGT(5)509>. There have been no reports of *O*-halogen carbothioates **167**, carboselenoates **168**, and carbottelluroates **169**. The reaction of *O*-trimethylsilyl thiopivalate (**133**, R = Bu^t) with NBS or Bu^tOCl resulted in the thiophilic attack of bromonium or chloronium ion giving Bu^tC(O)SBr or Bu^tC(O)SCl, respectively <1986TL4593>.



REFERENCES

- 1940JCS831 D. T. Lewis, *J. Chem. Soc.* **1940**, 831–832.
 1962BSB563 C. Collard-Charon, M. Renson, *Bull. Soc. Chim. Belg.* **1962**, 71, 563–578.
 1966JOC3439 G. A. Gornowicz, J. W. Ryan, *J. Org. Chem.* **1966**, 31, 3439–3441.
 1966MI74 B. Martel, N. Duffaut, *Compt. Rend., Ser. C* **1966**, 263, 74–76. (*Chem. Abstr.* **1966**, 65, 13746f).
 1967JHC54 G. Adembri, R. Nesi, *J. Heterocycl. Chem.* **1967**, 4, 54–60.
 1967JOC3709 C. M. Sharts, D.-W. Fong, *J. Org. Chem.* **1967**, 32, 3709–3710.
 1971S435 H. R. Kricheldorf, E. Leppert, *Synthesis* **1971**, 435–436.
 1972ACS1465 K. A. Jensen, L. Bøje, L. Henriksen, *Acta Chem. Scand.* **1972**, 26, 1465–1470.
 1972IJS(A)279 S. Kato, W. Akada, M. Mizuta, *Int. J. Sulfur Chem., Part A* **1972**, 2, 279–282.
 1972JCS(D)359 S. Cradock, E. A. V. Ebsworth, H. F. Jessep, *J. Chem. Soc., Dalton Trans.* **1972**, 359–364.
 1972MI223 H. R. Kricheldorf, E. Leppert, *Makromol. Chem.* **1972**, 158, 223–239.
 1972ZAAC78 R. Engler, G. Gattow, *Z. Anorg. Allg. Chem.* **1972**, 388, 78–88.
 1973BCJ244 S. Kato, W. Akada, M. Mizuta, Y. Ishii, *Bull. Chem. Soc. Jpn.* **1973**, 46, 244–248.
 1973JGU2635 M. A. Vasyanina, V. K. Khairullin, *J. Gen. Chem. USSR (Engl. Transl.)* **1973**, 2635–2638. (*Z. Obshch. Khim.* **1972**, 42, 2644–2648).
 1973MI47 H. R. Kricheldorf, E. Leppert, *Makromol. Chem.* **1973**, 167, 47–68.
 1974CB915 E. O. Fischer, S. Riedmüller, *Chem. Ber.* **1974**, 107, 915–919.
 1974JST123 S. Randhawa, C. N. R. Rao, *J. Mol. Struct.* **1974**, 21, 123–134.
 1975GEP(O)2410157 E. O. Fischer, S. Riedmüller, *Ger. Offen.* **1975**, 2410157. (*Chem. Abstr.* **1976**, 84, 30690b).
 1975JGU2421 M. G. Voronkov, R. G. Mirskov, O. S. Ishchenko, S. P. Sitnikova, *J. Gen. Chem. USSR (Engl. Transl.)* **1975**, 2421–2424. (*Zh. Obshch. Khim.* **1974**, 44, 2462–2465).
 1975JCS(P1)1574 D. H. R. Barton, S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585.
 1976CB1779 U. Dabrowska, J. Dabrowski, *Chem. Ber.* **1976**, 109, 1779–1786.
 1976JCS(D)1661 S. Cradock, E. A. V. Ebsworth, D. W. H. Rankin, W. J. Savage, *J. Chem. Soc., Dalton Trans.* **1976**, 1661–1667.
 1976JCS(P1)564 M. Mikolajczyk, P. Kielbasiński, *J. Chem. Soc., Perkin Trans. 1* **1976**, 564–569.
 1976JOC729 F. Malek-Yazdi, M. Yalpani, *J. Org. Chem.* **1976**, 41, 729–730.
 1976MI563 J. E. Drake, R. T. Hemmings, H. E. Henderson, *Inorg. Nucl. Chem. Lett.* **1976**, 12, 563–569.
 1977AG(E)725 C.-P. Klages, J. Voss, *Angew. Chem., Int. Ed. Engl.* **1977**, 16, 725–726.
 1977JCS(P1)1723 D. H. R. Barton, P.-E. Hansen, K. Picker, *J. Chem. Soc., Perkin Trans. 1* **1977**, 1723–1730.
 1977JHC1321 V. I. Cohen, S. Pourabass, *J. Heterocycl. Chem.* **1977**, 14, 1321–1323.
 1977JOC2645 V. I. Cohen, *J. Org. Chem.* **1977**, 42, 2645–2647.
 1977JST25 H. S. Randhawa, C. O. Meese, W. Walter, *J. Mol. Struct.* **1977**, 36, 25–34.
 1978ACS(B)780 A. Senning, K. Schank, *Acta Chem. Scand. Ser. B* **1978**, B32, 780.
 1978CC393 D. H. R. Barton, N. J. Cussans, S. V. Ley, *J. Chem. Soc., Chem. Commun.* **1978**, 393–394.
 1978JCS(P2)1167 R. F. Hudson, K. A. F. Record, *J. Chem. Soc., Perkin Trans. 2* **1978**, 1167–1171.
 1978JHC237 V. I. Cohen, *J. Heterocycl. Chem.* **1978**, 15, 237–240.
 1978JHC1415 V. I. Cohen, *J. Heterocycl. Chem.* **1978**, 15, 1415–1417.
 1979JHC365 V. I. Cohen, *J. Heterocycl. Chem.* **1979**, 16, 365–368.
 1979JCR(S)160 C.-P. Klages, W.-D. Malmberg, J. Voss, *J. Chem. Res. (S)* **1979**, 160–161.
 1979CC645 A. G. M. Barrett, D. H. R. Barton, R. W. Read, *J. Chem. Soc., Chem. Commun.* **1979**, 645–647.
 1979CC755 D. H. R. Barton, S. V. Ley, C. A. Meerholz, *J. Chem. Soc., Chem. Commun.* **1979**, 755–756.
 1979JGU940 E. P. Levedev, V. A. Baburina, M. D. Mizhiritskii, *J. Gen. Chem. USSR (Engl. Transl.)* **1979**, 940–943. (*Zh. Obshch. Khim.* **1979**, 49, 1081–1084).
 1979NKK1224 Y. Nakamura, N. Yoshioka, T. Ouchi, M. Imoto, *Nippon Kagaku Kaishi* **1979**, 1224–1226. (*Chem. Abstr.* **1980**, 92, 22875r).
 1980JCS(P1)1650 N. J. Cussans, S. V. Ley, D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1* **1980**, 1650–1653.
 1980JCS(P1)2191 A. G. M. Barrett, R. W. Read, D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1* **1980**, 2191–2195.
 1980JCS(P2)1557 L. Carlsen, H. Egsgaard, E. Schaumann, H. Mrozek, W.-R. Klein, *J. Chem. Soc., Perkin Trans. 2* **1980**, 1557–1562.
 1980MI193 W. Bett, S. Cradock, *Monatsh. Chem.* **1980**, 111, 193–198.
 1981T(S)213 S. V. Ley, C. A. Meerholz, D. H. R. Barton, *Tetrahedron, Suppl.* **1981**, 37, 213–223.

- 1982JOC3966 C. A. Bruynes, T. K. Jurriens, *J. Org. Chem.* **1982**, 47, 3966–3969.
 1982MI52 A. A. Turovskii, R. V. Kucher, N. A. Turovskii, A. A. Andrianov, V. V. Petrenko, *Dopov. Akad. Nauk. Ukr. RSR, Ser. B: Geol. Khim. Biol. Nauki* **1982**, 52–54. (*Chem. Abstr.* **1982**, 97, 55111v).
 1983JCS(P2)1471 T. C. Wong, F. S. Guziec Jr., C. A. Moustakis, *J. Chem. Soc., Perkin Trans. 2* **1983**, 1471–1475.
 1983JOC2635 B. A. Jones, J. S. Bradshaw, P. R. Brown, J. J. Christensen, R. M. Izatt, *J. Org. Chem.* **1983**, 48, 2635–2639.
 1984JA6084 M. V. Lakshmikantham, P. Carroll, G. Furst, M. I. Levinson, M. P. Cava, *J. Am. Chem. Soc.* **1984**, 106, 6084–6085.
 1984JCS(D)2301 E. A. V. Ebsworth, C. M. Huntley, D. W. H. Rankin, *J. Chem. Soc., Dalton Trans.* **1984**, 2301–2304.
 1985AG(E)1041 T. Severengiz, W.-W. du Mont, D. Lenoir, H. Voss, *Angew. Chem., Int. Ed. Engl.* **1985**, 24, 1041–1042.
 1985JOC1741 W. J. Hennen, B. C. Hinshaw, T. A. Riley, S. G. Wood, R. K. Robins, *J. Org. Chem.* **1985**, 50, 1741–1746.
 1986S142 Z. Machon, J. Cieplik, *Synthesis* **1986**, 142–144.
 1986TL4593 T. Murai, S. Oida, S. Min, S. Kato, *Tetrahedron Lett.* **1986**, 27, 4593–4594.
 1987CC820 T. Severengiz, W.-W. du Mont, *J. Chem. Soc., Chem. Commun.* **1987**, 820–821.
 1987NKK1430 Y. Hirabayashi, H. Ishihara, M. Echigo, *Nippon Kagaku Kaishi* **1987**, 1430–1436. (*Chem. Abstr.* **1988**, 108, 55604d).
 1987S363 A. Couture, P. Grandclaudon, E. Huguier, *Synthesis* **1987**, 363–364.
 1989JA4746 M. V. Lakshmikantham, W. Chen, M. P. Cava, *J. Org. Chem.* **1989**, 54, 4746–4750.
 1989JCS(F2)1945 R. Fausto, L. A. E. Batista de Carvalho, J. J. C. Teixeira-Dias, M. N. Ramos, *J. Chem. Soc., Faraday Trans. 2* **1989**, 85, 1945–1962.
 1989JGU1548 V. A. Al'fonsov, D. A. Pudovik, R. Z. Musin, V. N. Nazmutdinova, Yu. Ya. Efremov, É. S. Batyeva, A. N. Pudovik, *J. Gen. Chem. USSR (Engl. Transl.)* **1989**, 1548–1553. (*Zh. Obshch. Khim.* **1988**, 58, 1734–1740).
 1990BCJ835 H. Ishihara, M. Yoshimi, N. Hara, H. Ando, S. Kato, *Bull. Chem. Soc. Jpn.* **1990**, 63, 835–841.
 1990JA3029 K. C. Nicolaou, S. A. DeFrees, C.-K. Hwang, N. Stylianides, P. J. Carroll, J. P. Snyder, *J. Am. Chem. Soc.* **1990**, 112, 3029–3039.
 1990JA3040 K. C. Nicolaou, C.-K. Hwang, B. E. Marron, S. A. DeFrees, E. A. Couladouros, Y. Abe, P. J. Carroll, J. P. Snyder, *J. Am. Chem. Soc.* **1990**, 112, 3040–3054.
 1990JA6263 K. C. Nicolaou, D. G. McGarry, P. K. Somers, B. H. Kim, W. W. Ogilvie, G. Yiannikouros, C. V. C. Prasad, C. A. Veale, R. R. Hark, *J. Am. Chem. Soc.* **1990**, 112, 6263–6276.
 1990JST67 R. Fausto, L. A. E. Batista de Carvalho, J. J. C. Teixeira-Dias, *J. Mol. Struct. (Theochem.)* **1990**, 207, 67–83.
 1990TL3587 S. Kato, H. Kageyama, T. Kanda, T. Murai, T. Kawamura, *Tetrahedron Lett.* **1990**, 31, 3587–3590.
 1991TL7411 M. Lemarié, T.-N. Pham, P. Metzner, *Tetrahedron Lett.* **1991**, 32, 7411–7414.
 1992CB417 S. Kato, H. Kageyama, Y. Kawahara, T. Murai, H. Ishihara, *Chem. Ber.* **1992**, 125, 417–422.
 1992CL1843 K. Shimada, N. Jin, M. Fujimura, Y. Nagano, E. Kudoh, Y. Takikawa, *Chem. Lett.* **1992**, 1843–1846.
 1992TL7865 M. Segi, T. Takahashi, H. Ichinose, G. M. Li, T. Nakajima, *Tetrahedron Lett.* **1992**, 33, 7865–7868.
 1993CB1119 S. Channareddy, B. Glaser, E. P. Mayer, H. Nöth, S. W. Helm, *Chem. Ber.* **1993**, 126, 1119–1125.
 1993JA5823 T. Murai, T. Mizutani, T. Kanda, S. Kato, *J. Am. Chem. Soc.* **1993**, 115, 5823–5824.
 1993CC277 Y. Kawahara, S. Kato, T. Kanda, T. Murai, H. Ishihara, *J. Chem. Soc., Chem. Commun.* **1993**, 277–278.
 1994BCJ876 Y. Takikawa, H. Watanabe, R. Sasaki, K. Shimada, *Bull. Chem. Soc. Jpn.* **1994**, 67, 876–878.
 1994BCJ1881 Y. Kawahara, S. Kato, T. Kanda, T. Murai, *Bull. Chem. Soc. Jpn.* **1994**, 67, 1881–1885.
 1994JA2195 H. Kageyama, T. Murai, T. Kanda, S. Kato, *J. Am. Chem. Soc.* **1994**, 116, 2195–2196.
 1994JA8358 Y. Chiang, J. Jones Jr., A. J. Kresge, *J. Am. Chem. Soc.* **1994**, 116, 8358–8359.
 1994JCS(P1)1083 H. Kageyama, K. Kido, S. Kato, T. Murai, *J. Chem. Soc., Perkin Trans. 1* **1994**, 1083–1084.
 1994S483 J. Moussounga, J. Bouquant, J. Chucho, *Synthesis* **1994**, 483–485.
 1994TL1331 S. W. Wright, *Tetrahedron Lett.* **1994**, 35, 1331–1334.
 1995AX(C)2691 R. Jones, A. Graham, M. Rattray, J. R. Scheffer, J. Trotter, *Acta Crystallogr. Sect. C* **1995**, C51, 2691–2694.
 1995BCJ3507 Y. Kawahara, S. Kato, T. Kanda, T. Murai, M. Ebihara, *Bull. Chem. Soc. Jpn.* **1995**, 68, 3507–3517.
 1995CB883 H. Fischer, K. Treier, C. Troll, *Chem. Ber.* **1995**, 128, 883–889.
 1995CB1149 H. Fischer, K. Treier, C. Troll, *Chem. Ber.* **1995**, 128, 1149–1156.
 1995CC1583 K. C. Nicolaou, M. Sato, E. A. Theodorakis, N. D. Miller, *J. Chem. Soc., Chem. Commun.* **1995**, 1583–1585.
 1995COFGT(5)505 A. Ishii, J. Nakayama, Thio, seleno, and telluro acyloxy functions, $R^1C(S)OR^2$, $R^1C(Se)OR^2$, $R^1C(Te)OR^2$, etc, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 505–544.
 1995COFGT(5)509 A. Ishii, J. Nakayama, Thio, seleno, and telluro acyloxy functions, $R^1C(S)OR^2$, $R^1C(Se)OR^2$, $R^1C(Te)OR^2$, etc, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 505–544.
 1995JOC2942 T. Murai, Y. Ogino, T. Mizutani, T. Kanda, S. Kato, *J. Org. Chem.* **1995**, 60, 2942–2945.
 1995PS(101)173 A. Couture, P. Grandclaudon, D. Ionescu, L. Ivan, *Phosphorus, Sulfur, Silicon* **1995**, 101, 173–177.
 1996BSF1127 J.-B. Baudin, M.-G. Commenil, S. A. Julia, R. Lorne, O. Reul, *Bull. Soc. Chim. Fr.* **1996**, 133, 1127–1141.
 1996JA1262 S. Kato, Y. Kawahara, H. Kageyama, R. Yamada, O. Niyomura, T. Murai, T. Kanda, *J. Am. Chem. Soc.* **1996**, 118, 1262–1267.
 1996PS(108)289 B. F. Bonini, M. W. J. Beulen, M. Comes-Frncini, G. Mazzanti, H. H. J. M. van de Voort, B. Zwanenburg, *Phosphorus, Sulfur, Silicon* **1996**, 108, 289–293.

- 1996JCS(D)79 Y. Kawahara, S. Kato, T. Kanda, T. Murai, K. Miki, *J. Chem. Soc., Dalton Trans.* **1996**, 79–85.
- 1996S986 A. Couture, E. Deniau, P. Grandclaudeon, C. Simion, *Synthesis* **1996**, 986–990.
- 1997BCJ197 K. Shimada, N. Jin, M. Kawaguchi, K. Dobashi, Y. Nagano, M. Fujimura, E. Kudoh, T. Kai, N. Saito, J. Masuda, M. Iwaya, H. Fujisawa, S. Aoyagi, Y. Takikawa, *Bull. Chem. Soc. Jpn.* **1997**, 70, 197–206.
- 1998PS(136-138)295 S. Kato, H. Kageyama, Y. Kawahara, T. Kanda, *Phosphorus, Sulfur, Silicon* **1998**, 136–138, 295–298.
- 1998MI173 J. D. Reid, S. Sreedharan, A. Cole, S. Maskell, A. Bokth, E. W. Thomas, K. Brocklehurst, *Biochem. Soc. Trans.* **1998**, 26, S173.
- 1999IC507 O. Niyomura, S. Kato, T. Kanda, *Inorg. Chem.* **1999**, 38, 507–518.
- 1999JOC1065 M. A. Shalaby, H. Rapoport, *J. Org. Chem.* **1999**, 64, 1065–1070.
- 1999JPC(A)431 M. Remko, B. M. Rode, *J. Phys. Chem. A* **1999**, 103, 431–435.
- 1999OL697 R. S. Varma, D. Kumar, *Org. Lett.* **1999**, 1, 697–700.
- 1999S1109 T.-B. Huang, J. Zhang, D. Zhu, W. Yao, X. Qian, *Synthesis* **1999**, 1109–1111.
- 1999SC599 I. Furukawa, H. Fujisawa, T. Abe, T. Ohta, *Synth. Commun.* **1999**, 29, 599–606.
- 1999T3479 D. O. Jang, S. H. Song, D. H. Cho, *Tetrahedron* **1999**, 55, 3479–3488.
- 1999TL7651 H. Lee, M. Diaz, M. F. Hawthorne, *Tetrahedron Lett.* **1999**, 40, 7651–7655.
- 2000BCJ1861 T. Ohta, H. Fujisawa, Y. Nakai, I. Furukawa, *Bull. Chem. Soc. Jpn.* **2000**, 73, 1861–1864.
- 2000CC2093 L. Doszczak, J. Rachon, *J. Chem. Soc., Chem. Commun.* **2000**, 2093–2094.
- 2000IZV933 I. V. Borisova, N. N. Zemlyanskii, A. K. Shestakova, V. N. Khrustalev, Y. A. Ustynyuk, E. A. Chernyshev, *Izv. Akad. Nauk, Ser. Khim.* **2000**, 935–942. (*Engl. Trans. Russ. Chem. Bull.* **2000**, 49, 933–941, *Chem. Abstr.* **2000**, 133, 321940).
- 2000MP709 M. Remko, M. Smiesko, P. T. Van Duijnen, *Mol. Phys.* **2000**, 98, 709–714.
- 2000SL811 D. O. Jang, S. H. Song, *Synlett* **2000**, 811–812.
- 2000T5579 G. A. Brown, K. M. Anderson, M. Murray, T. Gallagher, N. J. Hales, *Tetrahedron* **2000**, 56, 5579–5586.
- 2001BJ343 J. D. Reid, S. Hussain, S. K. Sreedharan, T. S. F. Bailey, S. Pinitglang, E. W. Thomas, C. S. Verma, K. Brocklehurst, *Biochem. J.* **2001**, 357, 343–352.
- 2001JCS(D)518 K. Tani, S. Hanabusa, S. Kato, S. Mutoh, S. Suzuki, M. Ishida, *J. Chem. Soc., Dalton Trans.* **2001**, 518–527.
- 2002JCS(P1)1271 L. Doszczak, J. Rachon, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1271–1279.
- 2002JCS(P2)1747 L. Doszczak, W. Przychodzen, D. Witt, J. Rachon, *J. Chem. Soc., Perkin Trans. 2* **2002**, 1747–1751.
- 2002JOC3682 B. Föhlisch, D. A. Bakr, P. Fischer, *J. Org. Chem.* **2002**, 67, 3682–3686.
- 2002OM1487 K. Tani, R. Yamada, T. Kanda, M. Suzuki, S. Kato, T. Murai, *Organometallics* **2002**, 21, 1487–1492.
- 2002PS(177)1851 L. Doszczak, W. Przychodzen, D. Witt, J. Rachon, *Phosphorus, Sulfur, Silicon* **2002**, 177, 1851–1854.
- 2002S1047 L. Doszczak, J. Rachon, *Synthesis* **2002**, 1047–1052.
- 2002TL371 T. J. Curphey, *Tetrahedron Lett.* **2002**, 43, 371–373.
- 2003EJO1784 W. Yao, M. Liao, X. Zhang, H. Xu, J. Wang, *Eur. J. Org. Chem.* **2003**, 1784–1788.
- 2003SC1797 L. Doszczak, V. C. Kravtsov, J. F. Biernat, J. Rachon, *Synth. Commun.* **2003**, 33, 1797–1808.

Biographical sketch



Akihiko Ishii was born in Tokyo. He received his Ph.D. degree in 1987 from the University of Tokyo under the direction of Professor N. Inamoto. He was appointed as Assistant Professor of Department of Chemistry of Saitama University in 1987, and promoted to Associate Professor in 1994 and Professor in 2004. He was a visiting Professor of the University of Caen, France 1997. He received the 1996 Progress Award of the Society of Synthetic Organic Chemistry, Japan, on the study of the chemistry of isolable dithiiranes. His research interest is in the area of synthesis and reactivities of organosulfur and organoselenium compounds, in particular, cyclic sulfur compounds (dithiiranes, 1,2,4-trithiolanes, tetra-thiolanes, etc.), α -disulfoxides, and hydrodichalcogenides (selenenic and thioselenenic acids and related compounds).



Juzo Nakayama is a Professor of the Department of Chemistry, Faculty of Science, Saitama University. He obtained his Ph.D. degree from the University of Tokyo in 1973. He worked for the Institute of Physical and Chemical Research as a postdoctoral fellow, prior to joining the present institution in 1975, and also worked with Professor Paul D. Bartlett as a postdoctoral fellow from 1977 to 1978. He received an Award of the Society of Synthetic Organic Chemistry, Japan and the International Council on Main Group Chemistry Award for Excellence in Main Group Chemistry (ICMGC Award). His research interests include the chemistry of a range of sulfur-containing heterocycles (dithiiranes, thiirenes, dithietes, thiophenes, etc.) and sulfur-containing inner salts.

5.13

Functions with Two Chalcogens Other Than Oxygen

T. MURAI

Gifu University, Yanagido, Japan

5.13.1	INTRODUCTION	493
5.13.2	DITHIOIC ACIDS AND ESTERS	494
5.13.2.1	Dithioic Acid Alkali Metal and Mg Salts	494
5.13.2.2	Inner Salts of Dithioic Acids	495
5.13.2.3	Dithioic Acid Esters	496
5.13.2.3.1	<i>Dithioalkanoic acid esters and aromatic and heteroaromatic acid esters</i>	497
5.13.2.3.2	<i>α,β-Unsaturated dithioic acid esters</i>	502
5.13.2.3.3	<i>α,β-Acetylenic dithioic acid and esters</i>	505
5.13.2.3.4	<i>Dithioic acid esters having sulfur in higher oxidation states</i>	505
5.13.2.3.5	<i>Dithioic acid Si, Ge, Sn, Pb esters</i>	506
5.13.2.4	Dithiocarbamyl-azo Dyes, Thioacylsulfanylphosphines and -arsines	508
5.13.2.5	Trithioperesters	509
5.13.2.6	Thioacylsulfanyl Bromide	510
5.13.3	SELENOTHIOIC AND DISELENOIC ACIDS AND ESTERS	510
5.13.3.1	Selenothioic and Diselenoic Acid Esters	510
5.13.3.2	Selenothioic and Diselenoic Acid Salts	513

5.13.1 INTRODUCTION

The functionalities belonging to this category have been shown in [Table 1](#) in the acid form along with the nomenclature based on the IUPAC recommendations. A variety of synthetic methods for dithioic acids and their derivatives were already established in the 1990s. Some of the more conventional methods have been utilized since the 1990s. Alternatively, synthetic efforts to provide complex molecules involving a dithiocarboxyl group and transition metal complexes bearing dithiocarboxyl ligands have been made, but this chapter does not cover these topics. Instead, a variety of dithioic acid derivatives in which main group elements having organic substituents are attached to the sulfur atom will be discussed. The selenium and tellurium isologs of dithioic acid and their derivatives have been considered to be difficult to be isolated in a stable form for the following reason. The introduction of heavier elements has been predicted to enhance the energy level of high-lying π orbital and to lower that of low-lying π^* orbital. As a result, the stability of the compounds is reduced on going from the first row to the third row in [Table 1](#). In addition, hydrogen-bonding stabilization is dramatically decreased, and the chalcogen hydrogen bond such as S—H, Se—H, and Te—H becomes more susceptible to air oxidation on going from the left column to right column in [Table 1](#). However, recent synthetic efforts to synthesize selenium isologs of dithioic acid salts allowed for the isolation of inner salts of selenothioic and diselenoic acids. Furthermore, the first successful isolation of aliphatic and

Table 1 Acid analogs with two chalcogens other than oxygen

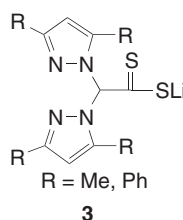
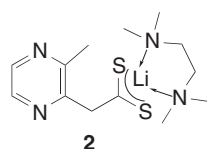
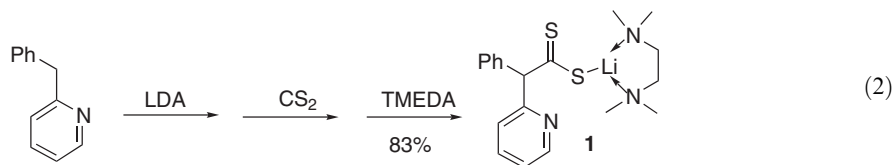
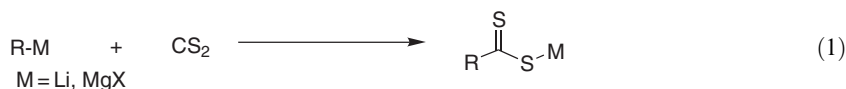
$\begin{array}{c} \text{S} \\ \parallel \\ \text{R}-\text{S}-\text{H} \end{array}$ Dithioic acid	$\begin{array}{c} \text{S} \\ \parallel \\ \text{R}-\text{Se}-\text{H} \end{array}$ Selenothioic Se-acid	$\begin{array}{c} \text{S} \\ \parallel \\ \text{R}-\text{Te}-\text{H} \end{array}$ Tellurothioic Te-acid
$\begin{array}{c} \text{Se} \\ \parallel \\ \text{R}-\text{S}-\text{H} \end{array}$ Selenothioic S-acid	$\begin{array}{c} \text{Se} \\ \parallel \\ \text{R}-\text{Se}-\text{H} \end{array}$ Diselenoic acid	$\begin{array}{c} \text{Se} \\ \parallel \\ \text{R}-\text{Te}-\text{H} \end{array}$ Selenotelluroic Te-acid
$\begin{array}{c} \text{Te} \\ \parallel \\ \text{R}-\text{S}-\text{H} \end{array}$ Tellurothioic S-acid	$\begin{array}{c} \text{Te} \\ \parallel \\ \text{R}-\text{Se}-\text{H} \end{array}$ Selenotelluroic Se-acid	$\begin{array}{c} \text{Te} \\ \parallel \\ \text{R}-\text{Te}-\text{H} \end{array}$ Ditelluroic acid

aromatic selenothioic acid salts was achieved. Nevertheless, Te-containing acid analogs are not reported as yet in spite of their potential importance from a synthetic and spectroscopic point of view.

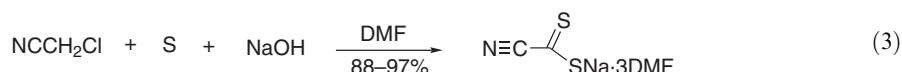
5.13.2 DITHIOIC ACIDS AND ESTERS

5.13.2.1 Dithioic Acid Alkali Metal and Mg Salts

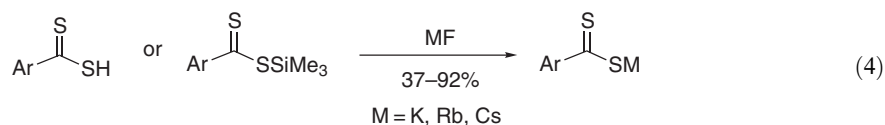
The most relevant methods for the synthesis of dithioic acid metal salts are the reactions of organolithium reagents or Grignard reagents with carbon disulfide (CS_2) (Equation (1)), and details of these methods are described in chapter 5.13.2.1 in <1995COFGT(5)545>. For example, 2-benzylpyridine was treated with lithium diisopropylamide (LDA), CS_2 , and tetramethylethylenediamine[1,2-bis(dimethylamino)ethane] (TMEDA) to afford the corresponding Li salt **1** as red crystals (Equation (2)) <1996CC1581>. A similar reaction of 2,3-dimethylpyrazine gave Li salt **2**. X-Ray molecular structures of these Li salts were elucidated. In Li salt **1**, only one sulfur atom of the dithiocarboxyl group is bonded to Li metal since the nitrogen atom of the pyridyl group also coordinated to Li metal. In contrast, two sulfur atoms of the dithiocarboxyl group of Li salt **2** are bonded to Li metal, and the C—S distances of the two C—S bonds were similar. Dithioic acid Li salts **3** were synthesized from bis(3,5-disubstituted pyrazol-1-yl)methane in 90–95% yields as a brown or orange solid, and their molecular structures were also elucidated <2002IC5193>.



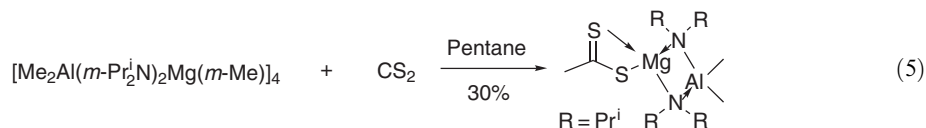
The reaction of chloroacetonitrile with NaOH and sulfur in DMF produced sodium cyano-dithioformate in 98% yield (Equation (3)) <1998JPR269>.



Aromatic dithioic acid potassium, rubidium, and caesium salts were prepared in 55–92% yields by reaction of the corresponding dithioic acids or dithioic acid silyl esters with metal fluorides (Equation (4)) <1999IC496>. They were purified by recrystallization with EtOH/ether or hexane. The salts obtained have a dimeric structure in which the two dithiocarboxyl groups are chelated to the metal cations located on the upper and lower sides of the plane involving the two opposing dithiocarboxyl groups.

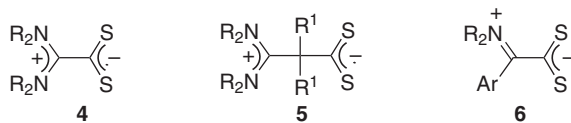


The insertion reaction of CS₂ into the C—Mg bond of [Me₂Al(μ-*i*-Pr₂N)₂Mg(μ-Me)]₄ resulted in the formation of 30% yield of dithioacetic acid Mg salt (Equation (5)) <1997OM4980>.

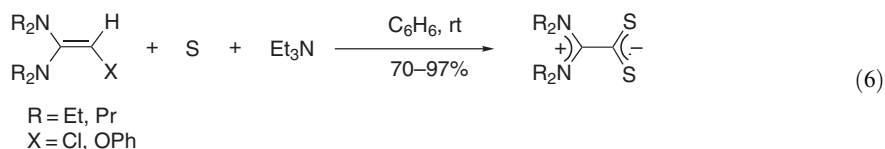


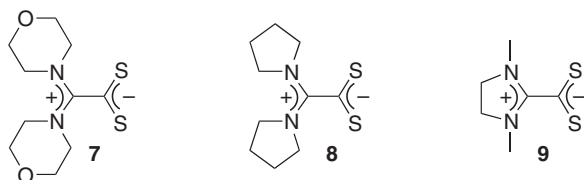
5.13.2.2 Inner Salts of Dithioic Acids

Three types of inner salts of dithioic acids 4–6 were introduced in the 1990s, although the first synthesis of these salts was achieved in the 1960s <1965JA2776>. Some improved methods were developed, and some of the salts were characterized by X-ray molecular structure analysis.

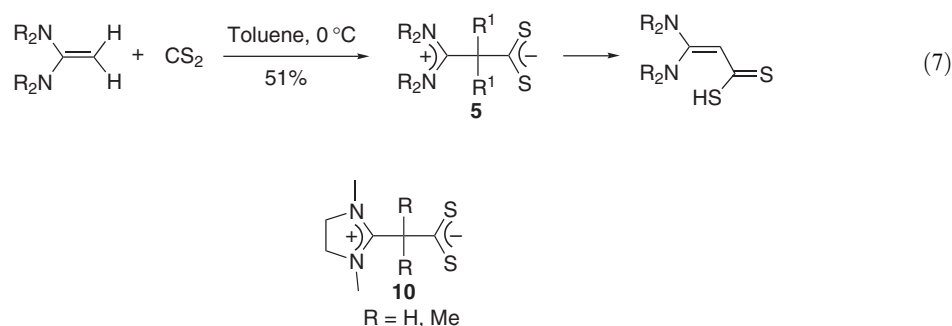


The reaction of 2-chloro or 2-phenoxy 1,1-bis(diamino)ethenes with elemental sulfur gave the inner salts in 70–97% yields (Equation (6)) <1995HAC45>. As for the reaction of 2-chloro derivatives, Et₃N was necessary to capture hydrogen chloride, whereas in the reaction of 2-phenoxy derivatives the use of Et₃N did not affect the yields of the product. The N—C—N plane and S—C—S plane of the salts were revealed to be nearly orthogonal, and the positive and negative charges were delocalized over these moieties. Alternatively, 1,1-dimorpholino- and 1,1-dipyrrolidino-ethenes and 2-methylene-1,3-dimethylimidazolidine were treated with disulfur dichloride in the presence of Et₃N to give the inner salts 7–9 in good yields <1997HAC505>.

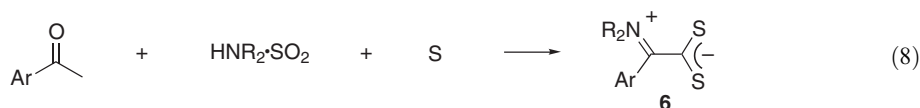




The inner salts **5**, where N—C—N and S—C—S moieties are insulated by an sp^3 carbon atom, were prepared by reacting 1,1-diaminoethenes with CS_2 (Equation (7)) <1997BCJ471>. However, the salts easily tautomerized to β,β -diamino- α,β -unsaturated dithioic acids when $R^1 = H$ and the two amino groups are not in the same cyclic ring. When 2-alkylidene-1,3-dimethylimidazolidine was reacted with CS_2 , the stable inner salts **10**, where no tautomerization took place, were obtained in 71% ($R = H$) and 92% ($R = Me$) yields <1998TL5587>.

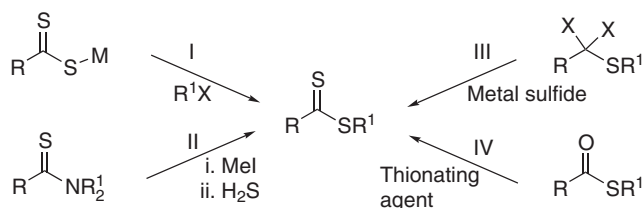


The treatment of acetophenones with amines, sulfur dioxide, and elemental sulfur produced inner salts **6** (Equation (8)) <1996PS(118)155>.



5.13.2.3 Dithioic Acid Esters

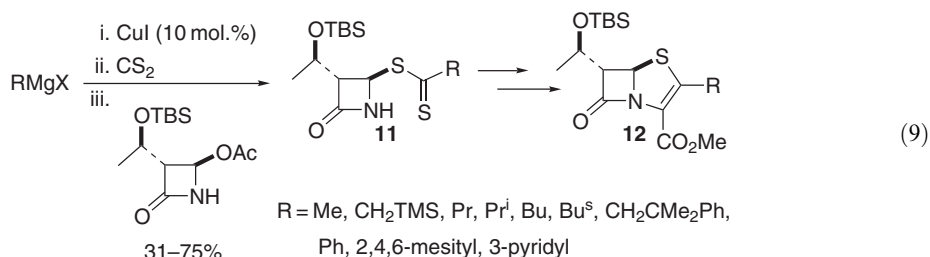
The synthetic methods for dithioic acid esters are mainly classified into four types of reactions as shown in Scheme 1. The most common method is the alkylation of dithioic acid salts derived from the reaction of organometallic reagents with CS_2 (route I). The addition reaction of hydrogen sulfide to thioiminium salts, derived from thioamides and methyl iodide, leads to esters (route II). Thionation of 1,1-dihalo-1-sulfides with metal sulfides also gives esters (route III). Finally, the conversion of the C=O group of thioic acid esters into a C=S group is achieved with thionating agents such as Lawesson's reagent (route IV). A variety of new derivatives have been synthesized by modifying these methods. Additionally, the manipulation of carbon skeletons of dithioic acid esters affords new dithioic acid esters.



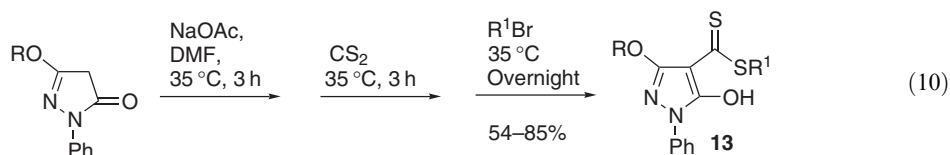
Scheme 1

5.13.2.3.1 Dithioalkanoic acid esters and aromatic and heteroaromatic acid esters

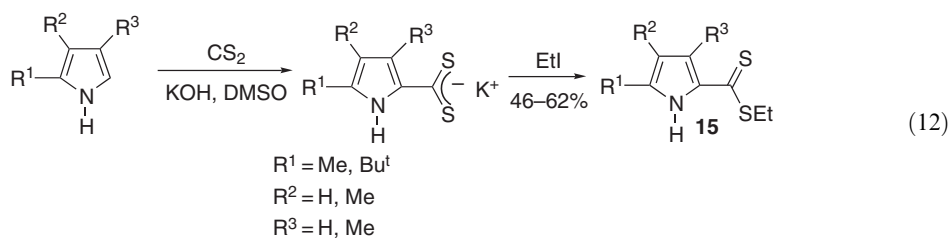
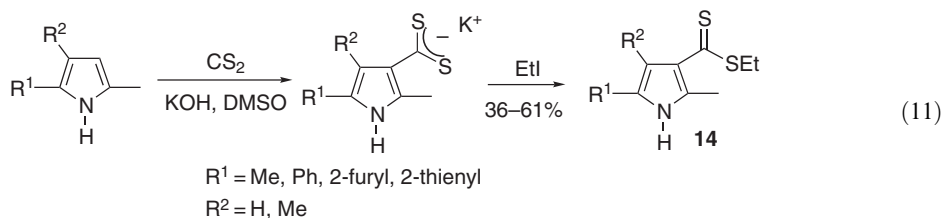
As an example of route I, dithioic acid copper salts, which were generated by reacting organo-copper reagents with CS₂, were reacted with 4-acetoxiazetidinone to afford azetidinone dithioic acid esters **11** in moderate-to-good yields (Equation (9)) <1995TL771>. The azetidinone dithioic acid esters were further converted into the corresponding penems **12** by treating with methyl oxalyl chloride and MeP(OEt)₂.

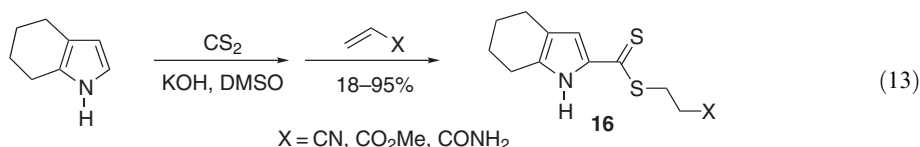


3-Hydroxy- <1996SC611> or 3-alkoxy- <1996MI423> 1-phenyl-2-pyrazoline-5-ones were treated with sodium acetate, and the mixture was reacted with CS₂, followed by alkylation to give dithioic acid esters **13** (Equation (10)). In this type of reaction, dialkylation often takes place to form ketene dithioacetals as the major product, but the reaction shown in Equation (10) selectively gave esters **13**.

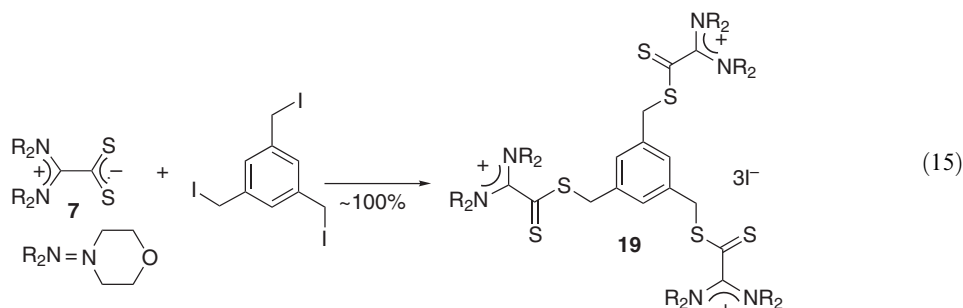
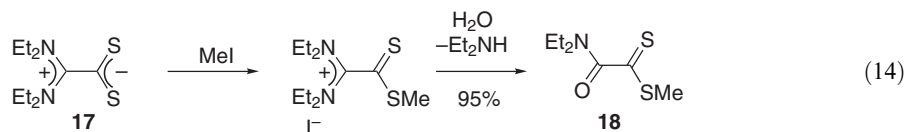


The synthesis of dithioic acid esters from a variety of pyrrole anions was studied <2000T7325>. The reaction of 2,5-di- or 2,4,5-trisubstituted pyrroles with KOH and CS₂ in dimethyl sulfoxide (DMSO) was carried out. Ethyl iodide was added to the reaction mixture to give selectively ethyl pyrrole-3-carbodithioates **14** in moderate yields (Equation (11)). In contrast a similar reaction of 3,5-di- or 3,4,5-trisubstituted pyrroles afforded pyrrole-2-carbodithioates **15** (Equation (12)). In these reactions the formation of regioisomers was not observed. Dithioic acid potassium salts derived from 4,5,6,7-tetrahydroindole were added to activated alkenes to form 2-cyanoethyl or 2-alkoxycarbonyl ethyl or 2-aminocarbonyl ethyl esters **16** in low-to-good yields (Equation (13)) <2001S293>.

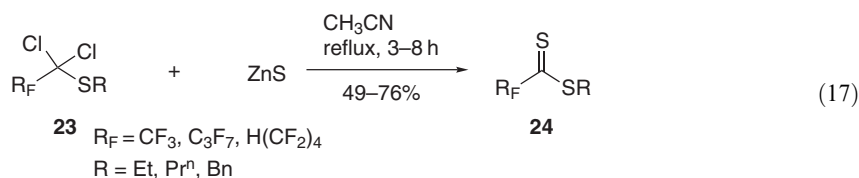
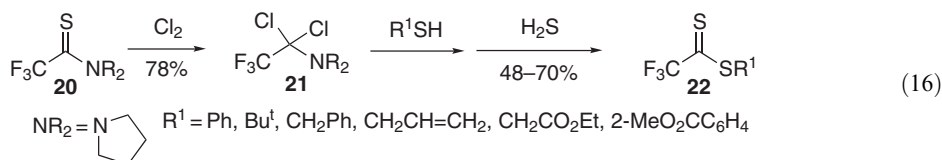


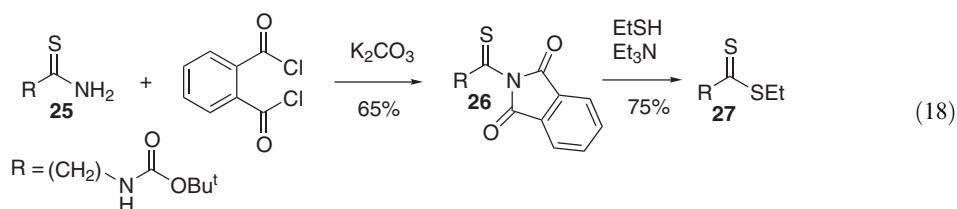


Alkylation of the inner salts of dithioic acids was also studied [\[1995HAC45\]](#). For example, methylation of the inner salt **17** took place smoothly to form a carbenium salt, followed by alkaline hydrolysis to form α -oxo dithioic acid ester **18** (Equation (14)) [\[1997TL5013\]](#). The inner salt **7** was reacted with 1,3,5-tris(iodomethyl)benzene to form the carbenium salt **19** as orange-red needles (Equation (15)) [\[2001CL768\]](#). A similar reaction with hexakis(bromomethyl)benzene was successful to give the carbenium salt bearing six dithiocarboxyl groups.

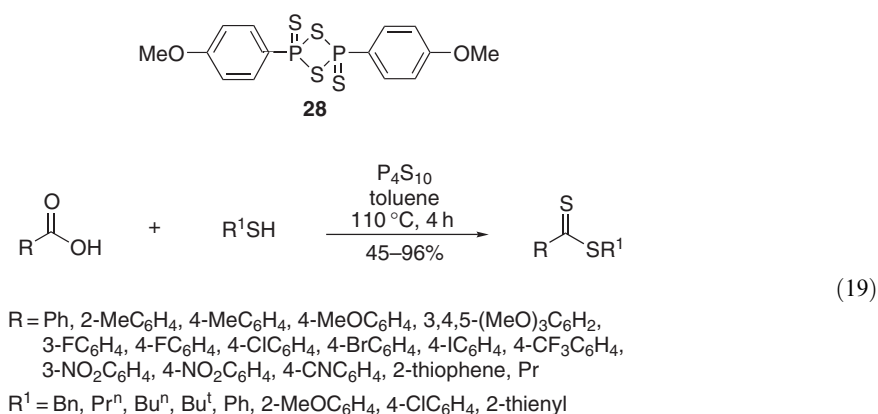


Readily available thioamides [\[1996JPR251\]](#) and thioiminium salts [\[1996CJC341\]](#) were used as precursors leading to dithioic acid esters. *C*-Glycosyl ethanethioamides were methylated with MeI to form thioiminium salts, then reacted with hydrogen sulfide in the presence of pyridine to give *C*-glycosyl ethanedithioic acid esters [\[1998TL2755\]](#). For the conversion of trifluoromethyl thioamides into the corresponding dithioic acid esters, methyl triflate or dimethyl sulfate was used to form the thioiminium salts [\[1997JPR697\]](#). Alternatively, treatment of thioamide **20** with chlorine gave amine **21**, which was treated with thiols and hydrogen sulfide successively at 0 °C to afford the ester **22**. A variety of thiols was used, and *S*-aryl-, *S*-alkyl-, *S*-benzyl-, *S*-allyl-, and *S*-alkoxymethyl esters were obtained (Equation (16)) [\[1997BSCF697\]](#). The 1,1-dichloro sulfides **23** derived from perfluoroalkyl sulfides with sulfuryl chloride were reacted with ZnS under reflux in CH₃CN (Equation (17)). The ZnS prepared from ZnCl₂, Na₂S, and NH₄OH, contained some impurities, and its purity was essential to obtain **24** in good yields. Primary thioamide **25** was reacted with phthaloyl dichloride in the presence of K₂CO₃ to form *N*-thioacylphthalimide **26** (Equation (18)) [\[1999S404\]](#). The phthalimide worked as a good leaving group and ethanethiol was directly introduced to the carbon atom of thiocarbonyl group of **26** to give ester **27**.

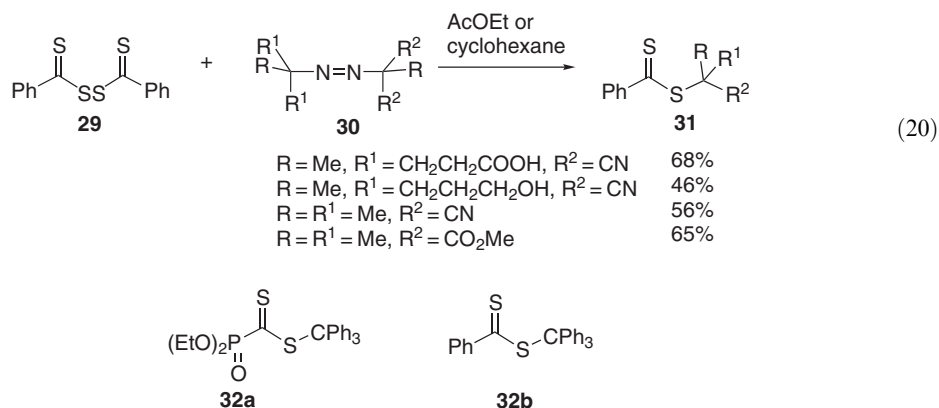




The conversion of the carbonyl group of thioic acid *S*-esters into a thiocarbonyl group is also a useful method for the synthesis of dithioic acid esters (route IV in [Scheme 1](#)). As a thionating agent, 1,3-dithia-2,4-diphosphetane-2,4-disulfide **28**, which was developed by Lawesson and co-workers in the 1970s, is available. Thionation of aromatic thioic acid *S*-benzyl esters with **28** was carried out with toluene as the solvent at 110 °C for 4 h to give the corresponding dithioic acid esters in good-to-high yields [<2001TL3791>](#). Phosphorus pentasulfide (P₄S₁₀) is also a good thionating agent. The reaction of carboxylic acids with thiols in the presence of P₄S₁₀ in toluene was found to afford dithioic acid esters ([Equation \(19\)](#)) [<2000OL3213>](#). Aromatic acids bearing electron-withdrawing and -donating groups and aliphatic acids have been employed. Benzylthiol, aliphatic and aromatic thiols when reacted gave generally good-to-high yields of the corresponding esters, although the yield slightly decreased in the reaction with *t*-butanethiol.

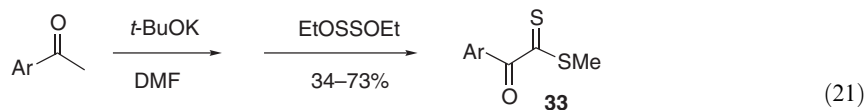


The reaction of bis(thiobenzoyl)disulfide **29** with diazo compounds **30** in ethyl acetate [<1999TL277>](#) or cyclohexane [<1999TL2435>](#) was used for the synthesis of *S*-cyano- or methoxycarbonylalkyl esters **31** ([Equation \(20\)](#)). Dithioic acid *S*-triphenylmethyl esters **32a**, **32b** were also reacted with diazo compounds under reflux in toluene to give *S*-cyanoalkyl esters **31** in good-to-high yields [<2002JOC7911>](#).

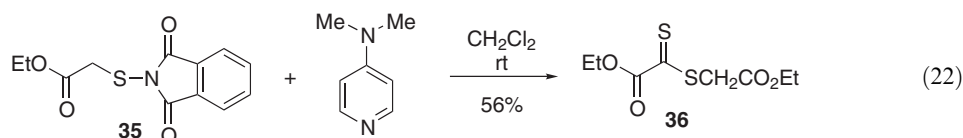
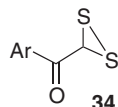


The synthesis of α -oxodithioic acid esters **33** was achieved by reacting acetophenones with a base and diethoxy sulfane followed by trapping with methyl iodide ([Equation \(21\)](#)) [<1994BSB389>](#). Dithiiranes **34** have been postulated as intermediates of the reaction. Pinacolone, toluenes bearing

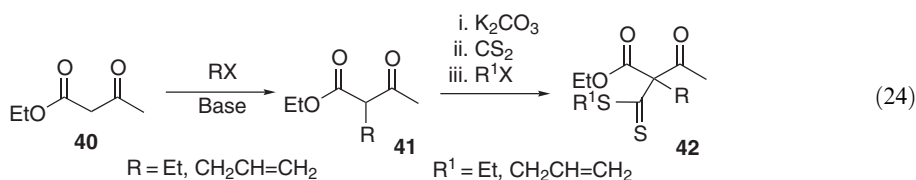
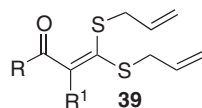
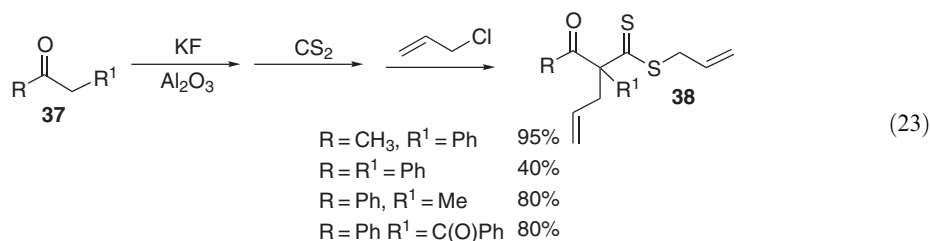
electron-withdrawing groups, and 2-methylbenzoxazole were also employed as starting materials in the reaction shown in Equation (21), but the corresponding dithioic acid esters were obtained in only low yields. Self-condensation of ethyl phthalimidodisulfanylacetate **35** in the presence of 4-dimethylaminopyridine (DMAP) also gave α -oxo dithioic acid ester **36** (Equation (22)) <1996JCS(P1)977>.

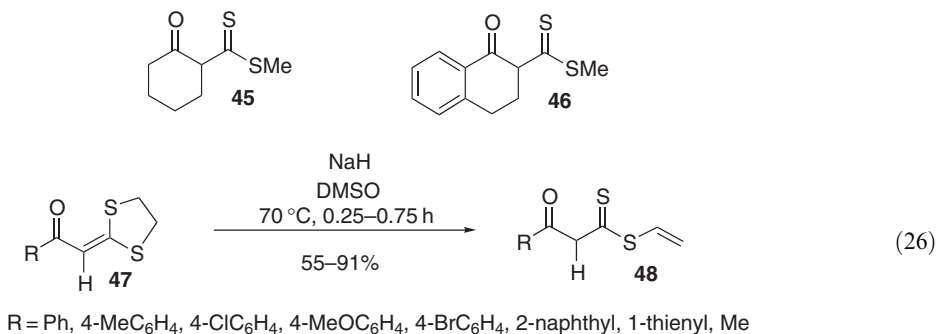
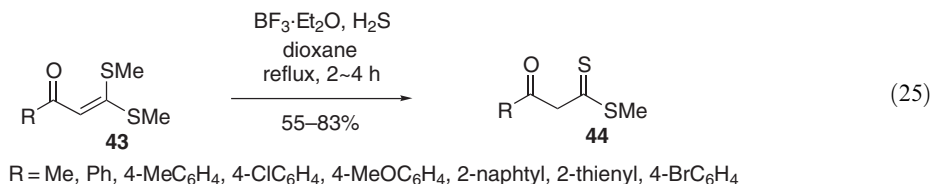


Ar = Ph, 4-NO₂C₆H₄, 2,5-(MeO)₂C₆H₄, 4-ClC₆H₄, 2-BrC₆H₄,
4-MeC₆H₄, 3-MeC₆H₄, 4-Bu^tC₆H₄

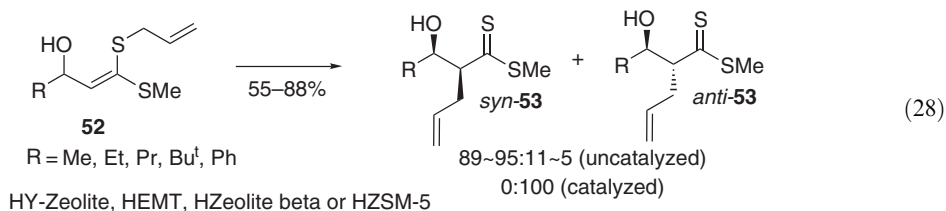
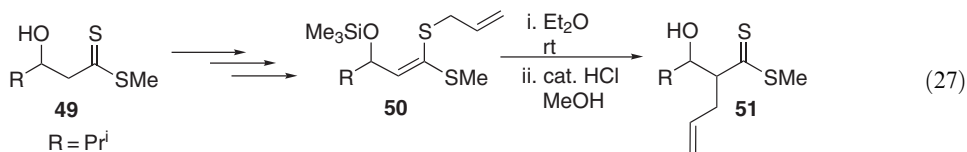


β -Oxo dithioic acid esters **38** were synthesized by the reaction of ketones **37** with KF in the presence of aluminum oxide followed by CS₂ and allylation (Equation (23)) <1995SC2305>. In the initial stage of the reaction *S,S*-diallyl ketenedithioacetals **39** may be formed, and undergo thio-Claisen rearrangement, which generally occurs under mild reaction conditions, to give **38**. Active methylene compounds such as **40** were initially alkylated, then the products **41** were treated with a base and CS₂ followed by alkylation to give β -oxo dithioic acid esters **42** (Equation (24)) <2002SC2369>. α -Oxo ketenedithioacetals are also used as precursors of β -oxo dithioic acid esters. Sulfhydrylolytic of α -oxo ketenedithioacetals **43** in the presence of Lewis acids gave esters **44** in 55–83% yields (Equation (25)) <1999SC791>. The reaction was applied to the synthesis of esters **45** and **46**. Alternatively, base-mediated cleavage of α -oxo ketenedithioacetals **43** with NaH in DMSO was developed for the synthesis of β -oxo dithioic acid esters **44–46** <2001S573>. The use of 2-arylmethylene-1,3-dithiolanes **47** gave *S*-vinyl β -oxo dithioic acid esters **48** (Equation (26)).

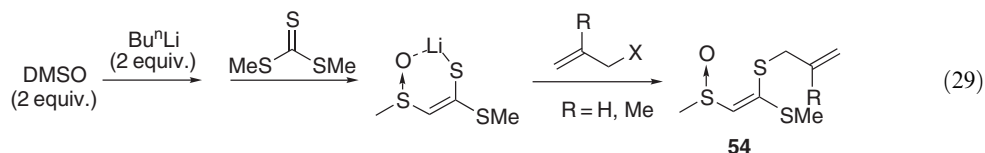


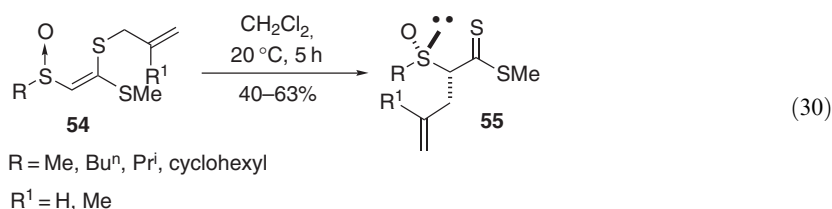


β -Hydroxy dithioic acid esters have been prepared by the aldol condensation of lithium enthiolates, generated from dithioacetic acid esters and LDA, with aldehydes [<1995TL6225>](#). The allylation of the obtained esters has been carried out to give α -allyl β -hydroxy dithioic acid esters. For example, the treatment of β -hydroxy esters **49** with LDA followed by allylation gave ketene dithioacetals **50**, which underwent thio-Claisen rearrangement to give esters **51** (Equation (27)) [<1994PS\(95-96\)383>](#). The stereochemistry of thio-Claisen rearrangement of *S*-allyl β -hydroxy ketene dithioacetals **52** was tested in the absence or presence of various zeolites (Equation (28)) [<1997TL2413>](#). The rearrangement of **52** without zeolite catalysts predominantly gave *syn*-**53** in 38–68% yields, whereas *anti*-**53** was selectively obtained in the presence of zeolites in better yields.

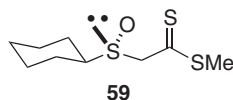
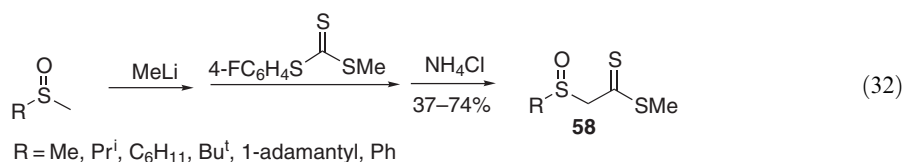
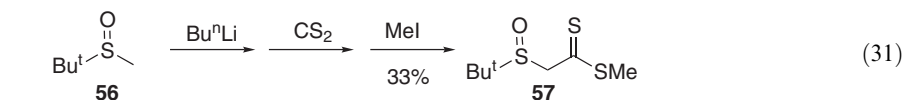


Stereoselective reactions utilizing the thio-Claisen rearrangement of *S*-allyl α -sulfinyl ketene dithioacetals has been elucidated. The starting acetals **54** were prepared from methyl phenyl trithiocarbonate and DMSO and subsequent allylation (Equation (29)) [<1994PS\(95-96\)421>](#). The rearrangement of **54** was examined at 20 °C for 5 h, and the products **55** were obtained in a diastereomer ratio of 93:7 (R = H) and 94:6 (R = Me) in 50–63% yields. As a starting material in Equation (29), not only DMSO but also alkyl methyl sulfoxides were used, and the additional alkyl groups in **54** did not affect the diastereoselectivity of the thio-Claisen rearrangement (Equation (30)) [<1997AG\(E\)371>](#).

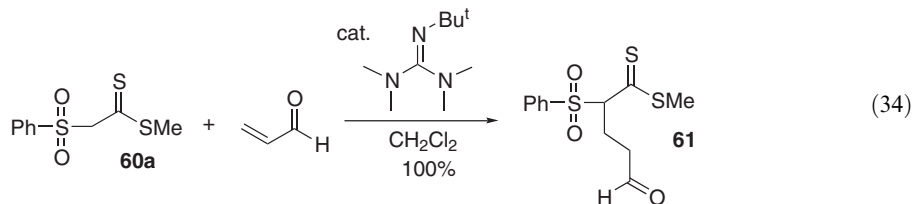
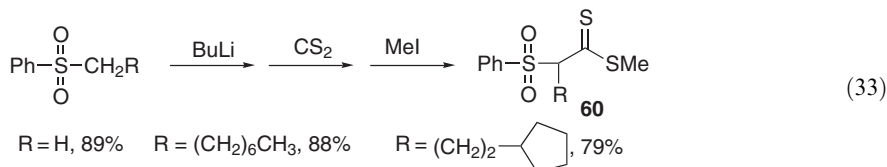




The deprotonation of *t*-butyl methyl sulfoxide **56** and subsequent reaction with carbon disulfide and methyl iodide gave α -sulfinyl dithioic acid ester **57** in 33% yield (Equation (31)) <1999S669>. When 4-fluorophenyl methyl trithiocarbonate was employed instead of carbon disulfide, the corresponding esters **58** were obtained in 30–72% yields depending on the substituents attached to the sulfinyl group (Equation (32)). The enantiopure α -sulfinyl dithioic acid ester **59** was synthesized by using the reaction of Equation (32) <1999PS(153–154)317>.



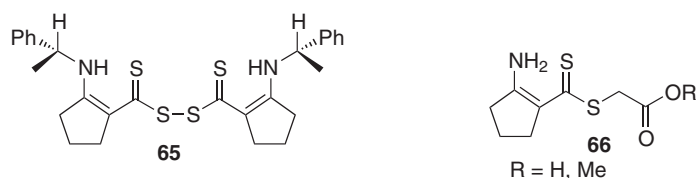
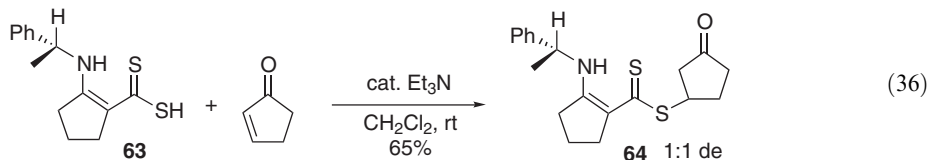
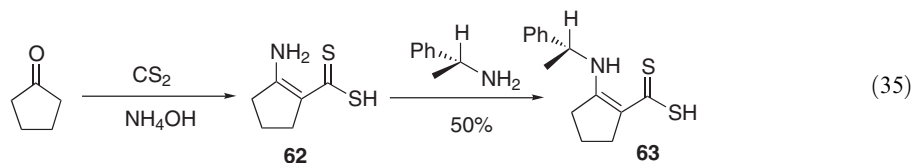
α -Sulfonyl dithioic acid esters **60** were synthesized from alkyl phenyl sulfones, CS_2 , and methyl iodide with high efficiency (Equation (33)) <1995T1887>. *t*-Butyl tetramethyl guanidine-catalyzed Michael addition of α -sulfonyl ester **60a** to acrolein took place to give δ -oxo- α -sulfonyl ester **61** quantitatively (Equation (34)).



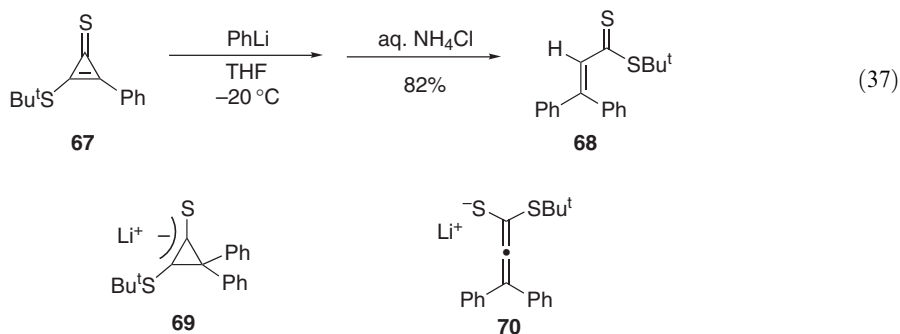
5.13.2.3.2 α,β -Unsaturated dithioic acid esters

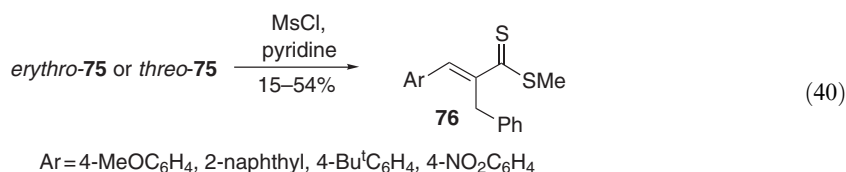
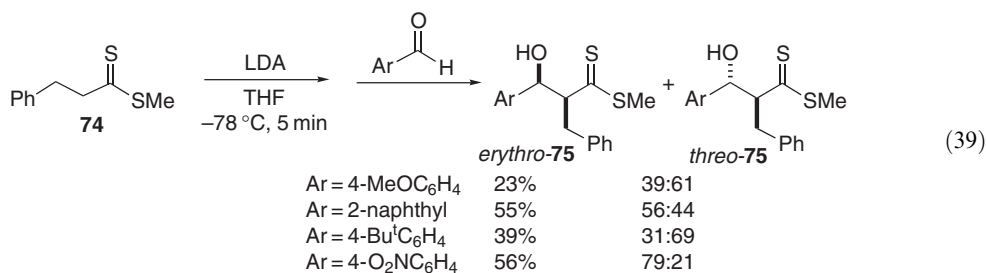
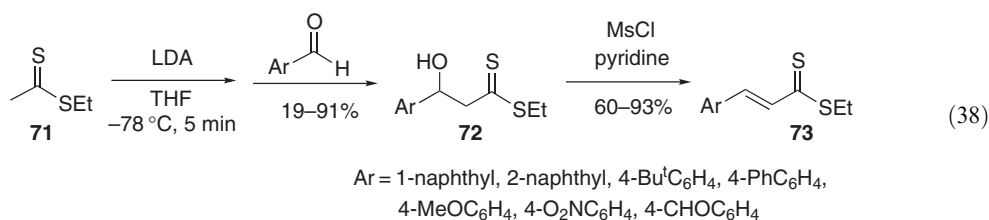
As α,β -unsaturated dithioic acids and esters, 2-amino-1-cyclopentenedithioic acid **62** was prepared by reacting cyclopentanone with CS_2 and NH_4OH (Equation (35)) <1996TA2603>. The amine exchange reaction of **62** with (R)-*N*-(1-phenylethyl)amine was carried out to give acid **63** as a yellow oil. The triethylamine-catalyzed addition reaction of acid **63** to cyclopentenone proceeded at room temperature to give ester **64** in good yields (Equation (36)), although exposure of

63 to air resulted in the formation of a disulfide **65** <1999TA3337>. X-Ray molecular structure analyses of 2-aminocyclopentene-1-dithioic acid and its methyl ester were carried out <2000IJC177>. The structure of **66** (R = H) was dimeric, whereas **66** (R = Me) was monomeric.

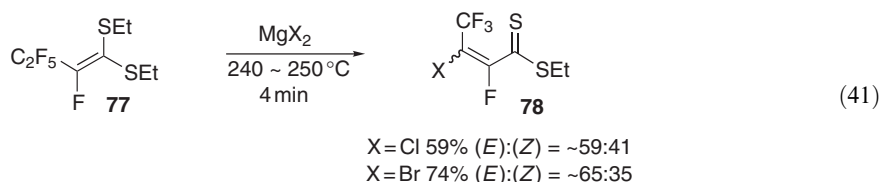


Ring-opening reaction of 2-*t*-butylsulfanyl-1-phenyl-cyclopropenethione **67** with PhLi proceeded smoothly, and the work-up of the reaction mixture with aqueous NH₄Cl gave α,β -unsaturated ester **68** (Equation (37)) <1996JCR(S)272>. The reaction may initially occur by the addition of phenyllithium to the carbon atom of **67** carrying the phenyl group to form **69**. Then, ring-opening of **69** accompanied by 1,2-migration of the *t*-butylthio group may lead to ketene **70**. Dehydration of β -hydroxy dithioic acid esters **72**, prepared by the aldol reaction of dithioacetic acid *S*-ethyl ester **71**, with aromatic aldehydes was used in an efficient synthetic method for α,β -unsaturated dithioic acid esters **73** (Equation (38)) <1999BCJ805>. *trans*-Cinnamaldehyde was also used as an aldehyde to give the corresponding $\alpha,\beta,\gamma,\delta$ -unsaturated ester in 72% yield. In contrast, dehydration of the β -hydroxy dithioic acid ester derived from 3-phenylpropanal was not successful. From the aldol reaction of 3-phenylpropanedithioic acid methyl ester **74** with aromatic aldehydes, two diastereomers **75** were formed (Equation (39)). Nevertheless, dehydration of both diastereomers proceeded stereoselectively to form only (*E*)-isomers **76** in moderate yields (Equation (40)). The aldol reaction of **71** with methylphenylglyoxylate followed by dehydration gave stereoisomeric mixtures ((*E*):(*Z*) = 56:44) of β -methoxycarbonyl β -phenyl α,β -unsaturated dithioic acid ester in 81% combined yield.

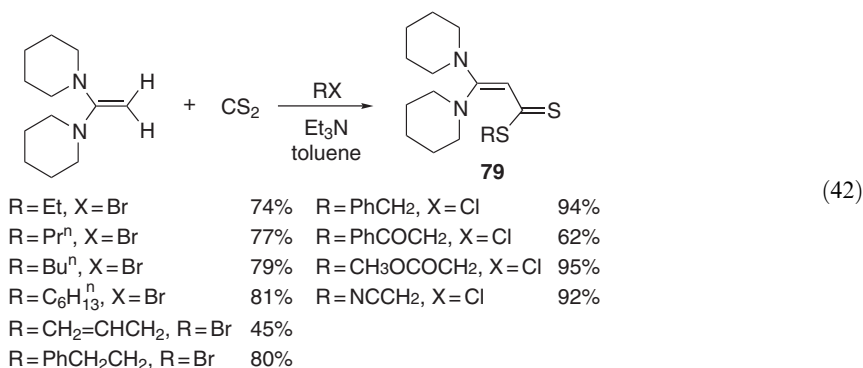




Perfluoro α,β -unsaturated dithioic acid esters **78** were prepared as stereoisomeric mixtures by thermal reaction of ketenedithioacetal **77** with magnesium halides (Equation (41)) <2001TL2133>. In the reaction with magnesium chloride, the thioic acid ester was formed as a by-product in 26% yield.

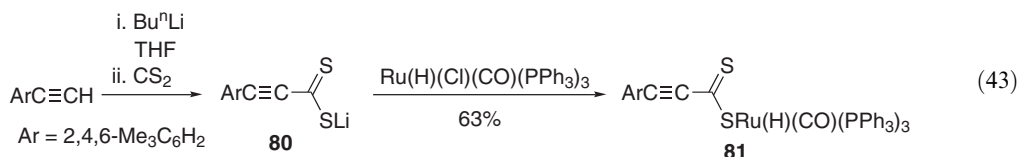


The successive reaction of 1,1-piperidinoethene with CS₂ and alkyl halides has been examined to prepare β,β -diamino α,β -unsaturated esters **79** (Equation (42)) <1997BCJ471>. The yields of **79** are highly dependent on the alkyl halides. The reaction with alkyl chlorides was sluggish, whereas in the reaction with alkyl iodides further alkylation of **79** took place, and **79** was obtained in only low yields. Thus, simple alkyl bromides and reactive chlorides were the most suitable reagents.



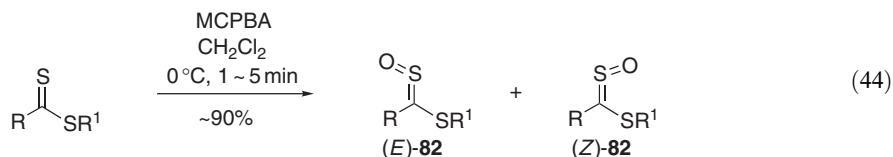
5.13.2.3.3 α,β -Acetylenic dithioic acid and esters

No examples of α,β -acetylenic esters have been reported since the 1990s. Insertion reaction of CS_2 to acetylenic Fe <1996JOM(510)207> or Ru complexes <1998JCS(D)1793> gave α,β -acetylenic dithioic acid Fe or Ru complexes. The reaction of lithium acetylides with CS_2 is known to give lithium alkyne carbodithioates. For example, lithium acetylide **80** generated from mesitylacetylene was reacted with CS_2 to give the dark red α,β -acetylenic dithioic acid lithium salt **80** (Equation (43)) <2001JOM(619)209>. The salt **80** was used for the synthesis of Ru complex **81**.



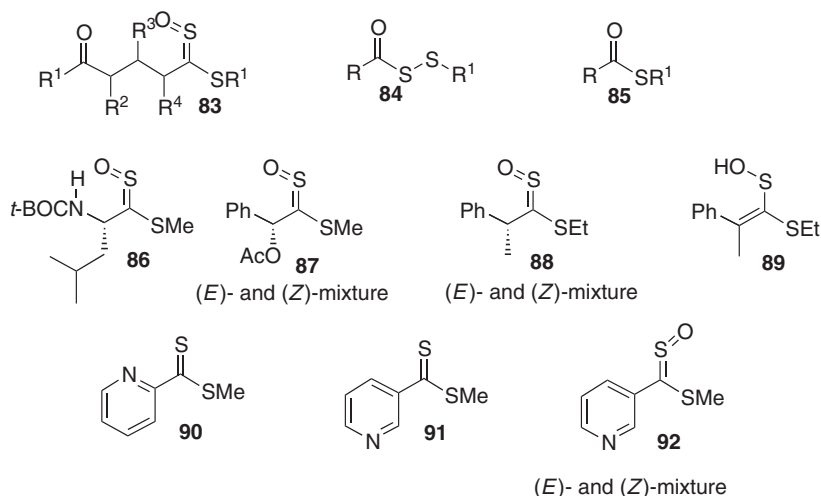
5.13.2.3.4 Dithioic acid esters having sulfur in higher oxidation states

Oxidation of dithioic acid esters gives sulfoxines. The reaction was applied to enolizable dithioic acid esters with 3-chloroperoxybenzoic acid (MCPBA) (Equation (44)) <1995BSCF67>. The reaction was complete within 5 min, and aqueous work-up and concentration of the reaction mixture gave crude products **82** in ~90% yield with 95% purity. The sulfoxines initially obtained adopted the (*E*)-configuration, but they were in equilibrium with (*Z*)-isomers within a few hours. The chemoselectivity of the oxidation was also disclosed. In the oxidation of dithioic acid esters bearing alkenyl, amino, and carbonyl groups, these functional groups were inert and selective oxidation proceeded leading to sulfoxines **82**. For example, δ -oxo dithioic acid esters were selectively converted into the corresponding sulfoxines **83** <1999TL2319>. When sulfoxines **82** were stored for some days, they further changed to dithioperoxyesters **84** and thioic acid esters **85**, the ratio of which was dependent on the substituents.



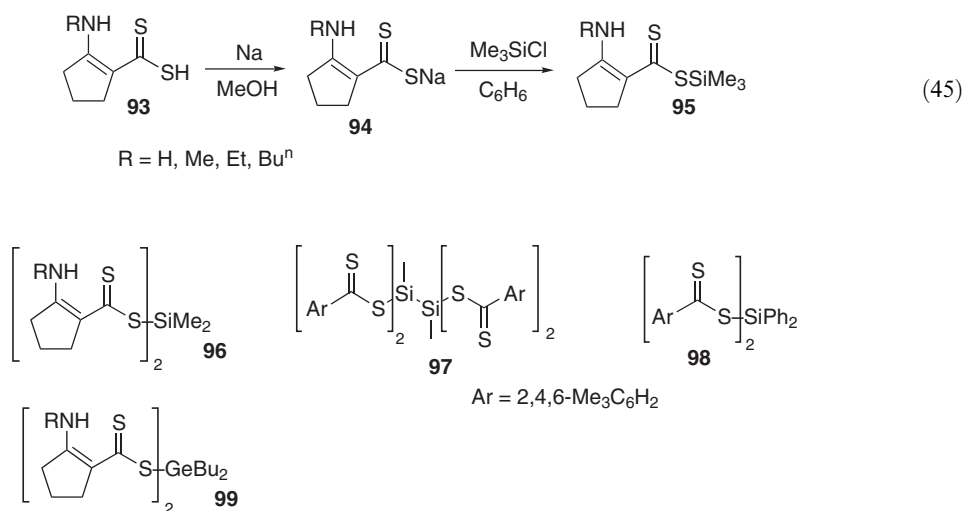
The synthesis of chiral sulfoxines **86–88** was reported <1995RTC91>. The sulfoxine **86** was obtained in 63% yield as a single isomer and was stable for a few years. No racemization of **86** was observed probably because an intramolecular hydrogen-bonding interaction was present between the oxygen atom and the hydrogen atom attached to the nitrogen atom. The dithioic acid ester derived from mandelic acid was oxidized with MCPBA to give sulfoxine **87** as a stereoisomeric mixture ((*E*):(*Z*) = 47:53) in 78% yield. The rearrangement and racemization of **87** was slow. However, when **87** was stored in solution for 7 months, it rearranged to thioic acid *S*-methyl ester and dithioperoxy ester. In contrast, the optical rotation of the sulfoxine **88**, which was obtained as a stereoisomeric mixture ((*E*):(*Z*) = 41:59), completely disappeared after standing for 24 h. This is most likely due to the racemization of **88** via a sulfenic acid **89**.

Two dithioic acid esters bearing pyridyl groups were oxidized with MCPBA <1998H2019>. Although aromatic sulfoxines are known as stable compounds, the reaction of 2-pyridyl ester **90** did not give the sulfoxine, but gave thioic acid ester. In contrast, the treatment of 3-pyridyl ester **91** with MCPBA afforded sulfoxine **92** ((*E*):(*Z*) = 79:21), which could be purified by chromatography on silica gel, in 79% yield.



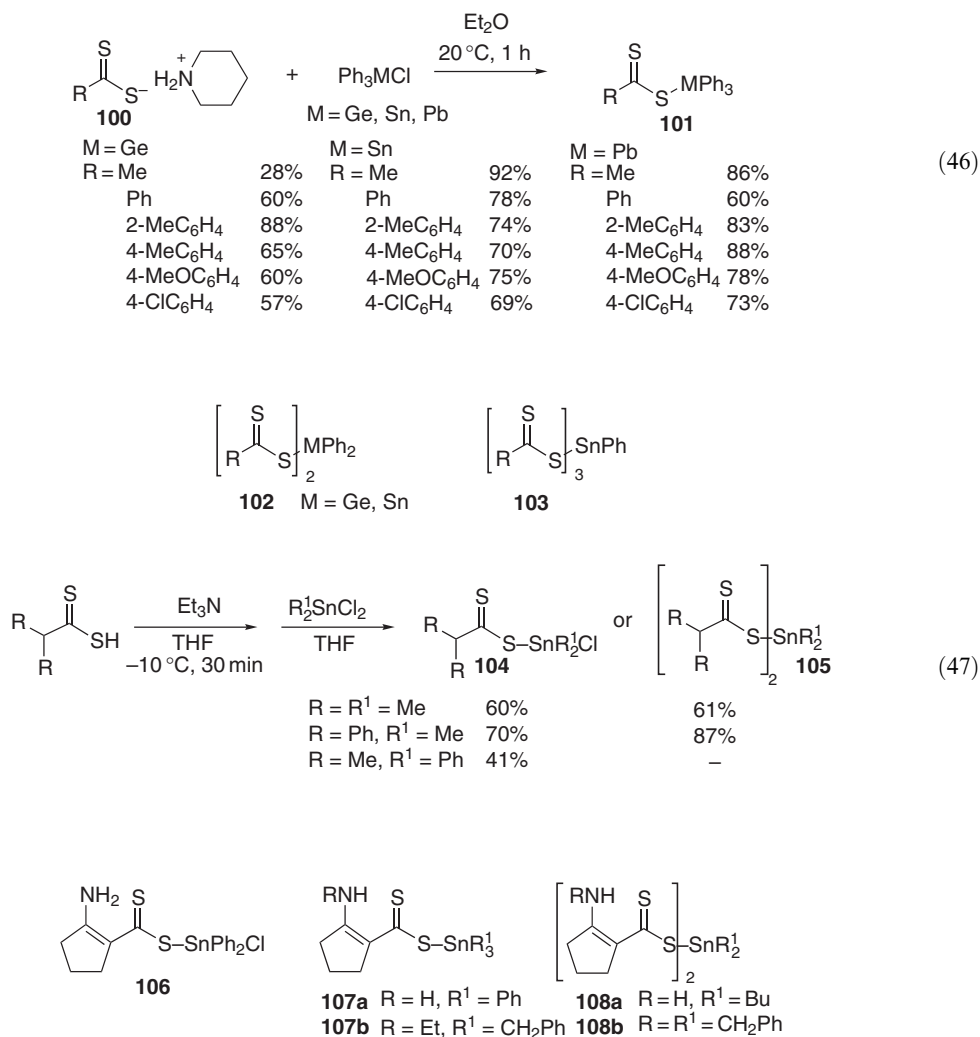
5.13.2.3.5 Dithioic acid Si, Ge, Sn, Pb esters

The reaction of 2-aminocyclopentene-1-carbodithioic acid sodium salts **94**, prepared from the acid **93** and Na, with trimethylsilyl chloride was reported to give *S*-silyl ester **95** (Equation (45)) <1998PS(142)249>. When dichlorosilane was used, two molecules of **93** were introduced to the silicon atom to form **96** <1999IJC604>, although the yields of **95** and **96** in these reactions were not clear. Four equivalents of potassium 2,4,5-trimethyldithiobenzoate were reacted with 1,1,2,2-tetrachloro-1,2-dimethyldisilane in tetra hydrofuran (THF) at room temperature to give the product **97** in 55% yield <2001AG(E)3450>. In the reaction with dichlorodiphenylsilane, two molecules of potassium salt were incorporated to form the product **98** in 44% yield. The X-ray structure analyses of **97** and **98** indicated that intramolecular interactions between the silicon atom and the sulfur atom of the thiocarbonyl group were present. Furthermore, the two silicon atoms of **97** were hepta-coordinated, whereas the silicon atom of **98** was hexa-coordinated. Theoretical studies on the hepta-coordinate disilane were also carried out <2002TL5759>.

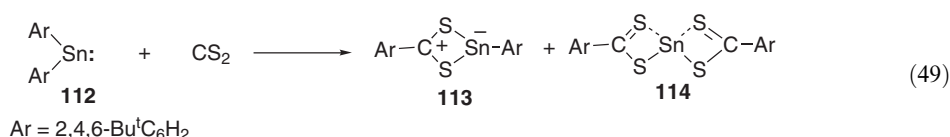
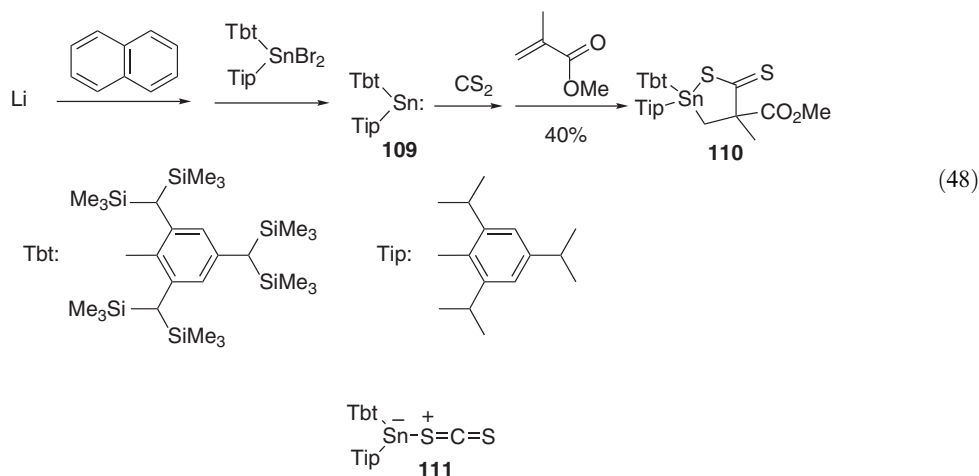


The germanium esters **99** were prepared by reacting sodium salt **94** with dibutylgermanium dichloride <2000SRI695>. Dithioic acid piperidinium salts **100** were used as a starting material to synthesize Ge, Sn, and Pb esters (Equation (46)) <2000JOM(611)190>. The corresponding esters **101**, which

were purified by recrystallization, were obtained in good-to-high yields. Germanium and tin dichlorides were also reacted with **100** to afford bis(dithiocarboxyl) Ge and Sn esters **102**. The reaction with tin trichlorides led to the esters **103**, where three molecules of dithiocarboxyl groups were introduced to the tin atom. X-Ray molecular structure analyses of some of these derivatives were performed. The coordination numbers of Ge, Sn, and Pb and the degree of intramolecular interaction between these elements and the sulfur atom of thiocarbonyl groups are discussed. In the Et_3N -mediated reaction of aliphatic dithioic acids with dimethyltin and diphenyltin dichlorides, two types of products **104** and **105** were selectively obtained (Equation (47)) <1996CB663>. The use of 0.5 equiv. of dithioic acids gave **104** as a sole product, whereas the reaction of 2 equiv. of acids afforded **105**. The stannylation of 2-aminocyclopentene-1-carbodithioic acids **93** was elucidated <2000PS(166)221>. The X-ray molecular structure analyses of the products **106–108** were carried out <2001ICA15, 2002JOM(645)105>.

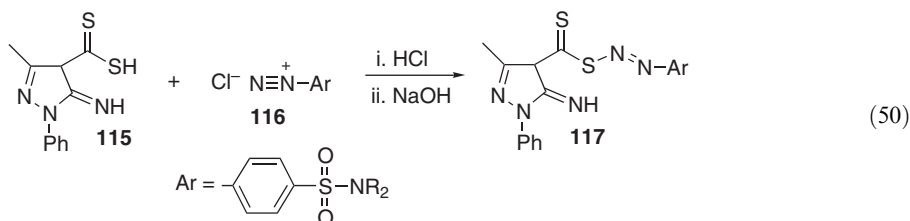


The stannylene **109** generated from $\text{Tbt}(\text{Tip})\text{SnBr}_2$ and lithium naphthalenide in THF was reacted with CS_2 followed by the addition of methyl acrylate to form 1,2-thiastannolane-5-thione **110** in 40% yield (Equation (48)) <1995OM3620>. The reaction may proceed via [2 + 3]-cycloaddition of a tin-containing 1,3-dipole **111**, which was formed by the nucleophilic attack of the sulfur atom of CS_2 onto stannylene **109**, with methyl acrylate. In the reaction of bis[2,4,6-tris(*t*-butyl)phenyl]stannylene **112** with 10 equiv. of CS_2 for 3 days at 60°C , a mixture of 1:1 adduct **113** and 2:1 adduct **114** was formed in 51% combined yield, whereas the reaction for 6 days at 60°C gave selectively **114** in 40% yield (Equation (49)) <1995OM3620>.

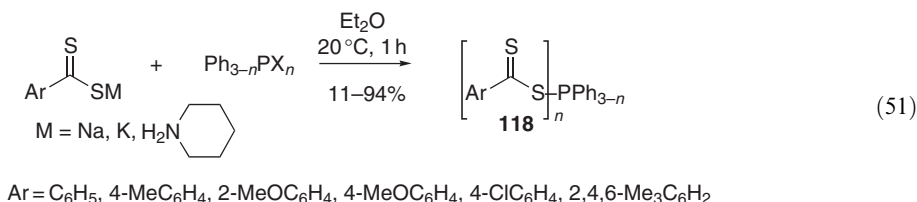


5.13.2.4 Dithiocarbamyl-azo Dyes, Thioacetylsulfanylphosphines and -arsines

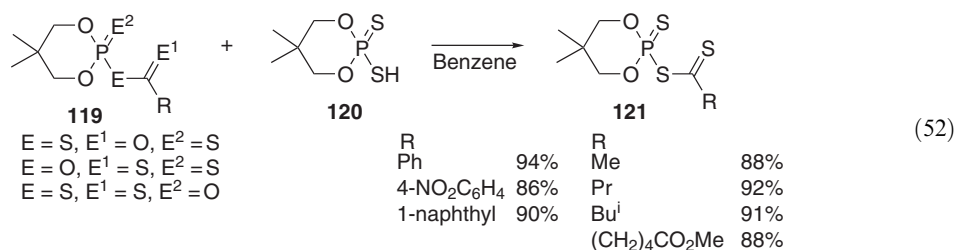
The reaction of dithioic acid **115** in 50% NaOH solution with diazonium salts **116** in HCl solution at 0 °C gave dithiocarbamyl-azo dyes **117** (Equation (50)) <1996PS(114)17>. The obtained dyes were used for the preparation of metal chelates, and their antibacterial activity was tested.



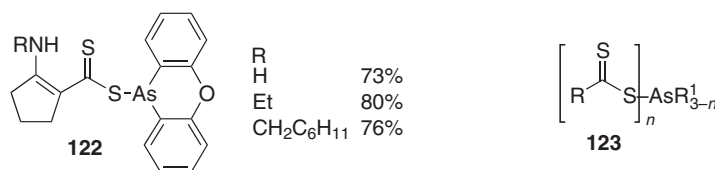
Thioacetylsulfanylphosphines **118** were prepared by treating aromatic dithioic acid salts with Ph_2PCl , PhPCl_2 , and PBr_3 in moderate-to-good yields (Equation (51)) <2000BCJ1243>. The compounds **118** are thermally less stable and moisture sensitive. In particular, the compounds, where two or three dithiocarboxyl groups were introduced to the phosphorus atom, are readily hydrolyzed even in Et_2O .



Mixed anhydrides **119** derived from acid chlorides and dithiophosphoric acid **120** were reacted with **120** under reflux in benzene for 1.5–6 h to give *S*-thioacyl dithiophosphates **121** (Equation (52)) <2000CC2093, 2002JCS(P1)1271>. The dithiophosphates **121** are stable and are isolated without any special precautions. The thioacylation of amines with **121** gave thioamides. The reaction of **121** with hydroxylamines was used for the synthesis of thiohydroxamic acids and *O*-thioacylhydroxylamines <2002PS(177)1851, 2002S1047>.

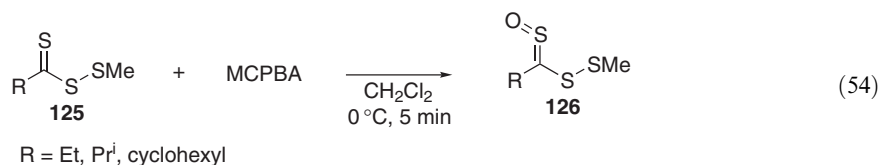
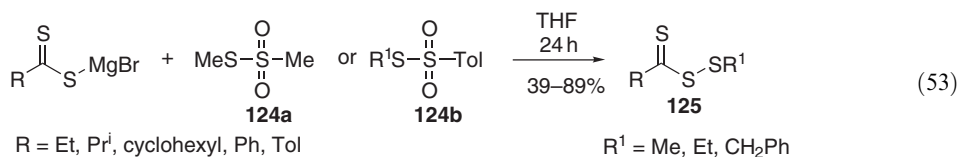


The reaction of 2-aminocyclopentene-1-carbodithioic acids **93** with 10-chlorophenoxarsine was carried out with ethanol as a solvent for 24 h to give thioacysulfanylarisines **122** in good yields <1995APOC133>. The molecular structure of **122** (R = H) was determined by X-ray crystallography. The intramolecular hydrogen-bonding interaction between the hydrogen atom attached to the nitrogen atom and the sulfur atom of the thiocarbonyl group was discussed. Thioacysulfanylarisines **123** (R¹ = Ph) were also prepared by the reaction similar to that of Equation (51) <2001JCS(D)518>. For **123** dithioic acid piperidinium salts were used in CH₂Cl₂, and both aliphatic and aromatic dithioic acid salts gave the corresponding arsines **123** in 70–90% yields. Arsines **123** were stored under air for 3 months, and their stability toward heating, oxygen, and moisture was higher than that of the corresponding phosphines **118**. Some of the arsines **123** were characterized by X-ray molecular structure analysis. To evaluate the degree of the intramolecular interaction between the thiocarbonylsulfur atom and the arsenic atom, natural bond orbital analyses were performed on the model compounds **123** (R = R¹ = Me). Consequently, the presence of several types of nonbonding interaction between lone pair electrons of the sulfur atom and σ* orbitals of S—As and C—As bonds has been suggested.

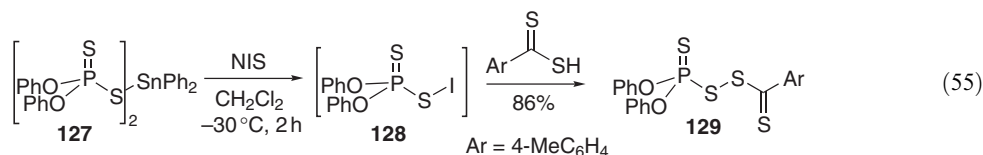


5.13.2.5 Trithioperesters

Dithioic acid derivatives, where an alkylthio or dithiophosphoryl group is attached to the sulfur atom, are known. The reaction of dithioic acid magnesium salts with alkylthiolating agents **124** proceeded smoothly to give trithioperesters **125** in 48–70% yields (Equation (53)) <1994TL5229>. Both aliphatic and aromatic derivatives were used as the magnesium salts. By using **124b**, ethylthio and benzylthio groups were introduced into **125**, and the compounds **125** were purified by column chromatography. The oxidation of **125** with MCPBA was also examined. As an initial product, sulfoxines **126** were obtained as a stereoisomeric mixture (Equation (54)), although the yields and ratio of stereoisomers were not reported.

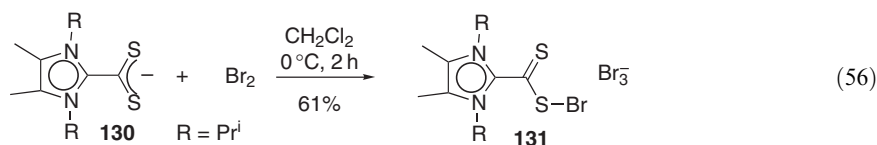


Phosphorothioylsulfenyl iodide **128** generated *in situ* from stannane **127** and *N*-iodosuccinimide was trapped with dithioic acid to give **129** as a red oily product (Equation (55)) <2002HCA2559>.



5.13.2.6 Thioacylsulfanyl Bromide

The inner salt **130**, which was prepared from imidazol-2-ylidene and CS₂, was reacted with bromine in CH₂Cl₂ at 0°C for 2 h to give sulfanyl bromide **131** as a red solid (Equation (56)) <1994ZN(B)1473>. The structure of **131** was clearly disclosed by X-ray molecular structure analysis. A similar reaction with iodine gave the charge transfer complex.

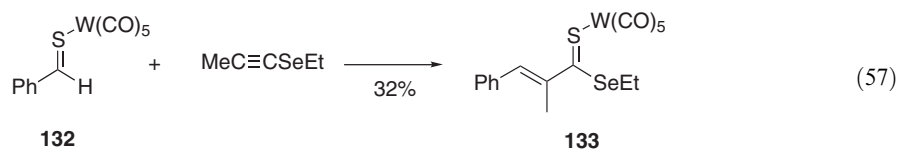


5.13.3 SELENOTHIOIC AND DISELENOIC ACIDS AND ESTERS

Only a few examples of selenium counterparts of dithioic acid esters, i.e., selenothioic *S*- or *Se*-esters and diselenoic acid esters <1998SR397>, had been known before 1993 mainly because of the lack of the appropriate synthetic procedures. The compounds belonging to this category have been believed to be labile and not able to be handled in air. However, several types of new synthetic procedures for the esters have been established, and these results have shown that the stability of the esters is highly dependent on the substituents attached to the carbon atom of C–Se double bonds and to the selenium or sulfur atom. More importantly, the introduction of aromatic rings to the esters does not necessarily enhance their stability. As has been mentioned before in this chapter, the most common starting material leading to dithioic acid esters is CS₂. The selenium isologs of carbon disulfide, such as carbon diselenide, are known, but cannot be easily handled because of their lability and high toxicity. Furthermore, even when organometallic reagents react with carbon diselenide, the stability of the metal salts obtained is questionable. Thus, a variety of synthetic routes to selenothioic and diselenoic acid esters, not via their corresponding acid salts, have been developed. Their acid salts were then synthesized from the esters.

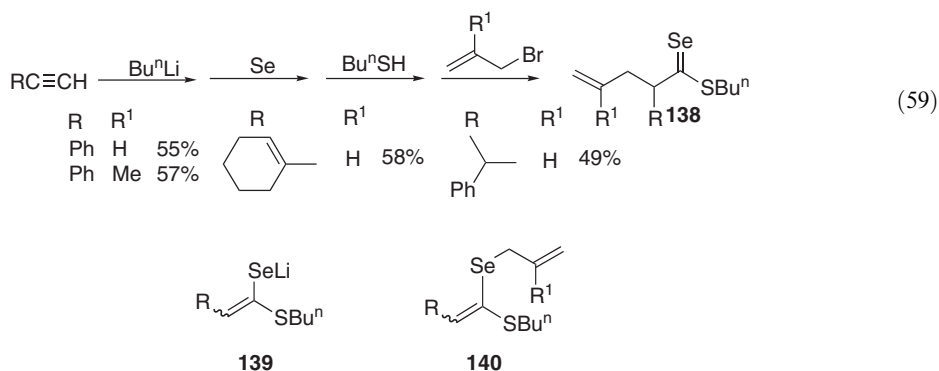
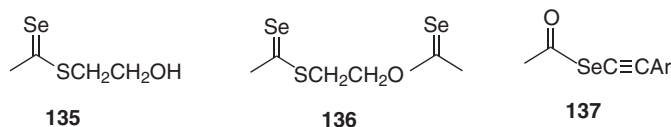
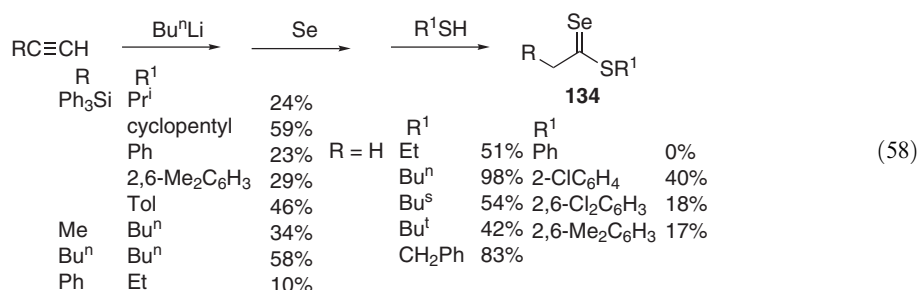
5.13.3.1 Selenothioic and Diselenoic Acid Esters

No new examples of selenothioic acid *Se*-esters have appeared since the 1990s except for the alkylation of selenothioic acid salts as described later. Instead, tungsten complex **133** was synthesized by the reaction of tungsten complex of thiobenzaldehyde **132** with methylethynyl ethyl selenide (Equation (57)) <1995CB883>. The product **133** was purified by column chromatography at –78°C.



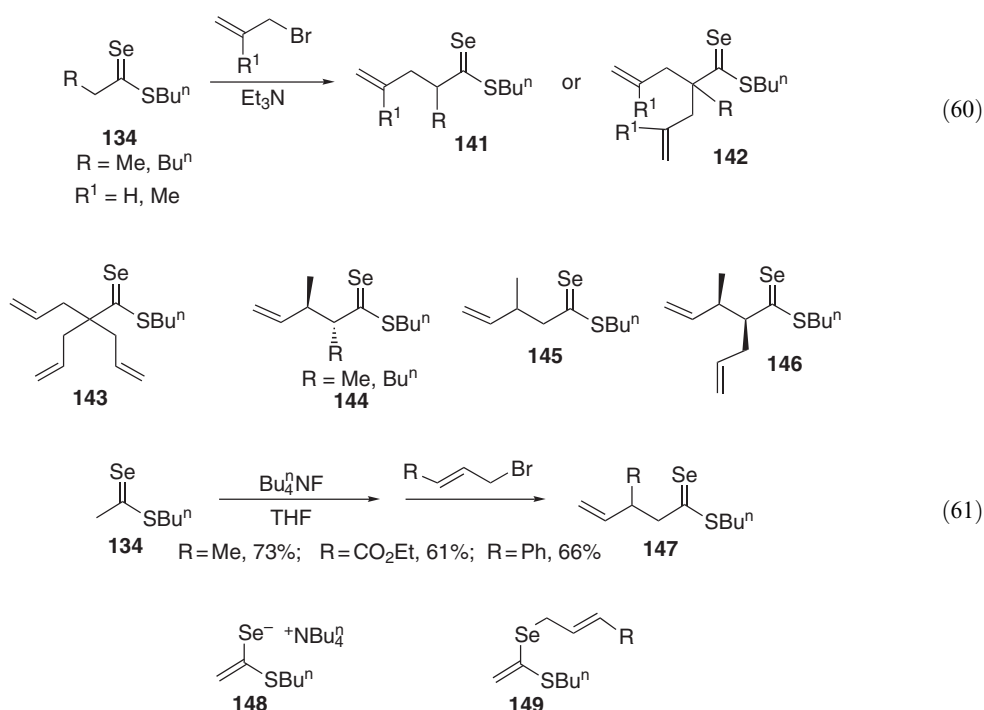
In contrast to selenothioic acid *Se*-esters, a variety of synthetic procedures for selenothioic acid *S*-esters have been developed <1998SR397>. The most efficient one-pot synthetic methods for *S*-esters is the reaction of lithium alkyne selenolates prepared from terminal

acetylenes, BuLi, and elemental selenium with thiols (Equation (58)) <1997JA8592>. The use of (trimethylsilyl)acetylene gave selenothioacetic acid *S*-esters **134** ($R = H$). The reaction with aliphatic thiols proceeded smoothly to give **134** as stable compounds in good-to-high yields, whereas the reaction with aromatic thiols gave **134** in low yields. This is mainly due to the lability of *S*-aryl esters **134**, which gradually decomposed during column chromatography. For example, the reaction mixture with benzenethiol initially showed a blue color, which was indicative of the formation of **134** ($R = H$, $R^1 = Ph$), but it changed to yellow during the aqueous work-up to result in the formation of the dimer of **134**. (Triphenylsilyl)acetylene and aliphatic acetylenes were also used as starting materials to give α -monosubstituted selenothioic acid *S*-esters **134**. Although these esters could be stored in the refrigerator, they were less stable than selenothioacetic acid *S*-esters **134** ($R = H$, $R^1 = \text{alkyl}$). When 2-hydroxyethanethiol was used as the thiol in the reaction of (trimethylsilyl)acetylene, not only selenothioacetic acid ester **135**, but also ester **136** were obtained in a ratio of 52:48 in 85% combined yields. This is in marked contrast to the reaction of Equation (58) with an alcohol instead of thiols, which gave only selenafulvenes. Acid-catalyzed reaction of selenoic acid *Se*-alkynyl esters **137** with thiols gave α -arylselenothioic acid *S*-esters in better yields, although the reaction took more than 2 days. The successive reaction of terminal acetylenes with BuLi, elemental selenium, thiols, and allylic bromides gave γ,δ -unsaturated selenothioic acid *S*-esters **138** (Equation (59)) <1996T2839>. The lithium eneselenolates **139** may be initially formed in the reaction mixture of Equation (59), then allylation takes place at the selenium atom to form allyl vinyl selenides **140**. The allyl vinyl selenides **140** undergo seleno-Claisen rearrangement, which proceeds more quickly than thio-Claisen rearrangement and leads to **138**.

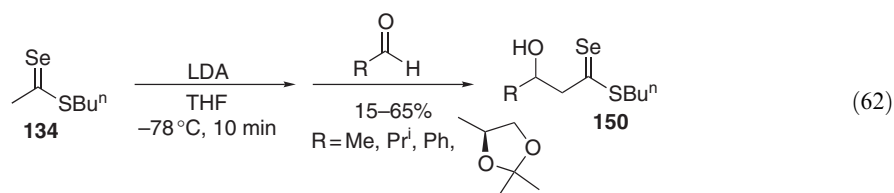


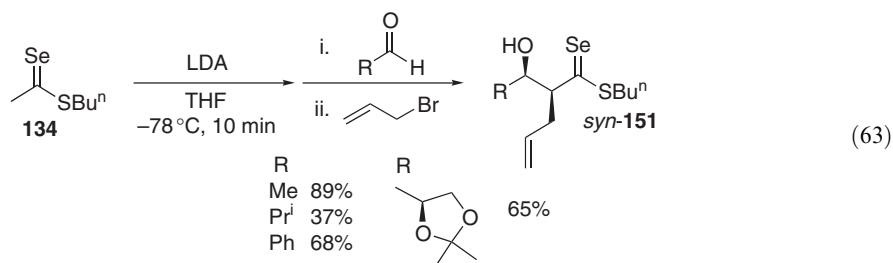
The rapid seleno-Claisen rearrangement was utilized for the allylation of selenothioic acid *S*-esters (Equation (60)) <1995CL1057>. In the reaction of selenothioacetic acid esters **134** ($R = H$, $R^1 = n\text{-Bu}$) with 2 equiv. of allyl bromide in the presence of Et₃N at 0 °C for 2 h, two

molecules of allyl groups were introduced to give **142** ($R = R^1 = H$) in 80% yields. The monoallylated product **141** ($R = R^1 = H$) was not obtained even in the reaction with 1 equiv. of allyl bromide. Triallylation of **134** ($R = H$, $R^1 = n\text{-Bu}$) was achieved at 66°C for 48 h with 3 equiv. of allyl bromide to give **143** in 90% yield. Monoallylation of **134** ($R = \text{Me}$, $n\text{-Bu}$, $R^1 = n\text{-Bu}$) with 1 equiv. of allylic bromide proceeded selectively at 0°C to give **141** in good yields, whereas the reaction with 2 equiv. of allylic bromide at 66°C for 48 h gave only diallylated products **142** in moderate-to-good yields <1997T12237>. Monoallylation of **134** ($R = \text{Me}$, $n\text{-Bu}$, $R^1 = n\text{-Bu}$) with crotyl bromide showed high stereoselectivity to give *anti*-**144** in 47% and 48% yields. *syn*-Selective allylation was observed for the reaction of *S*-ester **145** with allyl bromide at 66°C for 24 h to give **146** in 51% yield. Monoallylation of selenothioacetic acid *S*-ester **134** ($R = H$, $R^1 = n\text{-Bu}$) was achieved to afford **147** by using 1.5 equiv. of $n\text{-Bu}_4\text{NF}$ as a base (Equation (61)) <2000CL368>. In the reaction ammonium eneselenolate, **148** was formed almost quantitatively and instantly trapped with 1 equiv. of allylic bromides to give **149** <2001JOC8101>. The intermediates **149** undergo seleno-Claisen rearrangement to give **147**. Even when further deprotonation from **147** with $n\text{-Bu}_4\text{NF}$ occurred, no allylic bromides were present and aqueous work-up led to **147**.

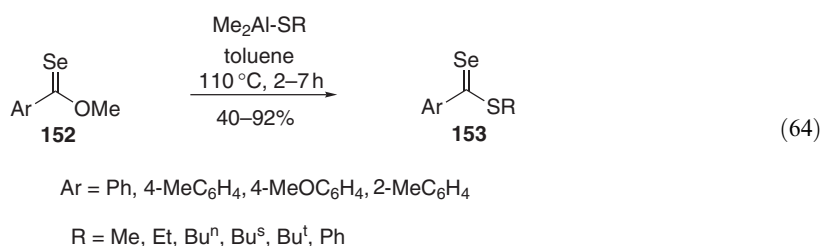


Aldol-type condensation reaction of **134** ($R = H$, $R^1 = n\text{-Bu}$) with aldehydes produced β -hydroxy selenothioic acid *S*-esters **150** (Equation (62)) <1999JOC2130>. In the reaction with acetaldehyde, the corresponding product **150** was obtained as a crude product, but it could not be purified by column chromatography. The use of isobutyraldehyde, benzaldehyde, and 2,3-isopropylidene-D-glyceraldehyde gave the corresponding β -hydroxy *S*-esters **150** in pure form. When allyl bromide was added to the reaction mixture prior to the aqueous work-up, α -allylated β -hydroxy *S*-esters **151** were obtained in 37–68% yields (Equation (63)). The allylation proceeded with 99% *syn*-selectivity.

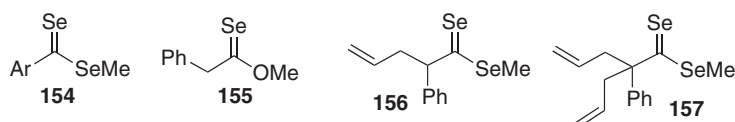




Aromatic selenothioic acid *S*-esters **153** were synthesized by reacting selenoic acid *O*-methyl esters **152** with aluminum thiolates (Equation (64)) <1995JOC2942>. Aromatic *S*-esters **153** were more labile than aliphatic esters. In particular, aromatic selenothioic acid *S*-phenyl esters **153** ($R = \text{Ph}$) were not isolated, although the deep blue color of the reaction mixture indicated the formation of **153** ($R = \text{Ph}$). These trends in the stability of aromatic derivatives are consistent with those of aliphatic derivatives. Namely, in both cases, *S*-aryl esters are too labile to be isolated.



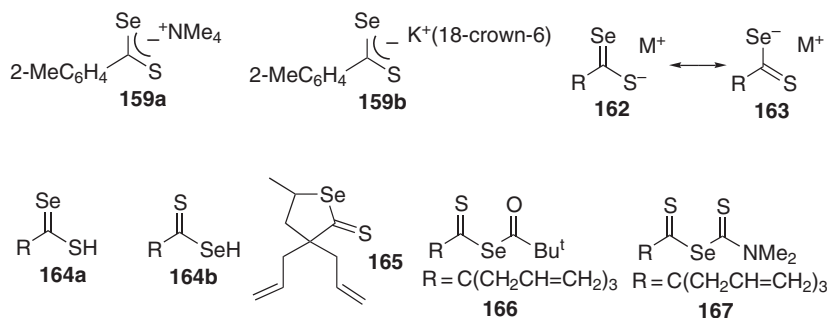
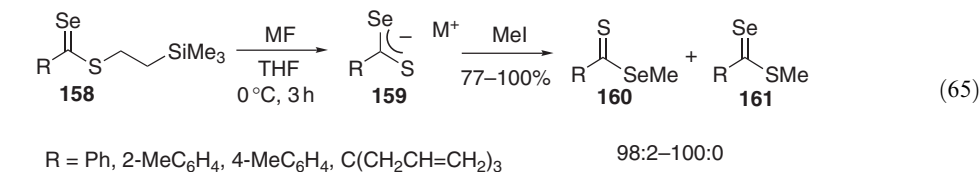
Aluminum selenolates were utilized for the synthesis of diselenoic acid esters. The reaction similar to Equation (64) with aluminum methylselenolate gave diselenoic acid methyl esters **154**. Interestingly, aromatic diselenoic acid esters **154** are more stable than selenothioic acid *S*-esters **153** <1998PS(136,137&138)561>. For the synthesis of aliphatic derivatives, *O*-ester **155** was reacted with aluminum methylselenolate but the corresponding diselenoic acid ester was not isolated. The ester formed *in situ* was then allylated. The allylation at room temperature for 2 h gave **156** in 69% yield, whereas allylation at 70 °C for 2 h produced **157** in 35% yield.



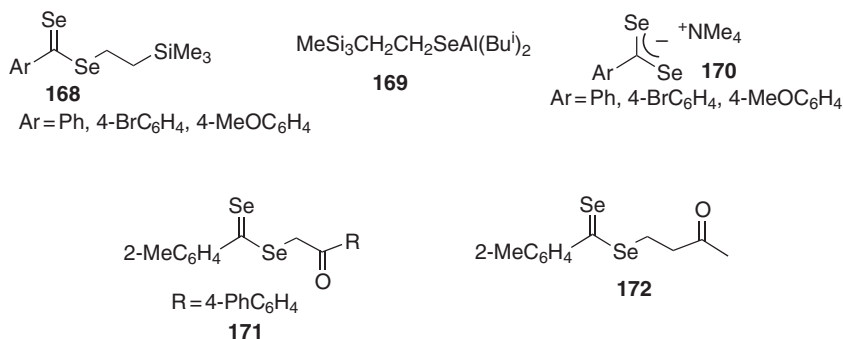
5.13.3.2 Selenothioic and Diselenoic Acid Salts

In contrast to the extensive literature of dithioic acids and their salts, no example of their selenium isologs was known. However, the efficient synthetic procedure for selenothioic and diselenoic acid esters described above has provided new synthetic routes to selenothioic and diselenoic acid salts. Selenothioic acid *S*-2-trimethylsilyl esters **158**, which were prepared by reactions similar to those of Equations (58), (60), and (64), were treated with ammonium fluoride <2000JA9850> or alkali metal fluorides <2001CL968> (Equation (65)). For the reaction with alkali metal fluorides, the addition of 18-crown-6 ether gave the salts **159** in higher yields. The salts **159** could be stored for several months in the refrigerator unless they were exposed to air. X-Ray molecular analyses of salts **159a** and **159b** were performed, but the position of the sulfur and selenium atoms was disordered. Although the properties of resonance hybrid **159** were not precisely discussed on the basis of X-ray analyses, they were elucidated by using ^{77}Se NMR spectroscopy. Consequently, if resonance hybrid **159** is expressed as two resonance structures, **162** and **163**, the importance of the resonance structure **162** in which the C—Se double bond was present was suggested. Methylation of the salts **159** took place almost exclusively at the selenium

atom of **159** to give *Se*-esters **160**, and only a small amount of *S*-esters **161** were observed. Attempts to generate selenothioic acids **164** were not successful, but the acidolysis of **159** ($R = C(CH_2CH=CH_2)_3$) gave selenothiolactone **165**, which may be formed via a selenothioic acid. Acylation and thiocarbamoylation of salts **159** were carried out to give unprecedented mixed anhydrides, **166** and **167**, in 61% and 39% yields, respectively.

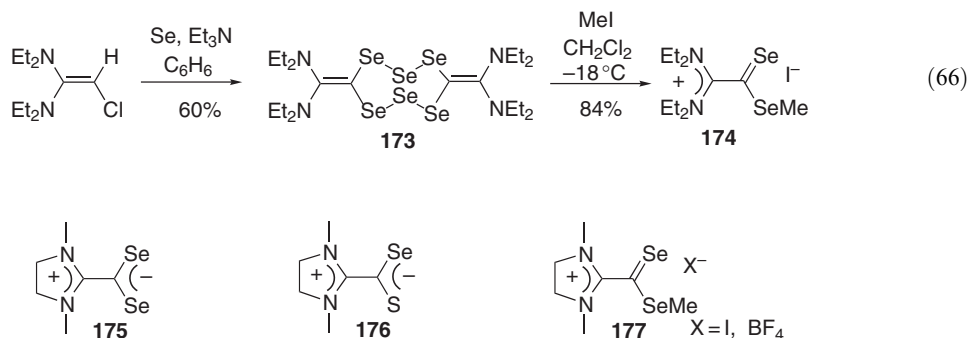


The reaction in Equation (65) was applied to the synthesis of diselenoic acid salts <2002JA5960>. As a starting material, 2-trimethylsilylethyl diselenoates **168** were prepared from selenoic acid *O*-methyl esters **152** and aluminum selenide **169**. Then, the esters **168** were reacted with ammonium fluoride. The salts derived from Bu_4NF were not stable, but the use of Me_4NF gave the corresponding salts **170** as a relatively stable green solid in 47–78% yields. In particular, the salt **170** ($\text{Ar} = 2\text{-MeC}_6\text{H}_4$) could be stored for a long time under an inert atmosphere in the refrigerator. X-Ray molecular structure analysis of the salt **170** ($\text{Ar} = \text{Ph}$) was carried out. Noteworthy is that the average length of the two $\text{C}-\text{Se}$ bonds is 1.830(4) Å, which is closer to the lengths of ordinary $\text{C}-\text{Se}$ double bonds. The reaction of salts **170** with a variety of electrophiles took place very rapidly to form diselenoic acid esters, but their stability is highly dependent on the substituents. For example, the alkylation with 4-phenylphenacyl bromide furnished the ester **171** as stable blue needles in 68% yield. Attempts to generate diselenoic acid failed again, but the trapping of the acid with methyl vinyl ketone gave diselenoic acid γ -oxobutyl ester **172** in 21% yield.



Since inner salts of dithioic acids **4** were synthesized from 1-chloro-2,2-diaminoethenes (Equation (6)), a similar reaction was expected to form inner salts of diselenoic acids. However, when 1-chloro-2,2-bis(diethylamino)ethene was reacted with elemental selenium and Et_3N under

reflux in benzene, hexaselenacyclooctane **173** was selectively obtained as the product (Equation (66)) <1998JA10027, 1998PS(136,137&138)569>. The compound **173** could be used as an equivalent to the inner salt of diselenoic acid. For example, methylation of **173** in CH_2Cl_2 gave carbenium salt **174**. Alternatively, the reaction of 2-methylene-1,3-dimethylimidazolidine with Se_2Cl_2 in the presence of Et_3N gave the desired inner salt of diselenoic acid **175** in 48% yield as thermally stable dark green crystals <2000JA9120>. The treatment of inner salt **175** with 0.2equiv. of elemental sulfur in CH_2Cl_2 at room temperature for 48 h gave inner salt **176** of selenothioic acid in 14% yield along with inner salt of dithioic acid **9**. The molecular structures and spectroscopic properties of a series of inner salts, i.e., dithioic acid **9**, selenothioic acid **176**, and diselenoic acid **175**, were studied in detail. To obtain free acids the protonation of inner salt **175** was attempted, but only decomposed products were formed along with red selenium even at low temperatures. In contrast, methylation with MeI or Me_3OBF_4 proceeded smoothly to give carbenium ion **177** in 91% or 86% yield.



In summary, synthetic procedures of dithioic, selenothioic, and diselenoic acid and their derivatives are described. For dithioic acid and their derivatives, a variety of practical synthetic methods appear to be already established. Nevertheless, environmentally more benign processes are required from the sustainable chemistry point of view. In many reactions unwanted co-products were formed along with desired products. Selenothioic and diselenoic acid and their derivatives could be isolated when appropriate substituents, which were not necessarily bulky, were introduced to their carbon skeletons. Several types of fundamental synthetic methods for them are provided, but the efficiency of some of them is still moderate. Examples of tellurium isologs of dithioic acid and derivatives are not known as yet. To synthesize them, new synthetic routes and feasible substituents to stabilize the compounds should be devised.

REFERENCES

- 1965JA2776 H. A. Wynberg, D. D. Coffman, *J. Am. Chem. Soc.* **1965**, 87, 2776–2777.
 1994BSB389 A. Hoepping, R. Mayer, *Bull. Soc. Chim. Belg.* **1994**, 103, 389–392.
 1994PS(95–96)383 P. Beslin, S. Perrio, *Phosphorus Sulfur Silicon* **1994**, 95–96, 383–384.
 1994PS(95–96)421 C. Fromont, P. Metzner, *Phosphorus Sulfur Silicon* **1994**, 95–96, 421–422.
 1994TL5229 C. Leriverend, P. Metzner, *Tetrahedron Lett.* **1994**, 35, 5229–5230.
 1994ZN(B)1473 N. Kuhn, H. Bohnen, G. Henkel, *Z. Naturforsch.* **1994**, 49b, 1473–1480.
 1995APOC133 R. Cea-Olivares, R.-A. Toscano, M. Estrada, C. Silvestru, P. G. y. García, M. López-Caredoso, G. Blass-Amador, *Appl. Organomet. Chem.* **1995**, 9, 133–140.
 1995BSCF67 F. Cerreta, A.-M. L. Nocher, C. Leriverend, P. Metzner, T. N. Pham, *Bull. Soc. Chim. Fr.* **1995**, 132, 67–74.
 1995CB883 H. Fischer, K. Treier, C. Troll, *Chem. Ber.* **1995**, 128, 883–889.
 1995CL1057 T. Murai, H. Takada, T. Kanda, S. Kato, *Chem Lett.* **1995**, 1057–1058.
 1995COFGT(5)545 T. Murai, S. Kato, Functions with two chalcogens other than oxygen, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, 1995, Vol. 2, pp. 545–564.
 1995HAC45 A. Nagasawa, I. Akiyama, S. Mashima, J. Nakayama, *Heteroatom Chem.* **1995**, 6, 45–49.
 1995JOC2942 T. Murai, Y. Ogino, T. Mizutani, T. Kanda, S. Kato, *J. Org. Chem.* **1995**, 60, 2942–2945.
 1995OM3620 M. Saito, N. Tokitoh, R. Okazaki, *Organometallics* **1995**, 14, 3620–3622.
 1995RTC91 J. B. van der Linden, J. L. Timmermans, B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **1995**, 114, 91–96.
 1995SC2305 D. Villemin, M. Hachemi, *Synth. Commun.* **1995**, 25, 2305–2310.
 1995T1887 D. H. R. Barton, K. A. D. Swift, C. Tachdjian, *Tetrahedron* **1995**, 51, 1887–1892.

- 1995TL771 D. S. Ennis, M. A. Armitage, *Tetrahedron Lett.* **1995**, 36, 771–775.
 1995TL6225 S. Tchertchian, Y. Vallée, *Tetrahedron Lett.* **1995**, 36, 6225–6226.
 1996CB663 K. Hartke, U. Wagner, *Chem. Ber.* **1996**, 129, 663–669.
 1996CC1581 S. C. Ball, I. Cragg-Hine, M. G. Davidson, R. P. Davies, P. R. Raithby, R. Snaith, *J. Chem. Soc., Chem. Commun.* **1996**, 1581–1582.
 1996CJC341 W. Neugebauer, E. Pinet, M. Kim, P. R. Carey, *Can. J. Chem.* **1996**, 74, 341–343.
 1996JCR(S)272 Y. Yagyu, N. Matsumura, H. Tanaka, H. Inoue, M. Yasui, F. Iwasaki, *J. Chem. Res. (S)* **1996**, 272–273.
 1996JCS(P1)977 G. W. Kirby, A. W. Lochead, S. Williamson, *J. Chem. Soc., Perkin Trans. 1* **1996**, 977–984.
 1996JOM(510)207 V. Cadierno, M. P. Gamasa, J. Gimeno, E. Lastra, *J. Organomet. Chem.* **1996**, 510, 207–211.
 1996JPR251 K. Hartke, S. Barrmeyer, *J. Prakt. Chem.* **1996**, 338, 251–256.
 1996MI423 A. Molinari, A. Oliva, L. Sanchez, *Bull. Soc. Chil. Quím.* **1996**, 41, 423–425.
 1996PS(114)17 I. M. A. Awad, *Phosphorus Sulfur Silicon* **1996**, 114, 17–28.
 1996PS(118)155 J. Hansen, F. W. Heinemann, *Phosphorus Sulfur Silicon* **1996**, 118, 155–180.
 1996SC611 A. Oliva, A. Molinari, R. Ariz, *Synth. Commun.* **1996**, 26, 611–616.
 1996T2839 T. Murai, K. Kakami, N. Itoh, T. Kanda, S. Kato, *Tetrahedron* **1996**, 52, 2839–2846.
 1996TA2603 P. de March, M. Figueredo, J. Font, L. González, A. Salgado, *Tetrahedron Asymmetry* **1996**, 7, 2603–2606.
 1997AG(E)371 C. Alayrac, C. Fromont, P. Metzner, N. T. Anh, *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 371–374.
 1997BCJ471 K. Akimoto, K. Masaki, J. Nakayama, *Bull. Chem. Soc. Jpn.* **1997**, 70, 471–476.
 1997BSF697 C. Portella, Y. G. Shermolovich, O. Tschenn, *Bull. Soc. Chim. Fr.* **1997**, 134, 697–702.
 1997HAC505 K. Akimoto, J. Nakayama, *Heteroatom Chem.* **1997**, 8, 505–508.
 1997JA8592 T. Murai, K. Kakami, A. Hayashi, T. Komuro, H. Takada, M. Fujii, T. Kanda, S. Kato, *J. Am. Chem. Soc.* **1997**, 119, 8592–8597.
 1997JPR697 F. Laduron, C. Nyns, Z. Janousek, H. G. Viehe, *J. Prakt. Chem.* **1997**, 339, 697–707.
 1997OM4980 C.-C. Chang, J.-H. Chen, B. Srinivas, M. Y. Chiang, G.-H. Lee, S.-M. Peng, *Organometallics* **1997**, 16, 4980–4984.
 1997T12237 T. Murai, H. Takada, K. Kakami, M. Fujii, M. Maeda, S. Kato, *Tetrahedron* **1997**, 36, 12237–12247.
 1997TL2413 R. Sreekumar, R. Padmakumar, *Tetrahedron Lett.* **1997**, 38, 2413–2416.
 1997TL5013 J. Nakayama, T. Otani, Y. Sugihara, A. Ishii, *Tetrahedron Lett.* **1997**, 38, 5013–5016.
 1998H2019 C. Lempereur, N. Plé, A. Turck, G. Quéguiner, F. Corbin, C. Alayrac, P. Metzner, *Heterocycles* **1998**, 48, 2019–2034.
 1998JA10027 J. Nakayama, I. Akiyama, Y. Sugihara, T. Nishio, *J. Am. Chem. Soc.* **1998**, 120, 10027–10031.
 1998JCS(D)1793 M. I. Bruce, B. C. Hall, N. N. Zaitseva, B. W. Skelton, A. H. White, *J. Chem. Soc., Dalton Trans.* **1998**, 1793–1803.
 1998JPR269 A. Hoepping, R. Mengel, R. Mayer, *J. Prakt. Chem.* **1998**, 340, 269–270.
 1998OM5206 M. Weidenbruch, U. Grobecker, W. Saak, *Organometallics* **1998**, 17, 5206–5208.
 1998PS(136,137&138)561 T. Murai, I. Mizutani, Y. Ogino, Y. Fujiwara, S. Kato, *Phosphorus Sulfur Silicon* **1998**, 136, 137 & 138, 561–564.
 1998PS(136,137&138)569 J. Nakayama, I. Akiyama, Y. Sugihara, *Phosphorus Sulfur Silicon* **1998**, 136, 137 & 138, 569–572.
 1998PS(142)249 R. Sharma, Singh, A. K. Rai, *Phosphorus Sulfur Silicon* **1998**, 142, 249–257.
 1998SR397 T. Murai, S. Kato, *Sulfur Reports* **1998**, 20, 397–418.
 1998TL2755 F. Sandrinelli, S. L. Roy-Gourvennec, S. Masson, P. Rollin, *Tetrahedron Lett.* **1998**, 39, 2755–2758.
 1998TL5587 J. Nakayama, K. Akimoto, Y. Sugihara, *Tetrahedron Lett.* **1998**, 39, 5587–5590.
 1999BCJ805 S. Furuta, M. Kuroboshi, T. Hiyama, *Bull. Chem. Soc. Jpn.* **1999**, 72, 805–819.
 1999IC496 S. Kato, N. Kitaoka, O. Niyomura, Y. Kitoh, T. Kanda, M. Ebihara, *Inorg. Chem.* **1999**, 38, 496–506.
 1999JJC604 R. K. Sharma, Y. P. Singh, A. K. Rai, *Indian J. Chem.* **1999**, 604–608.
 1999JOC2130 T. Murai, H. Endo, M. Ozaki, S. Kato, *J. Org. Chem.* **1999**, 2130–2133.
 1999PS(153–154)317 C. Alayrac, S. Nowaczyk, M. Lemarie, P. Metzner, *Phosphorus Sulfur Silicon* **1999**, 153–154, 317–318.
 1999S404 O. Josse, D. Labar, J. Marchand-Brynaert, *Synthesis* **1999**, 404–406.
 1999S669 C. Alayrac, S. Nowaczyk, M. Lemarié, P. Metzner, *Synthesis* **1999**, 669–675.
 1999SC791 S. K. Nair, C. V. Asokan, *Synth. Commun.* **1999**, 29, 791–798.
 1999TA3337 R. Cea-Olivares, V. García-Montalvo, S. Hernández-Ortega, C. Rodríguez-Narváez, P. G. y. García, M. López-Cardoso, P. de March, L. González, L. Elias, M. Figueredo, J. Font, *Tetrahedron Asymmetry* **1999**, 10, 3337–3340.
 1999TL277 G. Bouhadir, N. Legrand, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1999**, 40, 277–280.
 1999TL2319 F. Corbin, C. Alayrac, P. Metzner, *Tetrahedron Lett.* **1999**, 40, 2319–2322.
 1999TL2435 S. H. Thang, Y. K. Chong, R. T. A. Mayadunne, G. Moad, E. Rizzardo, *Tetrahedron Lett.* **1999**, 40, 2435–2438.
 2000BCJ1243 K. Tani, K. Matsuyama, S. Kato, K. Yamada, H. Mifune, *Bull. Chem. Soc. Jpn.* **2000**, 73, 1243–1252.
 2000CC2093 L. Doszczak, J. Rachon, *J. Chem. Soc., Chem. Commun.* **2000**, 2093–2094.
 2000CL368 T. Murai, S. Hayakawa, S. Kato, *Chem. Lett.* **2000**, 368–369.
 2000JJC177 V. García-Montalvo, M. A. Santana-Valdés, S. Hernández-González, G. Espinosa-Pérez, R. Cea-Olivares, *Indian J. Chem.* **2000**, 39B, 177–182.
 2000JA9120 J. Nakayama, T. Kitahara, Y. Sugihara, A. Sakamoto, A. Ishii, *J. Am. Chem. Soc.* **2000**, 122, 9120–9126.

- 2000JA9850 T. Murai, T. Kamoto, S. Kato, *J. Am. Chem. Soc.* **2000**, 122, 9850–9851.
2000JOM(611)190 S. Kato, K. Tani, N. Kitaoka, K. Yamada, H. Mifune, *J. Organomet. Chem.* **2000**, 611, 190–199.
- 2000OL3213 A. Sudalai, S. Kanagasabapathy, B. C. Benicewicz, *Org. Lett.* **2000**, 2, 3213–3216.
2000PS(166)221 R. Sharma, Y. Singh, A. K. Rai, *Phosphorus Sulfur Silicon* **2000**, 166, 221–230.
2000SR1695 R. K. Sharma, Y. P. Singh, A. K. Rai, *Synth. React. Inorg. Metal-Org. Chem.* **2000**, 30, 695–707.
- 2000T7325 B. A. Trofimov, L. N. Sobenina, A. I. Mikhaleva, A. P. Demenev, O. A. Tarasova, I. A. Ushakov, S. V. Zinchenko, *Tetrahedron* **2000**, 56, 7325–7329.
- 2001AG(E)3450 N. Kano, N. Nakagawa, T. Kawashima, *Angew. Chem., Int. Ed. Engl.* **2001**, 40, 3450–3452.
2001CL768 J. Nakayama, T. Otani, T. Tadokoro, Y. Sugihara, A. Ishii, *Chem. Lett.* **2001**, 768–769.
2001CL968 O. Niyomura, K. Sakai, T. Murai, S. Kato, S. Yamaguchi, K. Tamao, *Chem. Lett.* **2001**, 968–969.
- 2001ICA15 A. Tarassoli, T. Sedaghat, B. Neumüller, M. Ghassemzadeh, *Inorg. Chim. Acta* **2001**, 318, 15–22.
- 2001JCS(D)518 K. Tani, S. Hanabusa, S. Kato, S. Mutoh, S. Suzuki, M. Ishida, *J. Chem. Soc., Dalton Trans.* **2001**, 518–527.
- 2001JOC8101 T. Murai, S. Hayakawa, S. Kato, *J. Org. Chem.* **2001**, 66, 8101–8105.
2001JOM(619)209 H. Adams, P. E. McHugh, M. J. Morris, S. E. Spey, P. J. Wright, *J. Organomet. Chem.* **2001**, 619, 209–217.
- 2001S293 L. N. Sobenina, A. P. Demenev, A. I. Mikhaleva, V. N. Elokhina, A. G. Mal'kina, O. A. Tarasova, I. A. Ushakov, B. A. Trofimov, *Synthesis* **2001**, 293–299.
- 2001S573 S. K. Nair, R. Samuel, C. V. Asokan, *Synthesis* **2001**, 573–576.
- 2001TL2133 J.-P. Bouillon, Y. G. Shermolovich, C. Portella, *Tetrahedron Lett.* **2001**, 42, 2133–2135.
2001TL3791 S. Kanagasabapathy, A. Sudalai, B. C. Benicewicz, *Tetrahedron Lett.* **2001**, 42, 3791–3794.
2002HCA2559 M. Shi, S. Kato, *Helv. Chim. Acta* **2002**, 85, 2559–2563.
2002IC5193 A. Otero, J. Fernández-Baeza, A. Antinolo, F. Carrillo-Hermosilla, J. Tejada, A. Lara-Sánchez, L. Sánchez-Barba, M. Fernández-López, A. M. Rodríguez, I. López-Solera, *Inorg. Chem.* **2002**, 41, 5193–5202.
- 2002JA5960 K. Tani, T. Murai, S. Kato, *J. Am. Chem. Soc.* **2002**, 124, 5960–5961.
2002JCS(P1)1271 L. Doszczak, J. Rachon, *J. Chem. Soc., Perkin Trans. I* **2002**, 1271–1279.
2002JOC7911 A. Alberti, M. Benaglia, M. Laus, K. Sparnacci, *J. Org. Chem.* **2002**, 67, 7911–7914.
2002JOM(645)105 A. Tarassoli, A. Asadi, P. B. Hitchcock, *J. Organomet. Chem.* **2002**, 645, 105–111.
2002PS(177)1851 L. Doszczak, W. Przychodzen, D. Witt, J. Rachon, *Phosphorus Sulfur Silicon* **2002**, 177, 1851–1854.
- 2002S1047 L. Doszczak, J. Rachon, *Synthesis* **2002**, 1047–1052.
2002SC2369 Q. Zhang, Y.-l. Zhao, Y. Shi, L.-x. Wang, Q. Liu, *Synth. Commun.* **2002**, 32, 2369–2376.
2002TL5759 Y. Naruse, S. Inagaki, N. Kano, N. Nakagawa, T. Kawashima, *Tetrahedron Lett.* **2002**, 43, 5759–5762.

Biographical sketch

Toshiaki Murai was born in Osaka in 1957. He studied at Osaka University, where he obtained a B.Sc. in 1980, his M.Sc. in 1982, and his Ph.D. in 1986 under the direction of Professor N. Sonoda. He joined the faculty at Gifu University in 1983. From 1986 to 1988 he did postdoctoral work with Professor J. L. Sessler at the University of Texas at Austin. He was a recipient of Progress award in Synthetic Organic Chemistry, Japan in 1997. He is now Professor of Chemistry at Gifu University. His scientific interests include all aspects of organometallic chemistry, in particular, synthesis and elucidation of properties of new types of organochalcogen compounds, and development of new synthetic reactions with high efficiency.

5.14

Thionoamides and Their Se and Te Analogs

A. J. MOORE

University of Sunderland, Sunderland, UK

5.14.1	THIONOAMIDES	519
5.14.1.1	Thionoamides from Carboxamides	519
5.14.1.1.1	<i>Use of phosphorus pentasulfide</i>	520
5.14.1.1.2	<i>Use of Lawesson's reagent</i>	522
5.14.1.1.3	<i>Use of reagents related to Lawesson's</i>	526
5.14.1.1.4	<i>Miscellaneous reagents</i>	527
5.14.1.2	Thionoamides From Nitriles	529
5.14.1.3	Thioacylation of Amines	533
5.14.1.4	Thiocarbamoylation	539
5.14.1.5	Aminosulfuration/Sulfuration	543
5.14.1.6	Manipulation of an Existing Thionoamide	544
5.14.1.7	Miscellaneous Methods	549
5.14.2	THIONOAMIDE S-OXIDES AND S,S-DIOXIDES	551
5.14.3	SELENOAMIDES	551
5.14.3.1	Selenoamides from Carboxamides	552
5.14.3.2	Selenoamides from Nitriles	553
5.14.3.3	Manipulation of an Existing Selenoamide	555
5.14.3.4	Miscellaneous Methods	557
5.14.4	TELLUROAMIDES	560

5.14.1 THIONOAMIDES

In recent years, thionoamides have often appeared in the literature as versatile intermediates in synthetic transformations. For example, thionoamides are essential building blocks for the preparation of a number of biologically relevant heterocyclic scaffolds utilizing the Hantzsch thiazole synthesis. They have also attracted considerable interest in peptide chemistry, as the thionoamide bond is isosteric to the natural carboxamide peptide bond, yet possesses markedly different chemical and physical properties. This chapter covers advances in the synthesis of thionoamides since the publication of <1995COFGT(5)565>. In this chapter, all the methods for preparation of thionoamides have been surveyed in one section, 5.14.1, removing sections 5.14.2–5.14.6 from COFGT (1995), and consequently renumbering the subsequent sections.

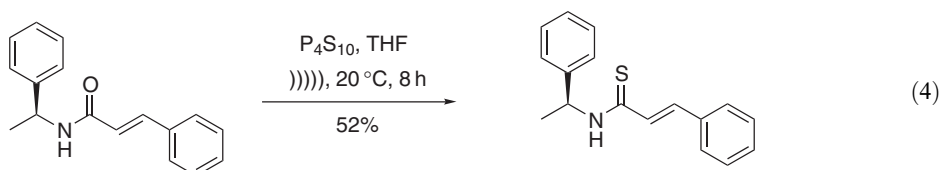
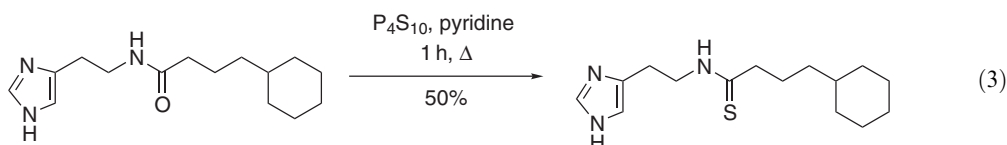
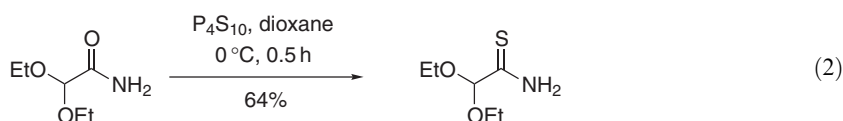
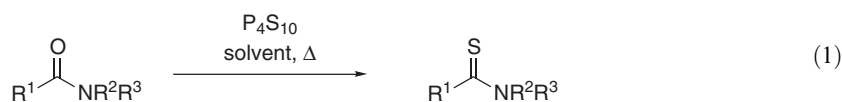
5.14.1.1 Thionoamides from Carboxamides

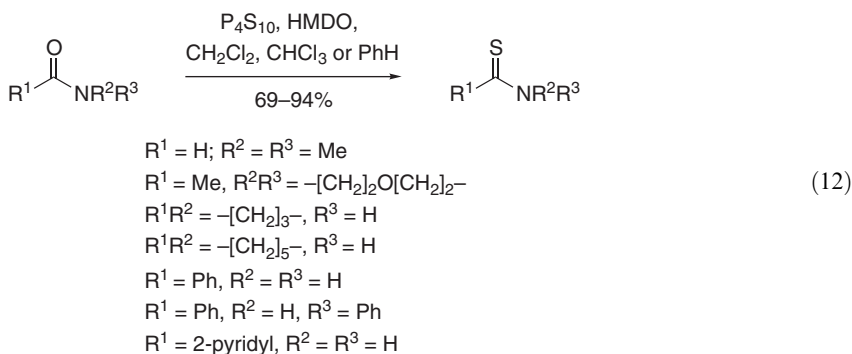
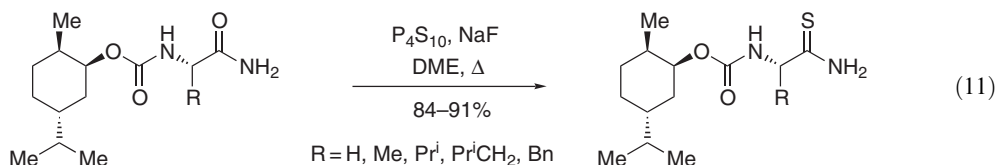
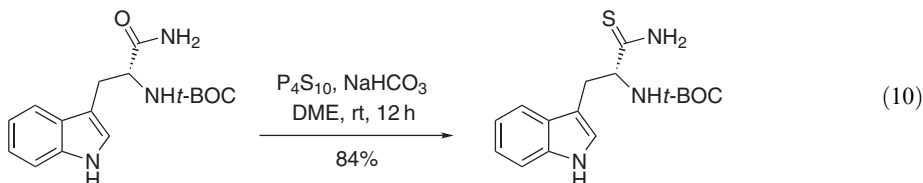
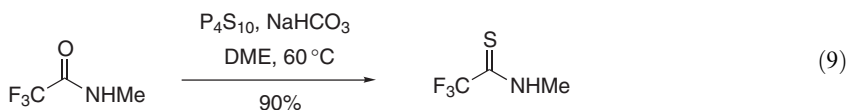
The carboxamide carbonyl group, either acyclic or cyclic, is generally the most easily thionated of the common carbonyl derivatives, and a number of reagents not otherwise useful for thionations

give good yields of thionoamides from carboxamides <1985T2567, 1992SR297>. Most commonly, however, conversion of an existing carboxamide into a thionoamide by O—S exchange is achieved using either phosphorus pentasulfide (P_4S_{10}) or Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide]. Other reagents which have been used for this transformation are described at the end of this section.

5.14.1.1.1 Use of phosphorus pentasulfide

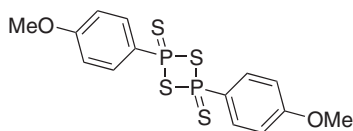
The conversion of carboxamides into thionoamides using phosphorus pentasulfide was first described in 1878, with the conversion of formanilide into thioformanilide <1878CB338>. Phosphorus pentasulfide has been subsequently used extensively for the conversion of carboxamides into thionoamides and a wide variety of examples have been described <1995COFGT(5)565>. The reaction is heterogeneous in nature and is normally carried out with an excess of phosphorus pentasulfide at elevated reaction temperatures. It is, therefore, necessary that both the starting material and the reaction product are thermally stable. Typical solvents include benzene, toluene, xylene, dioxan, DME, and pyridine (Equation (1)). More recently, dichloromethane has been shown to be an effective solvent for this conversion <2000EJOC3273>. One drawback with the use of phosphorus pentasulfide is that primary carboxamides are often converted into nitriles (via loss of hydrogen sulfide from the first formed primary thionoamide). Reaction times can be shortened dramatically and reaction temperatures often lowered significantly when thionation reactions are performed using ultrasound. Under ultrasound conditions, the use of phosphorus pentasulfide has been reported to be more selective than Lawesson's reagent, producing no reaction side-products <2000JCS(P1)3227>. Recent examples of the use of phosphorus pentasulfide in the conversion of carboxamides to thionoamides are shown in Equations (2)–(7), highlighting the range of functionality tolerated in the reaction <1996BMCL1543, 1998T3219, 1996TL123, 2000JCS(P1)3227, 1997PHA419, 1996JOC8701, 1994TA2313, 1995TL3781>. Several routes are known for preparation of the parent thionoformamide including reaction of formamide with phosphorus pentasulfide <1953JA4456, 2000JMC721, 2001BMC2035>. It is suggested that if further reaction of thionoformamide is required, it may be prepared and used without further purification by simply decanting the reaction mother liquor (Scheme 1) <2001BMC2035>. Occasionally, phosphorus pentasulfide is reported to thionate carboxamides when Lawesson's reagent fails (Equation (8)) <1995JHC1309>.





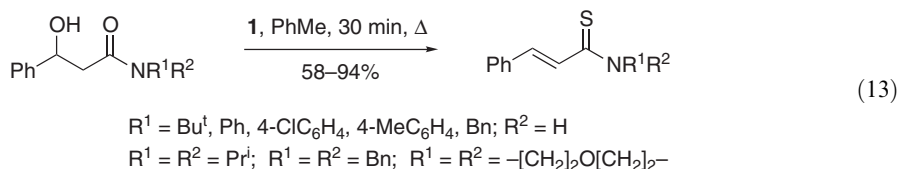
5.14.1.1.2 Use of Lawesson's reagent

Although first described in 1956 <1956JA5018>, the use of Lawesson's reagent [**1**, 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide] as an O—S transfer reagent did not develop until the late 1970s when a Danish group published their seminal work on the use of organophosphorus compounds as thionating agents <1995COFGT(5)565>. The mechanism of thionation has been shown to involve dissociation to ArPS_2 monomers followed by nucleophilic attack from the carbonyl oxygen toward the electrophilic phosphorus <1986TL3445, 1994TL4379>. This reagent, available commercially, has displaced phosphorus pentasulfide as the reagent of choice for many thionations of carbonyl-containing compounds <1985T5061>. Lawesson's reagent is both extremely efficient and also very versatile, thionating aliphatic, unsaturated, aromatic, and heterocyclic carboxamides <1995COFGT(5)565>; this is manifested in the number of citations for reactions using Lawesson's reagent when compared with other methods of thionating carboxamides. The reagent is reportedly free from a number of disadvantages associated with the use of phosphorus pentasulfide, primarily the conversion of primary carboxamides into nitriles (although this is still occasionally observed <1997TL1297>). As with phosphorus pentasulfide, the reaction is heterogeneous in nature and is often carried out at elevated reaction temperatures, although many reactions are efficient at room temperature and below; such mild conditions are important when, for example, thionating sensitive peptides where racemization is possible. Typical solvents include benzene, toluene, xylene, HMPA, dioxan, DME, and pyridine <1995COFGT(5)565>. It has been noted that when higher reaction temperatures are required, the formation of undesirable reagent-related by-products can occur <1995COFGT(5)565>, and isolation of the products from reaction mixtures can become extremely difficult by simple column chromatography.

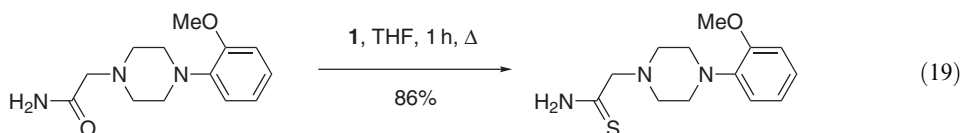
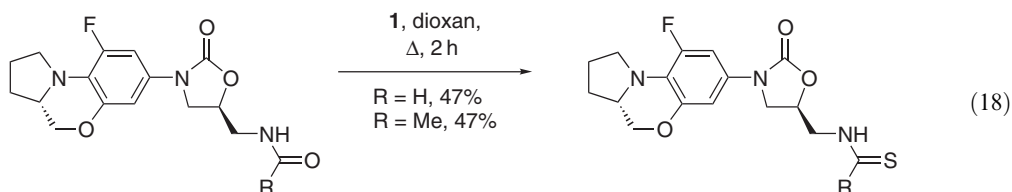
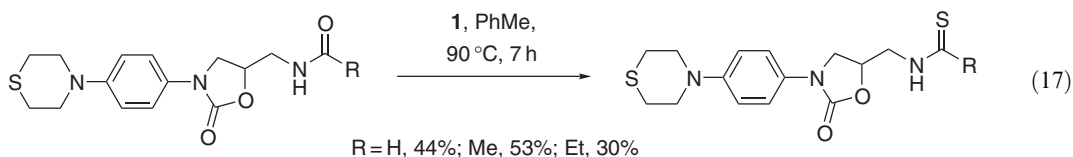
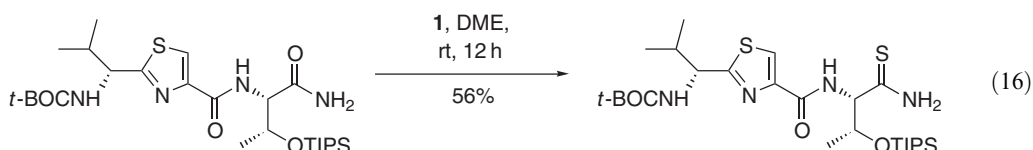
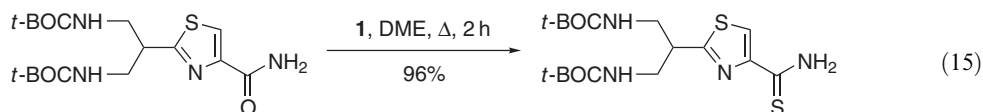
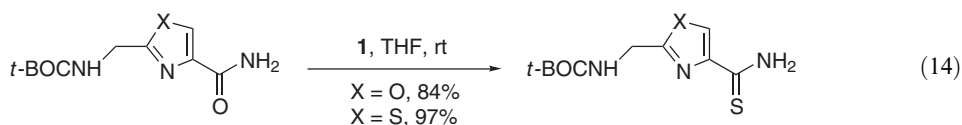


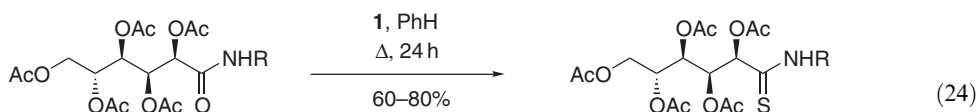
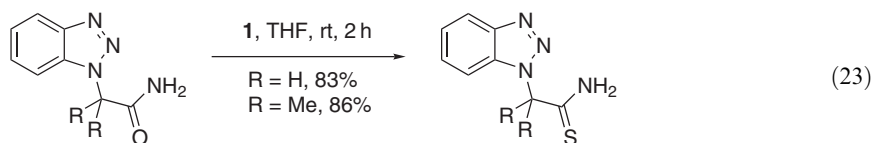
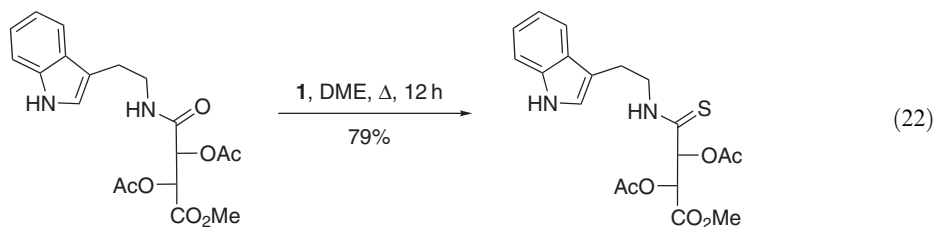
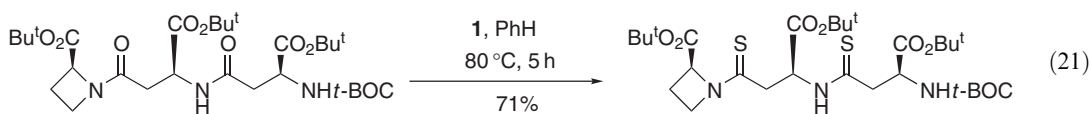
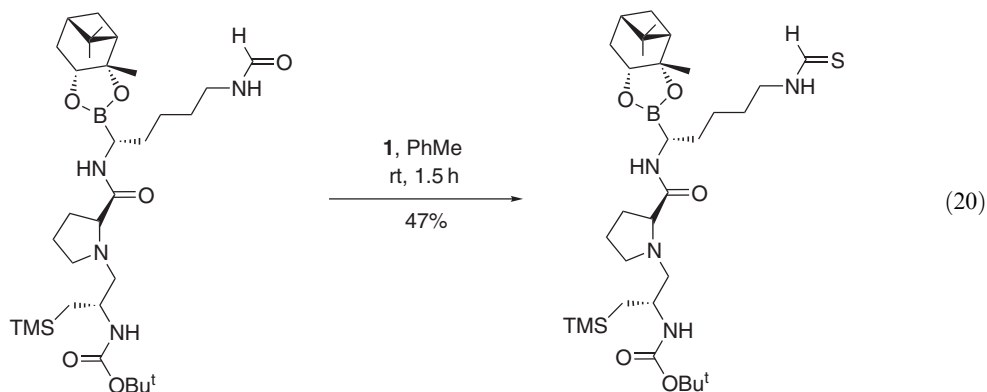
Lawesson's reagent, **1**

The carbonyl groups of common protecting groups used in peptide synthesis are generally unaffected by Lawesson's reagent, thionating only at elevated temperatures (e.g., urethanes $>110^{\circ}\text{C}$, esters $>140^{\circ}\text{C}$). Hence, Lawesson's reagent has seen widespread use in the synthesis of thionated amino acids and endotheopeptides [<1995BCJ3151, 1995COFGT\(5\)565, 1995JHC1309, 1995T12731, 1995TL67, 1996AG\(E\)1503, 1996JOC7671, 1996PS\(108\)257, 1996TL9107, 1997T13383, 1997TL2459, 1999BCJ1561, 1998JCS\(P1\)601, 1999BMCL2353, 1999T3007, 1999T11833, 2001CC717, 2001CC1934, 2001H835, 2003T2713>](#). It is, however, often necessary to protect nucleophilic functionalities such as amines or hydroxy groups, whereas carboxylic acids can be tolerated with carefully monitored reaction conditions. For example, thionation of β -hydroxycarboxamides with Lawesson's reagent gives exclusively *E*-thionoenamides ([Equation \(13\)](#)) [<1999T5017>](#). The authors suggest that the hydroxy group is converted into a thiol group, followed by loss of hydrogen sulfide (Lawesson's reagent is known to dehydrate alcohols via thiols [<1993JCS\(P1\)1113>](#)).

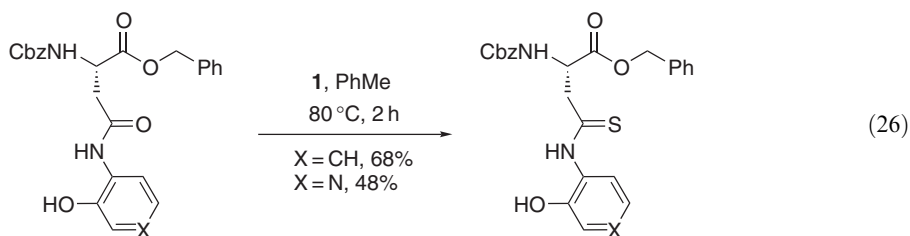
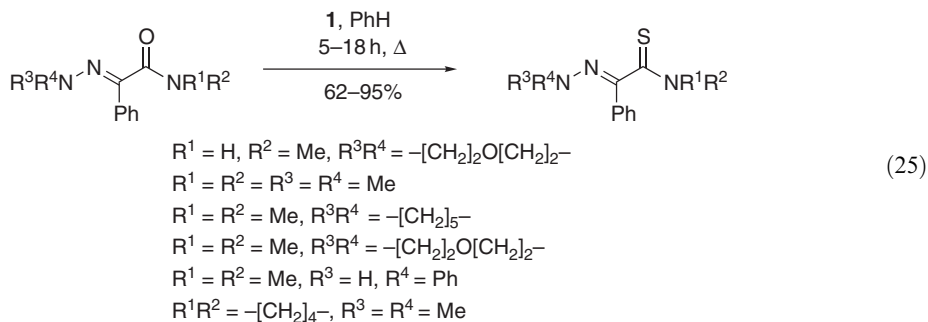


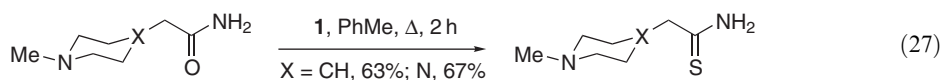
Lawesson's reagent may be successfully used to thionate carboxamides in the presence of many functional groups; the transformations of a variety of functionally interesting carboxamides are shown in [Equations \(14\)–\(27\)](#) [<1994PS\(97\)89, 1995MI77, 1995JA9107, 1995JOC5638, 1996AG\(E\)1503, 1996BMCL833, 1997PS\(126\)39, 1998H1319, 1998JMC4903, 1998TL89, 1999BCJ2483, 2000BMC2291, 2000BMCL1563, 2000TA1985, 2000TA2793, 2001CPB347, 2001TL3355, 2002JMC3953>](#).



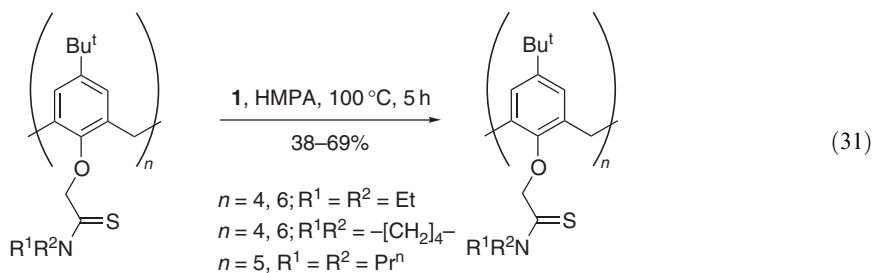
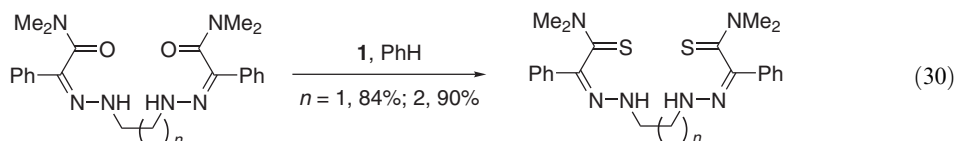
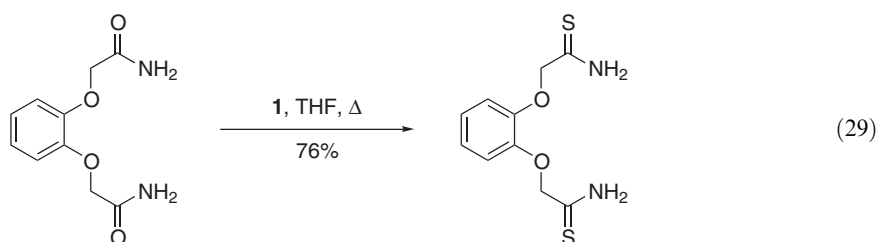
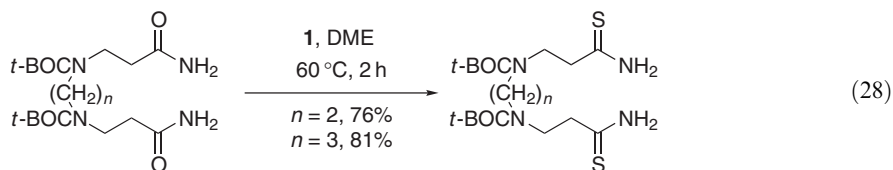


R = Me, Et, Prⁿ, Prⁱ, Ph, 4-MeC₆H₄, 4-BrC₆H₄

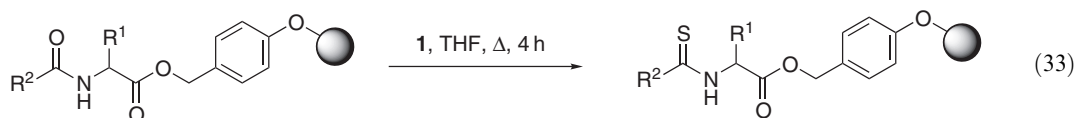




Compounds bearing more than one carboxamide group are effectively fully thionated using Lawesson's reagent. Representative examples include alkyl carboxamides (Equations (28) and (29)) <1997CPB189, 1998JHC177>, bis(hydrazonoamides) (Equation (30)) <1998TL8645, 2001JCS(P1)1212>, and calixarene carboxamides (Equation (31)) <1997JCS(P2)575, 1997JCS(P2)1353, 2001JCS(P2)2287, 2002JOC3165>.



Resin-bound carboxamides have been efficiently converted into thionoamides in refluxing THF using Rink amide resin (Equation (32)) <2000TL4965> and hydroxymethyl polystyrene resin (Equation (33)) <2003TL459>. In the latter case, cleavage from the resin to give the free thionoamide was also examined. The use of Lawesson's reagent in a microwave-assisted solvent-free parallel synthesis of thionoamides has also been described <2000TL7947>.



5.14.1.1.3 Use of reagents related to Lawesson's

Modifications to Lawesson's reagent have been investigated by a number of research groups in order to modify both its reactivity, in particular the selectivity, and solubility <1995COFGT(5)565>. The group of Belleau developed the phenoxy-substituted equivalent of Lawesson's reagent [**2**, 2,4-bis(4-phenoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide], prepared by heating phosphorus pentasulfide in an excess of diphenyl ether at 165–170 °C <1983TL3815>. This reagent is reportedly more soluble than Lawesson's reagent and is occasionally reported to give superior yields and reacts particularly well with amino acids and peptides (Equations (34) and (35)) <1996BMCL2253, 1999T12301>. As a result of improved solubility, reactions may often be conducted at lower temperatures than the equivalent reaction using Lawesson's reagent; this has the effect of enhancing optical purity of products from reactants containing easily racemizable chiral centers (Equation (36), Table 1) <1998JA591, 1995JOC4774>.

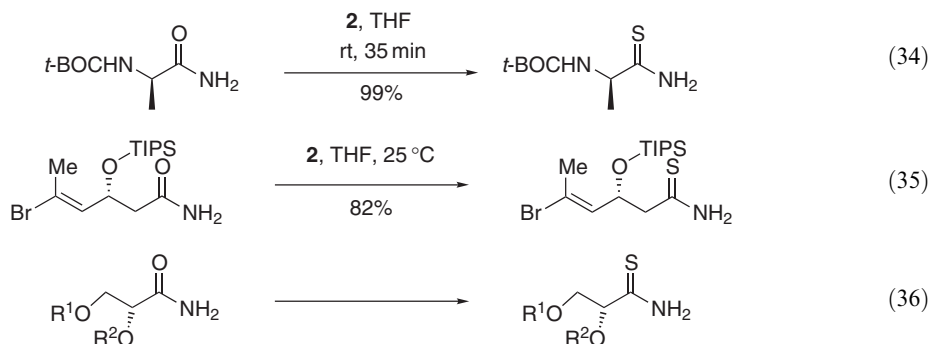
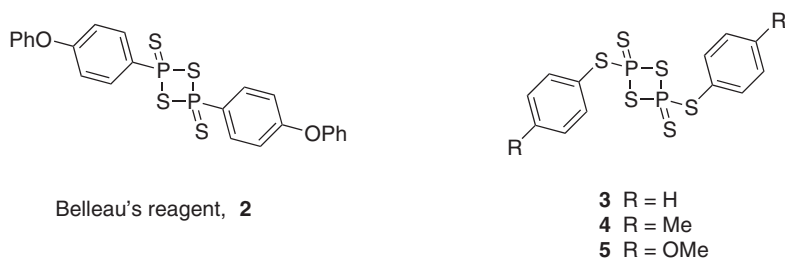


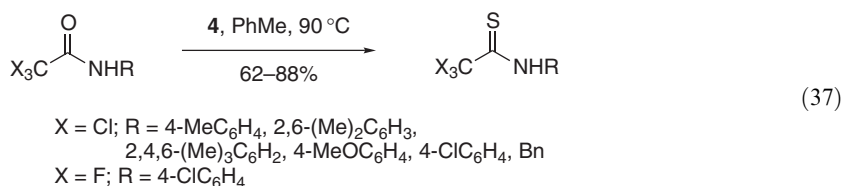
Table 1 Thionation with Lawesson's reagent **1** and Belleau's reagent **2**: a comparison (Equation (36))

R^1	R^2	Conditions	Yield (%)	ee (%)
$\text{CH}_3\text{C(O)}$	$\text{CH}_3\text{C(O)}$	1 , PhH, 70 °C	62	0
$\text{CH}_3\text{C(O)}$	$\text{CH}_3\text{C(O)}$	2 , THF, 0 °C	85	94
$-\text{CMe}_2-$	$-\text{CMe}_2-$	1 , PhH, 70 °C	92	96
$-\text{CMe}_2-$	$-\text{CMe}_2-$	2 , THF, 0 °C	97	>99

Source: <1995JOC4774>.

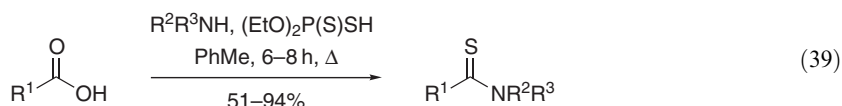
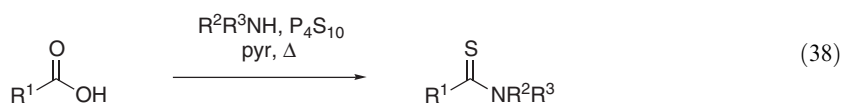
Further refinements to Lawesson's reagent saw the development of reagents **3–5** <1984S827, 1982CC457, 1987HCA1001>, which have good solubility in chloroform, THF, benzene, and toluene. They are reported to give superior yields to Lawesson's reagent under identical conditions <1995COFGT(5)565, 1989JCR(S)155> and it is speculated that enhanced solubility and reduced steric congestion due to the additional P–S bonds contribute to the success of the reaction. The Davy reagent [**4**, 2,4-bis(4-methylphenylthio)-1,3,2,4-dithiadiphosphetane-2,4-disulfide] <1982CC457, 1987HCA1001> has been shown to be useful for the preparation of trichloro- and trifluorothionoacetamides and also *N,N*-disubstituted trichlorothionoacetamides, when Lawesson's reagent failed (Equation (37)) <1998TL9259>. Similarly, when thionation of cyclic peptides using Lawesson's reagent failed, the Davy reagent was successful <1996JCS(P1)1749>.



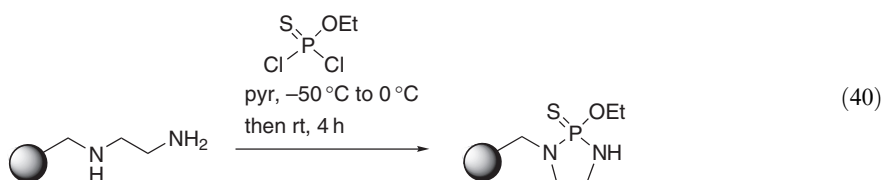


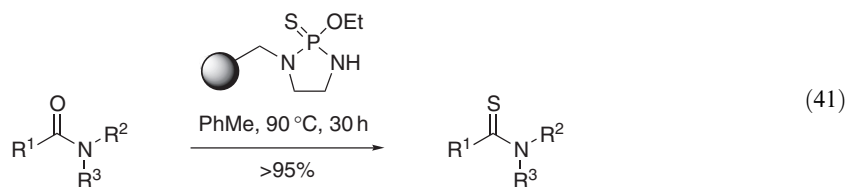
5.14.1.1.4 Miscellaneous reagents

A wide variety of alternative O—S exchange reagents have been used to convert carboxamides to thionoamides; these have been largely superceded by the use of the readily available phosphorus pentasulfide and Lawesson's reagent described above and have not found widespread application. Most alternatives also use phosphorus as oxygenophile, but examples using silicon and boron are also known <1995COFGT(5)565>. Monomeric thiophosphates have been demonstrated to be good thionating agents <1977BSB321>. Notably, the reaction of *O,O*-dialkyldithiophosphoric acids proceeds effectively with carboxamides and, in particular, *O,O*-diethyldithiophosphoric acid provides useful conversions of carboxamides into thionoamides (aromatic, primary, secondary, and tertiary) as long as reactions are carefully monitored. It has been reported that thionoamides can be prepared directly from carboxylic acids and amines in the presence of phosphorus pentasulfide (Equation (38)) <1869CB305, 1869CB494>. This reaction has recently been extended to the use of *O,O*-diethyldithiophosphoric acid (Equation (39)) <1995TL6745>. The ratio of reagents was found to be critical for efficient thionoamide formation.



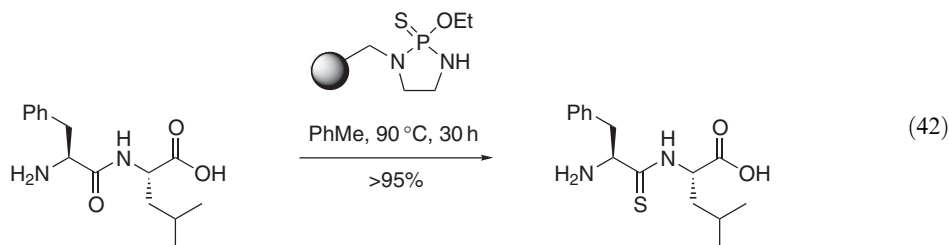
As Lawesson's reagent has a dimeric structure and is itself a poor candidate for tethering to a polymer support, monomeric thiophosphates have provided the basis for the first polymer-supported thionating agent <2001JCS(P1)358>. An aminothiophosphate resin (of low odor) was readily synthesized from commercially available *N*-(2-aminoethyl)aminomethyl polystyrene and ethyl dichlorothiophosphate (Equation (40)); this reagent has been shown to cleanly convert secondary and tertiary carboxamides to thionoamides at elevated temperatures (Equation (41), Table 2, Equation (42)) <2001JCS(P1)358>. In common with many supported reagent-mediated reactions, extended reaction times are required. Primary carboxamides were converted to nitriles under the reaction conditions; only benzamide gave the primary thionoamide, although in reduced yield due to dehydration to furnish the corresponding nitrile. Microwave heating in the presence of an ionic liquid (1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate) gives enhanced reaction rates and reduces reaction times considerably.



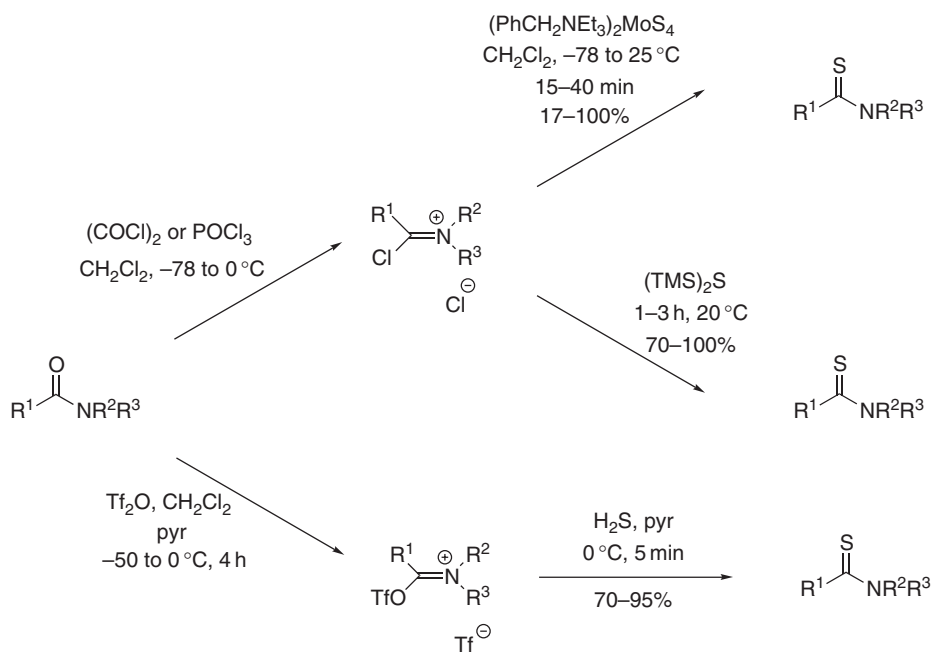
**Table 2** Thionation of amides using a polymer-supported thionating agent (Equation (41))

R^1	R^2	R^3	Method ^a	GC conversion (GC purity)
Me	H	Ph	A	99 (92)
Me	H	Ph	B	98 (92)
Me	Me	Me	B	99 (95)
Pr ⁿ	Me	Me	B	96 (95)
	–[CH ₂] ₃ –	Ph	B	99 (98)
	–[CH ₂] ₅ –	H	A	99 (93)
	–[CH ₂] ₅ –	H	B	99 (97)
Ph	H	H	A	68 (80)
Ph	H	Me	A	99 (88)
Ph	H	Me	B	96 (95)
Ph	Me	Me	A	99 (93)
Ph	Me	Me	B	99 (95)
PhCH ₂ CH ₂	Me	Me	B	96 (95)

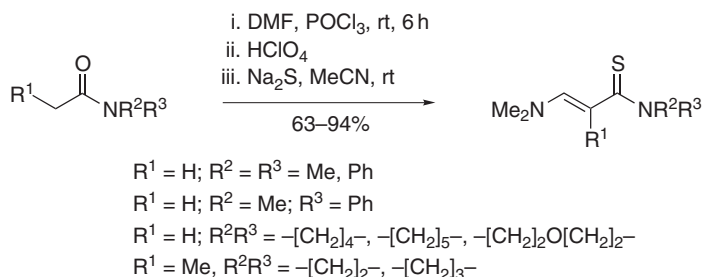
^a Method A: toluene, 90 °C, 30 h; Method B: toluene, 1-ethyl-3-methyl-1*H*-imidazolium hexafluorophosphate, 200 °C (microwave heating), 15 min.
Source: <2001JCS(P1)358>.



Chloroiminium salts, generated *in situ* from carboxamides and lactams using either phosphorus oxychloride or oxalyl chloride, react very rapidly with sulfur transfer reagents to afford the corresponding thionoamides and thiolactams in good yield. Benzyltriethylammonium tetrathiomolybdate [(PhCH₂NEt₃)₂MoS₄] <1995TL8311> and bis(trimethylsilyl) sulfide <1994JOC348> (Scheme 2) are both reported to proceed in good yield. In the absence of an activating agent, or in the presence of a Lewis acid, these reactions do not proceed due to the poor electrophilicity of the carbonyl carbon of the carboxamide. In both cases, the reaction yields are comparable to those reported using Lawesson's reagent. The former method is suggested to be preferable as the isolation of reaction products proceeds by simple extraction and bis(trimethylsilyl) sulfide is an expensive reagent with an obnoxious odor. Similarly, secondary and tertiary carboxamides generate imino and iminium triflates, respectively, when treated with trifluoromethanesulfonic anhydride. These imino and iminium triflates are strong electrophiles and react rapidly with hydrogen sulfide to afford thionoamides in good-to-excellent yield (Scheme 2) <1998TL245>. Reaction of *N,N*-disubstituted acetamides with the Vilsmeier reagent, prepared from DMF and phosphorus oxychloride, followed by reaction with sodium sulfide affords *N,N*-disubstituted 3-dimethylaminothioacrylamides (Equation (43)) <2000S805, 2000EJOC3273>. This reaction proceeds via an isolated 3-amino-3-chloropropenyldenedimethyliminium salt.



Scheme 2

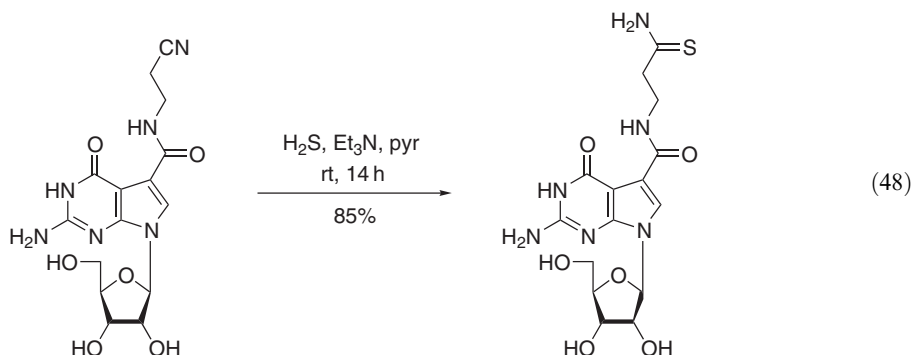
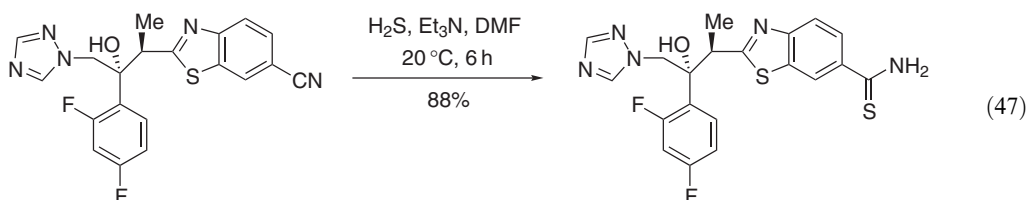
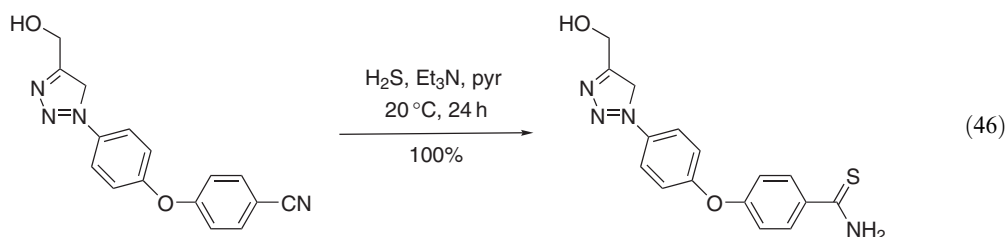
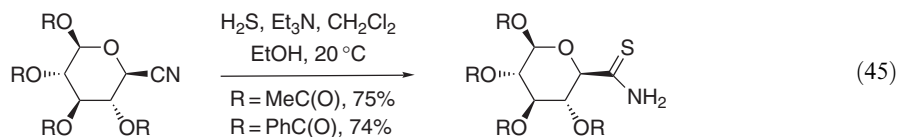
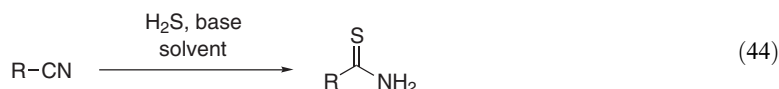


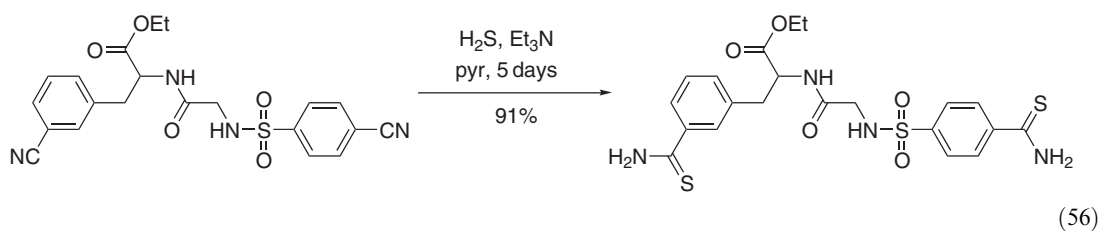
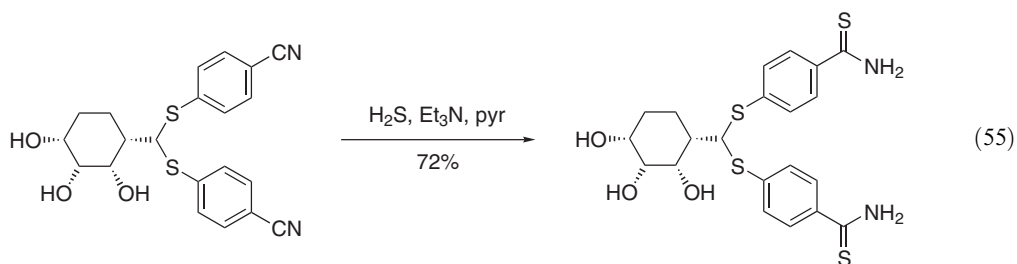
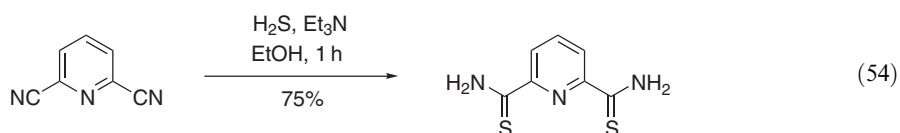
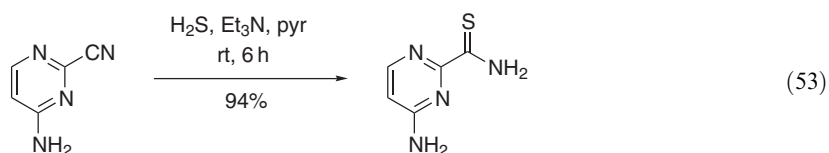
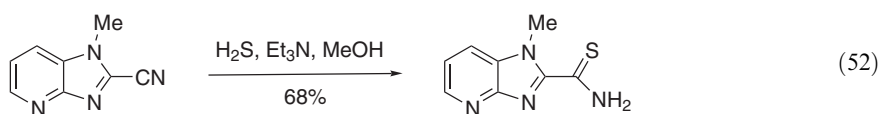
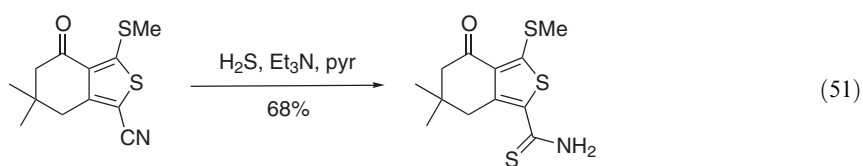
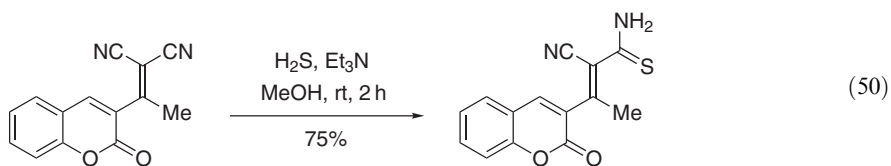
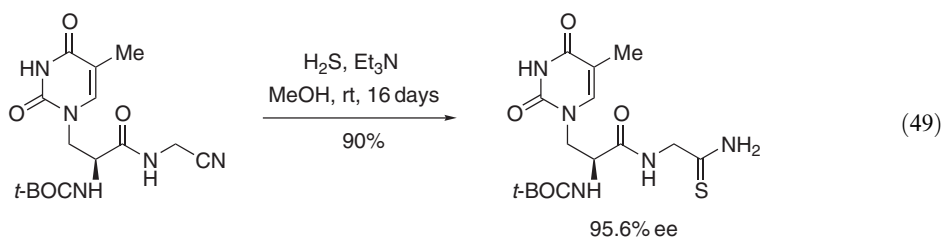
(43)

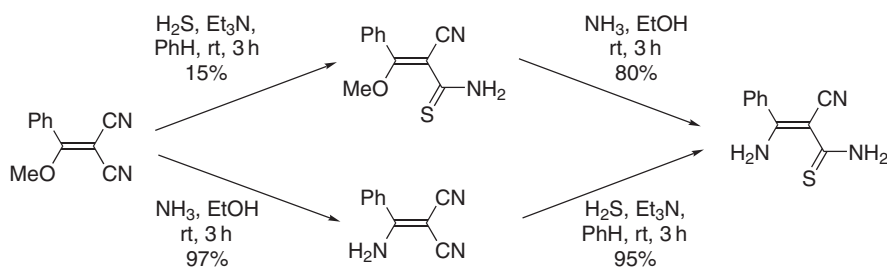
5.14.1.2 Thionoamides From Nitriles

The earliest reported method for the preparation of thionoamides involved the reaction of a nitrile with hydrogen sulfide gas in the presence of an amine. Whilst the use of hydrogen sulfide in the laboratory poses health and safety issues, researchers have continued to successfully use this method to prepare thionoamides (Equation (44)) <1995COFGT(5)565>. Early examples often required high pressures and elevated temperatures. The use of triethylamine in pyridine for the direct addition of hydrogen sulfide at atmospheric pressure <1952JCS742> has emerged as a workhorse preparation of thionoamides. The reaction is particularly suited to aromatic <1995JMC2378, 1996AP73, 1998CPB623, 1999BMCL3147, 1998M661, 1999MI666, 1999JMC3557, 1999JMC3572, 2000BMCL1971, 2000CAR25, 2000CAR525, 2000JMC3832, 2000JMC4063, 2001BMCL1289, 2002MI259, 2003T1317> and heteroaromatic <1995JMC4115, 1995JCS(P1)1543, 1995PHA794, 1996PHA27, 1998BCJ1391, 1999BMCL1167, 1999BMCL1973, 1999CCC417, 2000BMC363, 2001BMCL1379, 2001T2179, 2002BMCL491, 2003JMC2227> nitriles. Ammonia <1996HCA295, 1997PJC1060>, ammonium hydroxide <1996JOC778, 1996JOC7398>, potassium hydroxide <1999JMC1661>, diethylamine <1999BMC1559, 1999MI2345, 2000TL9493>, diisopropylethylamine <2000JMC2759>, *N,N*-dimethylaminopyridine <1996CL1025, 1999SC4113, 1999MI2425>, and sodium alkoxides <1960CB1511, 1996JMC3470, 1997ZN323, 1997RJOC569, 2000CAR25, 2001JOC4776> have all

been successfully utilized as base. Typical solvents include alcohols, diethyl ether, DMF, and dioxan. Whilst being particularly useful for aromatic nitriles, aliphatic nitriles also react, but often slowly <1995JA9107, 1995SI423, 1996CCA535, 1997JCS(P1)2983, 1997JOC3804, 1997TL4811, 1998JCR(S)84, 1998SL1077, 1999MI533, 1997BMCL861, 2000MI569, 2001T5429, 2001EJOC1695, 2002MI1292, 2003BMCL637>. This approach has been used for the preparation of some quite complex primary thionoamides (Equations (45)–(53)). The reaction is also applicable to multifunctional nitriles in which all nitrile functionality is converted to a thionoamide (e.g., Equations (54)–(56)) <1998JMC4240, 1999H277, 2001JCS(D)550, 2001CAR325, 2003JCR(S)225>. Interestingly, reaction of α -methoxybenzylidenemalononitrile with hydrogen sulfide afforded the corresponding thionoamide in only 15% yield, the major reaction product being 2-cyanothionoacetamide. Subsequent aminolysis afforded the desired thioacrylamide. However, reversing the order of reactions gave a significant improvement in overall yield (Scheme 3) <1994H1615>.

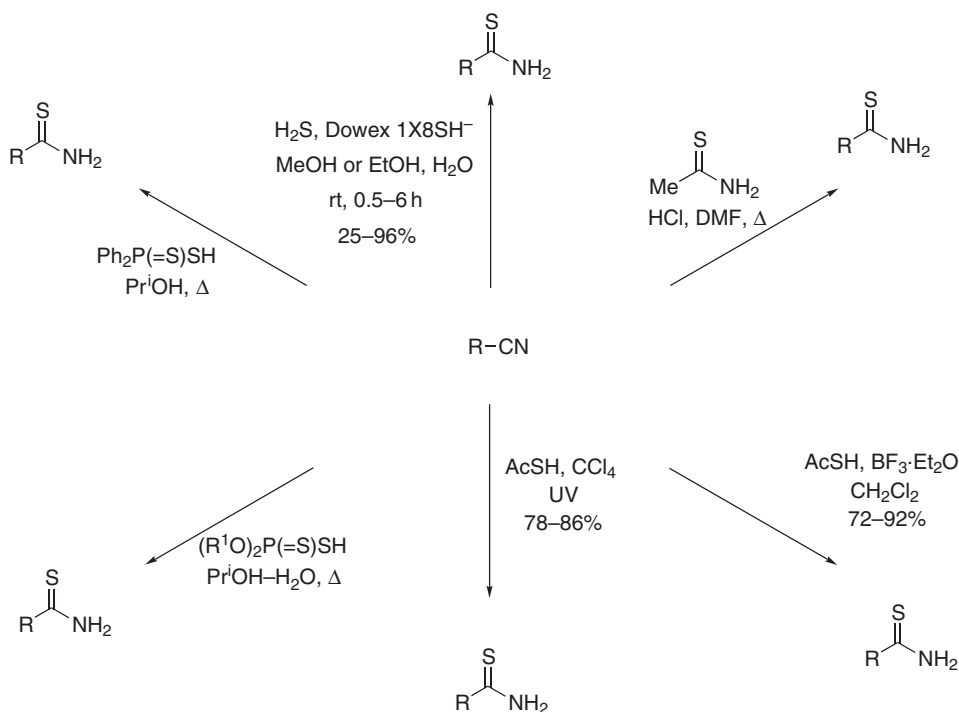






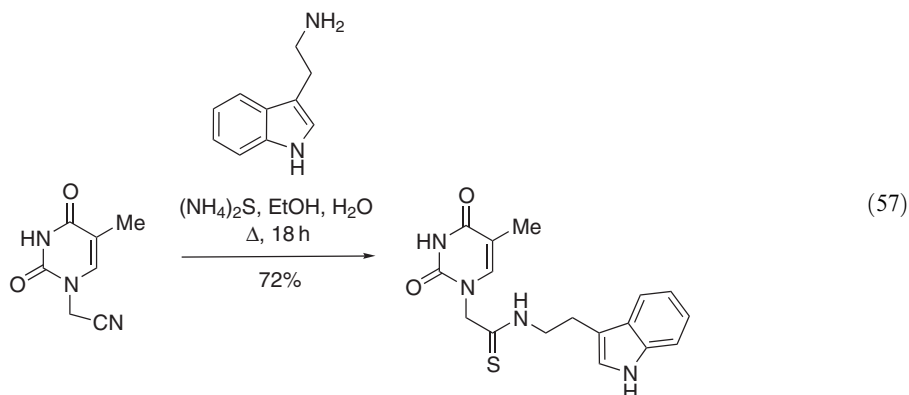
Scheme 3

The base-catalyzed synthesis of thionoamides from nitriles and hydrogen sulfide frequently suffers from the disadvantage of requiring the reaction to be performed at high temperature and/or under pressure. The reaction of nitriles with hydrogen sulfide in the presence of an anion exchange resin offers a convenient alternative, requiring only room temperature and atmospheric pressure using polar solvents (Scheme 4) <2002S1649>. This protocol is efficient for the preparation of primary thionoamides bearing various substituents. Several alternative methods for the conversion of nitriles into thionoamides have also been reported <1995COFGT(5)565>. Conversion of aliphatic nitriles into thionoamides can be performed with ammonium sulfide, or substituted ammonium sulfides <1995COFGT(5)565, 1996MI1102, 1997SC3431, 2000SC1083>. Sodium hydrogen sulfide hydrate has been similarly employed <1998JHC659, 1999MI693, 2003OL507>. Thionoacetamide was found to be a good source of hydrogen sulfide, converting aliphatic, aromatic, and heteroaromatic nitriles into thionoamides in DMF saturated with dry hydrogen chloride (Scheme 4) <1960JA2656, 1995JMC353, 1998H857, 1999BMCL569, 1999JMC5064, 2001JMC1741>. Thiobenzamide has reportedly also been used <2003CPB608>. The acid-catalyzed addition of thiolacetic acid to nitriles has been reported to yield thionoamides, although reactions are often sluggish <1995COFGT(5)565>. Reaction of nitriles with thiolacetic acid in the presence of a Lewis acid catalyst similarly produces the corresponding thionoamides (Scheme 4) <1994PS(95-96)325>. Irradiation (150 W floodlamp) of a mixture of a nitrile and thiolacetic acid in carbon tetrachloride enhances the reaction rate, and primary thionoamides can be isolated in good yield with negligible work-up (Scheme 4) <1994PS(95-96)325>. The authors maintain that this method provides a simple, mild, and apparently universal conversion of a wide range of structurally diverse nitriles into thionoamides.



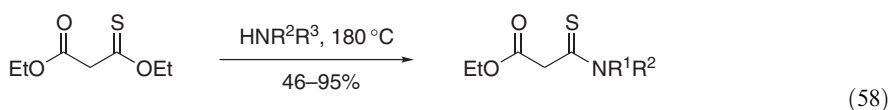
Scheme 4

The reaction of *O,O*-dialkylmonothiophosphoric acids with aromatic nitriles is known to produce primary thionoamides, although only in poor yield <1986ZOB2660>, whereas the reaction of the related *O,O*-dialkylthiophosphoric acids proceeds more effectively <1995COFGT(5)565>. The use of either water or an alcohol as a co-solvent allows the preparation of a range of thionoamides in good-to-excellent yields (Scheme 4) <1985PS(25)297, 1995MI833, 1996JMC1635, 1996MIP853426, 1996MI20, 1997MI741, 1997SC2393, 1998CPB623, 1999TL423, 2002BMC41, 2003BMC1493>. Similarly, diphenyldithiophosphoric acid has been used to effect this transformation using either water <1981TL1851, 1981TL1855> or an alcohol (Scheme 4) <2001BMCL1301> as co-solvent. The thionation reagents $P_4S_{11}Na_2$ (prepared *in situ* from phosphorus pentasulfide and sodium sulfide) <1992SC1397> and sodium trimethylsilanethiolate <1992S1219, 1993JOC4742, 1996BMCL139, 2001OL3655> have also been used for conversion of nitriles into thionoamides under mild conditions. Ammonium sulfide (Equation (57)) <2000T7981> and hydrogen sulfide <1999TL2841> have been used to effect the direct conversion of a nitrile into a secondary thionoamide by direct reaction with a primary amine.

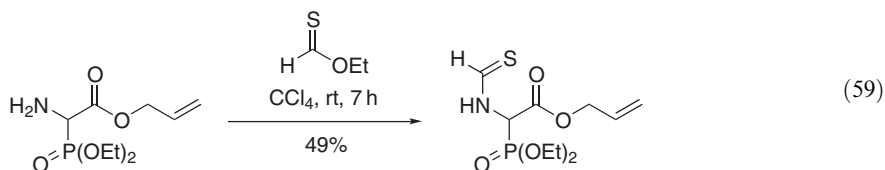


5.14.1.3 Thioacylation of Amines

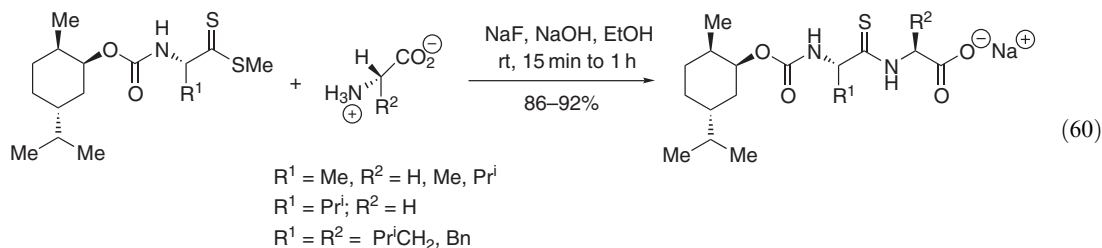
A wide variety of reagents have been utilized for the conversion of an amine into a thionoamide <1995COFGT(5)565>. Thioacyl halides have been used only to a limited extent, mainly as a result of the instability associated with this class of compounds. Trithiocarboxylic acid anhydrides bis(thioacyl)sulfides and related species have also received some attention <1995COFGT(5)565>. Thionoesters are well known as thioacylating agents <1995COFGT(5)565, 1998SL1243, 2002BMCL2427>. Amidation of β -carboalkoxy thionoesters with dialkylamines (morpholine, diethylamine) occurs at room temperature in the absence of solvent <1967CB1413>. This reaction has been extended to the synthesis of *N*-alkyl-*N*-arylthionoamidoacetates by using a slight excess of ester in the absence of a solvent at elevated temperature (Equation (58)) <2000SC565>. The corresponding acids were easily obtained by hydrolysis of the esters in excellent yield. Thioformylation of a primary amine in carbon tetrachloride has been demonstrated (Equation (59)) <1996T7691>.



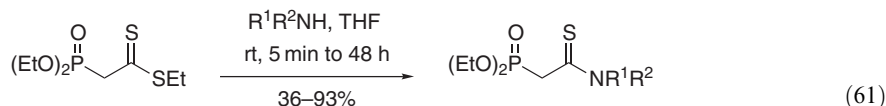
$R^1 = \text{Me}; R^2 = \text{Ph}, 4\text{-MeC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 3\text{-ClC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_4$
 $R^1 = -[\text{CH}_2]_2\text{OMe}, -[\text{CH}_2]_3\text{OMe}; R^2 = \text{Ph}$



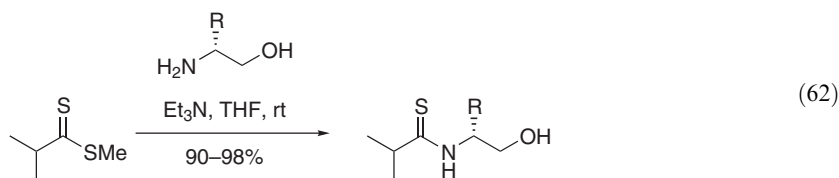
Thioacylation of amines by dithioesters is much faster than with thionoesters and esters, and has been shown to be a smooth and convenient method to prepare thionoamides <1972ZC133, B-1991MI419, 1995COFGT(5)565>. Not surprisingly, therefore, dithioesters have received great interest as thioacylating agents. The kinetics and mechanism of thioacylation using dithioesters and various amine substrates has been studied <1995JCS(P2)1169, 1998MI849, 2000JCS(P2)2306>. Thionoamides are efficiently synthesized by reacting dithioesters with primary amines <1998MI863>. The use of aqueous ammonia in DMF/toluene afforded primary thionoamides, although in diminished isolated yields <1998MI863>. Dithioesters are known to be very useful thioacylating agents in endotheiopeptide synthesis <1982JA5221, 1984JCS(P1)785, 1996PS(108)257>, although racemization is known to be a problem due to long reaction times <1992T8601>. Endotheiopeptides were prepared by condensation of *N*-protected α -amino dithioesters with α -amino acid derivatives (Equation (60)) <1996JPR251>. With sterically undemanding amino acids, such as glycine, the reaction is rapid; however, using higher amino acids led to longer reaction times and significant racemization. An improvement in reaction rate was realized using alkali salts of α -amino acids in the condensation reaction. Sterically demanding α -amino acids, such as valine or proline, reacted efficiently on addition of alkali metal fluorides as catalysts. The authors were, however, unable to monitor the extent of racemization in these reactions, suggesting instead that the short reaction times favored retention of configuration. Use of 4-(*N,N*-dimethylamino)pyridine in combination with caesium salts has also been reported to increase the reactivity of methyl dithioesters, whilst preserving stereochemistry during thioacylation <1995MI138>.

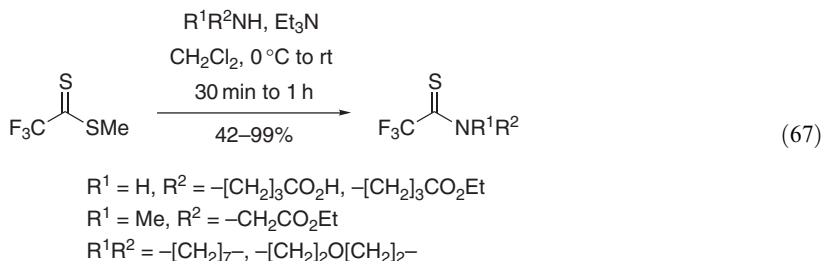
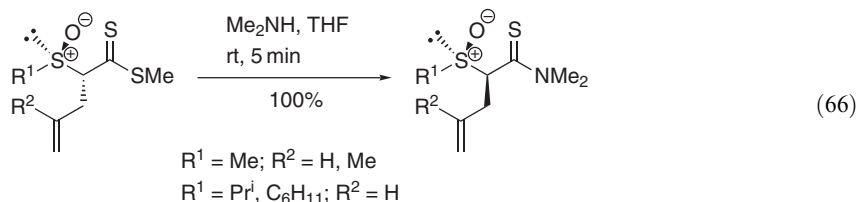
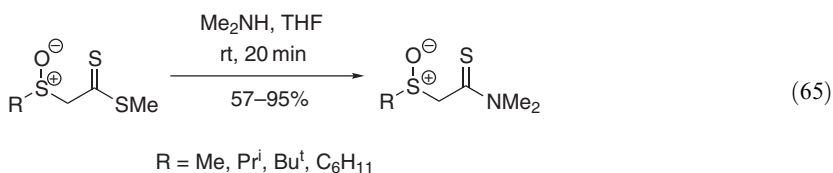
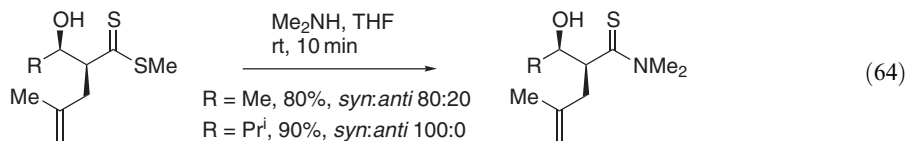
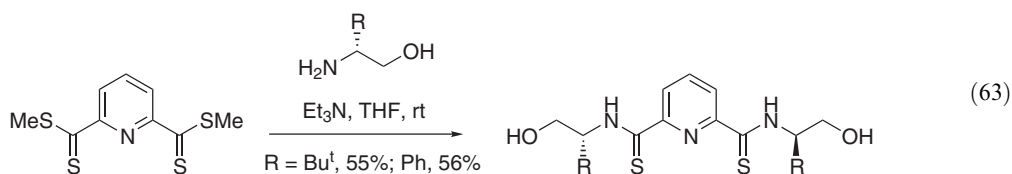


A variety of thioacylations using dithioesters have been reported in which minimal or no racemization is observed at the asymmetric center in either the amine (Equations (61)–(63)) <1994PS(89)119, 1995S1393, 2000S1143, 2001TA2851, 2002OL843> or the dithioester (Equation (64) and (65)) <1997T17253, 1999S669> precursor. Interestingly, aminolysis with dimethylamine of 2-methanesulfinylpent-4-enedithioic acid methyl esters proceeded under dynamic kinetic control to afford thionoamides with reverse configuration at the asymmetric carbon (Equation (66)) <2000TL2537>. Free amines react very quickly and amine hydrochlorides may be similarly coupled when triethylamine is used as a dehydrohalogenating agent. Methyl trifluorodithioacetate has been demonstrated to be a convenient and efficient trifluorothioacylating agent (Equation (67)) <1997JPR697>. *N*-Thioacylation of 2-amino-2-deoxyhexosamines and neuraminic acid methyl α -glycoside with *O*-ethyl thioformate, methyl dithioacetate, and methyl dithiopropionate afforded thioacylated derivatives in high yield <1993T10009, 1994T7445>.

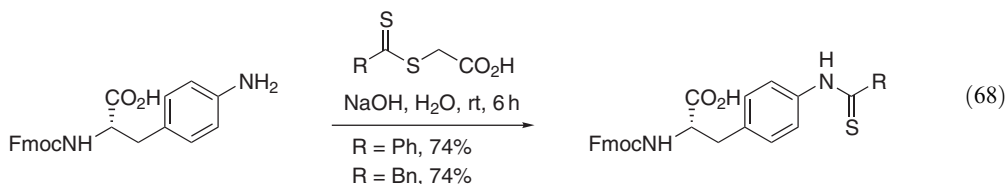


$\text{R}^1\text{R}^2\text{NH} = \text{methylamine, dimethylamine, ethanolamine, glycine}$
 $\text{L-alanine, L-phenylalanine, L-valine, L-methionine, L-proline}$

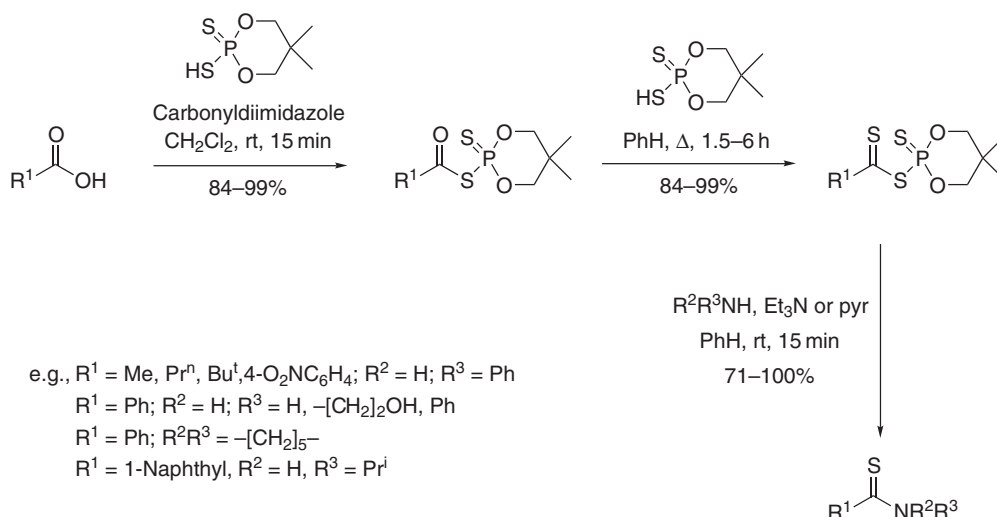




An alternative to the use of a classical alkyl dithioester has been reported; thioacylation of a phenylalanine derivative using either *S*-(thiobenzoyl)thioglycolic acid or *S*-(phenylthioacetyl)thioglycolic acid proceeded in excellent yield with retention of optical purity (Equation (68)) <2000JCS(P1)3227>.

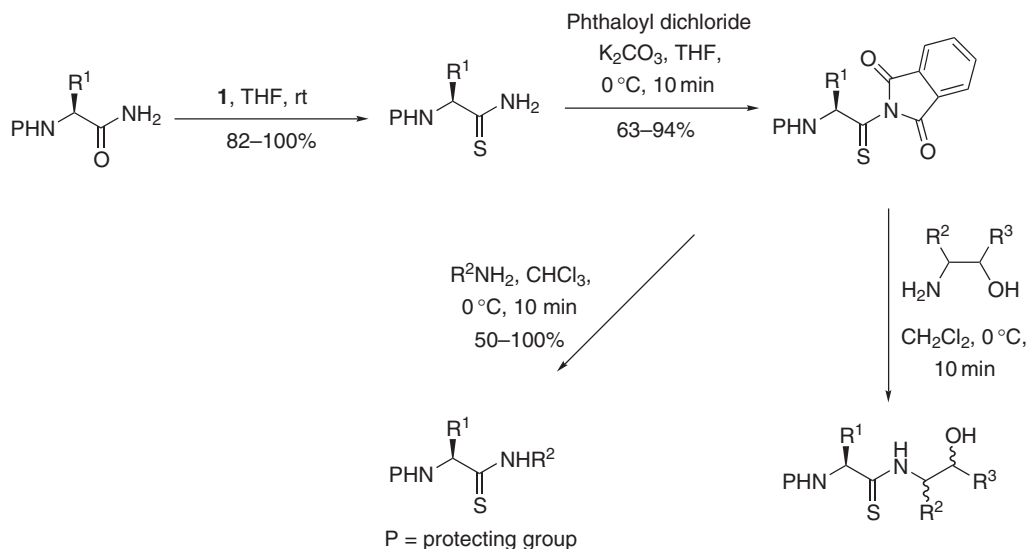


S-Thioacyl dithiophosphates have been shown to be efficient thioacylating agents, reaction proceeding efficiently with ammonia, primary, secondary, and unsaturated amines. *S*-Thioacyl dithiophosphates are formed exclusively when a benzene solution of an *S*-acyl dithiophosphate, derived from a carboxylic acid (Scheme 5), is refluxed with a dithiophosphoric acid and may be isolated or used *in situ* for thioacylation <2000CC2093, 2002JCS(P1)1271>. Due to the low reactivity of these *S*-thioacyl dithiophosphates toward oxygen nucleophiles, this method is applicable to the direct thioacylation of multifunctional nucleophiles containing unprotected hydroxy groups, allowing preparation of both hydroxy thionoamides and thiohydroxamic acids. This method represents a straightforward synthesis of a thioacylating agent from readily available carboxylic acid derivatives.



Scheme 5

N-Thioacylphthalimides are efficient *N*-thioacylating agents, reacting with amine nucleophiles under mild conditions to provide high yields of thionoamides with negligible epimerization during the thioacylation step <1997JOC3808, 1998TL127> (Scheme 6, Table 3). The *N*-thioacylphthalimides themselves are readily obtained in high yield and enantiopurity from the corresponding protected amino acid amides via an efficient two-step thionation activation sequence. In this case, thionation precedes the activation step ensuring that the sulfur is introduced under mild nonracemizing conditions.



Scheme 6

Amino acid thiobenzimidazolones appear to combine acceptable reactivity with stereochemical preservation (Equation (69)) <1993BMCL619, 1993T10489>. They were successfully utilized to prepare monothionated analogs of thymopentin (Arg-Lys-Asp-Val-Tyr) and tuftsin (Thr-Lys-Pro-Arg) <1993T10489>. Use of the thiobenzimidazolone of valine for thioacylation of an unprotected serine side-chain has been demonstrated <1995TL6153>. Fluorobenzimidazolones have also been used as thioacylating agents <1999JMC2046>. α -Amino thionoacids of nitrobenzotriazole were efficiently synthesized and used for thioacylation of amines and amino acids (Equation (70)) <1996JOC9045>. Under similar conditions, thionotriptides were efficiently synthesized

Table 3 Representative examples of endotheiopeptides prepared using *N*-thioacylphthalimides as *N*-thioacylating agents (Scheme 6)

Product	Yield (%)
<i>t</i> -BOC-Pheψ[CS-NH]Ala-NHBn	98
<i>t</i> -BOC-Pheψ[CS-NH]Ser-NHBn	81
<i>t</i> -BOC-Pheψ[CS-NH]Phe-Gly-NH ₂	73
<i>t</i> -BOC-Pheψ[CS-NH]Val-NHBn	69
<i>t</i> -BOC-Leuψ[CS-NH]Gly-NHBn	100
<i>t</i> -BOC-Leuψ[CS-NH]Phe-Gly-NH ₂	79
<i>t</i> -BOC-Leuψ[CS-NH]Val-NH ₂	72
<i>t</i> -BOC-Leuψ[CS-NH]Phe-NHBn	71
<i>t</i> -BOC-Valψ[CS-NH]Phe-NHBn	77
Fmoc-Alaψ[CS-NH]Gly-NHBn	100
Fmoc-Alaψ[CS-NH]Phe-NHBn	68
Fmoc-Alaψ[CS-NH]Phe-Gly-NHBn	55
<i>t</i> -BOC-Ser(Bn)ψ[CS-NH]Gly-NHBn	60
<i>t</i> -BOC-Proψ[CS-NH]Ala-NHBn	50

Source: <1997JOC3808>.

(Equation (71), Table 4) <2002JOC3266>. *N*-Protected amino monothioacids may be reacted with phosphorus-containing coupling reagents (PyBOP: benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate, PyNOP: 6-nitrobenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate, PyFOP: 6-trifluoromethylbenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate and PyAOP: 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate) in the presence of *N,N*-diisopropylethylamine (DIEA) to afford an activated thionoester which may be thioacylated *in situ* with stereochemical retention (Equation (72)) <1991TL7617, 1994JOC1257, 1996S383>. This method has been used both in solution and on a solid phase <1996MI190> to afford endotheiopeptides. The method appears to be quite general and tolerates both Fmoc and *t*-BOC protection; endotheiopeptides containing Gln and pGlu (unavailable by thionation techniques) may also be synthesized (e.g., pGluψ[CSNH]His-Pro-NH₂, Leu-Glnψ[CSNH]pLeu-Lys). A systematic study suggested that PyNOP is the activating reagent of choice <1996MI190>.

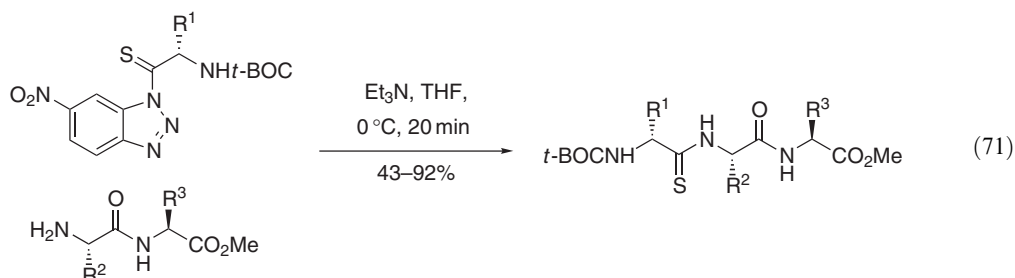
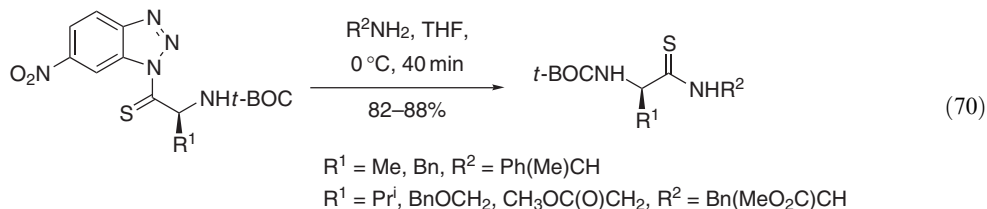
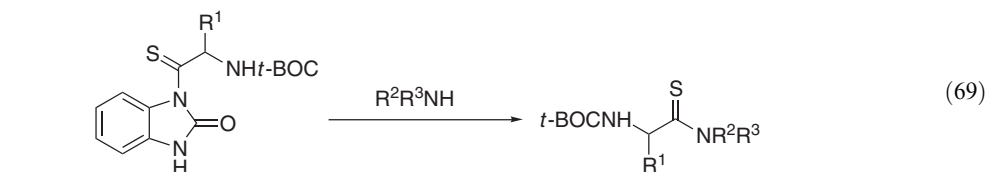
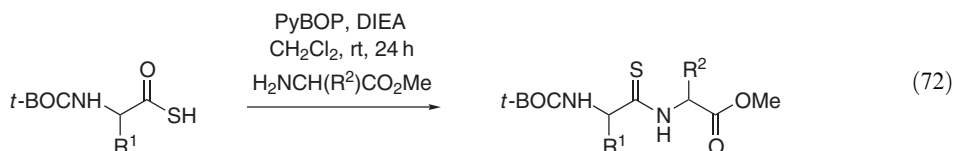
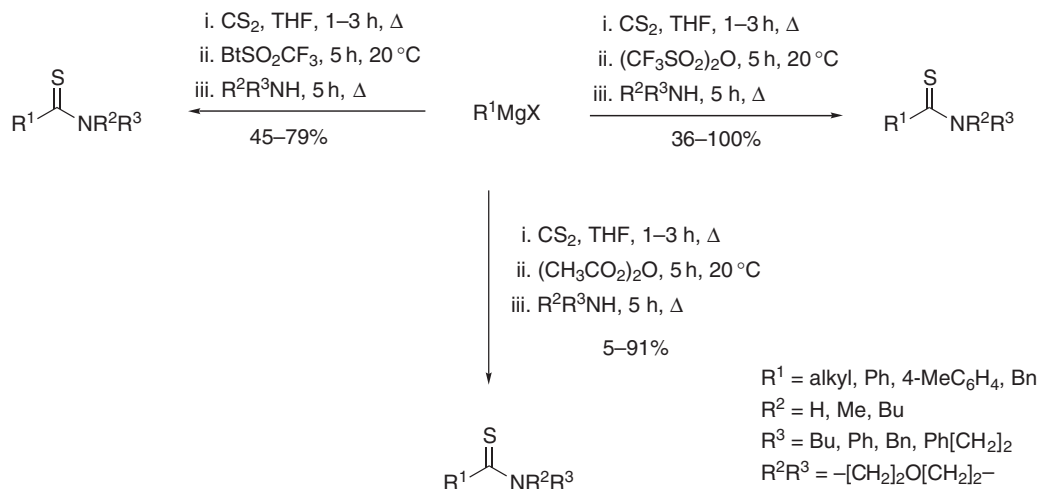
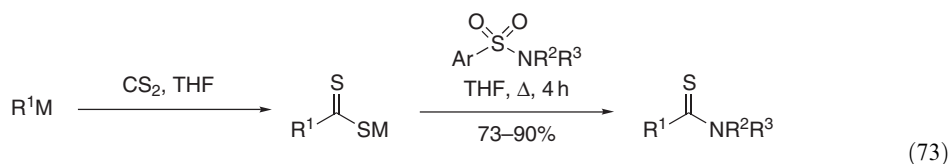


Table 4 Representative examples of endothiotriptides prepared using α -aminothionoacids of nitrobenzotriazole as thioacylating agents (Equation (71))

Product	Yield (%)
<i>t</i> -BOC-Ala ψ [CS-NH]Ala-Phe-OMe	91
<i>t</i> -BOC-Ala ψ [CS-NH]Gly-Phe-OMe	92
<i>t</i> -BOC-Ala ψ [CS-NH]Val-Phe-OMe	88
<i>t</i> -BOC-Ala ψ [CS-NH]Ala-Trp-OMe	73
<i>t</i> -BOC-Phe ψ [CS-NH]Ala-Phe-OMe	90
<i>t</i> -BOC-Phe ψ [CS-NH]Met-Phe-OMe	62
<i>t</i> -BOC-Phe ψ [CS-NH]Ala-Tyr-OMe	48
<i>t</i> -BOC-Val ψ [CS-NH]Val-Phe-OMe	91
<i>t</i> -BOC-Gly ψ [CS-NH]Ala-Phe-OMe	71



The one-pot successive reactions of Grignard reagents with carbon disulfide and amines mediated by 1-trifluoromethylsulfonylbenzotriazole provides an attractive and general route to thionoamides in good-to-moderate yield. The reaction proceeds via an intermediate thioacyloxybenzotriazole, which acts as an efficient thioacylating agent (Scheme 7) <1995SL99, 1995SI1497>. Alternatively, it has been demonstrated that triflic anhydride or acetic anhydride are effective. The reaction tolerates a wide variety of amines and Grignard reagents. Treatment of 2,4-dinitrobenzenesulfonamides with dithioacids (prepared *in situ* from carbon disulfide and an organometallic reagent), and subsequent heating gives thionoamides (Equation (73)) <1998TL1673>.

**Scheme 7**

$\text{R}^1 = \text{Ph}; \text{R}^2 = \text{H}; \text{R}^3 = 4\text{-MeOC}_6\text{H}_4; \text{M} = \text{MgBr}$

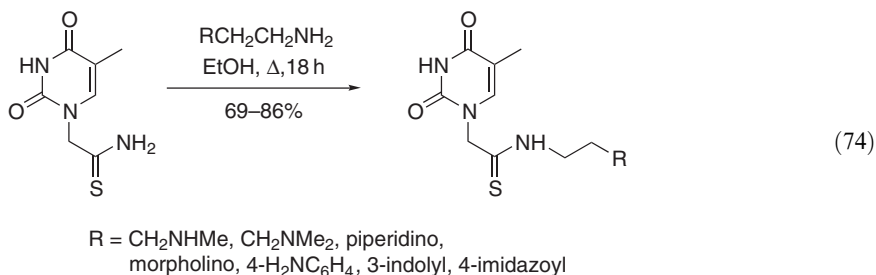
$\text{R}^1 = 4\text{-ClC}_6\text{H}_4; \text{R}^2 = \text{H}; \text{R}^3 = 4\text{MeOC}_6\text{H}_4; \text{M} = \text{MgBr}$

$\text{R}^1 = \text{Pr}^i, \text{CH}_2=\text{CH}; \text{R}^2 = \text{CH}_2\text{CH}_2\text{OMe}; \text{R}^3 = 4\text{-MeOC}_6\text{H}_4; \text{M} = \text{Li}$

$\text{Ar} = 2,4\text{-(O}_2\text{N)}_2\text{C}_6\text{H}_3$

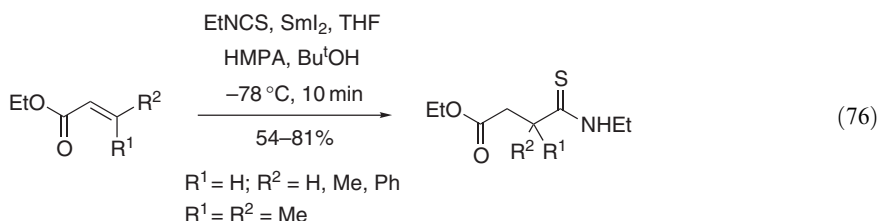
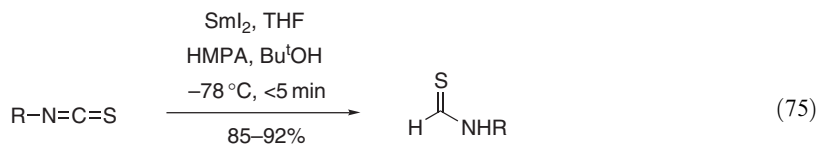
Historically, endothiopeptides have been prepared by first converting a preformed dipeptide into the corresponding thionopeptide with thionating agents followed by incorporation into the peptide sequence with traditional segment coupling <1981TL3635, 1983T3429, 1991HCA1953, 1992T8601>. Limitations of this approach include the lack of selectivity in thionation, and that carboxy-terminus activation of the thionodipeptide unit often leads to epimerization <1992AG(E)1229>. The thioacylation methods described above offer the significant advantage of regioselectivity and, additionally, the step-wise nature potentially makes them suited for application in solid-phase synthesis of endothiopeptides.

Thionoamides themselves can act as thioacylating agents <1995COFGT(5)565>. An impressive example of this was the transamination of a uracil thionoacetamide by a range of primary amines in ethanol at reflux to afford *N*-substituted thionoamides (Equation (74)) <2000T7981>.

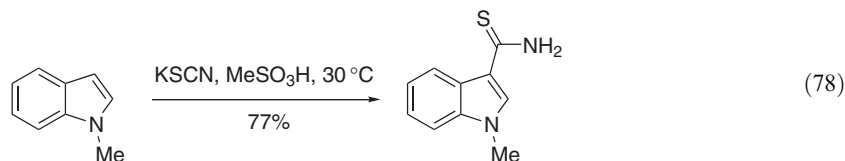
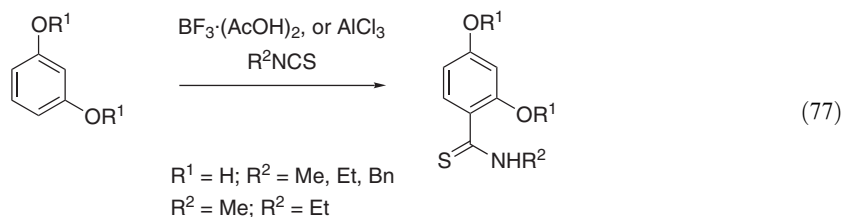


5.14.1.4 Thiocarbamoylation

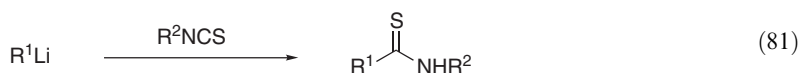
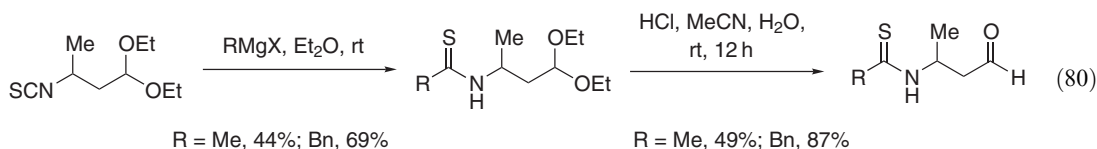
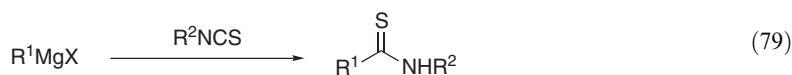
The addition of nucleophilic species to isothiocyanates or their synthetic equivalents has proved to be an efficient approach to thionoamides <1995COFGT(5)565> and continues to be used successfully. The simplest nucleophile, hydride ion, has been reported to add to aromatic and unsaturated isothiocyanates <1995COFGT(5)565>. Isothiocyanates may also be efficiently reduced using samarium iodide and *t*-butanol in the presence of HMPA to give *N*-monosubstituted thionoformamides in excellent yield under mild conditions (Equation (75)) <1996CC1805>. The reaction of α,β -unsaturated esters with isothiocyanates in the presence of samarium iodide, *t*-butanol and HMPA affords thionoamides (Equation (76)) <1998SC4517>. In the absence of a proton source, multicoupling products are observed.



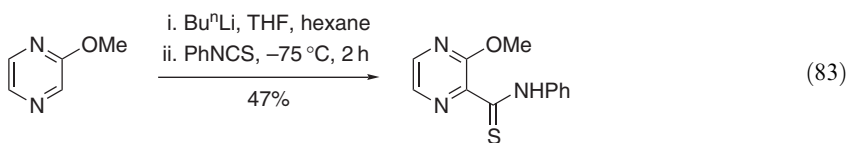
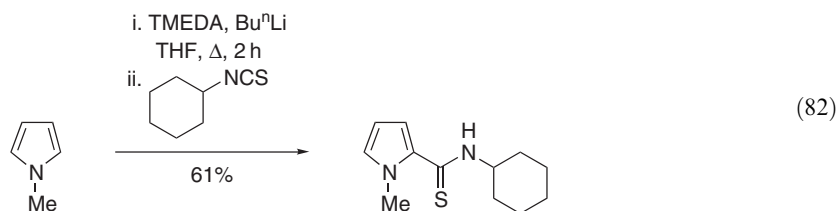
Friedel–Crafts reaction of electron-rich aromatic species with isothiocyanates and a Lewis acid proceeds to yield aromatic thionoamides (e.g., Equation (77)) <1995COFGT(5)565, 1999JHC1033, 2000RJOC1110, 2002EJOC2573, 2002H313>. Reaction with potassium thiocyanate in the presence of methanesulfonic acid is efficient for activated aromatic compounds and π -excessive heteroaromatic compounds (furan decomposed in the acidic reaction conditions) (e.g., Equation (78)) <2002BMCL2317>.

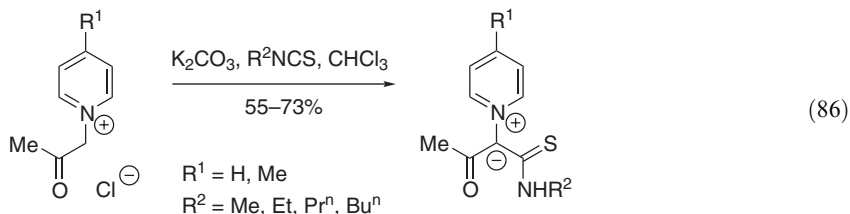
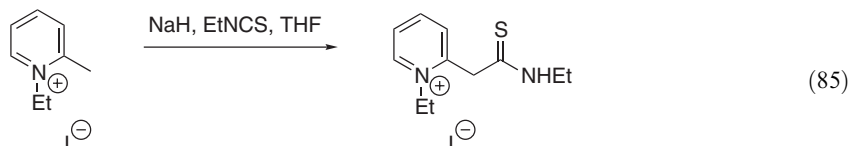
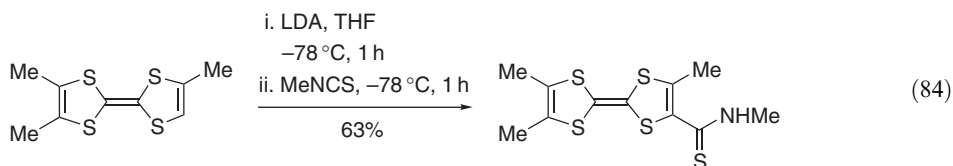


Nucleophilic addition of organometallic compounds to isothiocyanates has been investigated comprehensively [<1995COFGT\(5\)565>](#). Alkyl, aryl, and benzyl Grignard reagents have been shown to add to isothiocyanates to afford the expected thionoamides ([Equation \(79\)](#)). The reaction is equally applicable to the preparation of bis(thionoamide) derivatives [<1998JOC7481>](#). The reaction of 1,1-diethoxy-3-isothiocyanatobutane with Grignard reagents and subsequent hydrolysis of the acetal afforded the novel *N*-4-oxo-2-buthylthionoamides ([Equation \(80\)](#)) [<1997CHE805>](#). Organolithiums similarly react well with isothiocyanates ([Equation \(81\)](#)) [<1995COFGT\(5\)565, 1996SC3167, 1995S1033, 2001T8705>](#).

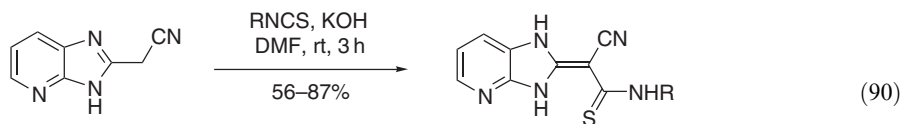
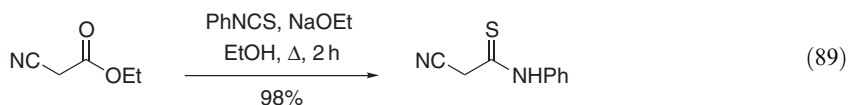
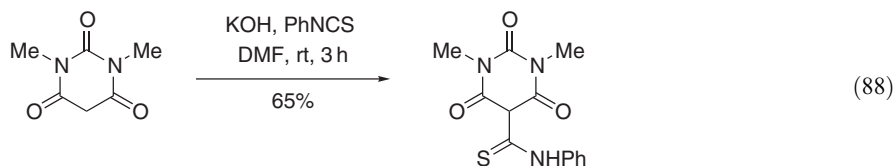
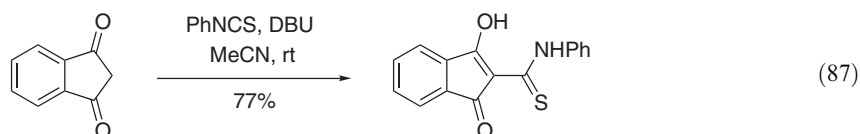


Direct metallation of *N*-methylpyrrole [<2001PJC1853>](#), thiazole [<1986KGS1405>](#), benzothiazole [<1986KGS1405>](#), 1*H*-quinolin-2-one [<1995S1362>](#), pyrazine [<1999H2349>](#), pyridazines [<2002T2743>](#), and tetrathiafulvalenes [<1995S8675, 1998JMAC1541>](#) with lithium bases and quenching with isothiocyanates leads to structurally interesting thionoamides ([Equations \(82\)–\(84\)](#)). Similarly, the reaction of the anion derived from *N*-ethyl-2-methylpyridinium iodide with ethyl isothiocyanate cleanly affords the corresponding thionoamide ([Equation \(85\)](#)) [<1998TL1763>](#). Acetyl[(*N*-alkyl)thiocarbamoyl](1-pyridino)methylides were prepared by reaction of isothiocyanates with the anion derived from 1-acetonylpyridinium chloride ([Equation \(86\)](#)) [<1995BCJ3573>](#). This procedure was also applied to pyrazinium derivatives [<1996JOC4655>](#).

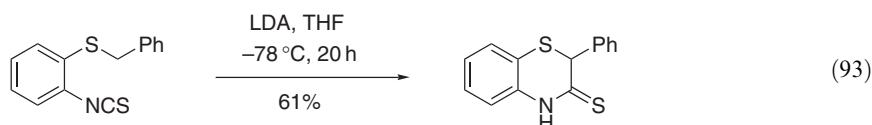
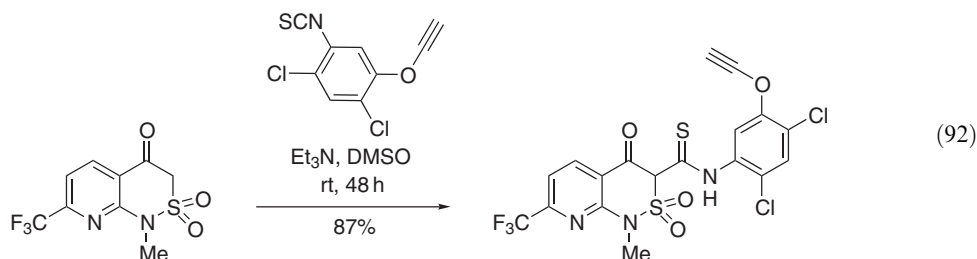
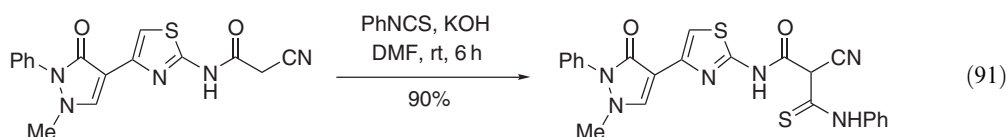




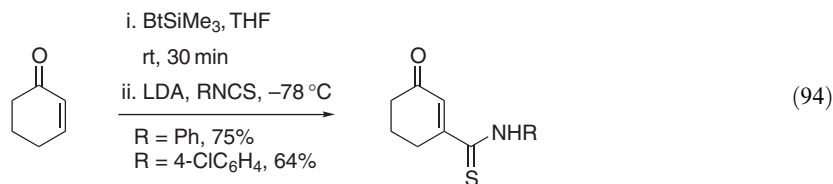
The reaction of anionic and enolic species derived from active methylene compounds with isothiocyanates is a useful synthetic route to thionoamides <1995COFGT(5)565>. Treatment of diethyl malonate with base followed by addition of isothiocyanates yields, after work-up, the expected thionoamides <1999H137, 2000H1171, 2002T9965>. Anions derived from ethyl acetoacetate, acetylacetone <1995MI445>, dimedone <1996MI45, 1995MI445, 2001PJC387>, indan-1,3-dione <1996MI45, 1998PJC439, 2001PJC387>, malononitrile <1995PS(105)213>, ethyl cyanoacetate <1999MI63>, and 1,2-diphenylethanone <1997MI615> all produce thionoamides. Decarboxylation, if possible, is occasionally observed <1999MI63>. Reactions of isothiocyanates with active methylene compounds bearing more diverse functionality have also been described <1996BSF587, 1996JOC1624, 1997JOC6215, 1997PHA346, 1998JHC499, 1998JOC1473, 1998PHA373, 1998MI2300, 1999JCR(S)184, 2000MI383, 2001PHA23, 2001PS(175)129, 2002BMCL2427, 2002HA248, 2002JA2137, 2002JOC8034, 2002PHA800>. Representative examples are given in Equations (87)–(92). Intramolecular thiocarbamoylations have also been demonstrated (Equation (93)) <1995H2263>. Simple ketone enolates also reacted with alkyl and aryl isothiocyanates to generate thionoamides <1995COFGT(5)565>.



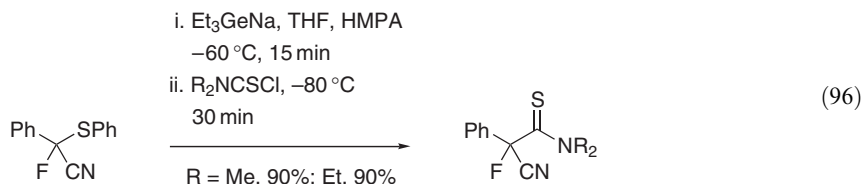
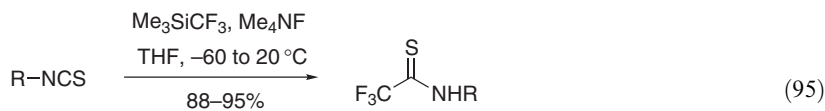
R = Me, C₆H₁₁, Ph, 4-MeC₆H₄, 4-ClC₆H₄, Bn



When the 1,4-adduct of 2-cyclohexenone and 1-trimethylsilylbenzotriazole is treated *in situ* with base, and the generated anion reacted with isothiocyanates, 3-thiocarbamoyl-2-cycloalkenones are formed in a simple one-pot procedure (Equation (94)) <1995TL5491>.

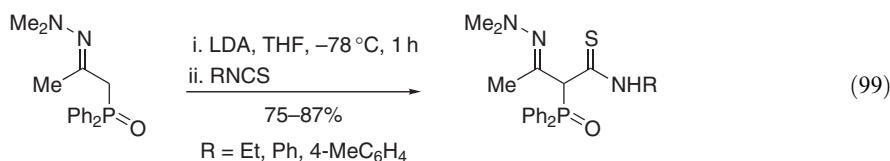
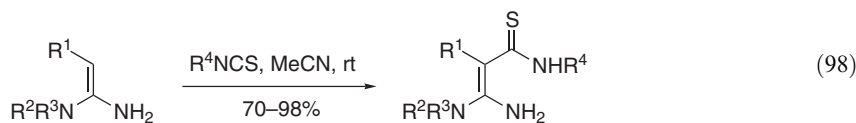
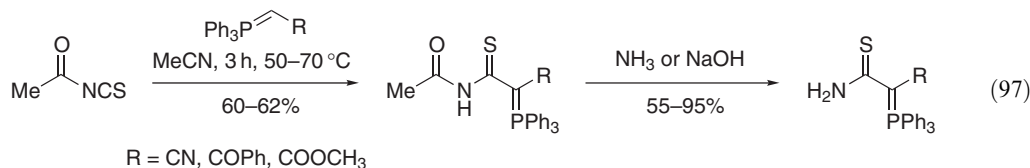


The trifluoromethyl anion generated from trimethyl(trifluoromethyl)silane in the presence of fluoride ions reacts with isothiocyanates under mild conditions to give trifluorothionoacetamides in high yield (Equation (95)) <2001TL8181>. This is highlighted as a simple procedure to access this often difficult-to-synthesize class of compounds <1976ZOR2213>. Reaction of dialkylated thio-carbamoyl chlorides with the α -cyano- α -fluoromethyl anion generated from 2-cyano-2-fluoro-2-phenylacetonitrile and Et_3GeNa efficiently affords cyanofluorinated thionoamides (Equation (96)) <1999S1319>.

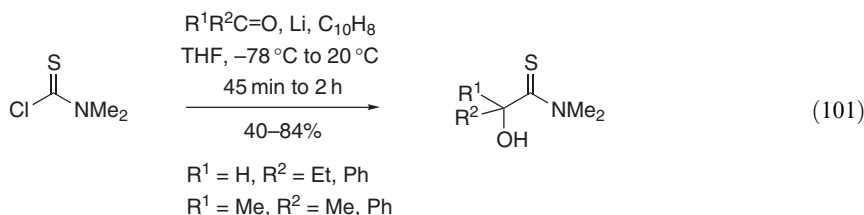
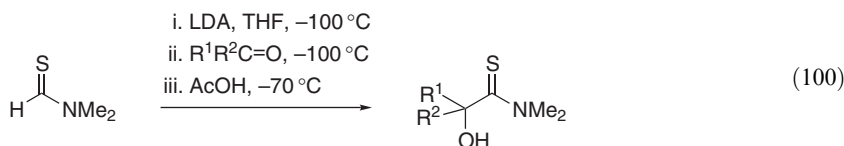


Phosphonium ylides react with isothiocyanates to afford stable thiocarbamoyl-substituted derivatives of phosphonium ylides <1995COFGT(5)565>. Reaction with acetyl isothiocyanate followed by deacetylation with either ammonia or sodium hydroxide afforded the corresponding thionoformamide phosphonium ylides (Equation (97)) <1995RJGC521>. Simple enamines and those bearing electron-withdrawing groups on the double bond reacted easily with isothiocyanates to afford the expected addition products (Equation (98)) <1995COFGT(5)565, 1995MI73, 1995JPR310, 1996SC1187, 1997HCA273, 1999JHC1183, 2003BMC495>. Regioselective addition

of metallated β -hydrazonophosphine oxides to isothiocyanates afforded functionalized thionoamides (Equation (99)) <1996T4123>.



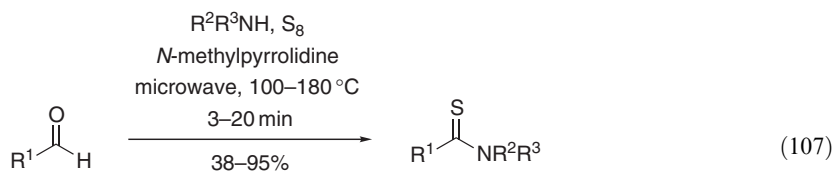
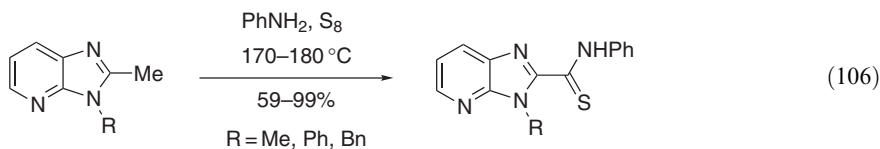
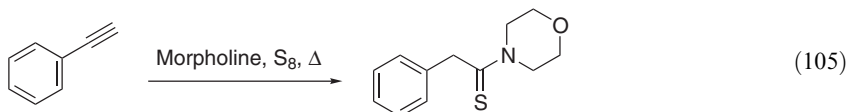
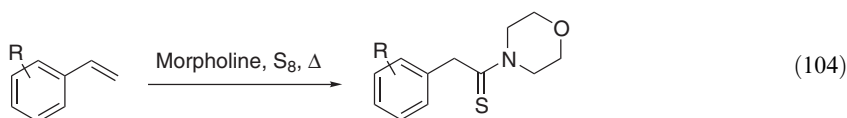
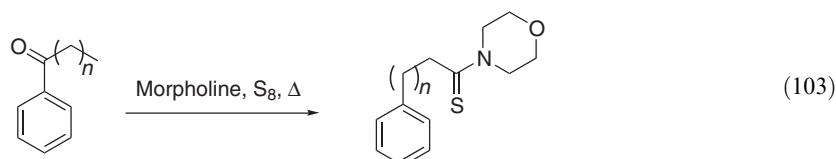
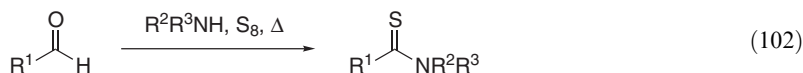
Deprotonation of tertiary thionoformamides has been described, offering a method for nucleophilic thiocarbamylation <1995COFGT(5)565>. In particular, deprotonated tertiary thionoamides added to alkyl halides, acyl halides, aldehydes, and ketones (e.g., Equation (100)) <1973AG(E)1014, 1976CB1309>. A recent alternative for the preparation of α -hydroxythionoamides involves the naphthalene-catalyzed lithiation of thiocarbamoyl chlorides using an excess of lithium powder in the presence of carbonyl compounds (Equation (101)) <1996T13739>. For best results, this process should be performed in the presence of the electrophile (Barbier-type conditions). The analogous reaction using *N,N*-diallylthiocarbamoyl chloride leads only to *N,N*-diallylthioformamide.



5.14.1.5 Aminosulfuration/Sulfuration

Aminosulfuration of a range of aromatic, benzylic, alkenic, and alkynic moieties represents a useful approach to the preparation of thionoamides <1995COFGT(5)565>. The three-component Kindler coupling of an aldehyde, elemental sulfur, and an amine allows for an easy introduction of diversity into the thionoamide backbone by simple variation of both the aldehyde and the amine component in the condensation step (Equation (102)). The related Willgerodt–Kindler reaction uses straight or branched-chain aryl alkyl ketones to give thionoamides with the same number of carbon atoms; however, an interesting facet of this reaction is that the thiocarbonyl group of the product is at the end of the alkyl chain (Equation (103)), with reaction yields often decreasing on increasing alkyl chain length. Both reactions generally afford good yields of the product thionoamides upon heating of the neat reagents or using suitable high boiling solvents, although long reaction times are often necessary <1996BSB17, 1999T1187, 2000EJOC3305, 2000OL2269, 2002MI653>. The protocols are, however, hampered

as volatile reagents cannot be realistically used without an autoclave. The reaction has also been successfully applied to various aromatic (Equation (104)) and heteroaromatic alkenes, phenylacetylene (Equation (105)) and, recently, imidazopyridine derivatives (Equation (106)) <1996RJOC586>. *para*-Toluenesulfonic acid has been used as an additive in the thermal reaction <1998JMC63, 2003SC59>. The use of microwave technology reduces the long reaction times <1999TL7549, 2000JCR(S)228, 2001SC53, 2001SC317, 2002PS(177)1189> and the use of microwaves combined with an autoclave allows for volatile reagents to be utilized successfully (Equation (107)) <2003MI145>.

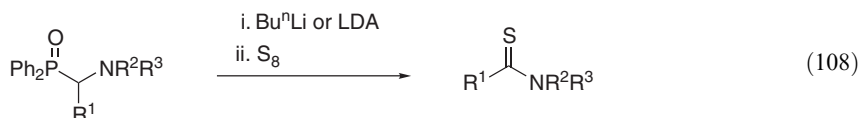


e.g., $\text{R}^1 = n\text{-C}_5\text{H}_{11}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Pr}^n$

$\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, Bn

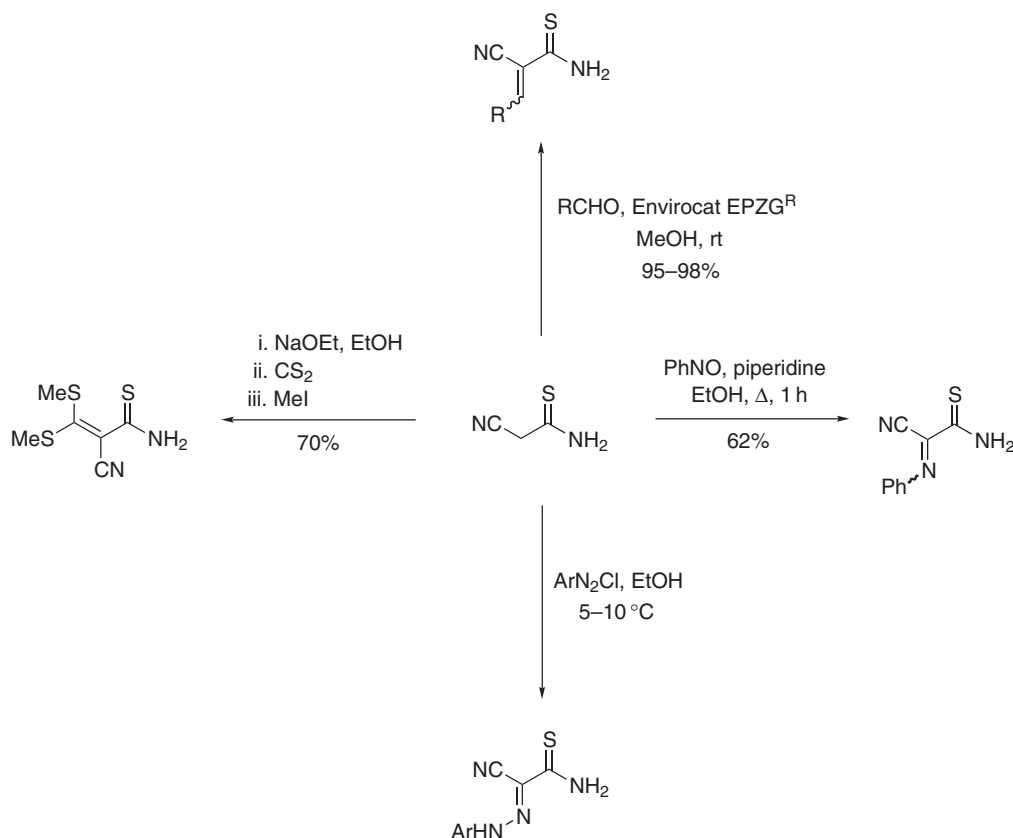
$\text{R}^1 = \text{Ph}$, Bn, 3-indolyl; $\text{R}^2\text{R}^3 = -[\text{CH}_2]_5-$

Stabilized phosphorus ylides and phosphonate anions both react with sulfur and secondary amines to produce tertiary thionoamides <1995COFGT(5)565>. Tertiary thionoamides have also been synthesized in good yields by simple reaction of the lithio-anions of α -amino-substituted diphenylphosphine oxides with 2 equiv. of elemental sulfur (Equation (108)) <1994RTC499, 1996PS(111)823, 1997CB49>.



5.14.1.6 Manipulation of an Existing Thionoamide

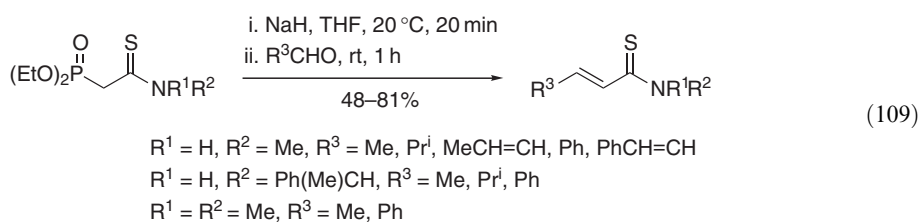
α -Cyanothionoacetamide is a versatile thionoamide derivative and has been utilized in a number of synthetic transformations (e.g., Scheme 8). α -Cyanothionoacetamide condenses with carbonyl-containing compounds in the presence of a variety of bases; examples include triethylamine <1995JHC819,

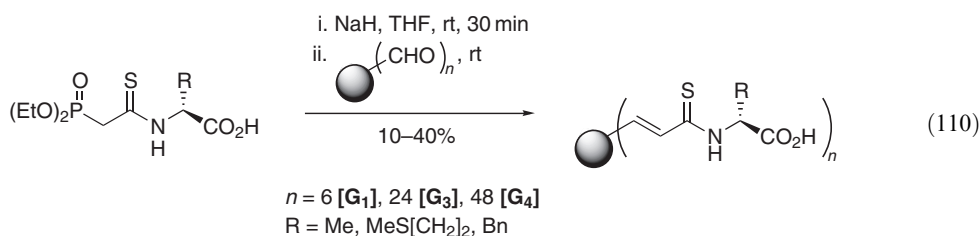


Scheme 8

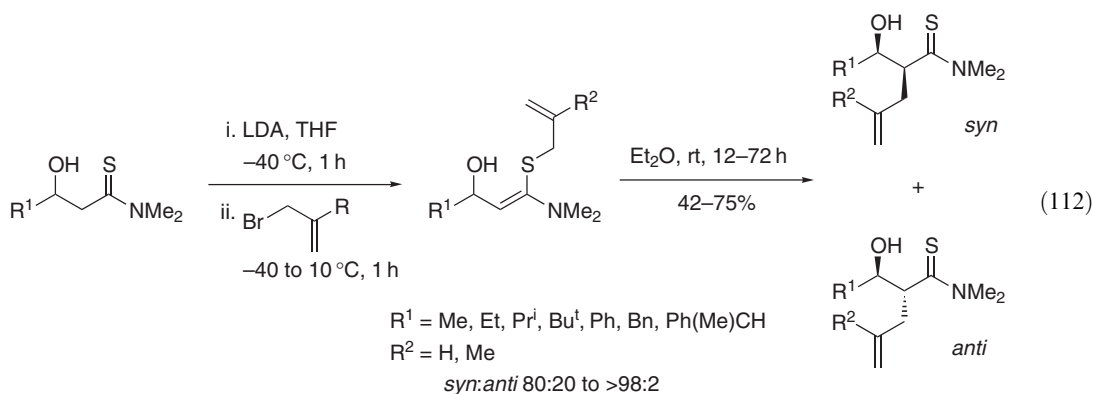
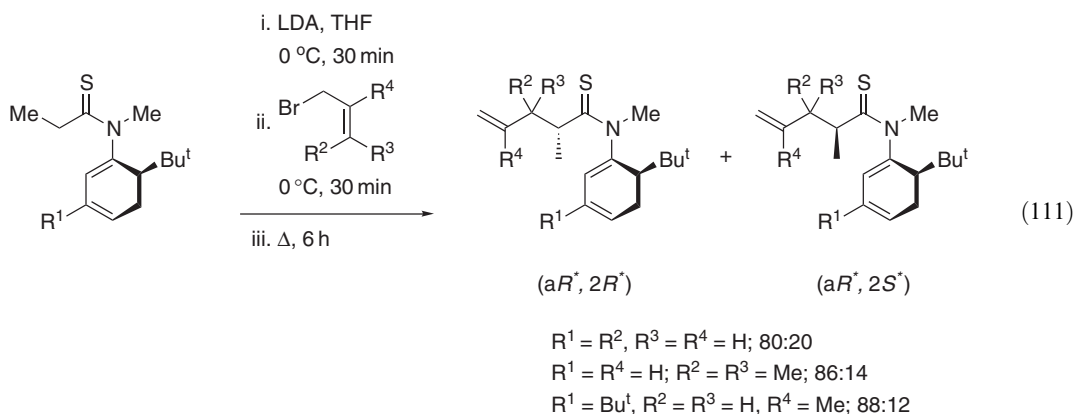
2002PS(177)115>, piperidine <1994JIC631, 1999JCR(S)696, 1999PHA106, 2000PS(167)289, 2000JMC1550>, *N*-methylmorpholine <1998CHE188>, β -alanine <1996JMC2170>, sodium methoxide <1996CPB2070>, and a piperazine bound to Merrifield resin <1999TL7031>. The condensation of α -cyanothioacetamide with aromatic aldehydes has also been successful using a novel heterogeneous acid catalyst, Envirocat EPZG^R <1997SC1153>. The reaction occurs either in methanol or in conditions with no solvent. The catalyst may be recovered by filtration and reactivated by azeotropic distillation. α -Cyanothioacetamide has been shown to react with nitroso compounds <1999JCS(P1)111> and with diazonium salts <1998JCR(S)672, 2000PS(167)161, 2003PS(178)1747>. Acetothionoamides have been used in an analogous reaction <1998JCS(P1)2133>. α -Cyanothioacetamide reacted with carbon disulfide in the presence of sodium ethoxide, followed by alkylation with methyl iodide to give a novel ketene dithioacetate <1997JCS(P1)3285>.

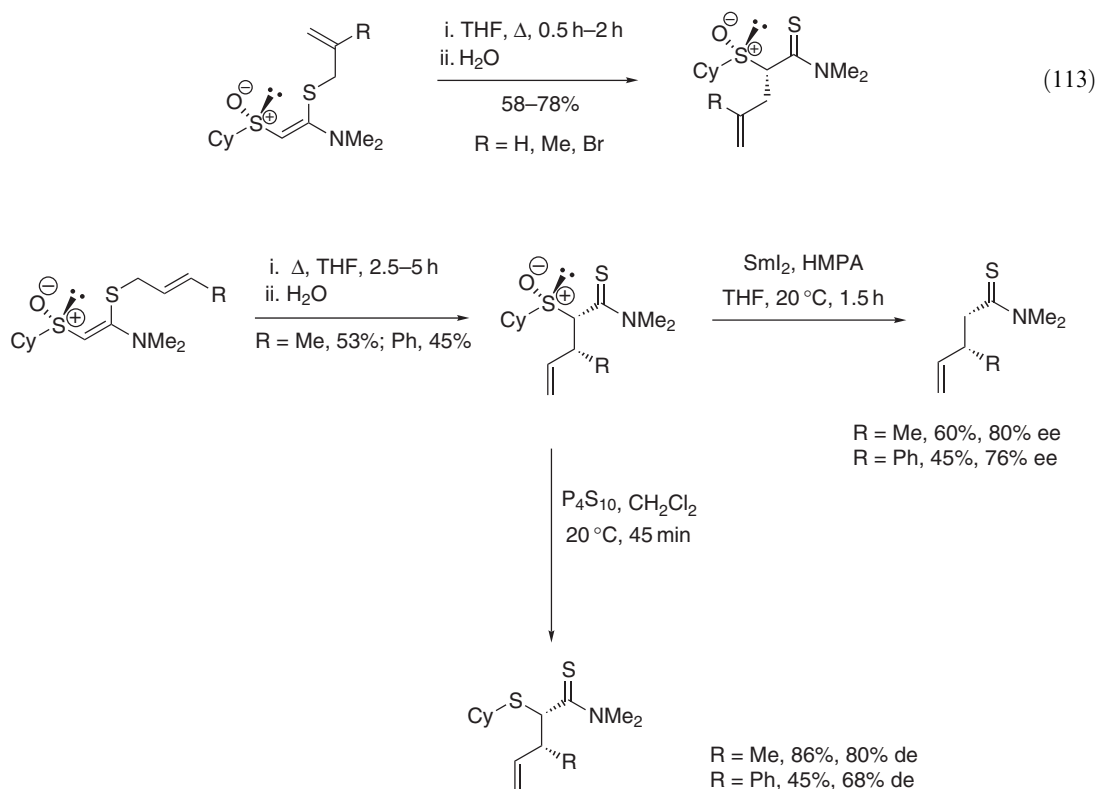
Phosphorylthionoamides have been prepared and their subsequent use as Horner–Emmons reagents was shown to be a general method for the preparation of α,β -unsaturated thionoamides (Equation (109)) <1994PS(89)119, 1995S1393, 2000S1143>. Notable examples include reaction with a protected D-mannofuranose in which C-anomeric olefination is followed by intramolecular cyclization to afford a separable mixture of α - and β -epimers of glycosyl ethanethionoamides <1998TL2755> and with first, third, and fourth generation aldehyde-terminated dendrimers (Equation (110)) <1997S1199>.





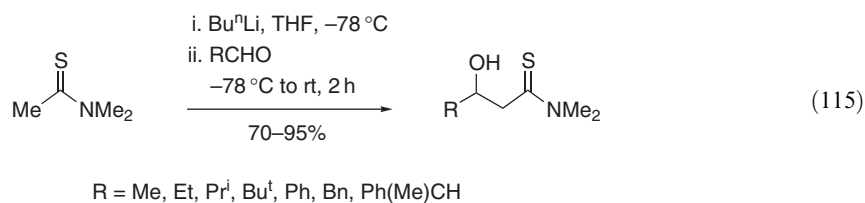
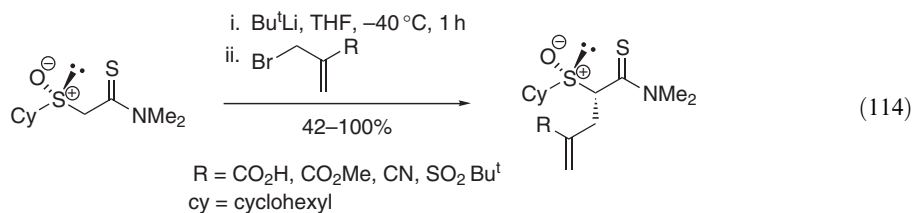
Deprotonation of thionoamides selectively leads to enethiolates. These intermediates exhibit soft character (as compared to enolates) and can react with alkyl halides by specific *S*-alkylation. Using this approach to prepare *S*-allylic ketene aminothioacetals, *in situ* thio-Claisen rearrangement to afford γ,δ -unsaturated thionoamides has been observed. Atropisomeric thionoamides were deprotonated with LDA and reacted with allyl halides to furnish *S*-allyl ketene aminothioacetals. Formation of these intermediates required elevated temperature and as a result they were not detected and underwent *in situ* asymmetric thio-Claisen rearrangement with good diastereoselectivity (Equation (111)) <2002CEJ632>. Similar reaction of β -hydroxythionoamides with LDA and allyl halides gave *S*-allylic ketene aminothioacetals, which rearranged slowly into γ,δ -unsaturated thionoamides; the *syn*-diastereoisomer was the major reaction product and the diastereomeric excess increased with steric hindrance (*syn/anti* ratio, 80:20 to >98:2) (Equation (112)) <1997T17253>. Ketene aminothioacetals bearing an enantiopure vinylic cyclohexylsulfinyl substituent have been isolated and subsequently shown to undergo asymmetric thio-Claisen rearrangement to afford α -sulfinyl- γ,δ -unsaturated thionoamides with excellent stereocontrol (Equation (113), Scheme 9, cy = cyclohexyl) <2001JOC7841>; a model was proposed to explain the stereochemical course of the reaction. Subsequent modification of the cyclohexylsulfinyl chiral auxiliary with either phosphorus pentasulfide or samarium iodide afforded novel thionoamides, without alteration of diastereopurity. Similar thio-Claisen rearrangement has also been used with chiral nonracemic bicyclic thiolactams <1994JA2633> and subsequently utilized to prepare a key intermediate in the asymmetric synthesis of (–)trichodiene <1998JA5453>.

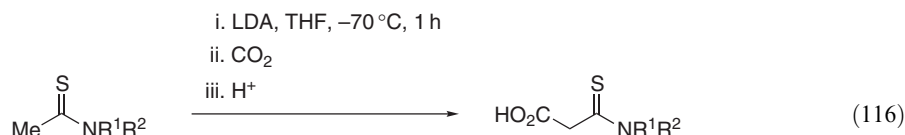




Scheme 9

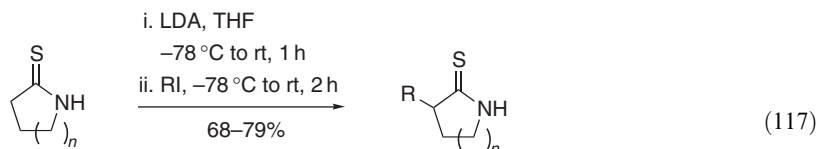
The alkylation of the lithium enethiolate of enantiopure α -cyclohexylsulfenylthionoacetamide with allyl bromides possessing an electron-withdrawing group occurred at the carbon center with modest-to-excellent 1,2-asymmetric induction (Equation (114)) <2002JOC6852>. Aldol reactions with thionoamides have been described by several groups and the diastereoselectivity and enantioselectivity studied <1995COFGT(5)565>. β -Hydroxy-*N,N*-dimethylthionoamides are readily prepared by reaction of *N,N*-dimethylthionoamide and various aldehydes (Equation (115)) <1997T17253>. Carboxylation of thionoacetamides occurred with LDA followed by quenching with carbon dioxide, although in low yield (Equation (116)) <2000SC565>. Alkylation α to the thiocarbonyl of thionolactams has been achieved using 1 equiv. of LDA and alkyl iodides as electrophiles (Equation (117)) <2000JOC2684>.





$\text{R}^1 = \text{Me}, \text{R}^2 = 2\text{-thienyl}, 38\%$

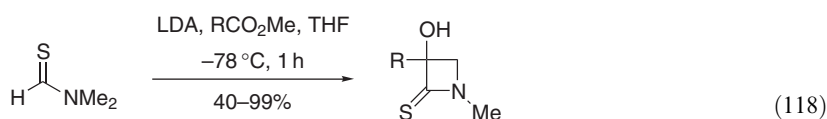
$\text{R}^1 = \text{Bu}^t, \text{R}^2 = \text{Ph}, 24\%$



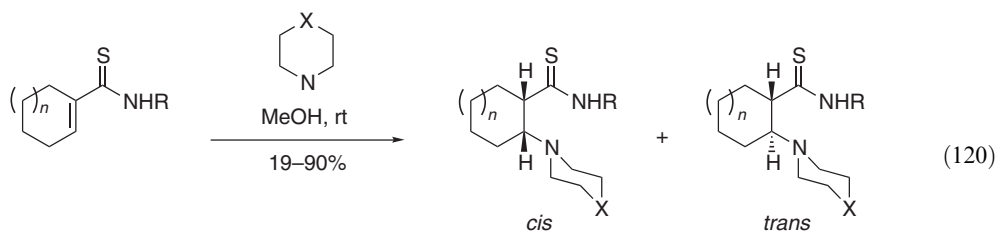
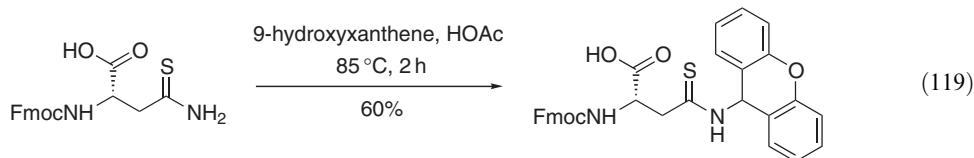
$\text{R} = \text{Ph}(\text{CH}_2)_2, n = 2$

$\text{R} = 3,4\text{-(MeO)}_2\text{C}_6\text{H}_2(\text{CH}_2)_2, n = 1, 2$

LDA-promoted condensation of *N,N*-dimethylthionoformamide with an ester afforded acylthionoamides, which cyclized in the presence of LDA to give β -thionolactams in good yield (Equation (118)). A mechanistic speculation was given <1995JA5859>. Reaction of primary (or secondary) thionoamides with a variety of agents to produce secondary (or tertiary) thionoamides is well described in the literature <1995COFGT(5)565>. The xanthen-9-yl moiety was successfully introduced by heating a primary thionamide with 9-hydroxyxanthene in the presence of acetic acid. This compound was successfully incorporated into a polypeptide using conventional Fmoc solid-phase coupling strategies (Equation (119)) <2000JCS(P1)3227>. Treatment of primary or secondary thionoamides with a base followed by the addition of a Michael acceptor bearing a β -leaving group allows the synthesis of *N*-alkenyl thionoamides <1995COFGT(5)565, 2001PS(170)75>. Heterocyclic and aliphatic amines add to acyclic and cyclic α,β -unsaturated thionoamides yielding β -amino-functionalized derivatives. For chiral 6-substituted α,β -unsaturated- δ -thionolactams diastereoselective addition was observed <1997JHC643>. In the case of cyclic acceptors, the formation of both kinetically (*cis*) and thermodynamically controlled (*trans*) products was observed, allowing tailoring of the reaction products (Equation (120)) <2001T8705>.



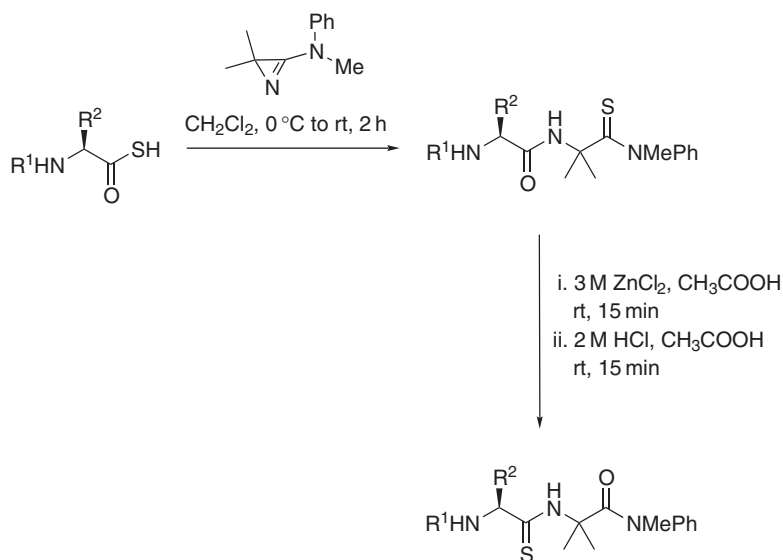
$\text{R} = \text{Pr}^i, \text{Bu}^t, \text{Me}(\text{MeO})_2\text{C}, \text{Ph}, 4\text{-MeC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 4\text{-F}_3\text{CC}_6\text{H}_4$



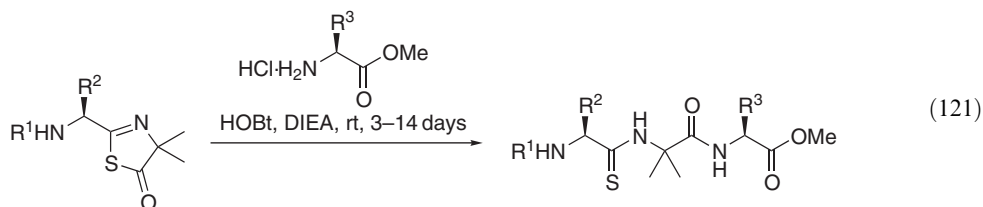
$n = 0, 1; \text{X} = \text{CH}_2, \text{O}; \text{R} = \text{Ph}, \text{Bn}$
cis:trans, 10:90 to 0:100

5.14.1.7 Miscellaneous Methods

Reaction of an *N*-protected α -amino thioacid with 2,2-dimethyl-3-(*N,N*-disubstituted)-2*H*-azirine yields α -alkylated endothiopeptides (Scheme 10), which are often difficult to synthesize by other methods. Under the conditions of “azirine/oxazolone” hydrolysis (3M HCl, THF, H₂O) <1991AG(E)238, 1996HCA527, 1996HCA1903>, rearrangement occurred in which the *C*-terminal thionoamide group shifted to the penultimate amino acid fragment <1998T8721, 1999HCA888, 1999HCA1899, 1999T5359, 2002HCA990>. In contrast to the corresponding dipeptide amides, this method led to extensive epimerization. However, using zinc chloride and hydrochloric acid in acetic acid, conditions were established by which this transformation could be achieved without epimerization. It was demonstrated that isomerization occurred via an intermediate 1,3-oxazole-5(4*H*)-thione, which itself undergoes spontaneous rearrangement to a 1,3-thiazole-5(4*H*)-one via spirocyclic intermediates <2001HCA786>. The acid-catalyzed conversion of endothiopeptides into a 1,3-thiazol-5(4*H*)-one and direct coupling with a *C*-protected α -amino acid using 1-hydroxybenzotriazole/*N,N*-diisopropylethylamine (DIEA) gave endothio-tripeptides in high yields without epimerization (Equation (121), Table 5). Using this approach, longer endothiopeptides could be assembled readily, with the thiocarbonyl next to a bulky Aib residue; this has been shown by the synthesis of the decaendothiopeptide *t*-BOC-Trp-Ile-Ala-Aib-Ile-Val ψ [CSNH]Aib-Leu-Aib-Pro-OMe, a zervamicin IIA analog <1998T8721>.



Scheme 10



(121)

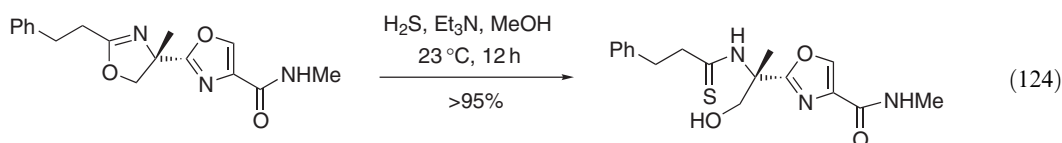
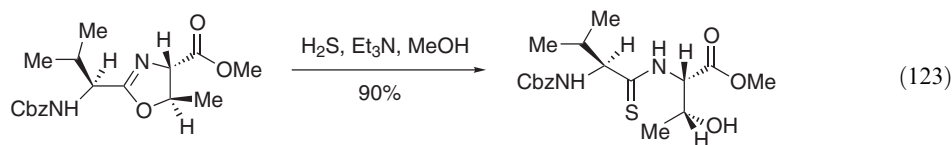
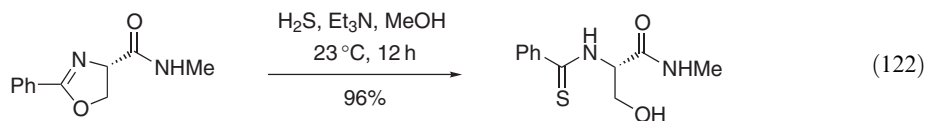
Ring opening of oxazolines occurs predominantly at *C*(2) under moderately basic or acidic conditions <1948JCS1919>. Thiolysis of oxazolines with hydrogen sulfide under slightly basic conditions in the presence of triethylamine affords thionoamides regioselectively and offers a synthetic alternative to the thionation of peptides for regiospecific preparation of the ψ [C(S)NH] peptide bond isosteres (Equations (122)–(124)) <1995TL6395, 1995JOC7224, 1996JA12358, 1997SL1, 2001TL2573, 2003T2713, 2000JA12041>. The presence of triethylamine is crucial, as it buffers the reaction medium; under more acidic conditions the yields of thionoamides drop significantly. Alternatively, DBU has been used as base <1997JOC1896>. Steric hindrance at the *C*(2)-exocyclic position of the oxazoline, as well as at *C*(4) and *C*(5) is tolerated to a high extent, and a wide range of functional groups are compatible with the reaction conditions. Illustrating the versatility of this method, total

Table 5 Representative examples of endotheopeptides prepared using azirine/oxazolone methodology (Equation (121))

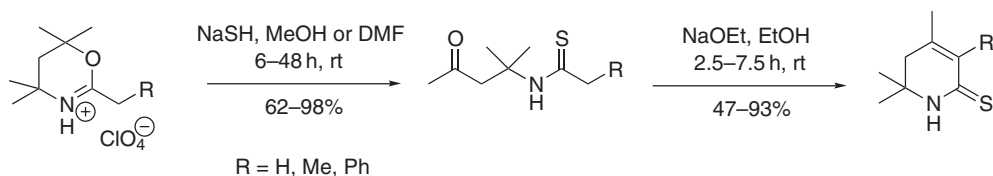
Product	Yield (%)
Z-Phe-Val ψ [CSNH]Aib-N(Me)Ph	91
N-Bn-N-t-BOC-Gly ψ [CSNH]Aib-N(Me)Ph	81
N-Me-N-t-BOC-Ala ψ [CSNH]Aib-N(Me)Ph	96
Z-Ile ψ [CS-NH]Aib-Gly-OMe	89
Z-Phe ψ [CS-NH]Aib-Ala-OEt	72
Fmoc-Ile ψ [CS-NH]Aib-Gly-OMe	92
Fmoc-Val ψ [CS-NH]Aib-Leu-OMe	65

Source: <1997JOC3808>.

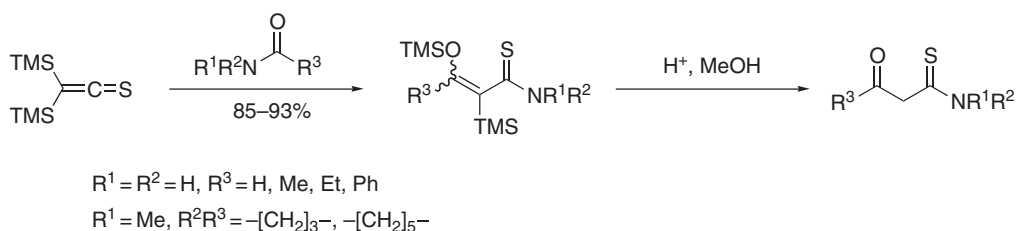
syntheses of (–)-thiangazole and lissoclinamide have incorporated the conversion of an oxazole into a thionoamide and subsequent ring closure to a thiazole as a pivotal step.



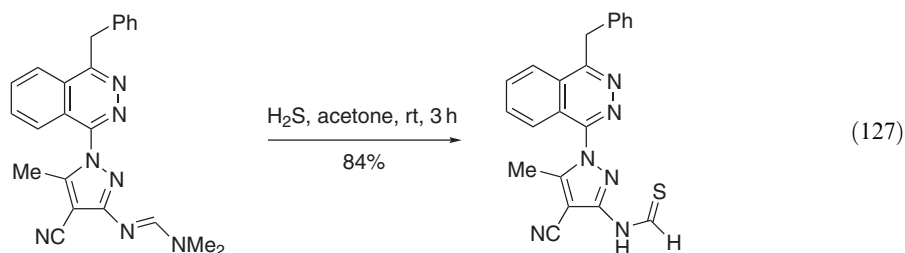
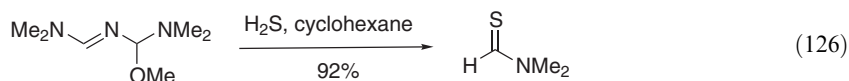
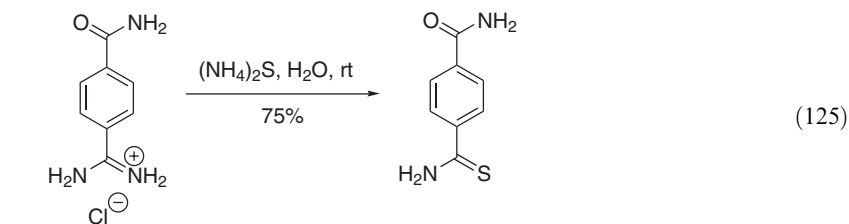
Reaction of 5,6-dihydro-4*H*-oxazinium salts with sodium hydrogen sulfide in methanol or DMF affords *N*-3-oxoalkylthionoamides in high yield (Scheme 11) <1996TL5203>; cyclization of the products in the presence of sodium ethoxide gives 5,6-dihydropyridine-2(1*H*)-thiones <1996TL5203>.

**Scheme 11**

N,N-Disubstituted alkanamides react cleanly, either at room temperature or elevated temperatures, with bis(trimethylsilyl)thioetene by an initial [2 + 2]-addition to form *N,N*-disubstituted 2-trimethylsilyl-3-trimethylsilyloxyalk-2-enethionoamides. These products were readily desilylated upon acid methanolysis to give *N,N*-disubstituted 3-oxothionoamides (Scheme 12) <1996CC1621>.

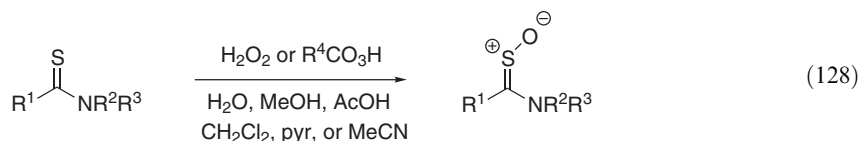
**Scheme 12**

Amidines react with ammonium sulfide to afford thionoamides (Equation (125)) <2000T7981>. Treatment of *N'*-(dimethylaminomethoxymethyl)-*N,N*-dimethylformamidine with hydrogen sulfide gives an excellent yield of *N,N*-dimethylthionoformamide (Equation (126)) <2000JPR682>. *N,N*-Dimethylaminomethyleneamino derivatives react smoothly with hydrogen sulfide in acetone in high yield to give primary thionoamides (Equation (127)) <1996PHA540>.



5.14.2 THIONOAMIDE S-OXIDES AND S,S-DIOXIDES

A wide variety of thionoamides may be converted into their corresponding thionoamide *S*-oxides by oxidation with either hydrogen peroxide or a peracid. There are some indications that the biotransformation of thionoamides involves sulfur oxidation <1984MI41> and thionoamide *S*-oxides have been observed as excretion products after administration of thionoamides <1982JOC4645>. Examples of the conversion of primary, secondary, tertiary, aromatic, benzylic, and heteroaromatic thionoamides are all documented (Equation (128)) <1995COFGT(5)565, 1995BSF67, 1999MI115>. An alternative oxidative method involves the treatment of imino-methyl disulfides with perbenzoic acid affording secondary thionoamide *S*-oxides <1969LA(727)50>. Conversion of secondary thionoamide *S*-oxides into *N*-methylated tertiary thionoamide *S*-oxides with diazomethane has been reported <1962LA(660)60>. To date there remains no report of an isolated thionoamide *S,S*-dioxide, although their intermediacy has been suggested in a number of reaction mechanisms <1995COFGT(5)565>.

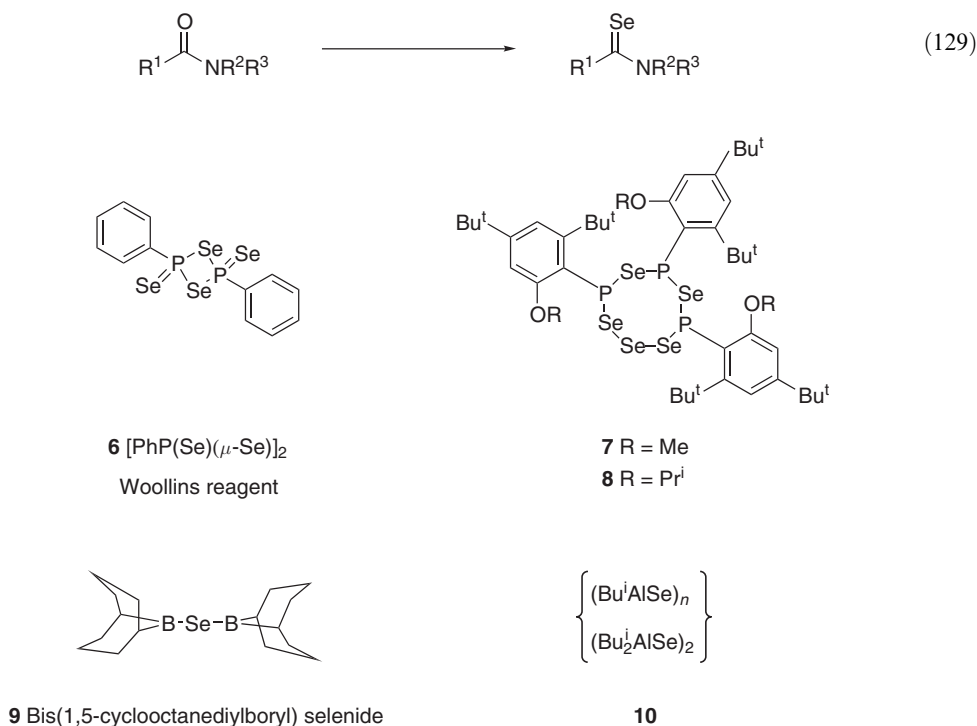


5.14.3 SELENOAMIDES

Although selenoamides were first reported over a century ago <1874CB1273>, their application has been greatly restricted due to the difficulties encountered in their preparation. In contrast to the homologous thionoamides, the synthesis of selenoamides is a synthetic challenge due to the lack of suitable, readily commercially available, and easy to handle selenating agents. Methods used for the preparation of selenoamides do, however, parallel those available for thionoamides <B-1991MI476, 2000TCC179>. Primary, secondary, and tertiary selenoamides are all available from the treatment of the corresponding carboxamide with phosphorus pentaselenide in a refluxing solvent such as benzene, xylene, or pyridine <1995COFGT(5)565>. Yields, however, are typically poor when compared to reactions with phosphorus pentasulfide, although it has been demonstrated that yields may be improved by the addition of barium carbonate <1976IJS519, 1999TA4123>.

5.14.3.1 Selenoamides from Carboxamides

Alongside the use of phosphorus pentaselenide, a number of new selenating agents **6–10** for the conversion of amides into selenoamides have been developed. Compound **6** <1988CC741, 1993PS(75)257, 1994PS(93)185, 2001TL5949, 2003TL6911> is a selenium analog of Lawesson's reagent **1** which provides a general and straightforward route to secondary and tertiary selenoamides <2001TL5949, 2003TL6911> (Equation (129), Table 6). It has been demonstrated that all four selenium atoms of **6** are transferred <2003TL6911> making it more effective in its selenium transfer ability than Lawesson's reagent in its ability to transfer sulfur (using Lawesson's reagent, only half the sulfur atoms are used to generate the thionoamide). Compound **6** is readily prepared by reaction of (PhP)₅ with 10 equiv. of gray selenium <2001MI1269>. Other heterocycles available from (PhP)₅ by treatment with different stoichiometries of selenium (namely, (PhP)₄Se, (PhP)₃Se₂, and (PhP)₃Se₃) have also been demonstrated to exhibit some selenation capability using *N,N*-dimethylbenzamide as substrate <2001TL5949>. Two new types of selenoxo phospholanes **7** <1995CL199> and **8** <1998CL17> have been prepared and shown to react with carboxamides to afford the corresponding selenoamides. The isolated yields using **7** were better than those using **8** and it is suggested that this is related to steric hindrance of the isopropoxy group compared to the methoxy group. Treatment of carboxamides with bis(1,5-cyclooctanediylboryl) selenide **9**, prepared *in situ* from 9-BBN and elemental selenium, afforded selenoamides in modest yields <1992CL1843, 1997BCJ197>. A novel Al–Se reagent **10** was prepared as a mixture of (BuⁱAlSe)₂ and (BuⁱAlSe)_{*n*}, along with small amounts of C–Se–Al type compounds when a solution of Buⁱ₂AlH was heated with powdered selenium. Owing to the instability, toxicity, and unpleasant odor of these reagents, they were neither purified nor fully characterized but used directly in the conversion of carboxamides into selenoamides in a one-pot procedure <1998PS(136-138)525, 1998JCS(P1)647>.



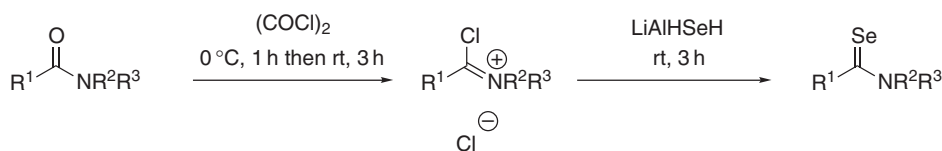
Procedures for the preparation of aromatic selenoamides via the imidoyl or iminium chloride were reported to be superior to the treatment of the carboxamide with phosphorus pentaselenide <1976IJS519>. Treatment of *N,N*-dimethylbenzamide with phosgene and *in situ* reaction with sodium hydrogen selenide, prepared by reaction of selenium with NaBH₄ in ethanol, afforded *N,N*-dimethylselenobenzamide in high yield <1996TL11163>. Previous preparations of this compound proceeded in only low-to-moderate yields <1966ACS597, 1985BCJ1448, 1979MI567>. *N,N*-Dialkylamides were similarly chlorinated with oxalyl chloride to afford imidoyl chloride

Table 6 Selected examples for the conversion of carboxamides into selenoamides (Equation (129))^a

<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	Yield (%) ^b	Method	References
H	Me	Me	82	A	<2003TL6911>
H	Me	Me	39	C	<1997BCJ197>
H	Me	Me	59	D	<1998JCS(P1)647>
H	Et	Et	77	A	<2003TL6911>
H	Pr ⁱ	Pr ⁱ	75	A	<2003TL6911>
H	Pr ⁱ	Pr ⁱ	16	C	<1997BCJ197>
H	Me	Ph	85	A	<2003TL6911>
H	Me	Ph	64	D	<1998JCS(P1)647>
H	–[CH ₂] ₅ –		65	D	<1998JCS(P1)647>
H	–[CH ₂] ₂ O[CH ₂] ₂ –		69	D	<1998JCS(P1)647>
H	–[CH ₂] ₂ NMe[CH ₂] ₂ –		64	D	<1998JCS(P1)647>
H	Ph	Ph	59	A	<2003TL6911>
H	Ph	Ph	60	D	<1998JCS(P1)647>
Me	Me	Me	66	A	<2003TL6911>
Me	Me	Me	34	C	<1997BCJ197>
Me	Me	Me	35	D	<1998JCS(P1)647>
Me	Me	Ph	48	D	<2003TL6911>
Ph	H	H	13	A	<2003TL6911>
Ph	H	Me	70	A	<2003TL6911>
Ph	Me	Me	72	A	<2003TL6911>
Ph	Me	Me	50	B	<1995CL199>
Ph	Me	Me	30	D	<1998JCS(P1)647>
4MeO-C ₆ H ₄	Me	Me	66	A	<2003TL6911>
4MeO-C ₆ H ₄	Me	Me	71	D	<1995CL199>
4NO ₂ -C ₆ H ₄	Me	Me	82	D	<1995CL199>
4MeOCO-C ₆ H ₄	Me	Me	80	D	<1995CL199>
Bn	Me	Me	51	D	<1995CL199>
	–[CH ₂] ₃ –	Me	74	A	<2003TL6911>
	–[CH ₂] ₃ –	Me	41	D	<1998JCS(P1)647>
	–[CH ₂] ₄ –	Me	61	A	<2003TL6911>
	–[CH ₂] ₅ –	H	44	A	<2003TL6911>

^a Reagents and conditions: Method A: carboxamide (4 equiv.), **6** (1 equiv.), PhH, rt, 12–20 h. Method B: carboxamide (5 equiv.), **7** (1 equiv.), PhH, Δ, 162–220 h (for equivalent reactions using **8**, see <1998CL17>). Method C: carboxamide (1 equiv.), **9** (1.1 equiv.), CH₂Cl₂ or CHCl₃, PhH, PhMe or mesitylene, rt or Δ, 5–24 h. Method D: BuⁱAlH (1 equiv.), Se (1 equiv.), carboxamide (1 equiv.), PhMe, 120–130 °C, 1 h. ^b Isolated yields.

salts; these were then reacted with LiAlHSeH <2001JA8408> to give the corresponding *N,N*-dialkylselenoamides in moderate-to-good yields (Scheme 13) <2002HC195>. When *N,N*-dialkylamides bearing bulky substituent groups on nitrogen were used (e.g., Prⁱ, Ph), these were not converted into their corresponding selenoamides due to steric hindrance.

**Scheme 13**

5.14.3.2 Selenoamides from Nitriles

One of the most convenient methods for the preparation of primary selenoamides is the reaction of nitriles with hydrogen selenide (or sodium hydrogen selenide) either by directly bubbling the gas into the reaction mixture or by generation *in situ*, although these methods are restricted mainly to aryl-substituted derivatives (e.g., from Al₂Se₃ <1978S668>, Se and NaBH₄ <1993S870, 1995TL237, 2002JOM274>, selenium and carbon monoxide <1985JOC384, 1985BCJ1448>). Recently, the reaction of nitriles with phosphorus pentaselenide has been demonstrated to afford

primary selenoamides in acceptable yields by slow release of hydrogen selenide when treated with water (Equation (130), Table 7) <2002SL1983>. Aliphatic and aromatic primary selenoamides were isolated by the reaction of the corresponding nitriles with either bis(trimethylsilyl) selenide <1990CL1403, 1995TL237> or potassium 4-methylselenobenzoate <1998CL1287> in the presence of boron trifluoride etherate in moderate-to-high yields. Selenoamides were also obtained as minor products when potassium 4-methylselenobenzoate was reacted with α,β -unsaturated nitriles <1998CL1287>. Reaction of aromatic and aliphatic nitriles with monoselenophosphate in aqueous acidic media directly, or generated *in situ* from *O,O,O*-tris(trimethylsilyl)monoselenophosphate, gives selenoamides <2001S1308>. *N*-Mono and *N,N*-disubstituted selenoamides are readily prepared in a one-pot procedure from nitriles, selenium metal, and NaBH₄ followed by transamination of the intermediate primary selenoamide with either primary or secondary amines (Scheme 14, Table 8) <1985BCJ1448, 1996SC2617>.

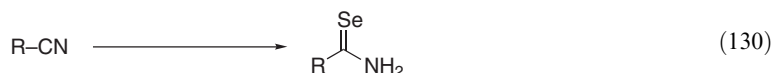
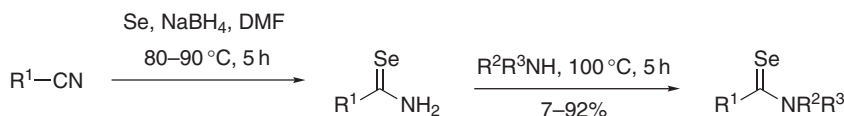


Table 7 Conversion of nitriles into primary selenoamides (Equation (130))

<i>R</i>	Method ^a	Yield (%) ^b	References
Me	A	27	<2002SL1983>
Me	E	79	<2001S1308>
Et	A	20	<2002SL1983>
Et	E	55	<2001S1308>
Pr	E	54	<2001S1308>
Pr ⁱ	C	41	<1998CL1287>
Bu ⁿ	C	70	<1998CL1287>
Bu ^t	A	42	<2002SL1983>
Bu ^t	C	65	<1998CL1287>
Ph	A	84	<2002SL1983>
Ph	C	72	<1998CL1287>
Ph	D	50	<2001S1308>
Ph	F	80	<2002OM274>
2-MeC ₆ H ₄	A	30	<2002SL1983>
2-MeC ₆ H ₄	C	63	<1998CL1287>
2-MeC ₆ H ₄	D	73	<2001S1308>
4-MeOC ₆ H ₄	C	65	<1998CL1287>
4-MeOC ₆ H ₄	F	98	<2002OM274>
4-EtOC ₆ H ₄	F	95	<2002OM274>
4-MeSC ₆ H ₄	F	97	<2002OM274>
4-ClC ₆ H ₄	C	86	<1998CL1287>
4-BrC ₆ H ₄	F	94	<2002OM274>
4-H ₂ NC ₆ H ₄	A	35	<2002SL1983>
Bn	A	40	<2002SL1983>
Bn	C	77	<1998CL1287>
Bn	D	59	<2001S1308>
4-ClC ₆ H ₄ CH ₂	A	48	<2002SL1983>
4-O ₂ NC ₆ H ₄ CH ₂	A	57	<2002SL1983>
Ph ₂ CH	A	81	<2002SL1983>
3-pyridyl	A	18	<2002SL1983>
3-pyridyl	E	70	<2001S1308>
(NC)CH ₂	A	41	<2002SL1983>
H ₂ NC(=O)CH ₂	A	47	<2002SL1983>
(EtO ₂ C)CH ₂	A	33	<2002SL1983>
H ₂ NC(=Se)CH ₂	A	55	<2002SL1983>
PhCH=CH	A	52	<2002SL1983>
H ₂ NCH ₂	A	59	<2002SL1983>

^a Reagents and conditions: Method A: nitrile (1 equiv.), P₂Se₅ (0.4 equiv.), EtOH, Δ , slow addition of water, 2–3 h. Method B: nitrile (1 equiv.), EtOH/water, Δ , slow addition of P₂Se₅ (0.4 equiv.), 2–3 h. Method C: nitrile, 4-MeC₆H₄C(O)SeK, BF₃·Et₂O, THF, 0°C, 5 h. Method D: nitrile, monoselenophosphate, water/MeOH or PrOH, rt, 12 h. Method E: nitrile, *O,O,O*-tris(trimethylsilyl)monoselenophosphate, MeOH, Δ , 5–96 h. Method F: (i) NaBH₄ (2 equiv.), Se (2 equiv.), EtOH, 1 h, (ii) pyridine, nitrile (1 equiv.), HCl, Δ , 2.5 h. ^b Isolated yields.



Scheme 14

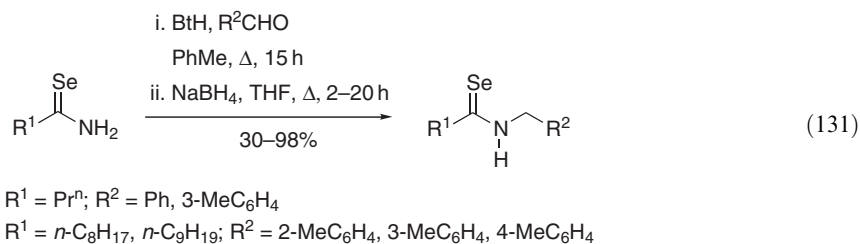
Table 8 Conversion of nitriles into primary and secondary selenoamides (Scheme 14)

R^1	R^2	R^3	Yield (%)
Pr ⁿ	$n-C_5H_{11}$	H	52
Pr ⁿ	—[CH ₂] ₅ —	H	59
Pr ⁿ	Bn	H	73
Ph	Bu ⁿ	H	89
Ph	$n-C_5H_{11}$	H	87
Ph	$n-C_8H_{17}$	H	86
Ph	$n-C_{11}H_{23}$	H	82
Ph	$n-C_{12}H_{25}$	H	82
Ph	Pr ⁱ	Pr ⁱ	7
Ph	$n-C_6H_{13}$	$n-C_6H_{13}$	43
Ph	—[CH ₂] ₅ —	H	58
Ph	Bn	H	92

Source: <1996SC2617>.

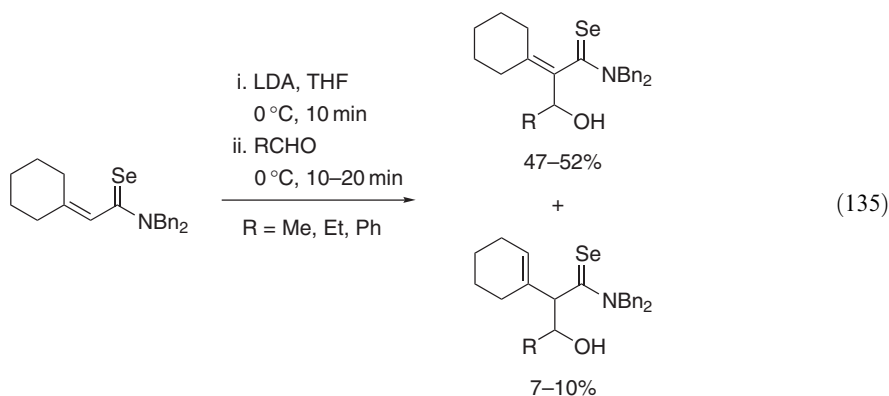
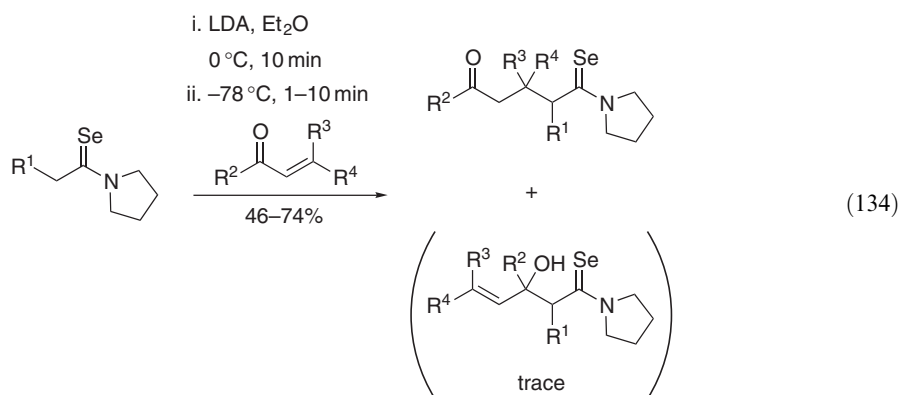
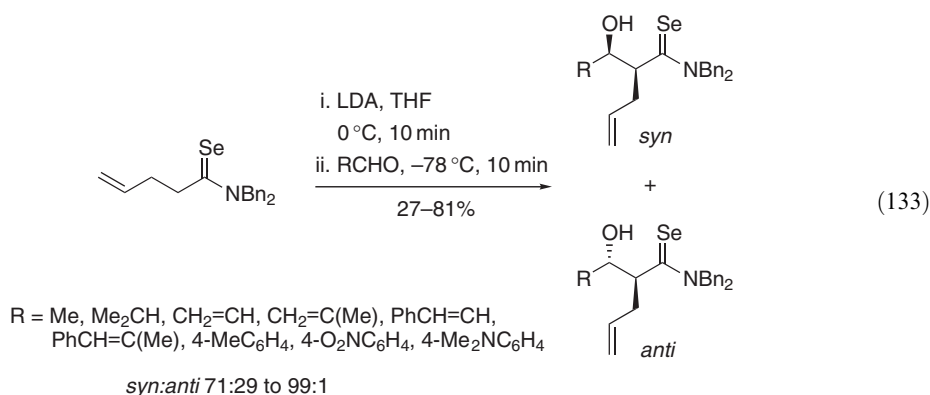
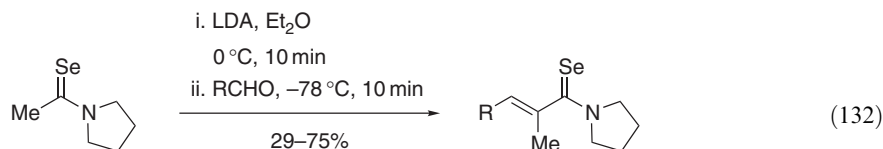
5.14.3.3 Manipulation of an Existing Selenoamide

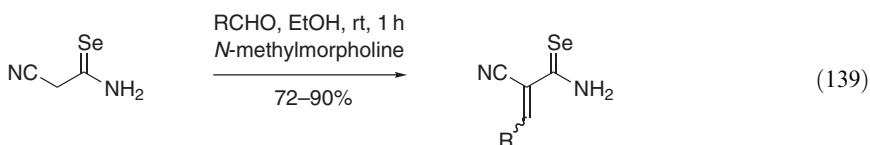
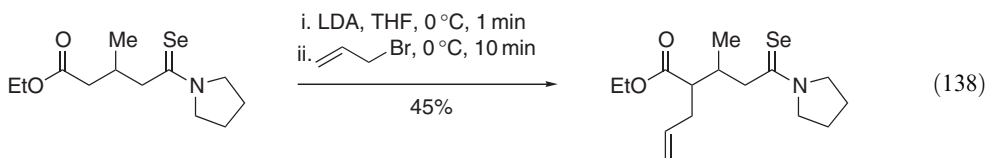
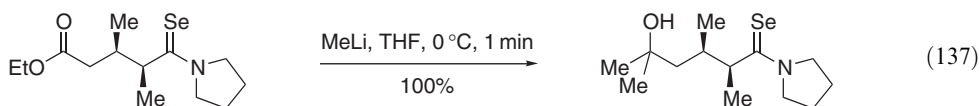
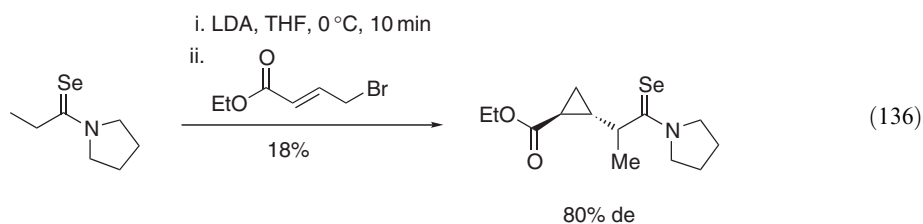
N-Substituted selenoamides have been prepared from primary selenoamides <1985BCJ1448, 1996SC2617, 2002MI891>. Reaction of aliphatic aldehydes with primary selenoamides and benzotriazole, followed by reduction with sodium borohydride afforded *N*-substituted selenoamides in good yield (Equation (131)) <2002MI891>. Similar reaction with aromatic aldehydes afforded *N*-substituted selenoamides in only low yields.



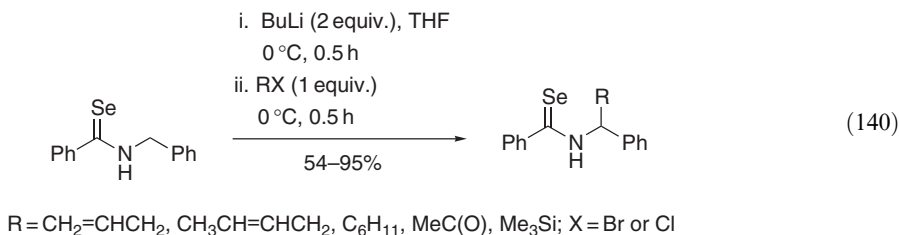
Reactions using metal enolates and enethiolates derived from amides and thionoamides, respectively have been well studied as synthetically important carbon—carbon bond forming reactions; the analogous reaction using a selenium counterpart has only recently been developed. Lithium eneselenolates have been prepared by deprotonation of enolizable selenoamides and used in subsequent quenching with a variety of electrophiles <1997MI29, 1997SL775, 2000OL311, 2001PS(172)101, 2001JCS(P1)2711>. Lithium eneselenolates reacted with aldehydes to give either α,β -unsaturated selenoamides (Equation (132)) <1997SL775>, or β -hydroxyselenoamides with diastereoselectivities in the range 71:29 to 99:1 (*syn:anti*) (Equation (133)) <2001PS(172)101, 2001JCS(P1)2711>. Similar reaction with aliphatic and aromatic ketones furnishes β -hydroxyselenoamides, in some cases with high diastereoselectivity <2002TL1343>. In the reaction of α -substituted lithium eneselenolates with α,β -unsaturated esters and ketones, Michael addition occurred in good yield to afford δ -oxoselenoamides with varying degrees of diastereoselectivity (Equation (134)) <2000OL311, 2001PS(172)101>. At lower reaction temperatures, a 1,2-adduct was also observed. Reaction of lithium dieneselenolates with aldehydes (Equation (135)) and allyl bromide proceeded smoothly to introduce substituents α - to the selenocarbonyl group <2001PS(172)101>. In these reactions, small amounts of β - γ -unsaturated selenoamides were also formed. Michael addition of the lithium eneselenolate of a

propaneselenoamide to 4-bromocrotonate followed by intramolecular cyclization gave a β -cyclopropylselenoamide, in which the substituents were *trans*-orientated (Equation (136)) <2000OL311>. The regioselectivity of reactions of δ -oxoselenoamides has been investigated <2000OL311>. Treatment with 2 equiv. of methyl lithium gave quantitatively a δ -hydroxysele-noamide (Equation (137)). Deprotonation with lithium diisopropylamide and subsequent alkylation occurred α to the carbon atom of the ester group with no evidence for deprotonation at the α -carbon to the selenocarbonyl group (Equation (138)). Knoevenagel condensation of cyanoselenoacetamide with aldehydes afforded aryl- and heteroarylmethylenecyanoselenoaceta-mides (Equation (139)) <1997MI29, 1998RJOC876, 1999RJOC1377>.



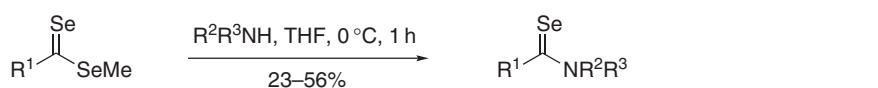
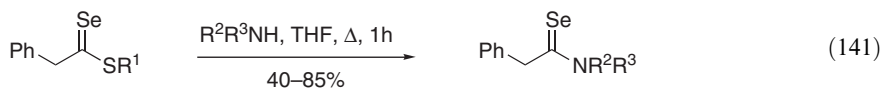


The preparation of secondary selenoamides has been demonstrated by selective generation of a selenoamide dianion from *N*-benzylselenobenzamide and subsequent trapping with various electrophiles (Equation (140)) <2002OL1407>.



5.14.3.4 Miscellaneous Methods

Selenothioesters (Equation (141)) <1993JA3000> and diselenoic acid methyl esters (Equation (142)) <1995HAC241> react with primary and secondary amines to afford selenoamides in moderate yield.

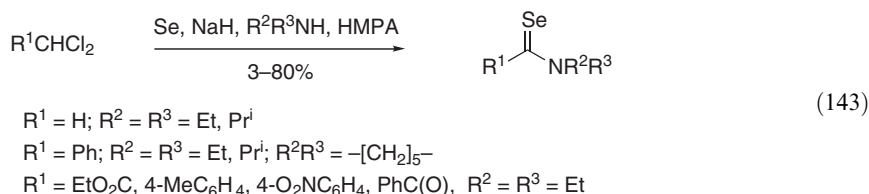


R¹ = Ph; R²R³ = –[CH₂]₄–, –[CH₂]₅–, –[CH₂]₂O[CH₂]₂–

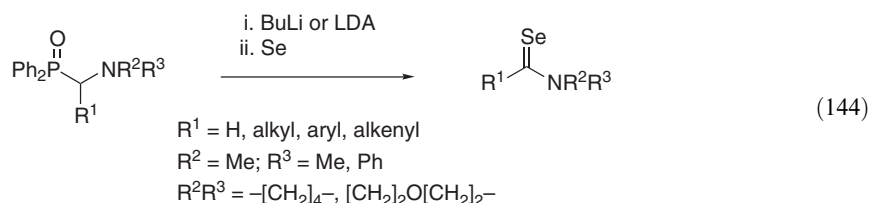
R¹ = 3-MeC₆H₄, 4-MeOC₆H₄; R²R³ = –[CH₂]₅–

R¹ = 4-MeC₆H₄; R²R³ = –[CH₂]₄–

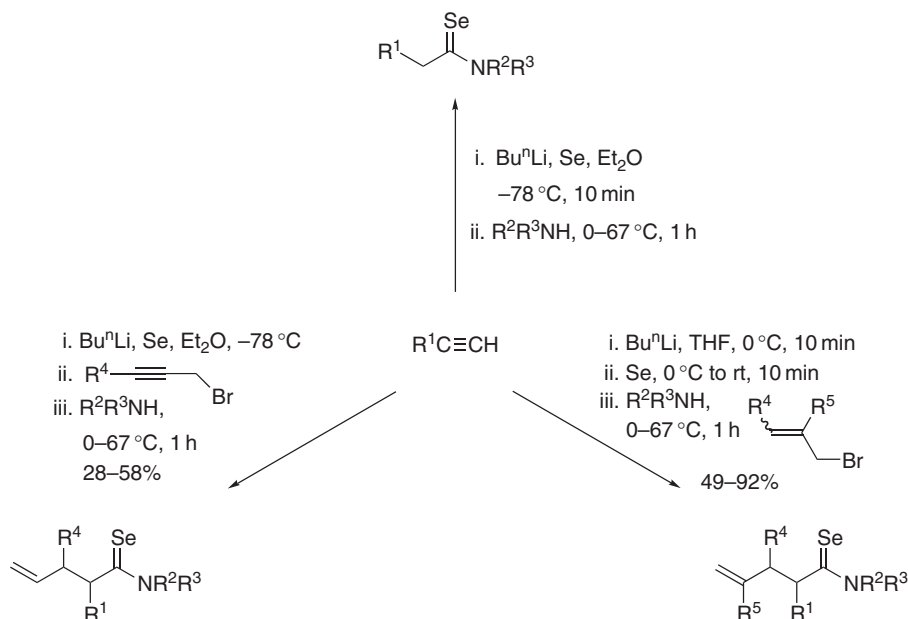
Treatment of dihalomethane derivatives with elemental selenium, sodium hydride, and an excess of an amine in a Willgerodt–Kindler-type selenation gave the corresponding selenoamide in modest yield (Equation (143)) <1996BCJ2235>. It is speculated that the reaction product is derived from a selenocarbonyl halide generated by the reaction of a dihalomethane selenolate with *N*-alkylated aminopolyselenide species $[R_2N-(Se)_n]^-$.



Reaction of phosphonate anions with elemental selenium and a secondary amine provides tertiary selenoamides <92CL131>. Tertiary selenoamides have also been synthesized in good yields by reaction of the lithio-anions of α -amino-substituted diphenylphosphine oxides with 2 equiv. of elemental selenium (Equation (144)) <1994RTC499, 1996PS(111)823, 1997CB49>.

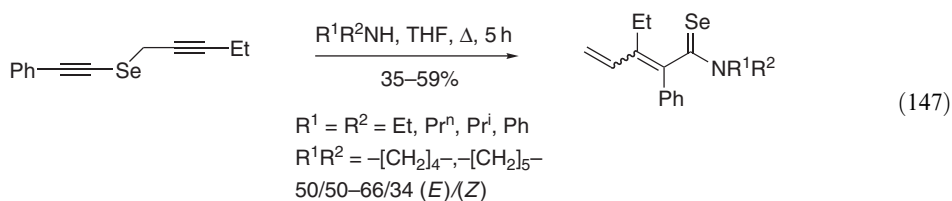
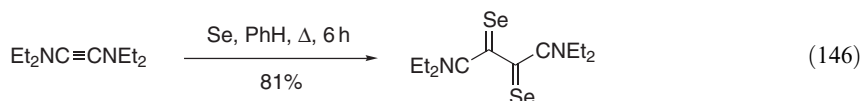
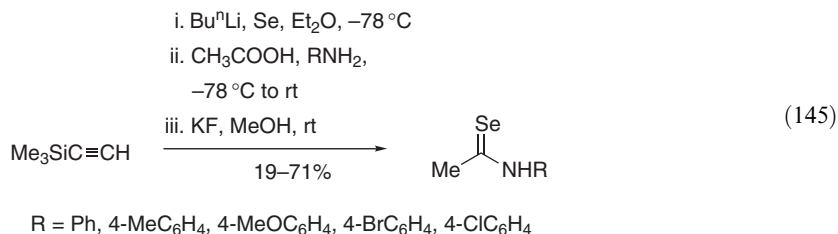


Alkynyl anions react efficiently with elemental selenium to form alkyneselenolates, which have been used as key intermediates in a number of preparations of selenoamides, reactions proceeding via selenoketene intermediates (Scheme 15, Equation (145)). The direct reaction of alkyneselenolates with secondary amines is an efficient route to selenoamides <1996SL865>. *N*-Aryl selenoamides were synthesized by reaction of trimethylsilylacetylene, *n*-butyllithium, selenium, acetic acid, and aryl amines (or the amine hydrochloride) followed by treatment with potassium fluoride in moderate-to-good yield <1998JOC374>. Similarly, trapping of alkyneselenolates with propargyl bromides <1994CL1743> or allylic bromides <1980TL4251, 1979RTC55, 1996CC1809, 1998BCJ1193> and subsequent reaction with amines affords unsaturated selenoamides in a one-pot procedure in good-to-high yields. For the allylic bromides, the reaction



Scheme 15

methodology was shown to be applicable to alkyl, alkenyl, aryl, and silyl acetylenes. The electron-rich ynediamine (Equation (146)) reacted with elemental selenium to form a selenoamide <1994CL77, 1998JA10027, 1998PS(136-138)569>. Pentynyl phenylethynyl selenide reacts with secondary amines to give $\alpha,\beta,\gamma,\delta$ -unsaturated selenoamides (Equation (147)) <2001JOC4099>.



When 6*H*-1,3,5-oxaselenazines are heated in the presence of a nucleophilic reagent, selenoamides are afforded as the 1,4-adduct of an intermediate 1,3-selenaza-1,3-butadiene formed by [4 + 2]-cycloreversion (Equation (148), Table 9) <1997CL701, 2001BCJ511>.

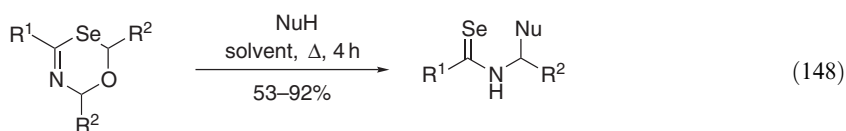
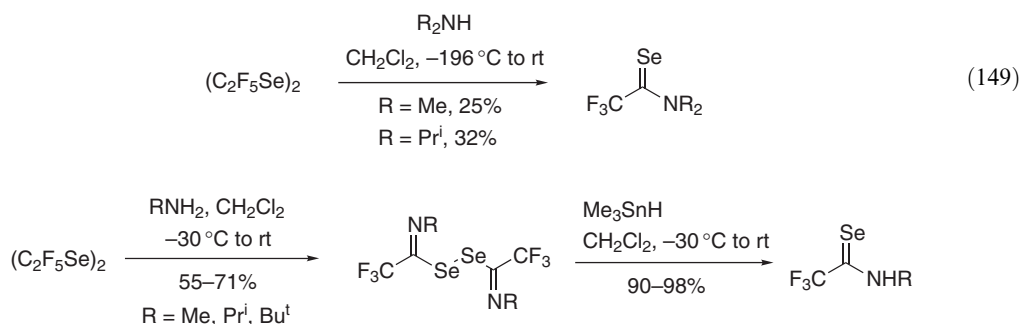


Table 9 Conversion of oxaselenazines into selenoamides (Equation (148))

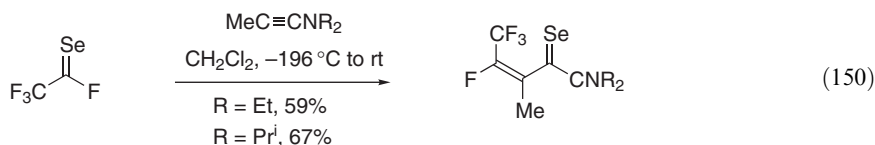
R^1	R^2	NuH	Solvent	Yield (%)
Ph	Me	MeOH	MeOH	62
Ph	Me	EtOH	EtOH	66
Ph	Bu ^t	EtOH	EtOH	53
4-ClC ₆ H ₄	Me	MeOH	MeOH	92
4-ClC ₆ H ₄	Me	EtOH	EtOH	85
Ph	Me	PhSH	PhH	85
Ph	Me	PhCH ₂ SH	PhH	82
Ph	Me	Pr ⁿ NH ₂	PhH	0

Source: <1997CL701, 2001BCJ511>.

The first representatives of the type $\text{Se}=\text{C}(\text{NR}_2)\text{CF}_3$ were prepared in 1990 by reaction of trifluoromethylselenocarbonyl fluoride with secondary amines <1990JOM321>. Diselenide $(\text{C}_2\text{F}_5\text{Se})_2$, selenol HSeC_2F_5 and the selenocarbonyl polymer $[\text{SeC}(\text{F})\text{CF}_3]_n$ are alternative starting reagents with reactions probably proceeding via a base-induced elimination of hydrogen fluoride to afford trifluoromethylselenocarbonyl fluoride as a highly reactive intermediate <1997CB913>. For example, diselenide $(\text{C}_2\text{F}_5\text{Se})_2$ reacted with secondary amines to form tertiary selenoamides as the major reaction product in moderate yields (Equation (149)). Reaction of the diselenide $(\text{C}_2\text{F}_5\text{Se})_2$ with primary amines afforded bis(trifluoromethylketiminoalkyl) diselenides which were cleaved with Me_3SnH to afford secondary selenoamides (Scheme 16) <1997CB913>. Trifluoromethylselenocarbonyl fluoride and its polymeric form $[\text{SeC}(\text{F})\text{CF}_3]_n$ react with ynamines to afford selenoacrylamides by [2 + 2]-cycloaddition and stereospecific electrocyclic ring-opening (Equation (150)) <1997CB913>.



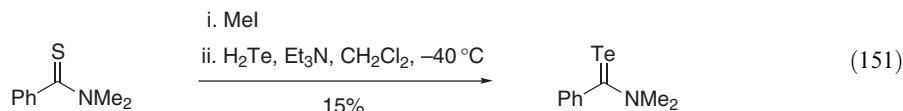
Scheme 16



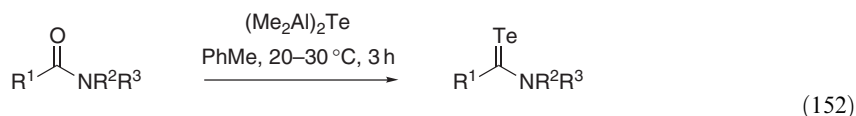
5.14.4 TELLUROAMIDES

Telluroamides, like other tellurocarbonyl compounds, are difficult to prepare due to the instability of the C=Te bond. To date, only a limited number of telluroamides have been described in the literature. In all cases, the isolated telluroamides have proved to be very unstable, decomposing on standing even at refrigeration temperatures. It has been noted that in air, or in damp solvents, decomposition to elemental tellurium and the parent amide occurs [\[1979CC1102\]](#). Isolated telluroamides have, however, given the expected spectral data, but due to decomposition, no satisfactory elemental analyses have been obtained. It is well known that telluroaldehydes and telluroketones may be stabilized by coordination to transition metals such as chromium, molybdenum, and tungsten. Investigation of the coordination of telluroamides with group 6 metals has shown that their stability is not significantly improved, and X-ray crystallographic studies have demonstrated that the bond between telluroamides and group 6 metals (chromium, molybdenum, and tungsten) is weak [\[1998HAC57\]](#).

N,N-Dimethyltelluroformamide was suggested to be the unstable product from the reaction of a steroidal iminium salt with sodium hydrogen telluride [\[1975JCS\(P1\)1574\]](#). *N,N*-Diethylphenyltelluroacetamide was suggested to be an intermediate in the reaction of phenylethyne with sodium in DMSO followed by the addition of tellurium, *t*-butyl chloride, and diethylamine, affording phenylacetic acid and elemental tellurium [\[1981ZOR2064\]](#). The first reaction resulting in an isolable, identifiable telluroamide is shown in [Equation \(151\)](#) [\[1979CC1102\]](#).

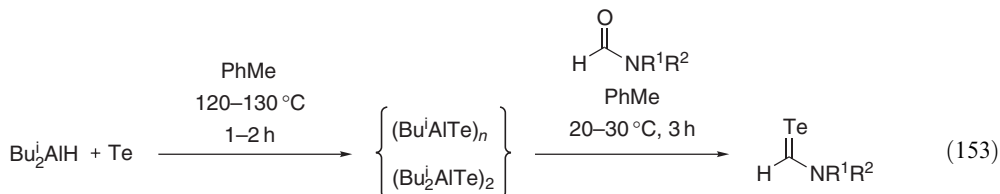


Bis(dimethylaluminum) telluride (Me₂Al)₂Te has been demonstrated to be an effective reagent for the conversion of carbonyl groups into tellurocarbonyls, the aluminum playing a key role in the replacement of the carbonyl oxygen with a Te atom [\[1989JA8749, 1990TL2095, 1992TL3515, 1992TL7865\]](#). Using this reagent, two telluroamides were successfully synthesized ([Equation \(152\)](#)) and their crystal structures established [\[1991SL105, 1997OM756\]](#). In a development of this reagent, a novel Al—Te reagent (analogous to the Al—Se reagent discussed in [Section 5.14.3](#)) was prepared as a mixture of (Buⁱ₂AlTe)₂ and (BuⁱAlTe)_{*n*}, along with small amounts of C—Te—Al type compounds. Owing to the instability, toxicity, and unpleasant odor of this reagent, it was neither purified nor fully characterized but used directly in the conversion of formamides into telluroformamides in a one-pot procedure ([Equation \(153\)](#)) [\[1998PS\(136-138\)525, 1998JCS\(P1\)647\]](#). Attempts to prepare *N,N*-dimethyltelluroacetamide and *N,N*-dimethyltellurobenzamide using this reagent were unsuccessful. It is suggested that this may be due to hindered attack of the Al—Te reagent into the carbonyl group [\[1998JCS\(P1\)647\]](#).



$\text{R}^1 = \text{H}, \text{R}^2 = -[\text{CH}_2]_2\text{O}[\text{CH}_2]_2-, 70\%$

$\text{R}^1\text{R}^2 = -[\text{CH}_2]_3-, \text{R}^3 = \text{Me}, 28\%$



$\text{R}^1 = \text{Me}; \text{R}^2 = \text{Me}, 25\%; \text{Ph}, 51\%$

$\text{R}^1\text{R}^2 = -[\text{CH}_2]_5-, 50\%; -[\text{CH}_2]_2\text{O}[\text{CH}_2]_2-, 66\%; -[\text{CH}_2]_2\text{NMe}[\text{CH}_2]_2-, 49\%$

REFERENCES

- 1869CB305 L. Henry, *Ber. Dtsch. Chem. Ges.* **1869**, 2, 305–308.
 1869CB494 L. Henry, *Ber. Dtsch. Chem. Ges.* **1869**, 2, 494–495.
 1874CB1273 F. V. Dechemd, *Chem. Ber.* **1874**, 7, 1273–1274.
 1878CB338 A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1878**, 11, 338–340.
 1948JCS1919 A. A. Goldberg, W. Kelly, *J. Chem. Soc.* **1948**, 1919–1926.
 1952JCS742 A. E. S. Fairfull, J. L. Lowe, D. A. Peak, *J. Chem. Soc.* **1952**, 742–744.
 1953JA4456 T. E. Londergan, N. L. Hause, W. R. Schmitz, *J. Am. Chem. Soc.* **1953**, 75, 4456–4458.
 1956JA5018 H. Z. Lecher, R. A. Greenwood, K. C. Whitehouse, T. H. Chao, *J. Am. Chem. Soc.* **1956**, 78, 5018–5022.
 1960CB1511 W. Walter, J. Curts, *Chem. Ber.* **1960**, 93, 1511–1517.
 1960JA2656 E. C. Taylor, J. A. Zoltewicz, *J. Am. Chem. Soc.* **1960**, 82, 2656–2657.
 1962LA(660)60 W. Walter, J. Voss, J. Curts, H. Pawelzik, *Liebigs Ann. Chem.* **1962**, 660, 60–73.
 1966ACS597 K. A. Jensen, P. H. Nielsen, *Acta Chem. Scand.* **1966**, 20, 597–629.
 1967CB1413 G. Barnikow, G. Strickmann, *Chem. Ber.* **1967**, 100, 1413–1427.
 1969LA(727)50 W. Walter, P.-M. Hell, *Liebigs Ann. Chem.* **1969**, 727, 50–60.
 1972ZC133 N. S. Tao, S. Scheithauer, R. Mayer, *Z. Chem.* **1972**, 12, 133–134.
 1973AG(E)1014 D. Enders, D. Seebach, *Angew. Chem., Int. Ed. Engl.* **1973**, 12, 1014–1016.
 1973SI49 J. W. Scheeren, P. H. J. Ooms, R. J. F. Nivard, *Synthesis* **1973**, 149–151.
 1975JCS(P1)1574 D. H. R. Barton, S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585.
 1976CB1309 D. Seebach, W. Lubosch, D. Enders, *Chem. Ber.* **1976**, 109, 1309–1323.
 1976JJS519 I. D. Rae, M. J. Wade, *Int. J. Sulfur Chem.* **1976**, 8, 519–528.
 1976ZOR2213 Y. L. Yagupolskii, B. K. Kerzner, L. M. Yagupolskii, *Zh. Org. Khim.* **1976**, 12, 2213–2217.
 1977BSB321 J. Perregaard, I. Thomsen, S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **1977**, 86, 321–328.
 1978S668 V. I. Cohen, *Synthesis* **1978**, 668–669.
 1979CC1102 K. A. Lerstrup, L. Henriksen, *J. Chem. Soc., Chem. Commun.* **1979**, 1102–1103.
 1979MI567 I. D. Rae, *Aust. J. Chem.* **1979**, 32, 567–573.
 1979RTC55 R. S. Sukhai, L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **1979**, 98, 55–58.
 1981TL3635 K. Clausen, M. Thorsen, S.-O. Lawesson, *Tetrahedron Lett.* **1981**, 37, 3635–3639.
 1980TL4251 E. Schaumann, F.-F. Grabley, *Tetrahedron Lett.* **1980**, 21, 4251–4254.
 1981TL1851 S. A. Benner, *Tetrahedron Lett.* **1981**, 22, 1851–1854.
 1981TL1855 S. A. Benner, *Tetrahedron Lett.* **1981**, 22, 1855–1858.
 1981ZOR2064 V. Z. Laishev, M. L. Petrov, A. A. Petrov, *Zh. Org. Khim.* **1981**, 17, 2064–2071. (*Chem. Abstr.* **1982**, 96, 122 329s)
 1982CC457 H. Davy, *J. Chem. Soc., Chem. Commun.* **1982**, 457–458.
 1982JA5221 P. Campbell, N. T. Nashed, *J. Am. Chem. Soc.* **1982**, 104, 5221–5226.
 1982JOC4645 J. R. Cashman, R. P. Hanzlik, *J. Org. Chem.* **1982**, 47, 4645–4650.
 1983T3429 M. Thorsen, B. Yde, U. Pedersen, K. Clausen, S.-O. Lawesson, *Tetrahedron* **1983**, 39, 3429–3435.
 1983TL3815 G. Lajoie, F. Lépine, L. Maziak, B. Belleau, *Tetrahedron Lett.* **1983**, 24, 3815–3818.
 1984JCS(P1)785 K. Clausen, M. Thorsen, S.-O. Lawesson, A. F. Spatola, *J. Chem. Soc., Perkin Trans. 1* **1984**, 785–798.
 1984MI41 E. Chieli, G. Malvaldi, *Toxicology* **1984**, 31, 41–52.
 1984S827 M. Yokoyama, Y. Hasegawa, H. Hatanaka, Y. Kawazoe, T. Imamoto, *Synthesis* **1984**, 827–829.
 1985BCJ1448 A. Ogawa, J. Miyake, N. Kambe, N. Sonoda, *Bull. Chem. Soc. Jpn.* **1985**, 58, 1448–1451.
 1985JOC384 A. Ogawa, J. Miyake, Y. Karasaki, S. Murai, N. Sonoda, *J. Org. Chem.* **1985**, 50, 384–386.
 1985PS(25)297 R. Shabana, S. O. Lawesson, H. J. Meyer, *Phosphorus Sulfur* **1985**, 25, 297–305.
 1985T2567 R. A. Cherkasov, G. A. Kuttyrev, A. N. Pudovik, *Tetrahedron* **1985**, 41, 2567–2624.

- 1985T5061 M. P. Cava, M. I. Levinson, *Tetrahedron* **1985**, 41, 5061–5087.
 1986KGS1405 T. Yagodzinski, T. Dzembovska, E. Yagodzinskaya, Z. Yablonski, *Khim. Geterotsikl. Soedin.* **1986**, 1405–1411.
 1986TL3445 T. B. Rauchfuss, G. A. Zank, *Tetrahedron Lett.* **1986**, 27, 3445–3448.
 1986ZOB2660 M. G. Zimin, N. G. Zabiroy, R. M. Kamalov, A. N. Pudovik, *Zh. Obshch. Khim. (Engl. Trans.)* **1986**, 56, 2660–2666. (*Chem. Abstr.* **1987**, 107, 236 844g).
 1987HCA1001 P. Wipf, C. Jenny, H. Heimgartner, *Helv. Chim. Acta* **1987**, 70, 1001–1011.
 1988CC741 J. C. Fitzmaurice, D. J. Williams, P. T. Wood, J. D. Woolins, *J. Chem. Soc., Chem. Commun.* **1988**, 741–743.
 1989JA8749 M. Segi, T. Koyama, Y. Takata, T. Nakajima, S. Suga, *J. Am. Chem. Soc.* **1989**, 111, 8749–8751.
 1989JCR(S)155 F. S. Guziec, Jr., L. M. Wasmund, *J. Chem. Res.(S)* **1989**, 155–156.
 1990CL1403 K. Shimada, S. Hikage, Y. Takeishi, Y. Takikawa, *Chem. Lett.* **1990**, 1403–1406.
 1990JOM321 J. Grobe, D. Le Van, J. Welzel, *J. Organomet. Chem.* **1990**, 386, 321–332.
 1990SC3085 D. Brillon, *Synth. Commun.* **1990**, 20, 3085–3095.
 1990TL2095 M. Segi, T. Koyama, T. Nakajima, S. Suga, S. Murai, N. Sonoda, *Tetrahedron Lett.* **1990**, 30, 2095–2098.
 1991AG(E)238 H. Heimgartner, *Angew. Chem., Int. Ed. Engl.* **1991**, 30, 238–264.
 1991HCA1953 D. Seebach, S. Y. Ko, H. Kessler, M. Köck, M. Reggelin, P. Schmieder, M. D. Walkinshaw, J. J. Bülsterli, D. Bevec, *Helv. Chim. Acta* **1991**, 74, 1953–1990.
 B-1991MI419 E. Schaumann, in *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming, Eds., Vol. 6, Pergamon Press, Oxford, **1991**.
 B-1991MI476 A. Ogawa, N. Sonoda, in *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming, Eds., Vol. 6, Pergamon Press, Oxford, **1991**.
 1991SL105 M. Segi, A. Kojima, T. Nakajima, S. Suga, *Synlett* **1991**, 2, 105–106.
 1991TL7617 T. Hoeg-Jensen, M. H. Jakobsen, C. E. Olsen, A. Holm, *Tetrahedron Lett.* **1991**, 32, 7617–7620.
 1992AG(E)1229 C. Unverzagt, A. Geyer, H. Kessler, *Angew. Chem., Int. Ed. Engl.* **1992**, 31, 1229–1230.
 1992CL131 K. Okuma, K. Ikari, H. Ohta, *Chem. Lett.* **1992**, 131–134.
 1992CL1843 K. Shimada, N. Jin, M. Fujimura, Y. Nagano, E. Kudoh, Y. Takikawa, *Chem. Lett.* **1992**, 9, 1843–1846.
 1992S1219 P.-Y. Lin, W.-S. Ku, M.-J. Shiao, *Synthesis* **1992**, 1219–1220.
 1992SC1397 D. Brillon, *Synth. Commun.* **1992**, 20, 1397–1401.
 1992SR297 D. Brillon, *Sulfur Rep.* **1992**, 12, 297–338.
 1992T8601 J. Jurayj, M. Cushman, *Tetrahedron* **1992**, 48, 8601–8614.
 1992TL3515 G. M. Li, M. Segi, T. Nakajima, *Tetrahedron Lett.* **1992**, 33, 3515–3518.
 1992TL7865 M. Segi, T. Takahashi, H. Ichinose, G. M. Li, T. Nakajima, *Tetrahedron Lett.* **1992**, 33, 7865–7868.
 1993BMCL619 B. Zacharie, R. Martel, G. Sauve, B. Belleau, *Bioorg. Med. Chem. Lett.* **1993**, 3, 619–624.
 1993JA3000 S. Kato, T. Komuro, T. Kanda, H. Ishihara, T. Murai, *J. Am. Chem. Soc.* **1993**, 115, 3000–3001.
 1993JCS(P1)1113 T. Nishio, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1113–1117.
 1993JOC4742 M.-J. Shiao, L.-L. Lai, W.-S. Ku, P.-Y. Lin, J. R. Hwu, *J. Org. Chem.* **1993**, 58, 4742–4744.
 1993PS(75)257 K. Karaghiosoff, K. Eckstein, *Phosphorus Sulfur* **1993**, 75, 257–260.
 1993S870 L.-L. Lai, D. H. Reid, *Synthesis* **1993**, 870–872.
 1994CL77 J. Nakayama, A. Mizumura, I. Akiyama, T. Nishio, I. Iida, *Chem. Lett.* **1994**, 77–80.
 1994CL1743 K. Shimada, S. Akimoto, H. Itoh, H. Nakamura, Y. Takikawa, *Chem. Lett.* **1994**, 1743–1746.
 1994H1615 C. O. Kappe, R. Flammang, C. Wentrup, *Heterocycles* **1994**, 37, 1615–1622.
 1994JA2633 P. N. Devine, A. I. Meyers, *J. Am. Chem. Soc.* **1994**, 116, 2633–2634.
 1994JIC631 M. Fawi, A. El-Latif, *J. Indian. Chem. Soc.* **1994**, 71, 631–633.
 1994JOC348 D. C. Smith, S. W. Lee, P. L. Fuchs, *J. Org. Chem.* **1994**, 59, 348–354.
 1994JOC1257 T. Hoeg-Jensen, C. E. Olsen, A. Holm, *J. Org. Chem.* **1994**, 59, 1257–1263.
 1993T10009 R. Isecke, R. Brossmer, *Tetrahedron* **1993**, 49, 10009–10016.
 1993T10489 B. Zacharie, G. Sauvé, C. Penney, *Tetrahedron* **1993**, 49, 10489–10500.
 1994PS(89)119 A. Bulpin, S. Le Roy-Gouvernec, S. Masson, *Phosphorus Sulfur* **1994**, 89, 119–132.
 1994PS(97)89 M. J. Gil, A. Reliquet, F. Reliquet, J. C. Meslin, *Phosphorus Sulfur* **1994**, 97, 89–94.
 1994PS(93)185 K. Karaghiosoff, K. Eckstein, R. Motzer, *Phosphorus Sulfur* **1994**, 93, 185–188.
 1994PS(95-96)325 J. Y. Gauthier, H. Lebel, *Phosphorus Sulfur* **1994**, 95–96, 325–326.
 1994RTC499 P. A. Otten, A. van der Gen, *Recl. Trav. Chim. Pays-Bas* **1994**, 113, 499–506.
 1994T7445 R. Isecke, R. Brossmer, *Tetrahedron* **1994**, 50, 7445–7460.
 1994TA2313 C. O. Mellet, A. M. Marin, J. M. G. Fernández, J. Fuentes, *Tetrahedron Asymmetry* **1994**, 5, 2313–2324.
 1994TL4379 M. Yoshifuji, D. L. An, K. Toyota, M. Yasunami, *Tetrahedron Lett.* **1994**, 35, 4379–4382.
 1995BCJ3151 C. Shin, Y. Nakamura, Y. Yamada, Y. Yonezawa, K. Umemura, J. Yoshimura, *Bull. Chem. Soc. Jpn.* **1995**, 68, 3151–3160.
 1995BCJ3573 A. Kakehi, S. Ito, S. Hayashi, T. Fujii, *Bull. Chem. Soc. Jpn.* **1995**, 68, 3573–3580.
 1995BSF67 F. Cerreta, A.-M. Le Nocher, C. Leriverend, P. Metzner, T. N. Pham, *Bull. Soc. Chim. Fr.* **1995**, 132, 67–74.
 1995CL199 D.-L. An, K. Toyota, M. Yasunami, M. Yoshifuji, *Chem. Lett.* **1995**, 199–200.
 1995COFGT(5)565 C. P. Dell, Thionoamides and their selenium and tellurium analogues, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 565–628.
 1995MI73 M. T. Cocco, C. Congiu, V. Onnis, M. L. Schivo, A. de Logu, *Farmaco* **1995**, 50, 73–76.
 1995MI77 R. Perrone, F. Berardi, N. A. Colabufo, V. Tortorella, M. D. Lograno, E. Daniele, S. Govoni, *Farmaco* **1995**, 50, 77–82.
 1995H2263 M. Takahashi, M. Ohba, *Heterocycles* **1995**, 41, 2263–2269.

- 1995HAC241 T. Murai, T. Mizutani, T. Kanda, S. Kato, *Heteroatom Chem.* **1995**, 6, 241–246.
1995JA5859 X. Creary, C. Zhu, *J. Am. Chem. Soc.* **1995**, 117, 5859–5860.
1995JA9107 S. A. Kane, H. Sasaki, S. M. Hecht, *J. Am. Chem. Soc.* **1995**, 117, 9107–9118.
1995JCS(P1)1543 B. K. Bhattacharya, T. S. Rao, G. R. Revankar, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1543–1550.
1995JCS(P2)1169 H. K. Oh, C. H. Shin, I. Lee, *J. Chem. Soc., Perkin Trans. 2* **1995**, 1169–1173.
1995JHC819 Y. W. Ho, I. J. Wang, *J. Heterocycl. Chem.* **1995**, 32, 819–825.
1995JHC1309 K. Koerber-Plé, G. Massiot, *J. Heterocycl. Chem.* **1995**, 32, 1309–1315.
1995JMC353 M. Chihara, H. Nagamoto, I. Takemura, K. Kitano, H. Komatsu, K. Sekiguchi, F. Tabusa, T. Mori, M. Tominaga, Y. Yabuuchi, *J. Med. Chem.* **1995**, 38, 353–358.
1995JMC2378 J. A. Zablocki, J. G. Rico, R. B. Garland, T. E. Rogers, K. Williams, L. A. Schretzman, S. A. Rao, P. R. Bovy, F. S. Tjoeng, R. J. Lindmark, M. V. Toth, M. E. Zupec, D. E. McMackins, S. P. Adams, M. Miyano, C. S. Markos, M. N. Milton, S. Paulson, M. Herin, P. Jacqmin, N. S. Nicholson, S. G. PanzerKnodel, N. F. Haas, J. D. Page, J. A. Szalony, B. B. Taite, A. K. Salyers, L. W. King, J. G. Campion, L. P. Feigen, *J. Med. Chem.* **1995**, 38, 2378–2394.
1995JMC4115 S. H. Krawczyk, T. E. Renau, M. R. Nassiri, A. C. Westerman, L. L. Wotring, J. C. Drach, L. B. Townsend, *J. Med. Chem.* **1995**, 38, 4115–4119.
1995JOC4774 H. Sone, T. Kondo, M. Kiryu, H. Ishiwata, M. Ojika, K. Yamada, *J. Org. Chem.* **1995**, 60, 4774–4781.
1995JOC5638 A. R. Katritzky, J. Chen, Z. Yang, *J. Org. Chem.* **1995**, 60, 5638–5642.
1995JOC7224 P. Wipf, S. Venkatraman, *J. Org. Chem.* **1995**, 60, 7224–7229.
1995JPR310 A. Rolfs, H. Brosig, J. Liebscher, *Prakt. Chem./Chem. Ztg.* **1995**, 337, 310–312.
1995MI138 H.-T. Le, M. Mayer, S. Thoret, R. Michelot, *Int. J. Peptide Protein Res.* **1995**, 45, 138–144.
1995MI445 M. Gütschow, S. Leistner, *Liebigs Ann. Org. Bioorg. Chem.* **1995**, 445–448.
1995MI833 H.-S. Lin, A. A. Rampersaud, J. E. Flokowitsch, W. E. Alborn, E. C. Y. Wu, D. A. Preston, *J. Chin. Chem. Soc.* **1995**, 42, 833–845.
1995PHA794 I. Simiti, O. Oniga, V. Zaharia, M. Horn, *Pharmazi* **1995**, 50, 794–796.
1995PS(105)213 M. G. Assy, H. Y. Moustafa, *Phosphorus Sulfur* **1995**, 105, 213–216.
1995S675 A. J. Moore, M. R. Bryce, A. S. Batsanov, J. C. Cole, J. A. K. Howard, *Synthesis* **1995**, 675–682.
1995S1033 C. Kiefl, A. Mannschreck, *Synthesis* **1995**, 1033–1037.
1995S1362 M. Fernández, E. de la Cuesta, C. Avendano, *Synthesis* **1995**, 1362–1364.
1995S1393 S. Le Roy-Gourvenec, S. Masson, *Synthesis* **1995**, 1393–1396.
1995S1423 K. Umemura, T. Tate, M. Yamaura, J. Yoshimura, Y. Yonezawa, C. Shin, *Synthesis* **1995**, 1423–1426.
1995S1497 A. R. Katritzky, J.-L. Moutou, Z. Yang, *Synthesis* **1995**, 1497–1505.
1995SL99 A. R. Katritzky, J.-L. Moutou, Z. Yang, *Synlett* **1995**, 99–100.
1995T12731 N. Irako, Y. Hamada, T. Shioiri, *Tetrahedron* **1995**, 51, 12731–12744.
1995TL67 J. A. Sowinski, P. L. Toogood, *Tetrahedron Lett.* **1995**, 36, 67–70.
1995TL237 D. Dubreuil, J. P. Pradère, N. Giraudeau, M. Goli, F. Tonnard, *Tetrahedron Lett.* **1995**, 36, 237–240.
1995TL3781 Y. Xiang, Q. Teng, C. K. Chu, *Tetrahedron Lett.* **1995**, 36, 3781–3784.
1995TL5491 A. R. Katritzky, J. Soloduchko, R. P. Musgrave, J. C. Breytenbach, *Tetrahedron Lett.* **1995**, 36, 5491–5494.
1995TL6153 C. D. J. Boden, G. Pattenden, *Tetrahedron Lett.* **1995**, 36, 6153–6156.
1995TL6395 P. Wipf, C. P. Miller, S. Venkatraman, P. C. Fritch, *Tetrahedron Lett.* **1995**, 36, 6395–6398.
1995TL6745 N. Borthakur, A. Goswami, *Tetrahedron Lett.* **1995**, 36, 6745–6746.
1995TL8311 P. Ilankumaran, A. R. Ramesha, S. Chandrasekaran, *Tetrahedron Lett.* **1995**, 36, 8311–8314.
1995RJGC521 O. B. Smolii, S. Ya Panchishin, E. A. Romanenko, B. S. Drach, *Russ. J. Gen. Chem. (Engl. Transl.)* **1995**, 65, 521–524.
1996AG(E)1503 G. Videnov, D. Kaiser, C. Kempter, G. Jung, *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 1503–1506.
1996AP73 W. von der Saal, R. A. Engh, A. Eichinger, B. Gabriel, R. Kucznier, J. Sauer, *Arch. Pharm. (Weinheim, Ger.)* **1996**, 329, 73–82.
1996BCJ2235 K. Shimada, M. Yamaguchi, T. Sasaki, K. Ohnishi, Y. Takikawa, *Bull. Chem. Soc. Jpn.* **1996**, 69, 2235–2242.
1996BMCL139 G. M. Coppola, H. Anjaria, R. E. Damon, *Bioorg. Med. Chem. Lett.* **1996**, 6, 139–142.
1996BMCL833 J. W. Clitherow, P. Beswick, W. J. Irving, D. I. C. Scopes, J. C. Barnes, J. Clapham, J. D. Brown, D. J. Evans, A. G. Hayes, *Bioorg. Med. Chem. Lett.* **1996**, 6, 833–838.
1996BMCL1543 P. L. Toogood, J. J. Hollenbeck, H. M. Lam, L. Li, *Bioorg. Med. Chem. Lett.* **1996**, 6, 1543–1546.
1996BMCL2253 L. G. Fisher, P. M. Sher, S. Skwish, I. M. Michel, S. M. Seiler, K. E. J. Dickinson, *Bioorg. Med. Chem. Lett.* **1996**, 6, 2253–2258.
1996BSB17 M. R. Kanyonyo, H. Ucar, M. Isa, P. Carato, D. Lesieur, P. Renard, J. H. Poupaert, *Bull. Soc. Chim. Belg.* **1996**, 105, 17–22.
1996BSF587 F. Cado, J. L. Di-Martino, P. Jacquault, J. P. Bazureau, J. Hamelin, *Bull. Soc. Chim. Fr.* **1996**, 133, 587–595.
1996CC1621 T. Tsuchiya, A. Oishi, I. Shibuya, Y. Taguchi, K. Honda, *J. Chem. Soc., Chem. Commun.* **1996**, 1621–1622.
1996CC1805 H. S. Park, I. S. Lee, Y. H. Kim, *J. Chem. Soc., Chem. Commun.* **1996**, 1805–1806.
1996CC1809 T. Murai, T. Ezaka, T. Kanda, S. Kato, *J. Chem. Soc., Chem. Commun.* **1996**, 1809–1810.
1996CCA535 P. Lohse, B. Oberhauser, B. Oberhauser-Hofbauer, G. Baschang, A. Eschenmoser, *Croat. Chem. Acta* **1996**, 69, 535–562.
1996CL1025 K. Okumura, M. Shigekuni, Y. Nakamura, C. Shin, *Chem. Lett.* **1996**, 1025–1026.
1996CPB2070 O. Uchikawa, K. Fukatsu, M. Suno, T. Aono, T. Doi, *Chem. Pharm. Bull.* **1996**, 44, 2070–2077.
1996HCA295 V.-M. Mukkala, P. Liitti, I. Hemmila, H. Takalo, C. Matachescu, J. Kankare, *Helv. Chim. Acta* **1996**, 79, 295–306.

- 1996HCA527 R. Luykx, C. B. Bucher, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1996**, 79, 527–540.
1996HCA1903 C. B. Bucher, H. Heimgartner, *Helv. Chim. Acta* **1996**, 79, 1903–1915.
1996JA12358 P. Wipf, P. C. Fritch, *J. Am. Chem. Soc.* **1996**, 118, 12358–12367.
1996JCS(P1)1749 Y. Hitotsuyanagi, Y. Matsumoto, S. Sasaki, J. Suzuki, K. Takeya, K. Yamaguchi, H. Itokawa, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1749–1755.
1996JMC1635 B. Dumaitre, N. Dodic, *J. Med. Chem.* **1996**, 39, 1635–1644.
1996JMC2170 A. Gazit, H. App, G. McMahon, J. Chen, A. Levitzki, F. D. Bohmer, *J. Med. Chem.* **1996**, 39, 2170–2177.
1996JMC3470 T. E. Renau, C. Kennedy, R. G. Ptak, J. M. Breitenbach, J. C. Drach, L. B. Townsend, *J. Med. Chem.* **1996**, 39, 3470–3476.
1996JOC1624 A. R. Katritzky, J. Li, *J. Org. Chem.* **1996**, 61, 1624–1628.
1996JOC778 G. Li, P. M. Warner, D. J. Jebaratnam, *J. Org. Chem.* **1996**, 61, 778–780.
1996JOC4655 J. M. Mínguez, M. I. Castellote, J. J. Vaquero, J. L. Garcia-Navio, J. Alvarez-Builla, O. Castano, J. L. Andrés, *J. Org. Chem.* **1996**, 61, 4655–4665.
1996JOC7398 D. M. Spero, S. R. Kapadia, *J. Org. Chem.* **1996**, 61, 7398–7401.
1996JOC7671 J. A. Sowinski, P. L. Toogood, *J. Org. Chem.* **1996**, 61, 7671–7676.
1996JOC8701 H. J. Schostarez, T. M. Schwartz, *J. Org. Chem.* **1996**, 61, 8701–8705.
1996JOC9045 M. A. Shalaby, C. W. Grote, H. Rapoport, *J. Org. Chem.* **1996**, 61, 9045–9048.
1996TL9107 D. J. Critcher, G. Pattenden, *Tetrahedron Lett.* **1996**, 37, 9107–9110.
1996JPR251 K. Hartke, S. Barrmeyer, *J. Prakt. Chem.* **1996**, 338, 251–256.
1996MI20 T. Naito, K. Hata, A. Tsuruoka, *Drugs of the Future* **1996**, 21, 20.
1996MI45 P. E. Hansen, F. Duus, S. Bolvig, T. S. Jagodzinski, *J. Mol. Struct.* **1996**, 378, 45–59.
1996MI190 T. Hoeg-Jensen, A. F. Spatola, A. Holm, *Int. J. Peptide Protein Res.* **1996**, 47, 190–200.
1996MI1102 M. Dolezal, J. Hartl, A. Lycka, V. Buchta, Z. Odlerova, *Collect. Czech. Chem. Commun.* **1996**, 61, 1102–1108.
1996MIP853426 T. Naito, K. Hata, Y. Kaku, A. Tsuruoka, I. Tsukada, M. Yanagisawa, T. Toyosawa, JP 0853426, **1996**.
1996PHA27 L. Bukowski, M. Janowiec, *Pharmazi* **1996**, 51, 27–30.
1996PHA540 S. A. El-Feky, Z. K. A. El-Samii, *Pharmazi* **1996**, 51, 540–543.
1996PS(108)257 T. Hoeg-Jensen, *Phosphorus Sulfur* **1996**, 108, 257–278.
1996PS(111)823 P. A. Otten, A. Van der Gen, *Phosphorus Sulfur* **1996**, 111, 823–823.
1996RJOC586 Y. M. Yutilov, L. I. Shcherbina, *Russ. J. Org. Chem. (Engl. Transl.)* **1996**, 32, 586–590.
1996S383 T. Hoeg-Jensen, A. Holm, H. Sorensen, *Synthesis* **1996**, 383–387.
1996SC1187 A. D. Moya, M. A. Cabrera, G. M. I. Trimino, V. H. Castro, *Synth. Commun.* **1996**, 26, 1187–1197.
1996SC2617 M.-D. Ruan, P.-F. Zhang, Y. Tao, W.-Q. Fan, *Synth. Commun.* **1996**, 26, 2617–2623.
1996SC3167 M. L. El Efrif, B. Hajjem, H. Zantour, B. Baccar, *Synth. Commun.* **1996**, 26, 3167–3173.
1996SL865 T. Murai, T. Ezaka, N. Niwa, T. Kanda, S. Kato, *Synlett* **1996**, 865–866.
1996T4123 F. Palacios, D. Aparicio, J. M. de los Santos, *Tetrahedron* **1996**, 52, 4123–4132.
1996T13739 D. J. Ramón, M. Yus, *Tetrahedron* **1996**, 52, 13739–13750.
1996T7691 T. Oberhauser, V. Meduna, *Tetrahedron* **1996**, 52, 7691–7702.
1996TL123 A. S. Bell, C. W. G. Fishwick, J. E. Reed, *Tetrahedron Lett.* **1996**, 37, 123–126.
1996TL5203 A. S. Fisyuk, M. A. Vorontsova, D. V. Temnikov, *Tetrahedron Lett.* **1996**, 37, 5203–5206.
1996TL11163 D. H. R. Barton, G. Fontana, *Tetrahedron Lett.* **1996**, 52, 11163–11176.
1997BCJ197 K. Shimada, N. Jin, M. Kawaguchi, K. Dobashi, Y. Nagano, M. Fujimura, E. Kudoh, T. Kai, N. Saito, J.-I. Masuda, M. Iwaya, H. Fujisawa, S. Aoyagi, Y. Takikawa, *Bull. Chem. Soc. Jpn.* **1997**, 70, 197–206.
1997BMCL861 Y. Saito, K. Umezawa, K. Kato, *Bioorg. Med. Chem. Lett.* **1997**, 7, 861–864.
1997CB49 P. A. Otten, S. Gorter, A. van der Gen, *Chem. Ber.* **1997**, 130, 49–54.
1997CB913 H. Blau, J. Grobe, D. Le Van, B. Krebs, M. Läge, *Chem. Ber.* **1997**, 130, 913–922.
1997CHE805 A. S. Fisyuk, L. V. Berdovich, D. V. Temnikov, L. N. Knyaz'kova, *Chem. Heterocycl. Compd. (Engl. Transl.)* **1997**, 33, 805–810.
1997CL701 K. Shimada, K. Aikawa, T. Fujita, S. Aoyagi, Y. Takikawa, C. Kabuto, *Chem. Lett.* **1997**, 701–702.
1997CPB189 H. Sasaki, A. Suehiro, Y. Nakamoto, *Chem. Pharm. Bull.* **1997**, 45, 189–193.
1997MI615 O. Bruno, S. Schenone, A. Ranise, F. Bondavalli, G. Falcone, W. Filippelli, I. Marabese, G. Motula, *Farmaco* **1997**, 52, 615–618.
1997HCA273 D. M. Argilagos, M. I. G. Trimino, A. M. Cabrera, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1997**, 80, 273–292.
1997JCS(P1)2983 V. Zoete, F. Bailly, J.-P. Catteau, J.-L. Bernier, *J. Chem. Soc., Perkin Trans. 1* **1997**, 2983–2988.
1997JCS(P1)3285 G. H. Elgemeie, A. H. Elghandour, A. M. Elzanate, S. A. Ahmed, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3285–3289.
1997JCS(P2)575 F. Arnaud-Neu, G. Barrett, D. Corry, S. Cremin, G. Ferguson, J. F. Gallagher, S. J. Harris, M. A. McKervey, M.-J. Schwing-Weill, *J. Chem. Soc., Perkin Trans. 2* **1997**, 575–579.
1997JCS(P2)1353 R. J. W. Lugtenberg, R. J. M. Egberink, J. F. J. Engbersen, D. N. Reinhoudt, *J. Chem. Soc., Perkin Trans. 2* **1997**, 1353–1357.
1997JHC643 J. G. Sósnicki, T. S. Jagodzinski, J. Liebscher, *J. Heterocycl. Chem.* **1997**, 34, 643–648.
1997JOC1896 M. D. Bachi, A. Melman, *J. Org. Chem.* **1997**, 62, 1896–1898.
1997JOC3804 M. A. Ciufolini, Y. C. Shen, *J. Org. Chem.* **1997**, 62, 3804–3805.
1997JOC3808 C. T. Brain, A. Hallett, S. Y. Ko, *J. Org. Chem.* **1997**, 62, 3808–3809.
1997JOC6215 A. R. Katritzky, L. Serdyuk, L. Xie, I. Ghiviriga, *J. Org. Chem.* **1997**, 62, 6215–6221.
1997JPR697 F. Laduron, C. Nyns, Z. Janousek, H. G. Viehe, *J. Prakt. Chem.* **1997**, 339, 697–707.
1997MI29 V. P. Litvinov, V. D. Dyachenko, *Dokl. Chem.* **1997**, 352, 29–33. (636–640).
1997MI741 T. Naito, A. Tsuruoka, H. Sakurai, R. Sakai, *J. Label. Compds. Radiopharm.* **1997**, 39, 741–746.

- 1997OM756 G. M. Li, R. A. Zingaro, M. Segi, J. H. Reibenspies, T. Nakajima, *Organometallics* **1997**, *16*, 756–762.
- 1997PHA346 N. S. Habib, S. M. Rida, E. A. M. Badawey, H. T. Y. Fahmy, H. A. Ghozlan, *Pharmazi* **1997**, *52*, 346–350.
- 1997PHA419 H. Stark, X. Ligneau, R. Lipp, J.-M. Arrang, J.-C. Schwartz, W. Schunack, *Pharmazi* **1997**, *52*, 419–423.
- 1997PJC1060 J. Kameníček, F. Kašpárek, M. Posolda, V. Bekárek, J. Marek, *Pol. J. Chem.* **1997**, *71*, 1060–1065.
- 1997PS(126)39 M. J. Gil, A. Reliquet, J. C. Meslin, *Phosphorus Sulfur* **1997**, *126*, 39–52.
- 1997RJOC569 K. V. Domasevich, *Russ. J. Org. Chem.* **1997**, *33*, 569–570.
- 1997SI199 D. Prévôté, S. Le Roy-Gourvennec, A.-M. Caminade, S. Masson, J.-P. Majoral, *Synthesis* **1997**, 1199–1207.
- 1997SC1153 B. P. Bandgar, S. M. Zirange, P. P. Wadgaonkar, *Synth. Commun.* **1997**, *27*, 1153–1156.
- 1997SC2393 K. Matsuda, I. Yanagisawa, Y. Isomura, T. Mase, T. Shibamura, *Synth. Commun.* **1997**, *27*, 2393–2402.
- 1997SC3431 J. Spychała, *Synth. Commun.* **1997**, *27*, 3431–3440.
- 1997SL1 P. Wipf, S. Venkatraman, *Synlett* **1997**, 1–10.
- 1997SL775 T. Murai, T. Ezaka, T. Ichimiya, S. Kato, *Synlett* **1997**, 775–776.
- 1997TI3383 V. Bavetsias, G. M. F. Bisset, R. Kimbell, F. T. Boyle, A. L. Jackmann, *Tetrahedron* **1997**, *53*, 13383–13396.
- 1997TI7253 P. Beslin, B. Lelong, *Tetrahedron* **1997**, *53*, 17253–17264.
- 1997TL1297 W. C. Patt, M. A. Massa, *Tetrahedron Lett.* **1997**, *38*, 1297–1300.
- 1997TL2459 N. Galéotti, E. Plagnes, P. Jouin, *Tetrahedron Lett.* **1997**, *38*, 2459–2462.
- 1997TL4811 K. Umemura, K. Watanabe, K. Ono, M. Yamaura, J. Yoshimura, *Tetrahedron Lett.* **1997**, *38*, 4811–4814.
- 1997ZN323 K. V. Domasevitch, V. V. Ponomareva, A. A. Mokhir, E. B. Rusanov, J. Sieler, E. Hoyer, *Z. Naturforsch.* **1997**, *52*, 323–330.
- 1998BCJ1193 T. Murai, T. Ezaka, S. Kato, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1193–1200.
- 1998BCJ1391 K. Umemura, H. Noda, J. Yoshimura, A. Konn, Y. Yonezawa, C. Shin, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1391–1396.
- 1998CHE188 V. D. Dyachenko, V. P. Litvinov, *Chem. Heterocycl. Compd. (Engl. Transl.)* **1998**, *34*, 188–194.
- 1998CL17 M. Yoshifuji, N. Higeta, D.-L. An, K. Toyota, *Chem. Lett.* **1998**, 17–18.
- 1998CL1287 H. Ishihara, K. Yosimura, M. Kouketsu, *Chem. Lett.* **1998**, 1287–1288.
- 1998CPB623 A. Tsuruoka, Y. Kaku, H. Kakinuma, I. Tsukada, M. Yanagisawa, K. Nara, T. Naito, *Chem. Pharm. Bull.* **1998**, *46*, 623–630.
- 1998H857 M. Hasegawa, *Heterocycles* **1998**, *47*, 857–864.
- 1998H1319 K. Okumura, A. Ito, D. Yoshioka, C. Shin, *Heterocycles* **1998**, *48*, 1319–1324.
- 1998HAC57 G. M. Li, J. H. Reibenspies, R. A. Zingaro, *Heteroatom Chem.* **1998**, *9*, 57–64.
- 1998JA591 R. M. Rzaa, H. A. Shea, D. Romo, *J. Am. Chem. Soc.* **1998**, *120*, 591–592.
- 1998JA5453 R. M. Lemieux, A. I. Meyers, *J. Am. Chem. Soc.* **1998**, *120*, 5453–5457.
- 1998JA10027 J. Nakayama, I. Akiyama, Y. Sugihara, T. Nishi, *J. Amer. Chem. Soc.* **1998**, *120*, 10027–10031.
- 1998JCR(S)84 M. R. Selim, *J. Chem. Res. (S)* **1998**, 84–85.
- 1998JCR(S)672 F. A. Attaby, S. M. Eldin, M. A. A. El-Neairy, *J. Chem. Res. (S)* **1998**, *10*, 672–673.
- 1998JCS(P1)601 C. J. Moody, M. C. Bagley, *J. Chem. Soc., Perkin Trans. 1* **1998**, 601–607.
- 1998JCS(P1)647 G. M. Li, R. A. Zingaro, *J. Chem. Soc., Perkin Trans. 1* **1998**, 647–650.
- 1998JCS(P1)2133 V. S. Berseneva, A. V. Tkachev, Y. Y. Morzherin, W. Dehaen, I. Luyten, S. Toppet, V. A. Bakulev, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2133–2136.
- 1998JHC177 H.-S. Kim, Y. K. Koh, J.-H. Choi, *J. Heterocycl. Chem.* **1998**, *35*, 177–181.
- 1998JHC499 F. T. Coppo, M. M. Fawzi, *J. Heterocycl. Chem.* **1998**, *35*, 499–501.
- 1998JHC659 H.-S. Lee, Y.-G. Chang, K. Kim, *J. Heterocycl. Chem.* **1998**, *35*, 659–668.
- 1998JMAC1541 A. J. Moore, M. R. Bryce, A. S. Batsanov, J. N. Heaton, C. W. Lehmann, J. A. K. Howard, N. Robertson, A. E. Underhill, I. F. Perepicka, *J. Mater. Chem.* **1998**, *8*, 1541–1550.
- 1998JMC63 K. Unverferth, J. Engel, N. Höfgen, A. Rostock, R. Günther, H.-J. Lankau, M. Menzer, A. Rolfs, J. Liebscher, B. Müller, H.-J. Hofmann, *J. Med. Chem.* **1998**, *41*, 63–73.
- 1998JMC4240 B. Gabriel, M. T. Stubbs, A. Bergner, J. Hauptmann, W. Bode, J. Stürzebecher, L. Moroder, *J. Med. Chem.* **1998**, *41*, 4240–4250.
- 1998JMC4903 R. Perrone, F. Berardi, N. A. Colabufo, M. Leopoldo, V. Tortorella, *J. Med. Chem.* **1998**, *41*, 4903–4909.
- 1998JOC374 T. Murai, N. Niwa, T. Ezaka, S. Kato, *J. Org. Chem.* **1999**, *63*, 374–376.
- 1998JOC1473 A. R. Katritzky, D. Feng, M. Qi, *J. Org. Chem.* **1998**, *63*, 1473–1477.
- 1998JOC7481 Y. Tobe, S. Sasaki, M. Mizuno, K. Hirose, K. Naemura, *J. Org. Chem.* **1998**, *63*, 7481–7489.
- 1998M661 O. Oniga, I. Grosu, S. Mager, I. Simiti, *Monatsh. Chem.* **1998**, *129*, 661–669.
- 1998MI849 H. K. Oh, S. Y. Woo, C. H. Shin, I. Lee, *Int. J. Chem. Kinet.* **1998**, *30*, 849–857.
- 1998MI863 F. Mévellec, F. Demaimay, A. Roucoux, A. Moisan, N. Noiret, H. Patin, *J. Labelled Cpd. Radiopharm.* **1998**, *XLI*, 863–869.
- 1998MI2300 M. A. Kukaniev, S. S. Shukurov, Y. Khodzhibaev, N. Kurbonova, S. G. Bandaev, *Russ. Chem. Bl.* **1998**, *47*, 2300–2301.
- 1998PHA373 L. Bukowski, M. Janowiec, Z. Zwolska-Kwiek, Z. Andrzejczyk, *Pharmazi* **1998**, *53*, 373–376.
- 1998PJC439 R. Anulewicz, T. M. Krygowski, T. Jagodzinski, *Pol. J. Chem.* **1998**, *72*, 439–448.
- 1998PS(136-138)525 G. M. Li, R. A. Zingaro, *Phosphorus Sulphur* **1998**, *136–138*, 525–530.
- 1998PS(136-138)569 J. Nakayama, I. Akiyama, Y. Sugihara, *Phosphorus Sulphur* **1998**, *136–138*, 569–572.
- 1998RJOC876 V. D. Dyachenko, S. G. Krivokolysko, V. P. Litvinov, *Russ. J. Org. Chem. (Engl. Transl.)* **1998**, *34*, 876–881.

- 1998SC4517 Y. H. Kim, H. S. Park, D. W. Kwon, *Synth. Commun.* **1998**, 28, 4517–4524.
 1998SL1077 V. A. Reader, *Synlett* **1998**, 1077–1078.
 1998SL1243 L. E. Kiss, J. Rabbi, L. Varga, I. Koevesdi, *Synlett* **1998**, 1243–1245.
 1998T3219 A. S. Bell, C. W. G. Fishwick, J. E. Reed, *Tetrahedron* **1998**, 54, 3219–3234.
 1998T8721 J. Lehmann, A. Linden, H. Heimgartner, *Tetrahedron* **1998**, 54, 8721–8736.
 1998TL89 S. S. Klair, H. R. Mohan, T. Kitahara, *Tetrahedron Lett.* **1998**, 39, 89–92.
 1998TL127 C. T. Brain, A. Hallett, S. Y. Ko, *Tetrahedron Lett.* **1998**, 39, 127–130.
 1998TL245 A. B. Charette, P. Chua, *Tetrahedron Lett.* **1998**, 39, 245–248.
 1998TL1673 T. Messeri, D. D. Sternbach, N. C. O. Tomkinson, *Tetrahedron Lett.* **1998**, 39, 1673–1676.
 1998TL1763 M. Kawakami, M. Suzuki, H. Kawai, K. Ogawa, T. Shishido, *Tetrahedron Lett.* **1998**, 39, 1763–1766.
 1998TL2755 F. Sandrinelli, S. Le Roy-Gourvennec, S. Masson, P. Rollin, *Tetrahedron Lett.* **1998**, 39, 2755–2758.
 1998TL8645 J.-D. Charrier, A. Reliquet, J.-C. Meslin, *Tetrahedron Lett.* **1998**, 39, 8645–8646.
 1998TL9259 S. Braverman, M. Cherkinsky, L. Kedrova, *Tetrahedron Lett.* **1998**, 39, 9259–9262.
 1999BCJ1561 K. Okumura, Y. Nakamura, C. Shin, *Bull. Chem. Soc. Jpn.* **1999**, 72, 1561–1569.
 1999BCJ2483 K. Okumura, T. Suzuki, Y. Nakamura, C. Shin, *Bull. Chem. Soc. Jpn.* **1999**, 72, 2483–2490.
 1999BMCI559 T. T. Sakai, N. R. Krishna, *Bioorg. Med. Chem.* **1999**, 7, 1559–1565.
 1999BMCL569 X.-H. Gu, X.-Z. Wan, B. Jiang, *Bioorg. Med. Chem. Lett.* **1999**, 9, 569–572.
 1999BMCL1167 J. S. Carter, D. J. Rogier, M. J. Graneto, K. Seibert, C. M. Koboldt, Y. Zhang, J. J. Talley, *Bioorg. Med. Chem. Lett.* **1999**, 9, 1167–1170.
 1999BMCL1973 G. Carvatti, J. Rahuel, B. Gay, P. Furet, *Bioorg. Med. Chem. Lett.* **1999**, 9, 1973–1978.
 1999BMCL2353 J. L. Buchanan, R. S. Bohacek, G. P. Luke, M. Hatada, X. Lu, D. S. Dalgarno, S. S. Narula, R. Yuan, D. A. Holt, *Bioorg. Med. Chem. Lett.* **1999**, 9, 2353–2358.
 1999BMCL3147 J. Stürzebecher, H. Vieweg, T. Steinmetzer, A. Schweinitz, M. T. Stubbs, M. Renatus, P. Wikström, *Bioorg. Med. Chem. Lett.* **1999**, 9, 3147–3152.
 1999CCC417 V. Klimesova, M. Svoboda, K. Waisser, M. Pour, J. Kaustova, *Collect. Czech. Chem. Commun.* **1999**, 64, 417–434.
 1999H277 K. Oda, M. Sakai, K. Ohno, M. Machida, *Heterocycles* **1999**, 50, 277–282.
 1999H2349 C. Fruit, A. Truck, N. Plé, G. Quéguiner, *Heterocycles* **1999**, 51, 2349–2365.
 1999HCA888 J. Lehmann, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1999**, 82, 888–908.
 1999MI533 K. Walczyński, H. Timmerman, O. P. Zuiderveld, M. Q. Zhang, R. Glinka, *Farmaco* **1999**, 54, 533–541.
 1999MI666 V. Klimesova, M. Svoboda, K. Waisser, M. Pour, J. Kaustova, *Farmaco* **1999**, 54, 666–672.
 1999H137 J. Bernat, I. Chomca, P. Kristian, K. Pihlaja, K. D. Klika, J. Imrich, *Heterocycles* **1999**, 51, 137–140.
 1999HCA1899 J. Lehmann, H. Heimgartner, *Helv. Chim. Acta* **1999**, 82, 1899–1915.
 1999JHC1183 M. T. Cocco, C. Congiu, V. Onnis, A. M. Bernard, P. P. Piras, *J. Heterocycl. Chem.* **1999**, 36, 1183–1188.
 1999JCS(P1)111 P. A. Koutentis, C. W. Rees, *J. Chem. Soc., Perkin Trans. 1* **1999**, 111–117.
 1999JCR(S)184 A. O. Abdelhamid, H. F. Zohdi, N. M. Rateb, *J. Chem. Res. (S)* **1999**, 184–185.
 1999JCR(S)696 F. M. Abd El Latif, M. A. Bary, E. A. Elrady, M. Hassan, *J. Chem. Res. (S)* **1999**, 12, 696–697.
 1999JHC1033 J. Sosnicki, T. Jagodzinski, M. Krolilowska, *J. Heterocycl. Chem.* **1999**, 36, 1033–1041.
 1999JMC1661 H. Matsumoto, K. Ikeda, N. Nagata, H. Takayanagi, Y. Mizuno, M. Tanaka, T. Sasaki, *J. Med. Chem.* **1999**, 42, 1661–1666.
 1999JMC2046 B. Zacharie, M. Lagraoui, M. Dimarco, C. L. Penney, L. Gagnon, *J. Med. Chem.* **1999**, 42, 2046–2052.
 1999JMC3557 W. R. Ewing, M. R. Becker, V. E. Manetta, R. S. Davis, H. W. Pauls, H. Mason, Y. M. Choi-Sledeski, D. Green, D. Cha, A. P. Spada, D. L. Cheney, J. S. Mason, S. Maignan, J.-P. Guilloteau, K. Brown, D. Colussi, R. Bentley, J. Bostwick, C. J. Kasiewski, S. R. Morgan, R. J. Leadley, C. T. Dunwiddie, M. H. Perrone, V. Chu, *J. Med. Chem.* **1999**, 42, 3557–3571.
 1999JMC3572 Y. M. Choi-Sledeski, D. G. McGarry, D. M. Green, H. J. Mason, M. R. Becker, R. S. Davis, W. R. Ewing, W. P. Dankulich, V. E. Manetta, R. L. Morris, A. P. Spada, D. L. Cheney, K. D. Brown, D. J. Colussi, V. Chu, C. L. Heran, S. R. Morgan, R. G. Bentley, R. J. Leadley, S. Maignan, J.-P. Guilloteau, C. T. Dunwiddie, H. W. Pauls, *J. Med. Chem.* **1999**, 42, 3572–3587.
 1999JMC5064 R. E. Boyd, J. B. Press, C. R. Rasmussen, R. B. Raffa, E. E. Codd, C. D. Connelly, D. J. Bennett, A. L. Kirifides, J. F. Gardocki, B. Reynolds, J. T. Hortenstein, A. B. Reitz, *J. Med. Chem.* **1999**, 42, 5064–5071.
 1999MI63 R. Adhikari, D. Jones, A. J. Liepa, M. F. Mackay, *Aust. J. Chem.* **1999**, 52, 63–67.
 1999MI693 J. Rohály, L. Novák, C. Szántay, *OPPI Briefs* **1999**, 31, 693–694.
 1999MI115 A. B. Corradi, C. Boga, L. Forlani, P. Sgarabotto, *J. Chem. Crystallogr.* **1999**, 29, 115–119.
 1999MI2345 R. P. Panzica, L. B. Townsend, *Nucleosides Nucleotides* **1999**, 18, 2345–2356.
 1999MI2425 K. S. Ramasamy, D. Averett, *Nucleosides Nucleotides* **1999**, 18, 2425–2431.
 1999PHA106 T. I. El-Emary, E. A. Bakhite, *Pharmazi* **1999**, 54, 106–111.
 1999RJOC1377 V. P. Litvinov, V. D. Dyachenko, *Russ. J. Org. Chem. (Engl. Transl.)* **1999**, 35, 1377–1384.
 1999S669 C. Alayrac, S. Nowaczyk, M. Lemarié, P. Metzner, *Synthesis* **1999**, 669–675.
 1999S1319 Y. Yokoyama, K. Mochida, *Synthesis* **1999**, 1319–1324.
 1999SC4113 H. Y. Zhang, Z. J. Yang, H. W. Yu, Z. S. Piao, L. T. Ma, J. M. Min, L. H. Zhang, *Synth. Commun.* **1999**, 29, 4113–4126.
 1999T1187 D. C. Harrowven, M. C. Lucas, P. D. Howes, *Tetrahedron* **1999**, 55, 1187–1196.
 1999T3007 D. Krumme, H. Tschesche, *Tetrahedron* **1999**, 55, 3007–3018.
 1999T5017 T. Nishio, H. Sekiguchi, *Tetrahedron* **1999**, 55, 5017–5026.
 1999T5359 J. Lehmann, A. Linden, H. Heimgartner, *Tetrahedron* **1999**, 55, 5359–5376.
 1999T11833 C. Gros, N. Galéotti, R. Pascal, P. Jouin, *Tetrahedron* **1999**, 55, 11833–11842.
 1999T12301 H. Kigoshi, S. Yamada, *Tetrahedron* **1999**, 55, 12301–12308.

- 1999TA4123 M. J. Milewska, T. Polónski, *Tetrahedron: Asymmetry* **1999**, *10*, 4123–4128.
1999TL423 D. Goff, J. Fernandez, *Tetrahedron Lett.* **1999**, *40*, 423–426.
1999TL2841 J. Spychała, *Tetrahedron Lett.* **1999**, *40*, 2841–2844.
1999TL7031 J. Simpson, D. L. Rathbone, D. C. Billington, *Tetrahedron Lett.* **1999**, *38*, 7031–7033.
1999TL7549 M. Nooshabadi, K. Aghapoor, H. R. Darabi, M. M. Mojtahedi, *Tetrahedron Lett.* **1999**, *40*, 7549–7552.
2000BMC363 B. Jiang, X.-H. Gu, *Bioorg. Med. Chem.* **2000**, *8*, 363–371.
2000BMC2291 A. von Matt, C. Ehrhardt, P. Burkhard, R. Metternich, M. Walkinshaw, C. Tapparelli, *Bioorg. Med. Chem.* **2000**, *8*, 2291–2303.
2000BMCL1563 U. Baettig, L. Brown, D. Brundish, C. Dell, A. Furzer, S. Garman, D. Janus, P. D. Kane, G. Smith, C. V. Walker, X. Cockcroft, J. Ambler, A. Mitchelson, M. D. Talbot, M. Tweed, N. Wills, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1563–1566.
2000BMCL1971 R. J. Mathvink, J. S. Tolman, D. Chitty, M. R. Candelore, M. A. Cascieri, L. F. Colwell Jr., L. Deng, W. P. Feeney, M. J. Forrest, G. J. Hom, D. E. MacIntyre, L. Tota, M. J. Wyvratt, M. H. Fisher, A. E. Weber, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1971–1973.
2000CAR25 E. Bozó, A. Medgyes, S. Boros, J. Kuszmann, *Carbohydr. Res.* **2000**, *329*, 25–40.
2000CAR525 E. Bozó, S. Boros, J. Kuszmann, *Carbohydr. Res.* **2000**, *329*, 525–538.
2000CC2093 L. Doszczak, J. Rachon, *J. Chem. Soc., Chem. Commun.* **2000**, 2093–2094.
2000EJOC3273 C. Heyde, I. Zug, H. Hartmann, *Eur. J. Org. Chem.* **2000**, 3273–3278.
2000EJOC3305 T. J. Zimmermann, O. Freundel, R. Gompper, T. J. J. Müller, *Eur. J. Org. Chem.* **2000**, 3305–3312.
2000MI383 S. Schenone, O. Bruno, A. Ranise, F. Bondavalli, G. Facone, W. Filippelli, B. Rivaldi, *Farmaco* **2000**, *55*, 383–388.
2000MI569 K. Walczyński, R. Guryn, O. P. Zuiderveld, M.-Q. Zhang, H. Timmerman, *Farmaco* **2000**, *55*, 569–574.
2000H1171 J. Bernát, P. Kristian, J. Guspanova, I. Chomča, *Heterocycles* **2000**, *53*, 1171–1174.
2000JA12041 M. Wu, T. Okino, L. M. Nogle, B. L. Marquez, R. T. Williamson, N. Sitachitta, F. W. Berman, T. F. Murray, K. McGough, R. Jacobs, K. Colsen, T. Asano, F. Yokokawa, T. Shioiri, W. H. Gerwick, *J. Am. Chem. Soc.* **2000**, *122*, 12041–12042.
2000JCR(S)228 F. M. Moghaddam, M. Ghaffarzadeh, M. G. Dakamin, *J. Chem. Res. (S)* **2000**, 228–229.
2000JCS(P1)3227 J. M. Sanderson, P. Singh, C. W. G. Fishwick, J. B. C. Findlay, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3227–3231.
2000JCS(P2)2306 H. K. Oh, S. K. Kim, I. H. Cho, H. W. Lee, I. Lee, *J. Chem. Soc., Perkin Trans. 2* **2000**, 2306–2310.
2000JMC721 T. D. Penning, N. S. Chandrakumar, B. B. Chen, H. Y. Chen, B. N. Desai, S. W. Djuric, S. H. Docter, A. F. Gasielki, R. A. Haack, J. M. Migashiro, M. A. Russel, S. S. Yu, D. G. Corley, R. C. Durley, B. F. Kilpatrick, B. L. Parnay, L. J. Askonas, J. K. Gierse, E. F. Harding, M. K. Highkin, J. F. Kachur, S. H. Kim, G. G. Krivi, D. Villani-Price, E. Y. Pyla, W. G. Smith, N. S. Ghoreishi-Haask, *J. Med. Chem.* **2000**, *43*, 721–735.
2000JMC1550 G. Wells, A. Seaton, M. F. G. Stevens, *J. Med. Chem.* **2000**, *43*, 1550–1562.
2000JMC2759 W. C. Stevens Jr., R. M. Jones, G. Subramanian, T. G. Metzger, D. M. Ferguson, P. S. Portoghese, *J. Med. Chem.* **2000**, *43*, 2759–2769.
2000JMC3832 R. J. Mathvink, J. S. Tolman, D. Chitty, M. R. Candelore, M. A. Cascieri, L. F. Colwell Jr., L. Deng, W. P. Feeney, M. J. Forrest, G. J. Hom, D. E. MacIntyre, R. R. Miller, R. A. Stearns, L. Tota, M. J. Wyvratt, M. H. Fisher, A. E. Weber, *J. Med. Chem.* **2000**, *43*, 3832–3836.
2000JMC4063 D. A. Dudley, A. M. Bunker, L. Chi, W. L. Cody, D. R. Holland, D. P. Ignasiak, N. Janiczek-Dolphin, T. B. McClanahan, T. E. Mertz, L. S. Narasimhan, S. T. Rapundalo, J. A. Trautschold, C. A. Van Huis, J. J. Edmunds, *J. Med. Chem.* **2000**, *22*, 4063–4070.
2000JOC2684 A. Padwa, L. S. Beall, T. M. Heidelbaugh, B. Liu, S. M. Sheehan, *J. Org. Chem.* **2000**, *65*, 2684–2695.
2000JPR682 W. Kantelehner, M. Hauber, E. Haug, C. Schallenmüller, C. Regele, *J. Prakt. Chem.* **2000**, *342*, 682–699.
2000OL311 T. Murai, A. Suzuki, T. Ezaka, S. Kato, *Org. Lett.* **2000**, *2*, 311–313.
2000OL2269 S. Greve, C. Näther, W. Friedrichsen, *Org. Lett.* **2000**, *2*, 2269–2270.
2000PS(167)161 M. A. A. Elneairy, F. A. Attaby, M. S. Elsayed, *Phosphorus Sulfur* **2000**, *167*, 161–179.
2000PS(167)289 M. A. A. Elneairy, S. M. Eldin, F. A. Attaby, A. K. K. El-Louh, *Phosphorus Sulfur* **2000**, *167*, 289–302.
2000RJOC1110 L. L. Dmitrieva, G. I. Sarapulova, L. V. Klyba, A. I. Albanov, V. P. Zinovyeva, S. V. Tolmachev, N. A. Nedolya, L. Brandsma, *Russ. J. Org. Chem. (Engl. Transl.)* **2000**, *36*, 1110–1115.
2000S805 H. Hartmann, C. Heyde, I. Zug, *Synthesis* **2000**, 805–808.
2000S1143 N. Leflemme, P. Marchand, M. Gulea, S. Masson, *Synthesis* **2000**, 1143–1147.
2000SC565 G. W. Spears, K. Tsuji, T. Tojo, H. Nishimura, T. Ogino, *Synth. Commun.* **2000**, *30*, 565–574.
2000SC1083 J. Spychała, *Synth. Commun.* **2000**, *30*, 1083–1094.
2000T7981 J. Spychała, *Tetrahedron* **2000**, *56*, 7981–7986.
2000TA1985 M. J. Arévalo, M. Avalos, R. Babiano, A. Cabanillas, P. Cintas, J. L. Jiménez, J. C. Palacios, *Tetrahedron Asymmetry* **2000**, *11*, 1985–1995.
2000TA2793 Z. Arány, Z. Czarnocki, K. Wojtasiewicz, J. K. Maurin, *Tetrahedron Asymmetry* **2000**, *11*, 2793–2800.
2000TCC179 T. Murai, S. Kato, *Top. Curr. Chem.* **2000**, *208*, 179–199.
2000TL2537 C. Alayrac, P. Metzner, *Tetrahedron Lett.* **2000**, *41*, 2537–2539.
2000TL4965 J.-F. Pons, Q. Mishir, A. Nouvet, F. Brookfield, *Tetrahedron Lett.* **2000**, *41*, 4965–4968.
2000TL7947 R. Olsson, H. C. Hansen, C.-M. Andersson, *Tetrahedron Lett.* **2000**, *41*, 7947–7950.
2000TL9493 D. L. Boger, B. M. Aquila, W. C. Tse, M. Searcey, *Tetrahedron Lett.* **2000**, *41*, 9493–7498.

- 2001BCJ511 K. Shimada, K. Aikawa, T. Fujita, M. Sato, K. Goto, S. Aoyagi, Y. Takikawa, C. Kabuto, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 511–525.
- 2001BMC2035 S. Kumar, A. L. Pearson, R. F. Pratt, *Bioorg. Med. Chem.* **2001**, *9*, 2035–2044.
- 2001BMCL1289 M. S. Smyth, J. Rose, M. M. Mehrotra, J. Heath, G. Ruhter, T. Schotten, J. Seroogy, D. Volkots, A. Pandey, R. M. Scarborough, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1289–1292.
- 2001BMCL1301 P. G. Wyatt, M. J. Allen, J. Chilcott, G. Hickin, N. D. Miller, P. M. Woollard, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1301–1305.
- 2001BMCL1379 N. L. Subasinghe, C. Illig, J. Hoffman, M. J. Rudolph, K. J. Wilson, R. Soll, T. Randle, D. Green, F. Lewandowski, M. Zhang, R. Bone, J. Spurlino, R. DesJarlais, I. Deckman, C. J. Molloy, C. Manthey, Z. Zhou, C. Sharp, D. Maguire, C. Crysler, B. Grasberger, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1379–1382.
- 2001CAR325 E. Bozó, S. Boros, J. Kuzmann, *Carbohydr. Res.* **2001**, *332*, 325–333.
- 2001CC717 G. Pattenden, T. Thompson, *J. Chem. Soc., Chem. Commun.* **2001**, 717–718.
- 2001CC1934 V.-A. Nguyen, C. L. Willis, W. H. Gerwick, *J. Chem. Soc., Chem. Commun.* **2001**, 1934–1935.
- 2001CPB347 R. Tokuyama, Y. Takahashi, Y. Tomita, T. Suzuki, T. Yoshida, N. Iwasaki, N. Kado, E. Okezaki, O. Nagata, *Chem. Pharm. Bull.* **2001**, *49*, 347–352.
- 2001EJOC1695 R. Ketcham, E. Schaumann, G. Adiwidjaja, *Eur. J. Org. Chem.* **2001**, 1695–1699.
- 2001H835 T. Suzuki, A. Nagasaki, K. Okumura, C. Shin, *Heterocycles* **2001**, *55*, 835–840.
- 2001HCA786 R. A. Breitenmoser, H. Heimgartner, *Helv. Chim. Acta* **2001**, *84*, 786–796.
- 2001JCS(D)550 C. R. Rice, S. Wörl, J. C. Jeffery, R. L. Paul, M. D. Ward, *J. Chem. Soc., Dalton Trans.* **2001**, 550–559.
- 2001JCS(P1)358 S. V. Ley, A. G. Leach, R. I. Storer, *J. Chem. Soc., Perkin Trans. 1* **2001**, 358–361.
- 2001JCS(P1)1212 J.-D. Charrier, D. Deniaud, A. Reliquet, J.-C. Meslin, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1212–1215.
- 2001JCS(P1)2711 T. Murai, A. Suzuki, S. Kato, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2711–2716.
- 2001JCS(P2)2287 G. Arena, A. Contino, E. Longo, D. Sciotto, G. Spoto, *J. Chem. Soc., Perkin Trans. 2* **2001**, 2287–2291.
- 2001JOC4099 M. Koketsu, M. Kanoh, E. Itoh, H. Ishihara, *J. Org. Chem.* **2001**, *66*, 4099–4101.
- 2001JOC4776 M. T. Migawa, L. B. Townsend, *J. Org. Chem.* **2001**, *66*, 4776–4782.
- 2001JOC7841 S. Nowaczyk, C. Alayrac, V. Reboul, P. Metzner, M.-T. Averbuch-Pouchot, *J. Org. Chem.* **2001**, *66*, 7841–7848.
- 2001JMC1741 C. E. Stephens, F. Tanious, S. Kim, W. D. Wilson, W. A. Schell, J. R. Perfect, S. G. Franzblau, D. W. Boykin, *J. Med. Chem.* **2001**, *44*, 1741–1748.
- 2001JMC2990 L. Poitout, P. Roubert, M.-O. Contour-Galcéra, C. Moinet, J. Lannoy, J. Pommier, P. Plas, D. Bigg, C. Thurieau, *J. Med. Chem.* **2001**, *44*, 2990–3000.
- 2001OL3655 Q. Qiao, S.-S. So, A. Robert, R. A. Goodnow, *Org. Lett.* **2001**, *3*, 3655–3658.
- 2001PHA23 L. Bukowski, *Pharmazi* **2001**, *56*, 23–27.
- 2001PS(170)75 A. M. El-Sayed, O. A. A. Allah, *Phosphorus Sulfur* **2001**, *170*, 75–86.
- 2001PS(175)129 H. M. Moustafa, *Phosphorus Sulfur* **2001**, *175*, 129–142.
- 2001S1308 R. Kaminski, R. S. Glass, A. Skowronska, *Synthesis* **2001**, 1308–1310.
- 2001SC53 M. Gupta, S. Paul, R. Gupta, A. Loupy, *Synth. Commun.* **2001**, *31*, 53–59.
- 2001SC317 F. M. Moghaddam, M. Ghaffarzadeh, *Synth. Commun.* **2001**, *31*, 317–321.
- 2001TA2851 I. Abrunhosa, M. Gulea, J. Levillain, S. Masson, *Tetrahedron Asymmetry* **2001**, *12*, 2851–2859.
- 2001TL3355 K. Miyakoshi, J. Oshita, T. Kitahara, *Tetrahedron* **2001**, *57*, 3355–3360.
- 2001TL5949 P. Bhattacharyya, J. D. Woollins, *Tetrahedron Lett.* **2001**, *42*, 5949–5951.
- 2001TL8181 N. V. Kirij, Y. L. Yagupolskii, N. V. Petukh, W. Tyrre, D. Naumann, *Tetrahedron Lett.* **2001**, *42*, 8181–8183.
- 2001JA8408 H. Ishihara, M. Koketsu, Y. Fukuta, F. Nada, *J. Am. Chem. Soc.* **2001**, *123*, 8408–8409.
- 2001MI1269 G. Grossmann, G. Ohms, K. Kruger, K. Karaghiosoff, K. Eckstein, J. Hahn, A. Hopp, O. L. Malkina, P. Hrobarik, *Z. Anorg. Allg. Chem.* **2001**, *627*, 1269–1278.
- 2001PJC387 A. Wesolowska, T. S. Jagodzinski, J. G. Sosnicki, P. E. Hansen, *Pol. J. Chem.* **2001**, *75*, 387–400.
- 2001PJC1853 T. S. Jagodzinski, T. Dziembowska, E. Jagodzinska, Z. Rozwadowski, *Pol. J. Chem.* **2001**, *75*, 1853–1861.
- 2001PS(172)101 T. Murai, A. Suzuki, M. Takagi, S. Kato, *Phosphorus Sulfur* **2001**, *172*, 101–109.
- 2001T2179 V. S. Berseneva, Y. Y. Morzherin, W. Dehaen, I. Luyten, V. A. Bakulev, *Tetrahedron* **2001**, *57*, 2179–2184.
- 2001T5429 E. Ósz, K. Czifrák, T. Deim, L. Szilágyi, S. Bényei, L. Somsák, *Tetrahedron* **2001**, *57*, 5429–5434.
- 2001T8705 J. G. Sośnicki, T. S. Jagodziński, P. E. Hansen, *Tetrahedron* **2001**, *57*, 8705–8718.
- 2001TL2573 B. McKeever, G. Pattenden, *Tetrahedron Lett.* **2001**, *42*, 2573–2577.
- 2002BMC41 J. Cui, F. Marankan, W. Fu, D. Crich, A. Mesecar, M. E. Johnson, *Bioorg. Med. Chem.* **2002**, *10*, 41–46.
- 2002BMCL491 M. J. Rudolph, C. R. Illig, N. L. Subasinghe, K. J. Wilson, J. B. Hoffman, T. Randle, D. Green, C. J. Molloy, R. M. Soll, K. Lewandowski, M. Zhang, R. Bone, J. C. Spurlino, I. C. Deckman, C. Manthey, C. Sharp, D. Maguire, B. L. Grasberger, R. L. DesJarlais, Z. Zhou, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 491–495.
- 2002BMCL2317 S. Aki, T. Fujioka, M. Ishigami, J. Minamikawa, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2317–2320.
- 2002BMCL2427 T. Tojo, G. W. Spears, K. Tsuji, H. Nishimura, T. Ogino, N. Seki, A. Sugiyama, M. Matsuo, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2427–2430.
- 2002CEJ632 S. Dantale, V. Reboul, P. Metzner, C. Philouze, *Chem. -Eur. J.* **2002**, *8*, 632–640.
- 2002EJOC2573 D. Ach, T. Reboul, P. Metzner, *Eur. J. Org. Chem.* **2002**, 2573–2586.
- 2002MI259 V. Klimesova, J. Koci, K. Waisser, J. Kaustova, *Farmaco* **2002**, *57*, 259–265.
- 2002H313 H. Tokuyama, T. Fukuyama, M. T. Reding, Y. Kaburagi, *Heterocycles* **2002**, *56*, 313–330.

- 2002HC195 M. Koketsu, Y. Okayama, H. Aoki, H. Ishihara, *Heteroatom Chem.* **2002**, *13*, 195–198.
2002HA248 Z. E. Kandeel, K. M. Dawood, E. A. Ragab, A. H. Farag, *Heteroatom Chem.* **2002**, *13*, 248–251.
2002HCA990 R. A. Breitenmoser, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2002**, *85*, 990–1018.
2002JA2137 S. Yokoshima, T. Ueda, S. Kobayashi, A. Sato, T. Kuboyama, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2002**, *124*, 2137–2139.
2002JCS(P1)1271 L. Doszczak, J. Rachon, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1271–1279.
2002JMC3953 N. Selvakumar, D. Srinivas, M. K. Khera, M. S. Kumar, R. N. V. S. Mamidi, H. Sarnaik, C. Charavaryamath, B. S. Rao, M. A. Raheem, J. Pas, J. Iqbal, R. Rajagopalan, *J. Med. Chem.* **2002**, *45*, 3953–3962.
2002JOC3165 K. No, J. H. Lee, S. H. Yang, S. H. Yu, M. H. Cho, M. J. Kim, J. S. Kim, *J. Org. Chem.* **2002**, *67*, 3165–3168.
2002JOC3266 Y. Hitotsuyanagi, S. Motegi, H. Fukaya, K. Takeya, *J. Org. Chem.* **2002**, *67*, 3266–3271.
2002JOC6461 T. J. Curphey, *J. Org. Chem.* **2002**, *67*, 6461–6473.
2002JOC6852 S. Nowaczyk, C. Alayrac, P. Metzner, M.-T. Averbuch-Pouchot, *J. Org. Chem.* **2002**, *67*, 6852–6855.
2002JOC8034 S. Schunk, D. Enders, *J. Org. Chem.* **2002**, *67*, 8034–8042.
2002JOM274 A. Z. Al-Rubaie, L. Z. Yousif, A. J. H. Al-Hamad, *J. Organomet. Chem.* **2002**, *656*, 274–280.
2002MI653 M. F. Kosterina, Y. Y. Morzherin, A. V. Tkachev, T. V. Rybalova, Y. V. Gatilov, V. A. Bakulev, *Russ. Chem. Bl., Int. Ed. Engl.* **2002**, *51*, 653–658.
2002MI891 H.-R. Zhao, Q.-S. Yu, *Chin. J. Chem.* **2002**, *20*, 891–894.
2002MI1292 Y. Y. Morzherin, M. F. Kosterina, V. S. Berseneva, W. Dehaen, V. A. Bakulev, *Russ. Chem. Bull., Int. Ed. Engl.* **2002**, *51*, 1292–1297.
2002OL843 E. Pfund, T. Lequeux, S. Masson, M. Vazeux, *Org. Lett.* **2002**, *4*, 843–846.
2002OL1407 T. Murai, H. Aso, S. Kato, *Org. Lett.* **2002**, *4*, 1407–1409.
2002PHA800 H. T. Y. Fahmy, A. A. Bekhit, *Pharmazi* **2002**, *57*, 800–803.
2002PS(177)115 Y. M. Elkholy, *Phosphorus Sulfur* **2002**, *177*, 115–122.
2002PS(177)1189 H. R. Darabi, K. Aghapoor, K. Tabar-Heydar, M. Nooshabadi, *Phosphorus Sulfur* **2002**, *177*, 1189–1192.
2002S1649 R. Liboska, D. Zyka, M. Bobek, *Synthesis* **2002**, 1649–1651.
2002SL1983 K. Geisler, A. Jacobs, A. Künzler, M. Mathes, I. Girrleit, B. Zimmermann, E. Bulka, W.-D. Pfeiffer, P. Langer, *Synlett* **2002**, 1983–1986.
2002T2743 C. Fruit, A. Turck, N. Plé, L. Mojovic, G. Quéguiner, *Tetrahedron* **2002**, *58*, 2743–2753.
2002T9965 D. Jeffery, R. H. Prager, D. Turner, M. Dreimanis, *Tetrahedron* **2002**, *58*, 9965–9972.
2002TL1343 T. Murai, M. Ishizuka, A. Suzuki, S. Kato, *Tetrahedron Lett.* **2002**, *43*, 1343–1346.
2003BMC495 M. T. Cocco, C. Congiu, V. Onnis, *Bioorg. Med. Chem.* **2003**, *11*, 495–503.
2003BMCL637 M. D. Gaul, Y. Guo, K. Affleck, G. S. Cockerill, T. M. Gilmer, R. J. Griffin, S. Guntrip, B. R. Keith, W. B. Knight, R. J. Mullin, D. M. Murray, D. W. Rusnak, K. Smith, S. Tadepalli, E. R. Wood, K. Lackey, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 637–640.
2003BMC1493 N. Imanishi, K. Iwaoka, H. Koshio, S. Nagashima, K. Kazuta, M. Ohta, S. Sakamoto, H. Ito, S. Akuzawa, T. Kiso, S. Tsukamoto, T. Mase, *Bioorg. Med. Chem.* **2003**, *11*, 1493–1502.
2003CPB608 K. Kazaoka, H. Sajiki, K. Hirota, *Chem. Pharm. Bull.* **2003**, *51*, 608–611.
2003JCR(S)225 S. H. Mashraqui, S. Kumar, K. R. Nivalkar, *J. Chem. Res. (S)* **2003**, 225–227.
2003JMC2227 M. S. Chambers, J. R. Attack, H. B. Broughton, N. Collinson, S. Cook, G. R. Dawson, S. C. Hobbs, G. Marshall, K. A. Maubach, G. V. Pillai, A. J. Reeve, A. M. MacLeod, *J. Med. Chem.* **2003**, *46*, 2227–2240.
2003MI145 O. I. Zbruyev, N. Stiasni, C. O. Kappe, *J. Comb. Chem.* **2003**, *5*, 145–148.
2003OL507 Y.-G. Chang, H. S. Cho, K. Kim, *Org. Lett.* **2003**, *5*, 507–510.
2003PS(178)1747 M. A. A. Elneairy, A. Abbas, Y. N. Mabkhout, *Phosphorus Sulfur* **2003**, *178*, 1747–1757.
2003SC59 M. M. Alam, S. R. Adapa, *Synth. Commun.* **2003**, *33*, 59–63.
2003T1317 N. Ikemoto, J. Liu, K. M. J. Brands, J. M. McNamara, P. J. Reider, *Tetrahedron* **2003**, *59*, 1317–1325.
2003T2713 B. McKeever, G. Pattenden, *Tetrahedron* **2003**, *59*, 2713–2727.
2003TL459 D. Boeglin, S. Cantel, J. Martinez, J.-A. Fehrentz, *Tetrahedron Lett.* **2003**, *44*, 459–462.
2003TL6911 J. Bethke, K. Karaghiosoff, L. A. Wessjohann, *Tetrahedron Lett.* **2003**, *44*, 6911–6913.

Biographical sketch

A. J. Moore was born in Scarborough, studied at Durham University, where he obtained a B.Sc. in 1986 and his Ph.D. in 1989 under the direction of Professor M. R. Bryce. He remained in Durham working as a Postdoctoral Research Fellow, leaving in 1998 to become an industrial consultant in process development chemistry working for Contrachem Ltd. He took up his present position of Senior Lecturer in the School of Health, Natural and Social Sciences at the University of Sunderland in November 2001. His scientific interests include all aspects of heterocyclic and organosulfur chemistry; in particular, their application to materials and supramolecular chemistry and the development of novel agents for cognition enhancement and anticancer activity.

5.15

N-Substituted Thionoamides and Their Se and Te Analogs

C. FLYNN and L. HAUGHTON

Eli Lilly and Company Ltd., Windlesham, UK

5.15.1	OTHER DERIVATIVES OF THIONOAMIDES (AND THEIR Se AND Te ANALOGS) WITH SINGLY BONDED CARBON ATTACHED TO NITROGEN	571
5.15.1.1	N-Acylthionoamides, N-Acylselenoamides, and N-Acyltelluroamides— $R^1C(S)NR^2COR^3$	571
5.15.1.2	N-Thionoacyl, N-Selenoacyl, and N-Telluroacylthionoamides (and Their Se and Te Analogs)— $R^1C(S)NR^2C(S)R^3$	573
5.15.1.3	Other Heteroanalogues of N-Acylthionoamides (and Their Se and Te Analogs)— $R^1C(S)NR^2C(Y)R^3$	574
5.15.2	SINGLY BONDED NITROGEN FUNCTIONS OTHER THAN AMIDES— $RC(S)N=Y$, $RC(S)N\equiv Z$	574
5.15.3	N-HALOTHIONOAMIDES AND THEIR Se AND Te ANALOGS— $RC(S)NHHal$	575
5.15.4	N-THIONOACYLHYDROXYLAMINES AND THEIR Se AND Te ANALOGS— $R^1C(S)NHOR^2$	575
5.15.5	N-THIONOACYLSULFENAMIDES, N-THIONOACYLSULFINAMIDES, AND N-THIONOACYLSULFONAMIDES (AND THEIR Se AND Te ANALOGS)— $R^1C(S)NHSR^2$	577
5.15.6	N-THIONOACYLHYDRAZINES AND N-THIONOACYLHYDRAZONES AND THEIR DERIVATIVES (AND THEIR Se AND Te ANALOGS)— $RC(S)NHNH_2$, $R^1C(S)NHN=CR_2^2$	577
5.15.7	OTHER N-HETEROSUBSTITUTED N-THIONOAMIDES (AND THEIR Se AND Te ANALOGS)	579
5.15.7.1	N-Phosphonothionoamides, N-Phosphonoselenoamides, and N-Phosphonotelluroamides— $R^1C(S)NHPR_2^2$	579
5.15.7.2	N-Silylthionoamides, N-Silylselenoamides, and N-Silyltelluroamides— $R^1C(S)NHSiR_2^2$	580
5.15.8	THIOACYL FUNCTIONS LINKED TO A GROUP 15 ELEMENT OTHER THAN NITROGEN (AND THEIR Se AND Te ANALOGS)	580

5.15.1 OTHER DERIVATIVES OF THIONOAMIDES (AND THEIR Se AND Te ANALOGS) WITH SINGLY BONDED CARBON ATTACHED TO NITROGEN

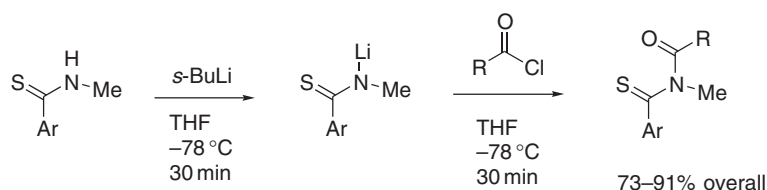
There are significant numbers of papers that report the use of compounds with structures that are similar to those described in this chapter but are contained in heterocycles. Such heterocycles are beyond the scope of this work, and therefore have not been included in this discussion. The preparation and reactions of heterocyclic compounds are described in publications such as *Comprehensive Heterocyclic Chemistry*.

5.15.1.1 N-Acylthionoamides, N-Acylselenoamides, and N-Acyltelluroamides— $R^1C(S)NR^2COR^3$

Overviews of N-acylthionoamides are referenced in the previous volume of this work <1995COFGT(5)629>. There have been no additional reviews published in the current review period.

Previously known methods of acylating primary and secondary thionoamides include the use of acyl halides, anhydrides, nitriles, ketene, or acetic acid <1995COFGT(5)629>. In the case of nitriles as acylating agents, hydrolysis of the intermediate *N*-thioacylamidine is required as an additional step to access the required *N*-acylthionoamides. Acylation of thionoamides with acyl halides proceeds via *S*-acylation followed by rearrangement to the *N*-acyl product. The isolation of *S*-acylated intermediates has been previously described <1995COFGT(5)629>.

Ach and co-workers <2002EJO2573> have described a method for the preparation of *N*-acylthionoamides via deprotonation of the corresponding secondary thioamide. The deprotonation was afforded using *s*-butyllithium (Scheme 1) and the resulting monoanion treated with benzoyl, propanoyl, or acetyl chloride to generate the required *N*-acylated product (Table 1).

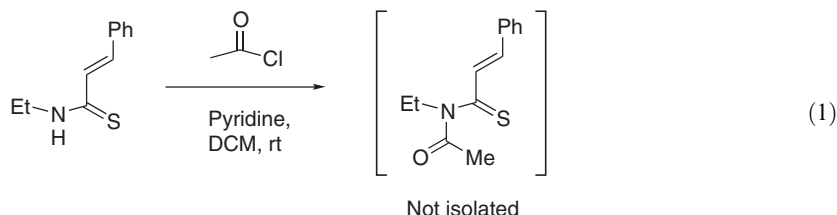


Scheme 1

Table 1 *N*-Acylation of thionoamides

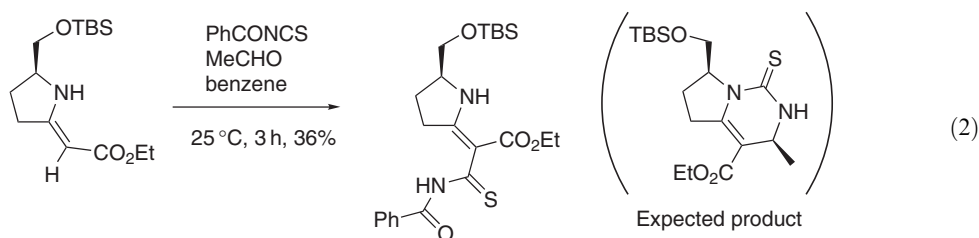
<i>Ar</i>	<i>R</i>	Yield (%)
2-MeC ₆ H ₄	Ph	91
2-MeC ₆ H ₄	Me	86
2-MeC ₆ H ₄	Et	86
2-MeNaphthyl	Ph	73

Bell and co-workers <1998T3219> have described the preparation of *N*-acyl α,β -unsaturated thionoamides with acid chlorides in the presence of pyridine (Equation (1)). The resultant *N*-acylthionoamides were then used directly in hetero-Diels–Alder reactions. Similar work has also been described by Gil *et al.* <1997PS(126)39>.

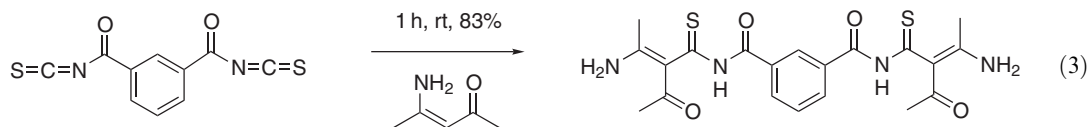


Reaction of an acid chloride with a thionoamide to generate *N*-acylated products was also described by Nagao <1996H517>.

Elliot and Long have reported the unexpected formation of an *N*-acylthionoamide upon treatment of the α,β -unsaturated ester shown with benzoyl isothiocyanate <2002TL9191>. The key annulation was initially attempted with benzoyl isocyanate and acetaldehyde. However, reaction at the α -position of the enamino-ester was observed, thus providing the *N*-acylthionoamide (Equation (2)). It is reported that the same compound can be obtained in a higher yield in the absence of acetaldehyde; however, no yield is given.



Reactions of aroyl isothiocyanates with a series of nucleophiles have been described by Bakhite <1999PHA491>. It has been reported that alcohols or amines can react with aroyl isothiocyanates to give *N*-acylthioureas and thiocarbamates, respectively (see also <1996IJC(B)608>). Further examples of these types of reactions have been described by Assy <1995PS(106)179, 1995PS213, 1995PJC1018>. Further to this, enaminones have also been used in reactions with aroyl isothiocyanates (Equation (3)) <1998PJC61>. The resultant intermediate was then converted into either the pyrimidine or the isothiazole, depending on the reaction conditions.



Acyl isothiocyanates are discussed by Assy <1996PS(108)15> as intermediates in the synthesis of pyrimidinones. Other examples of the preparation of acylthionoamides from isothiocyanates have been described by Hataba <1996IJC(B)144>.

No recent examples of *N*-acylated seleno- or telluroamides have been found. Acylation of selenoamides at selenium has been previously reported <1995COFGT(5)629>.

5.15.1.2 *N*-Thionoacyl, *N*-Selenoacyl, and *N*-Telluroacylthionoamides (and Their Se and Te Analogs)— $R^1C(S)NR^2C(S)R^3$

The previous volume of this work describes the preparation of *N*-thionoacylthionoamides by treatment with phosphorus(V) sulfide or Lawesson's reagent <1995COFGT(5)629>. Excess reagent and elevated temperatures are required to ensure complete conversion.

Dekeyser and co-workers <1996MI1177> have reported the preparation of a range of heterocyclic carbothioamides by reaction of heterocyclic thionoamides with alkyl isothiocyanates in the presence of potassium hydroxide. The desired *N*-thionoacylthionoamides were obtained in 53–81% yields (Equation (4) and Table 2).

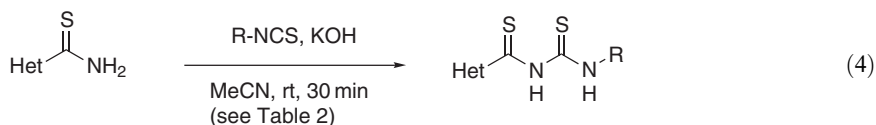
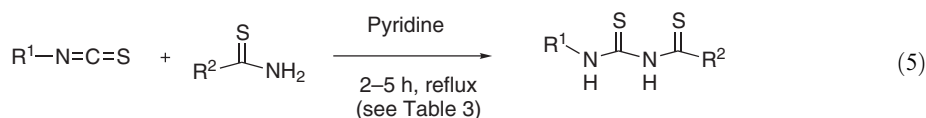


Table 2 Preparation of *N*-thionoacylthionoamides

<i>Het</i>	<i>R</i>	Yield (%)
3-Pyridinyl	Methyl	75
3-Pyridinyl	Ethyl	81
3-Pyridinyl	Isopropyl	72
Pyrazinyl	Methyl	64
Pyrazinyl	Ethyl	61
Pyrazinyl	Isopropyl	65
2-Furanyl	Methyl	70
2-Furanyl	Ethyl	62
2-Furanyl	Isopropyl	59
2-Thienyl	Methyl	54
2-Thienyl	Ethyl	53
2-Thienyl	Isopropyl	54

Chowdury <2002PS(177)497> has demonstrated that pyridine can also be used as a base in these types of transformations obtaining *N*-thionoacylthionoamides in similar yields (Equation (5) and Table 3).

**Table 3** Preparation of *N*-thionoacylthionoamides

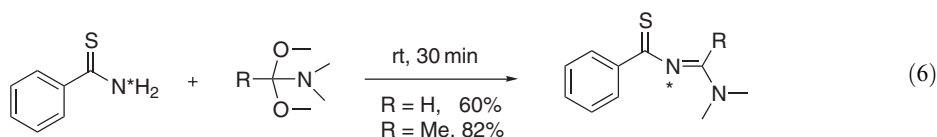
R^1	R^2	Yield (%)
Ph	Me	59
Me	Ph	63

5.15.1.3 Other Heteroanalogs of *N*-Acylthionoamides (and Their *Se* and *Te* Analogs)— $R^1C(S)NR^2C(Y)R^3$

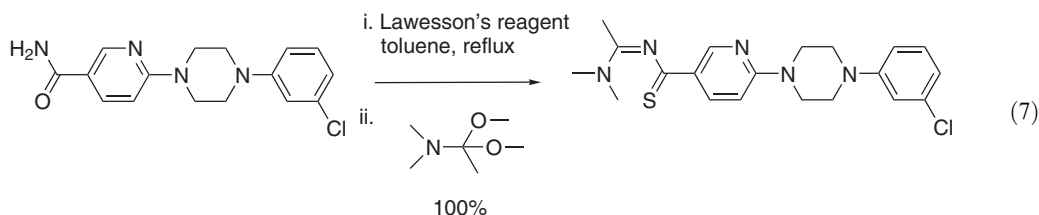
No further advances have occurred in this area since the publication of chapter 5.15.1.3 in COFGT (1995) <1995COFGT(5)629>.

5.15.2 SINGLY BONDED NITROGEN FUNCTIONS OTHER THAN AMIDES— $RC(S)N=Y$, $RC(S)N\equiv Z$

As described in COFGT (1995) <1995COFGT(5)629>, *N*-thionoacylamidines can be prepared by the condensation of thionoamides with amide dialkyl acetals <1997PS(131)147>. Pavlik <2002JHC237> has recently reported the reaction of ^{15}N -thiobenzamide with *N,N*-dimethylformamide dimethyl acetal or with *N,N*-dimethylacetamide dimethyl acetal in good yield at room temperature. This particular example used the ^{15}N -labeled starting material as these compounds were required for ^{15}N NMR studies and further elaborated to give 1,2,4-thiadiazoles (Equation (6)).

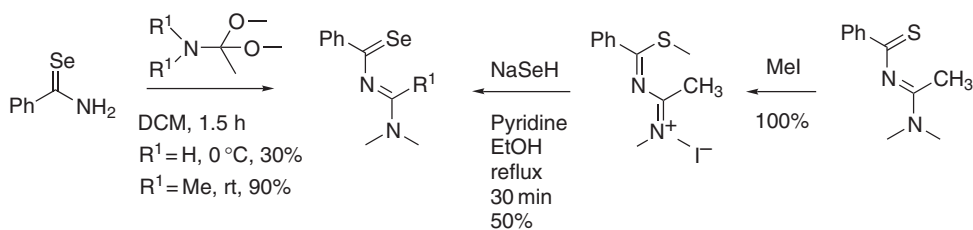


A similar method has also been used in the preparation of pharmaceutical targets by Bongartz and co-workers <2002BMC(L)589>. Quantitative yields were reported for the conversion into the thionoacylamidine from the corresponding amide (Equation (7)).



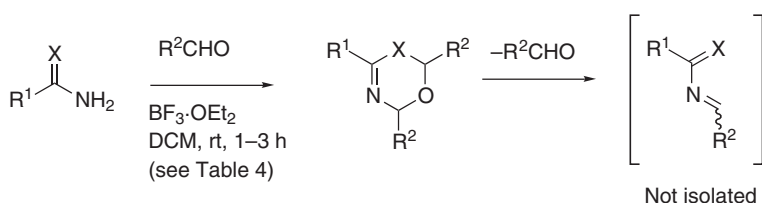
Selenoamides can likewise be converted into the corresponding *N*-selenoacylamidines by treatment with *N,N*-dimethylformamide dimethyl acetal or *N,N*-dimethylacetamide dimethyl acetal <1995TL237>.

The reaction of both *N*-thionoacyl- and *N*-selenoacylamidines to access 1-hetero-3-aza-dimethylaminobuta-1,3-dienes was reported in 1999. Conversion of the sulfur into the selenium analogs was also described (Scheme 2) <1999JCS(P1)2821>. *S*-Methylation was followed by substitution with sodium hydroselenide. These heterobutadienes have applications in [4 + 2]-cycloadditions and hence in heterocyclic systems <1996T10095>.



Scheme 2

1,3-Chalcogenaza-1,3-butadienes can also be prepared by thermal cycloreversion of 2,4,6-trisubstituted 6*H*-1,3,5-oxachalcogenazines formed from the thiono- or selenoamides and an aldehyde (Scheme 3 and Table 4) <2001BCJ511>. The resultant heterobutadienes can then directly undergo [4 + 2]-cycloaddition reactions. Both the thio and seleno analogs have been described.



Scheme 3

Table 4 Preparation of thiono- and selenoamides

X	R ¹	R ²	Yield (%)
S	Ph	Me	95
S	Ph	Bu ^t	43
S	<i>p</i> -Cl-C ₆ H ₄	Me	38
S	<i>p</i> -Cl-C ₆ H ₄	Bu ^t	32
Se	Ph	Me	56
Se	Ph	Bu ^t	32
Se	<i>p</i> -Cl-C ₆ H ₄	Me	53
Se	<i>p</i> -Cl-C ₆ H ₄	Bu ^t	44

No examples of tellurium analogs in this category have been found.

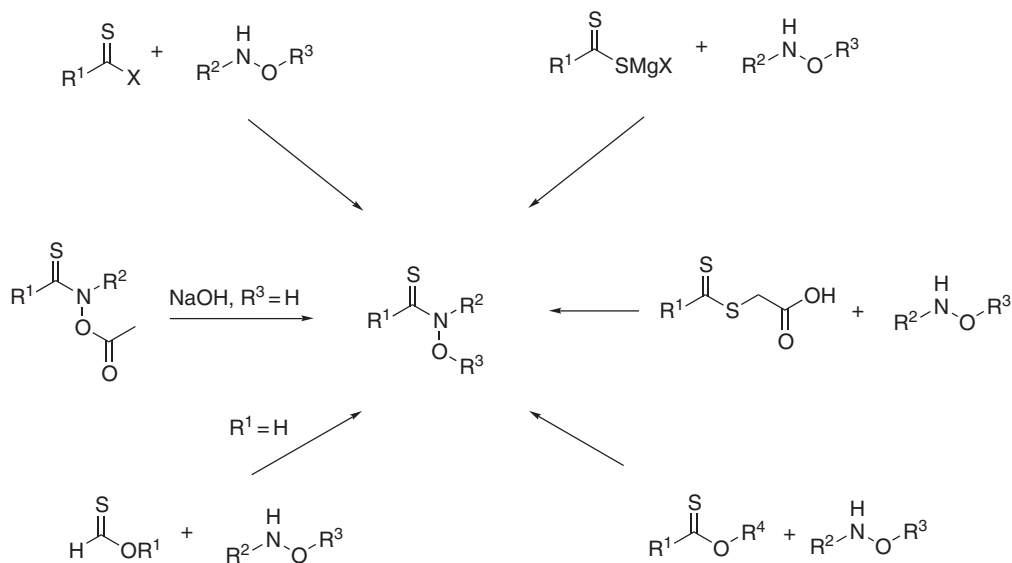
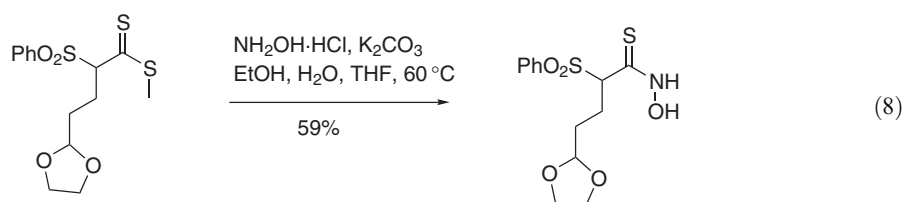
5.15.3 N-HALOTHIONOAMIDES AND THEIR Se AND Te ANALOGS—RC(S)NHHal

No advances have occurred in this area since the publication of the previous edition <1995COFGT(5)629>.

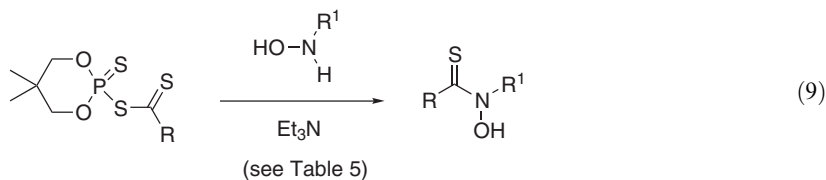
5.15.4 N-THIONOACYLHYDROXYLAMINES AND THEIR Se AND Te ANALOGS—R¹C(S)NHOH²

A wide range of reactions describing the synthesis and elaboration of *N*-thionoacyl hydroxylamines was discussed in the previous edition <1995COFGT(5)629>. A summary of these methods is shown in Scheme 4. There has been little new work in the current review period.

Thiohydroxamic acids can be prepared in moderate yields from treatment of dithiocarboxylic acid esters with hydroxylamine under basic conditions (Equation (8)) <1995T1887>.

**Scheme 4**

It has also been found that *S*-thioacyl dithiophosphates can be used to thioacetylate hydroxylamine (Equation (9) and Table 5) <2002PS(177)1851>.

**Table 5** Thioacylation of hydroxylamine

<i>R</i>	<i>R</i> ¹	Yield (%)
Ph	Me	68
Ph	Pr ⁱ	73
Ph	CH(Me)Ph	72
Pr	Me	83
Pr	Pr ⁱ	80
Pr	CH(Me)Ph	77
Pr	Bu ^t	57
MeOCO(CH ₂) ₄	Me	91
MeOCO(CH ₂) ₄	Pr ⁱ	91
MeOCO(CH ₂) ₄	CH(Me)Ph	94
MeOCO(CH ₂) ₄	Bu ^t	82
Bu ^t	Me	71

No references to seleno or telluro analogs were found in this category for the current review period or in COFGT (1995).

5.15.5 N-THIONOACYLSULFENAMIDES, N-THIONOACYLSULFINAMIDES, AND N-THIONOACYLSULFONAMIDES (AND THEIR Se AND Te ANALOGS)— $R^1C(S)NHSR^2$

No further advances have occurred in this area since the publication of chapter 5.15.5 in COFGT (1995) <1995COFGT(5)629>.

5.15.6 N-THIONOACYLHYDRAZINES AND N-THIONOACYLHYDRAZONES AND THEIR DERIVATIVES (AND THEIR Se AND Te ANALOGS)— $RC(S)NHNH_2$, $R^1C(S)NHN=CR^2$

There have been no recent new preparative methods for the synthesis of *N*-thionoacylhydrazides, although there have been a limited number of papers which have further exemplified Jensen's original work <1961ACS1087>.

For example, the 1-pyridinio(arenethiocarbonyl)amidates were prepared in 34–93% yields through the reactions of 1-aminopyridinium iodides with a series of dithiocarboxylate esters (Equation (10) and Table 6) <1997JOC7788>.

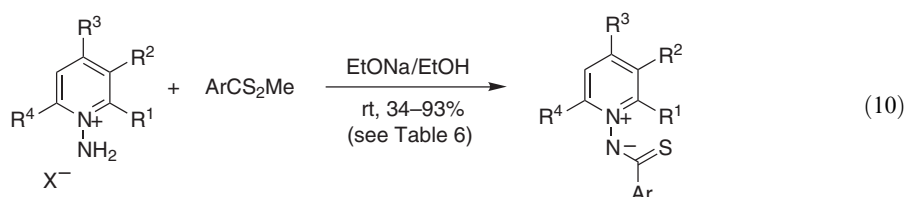


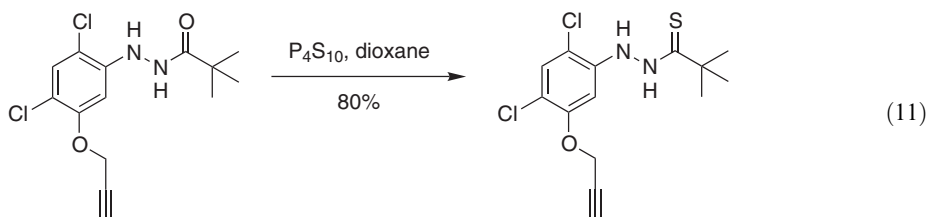
Table 6 Range of 1-pyridinio(arenethiocarbonyl)amidates prepared

R^1	R^2	R^3	R^4	Ar
H	H	H	H	C_6H_5
H	H	H	H	<i>p</i> -MeC ₆ H ₄
H	H	H	H	<i>p</i> -MeC ₆ H ₄
H	H	H	H	<i>o</i> -MeC ₆ H ₄
H	H	H	H	<i>p</i> -ClC ₆ H ₄
H	H	H	H	2-Thienyl
H	H	H	H	<i>p</i> -Me ₂ NC ₆ H ₄
H	H	Me	H	C_6H_5
H	H	Me	H	<i>p</i> -MeC ₆ H ₄
H	H	Me	H	<i>p</i> -MeOC ₆ H ₄
H	H	Me	H	<i>o</i> -MeOC ₆ H ₄
H	H	Me	H	<i>p</i> -ClC ₆ H ₄
H	H	Me	H	2-Thienyl
H	H	Me	H	<i>p</i> -Me ₂ NC ₆ H ₄
H	Me	H	H	C_6H_5
H	Me	H	H	<i>p</i> -MeC ₆ H ₄
H	Me	H	H	<i>p</i> -MeOC ₆ H ₄
H	Me	H	H	<i>p</i> -ClC ₆ H ₄

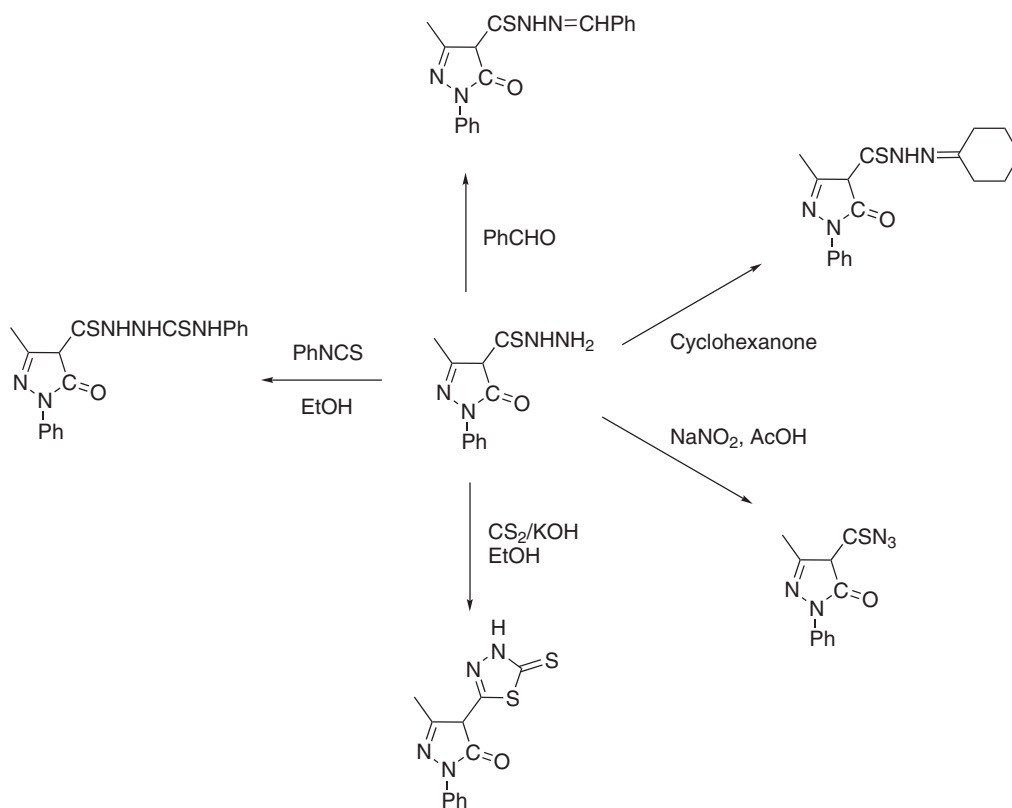
These compounds were obtained as pale yellow crystals having a characteristic sulfur odor, and their IR spectra showed an absorption band attributed to the carbon–sulfur double bond at near $1,150\text{ cm}^{-1}$. In addition, it was reported that when a chloroform solution of 1-pyridinio(thiobenzoyl)amidate and DMAD was heated at 50–60 °C for 11 h, a Diels–Alder reaction occurred, yielding a complex tricycle in a moderate 30% yield.

The thionation of acylhydrazides with P_4S_{10} is not, in general, a useful method giving thiadiazoles rather than the desired thionoacylhydrazides <1961ACS1097>. However, Dayan and co-workers <2001JAFC2302> have used this method in the synthesis of the herbicide IR 5790. They reported that P_4S_{10} can be added to a solution of *N'*-[2,4-dichloro-5-(2-propynyloxy)phenyl]-*N*-pivaloylhydrazine in

dioxane and the resultant mixture heated to 60 °C for 3 h to afford the required thionoacylhydrazine in 80% yield (Equation (11)).



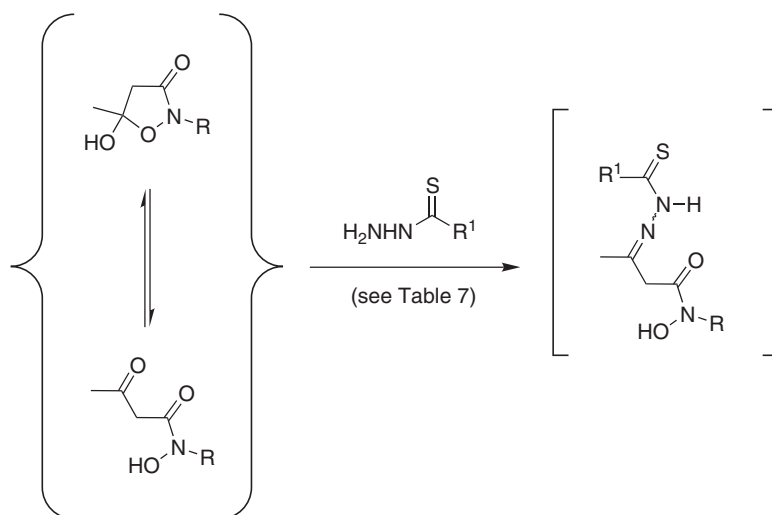
Work continues to be published on the reactions of hydrazines with electrophiles to synthesize the respective hydrazones. Youssef has reported further exemplifications of the reaction of hydrazines with isocyanate, nitrites, ketones, aromatic aldehydes, and carbon disulfide (Scheme 5).



Scheme 5

Sinkkonen and co-workers [<2002JHC805>](#) have studied the condensation of a series of hydrazines with 5-hydroxy-5-methyl-3-isoxazolidinones. The reaction products were studied by modern spectroscopic techniques. Interestingly, it was found that the choice of solvent used for NMR studies had a strong effect on the relative amounts of tautomers observed (Scheme 6 and Table 7).

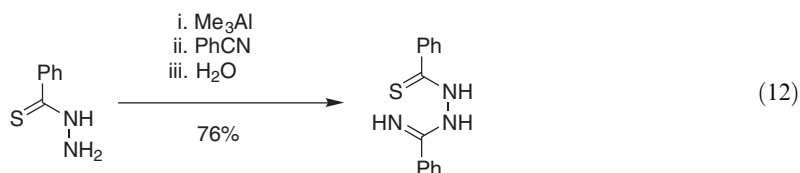
Kaszynski [<2000JOC931>](#) has developed a novel synthesis of *N*-thiobenzoylbenzamidrazone. This was achieved by the addition of thiobenzhydrazide to benzonitrile in the presence of 2 equiv. of trimethylaluminum to yield the benzamidrazone (Equation (12)).



Scheme 6

Table 7 Possible condensation products from thioaroylhydrazines

<i>R</i>	<i>R</i> ¹
CH ₂ Ph	Ph
CH ₂ Ph	4-CH ₃ C ₆ H ₄
4-MeOOCC ₆ H ₄	Ph
4-MeOOCC ₆ H ₄	4-CH ₃ C ₆ H ₄



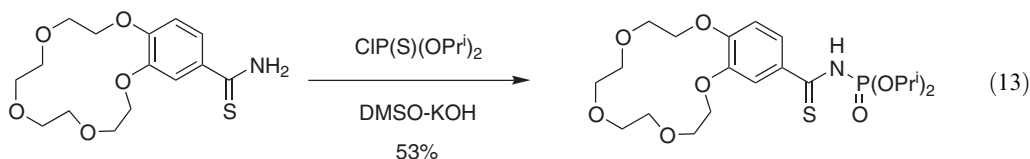
There have been no reports of the synthesis of selenium and tellurium analogs.

5.15.7 OTHER N-HETEROSUBSTITUTED N-THIONOAMIDES (AND THEIR Se AND Te ANALOGS)

5.15.7.1 N-Phosphonothionoamides, N-Phosphonoselenoamides, and N-Phosphonotelluroamides— $R^1C(S)NHPR_2^2$

There have been no new synthetic methods for the preparation of N-heterosubstituted N-thionoamides (and their selenium and tellurium analogs), although one paper has further exemplified the most common synthesis of these types of molecules.

Thus, Zabiroy [<2002MC154>](#) has reported the direct phosphorylation of a crown ether derivative of phenylacetamide with diisopropyl thiophosphate chloride in the presence of the superbases (DMSO-KOH) ([Equation \(13\)](#)). Full characterization of the product is described, although no X-ray data are presented.



5.15.7.2 N-Silylthionoamides, N-Silylselenoamides, and N-Silyltelluroamides— $R^1C(S)NHSiR_2^2$

No further advances have occurred in this area since the publication of chapter 5.15.7.2 in the previous edition <1995COFGT(5)629>.

5.15.8 THIOACYL FUNCTIONS LINKED TO A GROUP 15 ELEMENT OTHER THAN NITROGEN (AND THEIR Se AND Te ANALOGS)

No further advances have occurred in this area since the publication of chapter 5.15.8 in the previous edition <1995COFGT(5)629>.

REFERENCES

- 1961ACS1087 K. A. Jensen, C. Pedersen, *Acta Chem. Scand.* **1961**, 15, 1087–1090.
- 1995COFGT(5)629 M. W. Owton, in *N-Substituted thionoamides and their Se and Te analogues in Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 629–646.
- 1995PJC1018 M. G. Assy, A. A. Hataba, H. Y. Moustafa, *Pol. J. Chem.* **1995**, 69, 1018–1021.
- 1995PS(106)179 M. G. Assy, A. Haiekl, H. Y. Moustafa, *Phosphorus Sulfur Silicon* **1995**, 106, 179–185.
- 1995PS213 M. G. Assy, H. Y. Moustafa, *Phosphorus Sulfur Silicon* **1995**, 105, 213–216.
- 1995T1887 D. H. R. Barton, K. A. D. Swift, C. Tachdjian, *Tetrahedron* **1995**, 51, 1887–1892.
- 1995TL237 D. Dubreuil, J. P. Pradère, N. Giraudeau, M. Goli, F. Tonnard, *Tetrahedron Lett.* **1995**, 36, 237–240.
- 1996H517 Y. Nagao, K. Takahashi, K. Torisu, K. Kondo, N. Hamanaka, *Heterocycles* **1996**, 42, 517–523.
- 1996IJ(B)144 A. A. Hataba, M. G. Assy, R. M. Fikry, *Indian J. Chem.* **1996**, 35B, 144–146.
- 1996IJ(B)608 M. G. Assy, M. G. Abd-Ell Motti, *Indian J. Chem.* **1996**, 35B, 608–610.
- 1996MI1177 M. A. Dekeyser, P. T. McDonald, G. W. Angle, Jr., *J. Agric. Food Chem.* **1996**, 44, 1177–1179.
- 1996PS(108)15 M. G. Assy, *Phosphorus Sulfur Silicon* **1996**, 108, 15–20.
- 1996T10095 G. Morel, E. Marchand, J. P. Pradère, L. Toupet, S. Sinbandhit, *Tetrahedron* **1996**, 52, 10095–10112.
- 1997JOC7788 A. Kakehi, S. Ito, F. Ishida, Y. Tominaga, *J. Org. Chem.* **1997**, 62, 7788–7793.
- 1997PS(126)39 M. J. Gil, A. Reliquet, J. C. Meslin, *Phosphorus Sulfur Silicon* **1997**, 126, 39–52.
- 1997PS(131)147 C. Friot, A. Reliquet, J. C. Meslin, *Phosphorus Sulfur Silicon* **1997**, 131, 147–160.
- 1998PJC61 M. G. Assy, A. M. Amer, S. El-Bahaie, E. A. Halima, *Pol. J. Chem.* **1998**, 72, 61–65.
- 1998T3219 A. S. Bell, C. W. G. Fishwick, J. E. Reed, *Tetrahedron* **1998**, 54, 3219–3234.
- 1999JCS(P1)2821 G. B. Manh, F. Purseigle, D. Dubreuil, J. P. Pradère, A. Guingant, R. Danion-Bougot, D. Danion, L. Toupet, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2821–2828.
- 1999PHA491 E. A. Bakhite, Sh. M. Radwan, *Pharmazie* **1999**, 54, 491–498.
- 2000JOC931 J. M. Farrar, M. K. Patel, P. Kaszynski, *J. Org. Chem.* **2000**, 65, 931–940.
- 2001BCJ511 K. Shimada, K. Aikawa, T. Fujita, M. Sato, K. Goto, S. Aoyagi, Y. Takikawa, C. Kabuto, *Bull. Chem. Soc. Jpn.* **2001**, 74, 511–525.
- 2001JAF2302 F. E. Dayan, G. Meazza, F. Bettarini, E. Signorini, P. Piccardi, J. G. Romagni, S. O. Duke, *J. Agric. Food Chem.* **2001**, 49, 2302–2307.
- 2002BKCS41 M. M. Kandeel, M. S. Abbady, M. S. K. Youssef, *Bull. Korean Chem. Soc.* **2002**, 23, 41–47.
- 2002BMCL589 J. Bongartz, R. Stokbroekx, M. Van der Aa, M. Luyckx, M. Willems, M. Ceusters, L. Meerpoel, G. Smets, T. Jansen, W. Wouters, C. Bowden, L. Valletta, M. Herb, R. Tominovich, R. Tuman, *Bioorg. Med. Chem. Lett.* **2002**, 12, 589–591.
- 2002EJO2573 D. Ach, V. Reboul, P. Metzner, *Eur. J. Org. Chem.* **2002**, 2573–2586.
- 2002JHC237 J. W. Pavlik, C. Changtong, S. Tantayanon, *J. Heterocycl. Chem.* **2002**, 39, 237–239.
- 2002JHC805 K. N. Zelenin, I. V. Lagoda, V. V. Alekseyev, J. Sinkkonen, R. A. Shaikhutdinov, K. Pihlaja, *J. Heterocyclic Chem.* **2002**, 39, 805–810.
- 2002MC154 N. G. Zabirow, F. D. Sokolov, V. V. Brusko, A. K. Tashmukhamedova, N. J. Saifullina, R. A. Cherkasov, *Mendeleev Commun.* **2002**, 4, 154–155.
- 2002PS(177)497 A. Z. M. S. Chowdury, Y. Shibata, M. Morita, K. Kaya, *Phosphorus Sulfur Silicon* **2002**, 177, 497–509.
- 2002PS(177)1851 L. Doszczak, W. Przychodzen, D. Witt, J. Rachon, *Phosphorus Sulfur Silicon* **2002**, 177, 1851–1854.
- 2002TL9191 M. C. Elliot, M. S. Long, *Tetrahedron Lett.* **2002**, 43, 9191–9194.

Biographical sketch

Claire J. Flynn was born in Dundee, Scotland in 1974. She studied at Heriot-Watt University, where she obtained a B.Sc. in 1996. She moved to the University of Nottingham, where she completed a Ph.D. entitled “The Synthesis of Amino and Diamino-Sugars and the Evaluation of Sugar-Dye Conjugates,” under the direction of Dr. Mark Mascal, in collaboration with BASF. Currently she is working at Eli Lilly and Company as a Medicinal Chemist in the neuroscience therapeutic area.



Louise Haughton was born in the Lake District in 1973 and studied at Loughborough University, where she obtained a B.Sc. in 1996, working at Glaxo during her years of industrial placement. After spending the year 1997 in the laboratories of Professor Phillip Kocienski, University of Glasgow, she moved to University of Bath, where she completed a Ph.D. entitled “Kinetic and Dynamic Kinetic Resolutions Using Enzymes in Organic Synthesis,” under the direction of Professor J. M. J. Williams. Currently she is working at Eli Lilly and Company as a Medicinal Chemist in the neuroscience therapeutic area.

5.16

Thioacyl Functions Linked to a Metalloid (Si, Ge, or B) or Metal; and Their Seleno and Telluro Analogs

C. P. DELL

Eli Lilly and Company Ltd., Windlesham, UK

5.16.1	SINGLY BONDED METALLOID DERIVATIVES—RC(S)-METALLOID, RC(Se)-METALLOID, etc.	583
5.16.1.1	Singly Bonded Silicon Derivatives—R ¹ C(S)SiR ₃ ² , R ¹ C(Se)SiR ₃ ² , etc.	583
5.16.1.2	Singly Bonded Boron Derivatives—R ¹ C(S)BR ₂ ² , R ¹ C(Se)BR ₂ ² , etc.	586
5.16.1.3	Singly Bonded Germanium Derivatives—R ¹ C(S)GeR ₃ ² , etc.	586
5.16.2	SINGLY BONDED METAL DERIVATIVES—RC(S)-METAL, RC(Se)-METAL, etc.	586
5.16.2.1	General Comments and Methods	586
5.16.2.2	Group 1 and Group 2 Derivatives—RC(S)Li, RC(S)MgX, etc.	587
5.16.2.3	Lanthanide Derivatives	587
5.16.2.4	Transition Metal Derivatives	587
5.16.2.5	Group 3 and Group 4 Derivatives—RC(S)Ti, R ¹ C(S)SnR ₃ ² , etc.	587
5.16.2.6	Actinide Derivatives	587

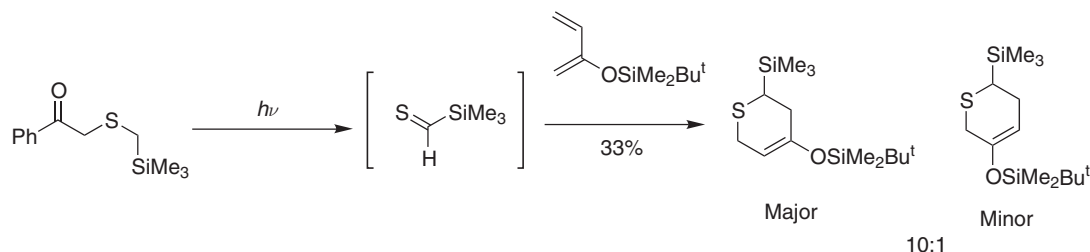
5.16.1 SINGLY BONDED METALLOID DERIVATIVES—RC(S)-METALLOID, RC(Se)-METALLOID, etc.

5.16.1.1 Singly Bonded Silicon Derivatives—R¹C(S)SiR₃², R¹C(Se)SiR₃², etc.

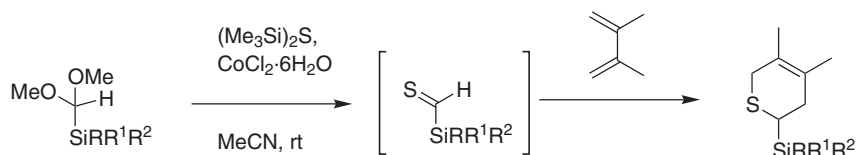
Thioformyltrimethylsilane has not been isolated, but has been trapped *in situ* as a Diels–Alder adduct <1983JA6999, 1986JOC1556>. The compound was made by the photofragmentation of a phenacyl sulfide (Scheme 1) <1986JOC1556>.

A more general approach to the preparation of thioformylsilanes involves treatment of silyl acetals with bis(trimethylsilyl) sulfide and cobalt(II) chloride hexahydrate. Selected examples are shown in Scheme 2 and Table 1 <1997SL361>. Again the compounds were not isolated but trapped as Diels–Alder adducts. This is typical of the behavior of α-silyl thioketones <1987JCS(P1)2643, 1987JCS(P1)2647, 1991TL2971, 1992MI41, 1993JCS(P1)1011, 1999HCO217>.

The synthesis and chemistry of α-silyl thioketones has been reviewed by Bonini <1997RHA47, 1993PS(74)31>, the key contributor to this area since the first α-silyl thioketone was prepared in 1981 <1981CCC822>. The methodology reported in COFGT (1995) for the conversion of α-silyl ketones to α-silyl thioketones using 2 equiv. of bis(trimethylsilyl) sulfide in the presence of 0.4 equiv. of cobalt(II) chloride hexahydrate in acetonitrile is probably in a “practical” sense the method of choice for this transformation <1989JOC19>. Bonini, however, favors the use of gaseous



Scheme 1

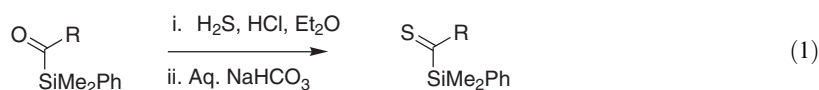


Scheme 2

Table 1 Preparation of thioformylsilanes from silyl acetals

<i>R</i>	<i>R</i> ¹	<i>R</i> ²	Yield (%)
Me	Me	Bu ^t	41
Me	Me	Ph	56
Me	Ph	Ph	62

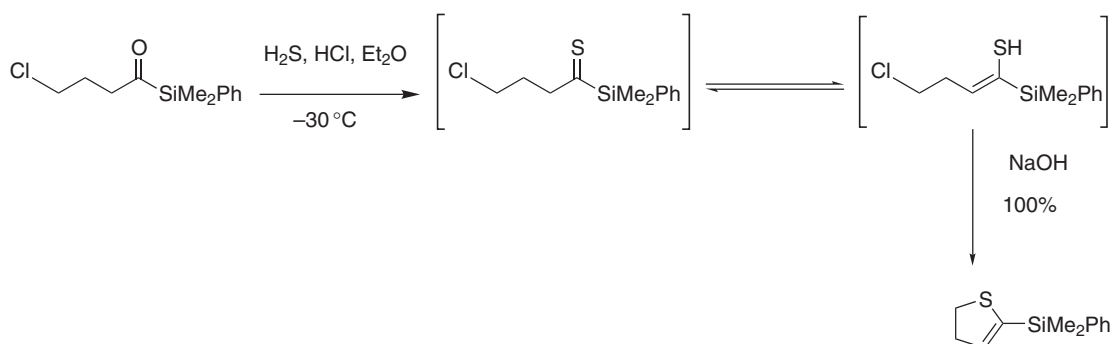
hydrogen sulfide and hydrogen chloride, followed by aqueous sodium hydrogen carbonate for the reaction <1997RHA47>. The utility of the latter method has been extended from aryl <1981CC822, 1986JCS(P1)381, 1988CC365, 2000JOM(611)449> and nonenolizable alkyl thio-ketones <1989JCS(P1)2083> to the thionation of cycloalkyl α -silyl ketones as exemplified in Equation (1) and Table 2 <1993JCS(P1)1011>.

**Table 2** Thionation of cycloalkyl α -trimethylsilyl ketones

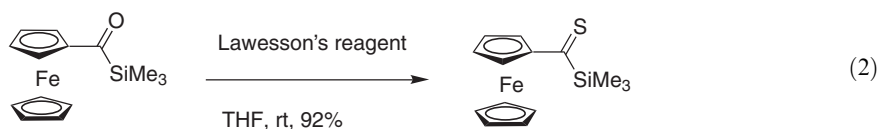
<i>R</i>	Yield (%)
Cyclopropyl	85
Cyclobutyl	95
Cyclohexyl	82

For more simple α -silyl thioketones bearing an acidic proton adjacent to the thiocarbonyl group, the result of attempted thionation is, in fact, enethiolization. With appropriate additional functionality, this enethiolization can be utilized in a breadth of synthetic chemistry <1994TL9227, 1996T4803, 1997T7897, 1997JCS(P1)3211, 1999SL486, 1999PS(153-154)315, 2000EJO2391>. An example is shown in Scheme 3.

The typical lack of thermal stability of α -silyl thioketones has meant that the use of Lawesson's reagent in toluene at reflux for the thionation had previously only really been successful with more thermally stable products such as (2,4,6-trimethylthiobenzoyl)trimethylsilane <1990JOC3744>. However, the enhanced reactivity of ferrocenylacetylsilanes has meant that transformation of these to ferrocenylthioacylsilanes has been effected with Lawesson's reagent in THF at room temperature (Equation (2)) <1999TL6473>. This has also been applied to the preparation of a novel planar chiral enantiomerically pure thioferrocenoylsilane <2001JOM(637-639)407>.



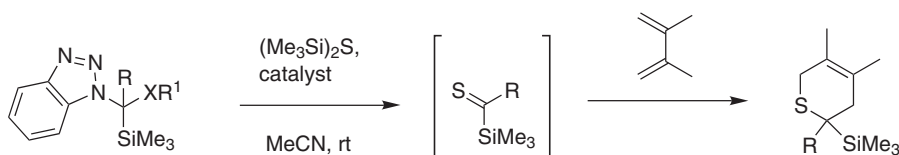
Scheme 3



(2)

Benzotriazole-mediated chemistry has been used in a recent synthetic approach to thioacylsilanes [<2000JOC9206>](#). The compounds were again trapped as Diels–Alder adducts (Scheme 4 and Table 3).

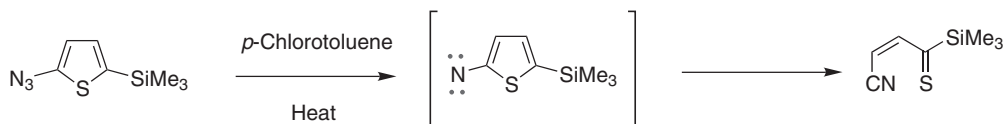
Thermolysis of 2-azido-5-trimethylsilylthiophene has been reported to provide an unsaturated thioacylsilane by loss of nitrogen and rearrangement of the intermediate nitrene (Scheme 5). However, the paper is principally concerned with elucidation of the mechanism and does not describe isolation of the product [<1999JCS\(P2\)623>](#).



Scheme 4

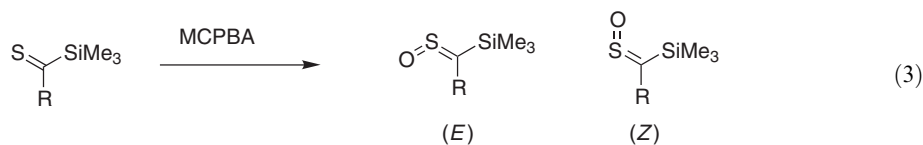
Table 3 Benzotriazole-mediated preparation of thioacylsilanes

<i>R</i>	<i>XR</i> ¹	<i>Catalyst</i>	<i>Yield (%)</i>
Me	OPh	TfOSiMe ₃	51
Bu ⁿ	SMe	CoCl ₂ · 6H ₂ O	64
Bn	SMe	CoCl ₂ · 6H ₂ O	58
Cyclopentyl	SPr	CoCl ₂ · 6H ₂ O	55
Me ₃ Si	SMe	CoCl ₂ · 6H ₂ O	55
H	OPh	HCl, MeOH	42



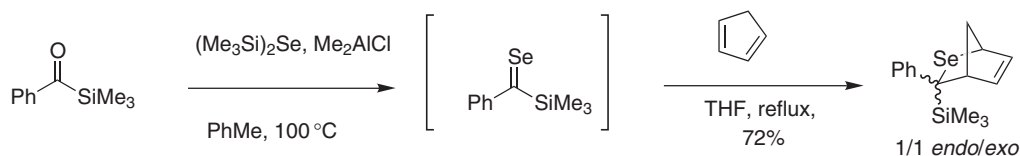
Scheme 5

Oxidation of thioacylsilanes with MCPBA yielded the corresponding *S*-oxides as exclusively or mainly the (*E*)-isomer (Equation (3) and Table 4) [<1986CC964, 1986JCS\(P1\)381, 1988CC365, 1989JCS\(P1\)2083, 1990JOC3744, 1993JCS\(P1\)1011>](#). The thioacylsilane *S*-oxides are more stable than the parent compounds but can show some lability on attempted purification.

**Table 4** Preparation of thioacylsilane *S*-oxides

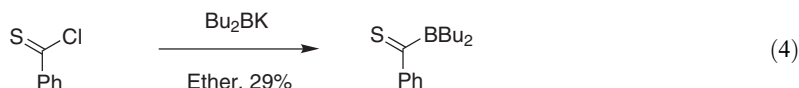
<i>R</i>	Yield (%)	(<i>E</i>)/(<i>Z</i>) ratio	Comments	References
Ph	65	100:0		<1990JOC3744>
Ph	42	100:0		<1986JCS(P1)381>
4-MeC ₆ H ₄	85	100:0		<1990JOC3744>
3-ClC ₆ H ₄	82	100:0	Labile	<1990JOC3744>
2,4,6-Me ₃ C ₆ H ₂	92	66:33	Labile on silica	<1990JOC3744>
Bu ^t	89	60:40	(<i>E</i>)-Isolated	<1989JCS(P1)2083>
Bu ^t	80	60:40	Labile on silica	<1990JOC3744>

Treatment of benzoyltrimethylsilane with bis(dimethylaluminum) selenide formed *in situ* is reported to provide the α -silyl selenoketone. The compound was trapped in good yield as its [4+2]-cycloadduct with cyclopentadiene (Scheme 6) <1989TL2095>. No other reports of the preparation of these species have appeared in the literature.

**Scheme 6**

5.16.1.2 Singly Bonded Boron Derivatives— $\text{R}^1\text{C}(\text{S})\text{BR}_2^2$, $\text{R}^1\text{C}(\text{Se})\text{BR}_2^2$, etc.

There is little preparative literature on α -boryl thioketones. Treatment of dibutylboron chloride with sodium–potassium alloy in ether followed by addition of thiobenzoyl chloride was reported to lead to a 29% yield of the α -boryl thioketone (Equation (4)) <1968CB2502>. The compound is distillable but very sensitive to oxidation.



Theoretical calculations (modified neglect of diatomic overlap (MNDO) geometry optimizations) have been carried out on a range of acyclic and cyclic α -boryl thioketones, but no synthetic chemistry was described <1989JST135>. The only literature appearing to exist on α -boryl selenoketones is similarly a theoretical paper, examining a gas-phase basicity scale for seleno-carbonyl compounds <1999JPC(A)1662>.

5.16.1.3 Singly Bonded Germanium Derivatives— $\text{R}^1\text{C}(\text{S})\text{GeR}_3^2$, etc.

No reports of such species have been found to date.

5.16.2 SINGLY BONDED METAL DERIVATIVES— $\text{RC}(\text{S})$ -METAL, $\text{RC}(\text{Se})$ -METAL, etc.

5.16.2.1 General Comments and Methods

No general methods for the synthesis of metal-bonded thioacyl compounds or their seleno and telluro analogs have been described.

5.16.2.2 Group 1 and Group 2 Derivatives—RC(S)Li, RC(S)MgX, etc.

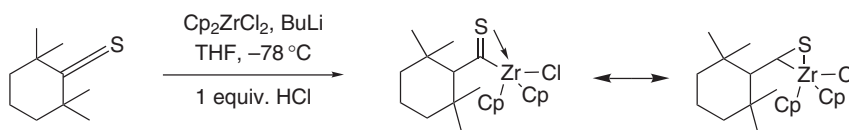
No reports of group 1 and group 2 bonded thioacyl compounds or their seleno or telluro analogs have appeared in the literature.

5.16.2.3 Lanthanide Derivatives

No articles related to lanthanide-bonded thioacyl compounds or their seleno and telluro analogs have been published <1999PS(153-154)315>.

5.16.2.4 Transition Metal Derivatives

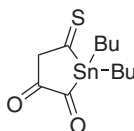
Many reports of thioacyl groups bonded to transition metals appear in the literature. The bonding may be depicted in a number of different ways. However, it appears from X-ray crystallographic data that the true nature of the complexes is described most accurately by a three-membered ring. This incorporates bonding from the metal to both the carbon and the sulfur and thus does not truly reflect chemistry of a thioacyl moiety singly bonded via carbon to a transition metal. An example is depicted in Scheme 7 <1991JA7782>. A small selection of the many related compounds and a description of the bonding can be found in the following references: <1988JA3171, 1990OM1650, 1994OM2147, 1995OM1104, 2001JOM(623)109>.



Scheme 7

5.16.2.5 Group 3 and Group 4 Derivatives—RC(S)Ti, $\text{R}^1\text{C}(\text{S})\text{SnR}_2^2$, etc.

Other than the cyclic α -stannyl thioketone **1** being included in a patent describing vulcanization accelerators for synthetic rubbers <1973JAP(K)48094743>, no other reports of group 3 and group 4 bonded thioacyl compounds have been uncovered.



1

5.16.2.6 Actinide Derivatives

No publications on this class of compounds have appeared.

REFERENCES

- 1968CB2502 G. Schmid, H. Nöth, *Chem. Ber.* **1968**, *101*, 2502–2505.
 1973JAP(K)48094743 K. Swatari, S. Oda, Y. Inoue, K. Rikumaru, *Jpn. Kokai* **1973**, 48094743. *Chem. Abstr.* **1974**, *80*, 146843.
 1981CC822 B. F. Bonini, G. Mazzanti, S. Sarti, P. Zanirato, G. Maccagnani, *J. Chem. Soc., Chem. Commun.* **1981**, 822–823.
 1983JA6999 E. Vedejs, D. A. Perry, K. N. Houk, N. G. Rondan, *J. Am. Chem. Soc.* **1983**, *105*, 6999–7001.

- 1986CC964 B. F. Bonini, G. Mazzanti, P. Zani, G. Maccagnani, G. Barbaro, A. Battaglia, P. Giorgianni, *J. Chem. Soc., Chem. Commun.* **1986**, 964–965.
- 1986JCS(P1)381 G. Barbaro, A. Battaglia, P. Giorgianni, G. Maccagnani, D. Macciantelli, B. F. Bonini, G. Mazzanti, P. Zani, *J. Chem. Soc., Perkin Trans. 1* **1986**, 381–385.
- 1986JOC1556 E. Vedejs, T. H. Eberlein, D. J. Mazur, C. K. McClure, D. A. Perry, R. Ruggeri, E. Schwartz, J. S. Stults, D. L. Varie, R. G. Wilde, S. Wittenberger, *J. Org. Chem.* **1986**, *51*, 1556–1562.
- 1987JCS(P1)2643 B. F. Bonini, A. Lenzi, G. Maccagnani, G. Barbaro, P. Giorgianni, D. Macciantelli, *J. Chem. Soc., Perkin Trans. 1* **1987**, 2643–2646.
- 1987JCS(P1)2647 P. Carisi, G. Mazzanti, P. Zani, G. Barbaro, A. Battaglia, P. Giorgianni, *J. Chem. Soc., Perkin Trans. 1* **1987**, 2647–2651.
- 1988JA3171 S. L. Buchwald, R. B. Nielsen, *J. Am. Chem. Soc.* **1988**, *110*, 3171–3175.
- 1988CC365 B. F. Bonini, G. Mazzanti, P. Zani, G. Maccagnani, *J. Chem. Soc., Chem. Commun.* **1988**, 365–367.
- 1989JCS(P1)2083 B. F. Bonini, G. Mazzanti, P. Zani, G. Maccagnani, *J. Chem. Soc., Perkin Trans. 1* **1989**, 2083–2088.
- 1989JOC19 A. Ricci, A. Degl'Innocenti, A. Capperucci, G. Reginato, *J. Org. Chem.* **1989**, *54*, 19–20.
- 1989JST135 P. V. Sudhakar, J. Chandrasekhar, *J. Mol. Struct.* **1989**, *194*, 135–147.
- 1989TL2095 M. Segi, T. Koyama, T. Nakajima, S. Suga, S. Murai, N. Sonoda, *Tetrahedron Lett.* **1989**, *30*, 2095–2098.
- 1990JOC3744 G. Barbaro, A. Battaglia, P. Giorgianni, B. F. Bonini, G. Maccagnani, P. Zani, *J. Org. Chem.* **1990**, *55*, 3744–3748.
- 1990OM1650 J. W. Park, L. M. Henling, W. P. Schaefer, R. H. Grubbs, *Organometallics* **1990**, *9*, 1650–1656.
- 1991JA7782 W. Ando, T. Ohtaki, T. Suzuki, Y. Kabe, *J. Am. Chem. Soc.* **1991**, *113*, 7782–7784.
- 1991TL2971 B. F. Bonini, A. Lenzi, G. Maccagnani, G. Barbaro, P. Giorgianni, D. Macciantelli, *Tetrahedron Lett.* **1991**, *32*, 2971–2974.
- 1992MI41 K.-T. Kang, C. H. Park, U. C. Yoon, *Bull. Korean Chem. Soc.* **1992**, *13*, 41–45.
- 1993JCS(P1)1011 B. F. Bonini, F. Busi, R. C. de Laet, G. Mazzanti, J. W. J. F. Thuring, P. Zani, B. Zwanenburg, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1011–1018.
- 1993PS(74)31 B. F. Bonini, *Phosphorus Sulfur* **1993**, *74*, 31–45.
- 1994OM2147 J. H. Shin, G. Parkin, *Organometallics* **1994**, *13*, 2147–2149.
- 1994TL9227 B. F. Bonini, M. Comes-Franchini, G. Mazzanti, A. Ricci, L. Rosa-Fauzza, P. Zani, *Tetrahedron Lett.* **1994**, *35*, 9227–9228.
- 1995OM1104 J. H. Shin, G. Parkin, *Organometallics* **1995**, *14*, 1104–1106.
- 1996T4803 B. F. Bonini, M. Comes-Franchini, M. Fochi, G. Mazzanti, A. Ricci, *Tetrahedron* **1996**, *52*, 4803–4816.
- 1997JCS(P1)3211 B. F. Bonini, M. Comes-Franchini, M. Fochi, G. Mazzanti, A. Ricci, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3211–3218.
- 1997RHA47 B. F. Bonini, M. Fochi, *Rev. Heteroatom. Chem.* **1997**, *16*, 47–67.
- 1997SL361 A. Degl'Innocenti, P. Scafato, A. Capperucci, L. Bartoletti, C. Spezzacatena, R. Ruzziconi, *Synlett* **1997**, 361–362.
- 1997T7897 B. F. Bonini, M. Comes-Franchini, M. Fochi, G. Mazzanti, A. Ricci, *Tetrahedron* **1997**, *53*, 7897–7910.
- 1999JCS(P2)623 F. Valenti, P. Zanirato, *J. Chem. Soc., Perkin Trans. 2* **1999**, 623–627.
- 1999JPC(A)1662 A. I. González, O. Mó, M. Yáñez, *J. Phys. Chem. A* **1999**, *103*, 1662–1668.
- 1999HCO217 B. F. Bonini, G. Mazzanti, P. Zani, *Heterocycl. Commun.* **1999**, *5*, 217–226.
- 1999PS(153-154)315 B. F. Bonini, M. Comes-Franchini, M. Fochi, S. Mangini, G. Mazzanti, A. Ricci, *Phosphorus Sulfur* **1999**, *153–154*, 315–316.
- 1999SL486 B. F. Bonini, M. Comes-Franchini, M. Fochi, G. Mazzanti, A. Ricci, *Synlett* **1999**, 486–488.
- 1999TL6473 B. F. Bonini, M. Comes-Franchini, M. Fochi, G. Mazzanti, A. Ricci, G. Varchi, *Tetrahedron Lett.* **1999**, *40*, 6473–6476.
- 2000EJO2391 B. F. Bonini, M. Comes-Franchini, M. Fochi, S. Mangini, G. Mazzanti, A. Ricci, *Eur. J. Org. Chem.* **2000**, 2391–2399.
- 2000JOC9206 A. Degl'Innocenti, A. Capperucci, D. C. Oniciu, A. R. Katritzky, *J. Org. Chem.* **2000**, *65*, 9206–9209.
- 2000JOM(611)449 K. Takeda, K. Sumi, S. Hagiwara, *J. Organomet. Chem.* **2000**, *611*, 449–454.
- 2001JOM(623)109 C. E. F. Rickard, W. R. Roper, S. D. Woodgate, L. J. Wright, *J. Organomet. Chem.* **2001**, *623*, 109–115.
- 2001JOM(637-639)407 B. F. Bonini, M. Comes-Franchini, M. Fochi, G. Mazzanti, A. Ricci, M. Tomasulo, G. Varchi, *J. Organomet. Chem.* **2001**, *637–639*, 407–417.

Biographical sketch

Colin Dell was born in London and studied at Imperial College, where he obtained a B.Sc. in 1981 and his Ph.D. in 1984 under the direction of Dr. E. H. Smith. After spending two years at Nottingham in the group of Dr. D. W. Knight, he moved to Ciba-Geigy Pharmaceuticals in Horsham, where he joined a group engaged in the design and synthesis of thrombin inhibitors. In 1989, he moved to Eli Lilly and Company, where he has worked ever since, with the last 10 years spent in the area of neuroscience.

5.17

Iminoacyl Halides and Oxy Functions

R. J. ANDERSON and P. W. GROUNDWATER

University of Sunderland, Sunderland, UK

and

M. NYERGES

Technical University of Budapest, Budapest, Hungary

5.17.1	IMIDOYL HALIDES	592
5.17.1.1	From Amides and Halogenating Reagents	592
5.17.1.1.1	Reactions with oxalyl chloride and phosgene	592
5.17.1.1.2	Reactions with phosphorus tri- and pentahalides	592
5.17.1.1.3	Reactions with thionyl chloride	595
5.17.1.2	From Nitriles and Isonitriles	595
5.17.1.3	From Amines	596
5.17.1.4	From Imidoyl Halides	597
5.17.1.5	Miscellaneous Methods	598
5.17.2	N-HALO-IMIDOYL HALIDES	599
5.17.3	HYDROXAMOYL HALIDES	599
5.17.3.1	General Remarks	599
5.17.3.2	Preparation Procedures	599
5.17.3.2.1	By halogenation of aldoximes	599
5.17.3.2.2	By halogenation of nitroalkanes and nitroalkenes	602
5.17.3.2.3	From hydroxamic acids or derivatives and halogen carriers	604
5.17.3.2.4	By nitrosation of amidoximes	604
5.17.3.2.5	From nitrile oxides	605
5.17.3.2.6	From hydroxamoyl halides	605
5.17.4	N-ORGANOTHIO-IMIDOYL HALIDES	605
5.17.5	HYDRAZONYL HALIDES (HYDRAZIDOYL HALIDES)	605
5.17.5.1	General Remarks	605
5.17.5.2	Preparation Methods	606
5.17.5.2.1	From carboxylic acid hydrazides and halogen carriers	606
5.17.5.2.2	From diazonium halides	606
5.17.5.2.3	By halogenation of hydrazones and azines	607
5.17.5.2.4	From hydrazidoyl halides	608
5.17.5.2.5	Miscellaneous methods	609
5.17.6	N-PHOSPHORYLATED IMIDOYL HALIDES	609
5.17.7	N-ORGANOELEMENTAL SUBSTITUTED IMIDOYL HALIDES	610
5.17.8	IMIDIC ACIDS	610
5.17.8.1	Imidic Acid Esters	610
5.17.8.1.1	From imidoyl halides	610
5.17.8.1.2	From carboxylic acid orthoesters or orthoamides	610
5.17.8.1.3	From nitriles and isonitriles	611
5.17.8.1.4	From heterocyclic compounds (ring-opening reactions)	612
5.17.8.1.5	From imidates and amidines	613
5.17.8.1.6	From metal complexes	614
5.17.8.1.7	Miscellaneous methods	615
5.17.8.2	N-Haloimides	616
5.17.8.3	N-Hydroxy- and N-Alkoxyimides (Hydroxamic Acid Esters)	616

5.17.8.3.1	From hydroxylamine and thioesters	616
5.17.8.3.2	From nitroalkenes or nitroacetate esters	617
5.17.8.3.3	By free-radical addition of trityl thionitrite to an alkene	617
5.17.8.3.4	From ethyl hydroxyacetimidate	617
5.17.8.3.5	By alkylation of an <i>N</i> -hydroxyamide or its ester	618
5.17.8.4	<i>N</i> -Organothioiminoesters and Related Compounds	619
5.17.8.4.1	General remarks	619
5.17.8.4.2	<i>N</i> -Sulfonylimidates	619
5.17.8.4.3	<i>N</i> -Sulfinylimidates	620
5.17.8.4.4	<i>N</i> -Sulfenylimidates	621
5.17.8.5	Hydrazonic Acid Esters (Hydrazonoates, <i>N</i> -Aminoimide Acid Esters)	621
5.17.8.5.1	From hydrazonoyl halides (hydrazidoyl halides)	621
5.17.8.5.2	From thioesters or iminoesters and hydrazine derivatives	622
5.17.8.5.3	Miscellaneous methods	622
5.17.8.6	<i>N</i> -Phosphorylated Imino-esters	623
5.17.8.7	Mixed Anhydrides from Carboximidic Acids and Inorganic or Organic Acids	624
5.17.8.8	Trialkylsilylimidates [<i>N</i> -Trialkylsilylimide Acid Esters, <i>O,N</i> -Bis(trialkylsilyl)imidates]	626
5.17.8.8.1	From carboxylic acid amides and their salts and silylating agents	626
5.17.8.8.2	From imidic acid derivatives	628

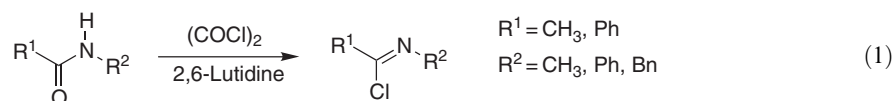
5.17.1 IMIDOYL HALIDES

5.17.1.1 From Amides and Halogenating Reagents

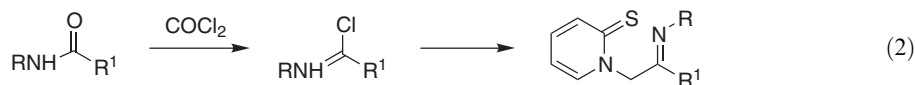
The activation of amides has remained the key method for the preparation of imidoyl halides since the publication of <1995COFGT(5)653>.

5.17.1.1.1 Reactions with oxalyl chloride and phosgene

A mild, practical, one-pot method for the generation of imidoyl chlorides from carboxylic acid amides has been described, involving the reaction of secondary amides with a stoichiometric amount of oxalyl chloride and 2,6-lutidine in CH_2Cl_2 at 0°C (Equation (1)). The isolation of pure compounds from this method does not involve fractional distillation or precipitation under anhydrous conditions and is, therefore, a significant improvement on many other methods for the generation of imidoyl chlorides <2002OL3127>.



Phosgene has been used to generate imidoyl chlorides from amides in the synthesis of several radical precursors such as (2-thiopyridin-1-yl)oxycarbonylimide esters (Equation (2)) <1998JA7738>.



5.17.1.1.2 Reactions with phosphorus tri- and pentahalides

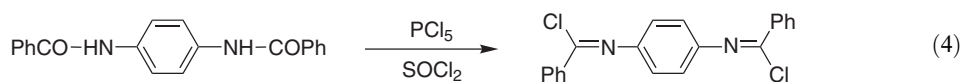
Imidoyl chlorides can be obtained from a range of aliphatic and aromatic amides by a general synthetic method involving the reaction with phosphorus penta- and trihalides in a variety of solvents (Equation (3)).



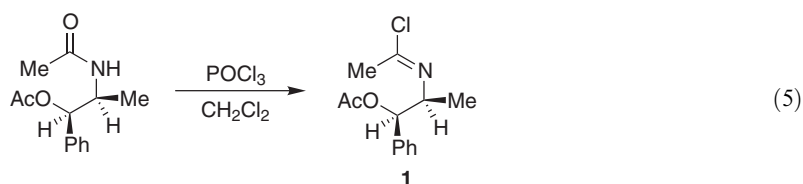
R^1	R^2	Reagent	Solvent	References
Me, Ph	Me	POCl ₃	CH ₂ Cl ₂	<1999SC1>
Me	Bn	POCl ₃	Et ₂ O	<2001TL2653>
	C ₆ H ₅ (CH ₂) ₄			
	C ₆ H ₁₁			
	ⁿ C ₄ H ₉			
	ⁱ C ₃ H ₇			
	Ph			
	4-O ₂ NC ₆ H ₄			
	4-BrC ₆ H ₄			
	4-MeC ₆ H ₄			
	4-MeOC ₆ H ₄			
Ph	Ph	PCl ₅	None	<1996S1428>
4-O ₂ NC ₆ H ₄	4-ClC ₆ H ₄			<2001IZV1562>
CF ₃	4-BrC ₆ H ₄			<2001MI1639>
	3-O ₂ NC ₆ H ₄			
	2,4-Br ₂ C ₆ H ₃			
	2,4-(O ₂ N) ₂ C ₆ H ₃			
	2-Pyridyl			
	3-Pyridyl			
	4-Pyridyl			
	Me			
Bu ^t	2,6-(Me) ₂ C ₆ H ₃	PCl ₅	Toluene	<1998T12007>
ⁿ C ₆ H ₁₃	ⁿ C ₈ H ₁₇			<1997TL8903>
Ph	CF ₃ CH ₂			<2001JCS(P2)1239>
4-O ₂ NC ₆ H ₄	(CF ₃) ₂ CH			
Ph	Bn	PCl ₅	Et ₂ O	<2001JCS(P1)2781>
2-PhC ₆ H ₄				
Ph ₂ C=CH				
Me	Me	PCl ₅	CHCl ₃	<2001IZV522>
				<2001MI545>
Ph	CF ₃	PCl ₅	POCl ₃	<2001EJO1225>
4-MeC ₆ H ₄	C ₄ F ₉			
4-FC ₆ H ₄				
4-ClC ₆ H ₄				
4-O ₂ NC ₆ H ₄				
Me ₃ C				

(3)

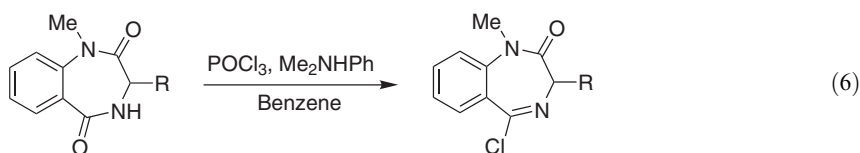
Thionyl chloride has also been used as a solvent with phosphorus pentachloride for the generation of imidoyl chlorides from carboxylic acid amides ($R^1 = 4\text{-BrC}_6\text{H}_4$, $4\text{-O}_2\text{NC}_6\text{H}_4$; $R^2 = \text{Ph}$, $4\text{-O}_2\text{NC}_6\text{H}_4$) and diamides (Equation (4)) <1996S1428>.



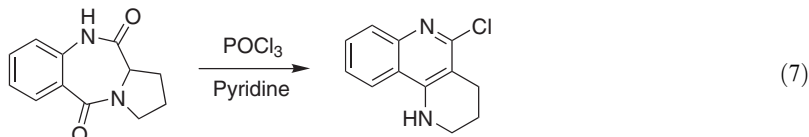
Chiral imidoyl chlorides, e.g., **1**, have been prepared under mild conditions with POCl₃ in dichloromethane (Equation (5)) <1999SC1>.



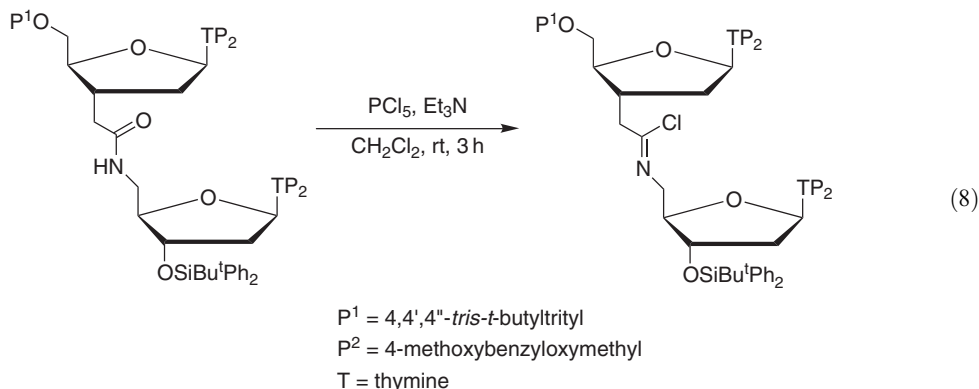
In the synthesis of 5-aryl-1,4-benzodiazepine derivatives, the corresponding imidoyl chloride was prepared <2003JOC2844> by an efficient procedure employing POCl₃ in the presence of *N,N*-dimethylaniline (Equation (6)) <1979JOC88>.



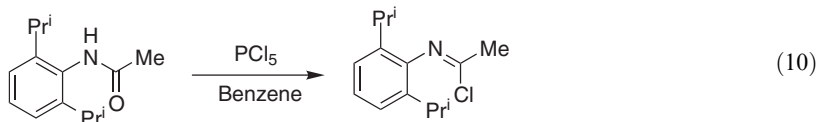
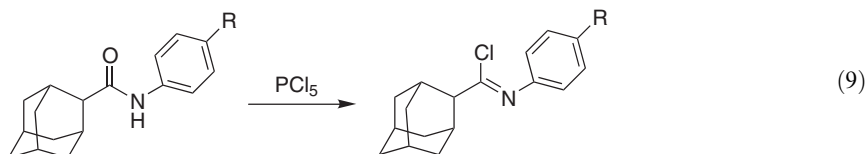
In an extension to earlier studies on rearrangements and aromatizations in the 1,4-benzodiazepine series, it has been reported that hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione and related compounds rearrange to 5-chlorotetrahydrobenzo[*h*][1,6]naphthyridine and related derivatives (Equation (7)) <2003JHC255> and not to cyclopenta[*b*][1,4]benzodiazepine as was previously described <1997TL2271, 1997TL6771, 2000T1361>.



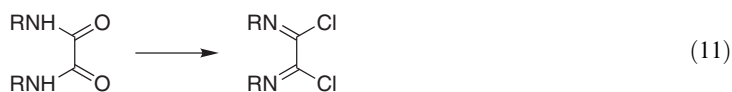
Imidoyl chlorides can be prepared by the reaction of amides with PCl_5 in the presence of Et_3N . Several other sets of conditions for this transformation were unsuccessful (Equation (8)) <1997BMCL447>.



Adamantyl-containing imidoyl chlorides were prepared by treatment of 1-adamantanecarboxanilides with PCl_5 (Equation (9)) <1996JOU1072, 1996ZOR1110>, while sterically hindered imidoyl chlorides were obtained from the corresponding amides with phosphorus pentachloride in refluxing benzene (Equation (10)) <1998JCS(D)4147, 2000CJC583>.

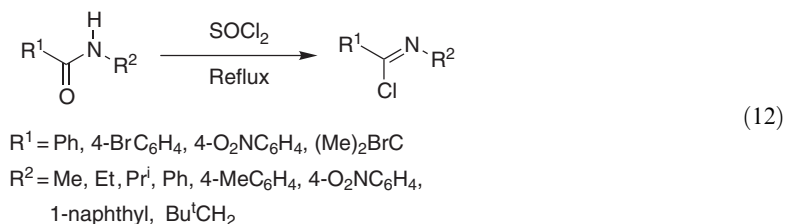


The reactions of bisimidoyl chlorides derived from oxalic acid and several aromatic and aliphatic amines have been investigated by numerous research groups (Equation (11)), most of which prepared these compounds using 1 equiv. of PCl_5 in refluxing dry toluene <1997PHA638, 1997MI617, 1997TL8017, 1998TL1135, 1999CC2439, 1999M1373, 1999EJO205, 1999JOC365, 1999SL1100, 1999SL468, 2000JOC729, 2000JOC3603, 2001EJI805, 2001EJO3953, 2001S601, 2001SL1437, 2002EJO686, 2002HET1257> by the method of Beckert <1995JPR143, 1998JPR323>.

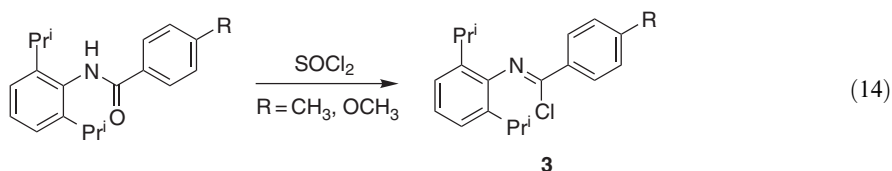
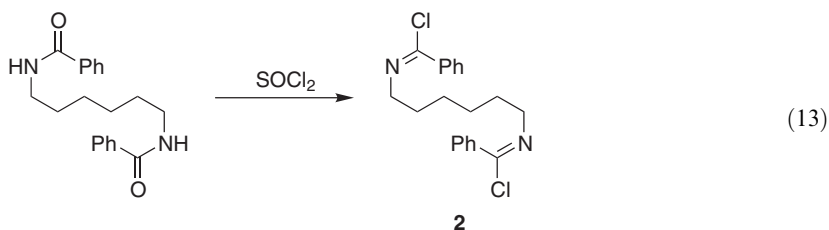


5.17.1.1.3 Reactions with thionyl chloride

Several groups have described the use of a general method for preparing benzimidoyl chlorides from the corresponding benzamides in thionyl chloride (Equation (12)), as solvent and reagent, at reflux <1996S1428, 1996LA87, 2001JCS(P2)1239, 2002T3003>.

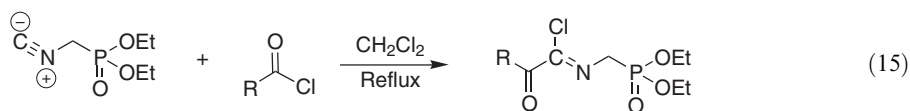


Bisimidoyl chlorides, e.g., **2**, (Equation (13)) <1999SC1> and sterically hindered imidoyl chlorides, e.g., **3**, (Equation (14)) <1998JCS(D)4147> have also been prepared in this way.

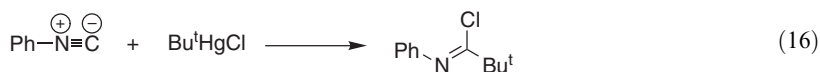


5.17.1.2 From Nitriles and Isonitriles

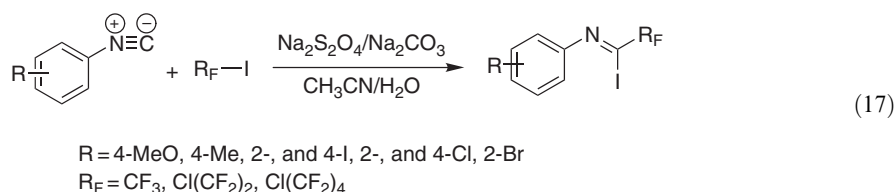
The reaction of primary, secondary, and tertiary acyl chlorides ($\text{R} = \text{Et}, \text{C}_6\text{H}_{11}, \text{Bu}^t$) with diethyl isocyanomethylphosphonate in refluxing dichloromethane, gave α -ketoimidoyl chlorides (Equation (15)) <1996JCS(P1)1893>.



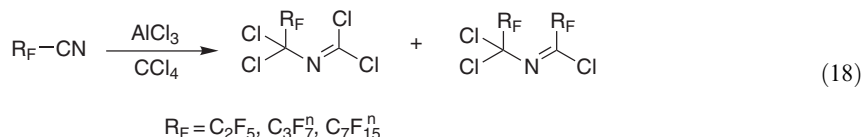
Photolysis of Bu^tHgCl with phenylisonitrile in benzene afforded the corresponding imidoyl chloride, which was detected by GC-MS before hydrolytic or reductive work-up (Equation (16)) <1998ACS528>.



Polyfluoroalkyl imidoyl iodides have been synthesized by the radical reaction of polyfluoroalkyl iodides with *N*-aryl isocyanides in the presence of a dehalogenation reagent such as $\text{Na}_2\text{S}_2\text{O}_4/\text{Na}_2\text{CO}_3$ (Equation (17)) <1996TL7999, 1997JFC65, 1997MI278, 1998JFC69>.

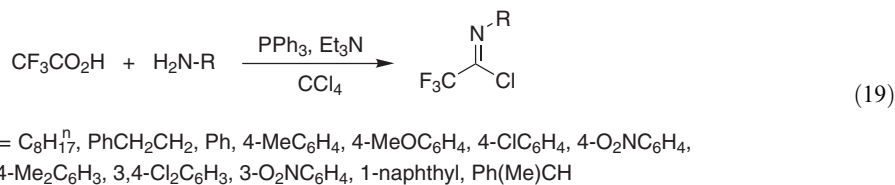


Perfluoronitriles react with a $\text{CCl}_4/\text{AlCl}_3$ mixture at elevated temperatures to give a mixture of almost equal amounts of imidoyl chlorides as shown in Equation (18), which could be separated by distillation <2001JFC123>.

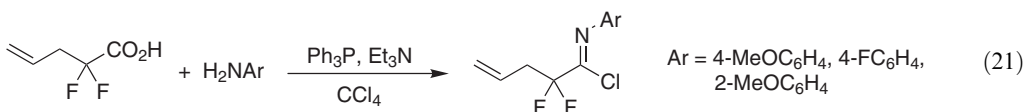
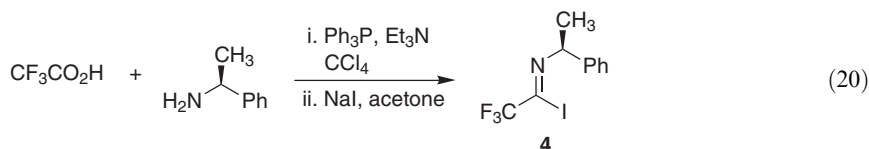


5.17.1.3 From Amines

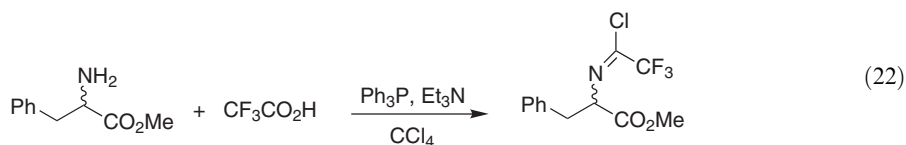
The chemistry of trifluoroacetimidoyl halides, including their preparation, reactions with nucleophiles, electrophiles, and radicals, and synthetic applications has recently been reviewed <1999JFC11>. These popular building blocks are stable compounds and are easily prepared in high yields by the one-pot procedure first described by Appel and co-workers <1973CB2093> and later improved by Uneyama <1993JOC32>. Refluxing a mixture of trifluoroacetic acid, an alkyl- or aryl amine, PPh_3 , and Et_3N in CCl_4 (Equation (19)) usually gives a high yield of the corresponding imidoyl halides <1996S511, 1998EJO435, 1998JOC6210, 1999JFC83, 2001OL1109>.



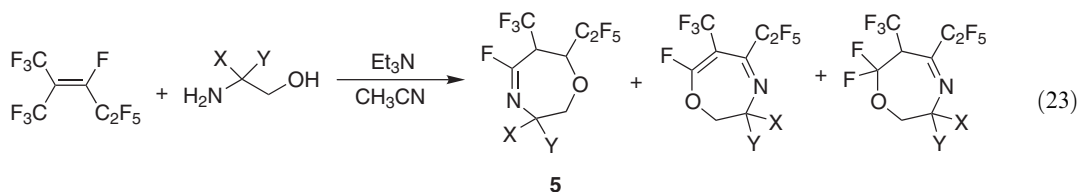
An imidoyl iodide **4** possessing a chiral moiety on the nitrogen atom was prepared from trifluoroacetic acid and (*S*)-phenylethylamine without any loss of optical purity (Equation (20)) <2003CC1752>. *N*-[2-(1-Alkynyl)phenyl]trifluoroacetimidoyl iodide and 2,2,2-trifluoro-*N*-(*p*-methoxyphenyl)acetimidoyl iodide have also been prepared by this method <1995BCJ1497>. *N*-(Aryl)-1-chloro-2,2-difluoro-4-penten-1-imines have been prepared by related methodology (Equation (21)) <2003OL2523, 2003OL2707>.



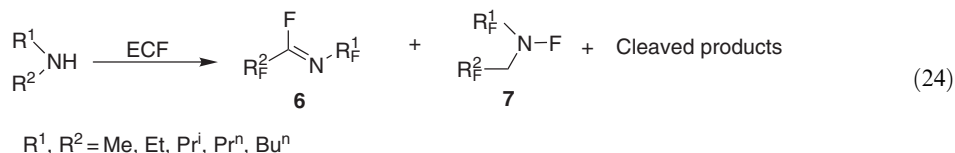
Phenylalanine methyl ester was reacted with trifluoroacetic acid in this manner to give an imidoyl chloride in good yield (Equation (22)) <2001JFC27>, which was then converted into stable enols of carboxylic esters via an Arbuzov rearrangement.



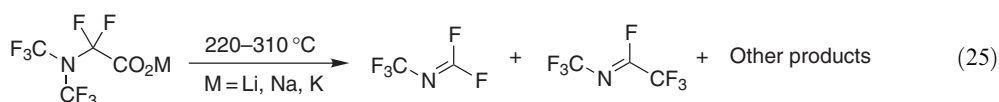
The reaction between perfluoro-2-methyl-2-pentene and compounds with the general formula $\text{H}_2\text{NC(X)(Y)CH}_2\text{OH}$ (Equation (23)) in the presence of triethylamine gives mixtures of seven-membered heterocycles, including an imidoyl fluoride **5** <2001JFC11>.



The electrochemical fluorination (ECF) of several secondary amines (Equation (24)) gives imidoyl fluorides **6** and *N*-fluoro-*N,N*-dialkylamines **7** in low yield, together with larger quantities of cleaved products. The combined yields of **6** and **7** were in the range 3–16%, depending greatly upon the type of alkyl groups present <2000JFC35>.

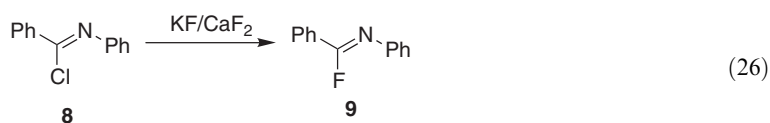


The thermal decomposition of perfluorodimethyl aminoacetate salts (Equation (25)) to give imidoyl fluorides has been investigated in detail. Variation of the counterion greatly affects the pyrolysis products and their yields, while changes in temperature had little effect upon the nature of the product and the yield in these reactions. Perfluoro-2-azapropene was prepared in moderate yield by the pyrolysis of perfluoro(dimethylamino)acetic acid potassium salt <1999JFC161>.

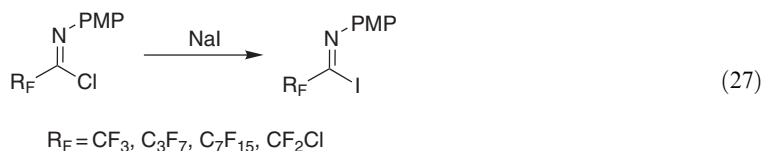


5.17.1.4 From Imidoyl Halides

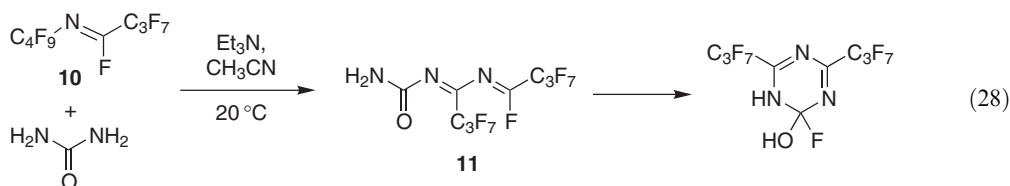
A new reagent, calcium-fluoride-supported potassium fluoride, has been used for the preparation of imidoyl fluorides. The imidoyl chloride **8** with an excess of this reagent in refluxing acetonitrile (Equation (26)) gave the halogen-exchanged compound **9** as an unstable, readily hydrolyzed liquid <1999AJC807>.



Perfluorinated imidoyl iodides were prepared by the substitution of the chloride atom of an imidoyl chloride by sodium iodide (Equation (27)) <2000JOC3404>.

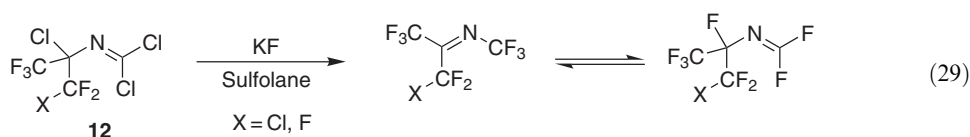


In the reaction of perfluoro-5-azanon-4-ene **10** with urea (Equation (28)), the imidoyl fluoride **11** was described as an intermediate which cyclized to a triazine <2000JFC105>.



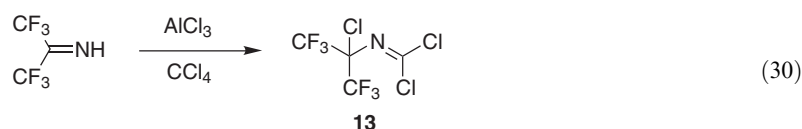
Treatment of the readily accessible phosphonium salt $\text{PhCCl}=\text{NCH}_2\text{P}^+\text{Ph}_3\text{Cl}^-$ with Et_3N yields an ylide $\text{PhCCl}:\text{NCH}:\text{PPh}_3$, which contains an electrophilic imidoyl chloride group together with a nucleophilic center (the $\text{P}=\text{C}$ bond), and can thus undergo cyclocondensations with carboxylic acid chlorides, CS_2 , or acyl isothiocyanates <1999JGU1583, 1999ZOB1652>.

The reaction of imidoyl chloride (**12**, $\text{X}=\text{F}$) with dry potassium fluoride in a polar solvent (Equation (29)) leads to the formation of a mixture of isomeric azaalkenes <2001JFC123>, which are reported to exist in equilibrium <1975IC592>. The analogous imidoyl chloride (**12**, $\text{X}=\text{Cl}$) also reacts with dry caesium fluoride to give a mixture of azaalkenes.

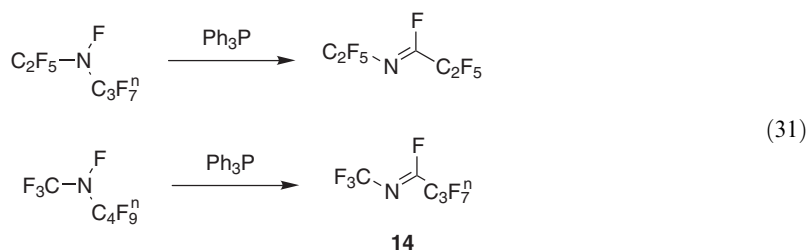


5.17.1.5 Miscellaneous Methods

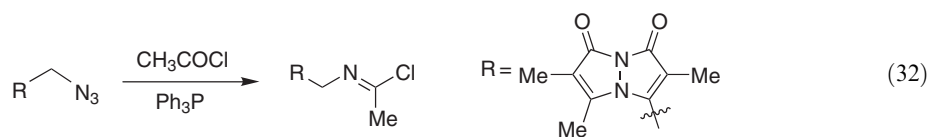
Hexafluoroacetoneimine reacts, on heating for several hours with a catalytic amount of AlCl_3 in carbon tetrachloride (Equation (30)), to give an imidoyl chloride **13**, with the evolution of hydrogen chloride. The imine of 1,3-dichlorotetrafluoroacetone behaves similarly <2001JFC123>.



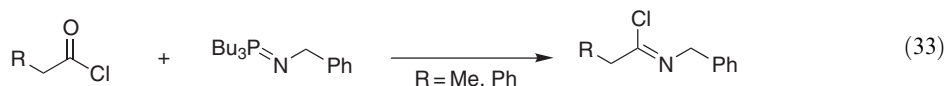
The reaction of *N*-fluoro secondary amines with Ph_3P proceeds smoothly, resulting in the formation of fluoroimines (imidoyl fluorides) in good yield (Equation (31)). It was found that only one of the possible regioisomeric imidoyl fluorides, e.g., **14**, was formed from fluoroamines with two different *N*-alkyl groups, with the $\text{C}=\text{N}$ bond of the imine being formed on the larger alkyl group <2000JFC35>.



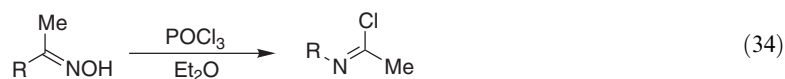
The addition of Ph_3P to a solution of an azide and a reactive acylating agent (such as acetyl chloride) leads to the formation of imidoyl chlorides (Equation (32)) via triazaphosphadiene adducts <1996JOC1689>.



The mechanism of the reaction of phosphazanes with acyl chlorides (Equation (33)) has been studied in detail by NMR spectroscopy <1996JOC5638>.



The Beckmann rearrangement of acetophenone derivatives (Equation (34)) has been used for the preparation of some simple imidoyl chlorides <2001TL2653>.



5.17.2 N-HALO-IMIDOYL HALIDES

N-Chloro- and *N*-bromo-imidoyl halides have been prepared by the reaction of chlorine or bromine with cyanogens or substituted nitriles. No further advances have occurred in this area since the publication of chapter 5.17.2 in <1995COFGT(5)653>, in which these syntheses were reviewed.

5.17.3 HYDROXAMOYL HALIDES

5.17.3.1 General Remarks

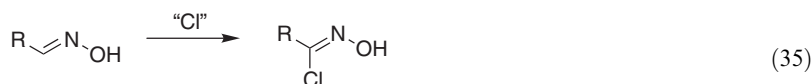
In recent years, as was the case at the time of publication of <1995COFGT(5)653>, hydroxamoyl halides have received much attention as precursors of nitrile oxides, e.g., references <1995H619, 1996CL455, 1996T8877, 1997T1787, 1997T6681, 1998JCS(P2)2413, 1998TL3233, 1998TL5869, 1999T14199, 2000T965, 2000TL3131>.

5.17.3.2 Preparation Procedures

The most frequently used procedures for the preparation of hydroxamoyl halides are based upon the halogenation of aldoximes, but in recent years the development of methods for the halogenation of nitroalkenes has also been reported.

5.17.3.2.1 By halogenation of aldoximes

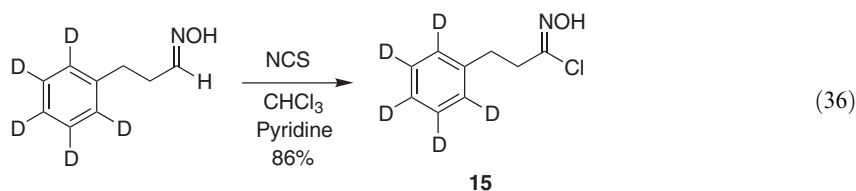
A variety of methods have been reported for the conversion of aldoximes into hydroxamoyl chlorides (Equation (35)) using chlorinating agents such as chlorine, nitrosyl chloride, *t*-butyl hypochlorite, and *N*-chlorosuccinimide (NCS) in attempts to improve the yield, simplify the experimental conditions, and avoid polyhalogenation.



R	Yield (%)	References
Ph	66–82	<2000T965, 2000TL3131, 1999T14199, 1998TL5869, 1998TL3233, 1997T6681, 1997T1787, 1998JCS(P2)2413, 1996CL455, 2000H579, 2002T9613, 1997TL1597, 2001JFC241, 2000JHC1505, 1998JMC4556>
2-ClC ₆ H ₄	Not reported	<1997TL1597>
3-ClC ₆ H ₄	Not reported	<1999T14199>
4-ClC ₆ H ₄	70–76	<2000T965, 1999T14199, 2000H579, 1998TL3233, 1997T1787, 1996CL455, 2002T9613, 1997TL1597, 2001JFC241>
2,4-ClC ₆ H ₃	Not reported	<1998JMC4556>
2,6-ClC ₆ H ₃	Not reported	<1997TL1597, 1998SC1879>
4-MeC ₆ H ₄	58–69	<2000T965, 1999T14199, 1998TL3233, 1997T1787, 1997TL1597, 2001JFC241, 2000JHC1505, 1998JMC4556>
2,4,6-Me ₃ C ₆ H ₂	Not reported	<1998TL3233, 1997TL1597>
4-MeOC ₆ H ₄	73–78	<2000T965, 2000TL3131, 1999T14199, 1998TL3233, 1997T1787, 1996CL455, 1997TL1597, 2001JFC241, 2000JHC1505, 1998JMC4556>
3,4-(MeO) ₂ C ₆ H ₃	Not reported	<1999T14199, 1998JMC4556>
4-F ₃ CC ₆ H ₄	Not reported	<2002T9613, 1997TL1597, 1998JMC4556>
3-O ₂ NC ₆ H ₄	Not reported	<1999T14199>
4-O ₂ NC ₆ H ₄	Not reported	<2000TL3131, 1998TL3233, 1997T1787, 1998JMC4556>
PhCH ₂ CH ₂	Not reported	<2002T9613>
PhCH ₂	Not reported	<1998TL3233, 2001JFC241, 1998JMC4556>
Ph ₂ CH	Not reported	<1997TL1597, 1998SC1879>
Ph(Me)CH	Not reported	<1997TL1597>
Me(CH ₂) ₄	Not reported	<1998TL3233, 1997TL1597>
Me(BnO ₂ CNH)CH	65	<1999SL873>
{Et(Me)CH}(BnO ₂ CNH)CHMe ₂ C	52	<1999SL873>
Me ₂ CHCH ₂ {(BnO ₂ CNH)}CH	71	<1999SL873>
PhCH ₂ (BnO ₂ CNH)CH	42	<1999SL873>
PhCH ₂ (Bu ^t O ₂ CNH)CH	48	<1999SL873>
Me(Bu ^t O ₂ CNH)CH	54	<1999SL873>
Me ₂ CHCH ₂ (Bu ^t O ₂ CNH)CH	75	<1999SL873>
{Et(Me)CH}(Bu ^t O ₂ CNH)CH	63	<1999SL873>

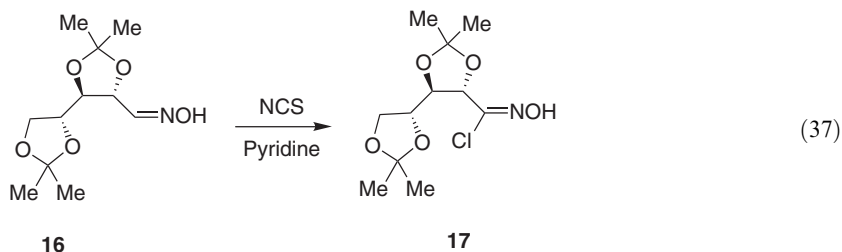
NCS in *N,N*-dimethylformamide (DMF) as solvent, which was first described by Bonini and co-workers <1980JOC3916>, has been used for the preparation of many hydroxamoyl chlorides. These conditions were also used for the preparation of bis(hydroxamic acid chlorides) <2000TL10055, 2001S2191>. Hydroxamoyl chloride precursors for intramolecular nitrile oxide cycloadditions have been prepared with this reagent in DMF as solvent <1996TL451>. Other solvents used include CHCl₃ (R = BnO₂CNHCH₂CH₂) <1999TL4085>, CH₂Cl₂ (R = 2-TBSOC₆H₄, Buⁿ, Prⁿ) <2003TL8901>, and MeCN (Bu^tO₂CCH₂N(*t*-BOC)(CH₂)_n) <2000JOC4289>. Mono-*ortho*-substituted *C*-chlorooximes can be readily prepared (NCS/pyridine), while the corresponding bis-*ortho*-substituted analogs are unstable and prone to decomposition <2003TL3555>.

The preparation of hydroxamoyl chlorides from benzaldoximes using NCS as the chlorinating agent has also been reported <1996T5739, 2003JMC284>, while the reaction of the corresponding oxime with NCS in chloroform/pyridine gave ethyl 8-chloro-8-hydroxyiminooctanoate <2001CAR295>. During the synthesis of deuterium-labeled desulfoglucosinolates the required hydroxamoyl chloride **15** was prepared with NCS in chloroform/triethylamine (Equation (36)) <1999T13269>.

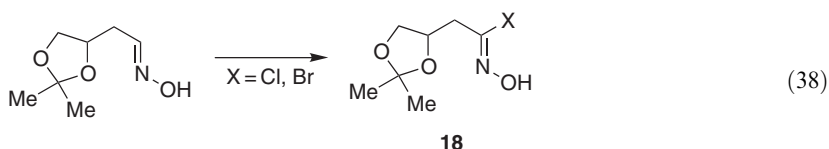


Hydroxamoyl chlorides anchored onto a solid phase were prepared from 4-hydroxybenzaldehyde attached to chlorotriptyl resin <1998TL2447> or to a polyethylene glycol support <2003TL4113>. The oxime resins were chlorinated with 4 equiv. of NCS in CH₂Cl₂.

2,3:4,5-Di-*O*-isopropylidene-D-arabinohydroxamoyl chloride **17** was prepared from the corresponding oxime **16** with NCS in pyridine (Equation (37)) <1999CAR1>, while in a cycloaddition approach to breynolide, the nitrile oxide precursor was obtained by the chlorination of the protected oxime <1997T8997>.

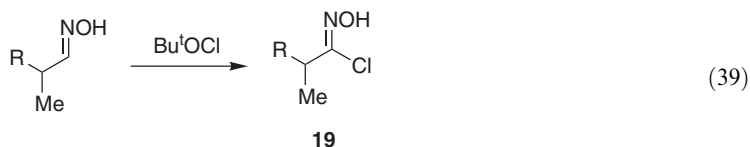


Chlorination with NCS in DMF was found to be a useful method in the synthesis of penam sulfones, a new class of β -lactamase inhibitor <2000OL3087>. A C-22-steroidal chlorooxime <2000JOC6231> and nitrile oxide precursor hydroxamoyl halides **18** have been prepared with different reagents (NaOCl, NCS, NBS, Bu^tOCl) in chloroform in various yields (Equation (38)) <2000TL6011>.

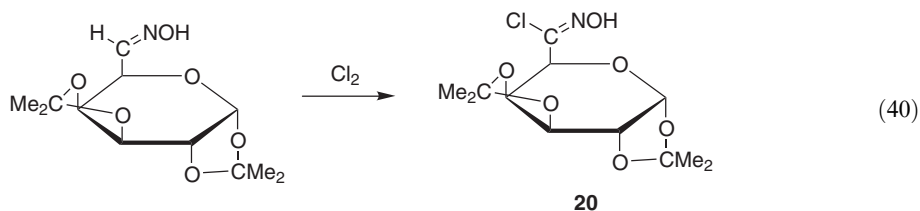


The HCl/DMF/Oxone[®] halogenating system was used for the preparation of simple hydroxamoyl chlorides (Equation (35); R = Ph, 2-ClC₆H₄, 4-ClC₆H₄, 2,6-Cl₂C₆H₃, 4-MeC₆H₄, 2,4,6-Me₃C₆H₂, 4-MeOC₆H₄, 4-F₃CC₆H₄, (C₆H₅)₂CH, C₆H₅(Me)CH, Me(CH₂)₄) <1992JOC6649, 1997TL1597>. The intermediate hydroxamoyl chlorides derived from *O*-benzylvanillin aldoxime and trichloroisocyanuric acid, were not isolated, but the nitrile oxide was trapped by several dipolarophiles <2001SC3075>.

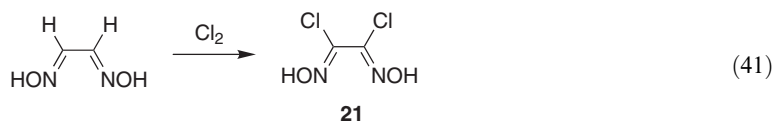
The preparation of the alanine-derived hydroxamoyl chloride (**19**, R = BOCNH) can be accomplished with NCS in chloroform, but more readily with *t*-butyl hypochlorite (CHCl₃, 0 °C) <2000TA3273>, while *t*-butyl hypochlorite (CH₂Cl₂, -78 °C) was also the reagent of choice in the synthesis of a highly sensitive hydroxamoyl chloride (**19**, R = (EtO)₂P(O)) (Equation (39)) <2001JOC6410>.



Hydroxamoyl chlorides can also be obtained by the direct chlorination of aldoximes. Five different protected sugar-derived oximes were reacted with chlorine gas in dichloromethane solution at low temperature (-30 °C) to produce the corresponding hydroxamoyl chlorides **20**, which were used directly (Equation (40)) <1995CAR321>. D-Galactose-, D-mannose-, and D-xylose-derived hydroxamoyl chlorides were prepared similarly by bubbling chlorine through a solution of the oxime in CH₂Cl₂ at -78 °C <2001TL4065>.



An oximinoyl chloride derived from *t*-butyl formylacetate was prepared in this way by the chlorination of the oxime at -40 °C <1997JMC2064>, as was dichloroglyoxime **21** (Equation (41)) <1996TL4137>.

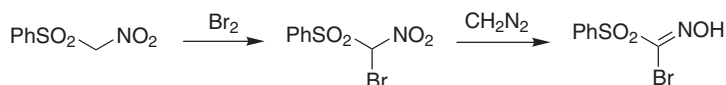


A very attractive protocol, originally reported by Tacconi [<1984G131>](#), which makes use of the easy and controlled generation of chlorine from hydrochloric acid and sodium hypochlorite, has been used to prepare several aliphatic hydroxamoyl chlorides from the aldoximes [<1999T10497>](#).

Benzyltrimethylammonium tetrachloroiodate (BTMAICl₄) is a convenient reagent for the conversion of aldoximes to hydroxamoyl chlorides. The aldoxime is treated with BTMAICl₄ in dichloromethane, the suspension of BTMAICl₄ disappears as the reaction proceeds, and the resulting by-product BTMAICl₂ can be precipitated out by adding diethyl ether. In addition to stable aromatic and heteroaromatic hydroxamoyl chlorides, less stable aliphatic hydroxamoyl chlorides can be generated *in situ* by this method [<2000T1057>](#).

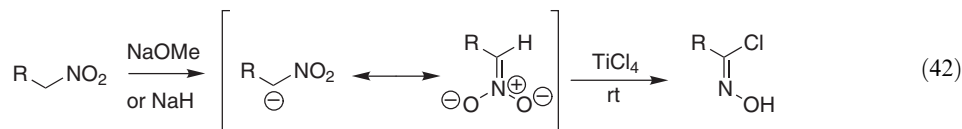
5.17.3.2.2 By halogenation of nitroalkanes and nitroalkenes

Nitroalkanes can be converted into hydroxamoyl bromides in two steps; for example, the bromination of phenylsulfonylnitromethane, followed by treatment with diazomethane at low temperatures, gave an unstable intermediate, which loses formaldehyde upon warming up to 40 °C ([Scheme 1](#)) [<1979JA1319, 1998CC1143>](#).

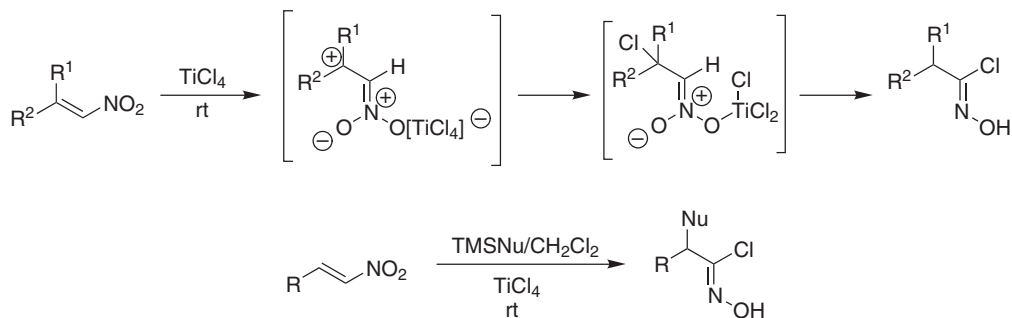


Scheme 1

Kumaran and Kulkarni reported the novel one-pot conversions into hydroxamoyl chlorides of nitroalkenes using TiCl₄ as the chlorinating agent, and of primary nitroalkanes using base (NaOMe or NaH) and TiCl₄ ([Equation \(42\)](#)) [<1994TL5517, 1996TL6407, 1997JOC1516>](#).



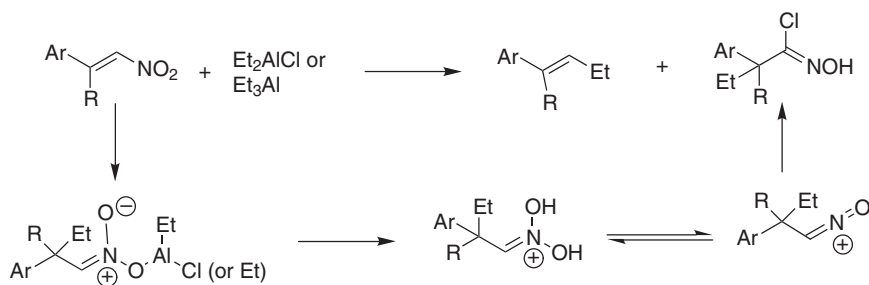
The mechanism suggested for the nitroalkene reaction involves a carbocation intermediate, which can be attacked by external nucleophiles ([Scheme 2](#)), so that treatment of a nitroalkene with TiCl₄ in the presence of Et₃SiH gives the corresponding hydroximoyl chlorides [<1994TL9099>](#), while with TMSNu—TiCl₄ (Nu = CN, N₃) the α-azido/cyano functionalized hydroximoyl chlorides were obtained [<1995SC3735>](#).



R = alkyl, aryl; Nu = CN, N₃

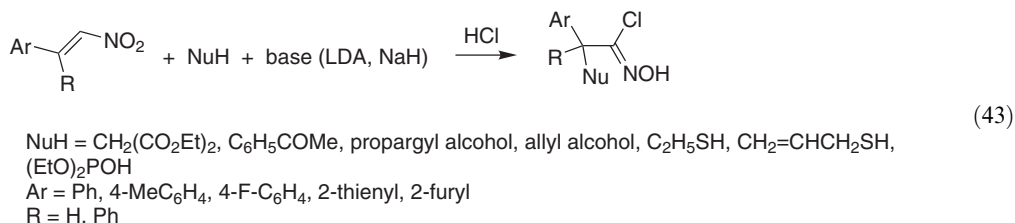
Scheme 2

β -Nitrostyrenes react with triethylaluminum or diethylaluminum chloride in diethyl ether to generate the alkenes and the hydroxamoyl chlorides after work-up with ice-cold, concentrated hydrochloric acid. The formation of the alkenes is proposed to be a free-radical reaction via NO_2 /alkyl substitution, since the yields of the alkenes are increased in the presence of benzoyl peroxide and decreased in the presence of galvinoxyl. The mechanism for the generation of the hydroxamoyl chlorides is proposed to proceed through a 1,4-addition pathway, producing nitronates. The protonated nitronates, or the nitroso cations, are then trapped by the chloride ion to form the final products. Yields are also improved by the presence of Lewis acids such as MgCl_2 (Scheme 3) <1999JCS(P1)47>.

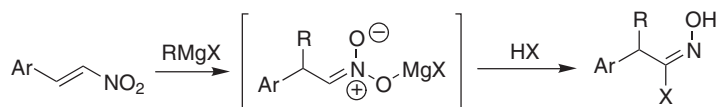


Scheme 3

β -Nitrostyrenes also react with stabilized nucleophiles, such as carbon nucleophiles, sulfur nucleophiles, alkoxides, and $(\text{EtO})_2\text{PO}^-$, to generate hydroxamoyl chlorides after work-up with ice-cold hydrochloric acid, in medium to high yields (Equation (43)) <1997TL6419, 1998T791, 1998T13997, 1999T12493>.

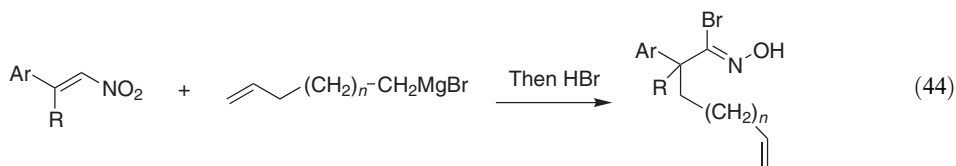


Various β -nitrostyrenes have been reacted with Grignard reagents to generate hydroxamoyl halides. In the first step the 1,4-addition gives the *aci*-anion, which is then added to ice-cold concentrated aqueous HBr or HCl solution (Scheme 4) <1996TL6339>.



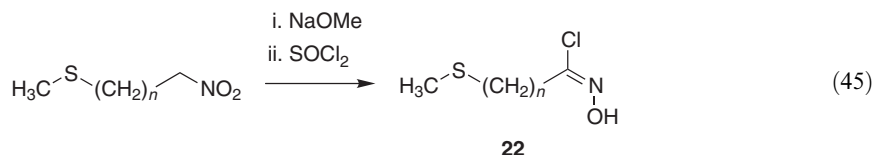
Scheme 4

Hydroxamoyl bromides have also been obtained using this methodology (Equation (44)) <1999T7115>.

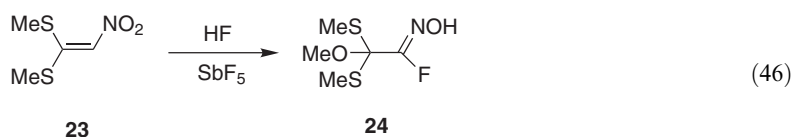


For a key step in a glucosinolate synthesis, it was necessary to prepare a hydroxamoyl halide **22** with a reactive methyl sulfide function, precluding the usual chlorine gas or NCS methodology <1980JOC3916>. This problem was overcome with an alternative nitronate methodology, in which

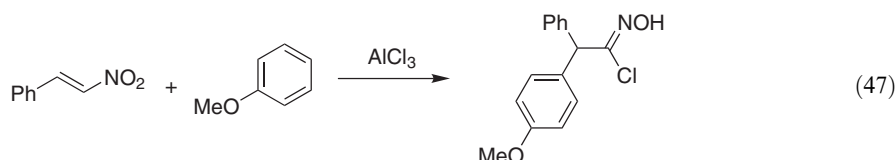
the nitronate salt was readily prepared using NaOMe, and was halogenated with thionyl chloride (Equation (45)) <1996TL5699>. A related method employs the halogenation with SOCl₂ of an anion formed from primary nitroalkanes with NaOMe <1990TL1417, 1995CAR257>.



Nitroketene-*S,S*-acetals having two electron-donating groups on the one end of the double bond and an electron-withdrawing group on the other are very prone to nucleophilic addition at the acetal carbon. When the nitroketene-*S,S*-acetal **23** was dissolved in HF/SbF₅ at low temperatures, and the solution was quenched with methanol, the halogenated orthoester **24** was obtained (Equation (46)) <1995T10929>.

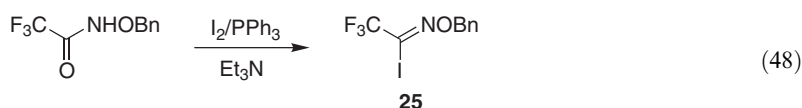


Finally, β -nitrostyrene was reacted with anisole in the presence of aluminum chloride to give a hydroxamoyl chloride (Equation (47)) <1997JCR(M)2459>.



5.17.3.2.3 From hydroxamic acids or derivatives and halogen carriers

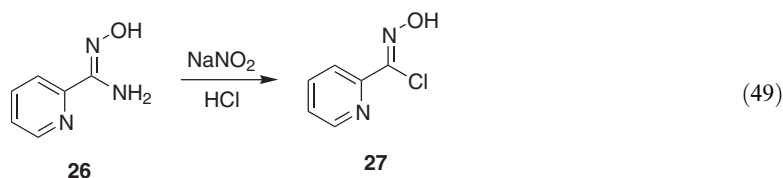
O-Alkylhydroxamic acids react with thionyl chloride <1980LA791, 1985JOC993>, or phosphorus pentachloride <1984JOC919>, or POCl₃/PCl₅ <1992JOC3245> resulting in the formation of the corresponding hydroxamoyl halides. Recently, Uneyama prepared the alkoxyimidoyl iodide **25** from *N*-(benzyloxy)-2,2,2-trifluoroacetamide by reaction with I₂/PPh₃/Et₃N (Equation (48)) <1996T233>.



N-Methoxyimidoyl bromides have been synthesized in a one-pot procedure from carboxylic acids, methoxyamine, and PPh₃/CBr₄ in 72–85% yield <1999MI222>.

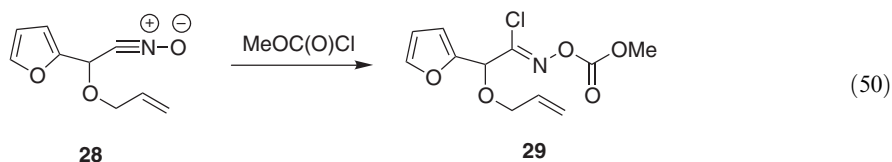
5.17.3.2.4 By nitrosation of amidoximes

Pyridine-2-amidoxime **26** gives pyridine-2-carbohydroximoyl chloride **27** upon treatment with sodium nitrite in the presence of hydrochloric acid (Equation (49)) <1995TL327> using the nitrosation method previously described by Kocivar <1988SC1427>.



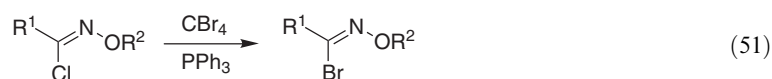
5.17.3.2.5 From nitrile oxides

The hydroxamoyl chloride **29** has been isolated by trapping of the intermediate nitrile oxide **28** with methyl chloroformate (Equation (50)) <1999T12493>.

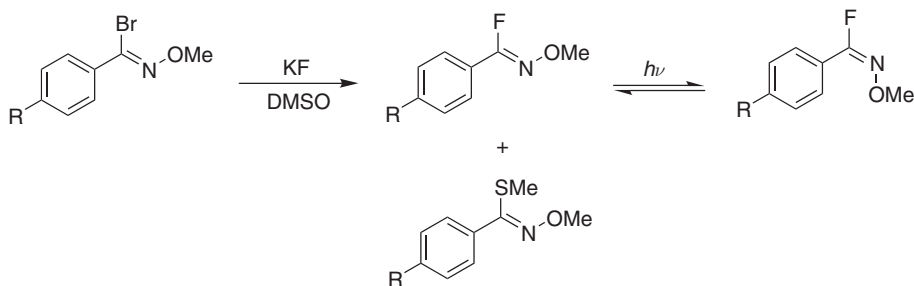


5.17.3.2.6 From hydroxamoyl halides

N-Alkoxyimidoyl bromides were prepared in good yields from the reaction of the corresponding *N*-alkoxyimidoyl chlorides with $\text{CBr}_4/\text{PPh}_3$ in acetonitrile using the method of Sakamoto (Equation (51)) <1991S750>, and used as coupling partners in Pd-catalyzed Stille reactions <2001SL1557>.



Heating of a (*Z*)-*N*-methoxy-(4-substituted-phenyl)carboximidoyl bromide with potassium fluoride in dimethyl sulfoxide at 150–170 °C gave the corresponding imidoyl fluorides along with varying amounts of methyl benzothiohydroxamates. The irradiation of solutions of the (*Z*)-hydroxamoyl fluorides in benzene gave a photostationary mixture of the (*E*)- and (*Z*)-isomers in an approximately 1:1 ratio (Scheme 5) <1999AJC807>.



Scheme 5

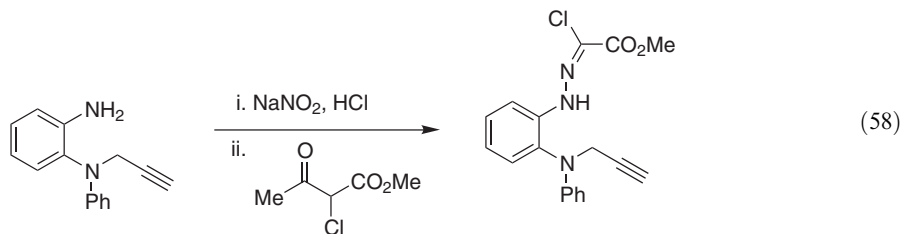
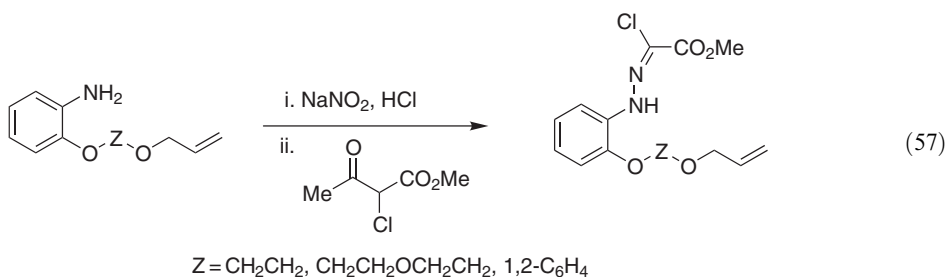
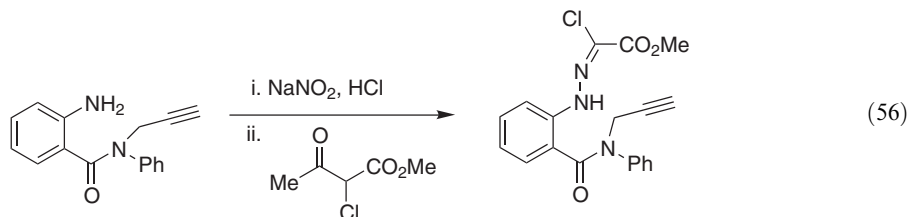
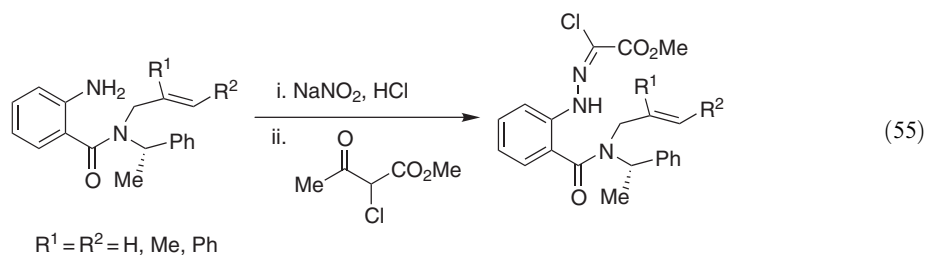
5.17.4 *N*-ORGANOTHIO-IMIDOYL HALIDES

No further advances have occurred in this area since the publication of chapter 5.17.4 in COFGT (1995).

5.17.5 HYDRAZONYL HALIDES (HYDRAZIDOYL HALIDES)

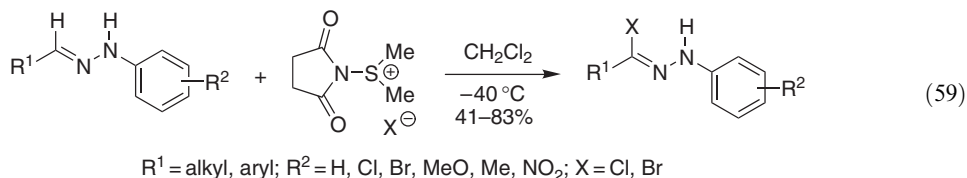
5.17.5.1 General Remarks

Hydrazonyl halides have been the subject of continuing attention over the last few decades, due to their importance as precursors of nitrile imines, which are used extensively in 1,3-dipolar cycloaddition reactions and related pericyclic processes, and of hydrazones of complex aliphatic ketones, which are important starting materials in the synthesis of a variety of heterocycles.

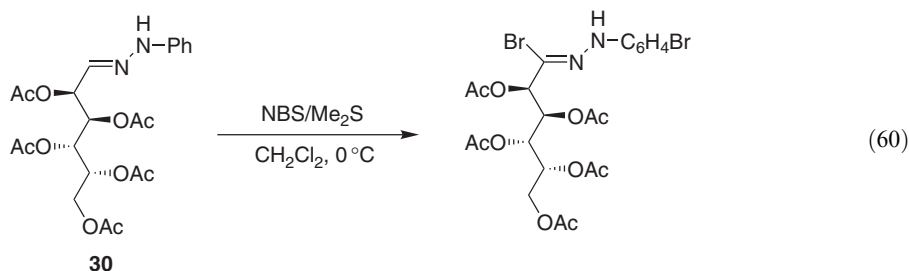


5.17.5.2.3 By halogenation of hydrazones and azines

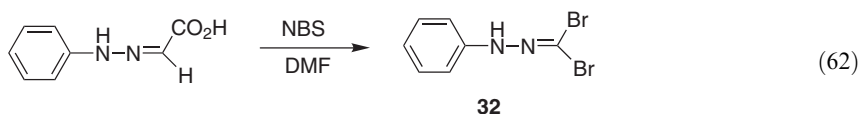
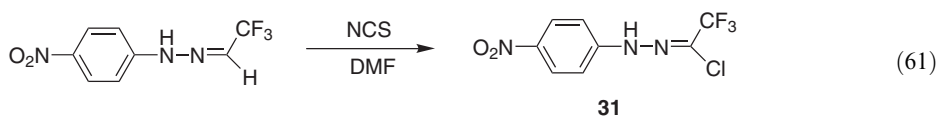
A new and convenient method has been described for the synthesis of hydrazonoyl halides, which involves the action of halosulfonium salts on hydrazones. This variation uses the NCS/NBS-dimethyl sulfide complex, the so-called Corey–Kim reagent [<1972JA7586>](#), at -40°C for the synthesis of a variety of aliphatic, aromatic, and substituted aromatic hydrazonoyl halides. Aromatic rings possessing electron-donating substituents are not halogenated because these halosulfonium salts, unlike chlorine or bromine, are not electrophilic ([Equation \(59\)](#)) [<1996T661>](#).



This method has been utilized for the synthesis of a carbohydrate-derived hydrazonoyl bromide ([Equation \(60\)](#)). D-Galactose phenylhydrazone penta-*O*-acetate **30** was treated with an excess of brominating reagent, and, in addition to the expected formation of the hydrazonoyl bromide, halogenation on the aromatic ring was observed [<1998TA3359, 2001TA469>](#).

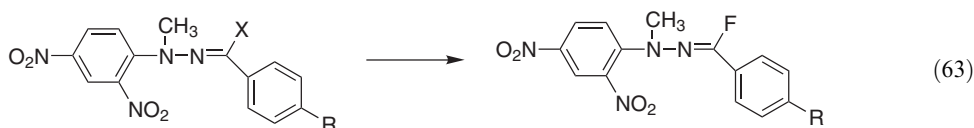


4-Nitrophenylhydrazonoyl chloride **31** was obtained by chlorination of the hydrazone by NCS in DMF (Equation (61)) <2000JMC2975>, while the phenylhydrazonoyl dibromide **32** was prepared from the hydrazone of glyoxalic acid (Equation (62)) <1999TL2605>.

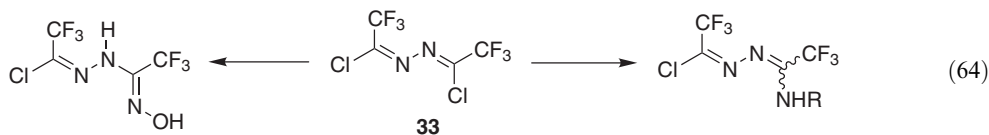


5.17.5.2.4 From hydrazidoyl halides

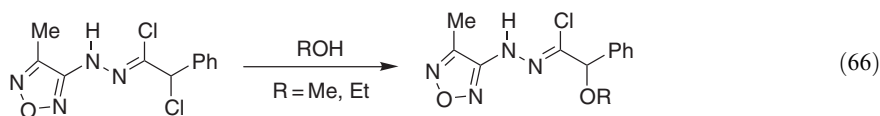
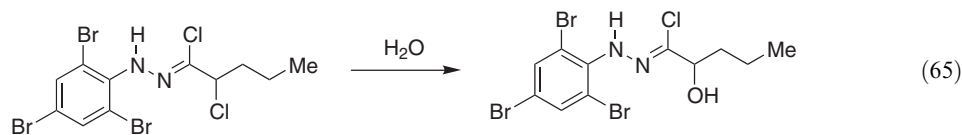
Hydrazonoyl fluorides (R = H, OMe) were prepared in reasonable yields by reacting the corresponding chloro- or bromo-compounds (X = Br, Cl) with an excess of CaF₂/KF in refluxing acetonitrile (Equation (63)) <1999AJC807>.



The reaction of dichloroazaine **33** with hydroxylamine (in 1:4 molar ratio) gave the (*E*),(*E*)-oxime but attempts to replace the remaining chlorine atom by further reaction with hydroxylamine were unsuccessful. The monoaminoazines from the reaction of a 2:1 mixture of amines and dichloroazaine were isolated as mixtures of two isomers (Equation (64)) <1995JFC95>.

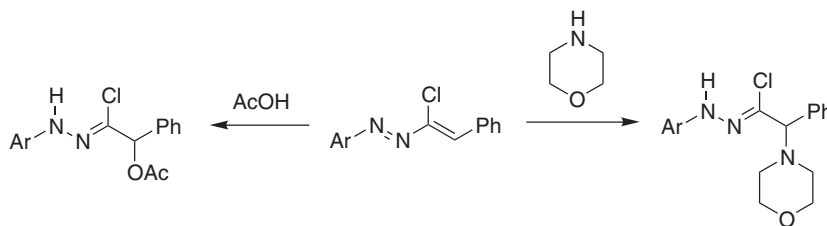


Nucleophiles such as water or alcohols substitute a halogen next to hydrazonoyl chloride, resulting in the formation of α -functionalized hydrazonoyl halides (Equations (65) and (66)) <1995IZV928, 1995MI901>.



5.17.5.2.5 Miscellaneous methods

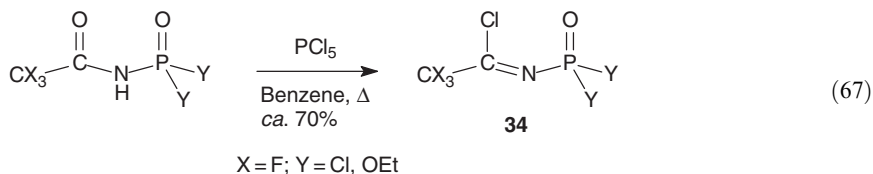
1-Aryl-2-(1-chloroalken-1-yl)diazenes react with amines, alcohols, and carboxylic acids to give arylhydrazonoyl chlorides with α -functional groups (Scheme 6) <1995MI890, 1995IZV917>.



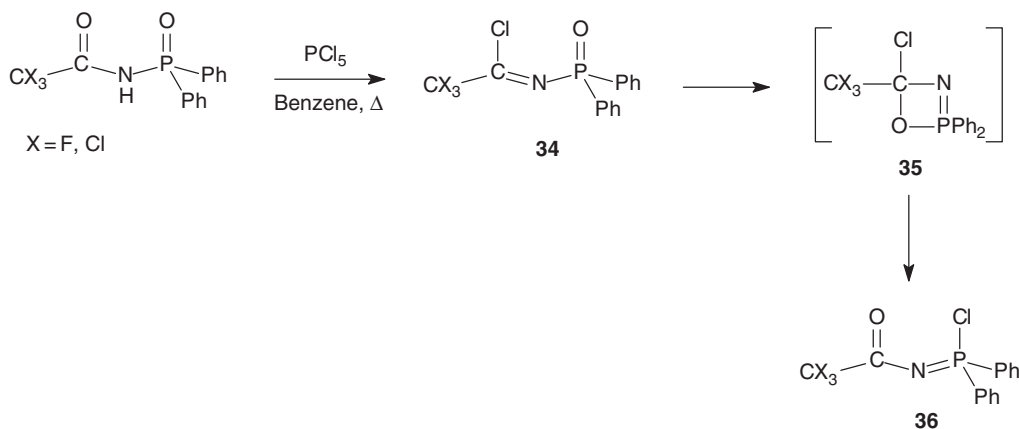
Scheme 6

5.17.6 N-PHOSPHORYLATED IMIDOYL HALIDES

N-Phosphorylated imidoyl chlorides **34** are readily prepared from *N*-phosphorylated amides by reaction with phosphorus pentachloride. Since the review of their synthesis in <1995COFGT(5)653>, the scope of this reaction has been shown to include a limited range of functionality in X and Y (Equation (67)), <1997JGU154, 1997ZOB160>.

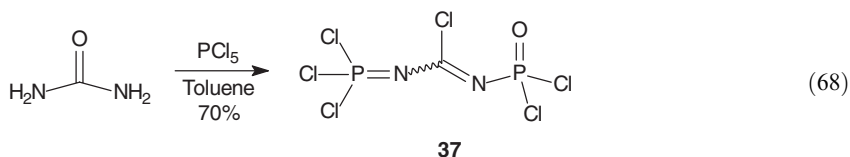


When $\text{X} = \text{Cl}$ or F and $\text{Y} = \text{Ph}$, the *N*-phosphorylated imidoyl chloride **34** is not isolated but reacts further to form the *N*-acyl-*P*-chlorophosphazo product **36** (Scheme 7), presumably through a four-centered intermediate **35**.



Scheme 7

When urea was treated in the same way, the corresponding *N*-phosphorylated imidoyl chloride **37** was formed (Equation (68)), from which *N*-phosphorylated urea derivatives can be prepared <1994JGU1551, 1994ZOB1746>.



N-Phosphorylated imidoyl chlorides are of interest as reactive synthons and have been shown to be useful in the syntheses of a range of phosphorus-containing organic targets <1994JGU359, 1994ZOB396, 1996PS736>.

5.17.7 *N*-ORGANOELEMENTAL SUBSTITUTED IMIDOYL HALIDES

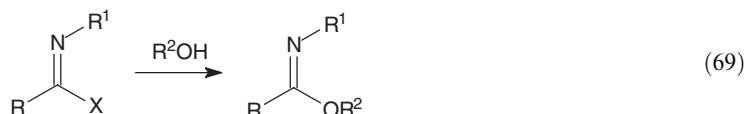
Dimeric *N*-boron-substituted imidoyl halides have been prepared from boron trichloride and α -fluorinated nitriles and cyano-imidoyl compounds. No further advances have occurred in this area since the publication of chapter 5.17.7 in <1995COFGT(5)653>, in which such reactions are described.

5.17.8 IMIDIC ACIDS

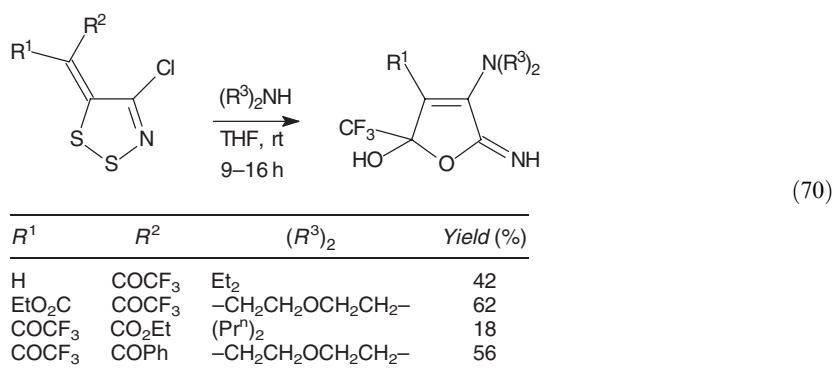
5.17.8.1 Imidic Acid Esters

5.17.8.1.1 From imidoyl halides

The general reaction of imidoyl halides with an alcohol under basic conditions yields the corresponding imidate (Equation (69)). There have been many reviews of these reactions prior to 1993, but there has been no further study of the scope of this reaction since <1995COFGT(5)653>.

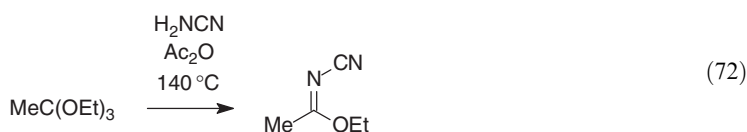
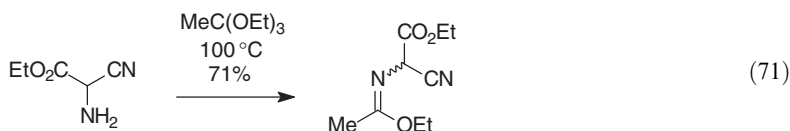


Imidates can be accessed from a dithiazolyl halide by reaction with a secondary alkylamine, followed by rearrangement (Equation (70)) <1998TL6895>.

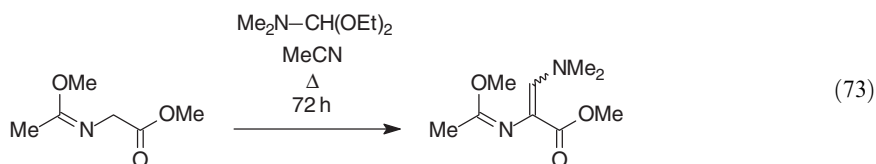


5.17.8.1.2 From carboxylic acid orthoesters or orthoamides

The acid-catalyzed condensation of amino compounds with carboxylic acid orthoesters is a common route to imidic acid esters <1995COFGT(5)653>. For example, the reaction of a 2-cyanoglycine ester with triethyl orthoacetate gives the imidate (Equation (71)) <1997JMC2196>, while the reaction of triethyl orthoacetate with cyanamide gives ethyl *N*-cyanoimide (Equation (72)) <1996JMC3019>.

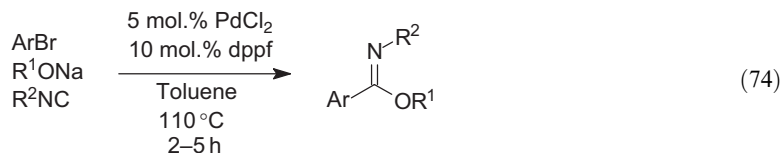


The condensation of an ethoxycarbonyl-*O*-methylimidate with an orthoamide (at the reactive methylene) gave an elaborated imidate (Equation (73)) <1999TL8097>.

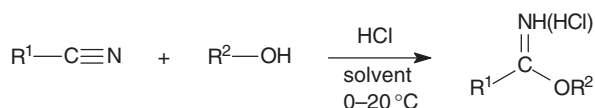


5.17.8.1.3 From nitriles and isonitriles

The palladium-catalyzed coupling of an aryl bromide, alkoxide (sodium ethoxide or phenoxide), and an isonitrile gives imidates in low to high yields (Equation (74)) <2001TL6191>.



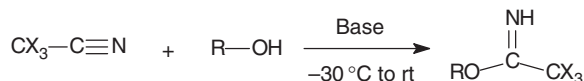
The Pinner synthesis is commonly employed in the preparation of imidate esters. Dry hydrogen chloride is passed through a dry solution of a nitrile in an appropriate solvent, such as diethyl ether, and the chosen alcohol is added to give the hydrochloride salt of the imidate ester (Equation (75)). The free base may be released by reaction with a mild base, such as sodium carbonate, or the imidate hydrolyzed to the ester if aqueous acid is used in the reaction. The reaction is suitable for the synthesis of aliphatic and aromatic imidates and is tolerant of a wide range of functionality on both the nitrile and the alcohol; representative examples are given in the table below.



R^1	R^2	Yield (%)	References
Me	Me	75	<2001SL1707>
Me	Et	>90	<2000TL8431, 2001JOC6756, 2003JMC314>
Et	Et	>80	<2001JOC6756>
Pr ⁱ	Me	89	<2001HCA3178, 2001JOC6756>
		98	<2001SL1707, 1993JCS(P1)1629>
Bu	Me	75	<1999JOC8084, 1997JOC8449>
Bu ^t	Me	85	<2001SL1707>
4-Bu ^t -C ₆ H ₄ CH ₂	Et	83	<1998JMC2243>
ⁿ C ₅ H ₁₁	Me	91	<2002CR105>
Cyclohexyl	Me	96	<2001SL1707>
(<i>E</i>)-MeCH=CHCH ₂	Me	95	<1994JCS(P1)3537>
MeOCH ₂ CH ₂	Me	88	<1995T8623>
BrCH ₂ CH ₂ CH ₂	Me	42	<1993TA2173>
N≡C-CH ₂	Et	>85	<2002T207>
EtO ₂ C	Et	95	<1997S301>
Ph	Et	>80	<2001JOC6756>
		62	<2001SL1707>
PhCH ₂	Me	97	<2001SL1707>
PhCH ₂	Et	100	<1998JOC8107, 2001JOC6756, 1995JMC3676>
PhCH(Me)	Et	99	<1998JOC8107>
PhCH(Et)	Me	100	<1999JCS(P1)2677>
3,4-(MeO) ₂ C ₆ H ₃	Et	99	<1998JOC8107>
3-HO-2,6-Me ₂ C ₆ H ₂ CH ₂	Et	60	<1998JMC2243>
3-BnO-2,4-Me ₂ C ₆ H ₂ CH ₂	Et	80	<1998JMC2243>
2-F-C ₆ H ₄	Et	>90	<1995JMC3676>
3-F-C ₆ H ₄	Et	>90	<1995JMC3676>
4-F-C ₆ H ₄	Et	>90	<1995JMC3676>
2,5-F-C ₆ H ₃	Et	>90	<1995JMC3676>
2,6-F-C ₆ H ₃	Et	>90	<1995JMC3676>

The versatility of this reaction has been demonstrated using nitriles derived from indoles <1993TL5623>, guanine analogs <1994TL4677>, tertiary amines <1993AP143>, and amides <1994S56>.

Imidate esters can also be prepared from the nitrile and alcohol under base-catalyzed conditions, usually in an ether solvent or CH_2Cl_2 . These reactions yield the free imidate directly and are used to prepare trihaloacetimidates from the corresponding trihaloacetonitrile (Equation (76)).



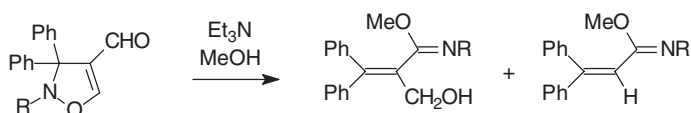
R	X	Base	Yield (%)	References
(E)-Me(CH ₂) ₆ CH=CH-CH ₂	Cl	Cs ₂ CO ₃	76	<1993TL5983>
CH ₂ =C(Me)CH ₂	Cl	NaH	36	<1999TL8785>
CH ₂ =C(Ph)CH ₂	Cl	NaH	52	<1999TL8785>
(E)-PhC(Me)=CH-CH ₂	Cl	NaH	56	<1999TL8785>
(E)-Pr-CH=CH-CH ₂	Cl	50% aq. KOH, (Bu ⁿ) ₄ NHSO ₄	85	<1996TL1481>
Me-C≡C-CH ₂	Cl	Na	70	<1993T1025>
PhCH ₂	Cl	50% aq. KOH, (Bu ⁿ) ₄ NHSO ₄	97	<1996TL1481>
(E)-Ph-CH=CH-CH ₂	Cl	NaH	95	<2003JMC2516, 2002T7275>
Me ₂ C=CH-CH ₂	Cl	NaH	93	<2003JMC2516>
4-MeO-C ₆ H ₄ CH ₂	Cl	NaH	60	<2001JOC6480>
3,4-(MeO) ₂ -C ₆ H ₃ CH ₂	Cl	NaH	66	<2001JOC6480>
(E)-Ph-CH=CHCH ₂	F	BuLi	83	<1999JCS(P1)3291>
(E)-MeCH=CH-CH=CHCH ₂	F	BuLi	77	<1999JCS(P1)3291>
(E)-Me ₂ C=CH(CH ₂) ₂ C(Me)=CHCH ₂	F	BuLi	88	<1999JCS(P1)3291, 2002T3579>
		DBU		

(76)

Many of the examples given above yield allylic acetimidates, which are intermediates for an Overman rearrangement leading to the corresponding allylic acetamides <1998JOC188, 1999JOM290>. The base-catalyzed synthesis of imidate esters can also be achieved using alcohols substituted with various functional groups, such as acetals and protected amines <1999JCS(P1)3291>, chiral alkenes <1993T5177>, phosphate esters <1993S497, 1998TL1465>, alcohols <1993TL6769>, and epoxides <1994LA541>.

5.17.8.1.4 From heterocyclic compounds (ring-opening reactions)

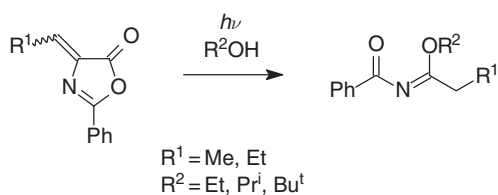
The ring opening of a number of five-membered heterocycles gives imidate esters. For example, the treatment of an isoxazolidine with Et₃N in refluxing methanol gave the imidate (Equation (77)) <1996TL917>.



(77)

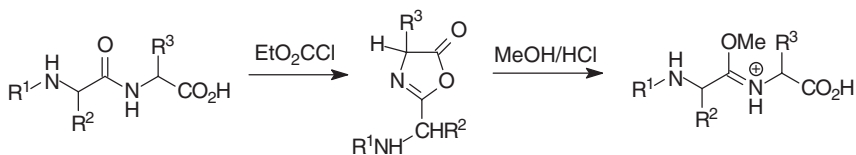
R=Me	60%	0%
R=Ph	2%	5%

The ring opening of 5(4*H*)-oxazolones under a variety of conditions also gives imidate esters; the irradiation of (*E*)- or (*Z*)-4-ethylidene-2-phenyl-5(4*H*)-oxazolones in various alcoholic solvents gives the imidates in good yield (Equation (78)) <1996TL4019>. Similar methodology, involving the irradiation of the oxazolones in the presence of allylic alcohols in acetonitrile, also gave the imidates <1998TL9711>.



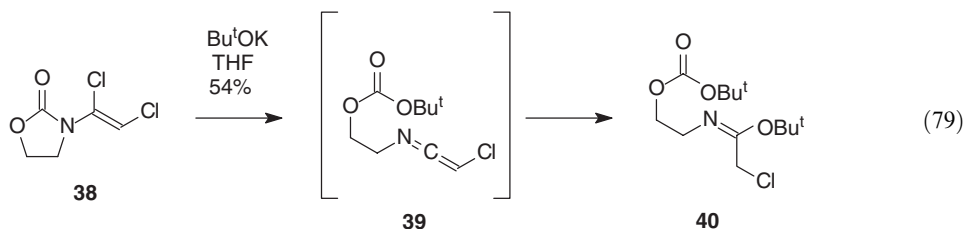
(78)

The alcoholysis of peptide-derived oxazolones gives the imidate hydrochlorides and this methodology has been employed for the removal of C-terminal residues (after subsequent hydrolysis) (Scheme 8) <1996TL7557>.

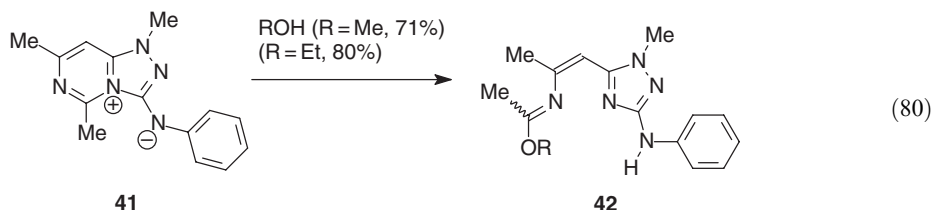


Scheme 8

Treatment of an oxazolidinone dichloroenamine **38** with Bu^tOK gave an imidate **40** via the chloroketene imine intermediate **39** (Equation (79)) <2001T459>.



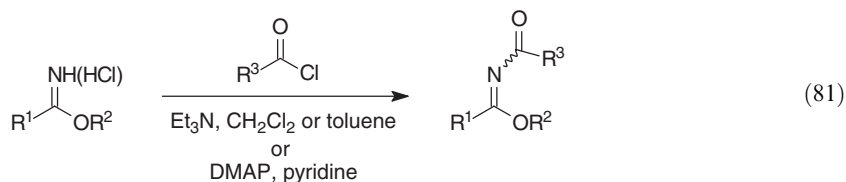
Ring opening of the [1,2,4]triazolo[4,3-*c*]pyridinium phenylaminide **41** with alcohols gave the imidates **42** in good yield (Equation (80)) <1997JCS(P2)49>.



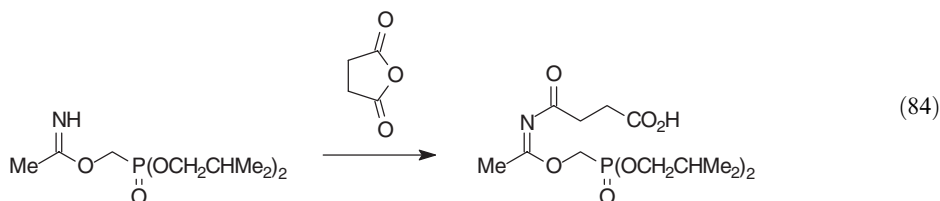
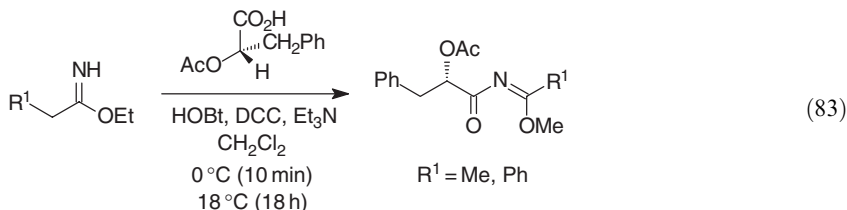
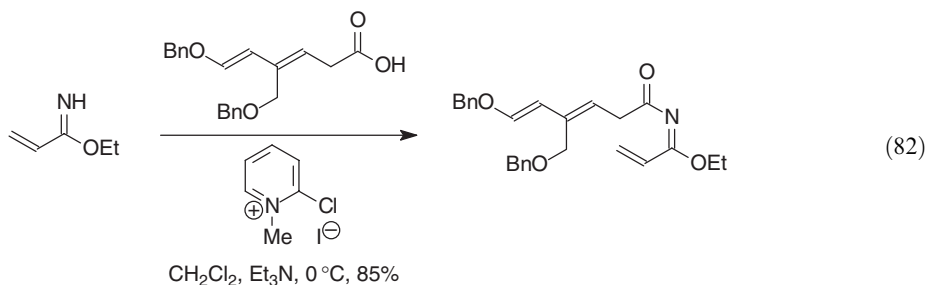
5.17.8.1.5 From imidates and amidines

Imidate esters can be obtained from simpler *N*-unsubstituted imidates via two main routes: acylation or transimination.

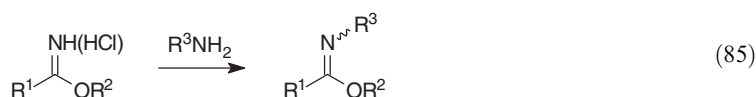
The acylation of *N*-unsubstituted imidates, to give a mixture of the (*E*)- and (*Z*)-isomers of the *N*-substituted imidates, generally involves the base-catalyzed reaction of the imidate hydrochloride with an acid chloride in an inert solvent, e.g., Et₃N/benzene or toluene <2000TL6721, 2001JGU1807, 2001ZOB1911>, Et₃N/CH₂Cl₂ <1993JMC2558, 1994JMC2808, 1995T11021, 1999JOC8084>, or DMAP/pyridine (Equation (81)) <1993TL6131>.



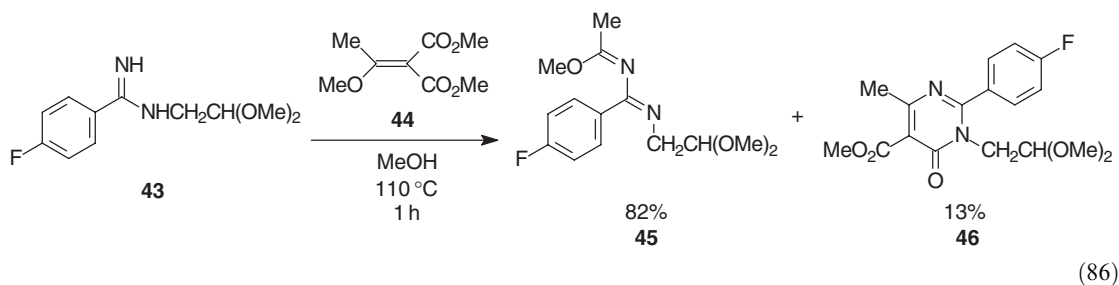
Alternative acylation procedures involve the coupling of the imidate with a carboxylic acid using 2-chloro-1-methylpyridinium iodide and Et₃N (Equation (82)) <2001OL2265> or DCC/HOBt/Et₃N (Equation (83)) <1997JCS(P1)1647>, or the reaction of an *N*-unsubstituted imidate with succinic anhydride (Equation (84)) <1996JGU1191, 1996ZOB1222>.



The preparation of more complex imidates from simpler *N*-unsubstituted imidates is a frequently employed method, involving the transimination of an imidate hydrochloride by reaction with an amine (Equation (85)) <1996JOC1761, 1998CPB973, 2002JOC188> under relatively mild conditions, e.g., Et₃N/CH₂Cl₂ <1993TL4639, 1995T6757, 2001CJC1562>, K₂CO₃/diethyl ether and water <2000JMC3168, 2000JCS(P1)2415>, or Na₂HPO₄/water <1993JMC2253>.

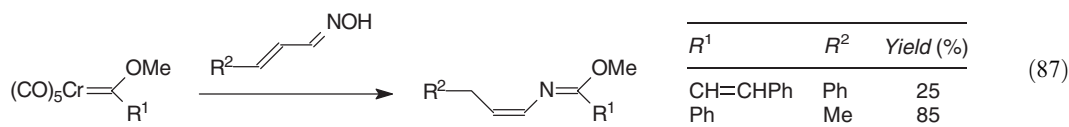


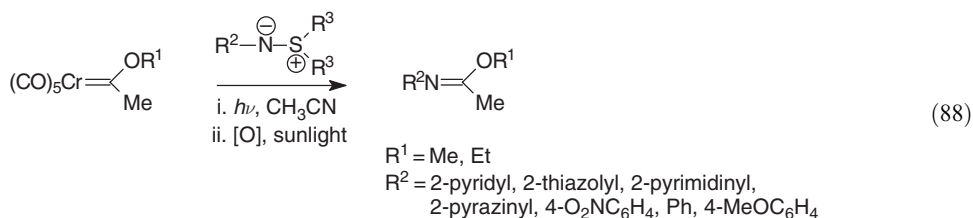
Finally, the reaction of an amidine **43** with an alkenylmalonate ester **44** in methanol gave a mixture of an imidate **45** and a dihydropyrimidine **46** (Equation (86)) <1993JOC4490>.



5.17.8.1.6 From metal complexes

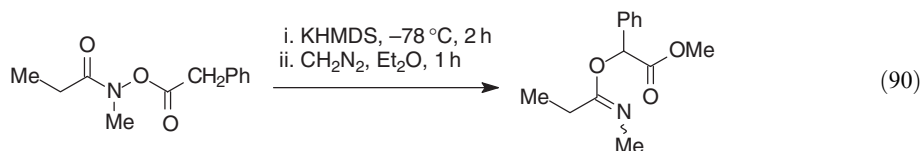
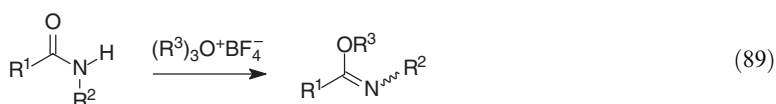
Imidic acid esters have been prepared by the reaction of Fischer carbene complexes with oximes (Equation (87)) <1996MI88> or sulfanilimines (Equation (88)) <1993JOC3886>.



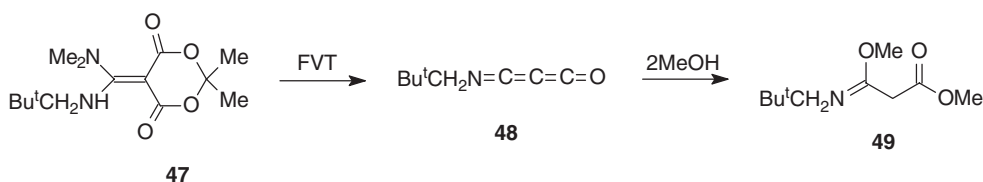


5.17.8.1.7 Miscellaneous methods

O-Alkylation of amides (Equation (89)), with trialkyloxonium tetrafluoroborate salts <1997SC923, 2000JOC4397> or methyl triflate <1994CB1699>, gives imidates, as does an anionic [3,3]-rearrangement followed by esterification (Equation (90)) <1994S1096, 1994CPB419>.

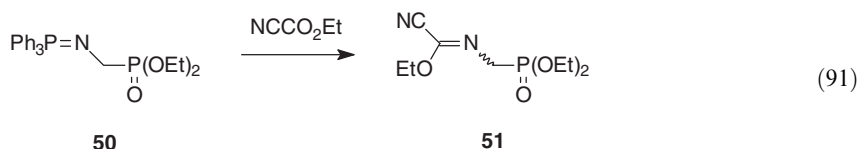


Flash vacuum thermolysis of a Meldrum's acid derivative **47** gave an iminopropadienone **48**, which gave an imidate **49** upon quenching with 2 equiv. of methanol (Scheme 9) <2002JOC2619>.

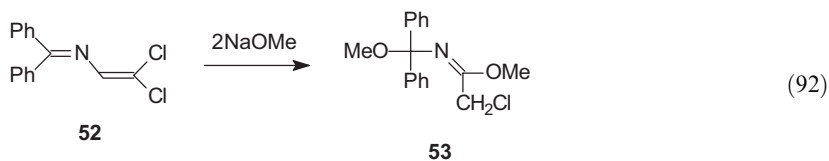


Scheme 9

The aza-Wittig reaction of a phosphazene **50** with ethyl cyanoformate gave a phosphonate-substituted imidate **51** (Equation (91)) <2003T2617>.

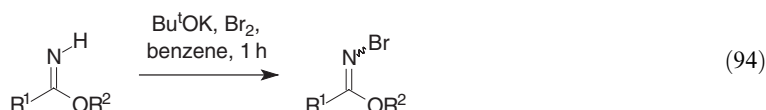
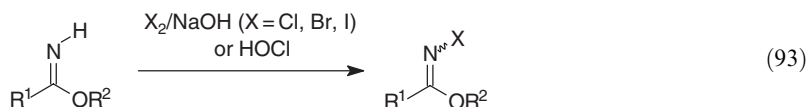


Treatment of a dichloroenamine **52** with sodium methoxide gives a good to excellent yield of the corresponding imidate **53** (Equation (92)) <2000EJO1235>.

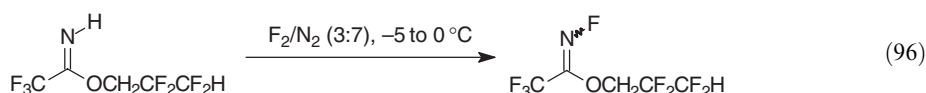
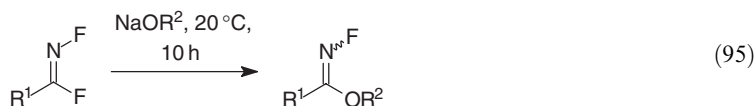


5.17.8.2 *N*-Haloimidates

N-Haloimidates were included in the original version of this work <1995COFGT(5)653>. The most general method for the preparation of *N*-chloro-, *N*-bromo-, and *N*-iodoimidates involves the reaction of *N*-unsubstituted imidic acid esters with hypohalites (Equation (93)) <1913CB3616, 1994JCS(P1)3537, 1998MI29>. *N*-Bromoimidates can also be prepared by the reaction of *N*-unsubstituted imidates with *t*-butyl hypobromite (Equation (94)) <1993AJC1213>.



N-Fluoroimidates are most readily prepared by the reaction of *N*-fluoroimidoyl fluorides with water or alkoxides (Equation (95)) <1971T51> or through the direct fluorination of *N*-unsubstituted imidic acid esters with mixtures of fluorine and nitrogen (Equation (96)) <1982IZV937, 1982BAU829>.

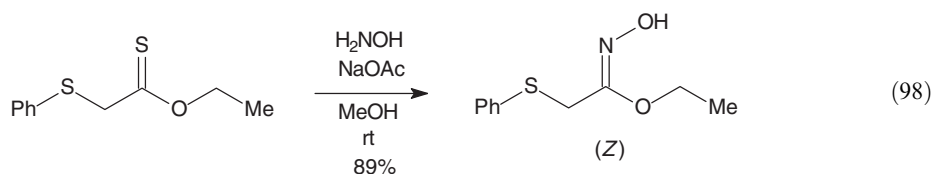
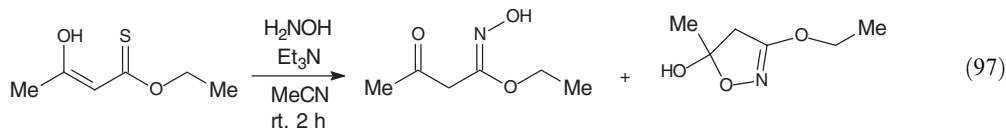


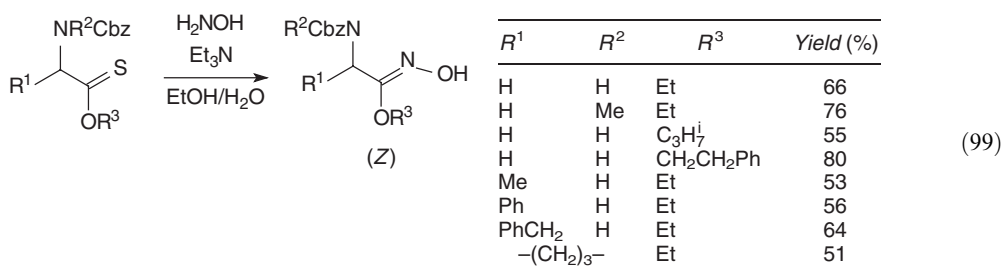
5.17.8.3 *N*-Hydroxy- and *N*-Alkoxyimidates (Hydroxamic Acid Esters)

Hydroxamic acid esters are reactive intermediates that are accessible through a variety of synthetic routes. They have been used in the preparation of sulfoalkylation agents <2001TL4285>, and in the synthesis of polyamines <1996T13751>, difluoroaminoxy compounds <1999IZV130, 1999MI131>, and lactones <1996TL229>, and to prepare phenoxyamines <1997OPP594>. In this review, synthetic routes to the *N*-hydroxyimidates will be discussed before those for the *N*-alkoxyimidates.

5.17.8.3.1 From hydroxylamine and thioesters

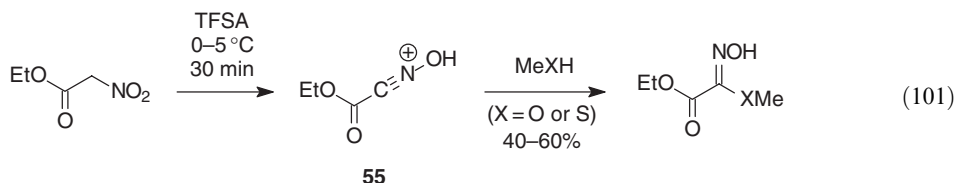
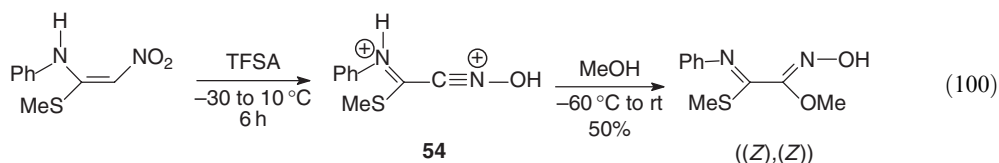
The reaction of hydroxylamine with a thionoester can be used to access *N*-hydroxyimidates. However, in cases when there are alternative products, separation can be problematic. Examples are given in Equations (97) <2000BCJ1861>, Equation (98) <1994BCJ2219>, and Equation (99) <2001ZN(B)547>.





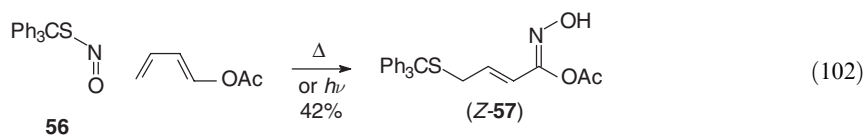
5.17.8.3.2 From nitroalkenes or nitroacetate esters

Treatment of a nitroalkene [<1996T9509>](#) or a nitroacetate ester [<1995T10929>](#) with the superacid, trifluoromethanesulfonic acid (TFSA), produces the corresponding hydroxynitrilium ion **54** or **55**, which may be trapped by an appropriate nucleophile to give the *N*-hydroxyimide, as illustrated in [Equations \(100\)](#) and [\(101\)](#), respectively.



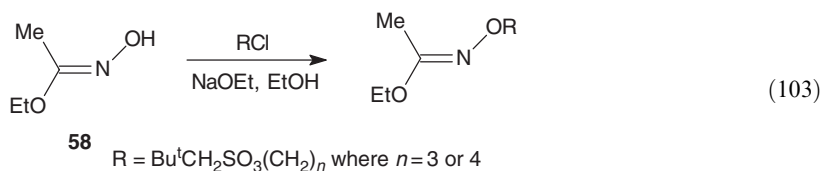
5.17.8.3.3 By free-radical addition of trityl thionitrite to an alkene

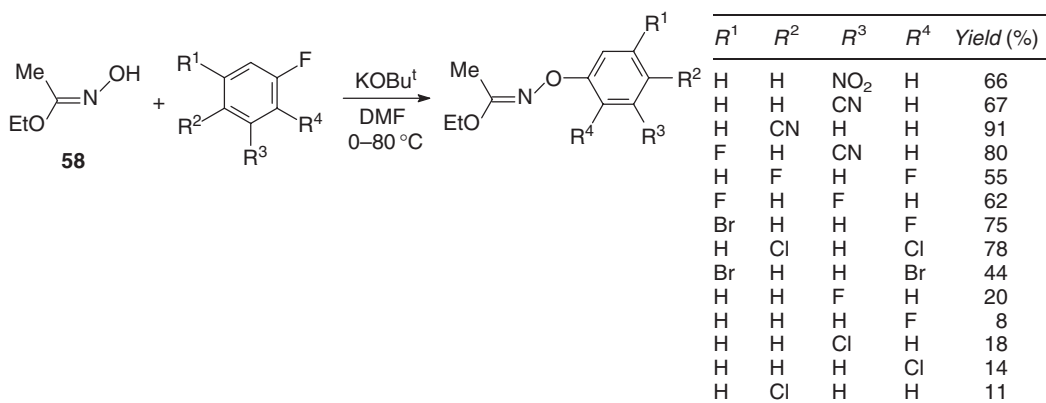
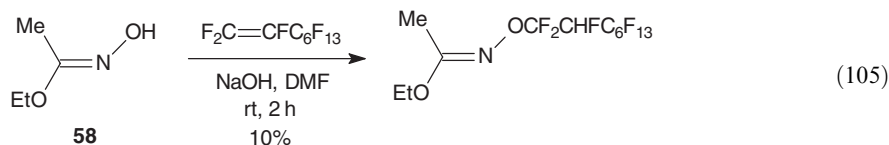
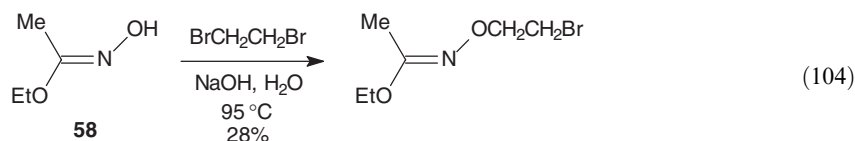
Free-radical addition of trityl thionitrite **56** to an alkene is a versatile reaction that produces a nitroso compound, which can tautomerize to give the oxime. A number of substituted alkenes have been shown to be useful in this reaction, although only one example yields an *N*-hydroxyimide **57** ([Equation \(102\)](#)) [<2001TL4377>](#).



5.17.8.3.4 From ethyl hydroxyacetimidate

Ethyl hydroxyacetimidate **58** can be alkylated by a variety of electrophilic reagents to give the corresponding hydroxamic acid esters. Examples are given in [Equations \(103\)](#) [<2001TL4285>](#), [Equation \(104\)](#) [<1996T13751>](#), [Equation \(105\)](#) [<1999MI131>](#), and [Equation \(106\)](#) [<1997OPP594>](#).

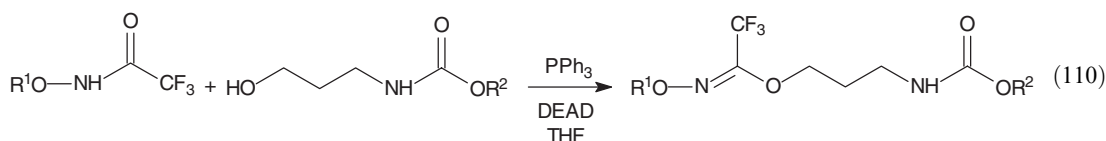
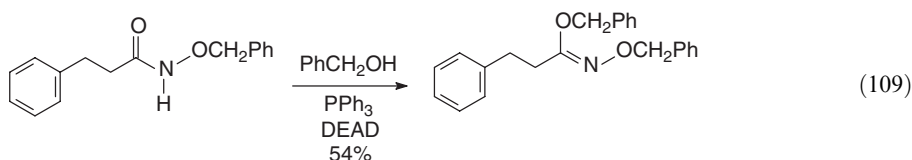
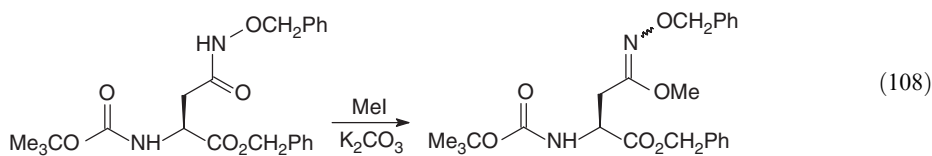
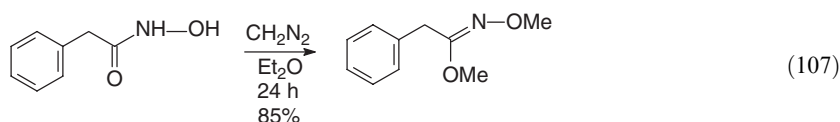




(106)

5.17.8.3.5 By alkylation of an *N*-hydroxyamide or its ester

An alternative method involves alkylation of the *N*-hydroxyamide or its ester using diazo-methane, methyl iodide, or an alcohol under Mitsunobu conditions. However, the presence of other nucleophilic groups can lead to a mixture of products. Specific examples of each are given in [Equations \(107\) <2001JOC2246>](#), [Equation \(108\) <1996JMC4197>](#), [Equation \(109\) <2000JA2995>](#), and [Equation \(110\) <1994TL3605>](#).



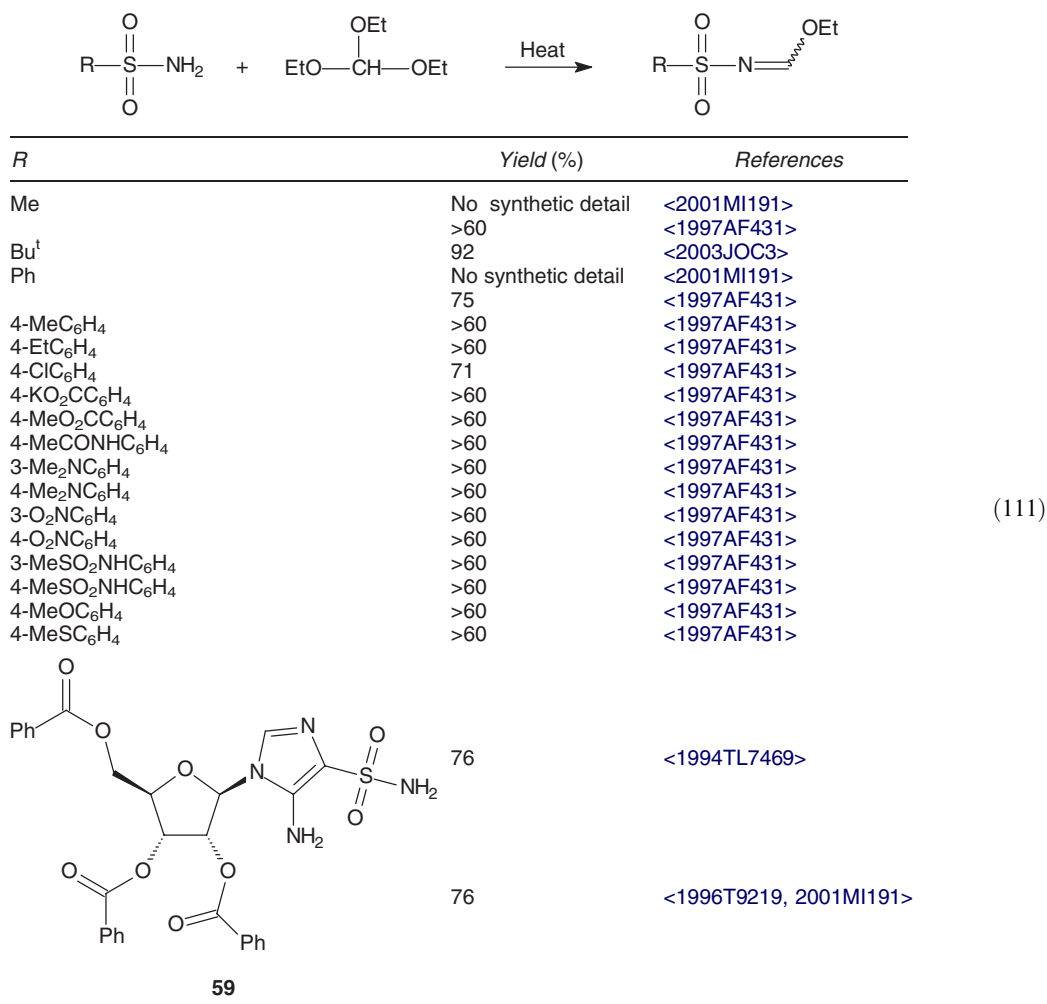
5.17.8.4 *N*-Organothioiminoesters and Related Compounds

5.17.8.4.1 General remarks

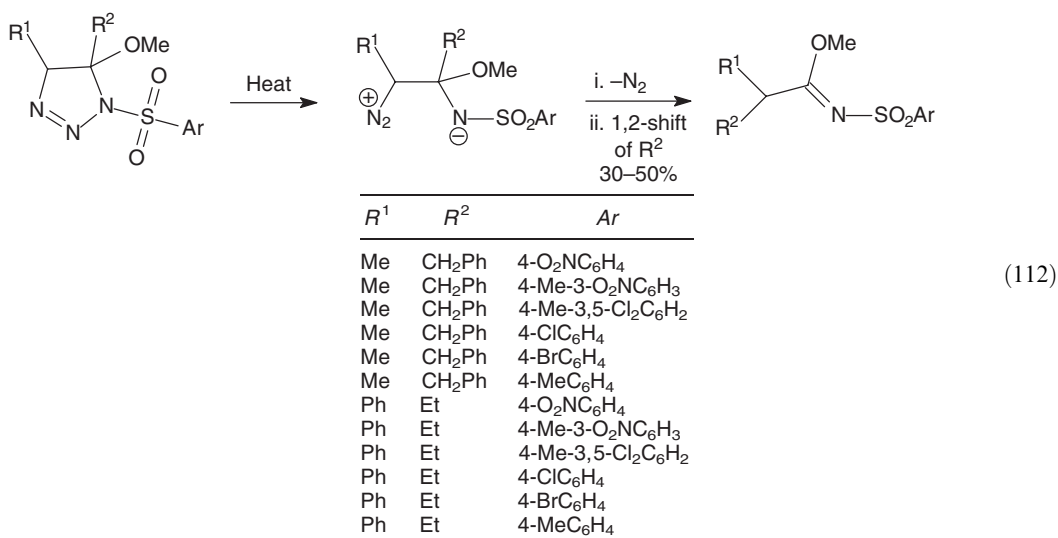
There are a number of organothioimidoyl esters which incorporate sulfur in various oxidation states: from the sulfonylimidoyl esters, through the corresponding sulfinylimidoyl esters to their sulfenyl analogs. The sulfonyl derivatives are the most studied and have found application in many areas, for example, as enzyme inhibitors <2000JMC1793, 1994TL7469, 2001MI191>.

5.17.8.4.2 *N*-Sulfonylimidates

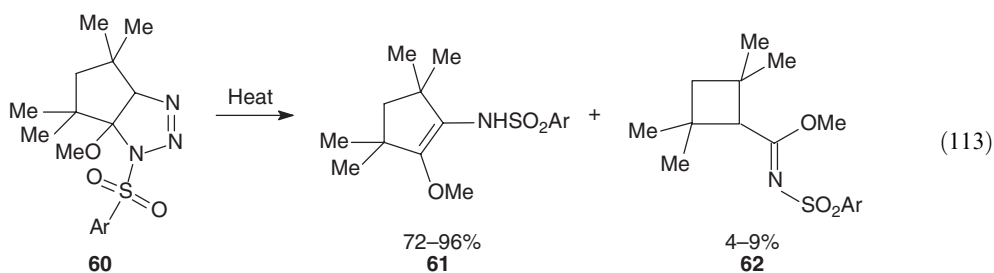
N-Sulfonylimidates are readily prepared by treatment of the appropriate sulfonamide with an orthoester. Substitution on the sulfonyl group is tolerated (Equation (111)).



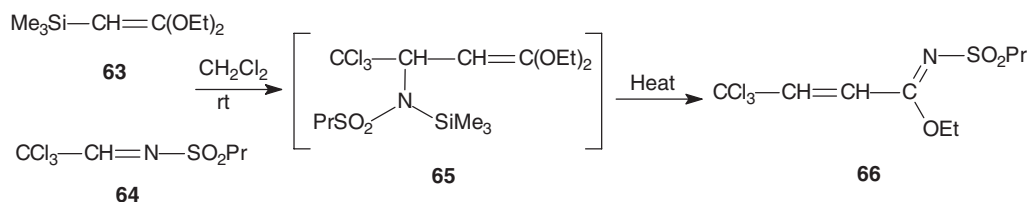
The preferential rearrangement of simple, substituted *N*-sulfonyltriazolines to the *N*-sulfonylimidates was unexpected; the corresponding aziridines were the expected products (Equation (112)) <1994JOU216, 1994ZOR210>.



A variation of this reaction was carried out with a series of bicyclic *N*-sulfonyltriazolines **60**. After heating, the major products were the corresponding *N*-sulfonylenamides **61** with trace amounts of the cyclic *N*-sulfonylimidates **62**, presumably via the corresponding *N*-sulfonylaziridine (Equation (113)) <1994JOU62, 1994ZOR59>.



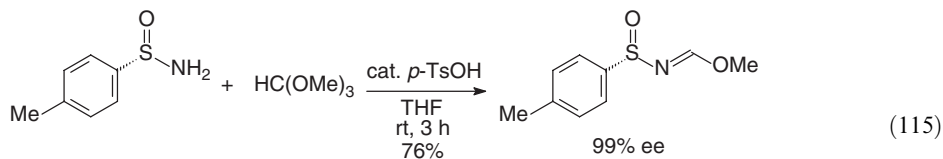
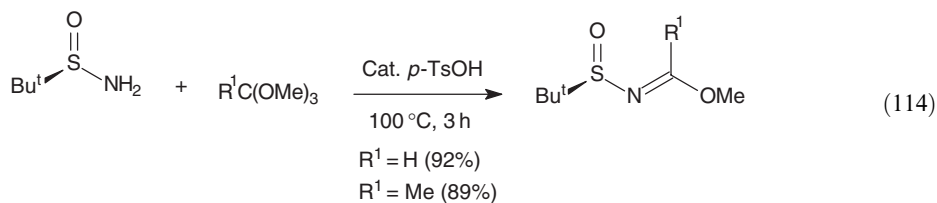
Reaction of the ketene acetal 1,1-diethoxy-2-trimethylsilyl ethene **63** with *N*-propylsulfonylchloraldimine **64** yields the linear adduct **65**, which cannot be isolated, but desilylates and rearranges to give the *N*-sulfonylimide **66** (Scheme 10) <1994JGU1554, 1994ZOB1750>.



Scheme 10

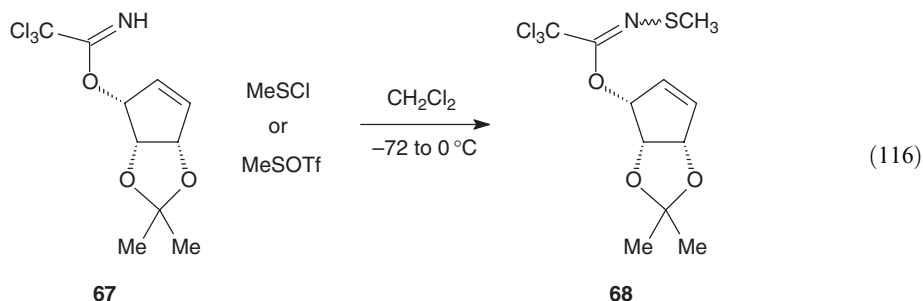
5.17.8.4.3 *N*-Sulfinylimidates

Chiral *N*-sulfinylimidate esters are accessed through the reaction of chiral *S*-substituted sulfonamides with an orthoester (Equations (114) and (115)) <2003JOC3>, although the range of substitution tolerated by this reaction has not been investigated.

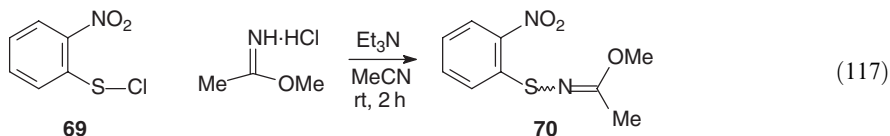


5.17.8.4.4 *N*-Sulfenylimidates

The first reported example of an *N*-sulfenylimidate **68** was prepared from the *N*-unsubstituted imidate **67** using either methanesulfonyl chloride or methanesulfonyl triflate (Equation (116)) <1994TL5121>.



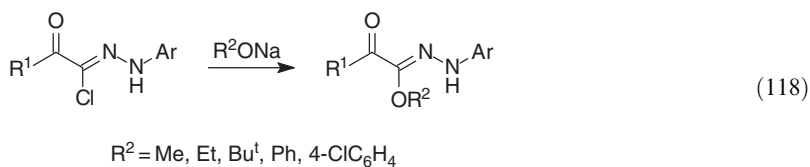
Similarly, the preparation of an *N*-sulfenylacetimidate **70** was achieved by reaction of a sulfenyl chloride **69** with methylacetimidate hydrochloride in the presence of triethylamine (Equation (117)) <2003T303>.



5.17.8.5 Hydrazonic Acid Esters (Hydrazonoates, *N*-Aminoimidic Acid Esters)

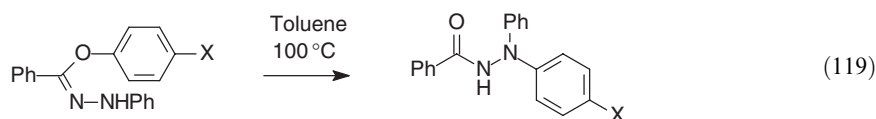
5.17.8.5.1 From hydrazonoyl halides (hydrazidoyl halides)

One of the most common routes to hydrazonoates is via the reaction of hydrazidoyl halides (especially chlorides) with alkali metal alkoxides (COFGT (1995)). For example, acyl-substituted hydrazonoates can be prepared by the reaction of either an acylhydrazonoyl chloride with an alcohol (as solvent and reactant) and sodium acetate, or with a solution of a sodium phenoxide in toluene (Equation (118)) <1995AP505>.



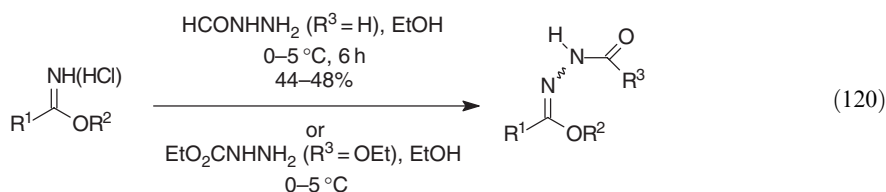
A similar procedure has been used to prepare an ethoxycarbonyl-substituted hydrazonoate by the reaction of the chloride with sodium ethoxide in refluxing ethanol <1995IJC(B)736>.

As mentioned in the original version of this work, the reaction conditions for this method should be chosen carefully since hydrazonoates undergo a Chapman-like rearrangement at temperatures above 100 °C (Equation (119)) <1971CC689>.



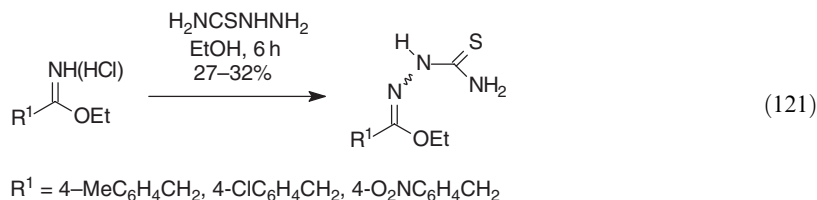
5.17.8.5.2 From thioesters or iminoesters and hydrazine derivatives

Another common route to hydrazonoates is via the reaction of imidates (or, more usually, their hydrochloride salts) with hydrazines, semicarbazides, and thiosemicarbazides. For example, the reaction of the imidate hydrochlorides ($\text{R}^1 = \text{Me}$, PhCH_2 , $4\text{-ClC}_6\text{H}_4\text{CH}_2$, Ph , $4\text{-MeC}_6\text{H}_4\text{CH}_2$) with formic acid hydrazide gives the hydrazonoates ($\text{R}^3 = \text{H}$) <1998JHC377>. Alternatively, the reaction of the imidate ($\text{R}^1 = \text{Bu}$, $\text{R}^2 = \text{Et}$), after generation of the free base, with ethyl carbazate in ethanol gave the hydrazonoate as a mixture of the *syn*- and *anti*-isomers (Equation (120)) <1993JMC2558, 1995JMC1799>.

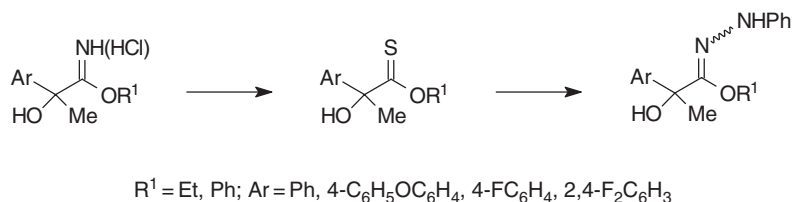


The 2-furanoyl derivative ($\text{R}^1 = \text{Bu}$, $\text{R}^2 = \text{Et}$, $\text{R}^3 = 2\text{-furanoyl}$) has been prepared by the reaction of the imidate hydrochloride with furoic acid hydrazide, in 58% yield, again as a mixture of the *syn* and *anti*-isomers <1993JMC591>.

The reaction of imidate hydrochlorides with thiosemicarbazide, in ethanol or dry DMF, gives imidate thiosemicarbazones (Equation (121)) <1993JMC591, 1997MI307>.



Finally, the reaction of thionoesters, prepared from imidates by reaction with H_2S , with phenylhydrazine in diethyl ether gave hydrazonoates (Scheme 11) <1994ZN(B)970>.

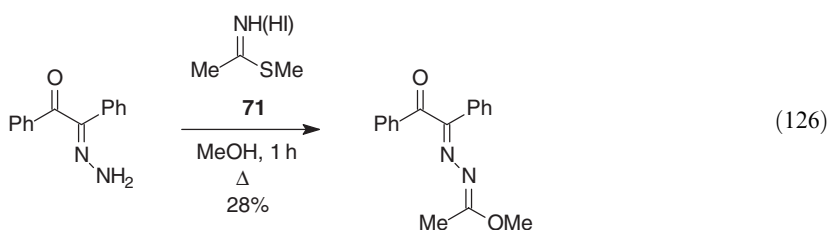
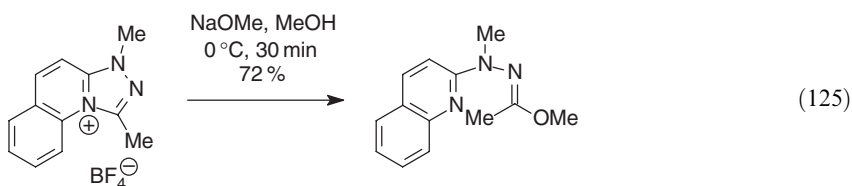
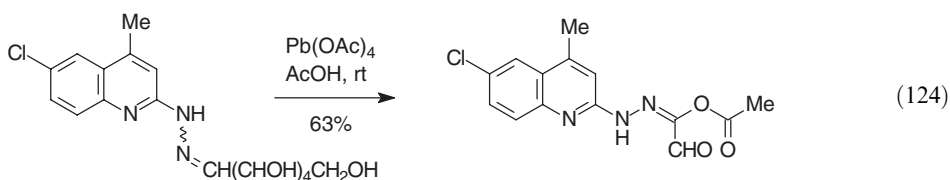
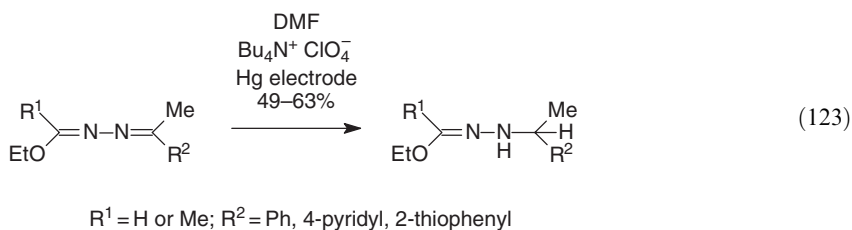
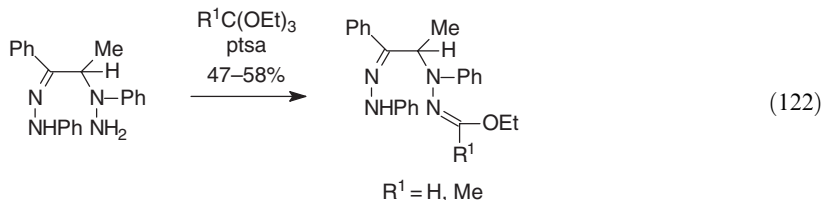


Scheme 11

5.17.8.5.3 Miscellaneous methods

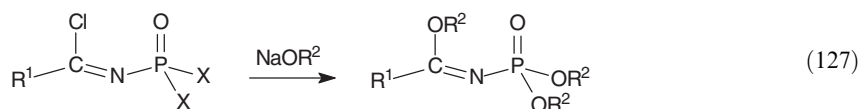
Hydrazonoates have also been prepared by the reaction of a carboxylic acid orthoester with hydrazines in the presence of *para*-toluenesulfonic acid (Equation (122)) <1993M299>, the electrochemical reduction of a hydrazonoate (Equation (123)) <2002SC225>, the oxidation of a sugar hydrazone

with lead tetraacetate (Equation (124)) <1998PHA294>, the base-catalyzed ring opening of a [1,2,4]-triazolo[4,3-*a*]quinolinium salt (Equation (125)) <1996T1399>, and the condensation of *S*-methylthioacetimidate hydroiodide **71** with benzil hydrazone (Equation (126)) <1996JHC1877>.

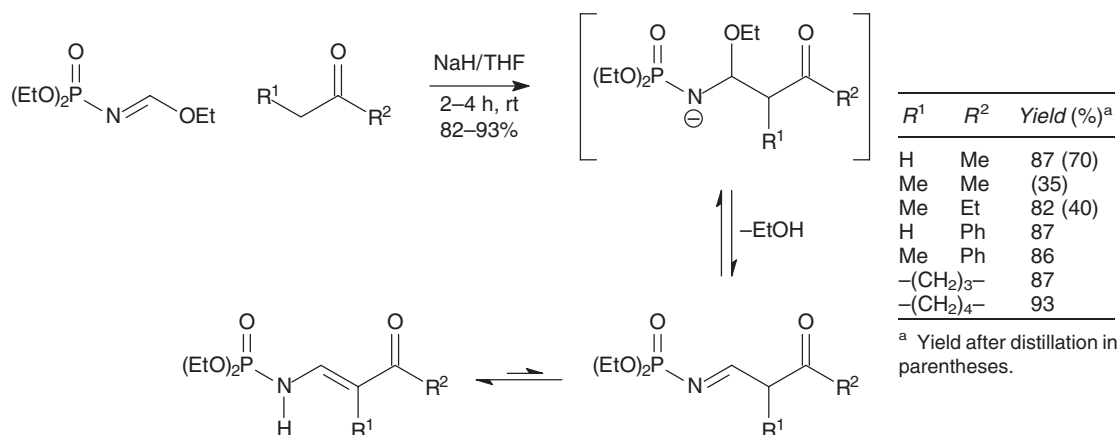


5.17.8.6 *N*-Phosphorylated Imino-esters

N-Phosphorylated imino-esters are easily accessible from the corresponding *N*-(dichlorophosphoryl)-imidoyl chlorides (as reviewed in <1995COFGT(5)653> (Equation (127))). The versatility of this reaction has been thoroughly investigated using a wide range of R¹ and R² substituents and was shown to accommodate many functionalities.

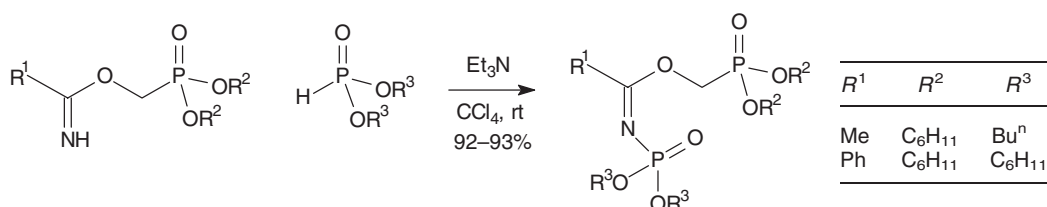


Simple *N*-phosphorylated imino esters have found utility as synthetic intermediates, for example, in the synthesis of diethyl 1-alkenyl phosphoramidates from a range of simple, enolizable ketones or diethyl malonate (Scheme 12) <2000T6299>.



Scheme 12

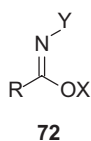
Alkyl-substituted *N*-phosphorylated imino esters may be obtained from the corresponding *C*-phosphorylated acetimidoyl methyl esters using the required dialkyl phosphonate ester (Equation (128)) <1997JGU162, 1997ZOB168>.



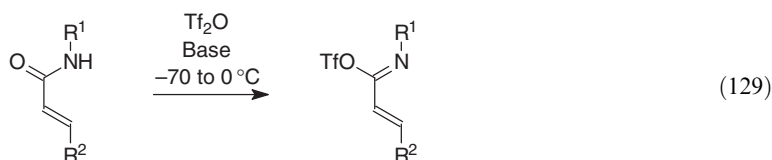
(128)

5.17.8.7 Mixed Anhydrides from Carboximide Acids and Inorganic or Organic Acids

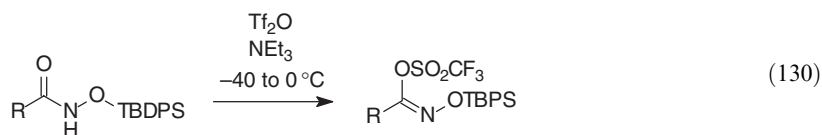
These mixed anhydrides, of general formula $RC(NY)OX$, are represented by the structure 72 shown below, where X is derived from an inorganic or organic acid.



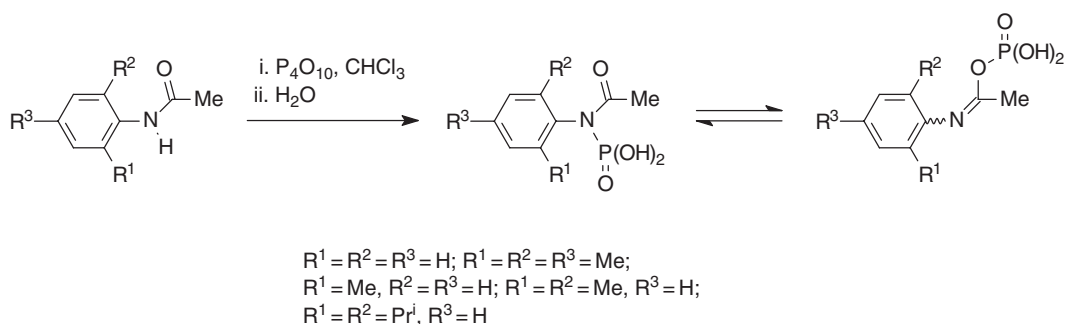
Mixed anhydrides of imidic and sulfonic acids ($Y = H$ or R^1 , $X = SO_2R^2$) are readily prepared *in situ* by the reaction of secondary amides with trifluoromethanesulfonic anhydride in the presence of a non-nucleophilic base (Equation (129)), e.g., 2,6-lutidine <2002OL3127> or Hünig's base <1994H509, 1996JOC3715, 1999TL7211, 1999TL7215>, in a non-polar solvent (CH_2Cl_2 or THF) at temperatures below $0^\circ C$.



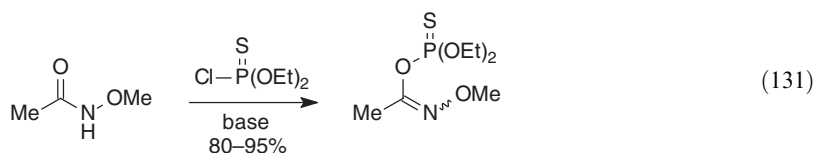
In a related procedure, silylhydroxamates, which are again generated *in situ* and are useful as nitrile oxide precursors, react with triflic anhydride at $-40^\circ C$, in the presence of triethylamine, to give *O*-silylimidic acid–sulfonic acid anhydrides ($Y = OR^1$, $X = SO_2R^2$) (Equation (130)) <2000OL539>.



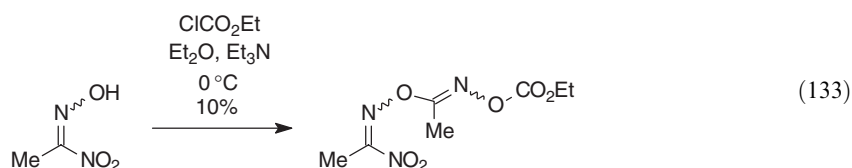
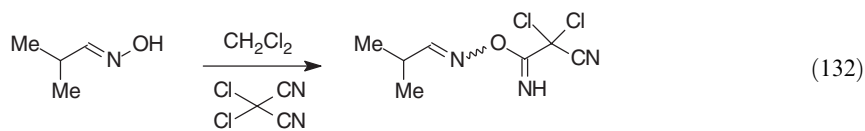
The reaction of acetanilides with phosphorus pentoxide gives an equilibrium mixture of *O*- and *N*-phosphorylated tautomers (Scheme 13) <1997JGU872, 1997ZOB932>, while the reaction of *N*-methoxyacetamide with a phosphorochloridithioate ester, in the presence of base, gives a mixture of the *syn*- and *anti*-isomers of the *N*-methoxyimidic acid—thiophosphoric acid anhydride (Equation (131)) <1993CL1835>, with the isomeric ratio being dependent upon the base employed. NaH, CaO, and K₂CO₃ give predominantly the *syn*-isomer; NaHCO₃/CuCl and NaOH/CuCl give predominantly the *anti*-isomer.



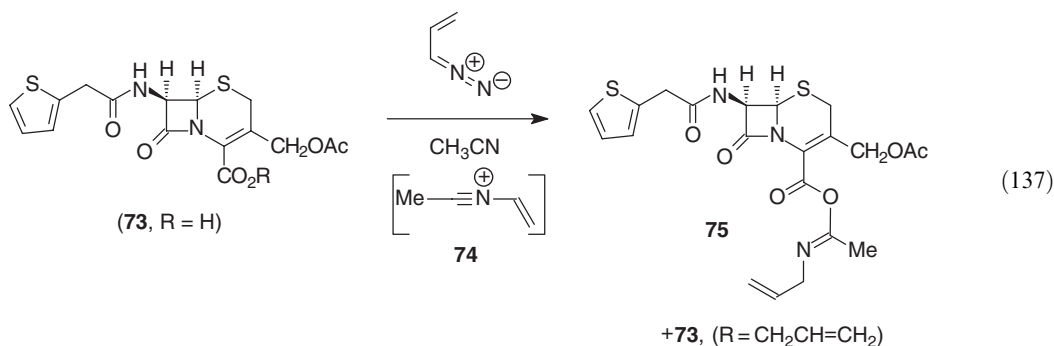
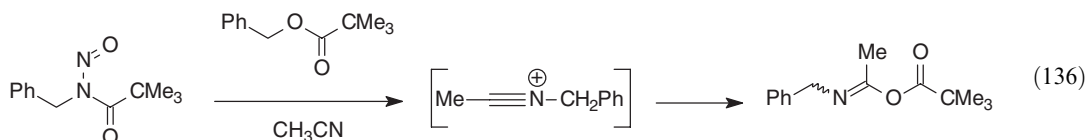
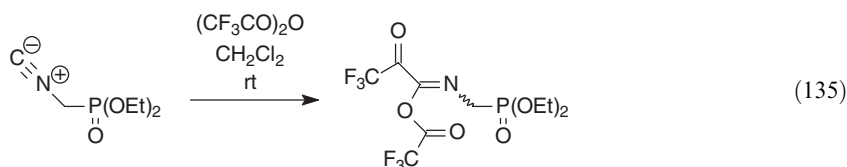
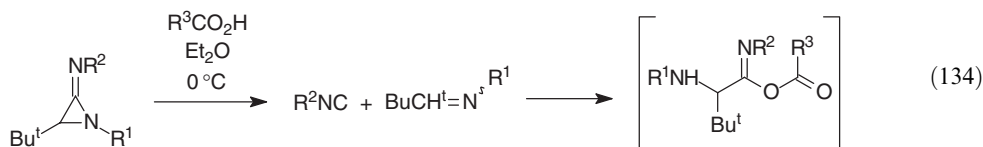
Scheme 13



Oxime—imidic acid anhydrides (Y = H or R¹, X = N(R²)OH), are prepared by the reaction of an oxime with either dichloromalononitrile (Equation (132)) <1994JOU85, 1994ZOR79> or ethyl chloroformate in the presence of Et₃N (Equation (133)) <1996AP83>.



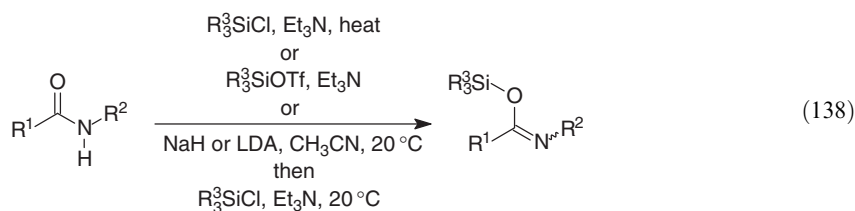
Imidic acid—carboxylic acid anhydrides are the products of a range of procedures, including the reaction of isonitriles and imines (from the thermolysis of iminoaziridines) with carboxylic acids (to give Ugi α-adducts) (Equation (134)) <1996MI462>, the reaction of isonitriles with trifluoroacetic anhydride (Equation (135)) <1996JCS(P1)1893>, and the three-component reaction of an ester, acetonitrile, and an *N*-nitrosoamide (via a nitrilium ion intermediate) (Equation (136)) <2000JOC1115>. The reaction of a cephalosporin carboxylic acid (**73**, R = H) with vinyl diazomethane in acetonitrile (Equation (137)) gave a mixture of the expected ester (**73**, R = CH₂CH=CH₂) and an imidate **75**, presumably via a nitrilium ion **74** generated *in situ* by the reaction of vinyl diazomethane with acetonitrile <1996TL1971>.



5.17.8.8 Trialkylsilylimidates [*N*-Trialkylsilylimidic Acid Esters, *O,N*-Bis(trialkylsilyl)imidates]

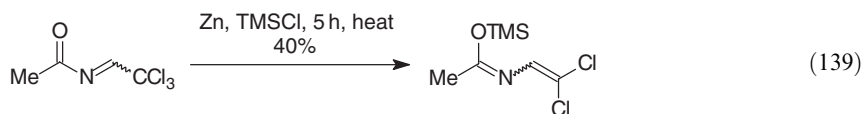
5.17.8.8.1 From carboxylic acid amides and their salts and silylating agents

The mono- and disilylation of simple carboxamides is readily achieved by treating the amides with trialkylchlorosilanes in the presence of a base, with triethylamine in ether, THF, or acetonitrile being commonly employed conditions <1963CB1473>. An alternative is the initial generation of the sodium or lithium salt of the amide, with sodium hydride or LDA in acetonitrile at ambient temperature, followed by reaction with the trialkylchlorosilane <2001CC2478, 2001MI573>. A similar method uses the reaction of a carboxamide with a trialkylsilyl triflate in the presence of triethylamine to prepare a range of *O*-trialkylsilylimidates (Equation (138)) <1994TL4235, 1999T3387>.

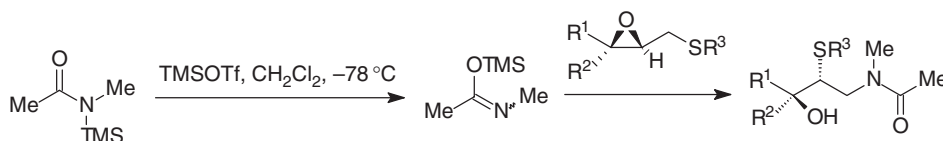


Monosilylated carboxamides generally exist as equilibrium mixtures of the *O*- and *N*-silylated compounds <1979JCS(P1)2478>.

The zinc-catalyzed reaction of *N*-(trichloroethylidene)acetamide with trimethylsilyl chloride gives the *N*-(2,2-dichlorovinyl)-*O*-trimethylsilylacetimidate (Equation (139)) <1993JOU1790, 1993ZOR2156>.

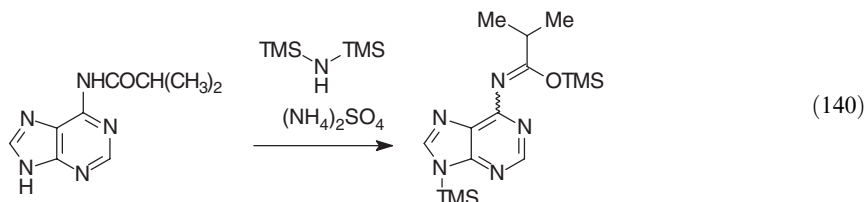


The reaction of *N*-methyl-*N*-trimethylsilylacetylamide with 1-mercapto-2,3-epoxides in the presence of trimethylsilyl triflate, gives the product of *N*-alkylation, and it has been proposed that this reaction proceeds via an initial trimethylsilyl triflate-catalyzed rearrangement of *N*-methyl-*N*-trimethylsilylacetylamide to *O*-trimethylsilyl-*N*-methylacetimidate under the reaction conditions (Scheme 14) <1997SL11>.

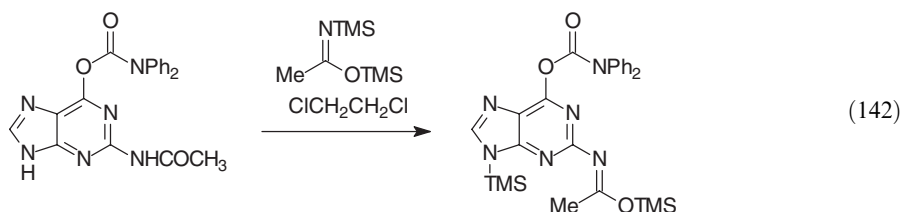
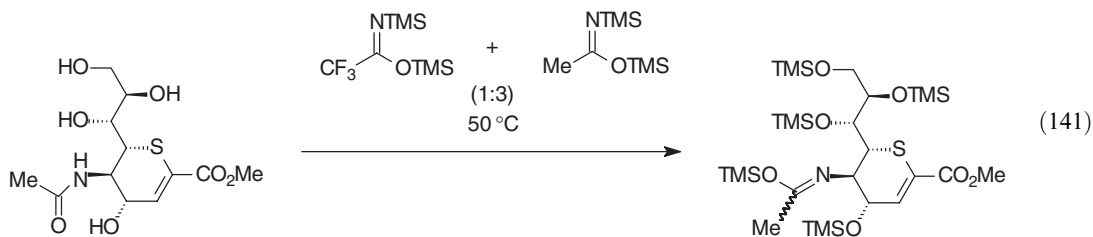


Scheme 14

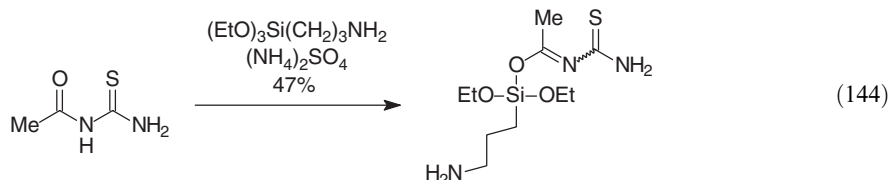
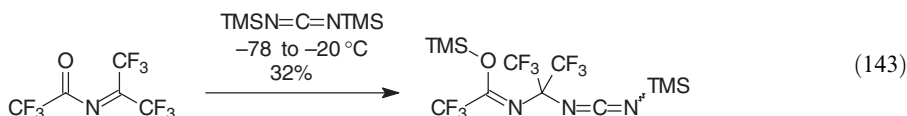
A range of *N*-purinyl- (Equation (140)) <1994JOC7653, 1994M1017> and *N*-pyrimidyl-*O*-trimethylsilylimidates <1991JOC4392, 1993JMC519, 1998MI1473, 2001MI976> has been prepared from the corresponding carboxamides and 1,1,1,3,3,3-hexamethyldisilazane in the presence of ammonium sulfate.



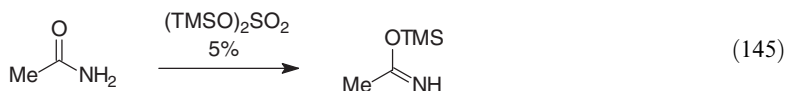
O,N-Bis(trimethylsilyl)imidates can also be used to prepare *O*-trimethylsilylimidates from carboxamides (Equations (141) and (142)) <1998T4521, 2000TL3577>.



O-Trialkylsilylimidates are also reported to be the products of the reaction of hexafluoroacetone trifluoroacetylamine with bis(trimethylsilyl)carbodiimide (Equation (143)) <1999IZV775, 1999MI771> and the reaction of triethoxysilanylpropylamine with acetylthiourea (Equation (144)) <1999JGU1391, 1999ZOB1446>.

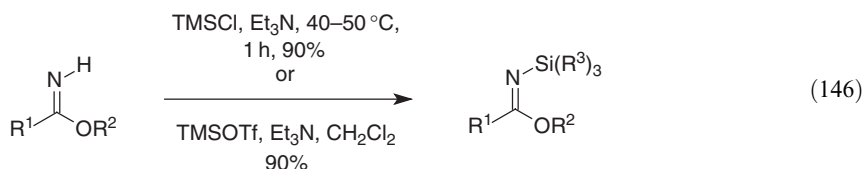


O-Trimethylsilylacetimide has been obtained, in very low yield, from the reaction of acetamide with bis(trimethylsilyl) sulfate (Equation (145)) <1998JGU397, 1998ZOB427>.



5.17.8.8.2 From imidic acid derivatives

N-Unsubstituted imidic acid esters or their hydrochloride salts are silylated by trialkylchlorosilanes/triethylamine <1997JGU1149, 1997ZOB1219> or trialkylsilyl triflates/triethylamine <1995T11021> to give the corresponding N-silylated imidates (Equation (146)).



REFERENCES

- 1913CB3616 J. Houben, E. Schmidt, *Chem. Ber.* **1913**, 46, 3616–3627.
 1963CB1473 L. Birkhofer, A. Ritter, H. Dickopp, *Chem. Ber.* **1963**, 96, 1473–1474.
 1971CC689 A. F. Hegarty, J. A. Kearny, M. P. Cashman, F. L. Scott, *J. Chem. Soc., Chem. Commun.* **1971**, 689.
 1971T51 B. L. Dyatkin, K. N. Makarov, I. L. Knunyants, *Tetrahedron* **1971**, 27, 51–62.
 1972JA7586 E. J. Corey, C. U. Kim, *J. Am. Chem. Soc.* **1972**, 94, 7586–7587.
 1973CB2093 R. Appel, K. Warning, K. D. Ziehn, *Chem. Ber.* **1973**, 106, 2093–2105.
 1975IC592 R. L. Kirchmeyer, U. I. Lassoers, J. M. Schreeve, *Inorg. Chem.* **1975**, 14, 592–594.
 1979JA1319 P. A. Wade, H. R. Hinney, *J. Am. Chem. Soc.* **1979**, 101, 1319–1320.
 1979JCS(P1)2478 S. A. Matlin, P. G. Sammes, R. M. Upton, *J. Chem. Soc., Perkin Trans. 1* **1979**, 2478–2480.
 1979JOC88 P. C. Wade, B. R. Vogt, B. Toeplitz, M. S. Puar, J. Z. Gougoutas, *J. Org. Chem.* **1979**, 44, 88–99.
 1980JOC3916 B. F. Bonini, M. Comes-Franchini, G. Mazzanti, K.-C. Liu, B. R. Shelton, R. K. Howe, *J. Org. Chem.* **1980**, 45, 3916–3918.
 1980LA791 J. C. Stowell, J. R. Christenson, *Liebigs Ann. Chem.* **1980**, 791–799.
 1981JMC532 D. L. Rector, S. D. Folz, R. D. Conklin, L. H. Nowakowski, G. Kaugars, *J. Med. Chem.* **1981**, 24, 532–538.
 1982BAU829 A. V. Fokin, Yu. N. Studnev, V. P. Stolyarov, N. N. Baranov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1982**, 31, 829–830.
 1982IZV937 A. V. Fokin, Yu. N. Studnev, V. P. Stolyarov, N. N. Baranov, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 937–939.
 1983JFC293 M. G. Barlow, D. Bell, N. J. O'Reilly, A. E. Tipping, *J. Fluorine Chem.* **1983**, 23, 293–299.
 1984G131 A. Corsico Coda, G. Tacconi, *Gazz. Chim. Ital.* **1984**, 114, 131–132.
 1984JHC797 H. M. Hassaneen, A. A. Fahmi, H. Abdelhamid, A. A. Yassin, A. S. Shawali, *J. Heterocycl. Chem.* **1984**, 21, 797–800.
 1984JOC919 W. J. Middleton, *J. Org. Chem.* **1984**, 49, 919–922.
 1984JOC3083 J. E. Rowe, A. F. Hegarty, *J. Org. Chem.* **1984**, 49, 3083–3087.
 1984S146 F. Pochat, *Synthesis* **1984**, 146–147.
 1985JOC993 J. E. Johnson, A. Ghafouripour, Y. K. Haug, A. W. Cordes, W. T. Pennington, O. Exner, *J. Org. Chem.* **1985**, 50, 993–997.
 1988SC1427 M. Kocovar, S. Polanc, M. Sollner, M. Tisler, B. Vercsek, *Synth. Commun.* **1988**, 18, 1427–1438.

- 1990TL1417 M.-C. Viand, P. Rollin, *Tetrahedron Lett.* **1990**, 31, 1417–1418.
- 1991JOC4392 M. Okabe, R.-C. Sun, G. Zenchoff, *J. Org. Chem.* **1991**, 56, 4392–4397.
- 1991S750 T. Sakamoto, H. Mori, M. Takizawa, Y. Kikugawa, *Synthesis* **1991**, 750–752.
- 1992JOC3245 T. Sakamoto, K. Okamoto, Y. Kikugawa, *J. Org. Chem.* **1992**, 57, 3245–3248.
- 1992JOC6649 J. N. Kim, E. K. Ryu, *J. Org. Chem.* **1992**, 57, 6649–6650.
- 1993AJC1213 S. A. Glover, G. P. Hammond, D. G. Harman, J. G. Mills, C. A. Rowbottom, *Aust. J. Chem.* **1993**, 46, 1213–1228.
- 1993AP143 V. Zingel, S. Elz, W. Schunack, *Arch. Pharm. (Weinheim Ger.)* **1993**, 326, 143–152.
- 1993CL1835 M. Sasaki, Y. Itoh, N. Yamamoto, Y. Yamada, *Chem. Lett.* **1993**, 1835–1838.
- 1993JCS(P1)1629 G. Pattenden, S. M. Thom, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1629–1636.
- 1993JMC519 H. O. Kim, R. F. Schinazi, K. Shanmuganathan, L. K. Jeong, J. W. Beach, S. Nampalli, D. L. Cannon, C. K. Chu, *J. Med. Chem.* **1993**, 36, 519–528.
- 1993JMC591 W. T. Ashton, C. L. Cantone, L. L. Chang, S. M. Hutchins, R. A. Strelitz, M. MacCoss, R. S. L. Chang, V. J. Lotti, K. A. Faust, T.-B. Chen, P. Bunting, T. W. Schorn, S. D. Kivlighn, P. S. Siegl, *J. Med. Chem.* **1993**, 36, 591–609.
- 1993JMC2253 I. Sircar, J. C. Hodges, J. Quin, A. M. Bunker, R. T. Winters, J. J. Edmunds, C. R. Kostlan, C. Connolly, S. J. Kesten, J. M. Hamby, J. G. Topliss, J. A. Keiser, R. L. Panek, *J. Med. Chem.* **1993**, 36, 2253–2265.
- 1993JMC2558 L. L. Chang, W. T. Ashton, K. L. Flanagan, R. A. Strelitz, M. MacCoss, W. J. Greenlee, R. S. L. Chang, V. J. Lotti, K. A. Faust, T.-B. Chen, P. Bunting, G. J. Zingaro, S. D. Kivlighn, P. K. S. Siegl, *J. Med. Chem.* **1993**, 36, 2258–2568.
- 1993JOC32 K. Tamura, H. Mizukami, K. Maeda, K. Watanabe, H. K. Uneyama, *J. Org. Chem.* **1993**, 58, 32–35.
- 1993JOC3886 H. Alcaide, L. Casarrubios, G. Dominguez, M. A. Sierra, *J. Org. Chem.* **1993**, 58, 3886–3894.
- 1993JOC4490 C. A. Veale, G. B. Steelman, M. M. Chow, *J. Org. Chem.* **1993**, 58, 4490–4493.
- 1993JOU1790 V. V. Shchepin, D. I. Efremov, *Russ. J. Org. Chem.* **1993**, 29, 1790–1794.
- 1993M299 J. G. Schantl, M. Preat, *Monatsh. Chem.* **1993**, 124, 299–308.
- 1993S497 E. Oehler, S. Kotzinger, *Synthesis* **1993**, 497–502.
- 1993T1025 S.-Y. Wei, K. Tomooka, T. Nakai, *Tetrahedron* **1993**, 49, 1025–1042.
- 1993T5177 R. Grigg, V. Santhakumar, S. Vijayaratnam, M. Thornton-Pett, A. W. Bridge, *Tetrahedron* **1993**, 49, 5177–5188.
- 1993TA2173 G. Solladie, J. Kovenski, F. Colobert, *Tetrahedron Asymmetry* **1993**, 4, 2173–2178.
- 1993TL4639 J. M. Lerestif, J. P. Bazureau, J. Hamelin, *Tetrahedron Lett.* **1993**, 34, 4639–4642.
- 1993TL5623 R. A. Bit, P. H. Crackett, W. Harris, C. H. Hill, *Tetrahedron Lett.* **1993**, 34, 5623–5626.
- 1993TL5983 R. W. Friesen, A. Giroux, K. L. Cook, *Tetrahedron Lett.* **1993**, 34, 5983–5986.
- 1993TL6131 H. Hioki, M. Okuda, W. Miyagi, S. Ito, *Tetrahedron Lett.* **1993**, 34, 6131–6134.
- 1993TL6769 A. Chen, I. Savage, E. J. Thomas, P. D. Wilson, *Tetrahedron Lett.* **1993**, 34, 6769–6772.
- 1993ZOR2156 V. V. Shchepin, D. I. Efremov, *Zh. Org. Khim.* **1993**, 29, 2156–2161.
- 1994BCJ2219 M. Yokoyama, Y. Menjo, M. Ubukata, M. Irie, M. Watanabe, H. Togo, *Bull. Chem. Soc. Jpn.* **1994**, 67, 2219–2226.
- 1994CB1699 H. Quast, S. Aldenkortt, E. Heller, P. Schaefer, E. Schmitt, *Chem. Ber.* **1994**, 127, 1699–1706.
- 1994CPB419 T. Uchida, Y. Endo, S. Hizatate, K. Shudo, *Chem. Pharm. Bull.* **1994**, 42, 419–421.
- 1994H509 C. Goulaouic-Dubois, D. R. Adams, A. Chiaroni, C. Riche, F. W. Fowler, D. S. Grierson, *Heterocycles* **1994**, 38, 509–512.
- 1994H1601 G. Brogini, L. Garanti, G. Molteni, G. Zecchi, *Heterocycles* **1994**, 38, 1601–1607.
- 1994JCS(P1)433 G. Brogini, L. Bruche, L. Garanti, G. Zecchi, *J. Chem. Soc., Perkin Trans. 1* **1994**, 433–438.
- 1994JCS(P1)3537 K. O. Hallinan, D. H. G. Crout, W. Errington, *J. Chem. Soc., Perkin Trans. 1* **1994**, 3537–3544.
- 1994JGU359 P. P. Onys'ko, T. V. Kolodka, N. V. Kolotilo, A. A. Kudryavtsev, A. D. Sinita, *Russ. J. Gen. Chem.* **1994**, 64, 359–364.
- 1994JGU1551 V. G. Rozinov, V. E. Kolbina, M. Yu Dmitrichenko, G. V. Dolgushin, V. I. Donskikh, *Russ. J. Gen. Chem.* **1994**, 64, 1551.
- 1994JGU1554 G. S. Zaitseva, L. I. Livantsova, O. P. Novikova, *Russ. J. Gen. Chem.* **1994**, 64, 1554–1555.
- 1994JMC2808 W. T. Ashton, L. L. Chang, K. L. Flanagan, S. M. Hutchins, E. M. Naylor, P. K. Chakravarthy, A. A. Patchett, W. J. Greenlee, T. B. Chen, K. A. Faust, R. S. L. Chang, V. J. Lotti, G. J. Zingaro, T. W. Schorn, P. K. S. Siegl, S. D. Kivlighn, *J. Med. Chem.* **1994**, 37, 2808–2826.
- 1994JOC7653 H. Sugimura, K. Osumi, Y. Kodaka, K. Sujino, *J. Org. Chem.* **1994**, 59, 7653–7660.
- 1994JOU62 V. P. Semenov, *Russ. J. Org. Chem.* **1994**, 30, 62–66.
- 1994JOU85 Yu. D. Smirnov, A. P. Tomilov, *Russ. J. Org. Chem.* **1994**, 30, 85–87.
- 1994JOU216 V. P. Semenov, *Russ. J. Org. Chem.* **1994**, 30, 216–221.
- 1994LA541 A. Bodenmueller, R. R. Schidt, *Liebigs Ann. Chem.* **1994**, 541–548.
- 1994M1017 A. A. El-Barvary, A. I. Khodair, E. B. Pedersen, C. Nielsen, *Monatsh. Chem.* **1994**, 125, 1017–1026.
- 1994S56 I. Jaafar, G. Francis, R. Danion-Bougot, D. Danion, *Synthesis* **1994**, 56–60.
- 1994S1096 Y. Endo, T. Uchida, S. Hizatate, K. Shudo, *Synthesis* **1994**, 1096–1105.
- 1994TL3605 P. K. T. Lin, N. Maguire, D. M. Brown, *Tetrahedron Lett.* **1994**, 35, 3605–3608.
- 1994TL4235 M. J. Martín-López, F. Bermeju-González, *Tetrahedron Lett.* **1994**, 35, 4235–4238.
- 1994TL4677 C. Shih, Y. Hu, *Tetrahedron Lett.* **1994**, 35, 4677–4680.
- 1994TL5121 C. Li, P. L. Fuchs, *Tetrahedron Lett.* **1994**, 35, 5121–5124.
- 1994TL5517 G. Kumaran, G. H. Kulkarni, *Tetrahedron Lett.* **1994**, 35, 5517–5518.
- 1994TL7469 A. S. Frame, G. Mackenzie, R. H. Wightman, *Tetrahedron Lett.* **1994**, 35, 7469–7472.
- 1994TL9099 G. Kumaran, G. H. Kulkarni, *Tetrahedron Lett.* **1994**, 35, 9099–9100.
- 1994ZN(B)970 D. Geffken, C. Holst, *Z. Naturforsch. B* **1994**, 49, 970–976.
- 1994ZOB396 P. P. Onys'ko, T. V. Kolodka, N. V. Kolotilo, A. A. Kudryavtsev, A. D. Sinita, *Zh. Obshch. Khim.* **1994**, 64, 396–402.

- 1994ZOB1746 V. G. Rozinov, V. E. Kolbina, M. Yu Dmitrichenko, G. V. Dolgushin, V. I. Donskikh, *Zh. Obshch. Khim.* **1994**, 64, 1746.
- 1994ZOB1750 G. S. Zaitseva, L. I. Livantsova, O. P. Novikova, *Zh. Obshch. Khim.* **1994**, 64, 1750–1751.
- 1994ZOR59 V. P. Semenov, *Zh. Org. Khim.* **1994**, 30, 59–62.
- 1994ZOR79 Yu. D. Smirnov, A. P. Tomilov, *Zh. Org. Khim.* **1994**, 30, 79–81.
- 1994ZOR210 V. P. Semenov, *Zh. Org. Khim.* **1994**, 30, 210–215.
- 1995AP505 P. Froberg, C. Kupfer, P. Stenger, U. Baumeister, P. Nuhn, *Arch. Pharm. (Weinheim Ger.)* **1995**, 328, 505–516.
- 1995BCJ1497 Y. Danoh, H. Matta, J. Uemura, H. Watanabe, K. Uneyama, *Bulletin of the Chemical Society of Japan* **1995**, 68, 1497–1507.
- 1995CAR257 H. Streicher, L. Latxague, T. Wiemann, P. Rollin, J. Thiem, *Carbohydr. Res.* **1995**, 278, 257–270.
- 1995CAR321 B. Joseph, P. Rollin, *Carbohydr. Res.* **1995**, 266, 321–325.
- 1995COFGT(5)653 W. Kantlehner, W. W. Mergen, Iminoacyl halide and oxy functions, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 653–724.
- 1995H619 R. Gandolfi, A. Gamba, P. Gruenanger, *Heterocycles* **1995**, 40, 619–638.
- 1995H777 L. Garanti, G. Molteni, G. Zecchi, *Heterocycles* **1995**, 40, 777–786.
- 1995IJC(B)736 H. H. Alnima, A. A. Ibrahim, W. F. Hammady, *Indian J. Chem., Sect. B* **1995**, 34, 736–739.
- 1995IZV917 A. Y. Tyurin, A. M. Churakov, E. L. Goncharova, S. L. Ioffe, Y. A. Strelenko, V. A. Tartakovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1995**, 917–923.
- 1995JCR(S)385 G. Broggini, L. Garanti, G. Molteni, G. Zecchi, *J. Chem. Res. (S)* **1995**, 385. (*M*) 2389–2397.
- 1995JFC95 M. M. Abdul-Ghani, A. E. Tipping, *J. Fluorine Chem.* **1995**, 72, 95–106.
- 1995JMC1799 L. J. Street, R. Baker, W. B. Davey, A. R. Guiblin, R. A. Jelley, A. J. Reeve, H. Routledge, F. Sternfeld, A. P. Watt, M. S. Beer, D. N. Middlemiss, A. J. Noble, J. A. Stanton, K. Scholey, R. J. Hargreaves, B. Sohal, M. I. Graham, V. G. Matassa, *J. Med. Chem.* **1995**, 38, 1799–1810.
- 1995JMC3676 J. L. Kelley, J. A. Linn, D. D. Bankston, C. J. Burchall, F. E. Soroko, B. R. Cooper, *J. Med. Chem.* **1995**, 38, 3676–3679.
- 1995JPR143 D. Lindauer, R. Beckert, M. Döring, P. Fehling, H. Görls, *J. Prakt. Chem./Chem.-Ztg.* **1995**, 337, 143–152.
- 1995MI890 A. Y. Tyurin, A. M. Churakov, E. L. Goncharova, S. L. Ioffe, Y. A. Strelenko, V. A. Tartakovsky, *Russ. Chem. Bl.* **1995**, 44, 890–896.
- 1995SC3735 G. Kumaran, G. H. Kulkarni, *Synth. Commun.* **1995**, 25, 3735–3740.
- 1995T6757 J. M. Lerestif, J. Perrocheau, F. Tonnard, J. P. Bazureau, J. Hamelin, *Tetrahedron* **1995**, 51, 6757–6774.
- 1995T8623 M. Lounasmaa, P. Hanhinen, R. Jokela, *Tetrahedron* **1995**, 51, 8623–8648.
- 1995T10929 J.-M. Coustard, *Tetrahedron* **1995**, 51, 10929–10940.
- 1995T11021 L. Ghosez, Ph. Bayard, P. Nshimyumukiza, V. Gouverneur, F. Sainte, R. Beaudegnies, H. Rivera, A. M. Frisquehbain, C. Wynants, *Tetrahedron* **1995**, 51, 11021–11042.
- 1995TL327 B. M. Kelly-Basetti, I. Krodziekwska, W. H. F. Sasse, G. P. Savage, G. W. Simpson, *Tetrahedron Lett.* **1995**, 36, 327–330.
- 1996AP83 K. Rehse, M. Herpel, D. Piechocki, *Arch. Pharm. (Weinheim, Ger.)* **1996**, 329, 83–86.
- 1996CL455 M. Shimizu, Y. Ukaji, K. Inomata, *Chem. Lett.* **1996**, 455–456.
- 1996JCS(P1)1893 W.-S. Huang, Y.-X. Zhang, C. Yuan, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1893–1896.
- 1996JGU1191 V. E. Shishkin, E. V. Mednikov, E. V. Zubareva, B. I. No, *Russ. J. Gen. Chem.* **1996**, 66, 1191–1193.
- 1996JHC1877 K.-J. Lee, D.-H. Song, D.-J. Kim, S.-W. Park, *J. Heterocycl. Chem.* **1996**, 33, 1877–1882.
- 1996JMC3019 Y. Naito, F. Akahoshi, S. Takeda, T. Okada, M. Kajii, H. Nishimura, M. Sugiura, C. Fukaya, Y. Kagitani, *J. Med. Chem.* **1996**, 39, 3019–3029.
- 1996JMC4197 D. V. Patel, M. G. Young, S. P. Robinson, L. Hunihan, B. J. Dean, E. M. Gordon, *J. Med. Chem.* **1996**, 39, 4197–4210.
- 1996JOC1689 D. E. Shalev, S. M. Chiacchiera, A. E. Radkowsky, E. M. Kosower, *J. Org. Chem.* **1996**, 61, 1689–1701.
- 1996JOC1761 A. Abbotto, S. Bradamante, G. A. Pagani, *J. Org. Chem.* **1996**, 61, 1761–1769.
- 1996JOC3715 N. J. Sisti, I. A. Motorina, M.-E. Tran Huu Dau, C. Riche, F. W. Fowler, D. S. Grierson, *J. Org. Chem.* **1996**, 61, 3715–3728.
- 1996JOC5638 I. Bosch, A. Gonzalez, F. Urpi, J. Vilarrasa, *J. Org. Chem.* **1996**, 61, 5638–5643.
- 1996JOU1072 B. I. No, E. V. Shishkin, T. V. Penskaya, V. E. Shishkin, *Russ. J. Org. Chem.* **1996**, 32, 1072.
- 1996LA87 H. Quast, S. Aldenkortt, B. Freudenreich, P. Schaefer, E.-M. Peters, K. Peters, H. G. von Schnering, E.-U. Würthwein, *Liebigs Ann. Org. Bioorg. Chem.* **1996**, 87–98.
- 1996MI88 J. Barluenga, M. Tomas, A. Ballesteros, J. Santamaria, R. Carbajo, F. LopezOrtiz, S. GarciaGranda, P. Pertierra, *Chem. -Eur. J.* **1996**, 2, 88–97.
- 1996MI462 H. Quast, S. Aldenkortt, *Chem. -Eur. J.* **1996**, 2, 462–469.
- 1996OPP699 G. Broggini, L. Garanti, G. Molteni, G. Zecchi, *Org. Prep. Proc. Int.* **1996**, 28, 699–711.
- 1996PS736 N. V. Kolotylo, P. P. Onys'ko, A. A. Sinita, *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, 111, 104.
- 1996S511 W. Huang, C. Yuan, *Synthesis* **1996**, 511–513.
- 1996S1076 G. Broggini, L. Garanti, G. Molteni, G. Zecchi, *Synthesis* **1996**, 1076–1078.
- 1996S1428 T. V. Artmonova, A. B. Zhivich, M. Y. Dubinskii, G. I. Koldobskii, *Synthesis* **1996**, 1428–1430.
- 1996T233 T. Sakai, F. Yan, S. Kashino, K. Uneyama, *Tetrahedron* **1996**, 52, 233–244.
- 1996T661 H. V. Patel, K. A. Vyas, S. P. Pandey, P. S. Fernandes, *Tetrahedron* **1996**, 52, 661–668.
- 1996T1399 A. Kotschy, G. Hajos, A. Messmer, G. Jones, *Tetrahedron* **1996**, 52, 1399–1410.
- 1996T5739 M. L. Miller, P. S. Ray, *Tetrahedron* **1996**, 52, 5739–5744.
- 1996T8877 J. R. Al-Dulayymi, M. S. Baird, V. A. Pavlov, A. I. Kurdjukov, *Tetrahedron* **1996**, 52, 8877–8888.
- 1996T9219 A. S. Frame, R. H. Wightman, G. Mackenzie, *Tetrahedron* **1996**, 52, 9219–9236.

- 1996T9509 J.-M. Coustard, *Tetrahedron* **1996**, 52, 9509–9520.
- 1996T13751 A. R. Khomutov, J. J. Vepsäläinen, A. S. Shvetsov, T. Hyvönen, T. A. Keinänen, V. N. Pustobaev, T. O. Eloranta, R. M. Khomutov, *Tetrahedron* **1996**, 52, 13751–13766.
- 1996TA1137 L. Grubert, G. Galley, M. Patzel, *Tetrahedron Asymmetry* **1996**, 7, 1137–1148.
- 1996TL229 O. Miyata, A. Nishiguchi, I. Ninomiya, T. Naito, K. Aoe, K. Okamura, *Tetrahedron Lett.* **1996**, 37, 229–232.
- 1996TL451 M. E. Jung, B. T. Vu, *Tetrahedron Lett.* **1996**, 37, 451–454.
- 1996TL917 R. Gandolfi, A. Gamba, M. Presutto, R. Oberti, N. Sardone, *Tetrahedron Lett.* **1996**, 37, 917–920.
- 1996TL1481 V. J. Patil, *Tetrahedron Lett.* **1996**, 37, 1481–1484.
- 1996TL1971 S. T. Waddell, G. M. Santorelli, *Tetrahedron Lett.* **1996**, 37, 1971–1974.
- 1996TL4019 B. Jung, H. Kim, B. S. Park, *Tetrahedron Lett.* **1996**, 37, 4019–4022.
- 1996TL4137 H. Irngatinger, A. Weber, *Tetrahedron Lett.* **1996**, 37, 4137–4140.
- 1996TL5699 M. Mavratzotis, V. Dourtoglou, C. Lorin, P. Rollin, *Tetrahedron Lett.* **1996**, 37, 5699–5700.
- 1996TL6339 C. F. Yao, W. C. Chen, Y. M. Lin, *Tetrahedron Lett.* **1996**, 37, 6339–6342.
- 1996TL6407 G. Kumaran, *Tetrahedron Lett.* **1996**, 37, 6407–6408.
- 1996TL7557 S. Yagisawa, M. Urakami, *Tetrahedron Lett.* **1996**, 37, 7557–7560.
- 1996TL7999 H.-B. Yu, W.-Y. Huang, *Tetrahedron Lett.* **1996**, 37, 7999–8000.
- 1996ZOB1222 V. E. Shishkin, E. V. Mednikov, E. V. Zubareva, B. I. No, *Zh. Obshch. Khim.* **1996**, 66, 1222–1223.
- 1996ZOR1110 J. I. No, E. V. Shishkin, T. V. Penskaya, V. E. Shishkin, *Zh. Org. Khim.* **1996**, 32, 1110.
- 1997AF431 L. Anglada, M. Raga, M. Marquez, A. Sacristan, J. M. Castello, *Arzneim.-Forsch.* **1997**, 47, 431.
- 1997BMCL447 A. Mesmaeker, C. Jouanno, W. M. Romain, S. Wendeborn, *Biorg. Med. Chem. Lett.* **1997**, 7, 447–452.
- 1997H1945 G. Brogini, L. Garanti, G. Molteni, G. Zecchi, *Heterocycles* **1997**, 45, 1945–1953.
- 1997JCR(M)2459 S. Baskaran, C. Baskaran, G. K. Trivedi, *J. Chem. Res. (M)* **1997**, 2459–2471.
- 1997JCS(P1)1647 A. D. Abell, J. W. Blunt, G. J. Foulds, H. G. Murray, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1647–1654.
- 1997JCS(P2)49 D. L. Crabb, D. A. Main, J. O. Morley, P. N. Preston, S. H. Wright, *J. Chem. Soc., Perkin Trans. 2* **1997**, 49–58.
- 1997JFC65 H.-B. Yu, W.-Y. Huang, *Journal of Fluorine Chemistry* **1997**, 84, 65–67.
- 1997JGU154 N. V. Kolotilo, P. P. Onys'ko, A. A. Sinita, *Russ. J. Gen. Chem.* **1997**, 67, 154–155.
- 1997JGU162 V. E. Shishkin, E. V. Mednikov, E. V. Zubareva, B. L. No, *Russ. J. Gen. Chem.* **1997**, 67, 162.
- 1997JGU872 P. M. Zavlin, D. A. Efremov, *Russ. J. Gen. Chem.* **1997**, 67, 872–877.
- 1997JGU1149 V. E. Shishkin, E. V. Mednikov, E. V. Isakova, B. I. No, *Russ. J. Gen. Chem.* **1997**, 67, 1149–1150.
- 1997JMC2064 C.-B. Xue, J. Wityak, T. M. Sielecki, D. J. Pinto, D. G. Batt, G. A. Cain, M. Sworin, A. L. Rockwell, J. J. Roderick, S. Wang, M. J. Orwat, V. E. Fietze, L. L. Bostrom, J. Liu, C. A. Higley, F. W. Rankin, A. E. Tobin, G. Emmett, G. K. Lalka, J. Y. Sze, S. V. Di Meo, S. A. Mousa, M. J. Thoolen, A. L. Racanelli, E. A. Hausner, T. M. Reilly, W. F. DeGrado, R. R. Wexler, R. E. Olson, *J. Med. Chem.* **1997**, 40, 2064–2084.
- 1997JMC2196 H.-S. Ahn, A. Bercovici, G. Boykow, A. Bronnenkant, S. Chackalamannil, J. Chow, R. Clevon, J. Cook, M. Czarniecki, C. Domalski, A. Fawzi, M. Green, A. Gundes, G. Ho, M. Laudicina, N. Lindo, K. Ma, M. Manna, B. McKittrick, B. Mirzai, T. Nechuta, B. Neustadt, C. Puchalski, K. Pula, L. Silverman, E. Smith, A. Stamford, R. P. Tedesco, H. G. Tsai, D. Tulshian, H. Vaccaro, R. W. Watkins, X. Y. Weng, J. T. Witkowski, Y. Xia, H. T. Zhang, *J. Med. Chem.* **1997**, 40, 2196–2210.
- 1997JOC1516 G. Kumaran, G. H. Kulkarni, *J. Org. Chem.* **1997**, 62, 1516–1520.
- 1997JOC8449 S. C. Shilcrat, M. K. Mokhallalati, M. D. Joseph, L. N. Pridgen, *J. Org. Chem.* **1997**, 62, 8449–8454.
- 1997MI278 H.-B. Yu, Q.-S. Zhang, W.-Y. Huang, *Chinese J. Chem.* **1997**, 15, 278–281.
- 1997MI307 A. A. Ikizler, B. Kahveci, C. B. Johansson, C. Celik, H. Yüsek, *Acta Pol. Pharm.* **1997**, 54, 307–312.
- 1997MI617 C. Kaepplinger, R. Beckert, W. Günther, H. Görls, *Liebigs Ann. Recl.* **1997**, 617–622.
- 1997OPP594 E. Miyazawa, T. Sakamoto, Y. Kikugawa, *Org. Prep. Proced. Int.* **1997**, 29, 594–600.
- 1997PHA638 R. Beckert, K. Waissner, C. Kapplinger, D. Lindauer, R. Walther, *Pharmazie* **1997**, 52, 638–639.
- 1997S301 A. McKillop, S. K. Chattopadhyay, A. Henderson, C. Avendano, *Synthesis* **1997**, 301–304.
- 1997SC923 A. J. Kiessling, C. K. McClure, *Synth. Commun.* **1997**, 27, 923–938.
- 1997SL11 C. M. Rayner, *Synlett* **1997**, 11–21.
- 1997T1787 P. Quadrelli, A. G. Invernizzi, M. Falzoni, P. Caramella, *Tetrahedron* **1997**, 53, 1787–1796.
- 1997T3005 G. Brogini, L. Garanti, G. Molteni, G. Zecchi, *Tetrahedron* **1997**, 53, 3005–3014.
- 1997T6681 A. Studer, D. P. Curran, *Tetrahedron* **1997**, 53, 6681–6696.
- 1997T8997 S. F. Martin, B. G. Anderson, D. Daniel, A. Gaucher, *Tetrahedron* **1997**, 53, 8997–9006.
- 1997TL1597 J. N. Kim, K. S. Jung, H. J. Lee, J. S. Son, *Tetrahedron Lett.* **1997**, 38, 1597–1598.
- 1997TL2271 A.-C. Gillard, F. Fabis, S. Jolivet-Fouchet, S. Rault, *Tetrahedron Lett.* **1997**, 38, 2271–2274.
- 1997TL6419 C.-F. Yao, C. S. Yang, H. Y. Fang, *Tetrahedron Lett.* **1997**, 38, 6419–6420.
- 1997TL6771 S. Fustero, B. Pina, A. Simon-Fuentes, *Tetrahedron Lett.* **1997**, 38, 6771–6774.
- 1997TL8017 R. Faust, B. Goebelt, *Tetrahedron Lett.* **1997**, 38, 8017–8020.
- 1997TL8903 E. Alonso, D. J. Ramon, M. Yus, *Tetrahedron Lett.* **1997**, 38, 8903–8906.
- 1997ZOB160 N. V. Kolotilo, P. P. Onys'ko, A. A. Sinita, *Zh. Obshch. Khim.* **1997**, 67, 160–161.
- 1997ZOB168 V. E. Shishkin, E. V. Mednikov, E. V. Zubareva, B. L. No, *Zh. Obshch. Khim.* **1997**, 67, 168.
- 1997ZOB932 P. M. Zavlin, D. A. Efremov, *Zh. Obshch. Khim.* **1997**, 67, 932–937.
- 1997ZOB1219 V. E. Shishkin, E. V. Mednikov, E. V. Isakova, B. I. No, *Zh. Obshch. Khim.* **1997**, 67, 1219–1220.
- 1998ACS528 G. A. Russell, R. Rajaratnam, P. Chen, *Acta Chem. Scand.* **1998**, 52, 528–532.
- 1998CC1143 S. Kim, J. H. Cheong, *J. Chem. Soc., Chem. Commun.* **1998**, 1143–1144.
- 1998CPB973 T. Okazaki, T. Watanabe, K. Kikuchi, A. Suga, M. Shibasaki, A. Fujimori, O. Inagaki, I. Yanagisawa, *Chem. Pharm. Bull.* **1998**, 46, 973–981.

- 1998EJO435 P. Bravo, M. Crucianelli, A. Farina, S. V. Meille, A. Volonterio, M. Zanda, *Eur. J. Org. Chem.* **1998**, 435–440.
- 1998JA7738 J. H. Horner, O. M. Musa, A. Bouvier, M. Newcomb, *J. Am. Chem. Soc.* **1998**, 120, 7738–7748.
- 1998JCS(D)4147 R. T. Boere, V. Klassen, G. Wolmershaeuser, *J. Chem. Soc., Dalton Trans.* **1998**, 4147–4154.
- 1998JCS(P2)2413 M. Freccero, R. Gandolfi, M. Sarzi-Amade, A. Rastelli, *J. Chem. Soc., Perkin Trans. 2* **1998**, 2413–2419.
- 1998JFC69 H.-B. Yu, W.-Y. Huang, *Journal of Fluorine Chemistry* **1998**, 87, 69–73.
- 1998JGU397 L. I. Belousova, N. N. Vlasova, M. G. Voronkov, *Russ. J. Gen. Chem.* **1998**, 68, 397–399.
- 1998JHC377 A. A. Ikizler, N. Yildirim, *J. Heterocycl. Chem.* **1998**, 35, 377–380.
- 1998JMC2243 H. Law, M. Dukat, M. Teitler, D. K. H. Lee, L. Mazzocco, R. Kamboj, V. Rampersad, T. Prinsinzano, R. A. Glennon, *J. Med. Chem.* **1998**, 41, 2243–2251.
- 1998JMC4556 T. D. Aicher, B. Balkan, P. A. Bell, L. J. Brand, H. S. Cheon, R. O. Deems, J. B. Fell, W. S. Fillers, J. D. Fraser, J. Gao, D. C. Knorr, G. G. Kahle, C. L. Leone, J. Nadelson, R. Simpson, H. C. Smith, *J. Med. Chem.* **1998**, 41, 4556–4566.
- 1998JOC188 T. Nishikawa, M. Asai, N. Ohyabu, M. Isobe, *J. Org. Chem.* **1998**, 63, 188–192.
- 1998JOC6210 S. Fustero, A. Navarro, B. Pina, A. Asensio, *J. Org. Chem.* **1998**, 63, 6210–6219.
- 1998JOC8107 P. I. Dalko, Y. Langlois, *J. Org. Chem.* **1998**, 63, 8107–8117.
- 1998JPR323 C. Kaepplinger, R. Beckert, W. Imhof, *J. Prakt. Chem./Chem.-Ztg.* **1998**, 340, 323–333.
- 1998MI29 M. F. Oldfield, N. P. Botting, *J. Labelled Compd. Radiopharm.* **1998**, 41, 29–36.
- 1998MI1473 L. S. Jeong, Y. A. Lee, H. R. Moon, M. W. Chun, *Nucleosides Nucleotides* **1998**, 17, 1473–1488.
- 1998PHA294 A. I. Khodair, E. S. I. Ibrahim, A. M. Diab, M. M. Abd-El Aziz, B. M. T. Omar, E. S. H. El Ashry, *Pharmazie* **1998**, 53, 294–300.
- 1998SC1879 K. S. Jung, H. J. Lee, H. N. Song, J. N. Kim, *Synth. Commun.* **1998**, 1879–1884.
- 1998T791 C.-F. Yao, K.-H. Kao, J.-T. Liu, C.-M. Chu, Y. Wang, W.-C. Chen, Y.-M. Lin, W.-W. Lin, M.-C. Yan, J.-Y. Liu, M.-C. Chuang, J.-L. Shiue, *Tetrahedron* **1998**, 54, 791–822.
- 1998T2843 G. Broggini, L. Garanti, G. Molteni, G. Zecchi, *Tetrahedron* **1998**, 54, 2843–2852.
- 1998T4521 H. Mack, R. Brossmer, *Tetrahedron* **1998**, 54, 4521–4538.
- 1998T12007 E. Alonso, D. J. Ramon, M. Yus, *Tetrahedron* **1998**, 54, 12007–12028.
- 1998T13997 K. H. Kao, C. S. Yang, J. T. Liu, W. W. Lin, H. Y. Fang, C.-F. Yao, K. Chen, *Tetrahedron* **1998**, 54, 13997–14014.
- 1998TA3359 A. Agócs, A. Bényei, L. Somogyi, P. Herczegh, *Tetrahedron Asymmetry* **1998**, 9, 3359–3363.
- 1998TL1135 J. Wückelt, M. Döring, P. Langer, H. Görls, R. Beckert, *Tetrahedron Lett.* **1998**, 39, 1135–1138.
- 1998TL1465 H. Shabany, C. D. Spilling, *Tetrahedron Lett.* **1998**, 39, 1465–1468.
- 1998TL2447 B. B. Shankar, D. Y. Yang, S. Gorton, A. K. Ganguly, *Tetrahedron Lett.* **1998**, 39, 2447–2448.
- 1998TL3233 P. Quadrelli, M. Mella, P. Caramella, *Tetrahedron Lett.* **1998**, 39, 3233–3236.
- 1998TL5869 A. J. Bicknell, N. W. Hird, S. A. Readshaw, *Tetrahedron Lett.* **1998**, 39, 5869–5872.
- 1998TL6895 H.-S. Lee, K. Kim, *Tetrahedron Lett.* **1998**, 39, 6895–6898.
- 1998TL9711 B. S. Park, C. M. Oh, K. H. Chun, J. O. Lee, *Tetrahedron Lett.* **1998**, 39, 9711–9714.
- 1998ZOB427 L. I. Belousova, N. N. Vlasova, M. G. Voronkov, *Zh. Obshch. Khim.* **1998**, 68, 427–429.
- 1999AJC807 J. E. Rowe, K. Lee, D. D. Dolliver, J. E. Johnson, *Aust. J. Chem.* **1999**, 52, 807–811.
- 1999CAR1 R. O. Gould, K. E. McGhie, R. M. Paton, *Carbohydr. Res.* **1999**, 322, 1–13.
- 1999CC2439 P. Langer, M. Döring, *J. Chem. Soc., Chem. Commun.* **1999**, 2439–2440.
- 1999EJO205 R. Faust, B. Goebelt, C. Weber, C. Krieger, M. Gross, J.-P. Gisselbrecht, C. Boudon, *Eur. J. Org. Chem.* **1999**, 205–214.
- 1999IZV130 A. V. Fokin, Y. N. Studnev, V. P. Stolyarov, R. S. Valiev, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1999**, 130–134.
- 1999IZV775 D. V. Romanov, T. V. Strelkova, Yu. A. Strelenko, N. V. Vasil'ev, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1999**, 775–777.
- 1999JCS(P1)47 C. M. Chu, J. T. Liu, W. W. Lin, C. F. Yao, *J. Chem. Soc., Perkin Trans. 1* **1999**, 47–52.
- 1999JCS(P1)2677 W. L. Neidhart, P. C. Anderson, G. J. Hart, A. R. Battersby, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2677–2690.
- 1999JCS(P1)3291 I. Savage, E. J. Thomas, P. D. Wilson, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3291–3304.
- 1999JFC11 K. Uneyama, *J. Fluorine Chem.* **1999**, 97, 11–25.
- 1999JFC83 J. Xiao, Z. X. Jingbo, D. Wang, C. Yuan, *J. Fluorine Chem.* **1999**, 99, 83–85.
- 1999JFC161 M. Nishida, H. Fukaya, E. Hayashi, T. Abe, *J. Fluorine Chem.* **1999**, 95, 161–165.
- 1999JGU1391 N. N. Vlasova, Yu. N. Pozhidaev, O. Yu. Belousova, M. G. Voronkov, *Russ. J. Gen. Chem.* **1999**, 69, 1391–1394.
- 1999JGU1583 O. B. Smolii, S. Y. Panchishin, E. A. Romanenko, B. S. Drach, *Russ. J. Gen. Chem.* **1999**, 69, 1583–1587.
- 1999JOC365 J. Wückelt, M. Döring, P. Langer, R. Beckert, H. Goerls, *J. Org. Chem.* **1999**, 64, 365–372.
- 1999JOC8084 G. J. Griffiths, M. B. Hauck, R. Imwinkelried, J. Kohr, C. A. Roten, G. C. Stucky, J. Gosteli, *J. Org. Chem.* **1999**, 64, 8084–8089.
- 1999JOM290 T. K. Hollis, L. E. Overman, *J. Organomet. Chem.* **1999**, 576, 290–299.
- 1999MI131 A. V. Fokin, Y. N. Studnev, V. P. Stolyarov, R. S. Valiev, *Russ. Chem. Bull.* **1999**, 48, 131–134.
- 1999MI222 L. Fu, X. Cui, Y. Xia, G. Shen, *Yanbian Daxue Xuebao, Ziran Kexueban* **1999**, 25, 222–226. (CAN 132:107516).
- 1999MI771 D. V. Romanov, T. V. Strelkova, Yu. A. Strelenko, N. V. Vasil'ev, *Russ. Chem. Bl.* **1999**, 48, 771–773.
- 1999M1373 M. Wenzel, F. Lehmann, R. Beckert, W. Guenther, H. Goerls, *Monatsh. Chem.* **1999**, 130, 1373–1382.
- 1999SC1 J. H. Teles, K. Breuer, D. Enders, H. Gielen, *Synth. Commun.* **1999**, 29, 1–9.
- 1999SL468 J. Wückelt, M. Döring, P. Langer, R. Beckert, *Synlett* **1999**, 468–470.
- 1999SL873 R. C. F. Jones, C. E. Dawson, M. J. O'Mahony, *Synlett* **1999**, 873–876.
- 1999SL1100 J. Wückelt, M. Döring, R. Beckert, P. Langer, *Synlett* **1999**, 1100–1102.

- 1999T3387 L. Ghosez, E. Jnoff, P. Bayard, F. Sainte, R. Beaudegnies, *Tetrahedron* **1999**, *55*, 3387–3400.
1999T7115 J.-T. Liu, W.-W. Lin, J.-J. Jang, J.-Y. Liu, M.-C. Yan, C. Hung, K.-H. Kao, Y. Wang, C.-F. Yao, *Tetrahedron* **1999**, *55*, 7115–7128.
- 1999T10497 P. Quadrelli, M. Mella, A. Invernizzi, A. Gamba, P. Caramella, *Tetrahedron* **1999**, *55*, 10497–10510.
1999T12493 M. C. Yan, J. Y. Liu, W. W. Lin, K. H. Kao, J. T. Liu, J. J. Jang, C. F. Yao, *Tetrahedron* **1999**, *55*, 12493–12514.
- 1999T13269 A. A. B. Robertson, N. P. Botting, *Tetrahedron* **1999**, *55*, 13269–13284.
1999T14199 V. Nair, K. V. Radhakrishnan, K. C. Sheela, N. P. Rath, *Tetrahedron* **1999**, *55*, 14199–14210.
1999TA487 G. Broggini, L. Garanti, G. Molteni, G. Zecchi, *Tetrahedron Asymmetry* **1999**, *10*, 487–492.
1999TA2203 G. Broggini, L. Garanti, G. Molteni, T. Pilati, A. Ponti, G. Zecchi, *Tetrahedron Asymmetry* **1999**, *10*, 2203–2212.
- 1999TA3873 G. Molteni, T. Pilati, *Tetrahedron Asymmetry* **1999**, *10*, 3873–3876.
1999TL2605 F. Foti, G. Grassi, F. Risitano, *Tetrahedron Lett.* **1999**, *40*, 2605–2606.
1999TL4085 R. C. F. Jones, C. E. Dawson, M. J. O'Mahony, P. Patel, *Tetrahedron Lett.* **1999**, *40*, 4085–4088.
1999TL7211 A. I. Motorina, D. S. Grierson, *Tetrahedron Lett.* **1999**, *40*, 7211–7214.
1999TL7215 A. I. Motorina, D. S. Grierson, *Tetrahedron Lett.* **1999**, *40*, 7215–7218.
1999TL8097 S. Jouneau, J. P. Bazureau, *Tetrahedron Lett.* **1999**, *40*, 8097–8098.
1999TL8785 M. Bujard, A. Briot, V. Gouverneur, C. Mioskowski, *Tetrahedron Lett.* **1999**, *40*, 8785–8788.
1999ZOB1446 N. N. Vlasova, Yu. N. Pozhidaev, O. Yu. Belousova, M. G. Voronkov, *Zh. Obshch. Khim.* **1999**, *69*, 1446–1449.
- 1999ZOB1652 O. B. Smolii, S. Y. Panchishin, E. A. Romanenko, B. S. Drach, *Zh. Obshch. Khim.* **1999**, *69*, 1652–1656.
- 2000BCJ1861 T. Ohta, H. Fujisawa, Y. Nakai, I. Furukawa, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1861–1864.
2000CJC583 R. T. Boere, V. Klassen, G. Wolmershauser, *Can. J. Chem.* **2000**, *78*, 583–586.
2000EJO1235 S. Jacquot, G. Schmitt, B. Laude, M. M. Kubicki, O. Blacque, *Eur. J. Org. Chem.* **2000**, 1235–1240.
2000H579 S. Manikandan, M. Shanmugasundaram, R. Raghunathan, E. J. P. Malar, *Heterocycles* **2000**, *53*, 579–584.
- 2000JA2995 H. Takahashi, Y. Hitomi, Y. Iwai, S. Ikegami, *J. Am. Chem. Soc.* **2000**, *122*, 2995–3000.
2000JCS(P1)2415 S. K. Chattopadhyay, J. Kempson, A. McNeil, G. Pattenden, M. Reader, D. E. Rippon, D. Waite, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2415–2428.
- 2000JFC35 T. Abe, E. Hayashi, H. Baba, *J. Fluorine Chem.* **2000**, *106*, 35–42.
2000JFC105 K.-W. Chi, G. G. Furin, Y. V. Gatilov, I. Y. Bagryanskay, E. L. Zhuzhgov, *J. Fluorine Chem.* **2000**, *103*, 105–115.
- 2000JHC1505 A. R. Katritzky, M. A. C. Button, S. Denisenko, *J. Heterocycl. Chem.* **2000**, *37*, 1505–1510.
2000JMC1793 C. T. Supuran, A. Scozzafava, F. Briganti, B. W. Clare, *J. Med. Chem.* **2000**, *43*, 1793–1806.
2000JMC2975 S. W. Djuric, N. Y. BaMaung, A. Basha, H. Liu, J. R. Luly, D. J. Madar, R. J. Sciotti, N. P. Tu, F. L. Wagenaar, P. E. Wiedeman, X. Zhou, S. Ballaron, J. Bauch, Y.-W. Chen, X. G. Chiou, T. Fey, D. Gauvin, E. Gubbins, G. C. Hsieh, K. C. Marsh, K. W. Mollison, M. Pong, T. K. Shaughnessy, M. P. Sheets, M. Smith, J. M. Trevillyan, U. Warrior, C. D. Wegner, G. W. Carter, *J. Med. Chem.* **2000**, *43*, 2975–2981.
- 2000JMC3168 I. K. Khanna, Y. Yu, R. M. Huff, R. M. Weier, X. Xu, F. J. Koszyk, P. W. Collins, J. N. Cogburn, P. C. Isakson, C. M. Koboldt, J. L. Masferrer, W. E. Perkins, K. Seibert, A. W. Veenhuizen, J. H. Yuan, D. C. Yang, Y. Y. Zhang, *J. Med. Chem.* **2000**, *43*, 3168–3185.
- 2000JOC729 P. Langer, J. Wückelt, M. Döring, *J. Org. Chem.* **2000**, *65*, 729–734.
2000JOC1115 R. W. Darbeau, E. H. White, N. Nunez, B. Coit, M. Daigle, *J. Org. Chem.* **2000**, *65*, 1115–1120.
2000JOC3404 H. Amii, Y. Kishikawa, K. Kageyama, K. Uneyama, *J. Org. Chem.* **2000**, *65*, 3404–3408.
2000JOC3603 P. Langer, J. Wückelt, M. Döring, H. Görls, *J. Org. Chem.* **2000**, *65*, 3603–3611.
2000JOC4289 T. Da Ros, M. Prato, V. Lucchini, *J. Org. Chem.* **2000**, *65*, 4289–4297.
2000JOC4397 N. A. Braun, M. Ousmer, J. D. Bray, D. Bouchu, K. Peters, E.-M. Peters, M. Ciufolini, *J. Org. Chem.* **2000**, *65*, 4397–4408.
- 2000JOC6231 B. Jiang, Y. Liu, W. S. Zhou, *J. Org. Chem.* **2000**, *65*, 6231–6236.
2000OL539 D. Muri, J. W. Bode, E. M. Carreira, *Org. Lett.* **2000**, *2*, 539–542.
2000OL3087 V. P. Sandanayaka, Y. Yang, *Org. Lett.* **2000**, *2*, 3087–3090.
- 2000T965 A. Zhang, Y. Kan, G.-L. Zhao, B. Jiang, *Tetrahedron* **2000**, *56*, 965–970.
2000T1057 S. Kanemasa, H. Matsuda, A. Kamimura, T. Kakinami, *Tetrahedron* **2000**, *56*, 1057–1064.
2000T1361 A. Hinschberger, A.-C. Gillard, I. Bureau, S. Rault, *Tetrahedron* **2000**, *56*, 1361–1367.
2000T6299 A. Napieraj, S. Zawadzki, A. Zwierzak, *Tetrahedron* **2000**, *56*, 6299–6305.
2000TA3273 R. C. F. Jones, S. J. Hollis, J. N. Iley, *Tetrahedron Asymmetry* **2000**, *11*, 3273–3276.
2000TL3131 H. Yamamoto, S. Watanabe, K. Kadotani, M. Hasegawa, M. Noguchi, S. Kanemasa, *Tetrahedron Lett.* **2000**, *41*, 3131–3136.
- 2000TL3577 M. E. Jung, A. Toyota, *Tetrahedron Lett.* **2000**, *41*, 3577–3582.
2000TL6011 G. J. McGarvey, J. A. Mathys, K. J. Wilson, *Tetrahedron Lett.* **2000**, *41*, 6011–6015.
2000TL6721 S. M. Sparks, K. J. Shea, *Tetrahedron Lett.* **2000**, *41*, 6721–6724.
2000TL8431 J. M. Mitchell, N. S. Finney, *Tetrahedron Lett.* **2000**, *41*, 8431–8434.
2000TL10055 G. T. Hwang, B. H. Kim, *Tetrahedron Lett.* **2000**, *41*, 10055–10060.
- 2001CAR295 N. E. Davidson, T. J. Rutherford, N. P. Botting, *Carbohydr. Res.* **2001**, *330*, 295–307.
2001CC2478 T. Misaki, M. Kurihara, Y. Tanabe, *J. Chem. Soc., Chem. Commun.* **2001**, 2478–2479.
2001CJC1562 O. P. Anderson, A. B. M. Barrett, J. J. Edmunds, S.-I. Hachiya, J. A. Hendrix, K. Horita, J. W. Malecha, C. J. Parkinson, A. VanSickle, *Can. J. Chem.* **2001**, *79*, 1562–1592.
- 2001EJI805 J. Wückelt, M. Döring, H. Görls, P. Langer, *Eur. J. Inorg. Chem.* **2001**, 805–811.
2001EJO1225 L. M. Yagupolskii, S. V. Shelyazhenko, I. I. Maletina, V. N. Petrik, E. B. Rusanov, A. N. Chernega, *Eur. J. Org. Chem.* **2001**, 1225–1233.

- 2001EJO3953 P. Langer, J. T. Anders, M. Döring, *Eur. J. Org. Chem.* **2001**, 3953–3959.
- 2001HCA3178 F. Glorius, M. Neuburger, A. Pfaltz, *Helv. Chim. Acta* **2001**, *84*, 3178–3196.
- 2001IZV522 R. R. Gataullin, L. S. Afon'kin, I. B. Abdrakhmanov, G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.* **2001**, 522–524.
- 2001IZV1562 D. V. Romanov, N. V. Vasil'ev, G. V. Zatonsky, *Izv. Akad. Nauk SSSR, Ser. Khim.* **2001**, 1562–1567.
- 2001JCS(P1)2781 P. W. Groundwater, I. Garnett, A. J. Morton, T. Sharif, S. J. Coles, M. B. Hursthouse, M. Nyerges, R. J. Anderson, D. Bendell, A. McKillop, W. Zhang, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2781–2787.
- 2001JCS(P2)1239 A. F. Hegarty, S. J. Eustace, N. M. Tynan, N.-N. Pham-Tran, M. T. Nguyen, *J. Chem. Soc., Perkin Trans. 2* **2001**, 1239–1246.
- 2001JFC11 K.-W. Chi, H.-A. Kim, G. G. Furin, E. L. Zhuzhgov, N. Protzuk, *J. Fluorine Chem.* **2001**, *110*, 11–20.
- 2001JFC27 J. Ding, P. Zhong, C. Yuan, *J. Fluorine Chem.* **2001**, *111*, 27–28.
- 2001JFC123 V. A. Petrov, *J. Fluorine Chem.* **2001**, *109*, 123–128.
- 2001JFC241 H.-J. Wang, W. Ling, L. Lu, *J. Fluorine Chem.* **2001**, *111*, 241–246.
- 2001JGU1807 B. I. No, Yu. L. Zotov, E. V. Shishkin, D. S. Klimov, *Russ. J. Gen. Chem.* **2001**, *71*, 1807–1810.
- 2001JOC2246 A. Leggio, A. Liguori, A. Napoli, C. Siciliano, G. Sindona, *J. Org. Chem.* **2001**, *66*, 2246–2250.
- 2001JOC6410 J. W. Bode, E. M. Carreira, *J. Org. Chem.* **2001**, *66*, 6410–6424.
- 2001JOC6480 A. Dahan, M. Portnoy, *J. Org. Chem.* **2001**, *66*, 6480–6482.
- 2001JOC6756 H. Emtenaes, L. Alderin, F. Almqvist, *J. Org. Chem.* **2001**, *66*, 6756–6761.
- 2001MI191 M. Böger, D. Dürr, L. Gsell, R. G. Hall, F. Karrer, O. Kristiansen, P. Maienfisch, A. Pascual, A. Rindlisbacher, *Post. Manage. Sci.* **2001**, *57*, 191–202.
- 2001MI545 R. R. Gataullin, L. S. Afon'kin, I. B. Abdrakhmanov, G. A. Tolstikov, *Russ. Chem. Bl.* **2001**, *50*, 545–547.
- 2001MI573 P. Langer, M. Döring, D. Seyferth, H. Görls, *Chem.-Eur. J.* **2001**, *7*, 573–584.
- 2001MI976 J. Wilson, J. A. Hadfield, J. Bailey, J. Zweit, N. Thatcher, R. Little, *J. Labelled Compd. Radiopharm.* **2001**, *44*, S976–S978.
- 2001MI1639 D. V. Romanov, N. V. Vasil'ev, G. V. Zatonsky, *Russ. Chem. Bl.* **2001**, *50*, 1639–1644.
- 2001OLI109 H. Amii, Y. Kishikawa, K. Uneyama, *Org. Lett.* **2001**, 1109–1112.
- 2001OL2265 S. M. Sparks, K. Shea, *Org. Lett.* **2001**, 2265–2268.
- 2001S601 D. Müller, R. Beckert, H. Görls, *Synthesis* **2001**, 601–606.
- 2001S2191 B. H. Kim, E. J. Jeong, G. T. Hwang, N. Venkatesan, *Synthesis* **2001**, 2191–2202.
- 2001SL1437 P. Langer, M. Döring, *Synlett* **2001**, 1437–1439.
- 2001SL1707 D. J. Conolly, P. J. Guiry, *Syn. Lett.* **2001**, 1707–1710.
- 2001SC3075 R. da Conceicao Rodrigues, A. P. de Aguiar, *Synth. Commun.* **2001**, *31*, 3075–3080.
- 2001SL1557 S. Chang, M. Lee, S. Kim, *Synlett* **2001**, 1557–1558.
- 2001T459 L.-L. Wei, J. A. Mulder, H. Xiong, C. A. Zificsak, C. J. Douglas, R. P. Hsung, *Tetrahedron* **2001**, *57*, 459–466.
- 2001TA469 A. Agócs, T. E. Gunda, G. Batta, Á. Kovács-Kulyassa, P. Herczegh, *Tetrahedron Asymmetry* **2001**, *12*, 469–476.
- 2001TL2653 A. Brunschweiler, D. Heber, *Tetrahedron Lett.* **2001**, *42*, 2653–2655.
- 2001TL4065 K. W. J. Baker, A. Gibb, A. R. March, R. M. Paton, *Tetrahedron Lett.* **2001**, *42*, 4065–4068.
- 2001TL4285 M. Adamczyk, Y.-Y. Chen, P. G. Mattingly, *Tetrahedron Lett.* **2001**, *42*, 4285–4287.
- 2001TL4377 M. Caverio, W. B. Motherwell, P. Potier, *Tetrahedron Lett.* **2001**, *42*, 4377–4379.
- 2001TL6191 C. G. Saluste, R. J. Whitby, M. Furber, *Tetrahedron Lett.* **2001**, *42*, 6191–6194.
- 2001ZOB1911 B. I. No, Yu. L. Zotov, E. V. Shishkin, D. S. Klimov, *Zh. Obshch. Khim.* **2001**, *71*, 1911–1914.
- 2001ZN(B)547 W. Thimann, D. Geffken, *Z. Naturforsch. B* **2001**, *56*, 547–553.
- 2002CR105 J. D. Rose, J. A. Maddy, R. N. Comber, W. J. Suling, L. N. Wilson, R. C. Reynolds, *Carbohydr. Res.* **2002**, *337*, 105–120.
- 2002EJO686 P. Langer, J. T. Anders, *Eur. J. Org. Chem.* **2002**, *4*, 686–691.
- 2002HET1257 D. Pufky, R. Beckert, M. Döring, O. Walter, *Heterocycles* **2002**, *57*, 1257–1264.
- 2002JOC188 R. J. Herr, P. F. Vogt, H. Meckler, M. P. Trova, *J. Org. Chem.* **2002**, *67*, 188–193.
- 2002JOC2619 H. Bibas, D. W. J. Moloney, R. Neumann, M. Shtaiwi, P. V. Bernhardt, C. Wentrup, *J. Org. Chem.* **2002**, *67*, 2619–2631.
- 2002OL3127 P. J. Manley, M. T. Bilodeau, *Org. Lett.* **2002**, *4*, 3127–3130.
- 2002SC225 T. Saied, M. L. Benkhoud, K. Boujlel, *Synth. Commun.* **2002**, *32*, 225–234.
- 2002T207 L. F. Basil, A. I. Meyers, A. Hassner, *Tetrahedron* **2002**, *58*, 207–213.
- 2002T3003 V. Nair, D. Sethumadhavan, S. M. Nair, S. Viji, N. P. Rath, *Tetrahedron* **2002**, *58*, 3003–3007.
- 2002T3579 N. Nakajima, M. Saito, M. Kudo, M. Ubukata, *Tetrahedron* **2002**, *58*, 3579–3588.
- 2002T7275 V. Boucard, H. Sauriat-Dorizon, F. Guibé, *Tetrahedron* **2002**, *58*, 7275–7290.
- 2002T9613 A. Kamimura, Y. Kaneko, A. Ohita, K. Matsuura, Y. Fujimoto, A. Kakehi, S. Kanemasa, *Tetrahedron* **2002**, *58*, 9613–9620.
- 2003CC1752 H. Amii, M. Kohda, M. Seo, K. Uneyama, *J. Chem. Soc., Chem. Commun.* **2003**, 1752–1753.
- 2003JHC207 A. S. Shawali, S. Elsheikh, C. Párkányi, *J. Het. Chem.* **2003**, *40*, 207–212.
- 2003JHC255 A. Hirschberger, F. Fabis, J. S. D. Santos, S. Rault, *J. Het. Chem.* **2003**, *40*, 255–259.
- 2003JMC284 M. R. Barbachyn, G. J. Cleek, L. A. Dolak, S. A. Garmon, J. Morris, E. P. Seest, R. C. Thomas, D. S. Toops, W. Watt, D. G. Wishka, C. W. Ford, G. E. Zurenko, J. C. Hamel, R. D. Schaadt, D. Stapert, B. H. Yagi, W. J. Adams, J. M. Friis, J. G. Slatter, J. P. Sams, N. L. Oien, M. J. Zaya, L. C. Wienkers, M. A. Wynalda, *J. Med. Chem.* **2003**, *46*, 284–302.
- 2003JMC314 S. L. Black, A. R. Jales, W. Brandt, J. W. Lewis, S. M. Husbands, *J. Med. Chem.* **2003**, *46*, 314–317.
- 2003JMC2516 M. D. Bachi, E. E. Korshin, R. Hoos, A. M. Szpilman, P. Ploypradith, S. J. Xie, T. A. Shapiro, G. H. Posner, *J. Med. Chem.* **2003**, *46*, 2516–2533.
- 2003JOC3 T. D. Owens, A. J. Souers, J. A. Ellman, *J. Org. Chem.* **2003**, *68*, 3–10.

- 2003JOC2844 A. Nadin, J. M. S. Lopez, A. P. Owens, A. C. Talbot, T. Harrison, *J. Org. Chem.* **2003**, *68*, 2844–2852.
- 2003OL2523 S. Fustero, A. Bartolome, J. F. Sanz-Cervera, M. Sanchez-Rosello, J. G. Soler, C. Ramírez de Arellano, A. S. Fuentes, *Org. Lett.* **2003**, *5*, 2523–2526.
- 2003OL2707 S. Fustero, J. G. Soler, A. Bartolome, M.-S. Rosello, *Org. Lett.* **2003**, *5*, 2707–2710.
- 2003T303 M. Bao, M. Shimizu, S. Shimada, M. Tanaka, *Tetrahedron* **2003**, *59*, 303–309.
- 2003T2617 F. Palacios, A. M. O. de Retana, E. M. de Marigorta, M. Rodriguez, J. Pagalday, *Tetrahedron* **2003**, *59*, 2617–2624.
- 2003T9315 G. Molteni, T. Pilati, A. Ponti, *Tetrahedron* **2003**, *59*, 9315–9322.
- 2003TL3555 J. W. Bode, Y. Hachisu, T. Matsuura, K. Suzuki, *Tetrahedron Lett.* **2003**, *44*, 3555–3558.
- 2003TL4113 X.-F. Lin, J. Zhang, Y.-G. Wang, *Tetrahedron Lett.* **2003**, *44*, 4113–4115.
- 2003TL8901 J. L. Stevens, T. D. Welton, J. P. Deville, V. Behar, *Tetrahedron Lett.* **2003**, *44*, 8901–8903.

Biographical sketch



Roz Anderson is a graduate of the University of Newcastle, where she obtained both her B.Sc. (1984) and Ph.D. (for work on the chemistry of cobaloximes, under the supervision of Prof. Bernard Golding) degrees. She then moved to Sunderland University to a post-doctoral position with Prof. Jeff Brown in the School of Pharmaceutical Sciences. In 1990 she was appointed to a Lectureship in Organic Chemistry and was promoted to Senior Lecturer in 1993 and Principal Lecturer in 2003. Her research interests include; the synthesis of novel chromogenic agents for enhanced bacterial detection, the investigation into the rôle of *tryptophan hydroxylase* in autism and the possible rôle of environmental factors in the symptomology, the design, and synthesis of improved cysteamine prodrugs, and molecular modeling in drug design and reaction mechanisms



Paul Groundwater was born in Edinburgh in 1962 and gained his B.Sc. (1983) and Ph.D. (1987) degrees from the University of Edinburgh. He was a post-doctoral fellow at the Australian National University, Canberra with Prof. Ron Warrener then returned to the U.K. to join Prof. Malcolm Stevens at the Cancer Research Campaign Experimental Chemotherapy Research Group, Aston University. In 1989 he was appointed to a Lectureship in the Department of Chemistry, Cardiff University. In 1996 he was appointed to a Readership in Organic Chemistry in the Institute of Pharmacy and Chemistry at the University of Sunderland and was promoted to Professor, in the Sunderland Pharmacy School, in 2001. He is the Centre Director of ChemiSPEC, a business providing spectroscopic services to industry and is currently the Research Director of the Sunderland Pharmacy School. His research interests include the generation and reactivity of dipolar intermediates, the design and synthesis of novel medicinal agents, the identification of the active principle of medicinal plants, and new assays for disease markers.



Miklós Nyerges was born in Budapest in 1967 and received his M.Sc. degree from the Technical University of Budapest in 1991 and his Ph.D. from the same Institution in 1996 (on research done partly at Cardiff University). He was a post-doctoral associate with Paul Groundwater at Sunderland University and then with Prof. Sir Derek Barton at Texas A & M. After a short visit to the Korean Research Institute of Chemical Technology, South Korea (C.S. Pak) in 1999 he returned to Sunderland as a NATO postdoctoral fellow. Currently he is a Senior Scientific researcher in the Research Group of the Hungarian Academy of Sciences, Department of Organic Chemical Technology, Technical University of Budapest. His research interests involve cycloaddition approaches to synthesis of natural products. He was a recipient of Zoltán Földi Award for Innovative Organic Chemistry (1995), a Junior Award of the Hungarian Academy of Sciences in Organic Chemistry (1997), the Géza Zemplén Award (2000) and a János Bolyai plaque (2002).

5.18

Iminoacyl Functions Linked to Chalcogens Other Than Oxygen

S. CHALLENGER

Pfizer Global Research and Development, Sandwich, UK

5.18.1	IMIDOYLSULFUR, -SELENIUM, AND -TELLURIUM DERIVATIVES	639
5.18.1.1	Thiolimidic Acids, $R^1C(NR^2)SH$	639
5.18.1.2	Thioimidic Esters and Anhydrides— $R^1C(NH)SR^2$, $R^1C(NR^2)SR^3$, and $R^1C(NR^2)SC(NR^2)R^1$	640
5.18.1.2.1	<i>Thioimidic esters and anhydrides from thioamides, thiolactams, and related compounds</i>	640
5.18.1.2.2	<i>Thioimidic esters and thioiminium salts from nitriles, nitrilium salts, isonitriles, and thiocyanates</i>	641
5.18.1.2.3	<i>Thioimidic esters from imidoyl halides, thioimidoyl chlorides, and imidoyl derivatives</i>	642
5.18.1.2.4	<i>Thioimidic esters from heterocumulenes, isothiocyanates, and ketenimines</i>	643
5.18.1.2.5	<i>Thioimidic esters from thioimidic esters</i>	643
5.18.1.2.6	<i>Thioimidic esters by miscellaneous methods</i>	644
5.18.1.3	Selenoimidic and Telluroimidic Esters, $R^1C(NR^2)SeR^3$ and $R^1C(NR^2)TeR^3$	644
5.18.1.3.1	<i>Selenoimidic esters from selenoamides, imidoyl derivatives, and isoselenocyanates</i>	644
5.18.1.3.2	<i>Telluroimidic esters, $R^1C(NR^2)TeR^3$</i>	646
5.18.1.4	Other Thioimidic Derivatives Where R^2 is Carbon Based, $R^1C(NR)SR^2$ (e.g., $R^2 = COR^3$)	647
5.18.1.5	<i>S</i> -Imidoyl Sulfenyl Halides, $R^1C(NR^2)SX$	647
5.18.1.6	<i>S</i> -Imidoyl Sulfenates, <i>S</i> -Imidoyl Sulfoxides, and <i>S</i> -Imidoyl Sulfones— $R^1C(NR^2)SOR^3$, $R^1C(NR^2)S(O)R^3$, and $R^1C(NR^2)SO_2R^3$	647
5.18.1.7	Imidoyl Disulfides and Diselenides, $R^1C(NR^2)SSR^3$ and $R^1C(NR^2)SeSeR^3$	647
5.18.1.7.1	<i>Imidoyl disulfides</i>	647
5.18.1.7.2	<i>Imidoyl diselenides</i>	648
5.18.1.8	<i>S</i> -Imidoyl Sulfenamides and Related Structures, $R^1C(NR^2)SNR^3R^4$ and $R^1C(NR^2)SN=CR^3$	648
5.18.1.9	Imidoylthiophosphorus Derivatives, $R^1C(NR^2)SP$	649
5.18.1.10	Imidoylthiometalloid Derivatives, $R^1C(NR^2)SSi$ and $R^1C(NR^2)SB$	649
5.18.1.11	Imidoylthiometals and Imidoylselenometals, $R^1C(NR^2)S$ Metal and $R^1C(NR^2)Se$ Metal	649
5.18.1.11.1	<i>S</i> -Imidoyl tin and mercury derivatives, $R^1C(NR^2)SSnR_3$ and $R^1C(NR^2)SHgSC(NR^2)CR^1$	649
5.18.1.11.2	<i>Se</i> -Imidoyl tin derivatives, $R^1C(NR^2)SeSnR_3$	650

5.18.1 IMIDOYLSULFUR, -SELENIUM, AND -TELLURIUM DERIVATIVES

5.18.1.1 Thiolimidic Acids, $R^1C(NR^2)SH$

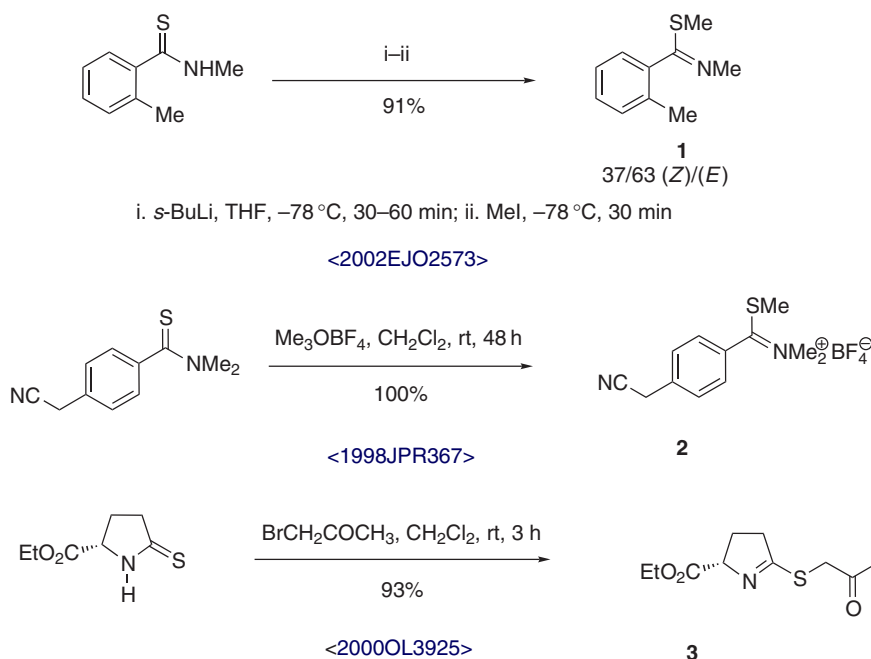
The methods of preparation of primary and secondary thioamides, which are tautomers of thiolimidic acids, are reviewed in Chapter 5.14 of this volume and will not be considered further here.

5.18.1.2 Thioimidic Esters and Anhydrides— $R^1C(NH)SR^2$, $R^1C(NR^2)SR^3$, and $R^1C(NR^2)SC(NR^2)R^1$

There are a number of methods available for the preparation of thioimidic esters and their salts. Examples are known of all three possible bond-forming transformations around the central imido carbon including formation of a C—C or C—S single bond and the C—N double bond. In the literature thioimidic esters are frequently referred to as thioimides and their salts as thioiminium salts. Thioimides can be considered as activated forms of amides and are useful intermediates in organic synthesis in, for example, the preparation of amidines and heterocyclic compounds. A number of general reviews on imido derivatives include the preparation of thioimides and their salts and cover the literature up to and including 1993 <1961CRV179, B-1972MI001, B-1975MI002, B-1979MI003, 1985HOU(E5/2)931, B-1991MI004, 1991COS(6)536, 1995COFGT(5)725>. This review also covers cyclic thioimidic ester derivatives (thiolactim ethers), which contain one heteroatom of the thioimido group in a ring, but does not include heterocyclic compounds in which both heteroatoms are part of a ring.

5.18.1.2.1 Thioimidic esters and anhydrides from thioamides, thiolactams, and related compounds

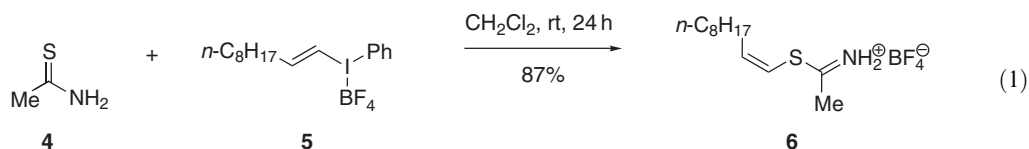
The most general and widely used method for the preparation of thioimidic esters, and their derivatives is via the *S*-alkylation or arylation of primary, secondary, or tertiary thioamides or thiolactams with alkylating or arylating agents <1995COFGT(5)725>. Some recent published examples of the synthesis of thioimides **1**, thioiminium salts **2**, and thiolactim ethers **3** are shown in Scheme 1. These examples demonstrate the scope of the method and the references include full experimental details.



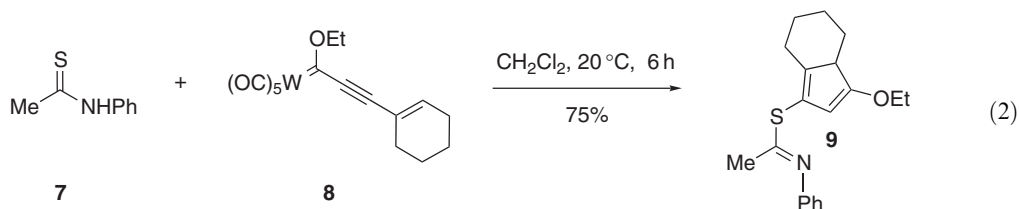
Scheme 1

Primary and secondary thioamides in the absence of added base give thioiminium salts, which are readily converted into thioimides with alkali metal hydroxides, carbonates, or tertiary amine bases. In most cases, mixtures of geometrical isomers are obtained. A variety of alkylating and arylating reagents have been used including alkyl halides <B-1979MI003>, dialkyl sulfates <1975LA1984>, trifluoromethanesulfonic acid esters <1989TL4443>, sultones <1964LA(676)114>, alkyl fluorosulfonates <1976TL143>, trialkyloxonium salts <1983SC753, 1998JPR367>, trialkylammonium salts <1995JOC2692>, diazoalkanes <1979TL4671, 1995MI4>, ethyl thiochloroformate <1973JOC2242, 1983JOC1544>, aryldiazonium salts <1970ZOR805>, and activated alcohol derivatives

<1985BCJ2721, 1992TL5117>. The alkylation of primary thioamides with alkyl halides has also been used to prepare stable polymer-supported thioimides, which have found an application in the synthesis of amidines <2001SL388>. There are examples of thioimides being prepared from thioamides under acidic reaction conditions using trimethyl orthoformate <1989JCS(P1)265, 2002JOC9304> and *N,N*-dimethylformamide dimethyl acetal <1968IZV576> as alkylating reagents. Some recent advances have been reported of the transformation of thioamides into *S*-alkenylthioimides. *S*-Alkenylation of thioacetamide **4** with (*E*)-alkenyl(phenyl)- λ^3 iodane reagent **5** stereoselectively provides the (*Z*)-*S*-alkenylthioiminium tetrafluoroborate salt **6** in good yield (Equation (1)) <2001OL2753>. The alkenylation at sulfur proceeds with exclusive inversion of configuration and is possible because of the very high leaving group ability of the phenyl- λ^3 iodanyl group. The application of this reagent has also been extended to tertiary thioamides and a thiolactam (nine examples, yields 91–98%) as part of a method for converting thioamides to amides <2002CC2802>. The product thioiminium salts were found to be labile and highly susceptible to hydrolysis.



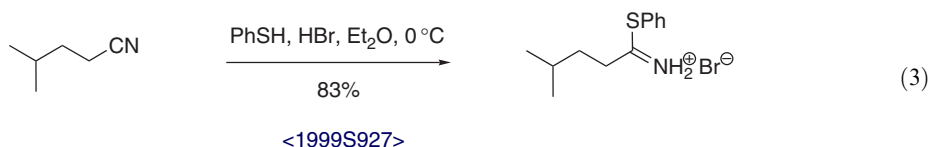
(*E*)-Thioimidic ester **9** has been obtained stereoselectively in 75% yield from the reaction of 2 equiv. of *N*-phenylthioacetamide **7** with (1-alkynyl)carbene tungsten complex **8** (Equation (2)) <2002EJO361>. Earlier examples of this reaction using 1 equiv. of thioamide gave tungsten and chromium complexes of thioimides (seven examples, yields 82–95%) <2000OM2373>.



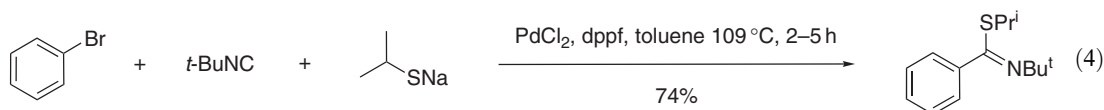
A limited number of radical additions to thioamides have been used to prepare thioimides. These include the arylation of secondary thioamides with the phenyl radical sources nitrosoacetanilide and phenylazotriphenylmethane <1982IZV2121> and the thermolytic decarboxylative rearrangement of a thiohydroxamic acid ester <1983TL5889>. The oxidation of thioamides with a variety of reagents has been reported to give different products, depending on the oxidizing reagent used, the reaction conditions and the nature of the thioamide <1961CRV45>. Symmetrical thioimidic anhydrides have been obtained under certain conditions; for example, the thioimidic anhydride derived from *N*-phenylthiobenzamide is obtained in 81% yield by oxidation with a molar equivalent of phenyliodosodiacetate under anhydrous conditions <1981MI11>. Symmetrical thioimidic anhydrides have also been prepared by the reaction of thioamides with imidoyl chlorides <1986IJC(B)357, 1990ZC320> or phenylsulfonyl chloride <1969LA(727)50>.

5.18.1.2.2 Thioimidic esters and thioiminium salts from nitriles, nitrilium salts, isonitriles, and thiocyanates

A general method (Pinner synthesis) for the preparation of *N*-unsubstituted thioiminium salts involves the addition of alkyl or aryl thiols to alkyl or aryl nitriles in the presence of hydrogen halides <1995COFGT(5)725>. A recent example is shown in Equation (3). Neilson discussed in detail the scope and limitations of this reaction in his 1975 review <B-1975MI002>.



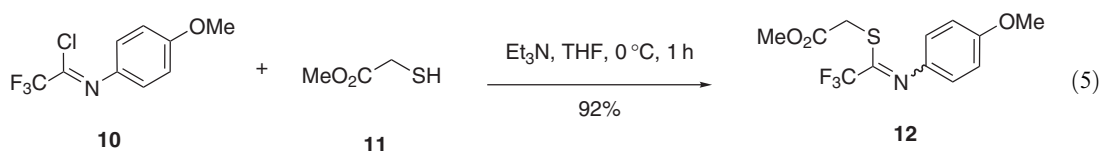
A major limitation of this methodology is that only *N*-unsubstituted thioiminium salts can be formed directly in the reaction. However, in an analogous process *N*-alkyl thioimide salts have been obtained from the reaction of nitrilium salts with thiols <1980CC1151, 1983JCS(P1)1067, 1985JOC4415>. A limited number of thioimides have been prepared by the base-catalyzed addition of thiols to nitriles with strongly electron-withdrawing α -substituents <1962JOC2858, 1976BSF667>. Often the thioimides formed are not isolated but react to form other products <1998JMC379>. This method has the advantage that free thioimides are formed, which are much less sensitive to hydrolysis compared with their salts. Thioimides <1970JOC2118, 1984T1075, 1988T3501> and thiolactim ethers <1994JOC7752, 1996SL60, 2003OL901> have also been prepared by the radical addition of thiols to isonitriles. In a more recent development, Whitby and co-workers have reported that a one-pot three-component palladium-catalyzed coupling reaction of bromobenzene, alkylisonitriles, and the sodium salt of 2-propanethiol provides thioimides (four examples, yields 40–74%) (Equation (4)) <2001TL6191>. The sodium salt of thiophenol was unsuccessful in this reaction. Isonitriles are isoelectronic with carbon monoxide and this reaction is analogous to the well-known palladium-catalyzed preparation of esters from aryl halides, carbon monoxide, and alcohols.



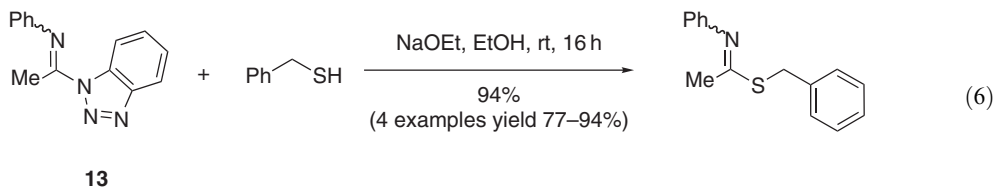
The Friedel–Crafts-type condensation of aliphatic and aromatic thiocyanates with electron-rich aromatic systems in the presence of protic or Lewis acids has been reported to give thioimide esters <1990SC71> and thiolactim ethers <1990KGS995>.

5.18.1.2.3 Thioimide esters from imidoyl halides, thioimidoyl chlorides, and imidoyl derivatives

The reaction of imidoyl halides with thiols in the presence of base is an established method for the preparation of thioimide esters and is the only method which has been used to prepare all three chalcogen imide esters <1995COFGT(5)725>. An example of this transformation is the reaction of imidoyl chloride **10** with thiol **11** to give the thioimide **12** (Equation (5)) <2001JOC1026>. Imidoyl chlorides have mainly been used but there is one report of the preparation of thioimides using an *in situ* generated imidoyl iodide <1983TL3255>.

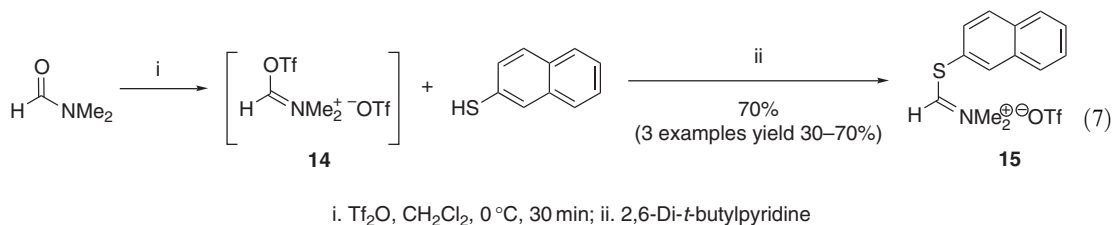


A disadvantage in the use of imidoyl chlorides is their inherent instability and sensitivity to hydrolysis. They are generally prepared by treatment of the corresponding amides with chlorinating agents and used *in situ*. Katritzky and co-workers have developed the use of 1-imidoylbenzotriazoles such as **13** (Equation (6)) as stable alternatives to imidoyl halides, and shown that they react with sodium thiolates to give thioimides in good yield <1995H231>. The method has subsequently been extended to the preparation of α -amino thioacetimidates <2001JOC2865>.



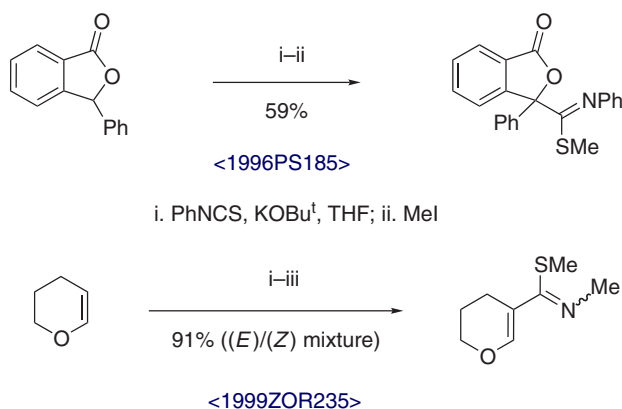
There have been a limited number of reports on the preparation of thioimides from the reaction of imidoyl derivatives containing oxygen leaving groups at the imidoyl carbon, e.g., the displacement of phenol from aryl imidates with thiols <1976CB922>. Thioiminium triflate salts **15** have been prepared by the reaction of aromatic and aliphatic thiols with iminium salts **14** derived from the *in situ* reaction of tertiary amides with trifluoromethanesulfonic anhydride

(Equation (7)) <1998TL711>. Thioimidic esters have also been prepared by the reaction of thioimidoyl chlorides <1977S626, 1985JOC771, 1989CL1261> and chloro thioformamidinium salts <1974AJC2635> with carbon nucleophiles.



5.18.1.2.4 Thioimidic esters from heterocumulenes, isothiocyanates, and ketenimines

The addition of carbon nucleophiles to the heterocumulene system of alkyl or aryl isothiocyanates, followed by subsequent *S*-alkylation of the primarily formed addition products, is an established method to prepare thioimides (Scheme 2) <1995COFGT(5)725>. A variety of carbon nucleophiles have been employed, including alkyl- <1984T1573>, aryl- <1996T12165>, alkenyl- <1999ZOR235, 2000T3373>, and allenyllithiums <1983CI(L)391, 1997TL6905, 1997ZOR1435, 1998TL1995, 1998TL2409, 1999EJO2663>, Grignard reagents <1978TL2715, 2000ZOR1146>, stabilized carbanions <1985S172, 1988LA471, 1996PS185, 2001JOC2850>, and ketene *O,N*-acetals <1974CB3589>. Intramolecular variants of this reaction are also known as a method to prepare thiolactim ethers <1981JCS(P1)40>. *N*-Arylthioimides have been prepared by the reaction of alkyl and aryl thiols with ketenimines <1954RTC695, 1971CJC1792, 1973JOC3951> and phosphacumulene ylides <1980CB912>.



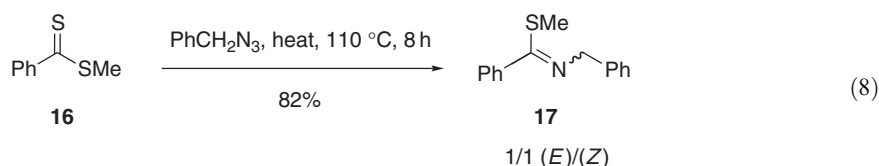
Scheme 2

5.18.1.2.5 Thioimidic esters from thioimidic esters

The methods of transformation of thioimidic esters and thiolactim ethers into more highly substituted derivatives were reviewed in chapter 5.18.1.2 in <1995COFGT(5)725>. Metallation of thioimides and subsequent alkylation at nitrogen <1984T1573> or at the carbon alpha to either the imido group <1984T1573, 1991JCS9(P1)2269> or sulfur atom <1980JA7929> has been used to prepare derivatives. The alkylation selectivity is dependent on the substrate and reaction conditions. Thioimidic esters have also been prepared by modification of functional groups, which are bound to the nitrogen of the thioimide group <1987JOC2523>, by thiol exchange reactions <1972JCS(P1)2326>, and by the *N*-alkylation of thioimides with (trimethylsilyl)methyl triflate <1989TL4443>.

5.18.1.2.6 Thioimidic esters by miscellaneous methods

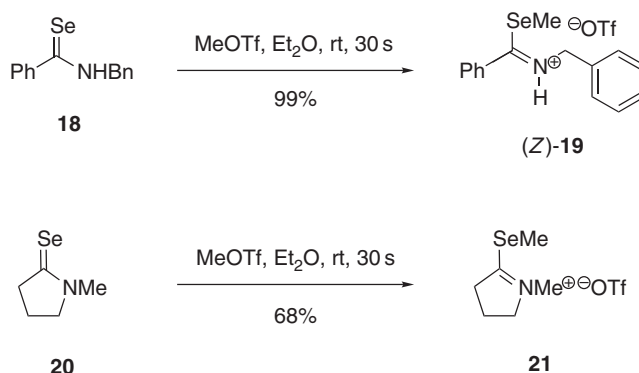
Some specific preparations of thioimidic esters and thiolactam ethers were described prior to 1992 and were reviewed in chapter 5.18.1.2.6 <1995COFGT(5)725>. These include the Beckmann rearrangement of oxime sulfonates in the presence of thiolates <1983JA2831>, the rearrangement of 1-azido-1-methyl-thiocycloalkanes <1980JA7929>, the sulfenylation of benzil dianils with 2,4-bis(phenylthio)-1,3-dithia-2,4-diphosphetane-2,4-disulfide <1992PS(66)87>, and the oxidation of *S,N*-acetals with lead tetraacetate or nitrosyl chloride <1988JCS(P1)169, 1987S547, 1988T1667>. There are two reports on the preparation of thioimides from dithioesters using *N*-sulfinyldimethylammonium tetrafluoroborate <1981LA65> and organic azides <1995HCA1499, 2001PJC975>, processes which formally involve the formation of a C—N double bond and loss of one sulfur atom from the dithioester. In the latter example, reaction of methyl dithiobenzoate **16** with benzyl azide gave the thioimide **17** in 82% yield after distillation (Equation (8)) <2001PJC975>. The mechanism of this transformation has been postulated to involve a 1,3-dipolar cycloaddition between the azide and dithioester followed by extrusion of nitrogen and sulfur.



5.18.1.3 Selenoimidic and Telluroimidic Esters, $\text{R}^1\text{C}(\text{NR}^2)\text{SeR}^3$ and $\text{R}^1\text{C}(\text{NR}^2)\text{TeR}^3$

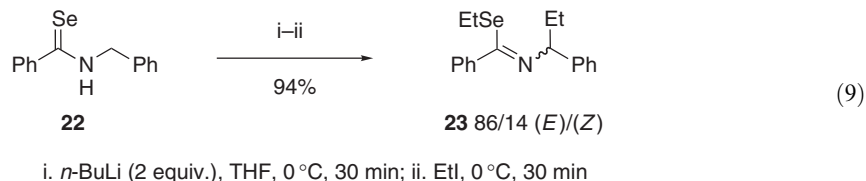
5.18.1.3.1 Selenoimidic esters from selenoamides, imidoyl derivatives, and isoselenocyanates

The methods of preparation of selenoimidic esters <B-1986MI005, 1995COFGT(5)725>, also called selenoimides, are analogous to those used for the corresponding thioimidic esters, but with fewer examples reflecting their greater reactivity. Selenoimides are potentially useful compounds in synthetic organic chemistry as precursors of imidoyl radicals. Methods for the preparation of selenoimides include the alkylation of selenoamides with alkyl halides <1966ACS597, 1975CC617, 1976CB956, 1996CC1809>, the reaction of imidoyl chlorides with selenolate anions <1976CB956, 1980JOC80>, and the reaction of imides with selenols <1976CB956>. Beckmann rearrangement of oxime mesylates with organoaluminum selenolates has been used to prepare cyclic and acyclic selenoimides <1983JA2831>. Recently, Mutoh and Murai have reported the preparation and isolation of selenoiminium salts **19** and **21** for the first time by reacting secondary **18** and tertiary selenoamides and a selenolactam **20** with methyl triflate at room temperature in diethyl ether (Scheme 3) <2003OL1361>. The salts **19** and **21** could be isolated in high yields by filtration (11 examples, yields 68–99%) were stable and could be stored under air at room temperature. Secondary selenoamides **18** gave selenoiminium salts **19** selectively as (*Z*)-isomers. Stereoisomers with respect to the C—Se bond were observed in the methylation of some of the tertiary selenoamides suggesting significant double-bond character.

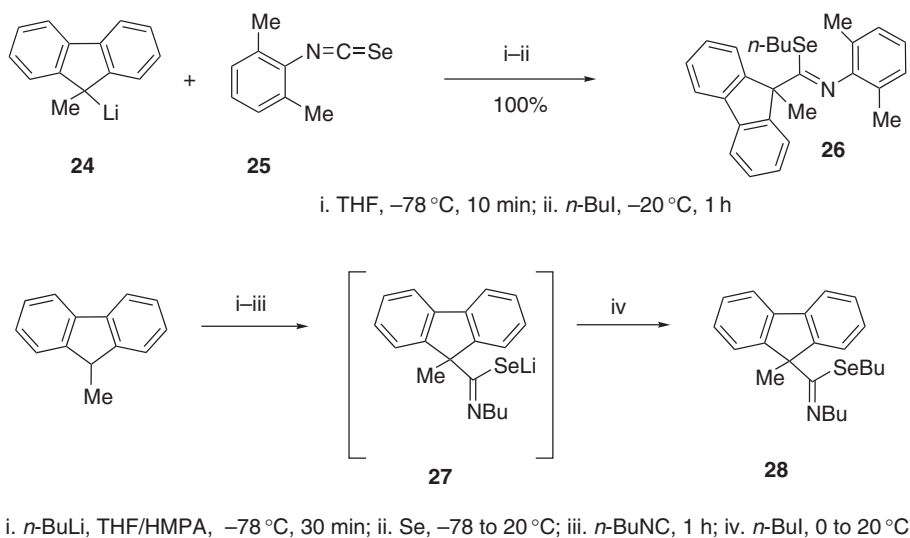


Scheme 3

Deprotonation of *N*-benzyl selenoamide **22** with 2 equiv. of *n*-BuLi to form the dianion, followed by trapping with 2 equiv. of ethyl iodide, gave the selenoimide **23** in 94% yield ((*E*)/(*Z*) = 86/14) (Equation (9)) <2002OL1407>. The use of 2 equiv. of base and 1 equiv. of ethyl iodide resulted in selective *C*-ethylation at the benzylic position.

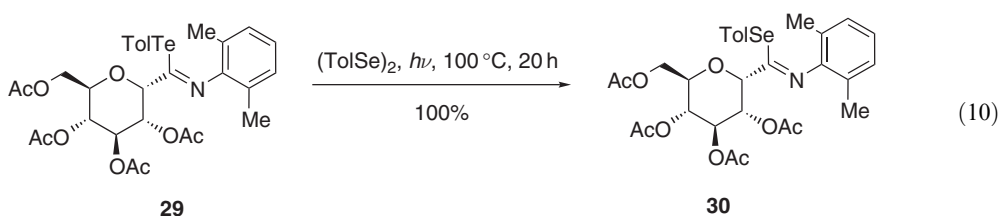


Selenoimides have also been prepared by the low-temperature reaction of 2,6-xylyl isoselenocyanate **25** at carbon with organolithiums followed by trapping with 1-iodobutane (Scheme 4) <1996T12165, B-1999MI006>. The reaction affords products resulting from attack at carbon or selenium, depending on the nature of the organolithium used. Thermodynamically more stable carbanions favor attack at carbon to produce selenoimides. For example, 9-methylfluorenyllithium **24** gave the selenoimide **26** in high yield. A related reaction involving selenoimidoylation of organolithiums with selenium and aryl or alkyl isocyanides has been reported to give selenoimide **28** after trapping the intermediate lithium selenocarboximides **27** with 1-iodobutane (13 examples, yields 29–92%) (Scheme 4) <2000JOC5022>. Selenoimides were obtained as single stereoisomers. In four examples, the (*Z*)-configuration was confirmed by NOE experiments or X-ray analysis.

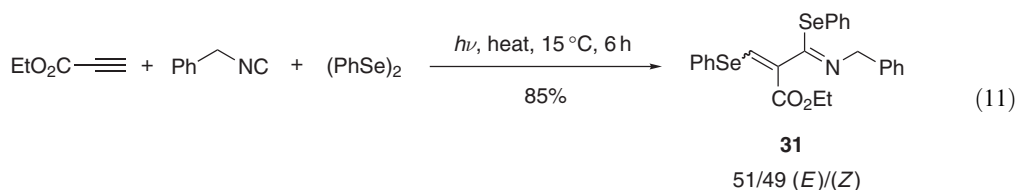


Scheme 4

Two transformations have been reported to give selenoimides <1999TL2347, 2001TL2317>, which have been postulated to involve the generation of imidoyl radicals followed by trapping with diselenides. Thermolysis of the telluroimidoylglycoside **29** in the presence of *p*-tolyl diselenide at 100 °C under UV irradiation gave the selenoimide **30** in quantitative yield (Equation (10)) <1999TL2347>.

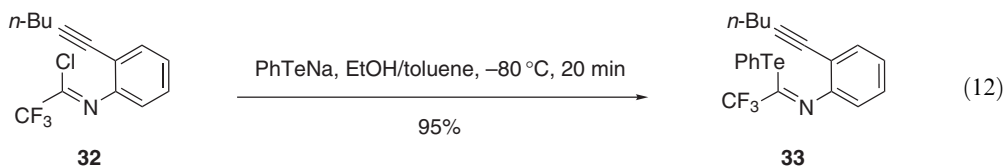


In a three-component coupling reaction, selenoimide **31** was obtained in 85% yield from the photochemical induced reaction of ethyl propiolate, benzyl isocyanide and diphenyl disulfide (Equation (11)) <2001TL2317>.

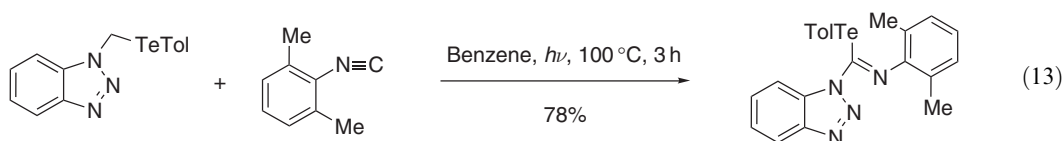


5.18.1.3.2 Telluroimidic esters, $R^1\text{C}(\text{NR}^2)\text{TeR}^3$

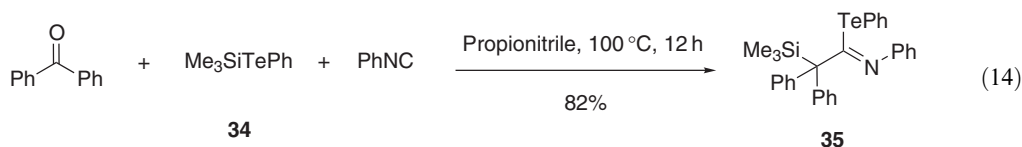
There have been a limited number of reports on the preparation of telluroimides. A series of *N*-aryltellurotrifluoroacetimidates has been prepared by the reaction of sodium phenyltelluroate with imidoyl chloride **32** (Equation (12)) <1993TL7933>. The telluroimide **33** was isolated in high yield (95%; four examples, yields 91–95%) and was stable to purification by silica chromatography.



Recent advances in the radical mediated group-transfer imidoylation of organotellurium compounds with isonitriles, has greatly increased the number of reported examples of this class of compounds (Equation (13)) <1999TL2347, 2001JA3697>. The method involves the photochemical or thermal generation of carbon-centered radicals from organotellurium compounds, which add to the C–N bond of isonitriles. The resulting imidoyl radicals undergo homolytic substitution reactions with the starting organotellurium compounds to give the product telluroimides and regenerate the carbon radical. Telluroimides have been prepared in moderate-to-high yields (23 examples, 40–90%) from alkyl, benzyl, α -amino, α -alkoxy, α -carboalkoxy, 1-glycosyl and acyl tellurides <2000TL7517, 2001TL5061>, and either phenyl or 2,6-dimethylphenylisonitrile. The use of aryl isonitriles is important to prevent β -fragmentation of the intermediate imidoyl radical to give nitriles. In all cases, a single (*Z*)-stereoisomer was obtained and in the case of telluroglycoside α -anomers were formed selectively.

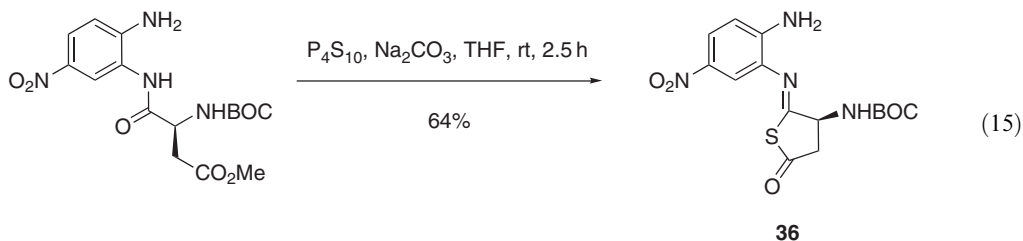


In a related process, a novel three-component coupling reaction involving phenyl trimethylsilyl telluride **34**, carbonyl compounds, and phenyl isocyanide has been reported to give telluroimides **35** (Equation (14)) <2000AG(E)3669>. The tellurium atom plays a crucial role in this reaction, the use of the corresponding silyl selenide or sulfide led to recovery of the starting materials. In an analogous process, α -aminotelluroimides have been prepared by the silyl telluride-mediated coupling of imines and isonitriles <2003AG(E)117>.



5.18.1.4 Other Thioimidic Derivatives Where R^2 is Carbon Based, $R^1C(NR)SR^2$ (e.g., $R^2 = COR^3$)

The acylation of primary and secondary thioamides with acyl chlorides in general leads to the formation of the more stable *N*-acylthioamides. *S*-Acyl derivatives have been obtained with certain substrates and experimental conditions <1985PS(25)63, 1985H2489, 1987JOC2523>. The cyclic thioimide **36** containing an *S*-acyl group as part of the ring has also been prepared by the intramolecular acylation of a thioamide generated *in situ* (Equation (15)) <1996JOC9045>.



5.18.1.5 *S*-Imidothio Sulfenyl Halides, $R^1C(NR^2)SX$

No further advances have occurred in this area since the publication of chapter 5.18.1.5 in <1995COFGT(5)725>. Tertiary thioamides react with bromine to give adducts which are unstable to moisture and storage at room temperature <1982SC865, 1984JCR(S)404, 1984JCS(P1)897>. The structures of the adducts have been investigated by ^{13}C NMR spectroscopy <1984OMR724>.

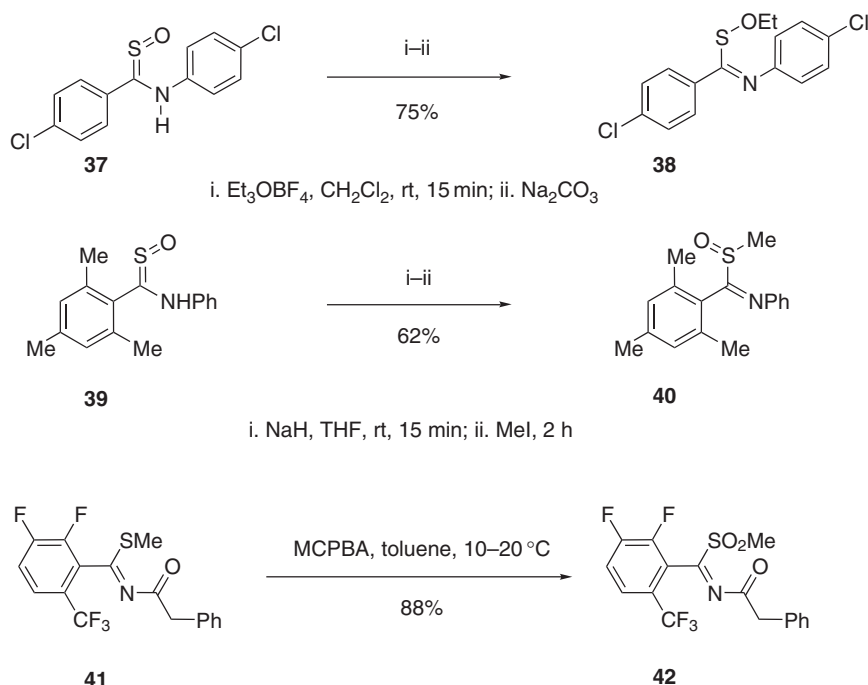
5.18.1.6 *S*-Imidothio Sulfenates, *S*-Imidothio Sulfoxides, and *S*-Imidothio Sulfones— $R^1C(NR^2)SOR^3$, $R^1C(NR^2)S(O)R^3$, and $R^1C(NR^2)SO_2R^3$

Selective *O*-alkylation of thioamide *S*-oxides **37** with triethyloxonium tetrafluoroborate followed by treatment with base lead to *S*-imidothio sulfenates **38** (Scheme 5) <1984RTC342>. These compounds have sufficient stability to be isolated and purified by silica chromatography. The structure of **38** was unambiguously established by an X-ray diffraction analysis. In the solid state the (*Z*)-isomer preferentially crystallizes. However, in solution a 4:1 mixture of (*Z*):(*E*)-isomers was observed by ^1H NMR spectroscopy. A limited number of the isomeric *S*-imidothio sulfoxides **40** have been prepared by the deprotonation of secondary thioamide *S*-oxides **39** with sodium hydride, followed by *S*-alkylation with alkyl halides (Scheme 5) <1984RTC342>. The *S*-imidothio sulfoxide products are sensitive to hydrolysis to the corresponding amides. Stability can be enhanced by introducing sterically hindered substituents to decrease the susceptibility of the imidothio carbon to nucleophilic attack. An *S*-imidothio sulfone derivative **42** has been prepared by the oxidation of *N*-acyl thioimide **41** with 3-chloroperbenzoic acid (Scheme 5) <1998JAP10273480>.

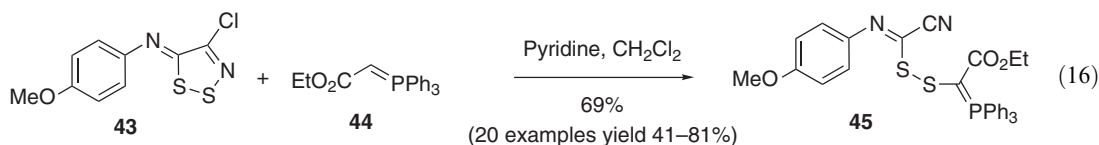
5.18.1.7 Imidothio Disulfides and Diselenides, $R^1C(NR^2)SSR^3$ and $R^1C(NR^2)SeSeR^3$

5.18.1.7.1 Imidothio disulfides

The methods of preparation of imidothio disulfides were reviewed in chapter 5.18.1.7 of <1995COFGT(5)565>. There are two principal methods of preparation of this class of compounds, which involve the reaction of thioamides with sulfonylating agents <1969LA(727)22, 1969LA(727)50, 1973LA462, 1974JCS(P1)853, 1991JOC6697> or in the case of symmetrical disulfides, oxidizing reagents <1961CRV45, 1967JOC392>. Some specific preparations of imidothio disulfides **45** (Equation (16)) have been described including the thermal Cope rearrangement of bis(thiobenzoyl)-*N*-methylhydrazine <1990ZOR214> and the reaction of 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles **43** with primary and secondary amines <1993JOC7001> or stabilized phosphoranes **44** <1996TL869>.

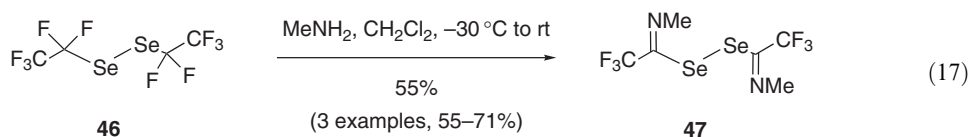


Scheme 5



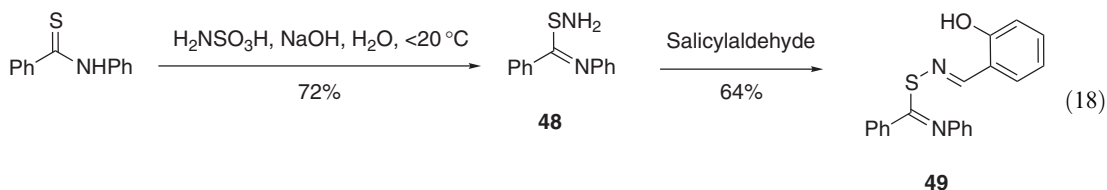
5.18.1.7.2 Imidoacyl diselenides

Bis(perfluoroethyl)diselenides **46** react with primary amines to give symmetrical imidoacyl diselenides **47** (Equation (17)) <1997CB913>. The structures of the products were assigned based on spectroscopic methods and on an X-ray diffraction study of the *N*-*t*-butyl derivative. Selenoamides were the major products of the reaction of diselenide **46** with secondary amines. Imidoacyl diselenides were also isolated as minor by-products (17–27% yields) from the reaction of *t*-butylamine with pentafluoroethylselenol, trifluoromethylselenocarbonyl fluoride, and a polymeric derivative <1997CB913>.



5.18.1.8 *S*-Imidoacyl Sulfenamides and Related Structures, $\text{R}^1\text{C}(\text{NR}^2)\text{SNR}^3\text{R}^4$ and $\text{R}^1\text{C}(\text{NR}^2)\text{SN}=\text{CR}^3$

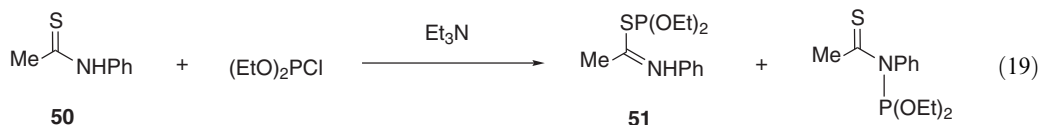
There are two methods available for the preparation of this class of compound which were reviewed in chapter 5.18.1.8 of <1995COFGT(5)725>. *S*-Imidoacyl sulfenamides **48** and their derivatives have been prepared by the reaction of primary and secondary thioamides with electrophilic aminating reagents, including *N*-chloroamines <1971LA(753)169, 2000USP6017947>, the sodium salt of hydroxylamine-*O*-sulfonic acid <1971USP3631071, 1972JOC3820>, and diethyl azodicarboxylate (Equation (18)) <1977CC220>.



The *S*-imidoyl sulfenamides can show instability and have been reacted with isocyanates or aldehydes to form stable urea and imine derivatives **49** <1972JOC3820>. In an alternative approach involving nucleophilic nitrogen, the reaction of *S*-imidoyl sulfenates with primary and secondary amines has been used to prepare *S*-imidoyl sulfenamides <1984RTC342>.

5.18.1.9 Imidoylthiophosphorus Derivatives, $R^1C(NR^2)SP$

The methods of preparation of imidoylthiophosphorus derivatives were reviewed in chapter 5.18.1.7 of <1995COFGT(5)725>, and no further advances have occurred since. The phosphorus(III) compounds, *S*-imidoylthiophosphites and *S*-imidoylthiophosphoramidate, have been prepared by the reaction of thioamides with phosphinyl chlorides (Equation (19)) <1985ZOB559, 1986ZOB1654>. For example, reaction of thioamide **50** with diethyl chlorophosphite gave an equal proportion of the *S*-imidoylthiophosphite **51** and *N*-phosphorylated analog (Equation (19)). The phosphorus(V) compounds, *S*-imidoyldithiophosphates, thiophosphates, and dithiophosphinates have been prepared either by the addition of dialkyl dithiophosphates to nitriles <1973DOK(211)113> and aryl isonitriles <1977JGU916> or the reaction of imidoyl chlorides with the salts of dithiophosphoric, thiophosphoric, or dithiophosphinic acids <1962USP3053876, 1979JGU2323, 1987EUP243970, 1990JGU1389>. The preparation of the corresponding *S*-imidoylthioarsenic, antimony, and bismuth derivatives has not been reported.



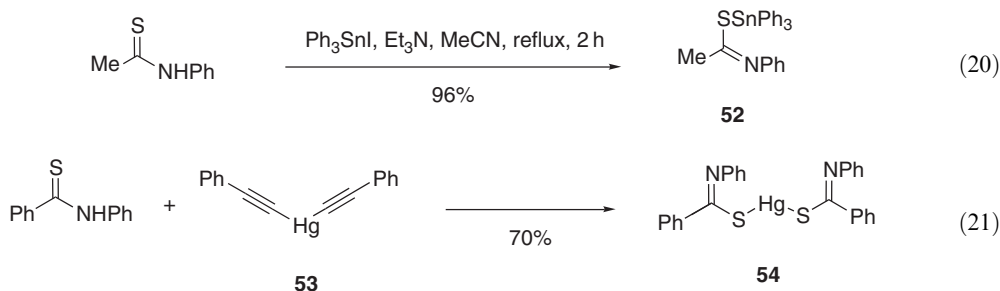
5.18.1.10 Imidoylthiometalloid Derivatives, $R^1C(NR^2)SSi$ and $R^1C(NR^2)SB$

The methods of preparation of imidoylthiometalloid derivatives were reviewed in chapter 5.18.1.8 of <1995COFGT(5)725>. Silylation of metallated secondary thioamides leads to an equilibrium mixture of the *S*- and *N*-silylated isomeric compounds <1975LA1808>. An analogous equilibrium has been reported for the reaction of thioamides with dibromophenylborane <1977JOM(141)241>.

5.18.1.11 Imidoylthiometals and Imidoylselenometals, $R^1C(NR^2)S$ Metal and $R^1C(NR^2)Se$ Metal

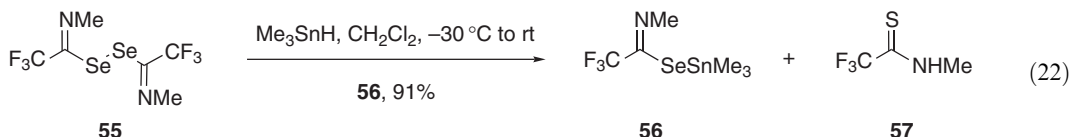
5.18.1.11.1 *S*-Imidoyl tin and mercury derivatives, $R^1C(NR^2)SSnR_3$ and $R^1C(NR^2)SHgSC(NR^2)CR^1$

Imidoylthiometals are known where the metal is tin or mercury. *S*-Stannyl thioimides **52** have been prepared by the reaction of secondary thioamides with trialkyl or triaryl tin halides (Equation (20)) <1975JOM(97)39, 1989JA1886>, the reaction of (stannylethynyl)amines with isothiocyanates <1978TL1951, 1985LA1669> and the reaction of Grignard reagents with phenylisothiocyanate followed by trapping with trialkyltin halides <1976JOM253>. The symmetrical mercury derivative **54** has been prepared by the reaction of mercury-bis(phenylalkyne) **53** with thiobenzanilide (Equation (21)) <1970CB32>.



5.18.1.11.2 Se-Imidoyl tin derivatives, $R^1\text{C}(\text{NR}^2)\text{SeSnR}_3$

The Se-imidoyl tin derivatives **56** have been prepared in good yields from a Se—Se bond cleavage reaction of imidoyl diselenide **55** with trimethyltin hydride (Equation (22)) <1997CB913>. The products are obtained as oils after removal of the co-product selenoamides **57** by vacuum distillation.



REFERENCES

- 1954RTC695 R. Dijkstra, H. J. Backer, *Recl. Trav. Chim. Pays-Bas* **1954**, 73, 695–703.
 1961CRV45 R. N. Hurd, G. DeLaMater, *Chem. Rev.* **1961**, 61, 45–86.
 1961CRV179 R. Roger, D. G. Neilson, *Chem. Rev.* **1961**, 61, 179–211.
 1962JOC2858 H. C. Brown, R. Pater, *J. Org. Chem.* **1962**, 27, 2858–2863.
 1962USP3053876 Malz, H.; Kuehle, E.; Bayer (Bayer A.G.), O. US Patent 3 053 876 (1962) (*Chem. Abstr.*, 1963, 58, 4470).
 1964LA(676)114 W. Ried, E. Schmidt, *Liebigs Ann. Chem.* **1964**, 676, 114–120.
 1966ACS597 K. A. Jensen, P. H. Nielson, *Acta Chem. Scand.* **1966**, 20, 597–629.
 1967JOC392 J. R. Schaeffer, C. T. Goodhue, H. A. Risley, R. E. Stevens, *J. Org. Chem.* **1967**, 32, 392–395.
 1968IZV576 I. A. Ivanova, B. P. Fedorov, F. M. Stoyanovich, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1968**, 3, 576–583. (*Chem. Abstr.* **1969**, 69, 96 579).
 1969LA(727)22 W. Walter, P. Hell, *Liebigs Ann. Chem.* **1969**, 727, 22–34.
 1969LA(727)50 W. Walter, P. Hell, *Liebigs Ann. Chem.* **1969**, 727, 50–60.
 1970CB32 W. Ried, W. Merkel, R. Oxenius, *Chem. Ber.* **1970**, 103, 32–36.
 1970JOC2118 T. Saegusa, S. Kobayashi, Y. Ito, *J. Org. Chem.* **1970**, 35, 2118–2121.
 1970ZOR805 E. P. Nesynov, M. M. Besprozvannays, P. S. Pel'kis, *Zh. Org. Khim.* **1970**, 6, 805–809. (*Chem. Abstr.* **1970**, 73, 14 400).
 1971CJC1792 R. Raap, *Can. J. Chem.* **1971**, 49, 1792–1798.
 1971LA(753)169 W. Walter, C. O. Meese, *Liebigs Ann. Chem.* **1971**, 753, 169–186.
 1971USP3631071 Raash, M.S. US Patent, 3 631 071 (1971) (*Chem. Abstr.*, 1971, 76, 1 114 541).
 1972JCS(P1)2326 M. D. Bachi, M. Rothfield, *J. Chem. Soc., Perkin Trans. 1* **1972**, 2326–2331.
 1972JOC3820 M. S. Raash, *J. Org. Chem.* **1972**, 27, 3820–3823.
 B-1972MI001 S. R. Sandler, W. Karo, in *Organic Functional Group Preparations*, E. C. Taylor, Ed., Vol. 9, Academic Press, New York, **1972**, pp. 314.
 1973DOK(211)113 A. N. Pudovik, R. A. Cherkasov, T. M. Sudokova, G. I. Evstafev, *Dokl. Akad. Nauk SSSR* **1973**, 211, 113–115. (*Chem. Abstr.* **1973**, 79, 92 330).
 1973JOC2242 S. L. Razniak, E. M. Flagg, F. Siebenthal, *J. Org. Chem.* **1973**, 38, 2242.
 1973JOC3951 M. W. Barker, S. C. Lauderdale, J. R. West, *J. Org. Chem.* **1973**, 38, 3951–3953.
 1973LA462 W. Walter, H. Meyer, *Liebigs Ann. Chem.* **1973**, 462–475.
 1974AJC2635 R. L. N. Harris, *Aust. J. Chem.* **1974**, 27, 2635–2643.
 1974CB3589 E. Schaumann, S. Sieveking, W. Walter, *Chem. Ber.* **1974**, 107, 3589–3601.
 1974JCS(P1)853 J. Almog, D. H. R. Barton, P. D. Magnus, R. K. Norris, *J. Chem. Soc., Perkin Trans. 1* **1974**, 853–857.
 1975CC617 M. P. Cava, L. E. Saris, *J. Chem. Soc., Chem. Commun.* **1975**, 617–618.
 1975JOM(97)39 E. J. Kupchik, H. E. Hanke, *J. Organomet. Chem.* **1975**, 97, 39–44.
 1975LA1808 W. Walter, H. W. Lueke, J. Voss, *Liebigs Ann. Chem.* **1975**, 1808–1821.
 1975LA1984 B. Zeeh, H. Kiefer, *Liebigs Ann. Chem.* **1975**, 1984–1993.
 B-1975MI002 D. G. Neilson, in *The Chemistry of Amidines and Imidates*, S. Patai, Ed., Vol. 9, Wiley, **1975**, pp. 385.
 1976BSF667 F. Raulin, G. Toupance, *Bull. Soc. Chim. Fr.* **1976**, 667–674.

- 1976CB922 W. Walter, C. O. Meese, *Chem. Ber.* **1976**, 109, 922–946.
 1976CB956 C. O. Meese, W. Walter, H. Mrotzek, H. Mirzai, *Chem. Ber.* **1976**, 109, 956–964.
 1976JOM253 E. W. Abel, I. D. H. Towle, *J. Organomet. Chem.* **1976**, 122, 253–260.
 1976TL143 H. A. Houwing, J. Wildeman, A. M. van Leusen, *Tetrahedron Lett.* **1976**, 17, 143–146.
 1977CC220 M. D. Dowle, *J. Chem. Soc., Chem. Commun.* **1977**, 220–221.
 1977JGU916 A. N. Pudovik, V. I. Nikitina, M. G. Zimin, I. N. Leont'eva, *J. Gen. Chem. USSR (Engl. Trans.)* **1977**, 47, 916–917.
 1977JOM(141)241 W. Maringele, A. Meller, *J. Organomet. Chem.* **1977**, 141, 241–248.
 1977S626 H. Yoshida, T. Ogata, S. Inokawa, *Synthesis* **1977**, 626–628.
 1978TL1951 G. Himbert, W. Schwickerath, *Tetrahedron Lett.* **1978**, 1951–1954.
 1978TL2715 P. Gosselin, S. Masson, A. Thuillier, *Tetrahedron Lett.* **1978**, 30, 2715–2716.
 1979JGU2323 M. G. Zimin, M. M. Afanasev, A. N. Pudovik, *J. Gen. Chem. USSR (Engl. Trans.)* **1979**, 49, 2323–2324.
 B-1979MI003 W. Kantlehner, in *Advances in Organic Chemistry*, H. Bohme, H. G. Viehe, Eds., Vol. 9, Wiley, **1979**, pp. 279.
 1979TL4671 H. Nishiyama, H. Nagase, K. Ohno, *Tetrahedron Lett.* **1979**, 20, 4671–4674.
 1980CB912 H. J. Bestmann, G. Schmid, D. Sandmeier, *Chem. Ber.* **1980**, 113, 912–918.
 1980CC1151 B. L. Booth, K. O. Jibodu, M. F. Proenca, *J. Chem. Soc., Chem. Commun.* **1980**, 1151–1153.
 1980JA7929 B. M. Trost, M. Vaultier, M. L. Santiago, *J. Am. Chem. Soc.* **1980**, 102, 7929–7932.
 1980JOC80 M. R. Detty, G. P. Wood, *J. Org. Chem.* **1980**, 45, 80–89.
 1981JCS(P1)40 R. C. Cambie, D. Chambers, P. S. Rutledge, P. D. Woodgate, *J. Chem. Soc., Perkin Trans. 1* **1981**, 40–51.
 1981LA65 M. A. Perez, M. Roessert, G. Kresze, *Liebigs Ann. Chem.* **1981**, 65–69.
 1981MI11 B. D. Podolov, B. Bogdanov, *Glasnik Hemijskog Drustra Beograd* **1981**, 46, 11–15. (*Chem. Abstr.* **1981**, 95, 61 700).
 1982IZV2121 I. I. Kandror, I. O. Bragina, *Iz. Akad. Nauk SSR, Ser. Khim.* **1982**, 9, 2121–2125. (*Chem. Abstr.* **1983**, 98, 16 383).
 1982SC865 A. Corsaro, A. Compagnini, M. Tarantello, S. Barbaro, G. Purrello, *Synth. Commun.* **1982**, 12, 865–860.
 1983CI(L)391 G. Darnault, M. Saquet, A. Thuillier, *Chem. Ind. (London)* **1983**, 391–392.
 1983JA2831 K. Maruoka, T. Miyazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori, H. Yamamoto, *J. Am. Chem. Soc.* **1983**, 105, 2831–2843.
 1983JCS(P1)1067 B. L. Booth, K. O. Jibodu, M. F. J. R. P. Proenca, *J. Chem. Soc., Perkin Trans. 1* **1983**, 1067–1073.
 1983JOC1544 D. Anderson, P. Zinke, S. L. Razniak, *J. Org. Chem.* **1983**, 48, 1544–1547.
 1983SC753 M. A. Casadei, B. Di Rienzo, *Synth. Commun.* **1983**, 13, 753–759.
 1983TL3255 Y. Ishida, S. Sasatani, K. Maruoka, H. Yamamoto, *Tetrahedron Lett.* **1983**, 24, 3255–3258.
 1983TL5889 D. H. R. Barton, G. Kretzschmar, *Tetrahedron Lett.* **1983**, 24, 5889–5892.
 1984JCR(S)404 A. Corsaro, A. Compagnini, G. Perrini, *J. Chem. Res. (S)* **1984**, 12, 404–405.
 1984JCS(P1)897 A. Corsaro, A. Compagnini, G. Perrini, G. Purrello, *J. Chem. Soc., Perkin Trans. 1* **1984**, 897–900.
 1984OMR724 U. Chiacchio, A. Corsaro, F. A. Bottino, *Org. Magn. Reson.* **1984**, 22, 724–726.
 1984RTC342 B. G. Lenz, B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **1984**, 103, 342–347.
 1984T1075 G. Morel, E. Marchand, K. H. Nguyen Thi, A. Foucaud, *Tetrahedron* **1984**, 40, 1075–1083.
 1984T1573 S. Masson, V. Mothes, A. Thuillier, *Tetrahedron* **1984**, 40, 1573–1580.
 1985BCJ2721 Y. Inoue, M. Taguchi, H. Hashimoto, *Bull. Chem. Soc. Jpn.* **1985**, 58, 2721–2722.
 1985H2489 O. Tsuge, S. Kanemasa, T. Yamada, K. Matsuda, *Heterocycles* **1985**, 23, 2489–2492.
 1985HOU(E5/2)931 W. Bauer, K. Kuhlein, *Methoden Org. Chem. (Houben-Weyl)* **1985**, E5/2, 931.
 1985JOC771 G. Morel, E. Marchand, A. Foucaud, *J. Org. Chem.* **1985**, 50, 771–778.
 1985JOC4415 N. J. Turro, Y. Cha, I. R. Gould, A. Padwa, J. R. Gasdaska, M. Tomas, *J. Org. Chem.* **1985**, 50, 4415–4417.
 1985LA1669 G. Himbert, *Liebigs Ann. Chem.* **1985**, 1669–1678.
 1985PS(25)63 W. Walter, C. R. Saha, *Phosphorus Sulfur* **1985**, 25, 63–77.
 1985S172 E. Schaumann, S. Fittkau, *Synthesis* **1985**, 172–174.
 1985ZOB559 V. A. Al'fonsov, D. A. Pudovik, E. S. Batyeva, A. N. Pudovik, *Zh. Org. Khim.* **1985**, 55, 559–562. (*Chem. Abstr.* **1985**, 103, 105 067).
 1986IJC(B)357 P. D. Baruah, G. Roy, R. Satsangi, M. P. Mahajan, *Indian J. Chem., Sect. B* **1986**, 25, 357–359.
 1986JCS(P1)39 D. H. R. Barton, D. Crich, G. Kretzschmar, *J. Chem. Soc., Perkin Trans. 1* **1986**, 39–53.
 B-1986MI005 C. Paulmier, in *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Oxford, **1986**, pp. 77.
 1986ZOB1654 D. M. Malenko, A. D. Sinita, *Zh. Obshch. Khim.* **1986**, 56, 1654–1655. (*Chem. Abstr.* **1987**, 106, 176 507).
 1987EUP243970 Baker, D. R.; Brownell, K. H. Eur. Patent 243 970 (1987) (*Chem. Abstr.* **1988**, 108, 94 402).
 1987JOC2523 O. Tsuge, S. Kanemasa, T. Yamada, K. Matsuda, *J. Org. Chem.* **1987**, 52, 2523–2530.
 1987S547 D. Pooranchand, H. Ila, H. Junjappa, *Synthesis* **1987**, 547–550.
 1988JCS(P1)169 J. N. Vishwakarma, A. Thomas, S. Apparao, H. Ila, H. Junjappa, *J. Chem. Soc., Perkin Trans. 1* **1988**, 169–173.
 1988LA471 C. Bruckner, B. Suchland, H. Reissig, *Liebigs Ann. Chem.* **1988**, 471–473.
 1988T1667 A. Thomas, J. N. Vishwakarma, S. Apparao, H. Ila, H. Junjappa, *Tetrahedron* **1988**, 44, 1667–1672.
 1988T3501 D. H. R. Barton, N. Ozbalik, B. Vacher, *Tetrahedron* **1988**, 44, 3501–3512.
 1989CL1261 Y. Ito, M. Inouye, M. Murakami, *Chem. Lett.* **1989**, 1261–1264.
 1989JA1886 M. D. Bachi, D. Denenmark, *J. Am. Chem. Soc.* **1989**, 111, 1886–1888.
 1989JCS(P1)265 D. M. Arnott, P. J. Harrison, G. B. Henderson, Z. Sheng, F. J. Leeper, A. R. Battersby, *J. Chem. Soc., Perkin Trans. 1* **1989**, 265–278.

- 1989TL4443 A. I. D. Alanine, C. W. G. Fishwick, *Tetrahedron Lett.* **1989**, 30, 4443–4446.
 1990JGU1389 P. P. Onysko, E. A. Suvalova, T. I. Chudakova, A. D. Sinita, *J. Gen. Chem. USSR (Engl. Transl.)* **1990**, 60, 1389–1391.
 1990KGS995 B. B. Aleksandrov, M. Y. Dormidontov, V. S. Shklyayev, Y. V. Shklyayev, *Khim. Geterotsikl. Soedin.* **1990**, 7, 995–996. (*Chem. Abstr.* **1991**, 114, 122 007).
 1990SC71 M. Adachi, T. Sugawara, *Synth. Commun.* **1990**, 20, 71–84.
 1990ZC320 G. Barnikow, J. Lehner, *Z. Chem.* **1990**, 30, 320.
 1990ZOR214 N. M. Przheval'skii, V. N. Drozd, *Zh. Org. Khim.* **1990**, 26, 214–215.
 1991COS(6)536 W. Kantlehner, *Comp. Org. Synth.* **1991**, 6, 536.
 1991JCS(P1)2269 N. Lage, S. Masson, A. Thuillier, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2269–2270.
 1991JOC6697 D. H. R. Barton, R. H. Hesse, A. C. O'Sullivan, M. M. Pechet, *J. Org. Chem.* **1991**, 56, 6697–6702.
 B-1991MI004 D. G. Neilson, in *The Chemistry of Amidines and Imidates*, S. Patai, Z. Rappoport, Eds., Vol. 2, Wiley, **1991**, pp. 425.
 1992PS(66)87 T. S. Hafez, *Phosphorus Sulfur* **1992**, 66, 87–93.
 1992TL5117 T. W. Hart, D. Guillochon, G. Perrier, B. W. Sharp, B. Vacher, *Tetrahedron Lett.* **1992**, 33, 5117–5120.
 1993JOC7001 H. Lee, K. Kim, *J. Org. Chem.* **1993**, 58, 7001–7008.
 1993TL7933 Y. Ueda, H. Watanabe, J. Uemura, K. Uneyama, *Tetrahedron Lett.* **1993**, 34, 7933–7934.
 1994JOC7752 M. D. Bachi, A. Balanov, N. Bar-Ner, *J. Org. Chem.* **1994**, 59, 7752–7758.
 1995COFGT(5)725 S. Challenger, Iminoacyl functions linked to chalcogens other than oxygen, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 725–740.
 1995H231 A. R. Katritzky, C. V. Stevens, G. Zhang, J. Jiang, N. De Kimpe, *Heterocycles* **1995**, 40, 231–240.
 1995HCA1499 G. Mloston, J. Romanski, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1995**, 78, 1499–1510.
 1995JOC2692 D. C. Smith, P. L. Fuchs, *J. Org. Chem.* **1995**, 60, 2692–2703.
 1995MI4 H. Kim, I. Kwon, J. Lee, *Bull. Korean. Chem. Soc.* **1995**, 16, 4–5.
 1996CC1809 T. Murai, T. Ezaka, T. Kanda, S. Kato, *J. Chem. Soc., Chem. Commun.* **1996**, 1809–1810.
 1996JOC9045 M. A. Shalaby, C. W. Grote, H. Rapoport, *J. Org. Chem.* **1996**, 61, 9045–9048.
 1996PS185 W. Dolling, T. Gildenast, M. Biedermann, H. Hartung, *Phosphorus Sulfur* **1996**, 116, 185–202.
 1996SL60 M. D. Bachi, A. Melman, *Synlett* **1996**, 60–62.
 1996T12165 H. Maeda, N. Kambe, N. Sonoda, S. Fujiwara, T. Shin-Ike, *Tetrahedron* **1996**, 52, 12165–12176.
 1996TL869 H. Lee, K. Kim, *Tetrahedron Lett.* **1996**, 37, 869–872.
 1997CB913 H. Blau, J. Grobe, D. Le Van, B. Krebs, M. Lage, *Chem. Ber.* **1997**, 130, 913–922.
 1997TL6905 L. Brandsma, N. A. Nedolya, H. D. Verkruijsse, N. L. Owen, D. Li, B. A. Trofimov, *Tetrahedron Lett.* **1997**, 38, 6905–6908.
 1997ZOR1435 N. A. Nedolya, L. Brandsma, A. S. H. T. M. Van der Kerk, V. Heerma, E. T. H. G. Luts, A. V. Afonin, R. J. de Lang, B. A. Trofimov, *Zh. Org. Khim.* **1997**, 33, 1435–1436.
 1998JAP10273480 Inoue, T.; Noda, K.; Takahashi, A.; Kuroki, T. Jpn. Patent 10 273 480 (1998)(*Chem. Abstr.* 1998, 129 330 538).
 1998JMC379 J. S. Ward, L. Merritt, D. O. Calligaro, F. P. Bymaster, H. E. Shannon, C. H. Mitch, C. Whitesitt, D. Brunsting, M. J. Sheardown, P. H. Olesen, M. D. B. Swedberg, L. Jeppesen, P. Sauerberg, *J. Med. Chem.* **1998**, 41, 379–392.
 1998JPR367 C. Former, G. Klärner, M. Wagner, K. Mullen, *J. Prakt. Chem.* **1998**, 340, 367–374.
 1998TL711 S. Sforza, A. Dossena, R. Corradini, E. Virgili, R. Marchelli, *Tetrahedron Lett.* **1998**, 39, 711–714.
 1998TL1995 N. A. Nedolya, L. Brandsma, A. H. T. M. van der Kerk, V. Y. Vvedensky, B. A. Trofimov, *Tetrahedron Lett.* **1998**, 39, 1995–1996.
 1998TL2409 N. A. Nedolya, L. Brandsma, O. A. Tarasova, H. D. Verkruijsse, B. A. Trofimov, *Tetrahedron Lett.* **1998**, 39, 2409–2410.
 1999EJO2663 L. Brandsma, N. A. Nedolya, B. A. Trofimov, *Eur. J. Org. Chem.* **1999**, 2663–2664.
 B-1999MI006 S. Fujiwara, N. Kambe, N. Sonoda, in *Organoselenium Chemistry: A Practical Approach*, T. G. Back, Ed., Oxford University Press, **1999**, pp. 233.
 1999S927 R. Baati, V. Gouverneur, C. Mioskowski, *Synthesis* **1999**, 6, 927–929.
 1999TL2347 S. Yamago, H. Miyazoe, R. Goto, J. Yoshida, *Tetrahedron Lett.* **1999**, 40, 2347–2350.
 1999ZOR235 L. Brandsma, N. A. Nedolya, V. P. Zinov'eva, G. I. Sarapulova, B. A. Trofimov, *Zh. Org. Kim.* **1999**, 35, 235–243.
 2000AG(E)3669 H. Miyazoe, S. Yamago, J. Yoshida, *Angew. Chem., Int. Ed Engl.* **2000**, 39, 3669–3671.
 2000JOC5022 S. Fujiwara, H. Maeda, T. Matsuya, T. Shin-Ike, N. Kambe, N. Sonoda, *J. Org. Chem.* **2000**, 65, 5022–5025.
 2000OM2373 H. Wu, R. Aumann, R. Frohlich, E. Wegelius, P. Saavenketo, *Organometallics* **2000**, 19, 2373–2381.
 2000OL3925 T. Honda, M. Kimura, *Org. Lett.* **2000**, 2, 3925–3927.
 2000T3373 A. Maercker, J. van de Fliert, U. Girreser, *Tetrahedron* **2000**, 56, 3373–3383.
 2000TL7517 S. Yamago, H. Miyazoe, T. Sawazaki, R. Goto, J. Yoshida, *Tetrahedron Lett.* **2000**, 41, 7517–7520.
 2000USP6017947 Brouwer, W. G.; Osika, E. M. US Patent, 6 017 947 (2000)(*Chem. Abstr.*, 2000, 132, 107 868)
 2000ZOR1146 L. L. Dmitrieva, G. I. Sarapulova, L. V. Klyba, A. I. Albanov, V. P. Zinov'yeva, S. V. Tolmachev, N. A. Nedolya, L. Brandsma, *Zh. Org. Khim.* **2000**, 36, 1146–1151.
 2001JA3697 S. Yamago, H. Miyazoe, R. Goto, M. Hashidume, T. Sawazaki, J. Yoshida, *J. Am. Chem. Soc.* **2001**, 123, 3697–3705.
 2001JOC1026 K. Uneyama, H. Ohkura, J. Hao, H. Amii, *J. Org. Chem.* **2001**, 66, 1026–1029.
 2001JOC2850 A. R. Katritzky, X. Wang, A. Denisenko, *J. Org. Chem.* **2001**, 66, 2850–2853.
 2001JOC2865 A. R. Katritzky, M. A. C. Button, S. Busont, *J. Org. Chem.* **2001**, 66, 2865–2868.
 2001OL2753 M. Ochiai, S. Yamamoto, T. Suefuji, D. Chen, *Org. Lett.* **2001**, 3, 2753–2756.
 2001PJC975 G. Mloston, J. Romanski, H. Heimgartner, *Polish J. Chem.* **2001**, 75, 975–982.

- 2001SL388 A. Ursini, M. Delpogetto, G. Guercio, A. Perboni, T. Rossi, *Synlett* **2001**, 388–390.
2001TL2317 A. Ogawa, M. Doi, K. Tsuchii, T. Hirao, *Tetrahedron Lett.* **2001**, 42, 2317–2319.
2001TL5061 S. Yamago, K. Iida, J. Yoshida, *Tetrahedron Lett.* **2001**, 42, 5061–5064.
2001TL6191 C. G. Saluste, R. J. Whitby, M. Furber, *Tetrahedron Lett.* **2001**, 42, 6191–6194.
2002CC2802 M. Ochiai, S. Yamamoto, *J. Chem. Soc., Chem. Commun.* **2002**, 2802–2803.
2002EJO361 H. Wu, R. Aumann, R. Frohlich, E. Wegelius, *Eur. J. Org. Chem.* **2002**, 361–368.
2002EJO2573 D. Ach, V. Reboul, P. Metzner, *Eur. J. Org. Chem.* **2002**, 2573–2586.
2002JOC9304 I. Ghosh, P. A. Jacobi, *J. Org. Chem.* **2002**, 67, 9304–9309.
2002OL1407 T. Murai, H. Aso, S. Kato, *Org. Lett.* **2002**, 4, 1407–1409.
2002TL257 G. Sommen, A. Comel, G. Kirsch, *Tetrahedron Lett.* **2002**, 43, 257–259.
2003AG(E)117 S. Yamago, H. Miyazoe, T. Nakayama, M. Miyoshi, J. Yoshida, *Angew. Chem., Int. Ed. Engl.* **2003**, 42, 117–120.
2003OL901 M. Minozzi, D. Nanni, J. C. Walton, *Org. Lett.* **2003**, 5, 901–904.
2003OL1361 Y. Mutoh, T. Murai, *Org. Lett.* **2003**, 5, 1361–1364.

Biographical sketch

Stephen Challenger was born in Llanhilleth, South Wales. He studied at University College Cardiff, where he obtained a B.Sc. in 1981 and his Ph.D. in 1984 under the direction of Professor G. Procter. After spending two years, as a NATO Postdoctoral fellow in the laboratories of Professor D. A. Evans at Harvard University he returned to the UK to take up a position in the Department of Chemical Research and Development at the Pfizer Global Research and Development Laboratories in Sandwich. His scientific interests include all aspects of process chemistry, in particular enantioselective reactions and the use of transition metal catalysis in synthesis.

5.19

Amidines and *N*-Substituted Amidines

P. J. DUNN

Pfizer Global Research and Development, Sandwich, UK

5.19.1	AMIDINES	656
5.19.1.1	Introduction and General Methods	656
5.19.1.1.1	Introduction	656
5.19.1.1.2	General methods	656
5.19.1.2	Formamidines ($\text{HC}(\text{NR}^1)\text{NR}_2^2$)	658
5.19.1.2.1	Preparation from formamides and thioformamides	658
5.19.1.2.2	Formamidines, prepared by reduction of carbodiimides and ureas	659
5.19.1.2.3	Formamidines from orthoformates, acetals, and amins	659
5.19.1.2.4	Formamidines from 1,3,5-triazine	660
5.19.1.2.5	Formamidines from isonitriles	661
5.19.1.2.6	Formamidines, prepared by miscellaneous methods	661
5.19.1.3	Aliphatic Amidines, $\text{R}^1\text{C}(\text{NR}^2)\text{NR}_3^3$ (R^1 = alkyl, allyl, propargyl, etc.)	662
5.19.1.3.1	Aliphatic amidines from nitriles	662
5.19.1.3.2	Aliphatic amidines from amides	665
5.19.1.3.3	Aliphatic amidines from thioamides and thioimide esters	666
5.19.1.3.4	Aliphatic amidines from orthoesters	667
5.19.1.3.5	Aliphatic amidines from compounds with cumulated double bonds	667
5.19.1.3.6	Aliphatic amidines, prepared by <i>N</i> -alkylation of simpler amidines	667
5.19.1.3.7	Aliphatic amidines, prepared by miscellaneous methods	668
5.19.1.4	Aromatic Amidines, $\text{ArC}(\text{NR}^1)\text{NR}_2^2$	668
5.19.1.4.1	Aromatic amidines from nitriles	668
5.19.1.4.2	Aromatic amidines from amides	671
5.19.1.4.3	Aromatic amidines from thioamides and thioimide esters	671
5.19.1.4.4	Aromatic amidines from compounds with cumulated double bonds	672
5.19.1.5	<i>N</i> -Acyl- and <i>N</i> -Heteroacylamidines	673
5.19.1.5.1	<i>N</i> -Acylamidines, $\text{R}^1\text{C}(\text{NR}^2)\text{NR}^3\text{COR}^4$	673
5.19.1.5.2	<i>N</i> -Thioacylamidines	673
5.19.1.5.3	<i>N</i> -Selenoacylamidines	674
5.19.2	AMIDINE-DERIVED STRUCTURES WITH AN <i>N</i> -HETEROATOM BOND	675
5.19.2.1	<i>N</i> -Haloamidines	675
5.19.2.1.1	<i>N</i> -Fluoroamidines	675
5.19.2.1.2	<i>N</i> -Chloroamidines	675
5.19.2.1.3	<i>N</i> -Bromoamidines	676
5.19.2.1.4	<i>N</i> -Iodoamidines	676
5.19.2.2	<i>N</i> -Imidoylhydroxylamines and Related Structures	676
5.19.2.2.1	<i>N</i> -Imidoylhydroxylamines from hydroxylamine	676
5.19.2.2.2	<i>N</i> -Imidoylhydroxylamines from amines and ammonia	677
5.19.2.2.3	<i>N</i> -Imidoylhydroxylamines by miscellaneous methods	678
5.19.2.3	<i>N</i> -Imidoylsulfenamides, -sulfimides, -sulfinamides, and -sulfonamides	678
5.19.2.3.1	<i>N</i> -Imidoylsulfenamides $\text{R}^1\text{C}(\text{NR}^2)\text{NR}^3\text{SR}^4$	678
5.19.2.3.2	<i>N</i> -Imidoylsulfimides	679
5.19.2.3.3	<i>N</i> -Imidoylsulfinamides	680
5.19.2.3.4	<i>N</i> -Imidoylsulfonamides	680
5.19.2.3.5	Amidine derivatives with an <i>N</i> -selenium or <i>N</i> -tellurium bond	682

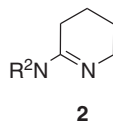
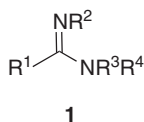
5.19.2.4	Amidrazones and Related Structures	683
5.19.2.4.1	Introduction and nomenclature	683
5.19.2.4.2	Primary amidrazones, $RC(NH)NHNH_2$	683
5.19.2.4.3	N-Alkyl-, aryl-, or alkenyl-substituted amidrazones	684
5.19.2.4.4	N-Acylamidrazones	685
5.19.2.5	Amidine Derivatives with an N—P, N—As, or N—Sb Bond	687
5.19.2.5.1	N-Phosphorylamidine derivatives	687
5.19.2.5.2	N-Phosphorus amidines (excluding N-phosphorylamidines)	688
5.19.2.5.3	Amidines with an N-arsenic bond	688
5.19.2.5.4	Amidines with an N-antimony bond	688
5.19.2.6	Amidine Derivatives with an N-Metalloid Bond	689
5.19.2.6.1	N-Silylamidines	689
5.19.2.6.2	N-Borylamidines	690
5.19.2.7	Amidine Derivatives with an N-Metal Bond, $R^1C(NR^2)NR^3-M$	691
5.19.2.7.1	Amidines with an N-metal bond, where M is a group 13 metal	691
5.19.2.7.2	Amidines with an N-metal bond where M is a group 14 metal	691
5.19.2.7.3	Amidines with an N-metal bond where M is a transition metal	692
5.19.2.7.4	Amidines with an N-metal bond, where M is a lanthanide or actinide metal	692

5.19.1 AMIDINES

5.19.1.1 Introduction and General Methods

5.19.1.1.1 Introduction

In this chapter the synthesis of amidines is reviewed. This review is restricted to compounds of structural formula **1** where R^1 is hydrogen or a carbon substituent. Thus, guanidines ($R^1 = NR_2$, etc.) and haloamidines are excluded along with cyclic amidines such as **2**, which are covered in *Comprehensive Heterocyclic Chemistry* <1984CHECI, 1996CHECII>. Some cyclic amidines may also be included when the method of synthesis is likely to be applicable to acyclic compounds.



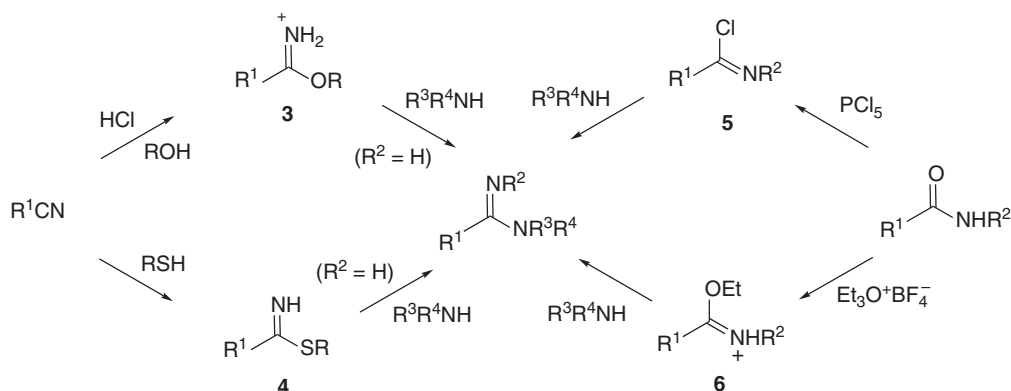
There are several reviews of amidine synthesis published in the literature <1944CRV351, 1958HOU(9)39, B-1975MI283, 1983RCR377, B-1991MI339, 1995COFGT(5)741>. The review by Boyd <B-1991MI339> includes haloamidines. The most structured review is provided in COFGT (1995) <1995COFGT(5)741>. Two small chapters in *Houben-Weyl* <1952HOU(8)702, 1985HOU(E5)1304> and related reviews on imidic ester chemistry <1961CRV179, B-1975MI385> also give useful information as does a review on additions to metal-activated organonitriles <2002CRV1771>. This review covers the years 1994–2003 as some 1994 references were not abstracted in time for COFGT (1995).

5.19.1.1.2 General methods

The most common methods of preparing amidines are from nitriles, amides, and thioamides. All these methods involve disconnection of the product to an iminium cation synthon and a nitrogen nucleophile.

Although discovered in 1877, the Pinner reaction <1961CRV179> remains the most common way of making primary amidines. In the review period (1994–2003), one-third of all publications, in which amidines were synthesized from nitriles, used a Pinner reaction. The nitrile is treated with an alcohol under anhydrous conditions in the presence of hydrogen chloride or hydrogen bromide to form the imidic ester salt **3** (Scheme 1). Subsequent reaction with ammonia or amines gives the amidine. As materials (alcohol, HCl and NH_3) are cheap, this method can be economical for large-scale synthesis. Recent examples of the Pinner reaction which contain

experimental details include the following <1999EJM575, 2000JA6382, 2000T5225, 2001JMC2695>. The Pinner reaction can also be used for synthesis of some substituted amidines <1958HOU(9)39, 2001H2085>. Amidine formation via base-catalyzed imidate formation is also common and works well for certain substrates <1996SC4351, 2000JMC4063>. Conversion of the nitrile into the amidoxime, by reaction with hydroxylamine, followed by reduction to give the amidine is a widely used synthetic method for making primary amidines <1996SC4351, 2000JMC4063>. The amidoxime method has also been used for large-scale synthesis <1995T12047, 2002WOP50076>. Forming primary amidines, by the reaction of a nitrile with methylchloroaluminum amide (ClMeAlNH₂), is a method of growing importance. This is an excellent general method which succeeds for hindered nitriles where the Pinner reaction fails or is less successful (see Sections 5.19.1.3.1 and 5.19.1.4.1) <1995TL8761, 2002BMCL865, 2002USP0013464>. The procedure is also reported to be more convenient in the laboratory than the Pinner method <1995TL8761>. Methylchloroaluminum amide may also be used to convert esters directly into amidines <1993BMC403>.



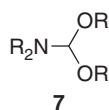
Scheme 1

A modification of the Pinner synthesis involves the formation of the thioimidic ester **4** (Scheme 1). Reaction of the isolable thioimidic ester with aromatic amines or the acetate salts of aliphatic amines or ammonium acetate reliably forms amidines. The thioimidic ester method can be used for acid-sensitive substrates, such as those with an *N*-BOC group <1981JOC2455>. A particularly useful variant of this reaction is the catalytic process with *N*-acetylcysteine <1999TL7067>.

A method which has been widely used to prepare *N*-substituted or *N,N*-disubstituted amidines is to heat the nitrile with a primary or secondary amine in the presence of aluminum chloride <1958HOU(9)39, 2000T9343>.

By definition, reactions from nitriles do not form tertiary amidines. Tertiary amidines and other substituted amidines are generally prepared from amides or thioamides. Activation of the mono-substituted amide to give the imidoyl chloride **5** is best achieved with phosphorus pentachloride though a variety of chlorination agents can be used <1998JCS(D)4147, 1999JCS(P1)705, 2001JHC425, 2001JMC2004>. The imidoyl chloride can then be reacted with a wide variety of mono- or disubstituted amines to produce amidines. Alternatively, the amide can be activated by alkylation and the alkoxy group displaced from the resulting imidic ester salt **6** <1968JOC1679, 2002T3499>.

The most common method of preparing formamidines is through the high yielding reaction of a formamidine acetal, such as **7**, with an amine or ammonia <1994SC1617, 1997TL7527>. Preparation from Vilsmeier reagents or equivalents is also very common <1959CB837, 2000T8253>.

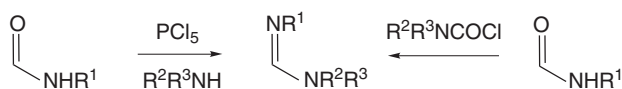


5.19.1.2 Formamidines (HC(NR¹)NR₂)

5.19.1.2.1 Preparation from formamides and thioformamides

(i) Formamidines from monosubstituted formamides

Di- or trisubstituted formamidines are readily prepared from monosubstituted formamides. The monosubstituted formamide can be activated by a reagent such as phosphorus pentachloride or dimethyl sulfate (Scheme 2). This chemistry was summarized in chapter 5.19.1.2.1 of <1995COFGT(5)741>. A variant on this method is the reaction between a monosubstituted formamide and a carbamoyl chloride (Scheme 2). Results from this chemistry were tabulated and summarized in COFGT (1995) <1983S35, 1995COFGT(5)741>.



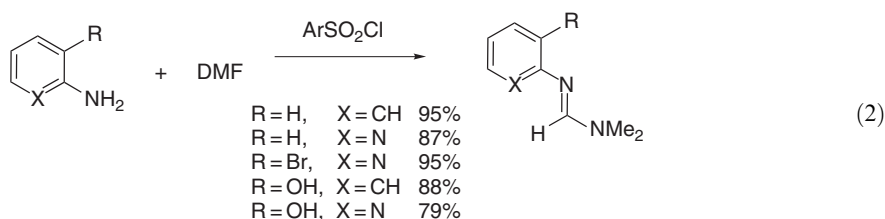
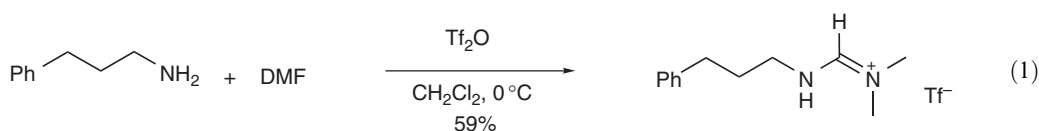
Scheme 2

(ii) Formamidines from disubstituted formamides, Vilsmeier reagents, and disubstituted thioformamides

Trisubstituted formamidines have been widely prepared from Vilsmeier reagents, most commonly from DMF and phosphorus oxychloride. The Vilsmeier salt forms amidines with both aliphatic and aromatic amines, and typical results are tabulated in COFGT (1995) <1959CB837, 1995COFGT(5)741>. Vilsmeier salts will also react with acylated amines to give formamidine hydrochlorides and carbon monoxide <1980S883>.

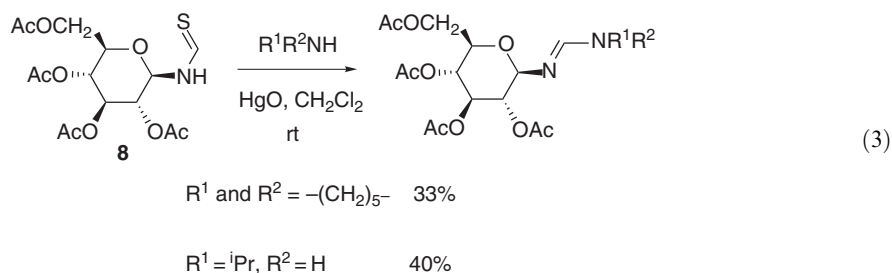
In the preparation of trisubstituted formamidines via a Vilsmeier reagent, it is reported to be more favorable to start from a disubstituted formamide and a primary amine as opposed to a monosubstituted formamide and a secondary amine <1995COFGT(5)741>.

Activation of DMF has also been achieved with triflic anhydride (Equation (1)) <1998TL711> and arylsulfonyl chlorides (Equation (2)) <1997TL5423, 2000T8253>. The arylsulfonyl chloride catalyzed reactions proceed in good yields (generally 80–95%) and are extremely rapid taking just 1–5 min at room temperature and this means that even hindered amines such as *t*-butylamine will form a formamidine (although in lower yield, 38%). Several arylsulfonyl chlorides were examined as potential activating agents and pyridine-2-sulfonyl chloride was found to be optimal <1997TL5423, 2000T8253>.



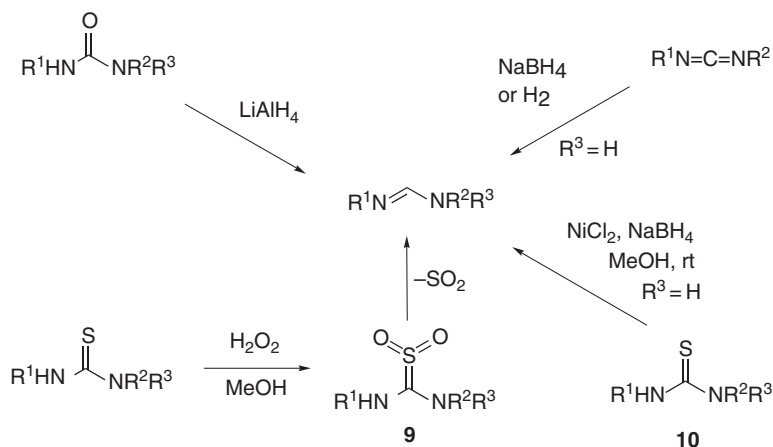
Other methods of activating DMF leading directly to dimethylformamidines are the use of Meerwein's reagent (Et₃OBF₄), phosgene or dimethyl sulfate <1993JMC1597>. Phosphorus trichloride has also been used for DMF activation giving formamidines <2000MI409>. Another recent method is the use of PyBroP (a common coupling agent in peptide synthesis), which gave formamidines in moderate yield <1999TL5487, 2001CPB933>.

Formamidines have been prepared by the reaction of amines and thioamides e.g., <1965CJC2640>. In the review period, it has been reported that this reaction may be catalyzed by mercury(II) oxide. Thus, thioamide **8** reacts with primary or secondary amines at room temperature to give moderate yields of formamidines (Equation (3)) <1995T8043>.



5.19.1.2.2 Formamidines, prepared by reduction of carbodiimides and ureas

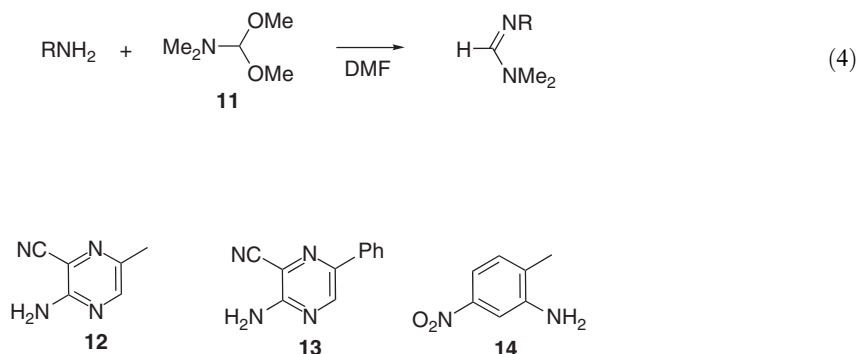
Formamidines can be prepared by reduction of ureas or carbodiimides and these methods are summarized in Scheme 3 and were covered in chapter 5.19.1.2.2 of COFGT (1995) <1995COFGT(5)741>. Also covered in COFGT (1995) was the preparation of formamidines from thioureas. The overall reaction from the thiourea is a reduction, though the reagent is hydrogen peroxide, and the reaction proceeds via the *S,S*-dioxide **9** followed by expulsion of sulfur dioxide. In the review period the reduction of *N,N'*-dialkyl thioureas (**10**, $\text{R}^1, \text{R}^2 = n\text{-Bu}$, cyclohexyl, *n*-Pr) with nickel borohydride (prepared *in situ* from nickel(II) chloride and sodium borohydride) was reported to give *N,N'*-dialkylformamidines <2002JCS(P1)2520>. Reduction of *N,N'*-diarylthioureas with nickel borohydride does not give *N,N'*-formamidines, instead further reduction to the arylamine and the *N*-methylarylamine was observed <2002JCS(P1)2520>.



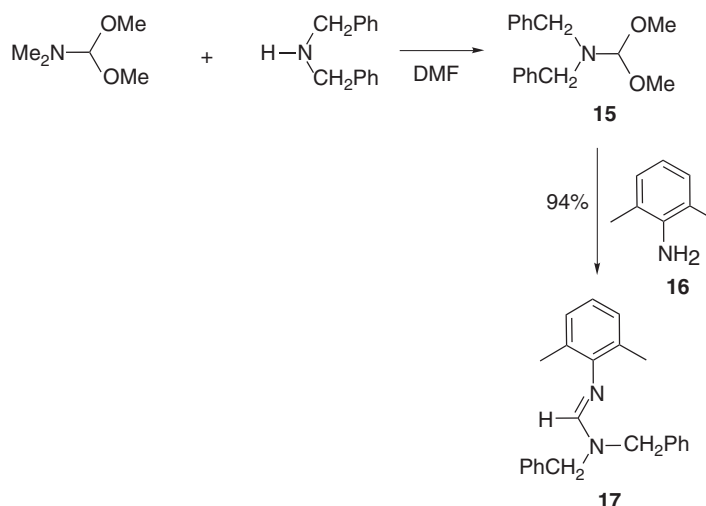
Scheme 3

5.19.1.2.3 Formamidines from orthoformates, acetals, and aminsals

An excellent and widely used method of preparing formamidines is the reaction of an amine with a formamide acetal such as **11** (Equation (4)). The method gives high yields under mild conditions and even works well for weakly basic amines such as **12** <1977JOC1523>, **13** <2000MI409>, and **14** <1994SC1617>.



To make a wide range of formamidines starting from DMF-dimethyl acetal, two strategies are possible. The first strategy is to react the DMF-dimethyl acetal first with an amine, such as dibenzylamine to give another acetal **15** which is subsequently reacted with a second amine, such as **16**, to give the *N,N'*-dibenzylformamidine **17** (Scheme 4) <1997TL7527>. This also illustrates that the formamidine acetal method works well for very hindered amines such as **16**. Dibenzylformamidines are very useful protecting groups for amines which can be removed by hydrolysis <1997TL7527>.

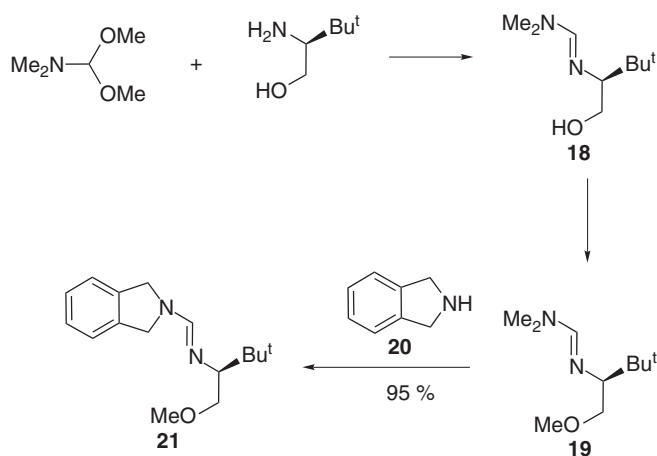


Scheme 4

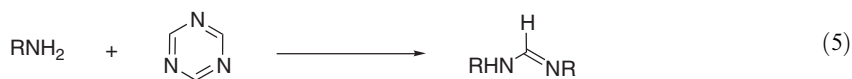
The second strategy is to react DMF-dimethyl acetal first with an amine to give the formamidine **18**. Subsequent amine exchange of the formamidine **19** with indoline **20** gave the chiral formamidine **21** with concomitant loss of dimethylamine (Scheme 5) <1992JOC4732, 1995TL5877>. The preparation of formamidines from aminals ($\text{HC}(\text{OR})(\text{NMe}_2)_2$) is covered in chapter 5.19.1.2.3 in <1995COFGT(5)741>.

5.19.1.2.4 Formamidines from 1,3,5-triazine

A high-yielding method of preparing *N,N'*-disubstituted formamidines is to heat 6 equiv. of an amine with 1 equiv. of 1,3,5-triazine (Equation (5)). This reaction is particularly effective using a primary aliphatic amine under neat conditions. This chemistry is summarized in chapter 5.19.1.2.4 of <1995COFGT(5)741>. In the review period most formamidine syntheses from 1,3,5-triazine formed polyformamidines.

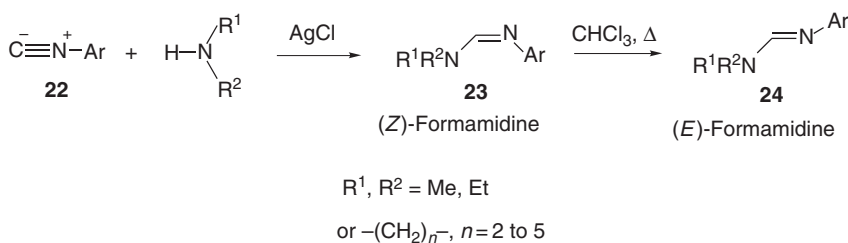


Scheme 5



5.19.1.2.5 Formamidines from isonitriles

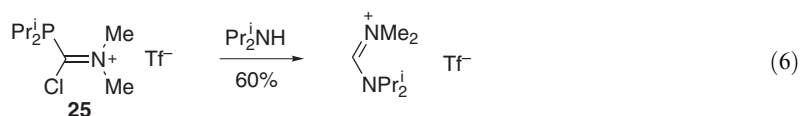
Arylisonitriles (**22**, Ar = Ph, *o*-, *m*-, *p*-ClC₆H₄; and *o*-, *p*-NO₂C₆H₄) can undergo reaction with 1 equiv. of secondary amine at -15°C in the presence of a catalytic amount of silver(I) chloride to give the (*Z*)-formamidine **23**. This product, characterized by infra-red and NMR spectroscopy, can be converted into the more stable (*E*)-isomer **24** by heating in boiling chloroform for 6 h or by treatment with acid at room temperature (Scheme 6) <1980CC130, 1980TL885>. Further examples of formamidines prepared from isonitriles are summarized in chapter 5.19.1.2.5 of COFGT (1995) <1995COFGT(5)741>. The reaction of isonitriles with amines may also be catalyzed by copper(II), zinc(II), and cadmium(II) salts.



Scheme 6

5.19.1.2.6 Formamidines, prepared by miscellaneous methods

A new method for preparing formamidines is the reaction of an amine with a carbene equivalent, the *C*-phosphanyl-*C*-chloroiminium salt **25**. The reaction takes place under mild conditions (dichloromethane, -78°C to rt) (Equation (6)) <2002CC2250>.

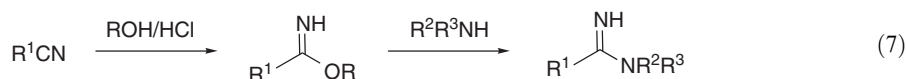


5.19.1.3 Aliphatic Amidines, $R^1C(NR^2)NR_2^3$ (R^1 = alkyl, allyl, propargyl, etc.)

Nearly all of the methods described in this section are equally applicable to aromatic amidines, and only when there are important differences will the synthesis of aromatic amidines be discussed separately in [Section 5.19.1.4](#).

5.19.1.3.1 Aliphatic amidines from nitriles

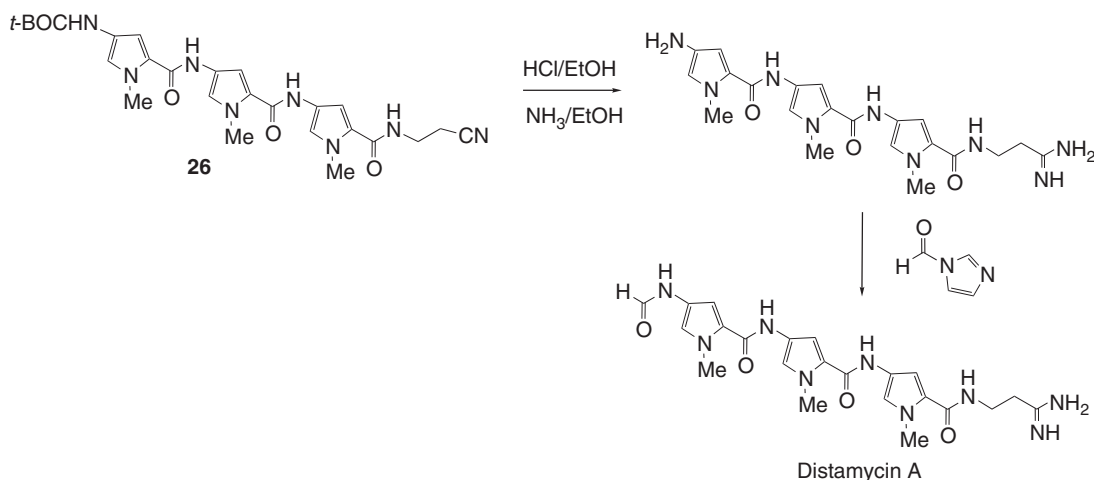
In 1877, Pinner described the synthesis of amidines from nitriles via the imidic ester ([Equation \(7\)](#)) [<1877CB1899>](#). As mentioned in the general methods, the Pinner method is still the most common method of preparing amidines (especially primary amidines) and during the review period (1994–2003) around one-third of all publications covering the preparation of amidines from nitriles used the Pinner method.



The nitrile is usually dissolved in anhydrous alcohol, typically ethanol [<2001JMC2695, 1996JMC2118, 2000T5225>](#) or methanol [<1997TA2679>](#), cooled and treated with excess of HCl gas to form the imidic ester hydrochloride. Subsequent reaction with an ammonium salt, alcoholic ammonia [<2001JMC2695, 2001JMC1217, 1996JMC2118>](#), or liquid ammonia [<2000T5225>](#) gives the primary amidine ([Equation \(7\)](#), $R^2, R^3 = H$). In the review period there were few reports of *N*-substituted or *N,N'*-disubstituted amidines being prepared from the imidate salt, but examples of such reactions were tabulated in *Houben–Weyl* [<1958HOU\(9\)39>](#).

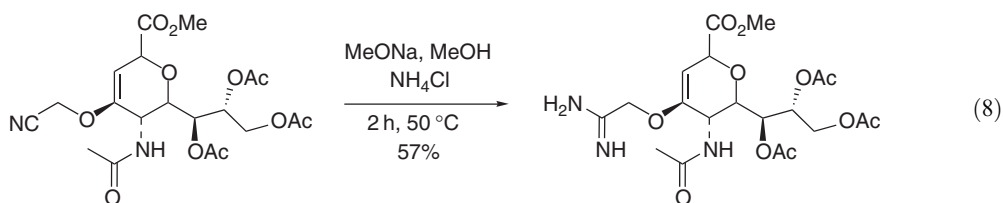
The Pinner reaction can be performed with reduced amount of ethanol (1–3 equiv.) in an inert solvent such as dioxan, ether, benzene, or chloroform and sometimes this is advantageous; for example, the extent of a side reaction to form orthoesters is reduced. Other side reactions include formation of *N,N'*-disubstituted amidines and hydrolysis of the nitrile to the amide (despite the supposedly anhydrous conditions).

The Pinner reaction was used to complete a total synthesis of Distamycin A ([Scheme 7](#)). Formation of the imidate takes place with concomitant deprotection of the *t*-BOC group. Following the formation of the amidine, the amine, liberated by the BOC removal, was formylated to give Distamycin A in 45% overall yield from **26** [<2000JA6382>](#).

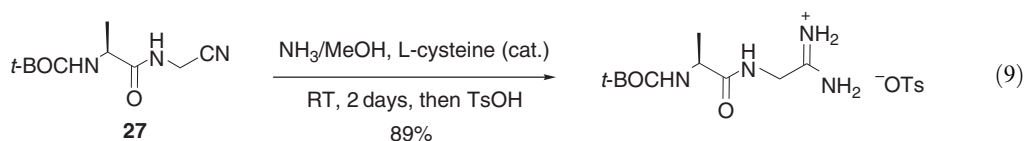


Scheme 7

For nitriles having an electron-withdrawing group in the α -position, the basicity of the nitrile nitrogen is decreased and the Pinner synthesis does not work well [<1995COFGT\(5\)653>](#). However, in these cases the base-catalyzed addition of alcohols to the nitrile works well. A recent example is shown in [Equation \(8\)](#) [<2001CAR31>](#).



A nitrile **27** with an electron-withdrawing group in the α -position was converted into the amidinium salt by Eschenmoser and co-workers. The reaction could be carried out without a catalyst but was significantly accelerated by using L-cysteine as catalyst (Equation (9)) <1986HCA1224>. The same reaction can also be carried out using *N*-acetylcysteine as catalyst <1999TL7067>. The *N*-acetylcysteine is particularly good for electron-poor aromatic nitriles (see Section 5.19.1.4.1).



Highly electrophilic nitriles such as trichloroacetonitrile will react directly with amines to give amidines in very high yields <2001SL135, 1995COFGT(5)741>.

Aliphatic and aromatic nitriles react with primary and secondary amines in the presence of aluminum chloride to give amidines. Examples with yields and references are tabulated in *Houben–Weyl* <1958HOU(9)39> and chapter 5.19.1.3.1 of <1995COFGT(5)741>. The reaction may also be catalyzed by tin(IV) chloride (see Equation (10), Table 1) <1993EJM955, 1995EJM809, 1998IJC(B)1283>, copper(I) chloride <1993TL6395>, or trimethylaluminum <2000JMC3168>. An environmentally friendly variant of the reaction is to use a Zeolite catalyst (Equation (10), Table 1) <1997TL3179>.

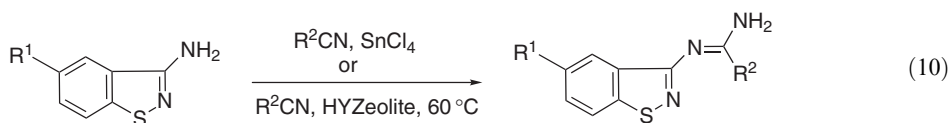
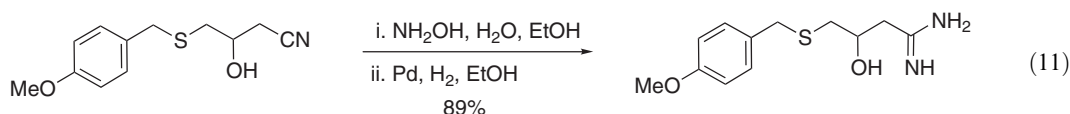


Table 1 The reaction of nitriles and amines catalyzed by SnCl_4 and zeolites

Substrate		Method	Yield (%)	References
R^1	R^2			
Me	Me	SnCl_4	80	<1993EJM955>
Me	Me	Zeolite	87	<1997TL3179>
H	Me	SnCl_4	80	<1993EJM955>
H	Me	Zeolite	85	<1997TL3179>
Me	CH_2Cl	SnCl_4	63	<1995EJM809>
Me	CH_2Cl	Zeolite	92	<1997TL3179>
H	CH_2Cl	SnCl_4	96	<1995EJM809>
H	CH_2Cl	Zeolite	90	<1997TL3179>

In some cases, the nitrile can be converted into the amidine by first forming the amidoxime followed by reduction of the N—O bond to give the amidine. A recent high-yielding example is shown in Equation (11) <1997JAP11193285>. Further examples of the preparation of aromatic amidines via this method can be found in Section 5.19.1.4.1.



Conversion of nitriles into amidines by reaction with methylchloroaluminum amide is a reaction that has been widely used since it was first reported by Garigipati (Equation (12)) <1990TL1969>. In a separate paper, a series of sterically hindered nitriles (**28–30**) was subjected to amidine formation via the classical Pinner reaction and reaction with methyl chloroaluminum amide. The results, in Table 2, show that the Garigipati method was superior both in terms of yield and much shorter reaction time, down from days to hours <1995TL8761>.

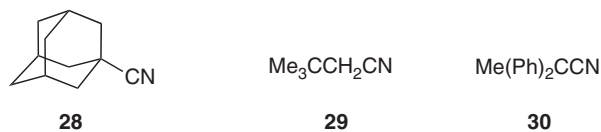
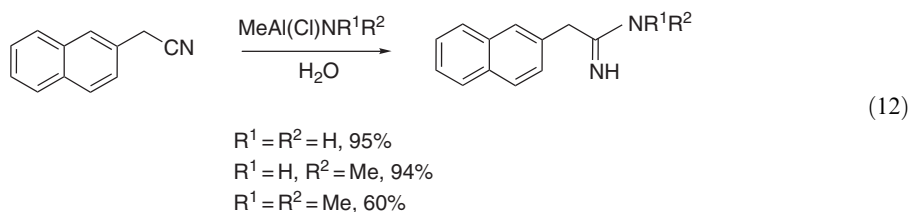
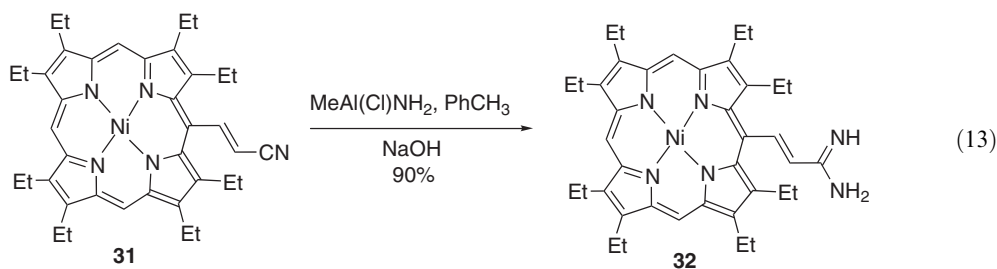


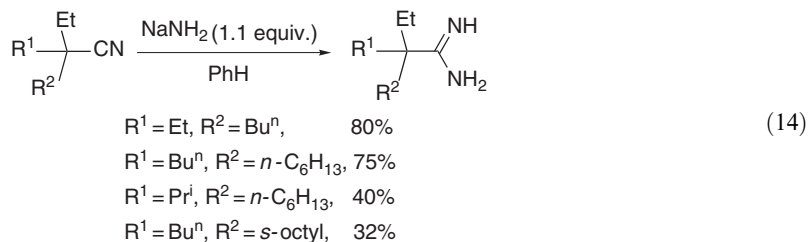
Table 2 Comparison of reaction times and yields for the Pinner and Garigipati methods

Starting nitrile	Pinner method		Garigipati method	
	Time (days)	Yield (%)	Time (h)	Yield (%)
28	21	40	18	64
29	14	38	15	70
30	15	<1	72	27

Another very impressive application of this methodology was the conversion of the porphyrin derivative **31** into the amidine **32** (Equation (13)). In spite of the high molecular weight and complexity of the starting nitrile, the product was isolated in very high yield <1995TL3477>. The equivalent reaction via the Pinner method was limited by the relative insolubility of porphyrin nitriles in alcohol. The Garigipati method has also been widely used for difficult aromatic substrates and will be covered in Section 5.19.1.4.1.

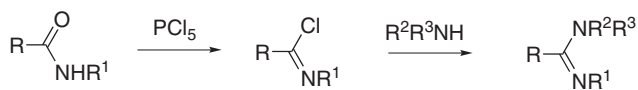


In COFGT (1995), the reaction of nitriles with strong bases such as sodium or potassium amide was reported to give primary amidines (e.g., Equation (14)). In the review period, the anion of hexamethyldisilazide was shown to react with nitriles to give primary amidines, but as the substrates are mostly aromatic nitriles this chemistry is discussed in Section 5.19.1.4.1.



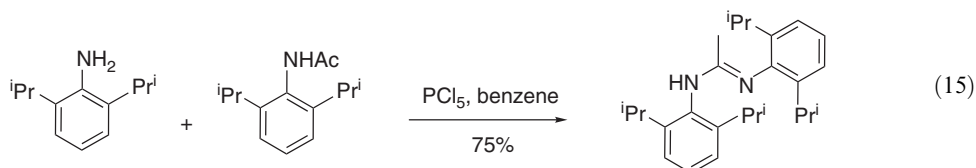
5.19.1.3.2 Aliphatic amidines from amides

Scheme 8 shows a method which is generally poor for making primary amidines <B-1975MI283> but is an excellent and general way of making di- and tri-substituted amidines. The secondary or tertiary amide can be activated by a number of methods but most commonly as the imidoyl chloride, subsequent reaction with primary or secondary amines yielding the corresponding amidine.



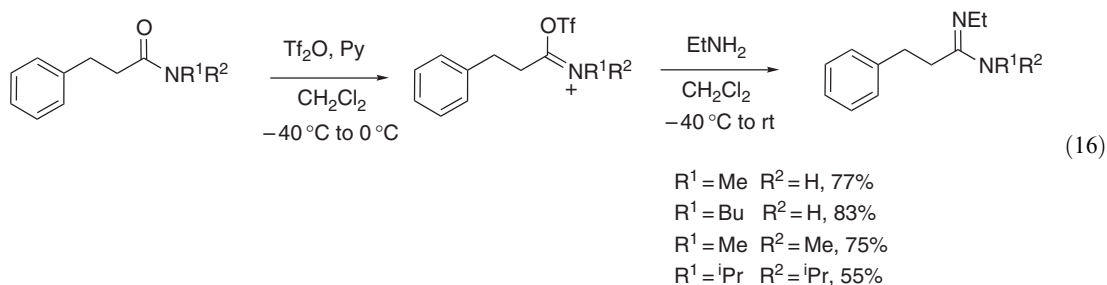
Scheme 8

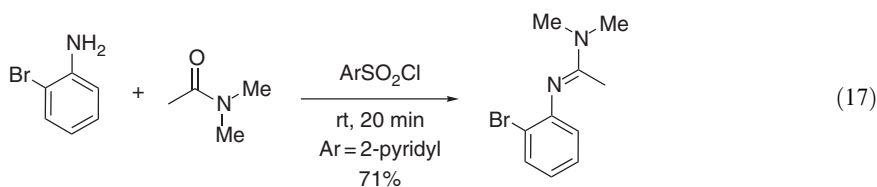
A classical procedure is to heat the amide and the amine with PCl_5 or POCl_3 in an inert solvent such as benzene or chloroform, and examples with conditions, yields, and references are tabulated in chapter 5.19.3.2 in <1995COFGT(5)741>. Surprisingly, in spite of the toxicity of benzene, PCl_5 in benzene has still been widely used in the review period (<2001ZOK834>, <1998JCS(D)4147>), and interestingly quite hindered amidines can be made via this method in good yield (Equation (15)) <1998JCS(D)4147>.



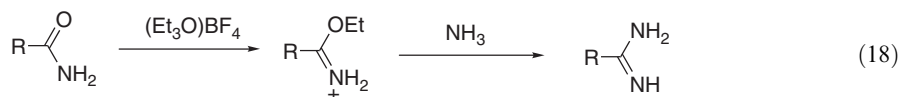
However, in the review period there have been more examples of the use of more “laboratory friendly” solvents, e.g., $\text{POCl}_3/\text{CH}_3\text{CN}$ <2001JMC2004> (see also <1978JMC273>), POCl_3 neat and then amine in DME <2001JHC425>, and $\text{SOCl}_2/\text{CH}_2\text{Cl}_2$ (see Section 5.19.1.4.2).

A more recent mild procedure for the activation of amides is to use triflic anhydride. Charette and Grenon reported 19 examples of which a selection is given in Equation (16) <2000TL1677> (see also <1998TL711>). Another recent procedure is to use an arylsulphonyl chloride as the activating agent (Equation (17)) <2000T8253>.



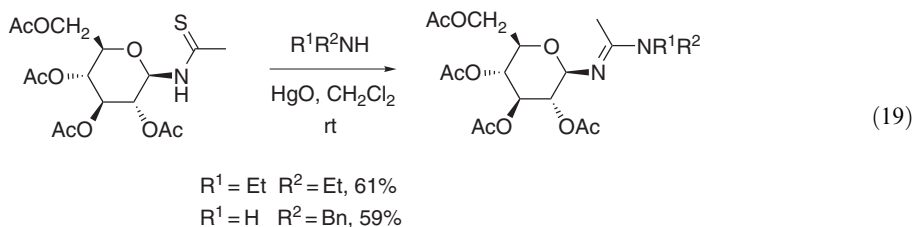


Another way of activating the amide is to use alkylation and this has the advantage that the method can be used to prepare primary as well as more highly substituted amidines (Equation (18)) <1968JOC1679>.

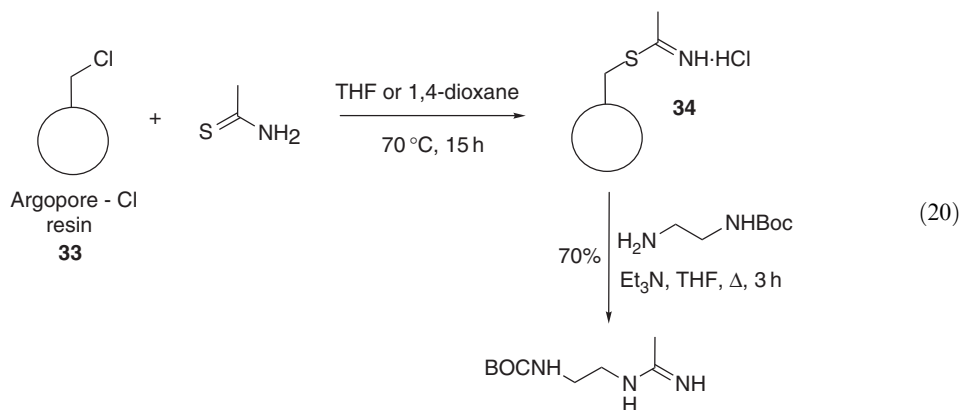


5.19.1.3.3 Aliphatic amidines from thioamides and thioimidic esters

The condensation of ammonia or an amine with a thioamide gives an amidine (sometimes as its H_2S salt). The reaction is improved by the addition of a mercury salt as a sulfide scavenger, e.g., HgCl_2 <1992TL2803> or HgO (Equation (19)) <1995T8043>.

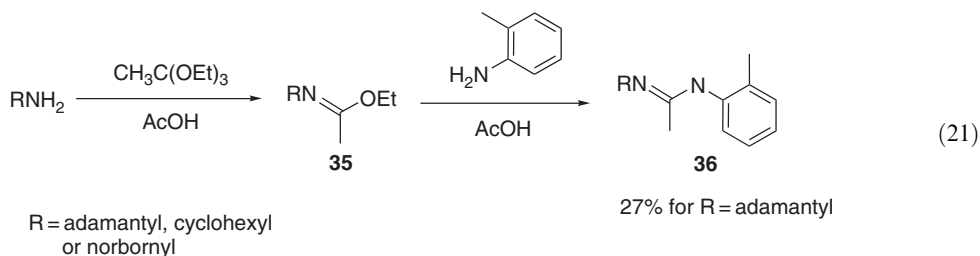


Alkylation of thioamides with alkyl halides or triethyloxonium tetrafluoroborate gives thioimidic esters which react more readily with amines or ammonia to give amidines (see Chapter 5.19.1.3.3 of <1995COFGT(5)741> and <1993JMC1811, 1999S927, 2001BMCL467>). In this review period, advances include the alkylation of thioamides with 2-naphthyl chloride to give a thioimide, which on subsequent reaction forms the amidine and a relatively nonodorous thiol by-product <1997TL179, 2001SL388>. Another advance has been to perform the reaction as part of a solid-phase synthesis. Hence, thioamides undergo reaction with the resin-bound reagent **33** to give resin-bound thioimides **34**. Subsequent reaction with an amine gave the free amidine (Equation (20)) <2001SL388>. A benefit is that a nonodorous thiol by-product is generated, in this case a polymer-bound thiol.



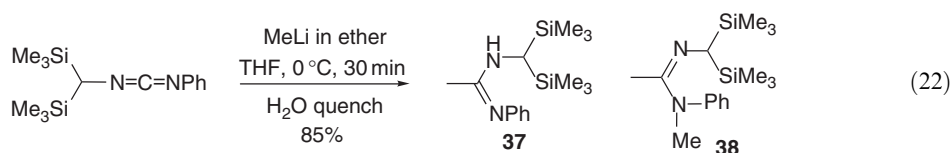
5.19.1.3.4 Aliphatic amidines from orthoesters

The preparation of symmetrical *N,N'*-substituted amidines from orthoesters is covered in chapter 5.19.1.3.4 in <1995COFGT(5)741> and other recent references include <1993BMCL2113, 1996JOC3902, 1997MI1968>. In addition, it is also possible to prepare unsymmetrical amidines, e.g., when an amine is heated with excess triethyl orthoacetate in acetic acid to give the imidic ester **35** which can then undergo reaction with a second amine to give the unsymmetrical amidine **36** (Equation (21)) <1993BMCL2113>.

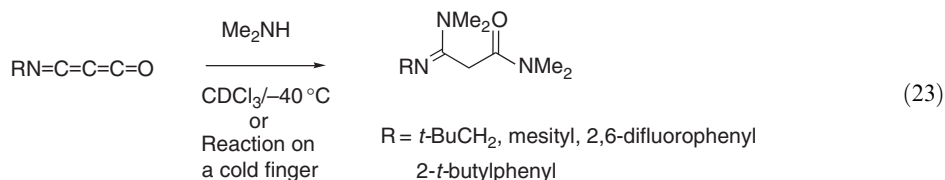


5.19.1.3.5 Aliphatic amidines from compounds with cumulated double bonds

The addition of organometallic compounds to carbodiimides is a relatively rare example of an amidine synthesis via C—C bond formation. Hence, methyllithium can be added to a carbodiimide followed by water quench to give the amidine **37**. If the water quench is replaced by a methyl iodide quench, a more substituted amidine **38** can be obtained (Equation (22)) <1995JOC6032>. Other organometallic nucleophiles may also add to carbodiimides including Grignard reagents <1995LA2171> and organozinc reagents. Further examples are given in chapter 5.19.1.3.5 of <1995COFGT(5)741>. Stabilized carbanions may also add to carbodiimides, e.g., the lithium anion of acetonitrile will add to a carbodiimide to give an amidine <2000BMCL2463>.



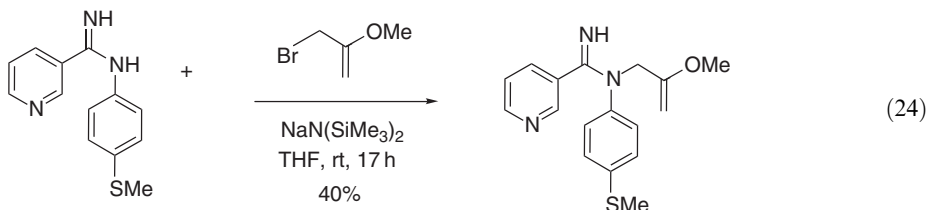
The preparation of amidines from isocyanates and ketenimines is covered in chapter 5.19.1.3.5 of <1995COFGT(5)741>. In the review period, the mechanism for the addition of amines to ketenimines has been studied by NMR spectroscopy and *ab-initio* calculation <2002JOC4298>. In a series of papers, Wentrup and co-workers have prepared amidines from iminopropadienones (Equation (23)) <1999JOC3608, 2002JOC2619, 2002JOC8558>.



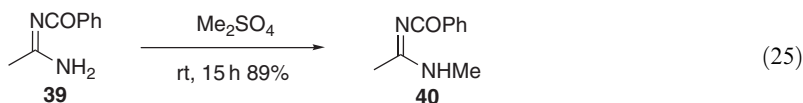
5.19.1.3.6 Aliphatic amidines, prepared by *N*-alkylation of simpler amidines

This method is most effective for the alkylation of symmetrical *N,N'*-disubstituted amidines <1998JCR(S)654, 2001MI97>, alkylation of *N,N*-disubstituted amidines, or monoalkylation of primary amidines (see chapter 5.19.1.3.6 of <1995COFGT(5)741>).

Attempts to monoalkylate monosubstituted amidines have attracted little synthetic interest as such reactions generally have poor regioselectivity <B-1975MI283>. The most useful results have been observed in the alkylation of *N*-aryl amidines which are alkylated predominantly on the nitrogen bearing the aryl groups (Equation (24)) <2000JMC3168> (see also <1971BCF478> and <1995JOC6032>).



In the absence of strong base, *N*-benzoylacetamide **39** is alkylated on the more nucleophilic nitrogen to give the alkylated amidine **40** (Equation (25)) <1996JOC2470>.



Acylated amidines may be alkylated on a nitrogen bearing an acyl group using Mitsunobu conditions <1995TL2045, 1998BMCL2961>.

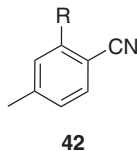
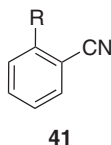
5.19.1.3.7 Aliphatic amidines, prepared by miscellaneous methods

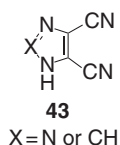
The preparation of amidines by reactions of carbanions with chloroformamidines is covered in chapter 5.19.1.3.7 of <1995COFGT(5)741>. The preparation of amidines from imines, hydrazones, aldoximes, ammonolysis, and by addition reactions to yneamines is covered in previous reviews <B-1975MI283, B-1991MI339>.

5.19.1.4 Aromatic Amidines, ArC(NR¹)NR₂²

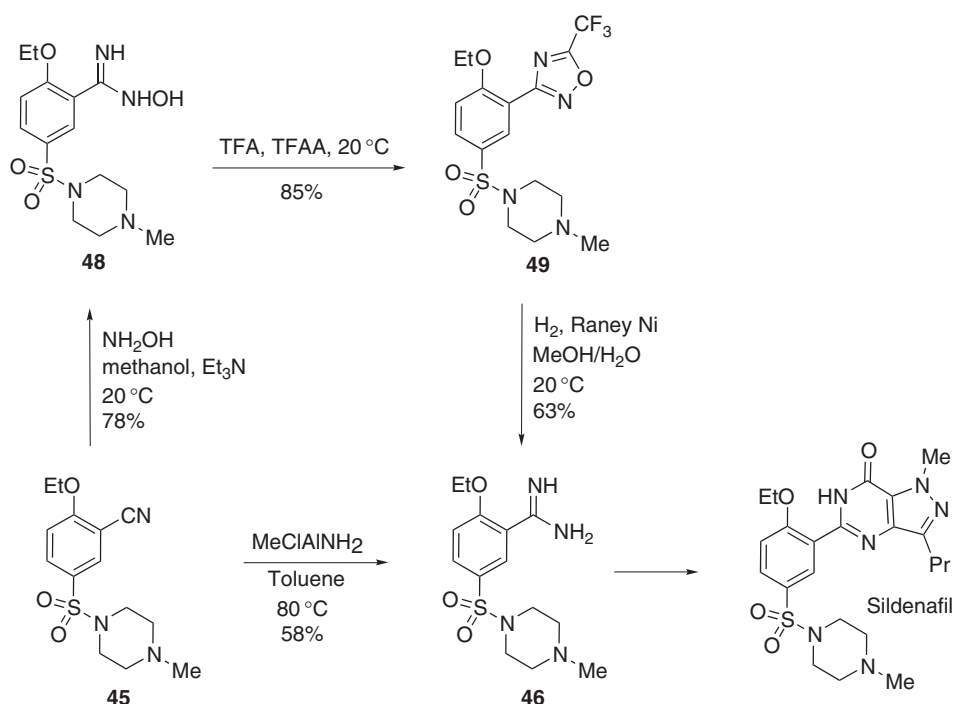
5.19.1.4.1 Aromatic amidines from nitriles

Nearly all of the synthetic methods described in Section 5.19.1.3.1 also apply to aromatic amidines. An important exception is the synthesis of aryl amidines from *ortho*-substituted aryl cyanides (**41**, R = Me, Cl, SO₂NH₂) (**42**, R = NO₂, NH₂) and 1-naphthonitrile which exhibit a “proximity effect” and do not form imidic esters when treated with ethanol and anhydrous HCl. Positional isomers where the positions *ortho*- to the nitrile are unoccupied behave normally and hence 4-methylbenzonitrile <1944CRV351> and 2-naphthonitrile <1978PHA568> form imidic esters, which are then converted into amidines. The proximity effect has some synthetic utility in differentiating between vicinal dinitriles; hence, symmetrical dinitriles such as **43** form salts of monoimidic esters which have been converted into amidines. Further examples of differentiating between vicinal dinitriles can be found in chapter 5.19.1.4.1 in <1995COFGT(5)741>.





If the desired product is the amidine, one way of solving the problem of the proximity effect is to use the Garigipati method [<1990TL1969>](#). Interestingly, two competing male erectile dysfunction drugs, sildenafil (the active ingredient in ViagraTM) and **44**, a key intermediate in the synthesis of vardenafil (the active ingredient in LevitraTM), both use the Garigipati method as a method of synthesis. For sildenafil, the nitrile **45** is converted into the amidine **46** in 58% yield by reaction with methylchloroaluminum amide (Scheme 9) [<2002USP0013464>](#). For vardenafil, 2-ethoxybenzonitrile is converted into 2-ethoxybenzamidine **47** with methylchloroaluminum amide in 76% yield. The amidine was subsequently converted into the intermediate **44** via the amidrazone (Scheme 10) [<2002BMCL865, 1999WOP24433>](#).

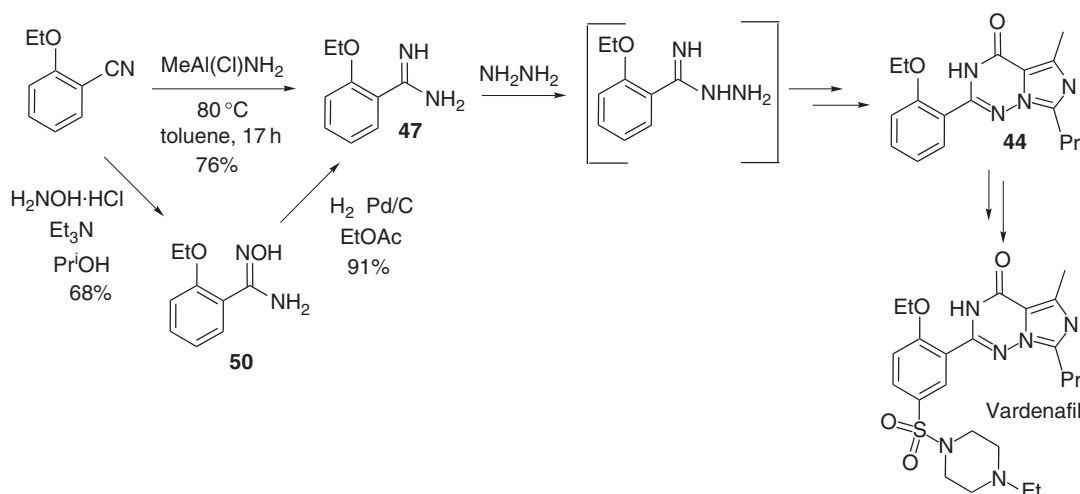


Scheme 9

Interestingly, the nitrile **45** (Scheme 9) will undergo a Pinner reaction [<2002USP0013464>](#) but in this case it was the conversion of the imidic ester into the amidine, which was problematic, the reverse of the general trend where formation of the imidate causes most problems. Workers at Pfizer were also able to convert the nitrile **45** into the amidine **46** by reaction with hydroxylamine to give the amidoxime **48** which was cyclized to give the oxadiazole **49** followed by hydrogenolysis [<2002USP0013464>](#). This work was based upon literature reports by Horwell and co-workers [<1998TL7619>](#) and Kohrt and co-workers [<2000TL6041>](#).

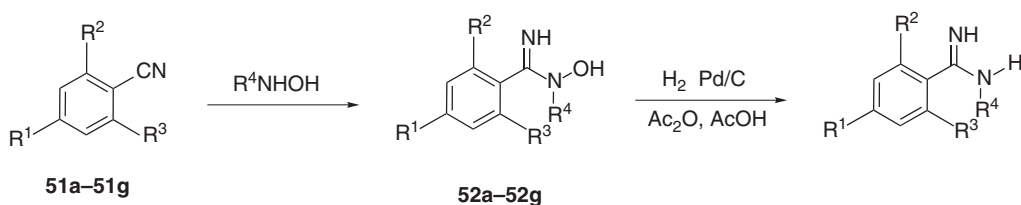
Workers at Bayer were also able to prepare the vardenafil intermediate, 2-ethoxybenzamidine via the amidoxime (Scheme 10). 2-Ethoxybenzonitrile was treated with hydroxylamine hydrochloride in the presence of triethylamine to give the amidoxime **50**, which was subjected to hydrogenolysis to give 2-ethoxybenzamidine **47** on a 136 Kg scale (Scheme 10) [<2002WOP50076>](#). Hence these methods proceeding via the amidoxime represent other ways of circumventing the proximity effect. Other multi-kg amidine syntheses via hydrogenolysis of an amidoxime have been reported [<1995T12047>](#) and [<1998SC4419>](#).

Sometimes the N—O bond can be difficult to reduce and in these cases *in situ* activation of the N—O bond by forming the acetate or trifluoroacetate ester followed by hydrogenolysis gives the desired



Scheme 10

amidine under mild conditions. A detailed study was reported by workers at Glaxo Wellcome and a selection of results is summarized in Scheme 11 and Table 3 <1996SC4351>. Formation of the amidoxime works well for a variety of electron-donating and withdrawing substituents and for systems containing an *ortho*-substituent, e.g., 51e. The yield from 2,6-dimethylbenzonitrile is significantly lower but it is worth noting that 2,6-dimethylbenzamidine had not been previously reported. Hydrogenolysis of 52d and 52c proceeded slowly (16 h) in the absence of an acylating agent but for 52a, hydrogenolysis without an acylating agent was so slow as to be impractical. However, hydrogenolysis after *in situ* activation to form the acetate gave excellent results for (52a–52f). For substrate 52g, more powerful activation as the trifluoroacetate was required to get a reasonable yield of the desired amidine. There are other reported examples of *in-situ* activation by forming the acetate <2000JOC8100, 2001BMCL1293> and the trifluoroacetate <2000JMC4063>. *In-situ* activation of the N–O bond is also possible using (*t*-BOC)₂O <1996BMCL111>.



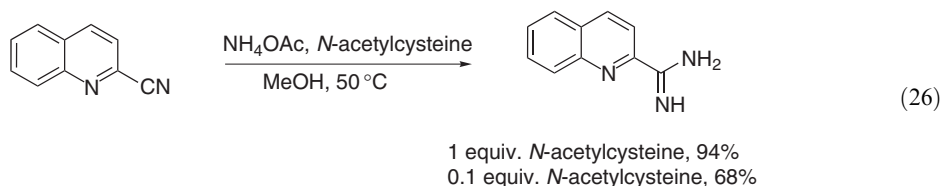
Scheme 11

Table 3 Synthesis of amidines by reduction of amidoximes

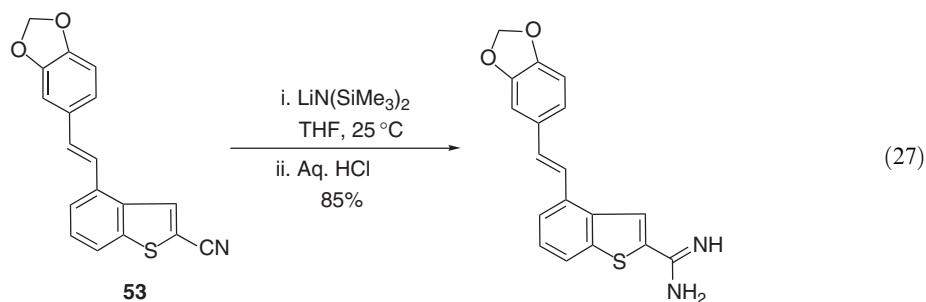
Substrate					Yield for amidoxime reaction (%)	Yield for amidine formation (%)	
R ¹	R ²	R ³	R ⁴	Ac ₂ O method		(CF ₃ CO ₂)O method	
a	F	H	H	H	90	84	“No better than Ac ₂ O”
b	MeO ₂ C	H	H	H	60	94	
c	Me ₂ N	H	H	H	81	90	
d	CF ₃	H	H	H	91	99	
e	H	Me	H	H	77	45	
f	H	Me	Me	H	16	56	59
g	F	H	H	Me	87	<5	

A very promising new method of preparing amidines from nitriles is to use an *N*-acetylcysteine-catalyzed reaction. The method works best for electron-deficient nitriles (Equation (26))

<1999TL7067> and also works well for some hindered nitriles, although reaction times are increased and yields reduced <1999TL7067>. Ammonium acetate may be substituted for gaseous ammonia to give a more convenient laboratory procedure.

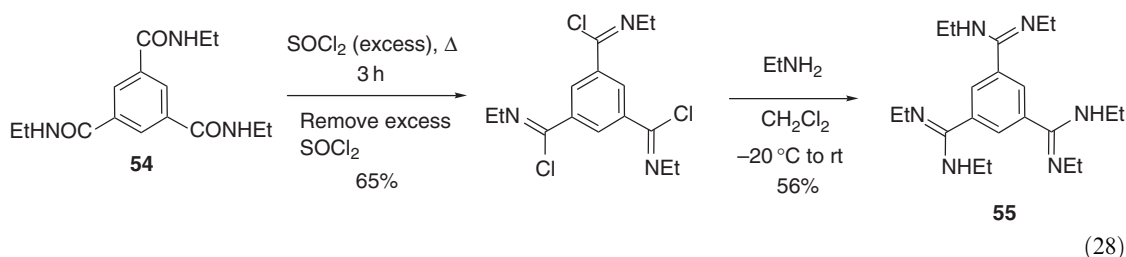


Reaction of the nitrile **53** with lithium hexamethyldisilazide followed by acid hydrolysis gave the desired amidine in 83% yield (Equation (27)) <1993BMC403>. Other examples of amidines prepared by the reaction of nitriles with lithium hexamethyldisilazide have been reported <1994JCS(D)3507, 2001WOP094333, 2002CC958>.



5.19.1.4.2 Aromatic amidines from amides

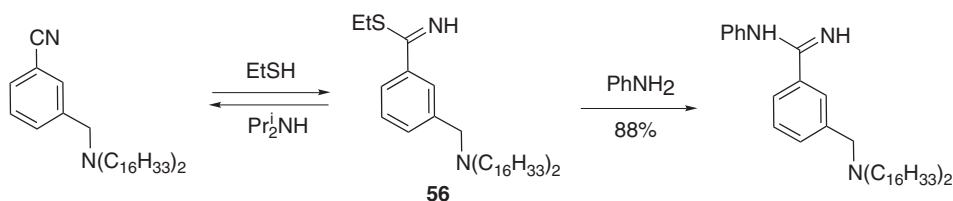
Aromatic amides are converted into amidines via the imidoyl chloride (normally by reaction with PCl_5 or POCl_3). The classical procedure is to heat an aryl amide, amine, and phosphorus chloride together in an inert solvent such as chloroform or benzene. A second classical method which can be used for arylamides or other amides which do not possess a β -hydrogen atom is to isolate the imidoyl chloride and then subsequently react with the amine. This procedure is tolerant of amines which react with phosphorus chlorides (e.g., aminophenols). Slightly more modern “laboratory-friendly” conditions are demonstrated by the conversion of the triamide **54** into the triamidine **55** (Equation (28)) <1999JCS(P1)705>. Other examples include <2001JMC2004>.



Aryl amides may be alkylated with Meerwein's reagent (Et_3OBF_4) and converted into primary or substituted amidines <1968JOC1679, 2002T3499>.

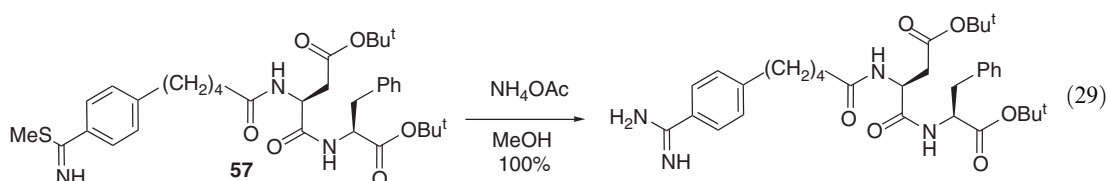
5.19.1.4.3 Aromatic amidines from thioamides and thioimidic esters

The reaction of aromatic thioimides with aromatic amines gives amidines in very good yield; hence, the reaction of thioimidic ester **56** with aniline leads to amidine formation in 88% yield (recrystallized) (Scheme 12). However with more basic aliphatic amines, elimination occurs to return the nitrile (Scheme 12).

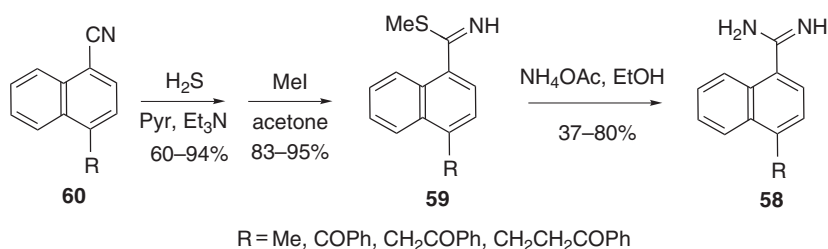


Scheme 12

The problem can be overcome by using a buffered system. Hence, the reaction of **56** with diisopropylamine in sodium acetate/acetic acid buffer gives the desired amidine [<1979JOC3726>](#). This principle also works for primary amidines; hence, the reaction of thiomidate **57** with ammonium acetate gives the desired amidine (Equation (29)) [<1993JMC1811>](#), whereas unbuffered conditions (alcoholic ammonia) can give elimination with aromatic thioimidates (see chapter 5.19.1.4.3 in [<1995COFGT\(5\)741>](#)).



The thioimidic ester method can be used to overcome the proximity effect. For example, 4-substituted-1-naphthamidines **58** can be prepared via the thioimidic esters **59**, whereas preparation from the nitriles **60** via the imidic ester (the Pinner reaction) failed (Scheme 13) [<1978PHA568>](#).

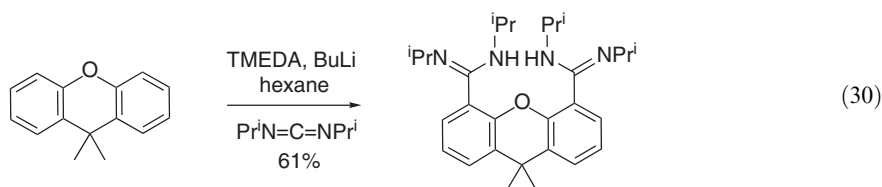


Scheme 13

Other recent syntheses of aromatic amidines from thioimidates include [<1993H1979, 1993JMC2168, 2001JMC1741, 2002BMCL1439>](#).

5.19.1.4.4 Aromatic amidines from compounds with cumulated double bonds

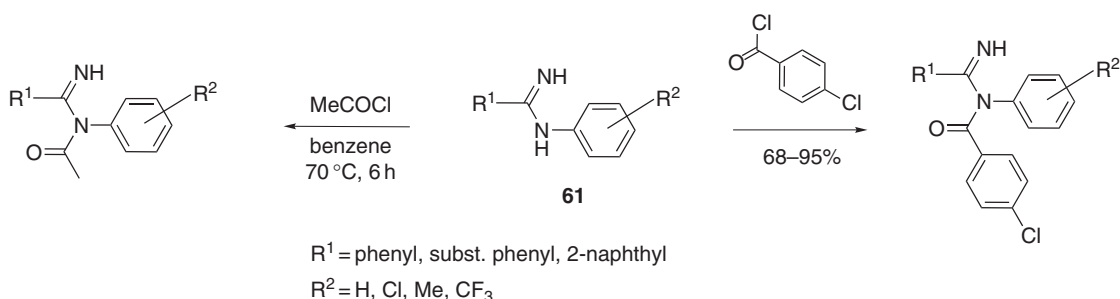
In the review period there have been a number of amidines prepared by adding an aryl anion to a carbodiimide. For example, both *ortho*-lithiation (Equation (30)) [<2003OM609>](#), and more frequently metal-halogen exchange [<2000JCS\(D\)967, 2001OM5532, 2002JCS\(D\)3919, 2002JOM\(662\)178>](#) have been used to generate the aryl anion.



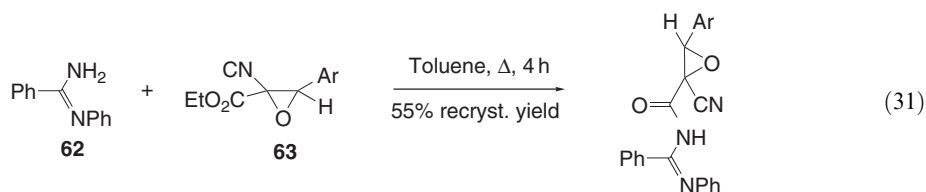
5.19.1.5 *N*-Acyl- and *N*-Heteroacylamidines5.19.1.5.1 *N*-Acylamidines, $R^1C(NR^2)NR^3COR^4$

Not surprisingly, the most common way of preparing acylamidines is via direct acylation. Direct acylation with acid chlorides, chloroformates, or phenolic esters is covered in chapter 5.19.1.5.1 of <1995COFGT(5)741>, and more recent references include <1998SC4419, 1999JMC3994> and <1996BMCL2425> (where the preparations of 24 acylated amidines are described). Several *t*-BOC-protected amidines were prepared by the reaction of an aryl amidine with (*t*-BOC)₂O <1997JMC2085, 1997JMC2843>.

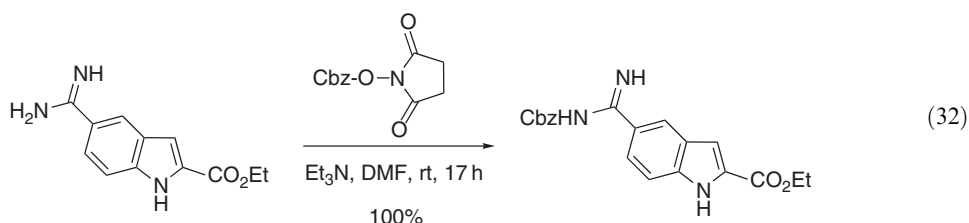
Amidines bearing an *N*-aryl substituent such as **61** are reported to undergo acylation with acid chlorides on the nitrogen bearing the aryl substituent as outlined in Scheme 14. A wide variety of benzamidines and naphthamidines have been prepared by this method <1972FRP2081556>. However, *N*-phenylbenzamidine **62** is reported to acylate on the other nitrogen when treated with the ester **63** (Equation (31)) <1995TL547>.



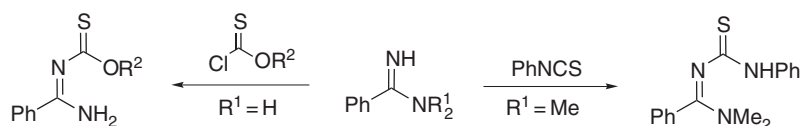
Scheme 14



Activated carbonates may also be used to acylate amidines in quantitative yield as shown in Equation (32) <1997JMC4308>.

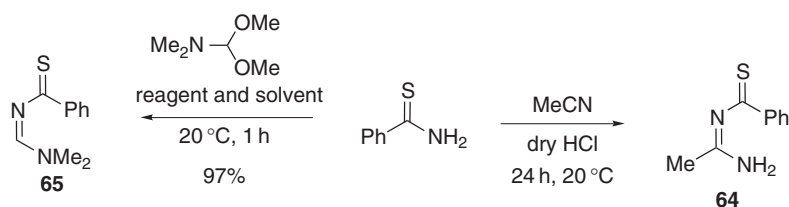
5.19.1.5.2 *N*-Thioacylamidines

Amidines can be thioacylated by reaction with thiochloroformates under phase-transfer conditions or by rt reaction with isothiocyanates (Scheme 15). Both methods were described in chapter 5.19.1.5.2 in <1995COFGT(5)741>. More recent literature reports of synthesis from isothiocyanates include <2001BMCL2225, 2001T153> (where reaction takes place at 0 °C).



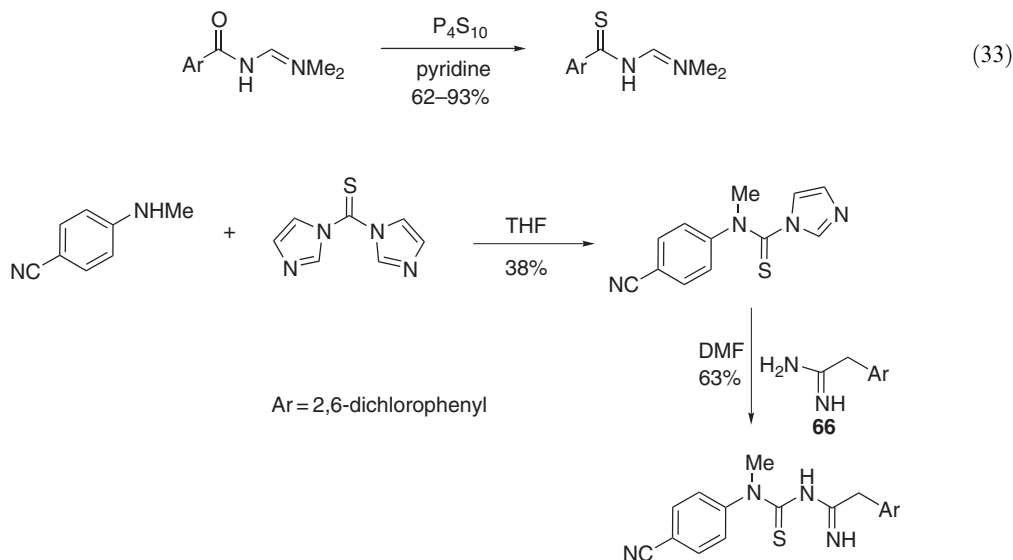
Scheme 15

Thiobenzamide undergoes reaction with protonated acetonitrile to give thiobenzoylacetamidine **64**. The reaction of thiobenzamide with dimethylformamide dimethyl acetal forms the thiobenzoylformamide **65** in excellent yield and under mild conditions (Scheme 16) <1980JOC3750>. Further references covering the preparation of thioacylamidines from formamide acetals can be found in <1995COFGT(5)741>.



Scheme 16

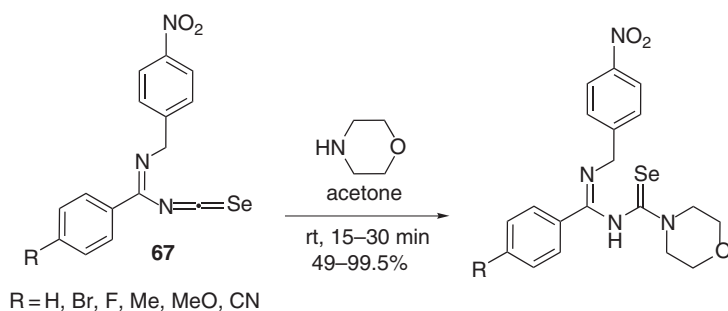
N-Thioacylamidines can also be prepared from the reaction of an *N*-acylamidine with phosphorus(V) sulfide (Equation (33)) <1988S655>. Another method involves sequential reaction of an amine with *N,N'*-thiocarbonyldiimidazole followed by displacement of the second imidazole with the amidine **66** (Scheme 17) <2001BMCL2225>.



Scheme 17

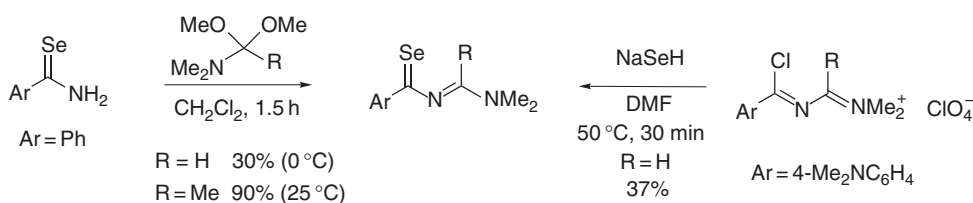
5.19.1.5.3 *N*-Selenoacylamidines

In <1995COFGT(5)741> the preparation of selenoacylamidines by the reaction of isoselenocyanates such as **67** with benzylamine was described. In the review period, the reaction has been extended to aliphatic amines such as morpholine, as shown in Scheme 18 <2000HCA1576> and <2002HCA1102>.



Scheme 18

Two other methods of preparing selenoacylamidines are shown in [Scheme 19](#) <1988S655, 1995TL237, 1998T2545>.



Scheme 19

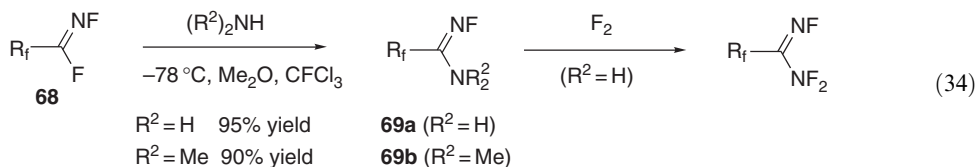
5.19.2 AMIDINE-DERIVED STRUCTURES WITH AN *N*-HETEROATOM BOND

5.19.2.1 *N*-Haloamidines

CAUTION: Nitrogen-halide compounds are potentially explosive; please read the primary literature carefully and take appropriate precautions.

5.19.2.1.1 *N*-Fluoroamidines

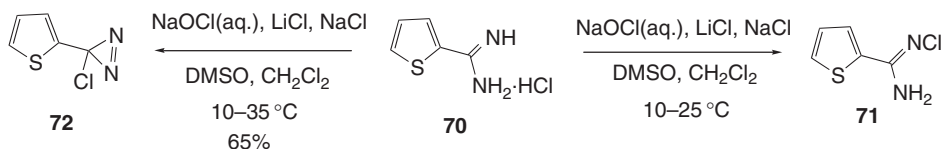
N-Fluoroamidines are formed in high yield by the action of ammonia or dimethylamine on the imidoyl fluoride **68** (Equation (34)) <1973JOC1075>. In addition, **69a** may further be fluorinated by elemental fluorine to give the trifluoroamidine <1973USP3726903>.



5.19.2.1.2 *N*-Chloroamidines

Baird and Bruce have shown that temperature control is important in influencing whether 2-amidinothiophene **70** is chlorinated with sodium hypochlorite to give the *N*-chloroamidine **71** or the chlorodiazirine **72**. At temperatures below 25 °C, the *N*-chloroamidine is the only isolated product. However, if the sodium hypochlorite is added rapidly and the temperature allowed to

rise to 35 °C, **72** is formed in 65% yield (Scheme 20) <1990JCR(S)134, 1990JCR(M)946> (see also <2003JPC3287>). Several examples of high-yielding methods to prepare *N*-chloroamidines were tabulated in chapter 5.19.2.1.2 of <1995COFGT(5)741>.



Scheme 20

5.19.2.1.3 *N*-Bromoamidines

N-Bromoamidines are prepared from the parent amidine with sodium hypobromite as described in chapter 5.19.2.1.3 in <1995COFGT(5)741>. No further advances have occurred since the publication of this chapter.

5.19.2.1.4 *N*-Iodoamidines

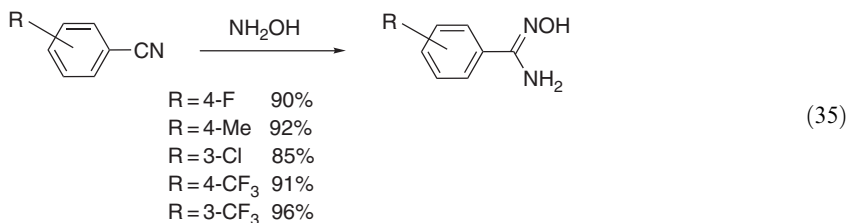
N-Iodobenzamidine may be prepared from benzamidine and potassium triiodide <1944CRV351>. No further advances have occurred since the publication of <1995COFGT(5)741>.

5.19.2.2 *N*-Imidoaldehydes and Related Structures

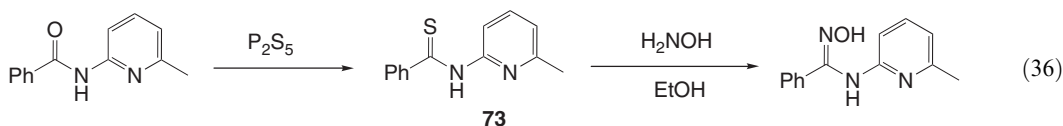
N-Imidoaldehydes are also known as amide oximes, hydroxamidines, and most commonly as amidoximes. The syntheses of *N*-imidoaldehydes have previously been reviewed in <1962CRV155, B-1992MI875> and <1995COFGT(5)741>, as well as a small section in a review by Abele and Lukevics <2001CHE141>.

5.19.2.2.1 *N*-Imidoaldehydes from hydroxylamine

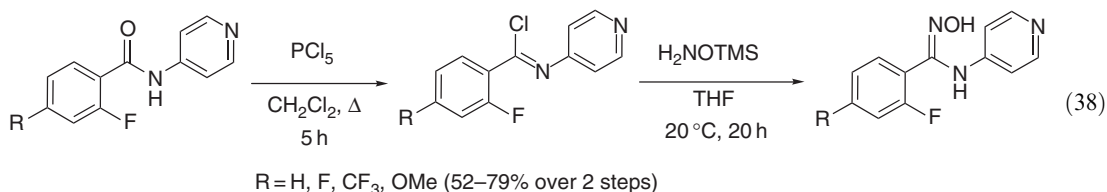
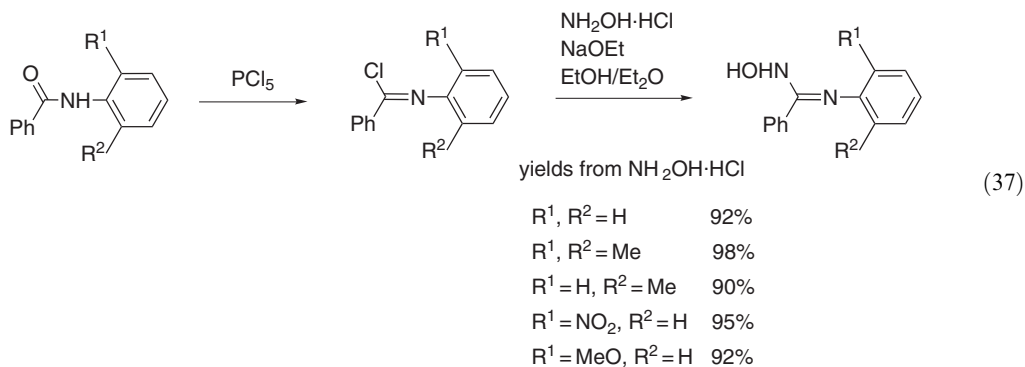
Hydroxylamine is sufficiently nucleophilic to undergo an addition reaction to a nitrile without the preformation of an imidic ester. This is the most common method of making *N*-imidoaldehydes with over 100 publications reporting this reaction in the review period. Some recent examples are shown in Equation (35) <1996SC4351, 2001JCS(P1)1321, 2001TL1495, 2002JMC944>. Further examples can be found in Sections 5.19.1.3.1 and 5.19.1.4.1.



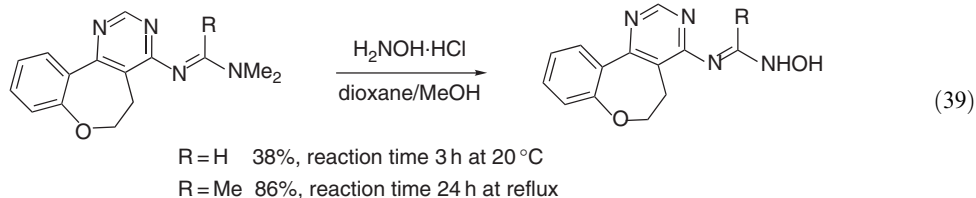
Hydroxylamine is also sufficiently nucleophilic to react directly with thioamides without the need for thioimide ester formation. The reaction of **73** with hydroxylamine gave the imidoaldehyde in 50% yield over two steps from the starting amide (Equation (36)) <1976JCS(P1)2166>.



N-Imidoylhydroxylamines may be prepared from the imidoyl chloride and hydroxylamine (Equation (37)) <1976AJC357>. In the review period, a modified reaction between the imidoyl chloride and *O*-trimethylsilylhydroxylamine was reported. A series of 12 amidoximes was prepared, a selection of which is shown in Equation (38). The trimethylsilyl group is removed under the reaction conditions <1996TL995>. The reaction of *N*-(2-methylphenyl)hydroxylamine with an imidoyl chloride also yields an amidoxime <2002MI1097>.

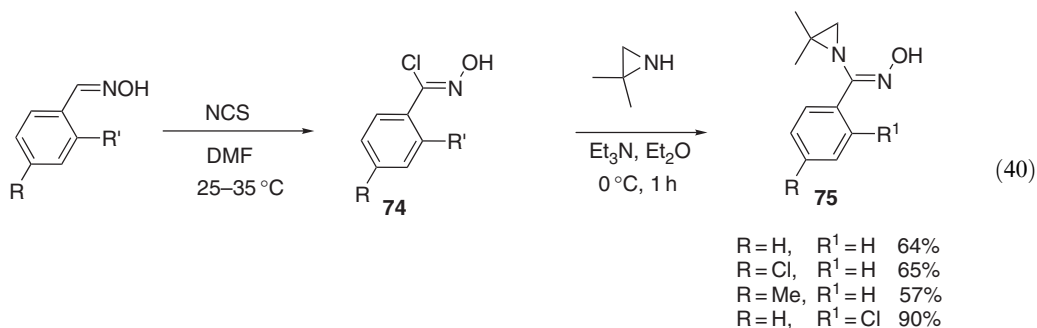


A further method for preparing *N*-imidoylhydroxylamines is the treatment of an amidine with hydroxylamine. This reaction is a common way of preparing formamidoximes (Equation (39)) <2001JHC425> (see also chapter 5.19.2.2.1 of <1995COFGT(5)741>).

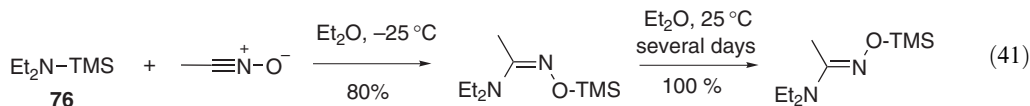


5.19.2.2.2 *N*-Imidoylhydroxylamines from amines and ammonia

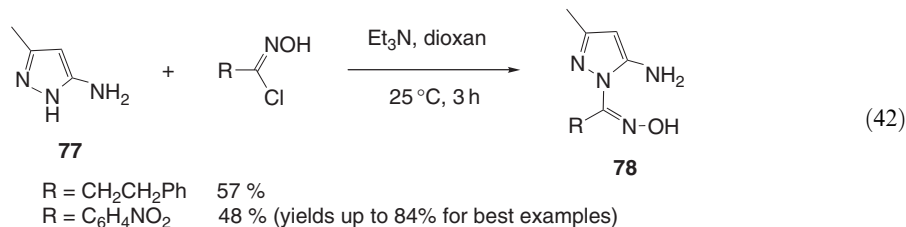
Chlorination of aldoximes gives oxyimide chlorides which readily react with amines or ammonia to give *N*-imidoylhydroxylamines (see chapter 5.19.2.2.2 in <1995COFGT(5)741>). The oxyimide chloride **74** reacts with 2,2-dimethylaziridine to give the (*Z*)-imidoylhydroxylamine **75** (Equation (40)) <1996JHC1583>. The reaction is thought to proceed via the stereospecific addition of the aziridine to the aryl nitrile oxide <1986JHC1861>. For other recent examples of *N*-imidoylhydroxylamines prepared from oxyimide chlorides (see <1997JCR(S)434, 1997T1787, 2000BMC601, 2002T10437>).



N-Trimethylsilyldiethylamine **76** undergoes facile addition to acetonitrile *N*-oxide to give the kinetically favored *O*-silylated (*Z*)-imidoylhydroxylamine. Over several days at room temperature, the (*Z*)-isomer rearranges to the thermodynamically more stable (*E*)-isomer (Equation (41)) <1985JOM(281)135>.

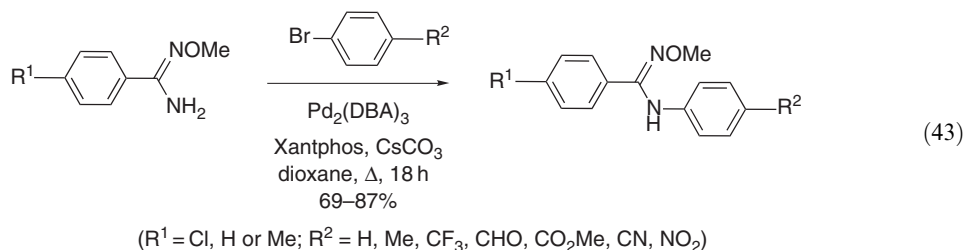


3-Alkyl-5-aminopyrazoles **77** undergo reaction with oxyimide chlorides at the pyrazole nitrogen rather than at the amino group to give **78** as the (*Z*)-isomer (Equation (42)) <1994LA1037>. This reaction also proceeds via the nitrile oxide.

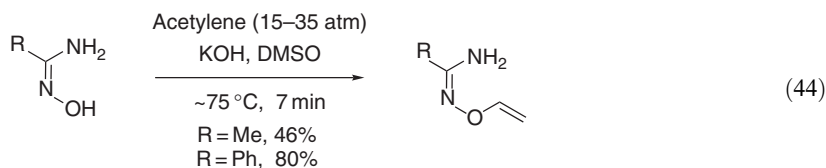


5.19.2.2.3 *N*-Imidoylhydroxylamines by miscellaneous methods

O-Alkylation and *O*-acylation of amidoximes are well known (see chapter 5.19.2.2.1 of <1995COFGT(5)741>). However during the review period, *N*-arylations of *O*-methylamidoximes have been reported by a palladium-catalyzed reaction of the *O*-methylamidoxime with an aryl bromide, iodide, or an activated aryl chloride. Twelve examples are reported, a selection of which is shown in Equation (43) <2002TL4221>.



The synthesis of *O*-vinylamidoximes has been reported using KOH/DMSO as base (Equation (44)) <2001S2427> (Note: *O*-vinylamidoximes can explode on heating).

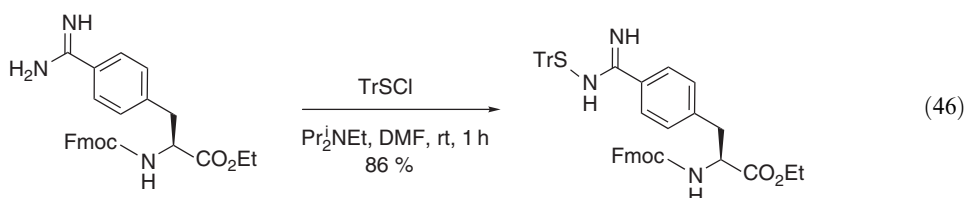
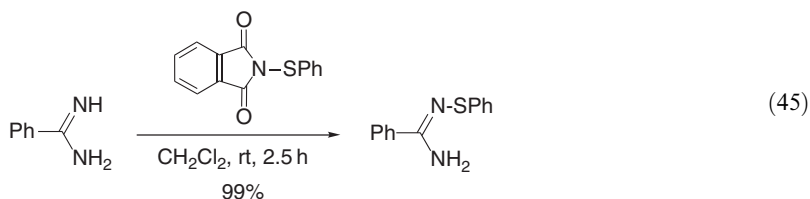


5.19.2.3 *N*-Imidoylsulfenamides, -sulfimides, -sulfinamides, and -sulfonamides

5.19.2.3.1 *N*-Imidoylsulfenamides $\text{R}^1\text{C}(\text{NR}^2)\text{NR}^3\text{SR}^4$

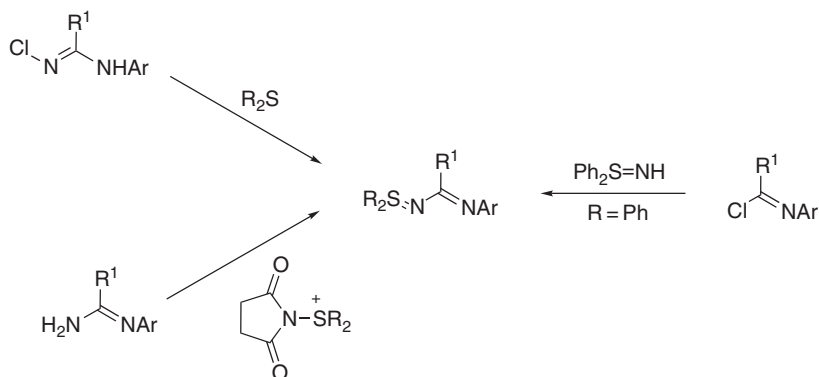
N-Imidoylsulfenamides, also known as sulfenylamidines, are stable materials which are often isolated as crystalline, sharp melting solids; are slowly hydrolyzed by aqueous alcohol. *N*-Imidoylsulfenamides are prepared by the reaction of an amidine with a sulfenyl chloride

or other sulfenating agent. Examples are tabulated in chapter 5.19.2.3.1 of <1995COFGT(5)741>. Recent examples include the high-yielding sulfenation of benzamidine with *N*-(phenylthio)phthalimide (Equation (45)) <1993JA7584>. Very hindered sulfenating agents such as tritylsulfonyl chloride also give good yields of the desired *N*-imidoylsulfenamide (Equation (46)) <1996JMC1372>.

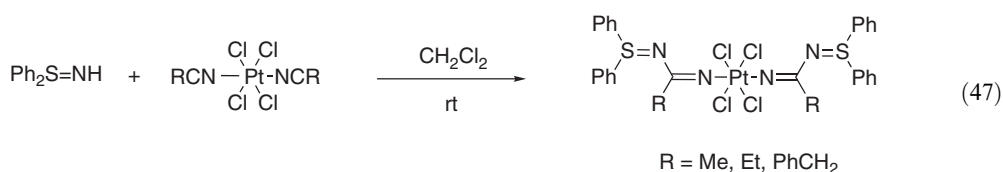


5.19.2.3.2 *N*-Imidoylsulfimides

N-Imidoylsulfimides are prepared by three general methods, from either *N*-chloroamidines, amidines, or imidoyl chlorides. These are shown in Scheme 21. References for these preparations can be found in chapter 5.19.2.3.2 of <1995COFGT(5)741> or in a review by Gilchrist and Moody <1977CRV409>. Since the publication of the chapter there has been little research activity into the preparation of *N*-imidoylsulfimides. One exception is the discovery that sulfimide ($\text{Ph}_2\text{S}=\text{NH}$) will undergo a platinum-mediated coupling reaction with a nitrile to give a platinum amidine complex (Equation (47)) <2003IC301> (see also <2001EJI263>).

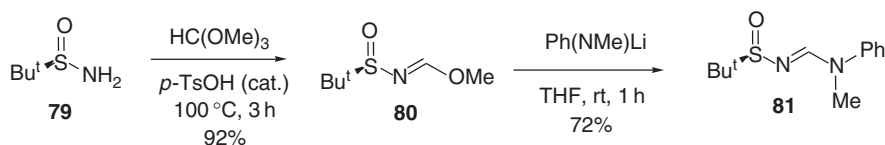


Scheme 21



5.19.2.3.3 *N*-Imidoysulfonamides

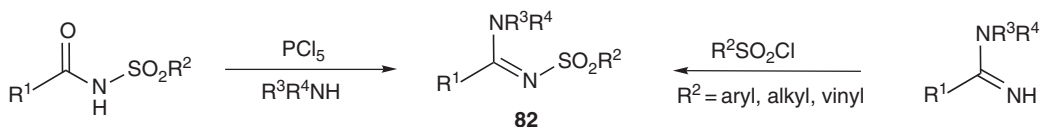
N-Imidoysulfonamides can be prepared by the reaction of a sulfonamide **79** with trimethyl orthoformate to give the imidate **80**, which subsequently undergoes reaction with the lithium salt of *N*-methylaniline to give the desired *N*-imidoysulfonamide **81** (Scheme 22) <2003JOC3>. The imidate **80** also undergoes reaction with dimethylamine in THF to give an imidoysulfonamide <2001JA1539>. The stereochemistry of the sulfonamide is maintained through the reaction sequence and this is important as these reactions are used to build up chiral ligands for catalysis. Racemic sulfonamides can be prepared by reaction of a silylated amidine with 4-toluenesulfinyl chloride <1997CJC1188>.



Scheme 22

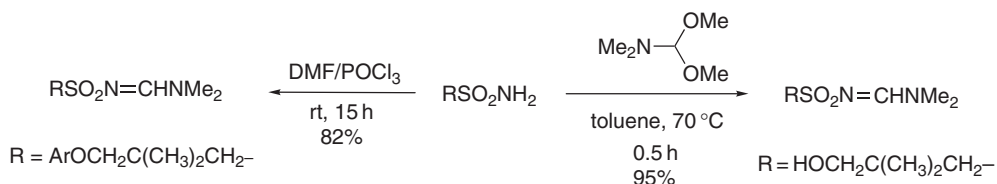
5.19.2.3.4 *N*-Imidoysulfonamides

Two of the most common ways of making *N*-imidoysulfonamides **82** are by direct sulfonation of the amidine (Scheme 23) or by converting an *N*-sulfonylcarboxamide into its imidoysulfonamide followed by reaction with an amine or ammonia to give the imidoysulfonamide **82** (Scheme 23). Both of these approaches were covered in chapter 5.19.2.3.4 of <1995COFGT(5)741>.



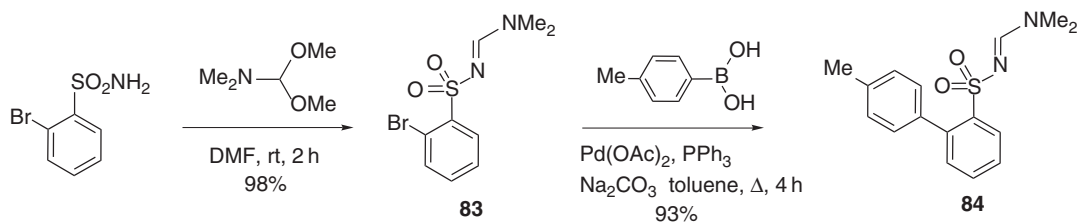
Scheme 23

The preparation of *N*-imidoysulfonamides from sulfonamides and imidates was also covered in chapter 5.19.2.3.4 of <1995COFGT(5)741>. In the review period, sulfonamides have also been shown to react under Vilsmeier conditions to give *N*-imidoysulfonamides (Scheme 24) <1996CPB122> (see also <1997JFC25>), and to react with DMF-dimethyl acetal to give *N*-imidoysulfonamides in very high or quantitative yields (Scheme 24) <1997CPB1447, 1997JHC43, 2002OPP545>. The reaction works for both aryl and alkyl sulfonamides but is only successful for primary sulfonamides (e.g., RSO₂NH₂). The reaction of secondary sulfonamides with DMF-dimethyl acetal does not form the *N*-imidoysulfonamide, instead *N*-methylation of the sulfonamide nitrogen takes place <1997JHC43, 2002OPP545>.



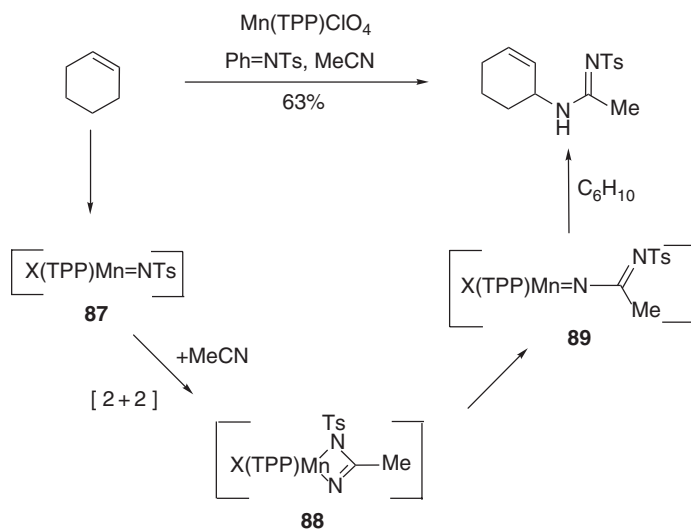
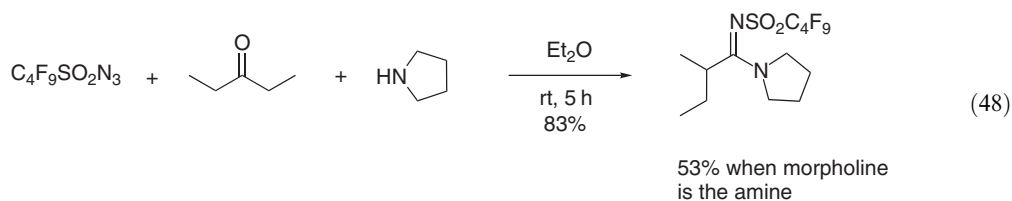
Scheme 24

A particularly useful variant of the DMF-dimethyl acetal chemistry was reported by workers at Hoechst Roussel. 2-Bromobenzenesulfonamide was treated with DMF-dimethyl acetal at room temperature to give the *N*-imidoysulfonamide **83** in 98% yield. Performing a Suzuki reaction on **83** gave **84** in 93% yield. Hence, this methodology could then give access to a wide variety of *N*-imidoysulfonamides by using different boronic acids (Scheme 25) <1995JMC2357>.

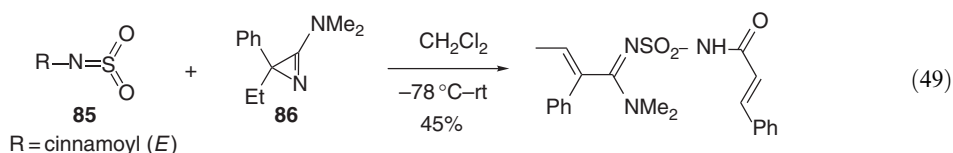


Scheme 25

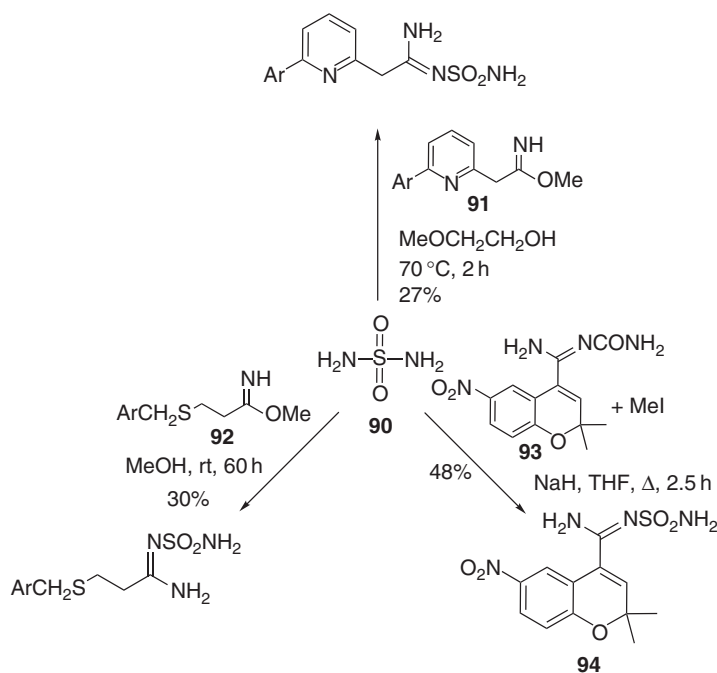
In the review period a number of new methods have been reported for making *N*-imidoyl-sulfonamides. These include the reaction of a ketone, an amine, and a fluoroalkanesulfonyl azide (Equation (48)) <2000S513>, the reaction an *N*-sulfonylamine **85** with a dimethylaminoazirine **86** (Equation (49)) <1996JCS(P1)1629> and through an insertion reaction of cyclohexene which was discovered by Evans and co-workers (Scheme 26) <1994JA2742>. Evans proposed that the initially formed metal catalyst **87** undergoes a [2+2]-reaction with the solvent acetonitrile to give **88** which rearranges to **89** prior to allylic insertion (Scheme 26) <1994JA2742>.



Scheme 26



A number of recent papers report the preparation of *N*-imidoylsulfonamides from sulfamide **90** and are shown in Scheme 27. The imidic esters **91** and **92** are prepared via a Pinner reaction, and subsequent reaction with sulfamide gives the *N*-imidoylsulfonamide <1994JMC57, 1997CPB116>. Sulfamide will also react with the methylation product of **93** to give the *N*-imidoylsulfonamide **94** (Scheme 27) <1994BMCL1995>.

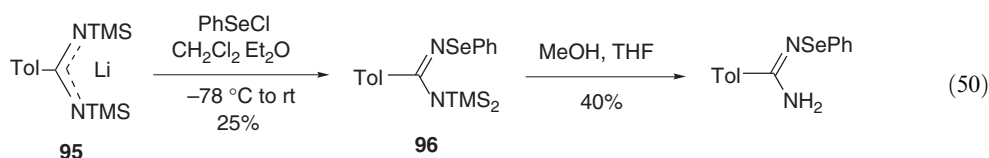


Scheme 27

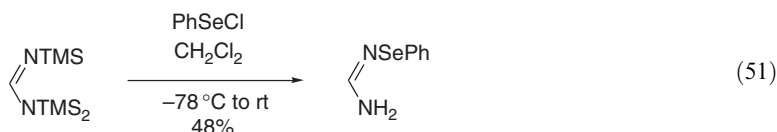
5.19.2.3.5 Amidine derivatives with an *N*-selenium or *N*-tellurium bond

(i) Amidine derivatives with an *N*-selenium bond

The number of amidine derivatives with an *N*-selenium bond has increased in recent years mainly due to the research efforts of the Chivers group. Treatment of the lithium salt of the disilylamidine **95** with phenylselenium chloride gave the selenium derivative **96** as an off-white solid in 25% isolated yield. The derivative **96** could be treated with 1 equiv. of methanol in THF, with gentle heating to give the desilylated compound as dark purple crystals (Equation (50)) <1995CJC1380>.

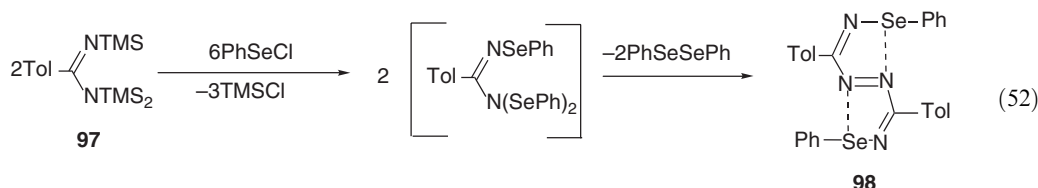


Tris(trimethylsilyl)formamidine was treated with phenylselenium chloride to give the selenium derivative with concomitant desilylation (Equation (51)) <1995CJC1380>. A single crystal X-ray structure was reported for the product.



Treatment of the tris(trimethylsilyl)amidine **97** with 3 equiv. of phenylselenium chloride produces an intensely colored purple solution upon warming to room temperature. The reaction is thought to proceed via the tris(seleno)amidine followed by “dimerization” with elimination of diphenyl diselenide to give the purple diazene **98** (Equation (52)) <1994IC2364> (see also <1996IC5836>). In a close analog, the diazene nitrogen–selenium bond distance is reported to

be around 2.65 Å (cf. 3.5 Å for the sum of the van der Waals radii for selenium and nitrogen) [<1990JA5373>](#) and the authors suggest there is some nitrogen–selenium bonding interaction (shown by the broken lines) for the diazene **98**.



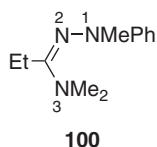
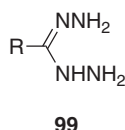
(ii) Amidines with an *N*-tellurium bond

Preparations of these derivatives were covered in chapter 5.19.2.3.5 of [<1995COFGT\(5\)741>](#) (see also [<1988JOM\(352\)C1>](#)). No major advances have been made since the publication of this chapter.

5.19.2.4 Amidrazones and Related Structures

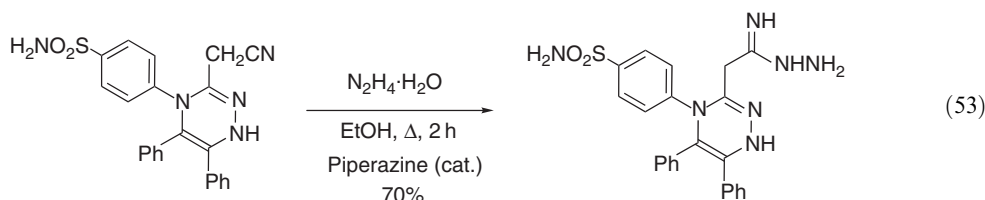
5.19.2.4.1 Introduction and nomenclature

Amidrazones are also known as hydrazidines, amide hydrazines, or *N*-imidoylhydrazines. In this review the name hydrazidines will be used for structures such as **99**. There have been two previous reviews on amidrazones by Neilson and co-workers [<1970CRV151, B-1975MI491>](#) as well as the review in [<1995COFGT\(5\)741>](#) (see also [<1995COFGT\(5\)805>](#)). This review in conformance with previous reviews will number the nitrogen atoms as shown for compound **100** and is therefore named *N*¹-phenyl-*N*¹,*N*³,*N*³-trimethylpropanamidrazone.



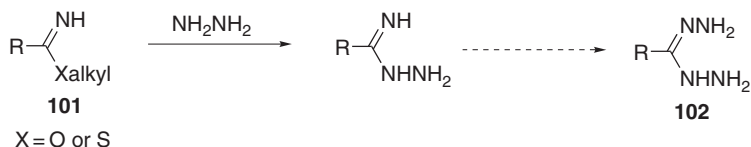
5.19.2.4.2 Primary amidrazones, *RC*(NH)NHNH₂

The preparation of primary amidrazones from the reaction of hydrazine with a nitrile is covered in chapter 5.19.2.4.2 of [<1995COFGT\(5\)741>](#). More recent examples include [<2000MI208>](#) as shown in [Equation \(53\)](#) and [<1993MI223, 1999MI176>](#).



The most common method of preparing primary amidrazones is through a substitution reaction of imidic esters (**101**, X = O) with hydrazine ([Scheme 28](#)) [<1961CRV179, 1970CRV151, B-1975MI385>](#). Care has to be taken with the hydrazine stoichiometry and the reaction temperature to avoid formation of the hydrazidine **102**.

The preparation of primary amidrazones from thioimidic esters (**101**, X = S) and from thioamides is covered in chapter 5.19.2.4.2 of [<1995COFGT\(5\)741>](#).

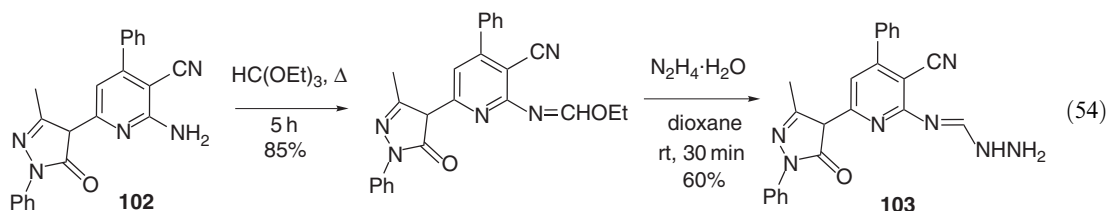


Scheme 28

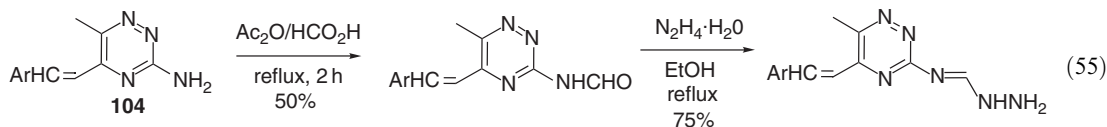
5.19.2.4.3 *N*-Alkyl-, aryl-, or alkenyl-substituted amidrazones

(i) *N*-Substituted amidrazones from hydrazines

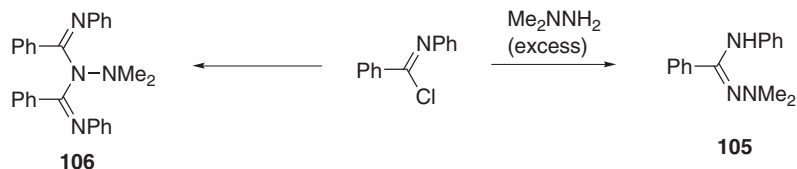
Imidic esters react with hydrazine, mono-, di-, and trisubstituted hydrazines to give substituted amidrazones. The reaction of imidic esters with monosubstituted and especially *N,N*-disubstituted hydrazines gives amidrazones with fewer side products than the equivalent reaction with hydrazine. A convenient method for preparing formamidrazones is to heat an amine such as **102**, with triethyl orthoformate to give the imidate, which can then undergo reaction with hydrazine, or a substituted hydrazine to give the formamidrazone **103** (Equation (54)) <2002JHC309>. For similar examples, see <1993S1129, 1997PHA28>.



Another option is to convert the amine such as **104** into the formamide. The formamide is reactive enough to form the formamidrazone directly with hydrazine (Equation (55)) <1999PHA667>.



Imidoyl chlorides are a very good source of amidrazones though the high reactivity of the imidoyl chloride can lead to some loss of selectivity. Hence, *N*-phenylbenzimidoyl chloride cleanly forms the trisubstituted amidrazone **105** with a large excess of 1,1-dimethylhydrazine, but with 2 equiv. of 1,1-dimethylhydrazine a mixture of **105** and **106** is obtained (Scheme 29) <1970CRV151>. For more recent examples of amidrazones prepared from imidoyl chlorides, see <1998JA2989, 2002JMC2942>.

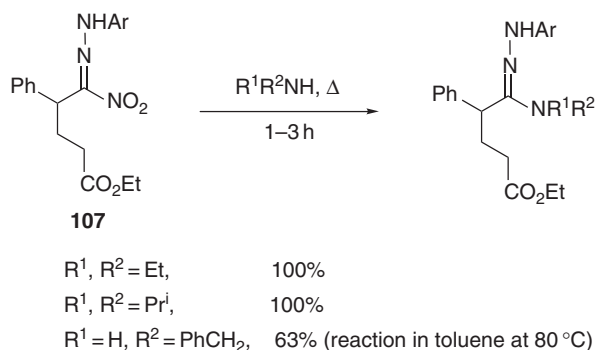


Scheme 29

The preparation of *N*-substituted amidrazones from the reaction of hydrazine with thioamides, triazine, formamide acetals, and ketenamines is covered in chapter 5.19.2.4.3 of <1995COFGT(5)741>.

(ii) *N*-Substituted amidrazones from amines and ammonia

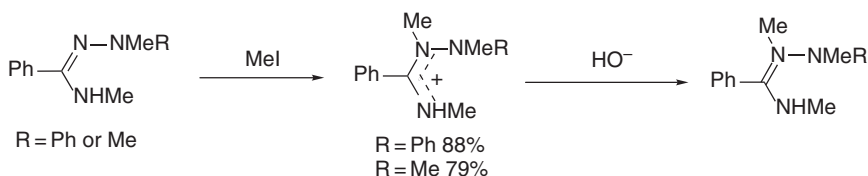
Amidrazones can be prepared by reaction of a primary or secondary amine with an α -nitrohydrazone **107** (Scheme 30) <2002TL8925> (see also <1977JOC2091>). α -Nitrohydrazones can also be hydrogenated over Raney nickel to give amidrazones <1951LA(574)85> and <1955CB1284>.



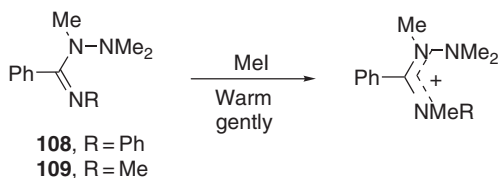
Scheme 30

(iii) *N*-Substituted amidrazones by *N*-alkylation of simpler amidrazones

The alkylation of amidrazones has been studied by Smith and co-workers <1971JOC1155, 1973JOC1344, 1977JOC1862>. Depending upon the substitution pattern, alkylation can occur on any of the three nitrogen atoms, but in most cases alkylation occurs at N^2 or N^3 so that an “amidinium like” delocalized cation is formed. Scheme 31 gives an example of N^2 alkylation via a delocalized cation, whereas in Scheme 32 amidrazones **108** and **109** are also alkylated to give a delocalized cation but via alkylation at the N^3 atom. Further examples are given in chapter 5.19.2.4.3 of <1995COFGT(5)741>, and there have been no significant advances since the publication of that chapter.



Scheme 31

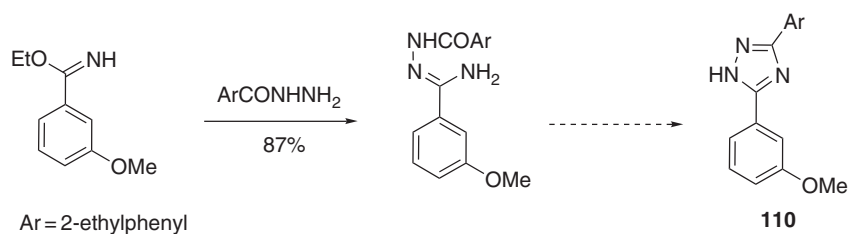


Scheme 32

5.19.2.4.4 *N*-Acylamidrazones(i) N^1 -Acylamidrazones

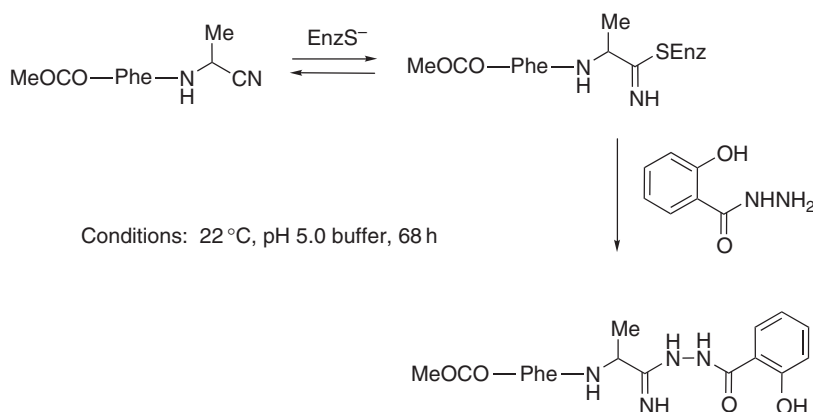
Primary amidrazones are generally acylated directly at N^1 in good yield <B-1975MI491>. N^3 -Phenylbenzamidrazone is also acylated at N^1 <1971CB639>. Another way of making N^1 -acylamidrazones is by the reaction of acylhydrazines with imidic esters. Not surprisingly,

the reaction is slower and much cleaner than the reaction of imidic esters with hydrazine. Some care must be taken to avoid cyclization to the triazole e.g., **110** (see Scheme 33) <1983JMC1187>.



Scheme 33

A new method of preparing N^1 -acylamidrazones from acyl hydrazines is to use an engineered papain nitrile hydratase (Scheme 34) <1998MI78>. The authors report that this method can avoid a number of the side products which can be formed from the reaction of nitriles with hydrazides.

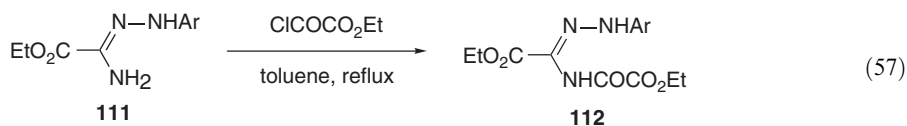
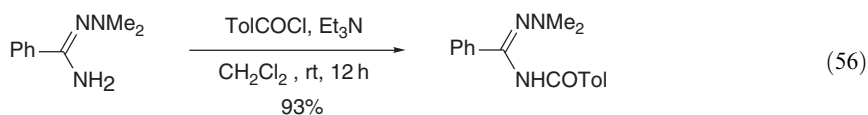


Scheme 34

Further examples of making N^1 -acylamidrazones and N^1 -acylformidrazones can be found in chapter 5.19.2.4.4 of <1995COFGT(5)741>.

(ii) N^3 -Acylamidrazones

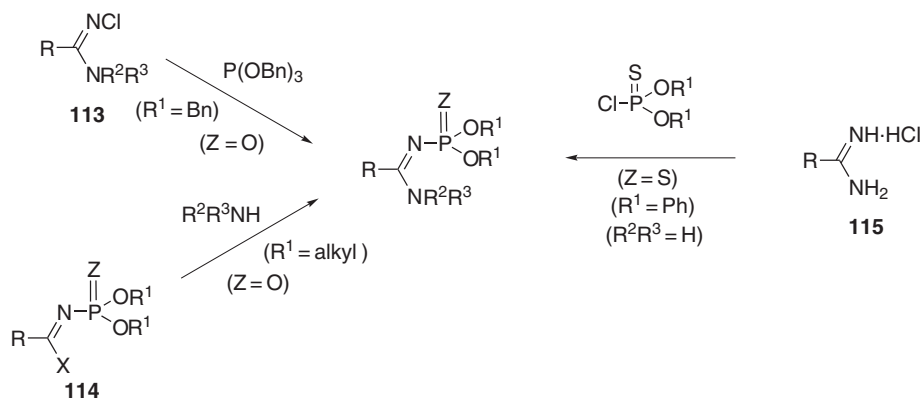
N^1, N^1 -Disubstituted amidrazones are acylated on the N^3 -atom (Equation (56)) <1983JHC69>. The N^1 -aryl-substituted amidrazone **111** was also reported to acylate on N^3 to give **112** (Equation (57)) <2001JMC3157>.



5.19.2.5 Amidine Derivatives with an N—P, N—As, or N—Sb Bond

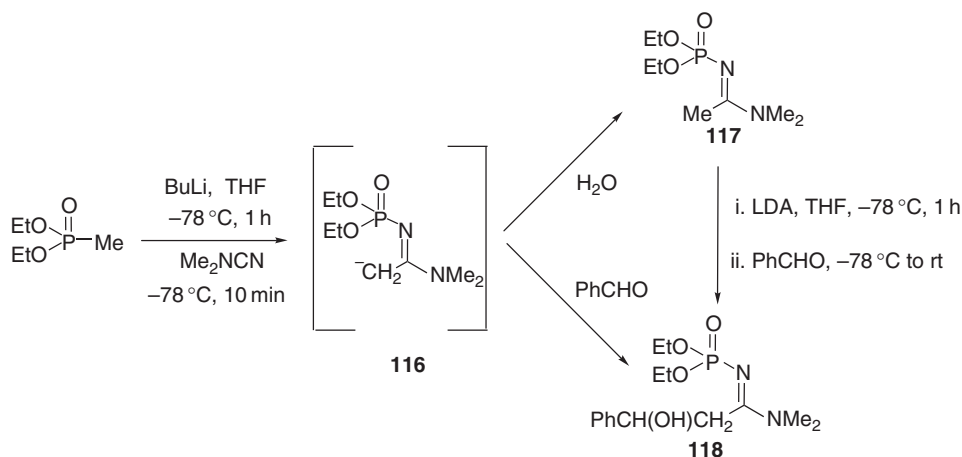
5.19.2.5.1 *N*-Phosphorylamidine derivatives

Several methods of preparing *N*-phosphorylamidine derivatives were outlined in chapter 5.19.2.5.1 of <1995COFGT(5)741>. Three of the most common methods are shown in Scheme 35. *N*-Phosphorylamidines can be prepared from *N*-chloroamidines **113** via an Arbusov-type reaction with tribenzyl phosphite. *N*-Phosphorylamidines may also be prepared from imidoyl esters (**114**, X = OR) or imidoyl chlorides (**114**, X = Cl) and amines, and from thiophosphorylation of amidines **115** (Scheme 35).



Scheme 35

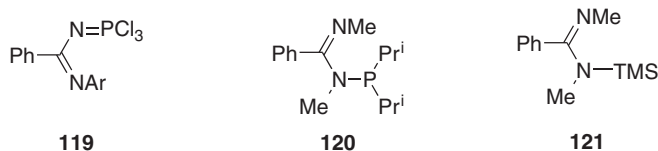
A new method of making *N*-phosphorylamidines involves the reaction of α -lithioalkyl phosphonates with cyanamides. Following initial addition to the nitrile, there is a migration of the phosphoryl group to give the anion of the *N*-phosphorylacetamidine **116**. This anion can be quenched with water to give **117** or benzaldehyde to give **118**. Quenching with other electrophiles such as methyl iodide, allyl bromide, or TMSCl is also possible <1998CC609>. The *N*-phosphorylacetamidine **117** can also be deprotonated and quenched with an electrophile (Scheme 36), hence giving access to a wide range of phosphorylamidines.



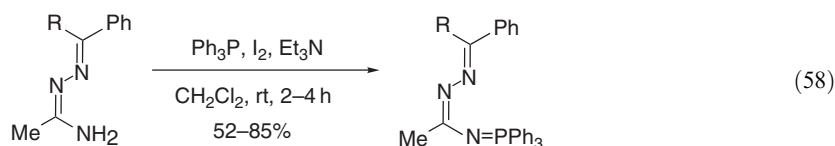
Scheme 36

5.19.2.5.2 *N*-Phosphorus amidines (excluding *N*-phosphorylamidines)

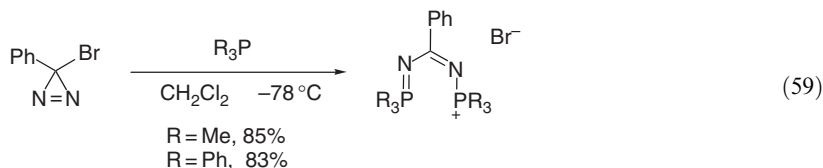
Chapter 5.19.2.5.2 of <1995COFGT(5)741> gives several methods of making these compounds; for example, the ylide **119** can be prepared from the corresponding *N*-chlorobenzamidine derivative by the high-yielding reaction with phosphorus trichloride. The phosphinoamidine **120** can be prepared by the reaction of diisopropylphosphorus chloride with the trimethylsilylamidine **121**.



An alternative way of preparing N—P ylides that has been reported in the review period is via the reaction of an amide with triphenylphosphine in the presence of iodine (Equation (58)) <2002JHC845>.



Reaction of a bromodiazirine with trimethyl or triphenylphosphine gave the bisphosphorus adducts in high yield (Equation (59)) <1994JA2159, 1996JA1060>. The π -electrons in the bisphosphorus adducts are fully delocalized over the nitrogen and phosphorus atoms and the amidine carbon.

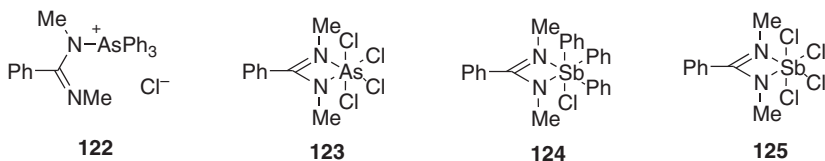


5.19.2.5.3 Amidines with an *N*-arsenic bond

Arsoranylbendamidine derivatives **122** and **123** are prepared from the reaction of *N*-chloro-*N,N'*-dimethylbenzamidine with triphenylarsane or arsenic trichloride, respectively, as described in chapter 5.19.2.5.3 of <1995COFGT(5)741>. No major advances have occurred since the publication of this chapter.

5.19.2.5.4 Amidines with an *N*-antimony bond

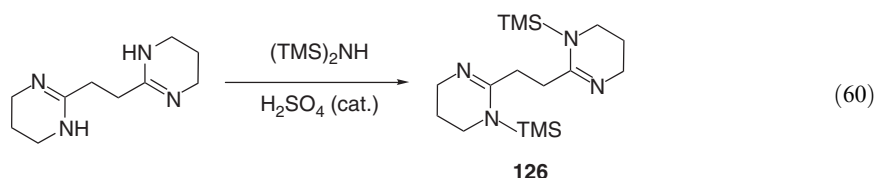
The antimony–benzamidine complexes **124** and **125** are prepared from *N*-chloro-*N,N'*-dimethylbenzamidine and triphenylantimony and antimony trichloride, respectively. Unlike the arsenic derivative **122**, antimony prefers the chelated structure **124** <1980CB1394>. No major advances have occurred since the publication of <1995COFGT(5)741>.



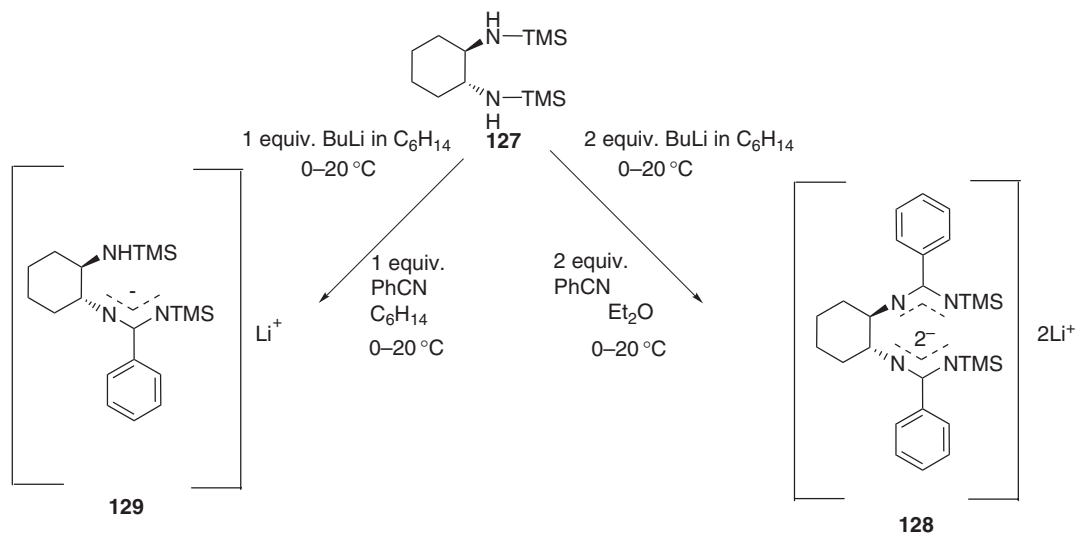
5.19.2.6 Amidine Derivatives with an *N*-Metalloid Bond5.19.2.6.1 *N*-Silylamidines

(i) Monosilylamidines

Examples of the preparation of monosilylamidines from the lithium salt of a silylated amine and an imidoyl chloride or by direct silylation of amidines with trimethylsilyl chloride are given in chapter 5.19.2.6.1 of <1995COFGT(5)741>. The diamidine is silylated with an excess of bis(trimethylsilyl)amide to give **126** (Equation (60)) <1981JA4186>.

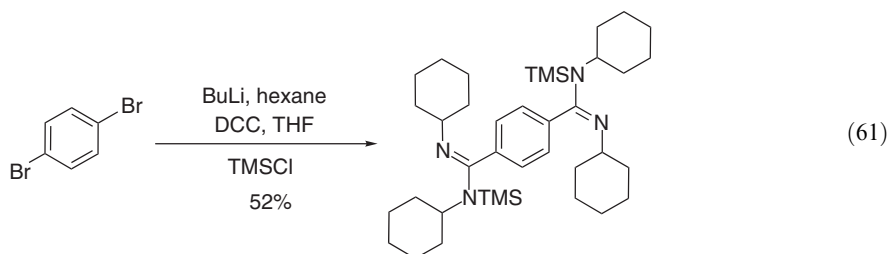


The bis-silylated diamine **127** undergoes deprotonation and reaction with 2 equiv. of benzonitrile in diethyl ether to give the bis(monosilyl)amidine **128** which can be isolated as the dilithium salt (Scheme 37) <2002JCS(D)1401> (see also <2002CC958>). With 1 equiv. of benzonitrile, the monoamidine salt **129** is formed and a crystal structure of this compound is available <2002JCS(D)1401>.



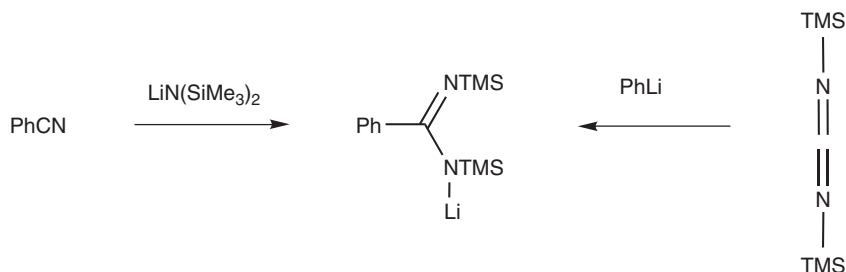
Scheme 37

When 1,4-dibromobenzene is treated with 2 equiv. of butyllithium, a double metal halogen exchange reaction occurs, and subsequent reaction with two molecules of dicyclohexylcarbodiimide followed by silylation produced the silylated amidine (Equation (61)) <2002JOM(662)178>.



(ii) *Disilylamidines*

The preparation of disilylamidines was covered in chapter 5.19.2.6.1. of <1995COFGT(5)741>. The main methods are the addition of the lithium or calcium salt of bis(trimethylsilyl)amide to a nitrile, or the addition of a lithium carbanion to *N*¹,*N*³-bis(trimethylsilyl)carbodiimide. Both approaches are shown in Scheme 38.



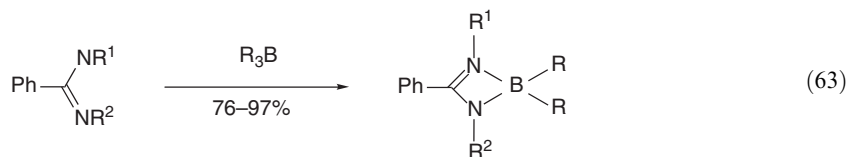
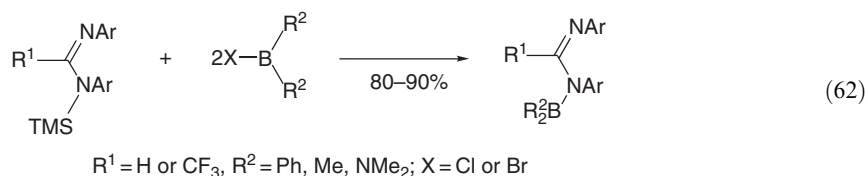
Scheme 38

(iii) *Trisilylamidines*

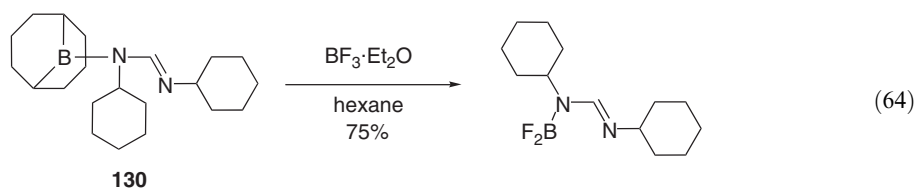
The preparations of *N,N,N'*-tris(trimethylsilyl)benzamidine and its derivatives are described in chapter 5.19.2.6.1 of <1995COFGT(5)741> (see also <2002IC2014>).

5.19.2.6.2 *N*-Borylamidines

A large number of borylamidines have been reported. These borylamidines may be mono-coordinate such as those prepared in Equation (62) <1978ZAAC(445)107>, a reference that gives the preparation of over 30 borylamidines, or di-coordinate such as those prepared by the method outlined in Equation (63) (Note: $\text{R}_2\text{B-S-alkyl}$ can also be used as the reagent) <1978BAU2304>. Many other methods of making borylamidines are given in chapter 5.19.2.6.2 of <1995COFGT(5)741>.



In the review period, the borylamidine **130** was prepared by a hydroboration reaction of a carbodiimide with 9-BBN. This compound undergoes a boron exchange reaction with boron trifluoride to give the difluoroborylamidine in 75% yield (Equation (64)) <1994ZN(B)1453>.

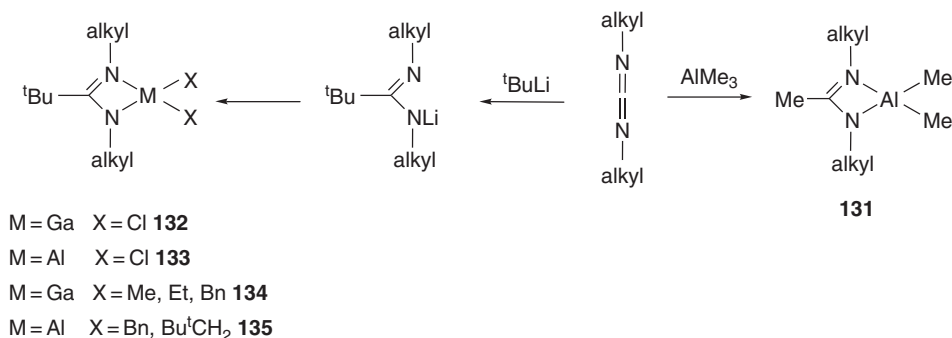


5.19.2.7 Amidine Derivatives with an *N*-Metal Bond, $R^1C(NR^2)NR^3-M$

Amidines form salts with alkali and alkaline earth metals and complexes with most other metals. The amidinato ligand can be either η^1 or η^2 with π -type or $N-M$ σ -bonding. A comprehensive 78 page review by Eldemann <1994CCR403> gives details of *N*-silylated benzamidine complexes with main group elements, transition metals, and actinide elements.

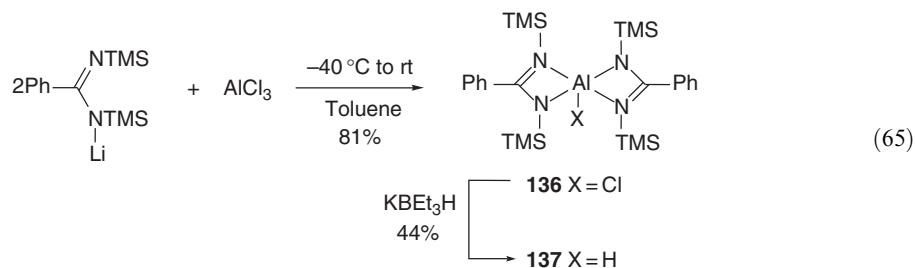
5.19.2.7.1 Amidines with an *N*-metal bond, where *M* is a group 13 metal

Amidine complexes with aluminum, gallium, indium, and thallium were reported in chapter 5.19.2.7.1 of <1995COFGT(5)741>. Since the publication of the chapter there has been a large number of publications which include amidine complexes of group 13 metals. One general method of preparing aluminum or gallium complexes is shown in Scheme 39. Treatment of carbodiimides with trimethylaluminum gives the dimethylaluminum acetamidine complex **131** (alkyl = *i*Pr, *t*Bu, cyclohexyl). Alternatively, the carbodiimide can be treated with an alkyl- or aryllithium to give the lithium salt of the amidine which can be further treated with gallium trichloride to give **132** or aluminum trichloride to give **133**. Treatment of either **132** or **133** with a Grignard reagent gave **134** and **135** respectively, in good yield <1997OM5183, 1999OM4619>, for examples starting from a carbodiimide and an aryllithium see <2001OM5532> and <2002OM2306>.



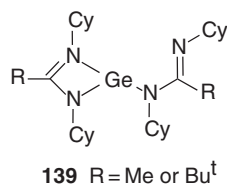
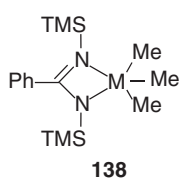
Scheme 39

N,N'-Bis(trimethylsilyl)benzamidine forms a 2:1 complex **136** with aluminum trichloride in high yield as shown in Equation (65). The chloroaluminum complex **136** can be converted into the hydroaluminum complex **137** by treatment with potassium triethylborohydride (Equation (65)) <1996CC223>. For examples of indium and thallium complexes, see <2002OM2145>.



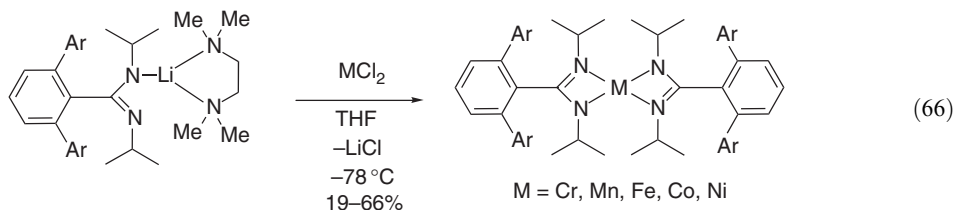
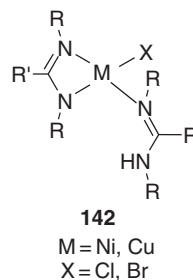
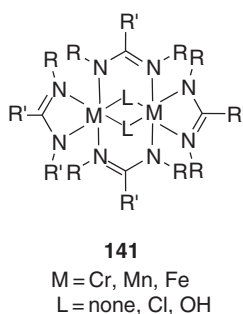
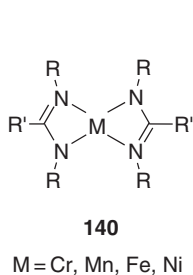
5.19.2.7.2 Amidines with an *N*-metal bond where *M* is a group 14 metal

In chapter 5.19.2.7.2 of <1995COFGT(5)741>, the preparation of the germanium, tin, or lead complexes (**138**, M = Ge, Sn, Pb) was reported. The germanium complexes (**139**, R = Me, Bu^t) are prepared from 2 equiv. of the lithium amidinate and a metal source <1997JA10359, 1999OM4700>. For other examples of tin and germanium complexes of amidines, see <1996JA10850, 1997IC501, 2000JCS(D)1663>.



5.19.2.7.3 Amidines with an *N*-metal bond where *M* is a transition metal

Amidines form complexes with most transition metals and with all first row transition metals. These complexes were reviewed in chapter 5.19.2.7.3 of <1995COFGT(5)741> and in more detail by Barker and Kilner <1994CCR219>. Since the publication of these two reviews there have been many further complexes reported. Common structural motifs for first row transition metals are **140–142** <2002JCS(D)3454>. A series of hindered amidine complexes were prepared from the corresponding lithium salts (Equation (66)) <2002JCS(D)3454>.



Lead references for amidine complexes of some common transition metals including all of the first row transition metals are given in Table 4.

5.19.2.7.4 Amidines with an *N*-metal bond, where *M* is a lanthanide or actinide metal

The preparation of lanthanide complexes with silylated amidines $\text{Ln}[4\text{-RC}_6\text{H}_4\text{C}(\text{N-TMS})_2]_3$ was described in chapter 5.19.2.7.4 of <1995COFGT(5)741>. In the review period the preparation of lanthanide complexes of *N,N'*-dicyclohexylacetamidine and *N,N'*-dicyclohexylbenzamidine have also been reported <2002JOM(662)144>. Carbodiimides can be inserted into the Ln—C bond of organolanthanide complexes as shown in Equation (67) <2002OM1420>. For other examples of amidinate lanthanide complexes see <1995CB395, 1997JCS(D)1945> and <1999OM5360>.

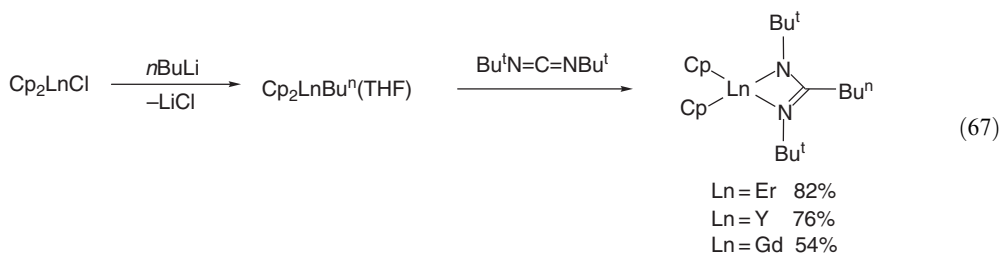
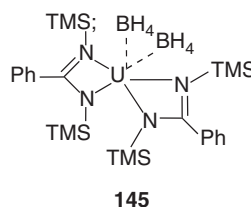
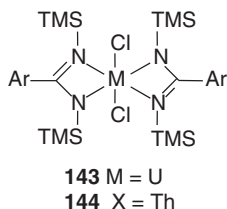


Table 4 Amidine complexes of some common transition metals

<i>Metal</i>	<i>References</i>
Ag	<2001JOM(634)167>
Co	<2002JCS(D)3454>
Cr	<2002CC2914, 2002JCS(D)3454, 1991ZN(B)1328>
Cu	<2002JCS(D)3454, 1993JOM(456)299>
Fe	<2002CC958, 2002JCS(D)3454, 1991ZN(B)1328>
Hg	<1991ZN(B)1328>
Hf	<2003OM21>
Mn	<2002JCS(D)3454, 1991ZN(B)1328>
Mo	<2002JOM(663)78, 1998JCS(D)4147>
Ni	<2002JCS(D)3454, 2001ZAAC1560>
Pd	<1996CJC2018>
Pt	<1996CJC2018>
Ru	<2002OM4315, 2001BCJ1927, 2001JOM(634)167>
Sc	<2002JCS(D)1694>
Ta	<2001OM3531, 2000JOM(607)227>
Ti	<2003EJC427, 2003OM609, 2002JCS(D)4175, 2001JCS(D)1392, 2000OM2823>
V	<1993OM1794>
W	<1998OM854>
Zn	<1991ZN(B)1328>
Zr	<2003OM21, 2002JA5932, 2001CC2144>

The preparation of amidinato complexes with the actinide elements, uranium and thorium was covered in chapter 5.19.2.7.4 of <1995COFGT(5)741>. With less sterically demanding amidinato ligands, complexes such as, $[4\text{-CF}_3\text{C}_6\text{H}_4\text{C}(\text{N-TMS})_2\text{MCl}]$ ($\text{M} = \text{U}, \text{Th}$) are formed with the metal in the +4 oxidation state. With sterically more demanding ligands complexes such as, **143** and **144** are formed <1990JOM(338)21>. During the review period the preparation of further uranium complexes for example, **145** <1998IC1315> has also been reported.



ACKNOWLEDGEMENTS

The author would like to thank Mr. D. F. Wood and Dr. S. Narayanaswami for conducting the computer literature searches for this review.

REFERENCES

- 1877CB1899 A. Pinner, F. Klein, *Ber. Dtsch. Chem. Ges.* **1877**, 10, 327.
 1944CRV351 R. L. Shriner, F. W. Neumann, *Chem. Rev.* **1944**, 35, 351–425.
 1951LA(574)85 D. Jerchel, H. Fischer, *Liebigs Ann. Chem.* **1951**, 574, 85–98.
 1952HOU(8)702 H. Henecka, P. Kurtz, *Methoden Org. Chem. (Houben-Weyl)* **1952**, 8, 702–706.
 1955CB1284 D. Jerchel, W. Edler, *Chem. Ber.* **1955**, 88, 1284–1295.
 1958HOU(9)39 H. Soll, *Methoden Org. Chem. (Houben-Weyl)* **1958**, 9, 39–69.
 1959CB837 H. Brederick, R. Gompper, K. Klemm, H. Rempfer, *Chem. Ber.* **1959**, 92, 837–849.
 1961CRV179 R. Roger, D. G. Neilson, *Chem. Rev.* **1961**, 61, 179–211.
 1962CRV155 F. Eloy, R. Lenaers, *Chem. Rev.* **1962**, 62, 155–183.
 1965CJC2640 G. R. Pettit, L. R. Garson, *Can. J. Chem.* **1965**, 43, 2640–2644.
 1968JOC1679 L. Weintraub, S. R. Oles, N. Kalish, *J. Org. Chem.* **1968**, 33, 1679–1681.
 1970CRV151 D. G. Neilson, R. Roger, J. W. M. Heatlie, L. R. Newlands, *Chem. Rev.* **1970**, 70, 151–170.
 1971BCF478 J.-A. Gautier, M. Miocque, C. Fauran, A. Y. Le Cloarec, *Bull. Soc. Chim. Fr.* **1971**, 478–482.

- 1971CB639 H. Reimlinger, W. R. F. Lingier, J. J. M. Vandewalle, *Chem. Ber.* **1971**, *104*, 639–644.
- 1971JOC1155 R. F. Smith, D. S. Johnson, C. L. Hyde, T. C. Rosenthal, A. C. Bates, *J. Org. Chem.* **1971**, *36*, 1155–1158.
- 1972FRP2081556 Gautier, J.-A.; Miocque, M.; Le Cloarec, A. Y.; Furan, C.; Raynaud, G.; Pourrias, B. Fr. Pat. 2 081 556 (1972) (*Chem. Abstr.* **1972**, *77*, 34 128c).
- 1973JOC1075 C. D. Wright, J. L. Zollinger, *J. Org. Chem.* **1973**, *38*, 1075–1080.
- 1973JOC1344 R. F. Smith, D. S. Johnson, R. A. Abgott, M. J. Madden, *J. Org. Chem.* **1973**, *38*, 1344–1348.
- 1973USP3726903 Kosher, R. J.; Wright, C. D.; Zollinger, J. L.; Dybvig, D. H.; Husted, D. R. U.S. Patent, 3726903 (1973) (*Chem. Abstr.* **1973**, *79*, 41987b).
- B-1975MI283 J.-A. Gautier, M. Miocque, C. C. Farnoux, in *The Chemistry of Amidines and Imidates*, S. Patai, Ed., Vol. 1, Wiley, New York, **1975**, pp. 283–349.
- B-1975MI385 D. G. Neilson, in *The Chemistry of Amidines and Imidates*, S. Patai, Ed., Vol. 1, Wiley, New York, **1975**, pp. 385–489.
- B-1975MI491 K. M. Watson, D. G. Neilson, in *The Chemistry of Amidines and Imidates*, S. Patai, Ed., Vol. 1, Wiley, New York, **1975**, pp. 491–545.
- 1976AJC357 L. H. Briggs, R. C. Cambie, I. C. Dean, P. S. Rutledge, *Aust. J. Chem.* **1976**, *29*, 357–366.
- 1976JCS(P1)2166 T. L. Gilchrist, C. J. Harris, D. G. Hawkins, C. J. Moody, C. W. Rees, *J. Chem. Soc., Perkin Trans. 1* **1976**, 2166–2170.
- 1977CRV409 T. L. Gilchrist, C. J. Moody, *Chem. Rev.* **1977**, *77*, 409–435.
- 1977JOC1523 E. C. Taylor, J. L. LaMattina, *J. Org. Chem.* **1977**, *42*, 1523–1527.
- 1977JOC1862 R. F. Smith, L. L. Kinder, D. G. Walker, L. A. Buckley, J. M. Hammond, *J. Org. Chem.* **1977**, *42*, 1862–1865.
- 1977JOC2091 H. Feuer, L. F. Spinicelli, *J. Org. Chem.* **1977**, *42*, 2091–2094.
- 1978BAU2304 B. M. Mikhailov, V. A. Dorokhov, L. I. Lavrinovich, *Bull. Acad. Sci. USSR, Div. Chim. Sci. (Eng. Transl.)* **1978**, *27*, 2304.
- 1978JMC273 P. F. Fabio, T. L. Fields, Y.-i. Lin, J. Burden, S. Carvajal, K. C. Murdock, S. A. Lang Jr., *J. Med. Chem.* **1978**, *21*, 273–276.
- 1978PHA568 G. Wagner, B. Voigt, *Pharmazi* **1978**, *33*, 568–572.
- 1978ZAAC(445)107 W. Maringgele, A. Meller, *Z. Anorg. Allg. Chem.* **1978**, *445*, 107–121.
- 1979JOC3726 R. C. Schnur, *J. Org. Chem.* **1979**, *44*, 3726–3727.
- 1980CB1394 K. Hartke, H.-M. Wolff, *Chem. Ber.* **1980**, *113*, 1394–1405.
- 1980CC130 A. F. Hegarty, A. Chandler, *J. Chem. Soc., Chem. Commun.* **1980**, 130–131.
- 1980JOC3750 Y.-i. Lin, S. A. Lang Jr., S. R. Petty, *J. Org. Chem.* **1980**, *45*, 3750–3753.
- 1980S883 J. Besan, L. Kulcsar, M. Kovacs, *Synthesis* **1980**, 883–884.
- 1980TL885 A. F. Hegarty, A. Chandler, *Tetrahedron Lett.* **1980**, *21*, 885–888.
- 1981JOC2455 P. L. Barker, P. L. Gendler, H. Rapoport, *J. Org. Chem.* **1981**, *46*, 2455–2465.
- 1981JA4186 H. Yamamoto, K. Maruoka, *J. Am. Chem. Soc.* **1981**, *103*, 4186–4194.
- 1983JHC69 R. F. Smith, K. J. Coffman, S. M. Geer, *J. Heterocycl. Chem.* **1983**, *20*, 69–71.
- 1983JMC1187 A. Omodei-Sale, P. Consonni, G. Galliani, *J. Med. Chem.* **1983**, *26*, 1187–1192.
- 1983RCR377 V. G. Granik, *Russ. Chem. Rev. (Engl. Transl.)* **1983**, *52*, 377.
- 1983S35 E. Haug, W. Kantlehner, P. Speh, H.-J. Brauner, *Synthesis* **1983**, 35–37.
- 1984CHECI A. R. Katritzky, C. W. Rees, Eds., *Comp. Heterocyclic Chem.* Pergamon, Oxford, **1984**.
- 1985HOU(E5)1304 D. Schumann, *Methoden Org. Chem. (Houben-Weyl)* **1985**, *E5*, 1304–1308.
- 1985JOM(281)135 R. F. Cunico, L. Bedell, *J. Organomet. Chem.* **1985**, *281*, 135–140.
- 1986HCA1224 H. Moser, A. Fliri, A. Steiger, G. Costello, J. Schreiber, A. Eschenmoser, *Helv. Chim. Acta* **1986**, *69*, 1224–1262.
- 1986JHC1861 J. E. Johnson, J. A. Maia, K. Tan, A. Ghafouripour, P. de Meester, S. S. Chu, *J. Heterocycl. Chem.* **1986**, *23*, 1861–1868.
- 1988JOM(352)C1 K. Dehnicke, C. Ergezinger, E. Hartman, A. Zinn, K. Hoesler, *J. Organomet. Chem.* **1988**, *352*, C1–C4.
- 1988S655 J. Liebscher, *Synthesis* **1988**, 655–669.
- 1990JA5373 V. Chadrasekhar, T. Chivers, J. F. Fait, S. S. Kumaravel, *J. Am. Chem. Soc.* **1990**, *112*, 5373–5374.
- 1990JCR(S)134 M. S. Baird, I. Bruce, *J. Chem. Res. (S)* **1990**, 134–135.
- 1990JCR(M)946 M. S. Baird, I. Bruce, *J. Chem. Res. (M)* **1990**, 946–965.
- 1990JOM(338)21 M. Wedler, F. Knoesel, M. Noltemeyer, F. T. Edelman, U. Behrens, *J. Organomet. Chem.* **1990**, *338*, 21–45.
- 1990TL1969 R. S. Garigipati, *Tetrahedron Lett.* **1990**, *31*, 1969–1972.
- B-1991MI339 G. V. Boyd, in *The Chemistry of Amidines and Imidates*, S. Patai, Z. Rappoport, Eds., Vol. 2, Wiley, New York, **1991**, pp. 339–366.
- 1991ZN(B)1328 J. K. Buijink, N. Noltemeyer, F. T. Edelmann, *Z. Naturforsch. Teil B* **1991**, *46*, 1328–1332.
- B-1992MI875 D. N. Nicolaides, E. A. Varella, in *The Chemistry of Acid Derivatives Supplement B: The Chemistry of Amidoximes*, S. Patai, Ed., Vol. 2, part 2, Interscience, New York, **1992**, pp. 875.
- 1992JOC4732 A. I. Meyers, T. R. Elworthy, *J. Org. Chem.* **1992**, *57*, 4732–4740.
- 1992TL2803 M. P. Foloppe, S. Rault, M. Robba, *Tetrahedron Lett.* **1992**, *33*, 2803–2804.
- 1993BMC403 A. J. Bridges, A. Lee, C. E. Schwartz, M. J. Towle, B. A. Littlefield, *Biorg. Med. Chem.* **1993**, *1*, 403–410.
- 1993BMCL2113 N. L. Reddy, J. B. Fischer, K. J. Burke-Howie, P. Barmettler, M. R. Rhodes, E. Weber, J. F. W. Keana, *Biorg. Med. Chem. Lett.* **1993**, *3*, 2113–2116.
- 1993EJM955 P. Vicini, L. Amoretti, V. Ballabeni, E. Barocelli, M. Chiavarini, *Eur. J. Med. Chem.* **1993**, *28*, 955–961.
- 1993H1979 Y. El-Ahmad, J.-D. Brion, P. Reynaud, *Heterocycles* **1993**, *9*, 1979–1988.
- 1993JA7584 X. Creary, A. F. Sky, G. Phillips, D. E. Alonso, *J. Am. Chem. Soc.* **1993**, *115*, 7584–7592.

- 1993JMC1597 H. J. Breslin, M. J. Kukla, R. W. Tuman, M. C. Rebarchak, C. R. Bowden, *J. Med. Chem.* **1993**, *36*, 1597–1603.
- 1993JMC1811 J. A. Zablocki, M. Miyano, R. B. Garland, D. Pireh, L. Schretzman, S. N. Rao, R. J. Lindmark, S. G. Panzer-Knodle, N. S. Nicholson, B. B. Taite, A. K. Salyers, L. W. King, J. G. Campion, L. P. Feigen, *J. Med. Chem.* **1993**, *36*, 1811–1819.
- 1993JMC2168 J. Stanek, G. Caravatti, J. Frei, P. Furet, H. Mett, P. Schneider, U. Regenass, *J. Med. Chem.* **1993**, *36*, 2168–2171.
- 1993JOM(456)299 F. Olbrich, G. Schmidt, E. Weiss, U. Behrens, *J. Organomet. Chem.* **1993**, *456*, 299–303.
- 1993MI223 E. A. Mohamed, R. M. Abdel-Rahman, A. M. Tawfik, M. M. Ismail, *Pak. J. Sci. Ind. Res.* **1993**, *36*, 223–227. (*Chem. Abstr.* **1994**, *121*, 83299).
- 1993OM1794 M. Vivanco, R. Ruiz, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *Organometallics* **1993**, *12*, 1794–1801.
- 1993SI129 H. Wamhoff, E. Kroth, C. Strauch, *Synthesis* **1993**, 1129–1132.
- 1993TL6395 G. Rousselet, P. Capdevielle, M. Maumy, *Tetrahedron Lett.* **1993**, *34*, 6395–6398.
- 1994BMCL1995 T. Ishizawa, H. Koga, H. Sato, T. Makino, N. Taka, T. Takahashi, T. Sato, H. Nabata, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1995–1998.
- 1994CCR219 J. Barker, M. Kilner, *Coord. Chem. Rev.* **1994**, *133*, 219–300.
- 1994CCR403 F. T. Edelmann, *Coord. Chem. Rev.* **1994**, *137*, 403–481.
- 1994IC2364 T. Chivers, K. McGregor, M. Parvez, *Inorg. Chem.* **1994**, *33*, 2364–2369.
- 1994JA2159 G. Alcaraz, A. Baceiro, M. Nieger, G. Bertrand, *J. Am. Chem. Soc.* **1994**, *116*, 2159–2160.
- 1994JA2742 D. A. Evans, M. M. Faul, M. T. Bilodeau, *J. Am. Chem. Soc.* **1994**, *116*, 2742–2753.
- 1994JCS(D)3507 M. S. Eisen, M. Kapon, *J. Chem. Soc., Dalton Trans.* **1994**, 3507–3510.
- 1994JMC57 Y. Katsura, Y. Inoue, T. Tomishi, H. Ishikawa, H. Takasugi, *J. Med. Chem.* **1994**, *37*, 57–66.
- 1994LA1037 K. Kirschke, E. Wolff, M. Ramm, G. Lutze, B. Schulz, *Liebigs Ann. Chem.* **1994**, 1037–1042.
- 1994SC1617 D. Toste, J. McNulty, I. W. J. Still, *Synth. Commun.* **1994**, *24*, 1617–1624.
- 1994ZN(B)1453 R. Boese, R. Koester, M. Yalpani, *Z. Naturforsch., Teil B* **1994**, *49*, 1453–1458.
- 1995CB395 H. Schumann, J. Winterfeld, H. Hemling, F. E. Hahn, P. Reich, K.-W. Brzezinka, F. T. Edelmann, U. Kilimann, M. Schaefer, R. Herbst-Irmer, *Chem. Ber.* **1995**, *128*, 395–404.
- 1995CJC1380 T. Chivers, K. McGregor, M. Parvez, I. Vargas-Baca, T. Ziegler, *Can. J. Chem.* **1995**, *73*, 1380–1385.
- 1995COFGT(5)653 W. Kantelehn, Iminoacyl halides and oxy functions, in *Comprehensive Organic Functional Group Transformations: Iminoacyl Halides and Oxy Functions*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Vol. 5, pp. 653–724, Elsevier, Oxford, **1995**.
- 1995COFGT(5)741 P. J. Dunn, Amidines and N-substituted amidines, in *Comprehensive Organic Functional Group Transformations: Amidines and N-Substituted Amidines*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Vol. 5, pp. 741–782, Elsevier, Oxford, **1995**.
- 1995COFGT(5)805 B. Stanovnik, N-Heterosubstituted iminoacyl functions, in *Comprehensive Organic Functional Group Transformations: N-Hetero-substituted Iminoacyl Functions*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Vol. 5, pp. 805–864, Elsevier, Oxford, **1995**.
- 1995EJM809 P. Vicini, L. Amoretti, V. Ballabeni, E. Barocelli, M. Chiavarini, *Eur. J. Med. Chem.* **1995**, *30*, 809–814.
- 1995LA2171 H. Quast, S. Aldenkort, P. Schaefer, E. Schmitt, E.-U. Wuerthwein, *Liebigs Ann. Chem.* **1995**, 2171–2188.
- 1995JMC2357 P. Depez, J. Guillaume, R. Becker, A. Corbier, S. Didierlaurent, M. Fortin, D. Frechet, G. Hamon, B. Heckmann, H. Heitsch, H.-W. Kleemann, J.-P. Vever, J.-C. Vincent, A. Wagner, J. Zhang, *J. Med. Chem.* **1995**, *38*, 2357–2377.
- 1995JOC6032 G. Barbaro, A. Battaglia, P. Giogianni, A. Guerrini, G. Seconi, *J. Org. Chem.* **1995**, *60*, 6032–6039.
- 1995T8043 M. Avalos, R. Babiano, P. Cintas, C. J. Duran, J. L. Jimenez, J. C. Palacios, *Tetrahedron* **1995**, *51*, 8043–8056.
- 1995T12047 H. Jendralla, B. Seuring, J. Herchen, B. Kulitzscher, J. Wunner, *Tetrahedron* **1995**, *51*, 12047–12068.
- 1995TL237 D. Dubreuil, J. P. Pradere, N. Giraudeau, M. Goli, F. Tonnard, *Tetrahedron Lett.* **1995**, *36*, 237–240.
- 1995TL547 M. Guillemet, A. Robert, M. Baudy-Floc'h, *Tetrahedron Lett.* **1995**, *36*, 547–548.
- 1995TL2045 J. Eustache, A. Grob, *Tetrahedron Lett.* **1995**, *36*, 2045–2046.
- 1995TL3477 J. P. Kirby, N. A. van Dantzig, C. K. Chang, D. G. Nocera, *Tetrahedron Lett.* **1995**, *36*, 3477–3480.
- 1995TL5877 A. I. Meyers, B. Santiago, *Tetrahedron Lett.* **1995**, *36*, 5877–5880.
- 1995TL8761 R. A. Moss, W. Ma, D. C. Merrer, S. Xue, *Tetrahedron Lett.* **1995**, *36*, 8761–8764.
- 1996BMCL111 P. L. Feldman, S. Chi, *Biorg. Med. Chem. Lett.* **1996**, *6*, 111–114.
- 1996BMCL2425 J. Gante, H. Juraszyk, P. Raddatz, H. Wurziger, S. Bernotat-Danielowski, G. Melzer, F. Rippmann, *Biorg. Med. Chem. Lett.* **1996**, *6*, 2425–2430.
- 1996CC223 R. Duchateau, A. Meetsma, J. H. Teuben, *J. Chem. Soc., Chem. Commun.* **1996**, 223–224.
- 1996CHECII A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Eds., *Comp. Heterocyclic. Chem. II*, Elsevier, Oxford, **1996**.
- 1996CJC2018 A. Singhal, V. K. Jain, *Can. J. Chem.* **1996**, *74*, 2018–2025.
- 1996CPB122 M. Kuwahara, Y. Kawano, H. Shimazu, Y. Ashida, A. Miyake, *Chem. Pharm. Bull.* **1996**, *44*, 122–131.
- 1996IC5836 T. Chivers, I. Krouse, M. Parvez, I. Vargas-Baca, T. Ziegler, P. Zoricak, *Inorg. Chem.* **1996**, *35*, 5836–5842.
- 1996JA1060 G. Alcaraz, V. Piquet, A. Baceiredo, F. Dahan, W. W. Schoeller, G. Bertrand, *J. Am. Chem. Soc.* **1996**, *118*, 1060–1065.
- 1996JA10850 Y. Zhou, D. S. Richeson, *J. Am. Chem. Soc.* **1996**, *118*, 10850–10852.
- 1996JCS(P1)1629 I. Tornus, E. Schaumann, G. Adiwidjaja, *J. Chem. Soc., Perkin Trans. 1* **1996**, 1629–1633.
- 1996JHC1583 J. E. Johnson, D. Nwoko, M. Hotema, N. Sanchez, R. Alderman, V. Lynch, *J. Heterocycl. Chem.* **1996**, *33*, 1583–1592.
- 1996JMC1372 D. A. Pearson, J. Lister-James, W. J. McBride, D. M. Wilson, L. J. Martel, E. R. Civitello, R. T. Dean, *J. Med. Chem.* **1996**, *39*, 1372–1382.

- 1996JMC2118 H. U. Stilz, B. Jablonka, M. Just, J. Knolle, E. F. Paulus, G. Zoller, *J. Med. Chem.* **1996**, 39, 2118–2122.
- 1996JOC2470 A. Guzman, M. Romero, F. X. Talamas, *J. Org. Chem.* **1996**, 61, 2470–2483.
- 1996JOC3902 M. Kobayashi, K. Uneyama, *J. Org. Chem.* **1996**, 61, 3902–3905.
- 1996SC4351 B. D. Judkins, D. G. Allen, T. A. Cook, B. Evans, T. E. Sardharwala, *Synth. Commun.* **1996**, 26, 4351–4367.
- 1996TL995 D. M. Fink, B. E. Kurys, *Tetrahedron Lett.* **1996**, 37, 995–998.
- 1997CJC1188 V. Chandrasekhar, T. Chivers, L. Ellis, I. Krouse, M. Parvez, I. Vargas-Baca, *Can. J. Chem.* **1997**, 75, 1188–1194.
- 1997CPB116 Y. Kawanishi, S. Ishihara, K. Takahashi, T. Tsushima, S. Hagishita, M. Ishikawa, Y. Ishihara, *Chem. Pharm. Bull.* **1997**, 45, 116–124.
- 1997CPB1447 M. Kuwahara, Y. Kawano, M. Kajino, Y. Ashida, A. Miyake, *Chem. Pharm. Bul.* **1997**, 45, 1447–1457.
- 1997IC501 Y. Zhou, D. S. Richeson, *Inorg. Chem.* **1997**, 36, 501–504.
- 1997JA10359 S. R. Foley, C. Bensimon, D. S. Richeson, *J. Am. Chem. Soc.* **1997**, 119, 10359–10363.
- 1997JAP11193285 Akiha, T.; Saito, T.; Kazuaki, K. *Japan Patent* 11193285 (**1997**) (*Chem. Abstr.* **1999**, 131, 102278).
- 1997JCR(S)434 N. Abe, H. Chijimatsu, S. Kondo, H. Watanabe, K. Sato, *J. Chem. Res. (S)* **1997**, 434.
- 1997JCS(D)1945 P. B. Hitchcock, M. F. Lappert, S. Tian, *J. Chem. Soc., Dalton Trans.* **2002**, 1945–1952.
- 1997JFC25 G. L. Xu, B. Xu, C. Y. Qin, S. Z. Zhu, *J. Fluorine Chem.* **1997**, 84, 25–28.
- 1997JHC43 M. Malesic, A. Krbavcic, A. Golobic, L. Golic, B. Stanovnik, *J. Heterocycl. Chem.* **1997**, 34, 43–48.
- 1997JMC2085 M. J. Fisher, B. Gunn, C. S. Harms, A. D. Kline, J. T. Mullaney, A. Nunes, R. M. Scarborough, A. E. Arfsten, M. A. Skelton, S. L. Um, B. G. Utterback, J. A. Jakubowski, *J. Med. Chem.* **1997**, 40, 2085–2101.
- 1997JMC2843 D. J. Sall, A. E. Arfsten, J. A. Bastian, M. L. Denney, C. J. Harms, J. R. McCowan, J. M. Morin Jr., J. W. Rose, R. M. Scarborough, M. S. Smyth, S. L. Um, B. G. Utterback, R. T. Vasileff, J. H. Wikel, V. L. Wyss, J. A. Jakubowski, *J. Med. Chem.* **1997**, 40, 2843–2857.
- 1997JMC4308 T. Su, M. A. H. Naughton, M. S. Smyth, J. W. Rose, A. E. Arfsten, J. R. McCowan, J. A. Jakubowski, V. L. Wyss, K. J. Ruterbories, D. J. Sall, R. M. Scarborough, *J. Med. Chem.* **1997**, 40, 4308–4318.
- 1997MI1968 P. R. Phillips, J. Barker, W. Errington, M. G. H. Wallbridge, *Acta. Crystallograph. Part C* **1997**, 53, 1968–1971.
- 1997PHA28 H. A. Abd El-Nabi, *Phamazi* **1997**, 52, 28–32.
- 1997OM5183 M. P. Coles, D. C. Swenson, R. F. Jordan, *Organometallics* **1997**, 16, 5183–5194.
- 1997T1787 P. Quadrelli, A. G. Invernizzi, M. Falzoni, P. Caramella, *Tetrahedron* **1997**, 53, 1787–1796.
- 1997TA2679 H. Nagata, T. Taniguchi, K. Ogasawara, *Tetrahedron Asymmetry* **1997**, 8, 2679–2681.
- 1997TL179 B. G. Shearer, J. A. Oplinger, S. Lee, *Tetrahedron Lett.* **1997**, 38, 179–182.
- 1997TL3179 R. Sreekumar, P. Rugmini, R. Padmadkumar, *Tetrahedron Lett.* **1997**, 38, 3179–3182.
- 1997TL5423 Y. Han, L. Cai, *Tetrahedron Lett.* **1997**, 38, 5423–5426.
- 1997TL7527 S. Vincent, S. Mons, L. Lebeau, C. Mioskowski, *Tetrahedron Lett.* **1997**, 38, 7527–7530.
- 1998BMCL2961 J. Eustache, A. Grob, C. Lam, O. Sellier, G. Schulz, *Biorg. Med. Chem. Lett.* **1998**, 8, 2961–2966.
- 1998CC609 W. B. Jang, K. Lee, C.-W. Lee, D. Y. Oh, *J. Chem. Soc., Chem. Commun.* **1998**, 609–610.
- 1998IC1315 M. Mueller, V. C. Williams, L. H. Doerrer, M. A. Leech, S. A. Mason, M. L. H. Green, K. Prout, *Inorg. Chem.* **1998**, 37, 1315–1323.
- 1998IJC(B)1283 B. S. Reddy, T. Sambaiah, K. K. Reddy, *Indian J. Chem., Sect. B* **1998**, 37B, 1283–1285.
- 1998JA2989 K. Hutchison, G. Srdanov, R. Hicks, H. Yu, F. Wudl, *J. Am. Chem. Soc.* **1998**, 120, 2989–2990.
- 1998JCR(S)654 M. A.-M. Goma, *J. Chem. Res. (S)* **1998**, 654–655.
- 1998JCS(D)4147 R. T. Boere, V. Klassen, G. Wolmershauser, *J. Chem. Soc., Dalton Trans.* **1998**, 4147–4154.
- 1998MI78 E. Dufour, W. Tam, D. K. Naegler, A. C. Storer, R. Menard, *FEBS Lett.* **1998**, 443, 78–82. (*Chem. Abstr.* **1998**, 129, 276292).
- 1998OM854 P. Legzdins, S. A. Lumb, V. G. Young Jr., *Organometallics* **1998**, 17, 854–871.
- 1998SC4419 C. Lila, P. Gloanec, L. Cadet, Y. Herve, J. Fournier, F. Leborgne, T. J. Verbeuren, G. De Nanteuil, *Synth. Commun.* **1998**, 28, 4419–4429.
- 1998T2545 F. Purseigle, D. Dubreuil, A. Marchand, J. P. Pradere, M. Goli, L. Toupet, *Tetrahedron* **1998**, 54, 2545–2562.
- 1998TL711 S. Sforza, A. Dossena, R. Corradini, E. Virgili, R. Marchelli, *Tetrahedron Lett.* **1998**, 39, 711–714.
- 1998TL7619 S. Menzler, J. A. Bikker, D. C. Horwell, *Tetrahedron Lett.* **1998**, 39, 7619–7622.
- 1999EJM575 D. A. Patrick, J. E. Hall, B. C. Bender, D. R. McCurdy, W. D. Wilson, F. A. Tanious, S. Saha, R. R. Tidwell, *Eur. J. Med. Chem.* **1999**, 34, 575–583.
- 1999JCS(P1)705 A. Kraft, *J. Chem. Soc., Perkin Trans. 1* **1999**, 705–714.
- 1999JMC3994 S. M. Rahmathullah, J. E. Hall, B. C. Bender, D. R. McCurdy, R. R. Tidwell, D. W. Botkin, *J. Med. Chem.* **1999**, 42, 3994–4000.
- 1999JOC3608 C. Wentrup, V. V. R. Rao, W. Frank, B. E. Fulloon, D. W. J. Moloney, T. Mosandl, *J. Org. Chem.* **1999**, 64, 3608–3619.
- 1999MI176 R. M. Abdel-Rahman, J. M. Morsy, H. A. Allimony, W. R. Abd El-Monem, *Boll. Chim. Farmaceutico* **1999**, 138, 176–185. (*Chem. Abstr.* **2000**, 132, 122587).
- 1999OM4619 S. Dagonne, R. F. Jordan, *Organometallics* **1999**, 18, 4619–4623.
- 1999OM4700 S. R. Foley, G. P. A. Yap, D. S. Richeson, *Organometallics* **1999**, 18, 4700–4705.
- 1999OM5360 K. Kincaid, C. P. Gerlach, G. R. Giesbrecht, J. R. Hagadorn, G. D. Whitener, A. Shafir, J. Arnold, *Organometallics* **1999**, 18, 5360–5366.
- 1999PHA667 R. M. Abdel-Rahman, J. M. Morsy, S. El-Edfawy, H. A. Amine, *Pharmazi* **1999**, 54, 667–671.
- 1999S927 R. Baati, V. Gouverneur, C. Miokowski, *Synthesis* **1999**, 927–929.
- 1999TL5487 S. Delarue, C. Sergheraert, *Tetrahedron Lett.* **1999**, 40, 5487–5490.

- 1999TL7067 U. E. W. Lange, B. Schaefer, D. Baucke, E. Buschmann, H. Mack, *Tetrahedron Lett.* **1999**, 40, 7067–7071.
- 1999WOP24433 Niewohner, U.; Es-Sayed, M.; Haning, H.; Schenke, T.; Schlemmer, K.-H.; Keldenich, J.; Bischoff, E.; Perzborn, E.; Dembowski, K.; Serno, P.; Nowakowski, M. World Patent 24433 (1999) (*Chem. Abstr.* **1999**, 130, 352283).
- 2000BMC601 J. A. Tucker, T. L. Clayton, C. G. Chidester, M. W. Schulz, L. E. Harrington, S. J. Conrad, Y. Yagi, N. L. Oien, D. Yurek, M.-S. Kuo, *Biorg. Med. Chem.* **2000**, 8, 601–615.
- 2000BMCL2463 K. Yoshiizumi, F. Nakajima, T. Kiyoi, H. Kondo, *Biorg. Med. Chem. Lett.* **2000**, 10, 2463–2466.
- 2000HCA1576 Y. Zhou, A. Linden, H. Heimgartner, *Helv. Chim. Acta.* **2000**, 83, 1576–1598.
- 2000JA6382 D. L. Boger, B. E. Fink, M. P. Hedrick, *J. Am. Chem. Soc.* **2000**, 122, 6382–6394.
- 2000JCS(D)967 C.-T. Chen, L. H. Doerrer, W. V. Cliff, M. L. H. Green, *J. Chem. Soc., Dalton Trans.* **2000**, 967–974.
- 2000JCS(D)1663 S. R. Foley, G. P. A. Yap, D. S. Richeson, *J. Chem. Soc., Dalton Trans.* **2000**, 1663–1668.
- 2000JMC3168 I. K. Khanna, Y. Yu, R. M. Huff, R. M. Weier, X. Xu, F. J. Koszyk, P. W. Collins, J. N. Cogburn, P. C. Isakson, C. M. Koboldt, J. L. Masferrer, W. E. Perkins, K. Seibert, A. W. Veenhuizen, J. Yuan, D.-C. Yang, Y. Y. Zhang, *J. Med. Chem.* **2000**, 43, 3168–3185.
- 2000JMC4063 D. A. Dudley, A. M. Bunker, L. Chi, W. L. Cody, D. R. Holland, D. P. Ignasiak, N. Janiczek-Dolphin, T. B. McClanahan, T. E. Mertz, L. S. Narashimhan, S. T. Rapundalo, J. A. Trautschold, C. A. Van Huis, J. J. Edmunds, *J. Med. Chem.* **2000**, 43, 4063–4070.
- 2000JOC8100 D. G. Batt, G. C. Houghton, W. F. Daneker, P. K. Jadhav, *J. Org. Chem.* **2000**, 65, 8100–8104.
- 2000JOM(607)227 S. M. Mullins, J. R. Hagadorn, R. G. Bergman, J. Arnold, *J. Organomet. Chem.* **2000**, 607, 227–232.
- 2000MI208 J. M. Morsy, F. Ismail, R. M. Abdel-Rahman, H. A. Amine, *Pak. J. Ind. Res.* **2000**, 43, 208–213. (*Chem. Abstr.* **2001**, 134, 56646).
- 2000MI409 W. Kraus, H. C. van der Plas, *Topics in Catalysis* **2000**, 11/12, 409–417. (*Chem. Abstr.* **2000**, 133, 173850).
- 2000OM2823 G. Bai, H. W. Roesky, M. Noltemeyer, H. Hao, H.-G. Schmidt, *Organometallics* **2000**, 19, 2823–2825.
- 2000S513 Y. Xu, Y. Wang, S. Zhu, *Synthesis* **2000**, 4, 513–516.
- 2000T5225 A. I. Khalaf, A. R. Pitt, M. Scobie, C. J. Suckling, J. Urwin, R. D. Waigh, R. V. Fishleigh, S. C. Young, W. A. Wylie, *Tetrahedron* **2000**, 56, 5225–5239.
- 2000T8253 L. Cai, Y. Han, S. Ren, L. Huang, *Tetrahedron* **2000**, 56, 8253–8262.
- 2000T9343 W. Szczepankiewicz, J. Suwinski, R. Bujok, *Tetrahedron* **2000**, 56, 9343–9349.
- 2000TL1677 A. B. Charette, M. Grenon, *Tetrahedron Lett.* **2000**, 41, 1677–1680.
- 2000TL6041 J. T. Kohrt, K. J. Filipinski, S. T. Rapundalo, W. L. Cody, J. J. Edmunds, *Tetrahedron Lett.* **2000**, 41, 6041–6044.
- 2001BCJ1927 H. Kondo, A. Kageyama, Y. Yamaguchi, M.-a. Haga, K. Kirchner, H. Nagashima, *Bull. Chem. Soc. Jap.* **2001**, 74, 1927–1937.
- 2001BMCL467 W. Guo, J. Hiratake, K. Ogawa, M. Yamamoto, S.-J. Ma, K. Sakata, *Biorg. Med. Chem. Lett.* **2001**, 11, 467–470.
- 2001BMCL1293 A. Pandey, J. Seroogy, D. Volkots, M. S. Smith, J. Rose, M. M. Mehrotra, J. Heath, G. Ruhter, T. Schotten, R. M. Scarborough, *Biorg. Med. Chem. Lett.* **2001**, 11, 1293–1296.
- 2001BMCL2225 D. W. Ludovici, M. J. Kukla, P. G. Grous, S. Krishnan, K. Andries, M.-P. de Bethune, H. Azijn, R. Pauwels, E. De Clercq, E. Arnold, P. A. J. Janssen, *Biorg. Med. Chem. Lett.* **2001**, 11, 2225–2228.
- 2001CAR31 K. Ikeda, K. Sano, M. Ito, M. Saito, K. Hidari, T. Suzuki, Y. Suzuki, K. Tanaka, *Carbohydrate Research* **2001**, 330(1), 31–41.
- 2001CC2144 J. R. Hagadorn, *J. Chem. Soc., Chem. Commun.* **2001**, 2144–2145.
- 2001CHE141 E. Abele, E. Lukevics, *Chem. Heterocycl. Compd.* **2001**, 37, 141–169.
- 2001CPB933 S. Delarue, S. Girault, F. D. Ali, L. Maes, P. Grellier, C. Sergheraert, *Chem. Pharm. Bull.* **2001**, 49, 933–937.
- 2001EJI263 P. F. Kelly, A. M. Z. Slawin, *Eur. J. Inorg. Chem.* **2001**, 1, 263–265.
- 2001H2085 L. Racane, V. Tralic-Kulenovic, L. Fiser-Jakic, D. W. Boykin, G. Karminski-Zamola, *Heterocycles* **2001**, 55, 2085–2098.
- 2001JA1539 T. D. Owens, F. J. Hollander, A. G. Oliver, J. A. Ellman, *J. Am. Chem. Soc.* **2001**, 123, 1539–1540.
- 2001JCS(D)1392 A. E. Guiducci, A. R. Cowley, M. E. G. Skinner, P. Mountford, *J. Chem. Soc., Dalton Trans.* **2001**, 1392–1394.
- 2001JCS(P1)1321 A. Reichert, R. Frohlich, R. Ferguson, A. Kraft, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1321–1328.
- 2001JHC425 K. Sasaki, Y.-X. Zhang, K. Okuda, T. Hirota, *J. Heterocycl. Chem.* **2001**, 38, 425–429.
- 2001JMC1217 S. D. Larsen, M. A. Connell, M. M. Cudahy, B. R. Evans, P. D. May, M. D. Meglasson, T. J. O'Sullivan, H. J. Schostarez, J. C. Sih, F. C. Stevens, S. P. Tanis, C. M. Tegley, J. A. Tucker, V. A. Vaillancourt, T. J. Vidmar, W. Watt, J. H. Yu, *J. Med. Chem.* **2001**, 44, 1217–1230.
- 2001JMC1741 C. E. Stephens, F. Tanious, S. Kim, W. D. Wilson, W. A. Schell, J. R. Perfect, S. G. Franzblau, D. W. Boykin, *J. Med. Chem.* **2001**, 44, 1741–1748.
- 2001JMC2004 X. Bu, L. W. Deady, G. J. Finlay, B. C. Baguley, W. A. Denny, *J. Med. Chem.* **2001**, 44, 2004–2014.
- 2001JMC2695 B. L. Mylari, P. J. Oates, D. A. Beebe, N. S. Brackett, J. B. Couter, M. S. Dina, W. J. Zembroski, *J. Med. Chem.* **2001**, 44, 2695–2700.
- 2001JMC3157 D. Catarzi, V. Colotta, F. Varano, G. Filacchioni, A. Galli, C. Costagli, V. Carla, *J. Med. Chem.* **2001**, 44, 3157–3165.
- 2001JOM(634)167 T. Hayashida, K. Yamaguchi, H. Nagashima, *J. Organomet. Chem.* **2001**, 634, 167–176.
- 2001MI97 M. I. Korotkikh, A. V. Kisel'ov, T. M. Pekhtereva, O. P. Shvaika, *Ukrainskii, Khimicheskii Zhurnal (Russian Edition)* **2001**, 67, 97–103. (*Chem. Abstr.* **2002**, 137, 33259).
- 2001OM3531 S. M. Pugh, D. J. M. Trosch, M. E. G. Skinner, L. H. Gade, P. Mountford, *Organometallics* **2001**, 20, 3531–3542.

- 2001OM5532 D. Abeysekera, K. N. Robertson, T. S. Cameron, J. A. C. Clyburne, *Organometallics* **2001**, *20*, 5532–5536.
- 2001S2427 B. A. Trofimov, E. Y. Schmidt, A. M. Vasil'tsov, A. I. Mikhaleva, A. B. Zaitsev, L. V. Morozova, A. G. Gorskikh, J. Henkelmann, J.-D. Arndt, *Synthesis* **2001**, 2427–2430.
- 2001SL135 M. Vuilhorgne, J. Bouquerel, J.-C. Hardy, S. Mignani, *Synlett* **2001**, 135–137.
- 2001SL388 A. Ursini, M. Delpogetto, G. Guercio, A. Perboni, T. Rossi, *Synlett* **2001**, 388–390.
- 2001T153 T. Masquelin, D. Obrecht, *Tetrahedron* **2001**, *57*, 153–156.
- 2001TL1495 R. F. Poulain, A. L. Tartar, D. P. Deprez, *Tetrahedron Lett.* **2001**, *42*, 1495–1498.
- 2001WOP094333 Antoine, L.; Bouquel, P.; Borghese, A.; Fisher, M.; Gorissen, H.; Jakubowski, J. A.; Khau, V. V.; Martinelli, M.; Merschaert, A.; Paal, M.; Ruhter, G.; Rypens, C.; Schotten, T.; Stenzel, W.; Van Hoeck, J. P. World Patent 01/094333 (**2001**) (*Chem. Abstr.* **2002**, *136*, 37511).
- 2001ZAAC1560 D. Wakther, M. Stollenz, L. Bottcher, H. Gorls, *Z. Anorg. Allg. Chem.* **2001**, *627*, 1560–1570.
- 2001ZOK834 R. R. Gataullin, I. S. Afon'kin, A. A. Fatykhov, L. V. Spirikhin, I. B. Abdrakhmanov, *Zh. Org. Khim.* **2001**, *37*, 834–840. (*English Translation*), (*Chem. Abstr.* **2002**, *136*, 216716).
- 2002BMCL865 H. Haning, U. Niewohner, T. Schenke, M. Es-Sayed, G. Schmidt, T. Lampe, E. Bischoff, *Biorg. Med. Chem. Lett.* **2002**, *12*, 865–868.
- 2002BMCL1439 J. J. Harnett, M. Auguet, I. Viossat, C. Dolo, D. Bigg, P.-E. Chabrier, *Biorg. Med. Chem. Lett.* **2002**, *12*, 1439–1442.
- 2002CC958 H. Kawaguchi, T. Matsuo, *J. Chem. Soc., Chem. Commun.* **2002**, 958–959.
- 2002CC2250 N. Merceron, A. Baceiredo, H. Gornitzka, G. Bertrand, *J. Chem. Soc., Chem. Commun.* **2002**, 2250–2251.
- 2002CC2914 A. J. Gallant, K. M. Smith, B. O. Patrick, *J. Chem. Soc., Chem. Commun.* **2002**, 2914–2915.
- 2002CRV1771 V. Y. Kukushkin, A. J. L. Pombeiro, *Chem. Rev.* **2002**, *102*, 1771–1802.
- 2002HCA1102 P. K. Atanassov, Y. Zhou, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2002**, *85*, 1102–1117.
- 2002IC2014 C. Knapp, E. Lork, P. G. Watson, R. Mews, *Inorg. Chem.* **2002**, *41*, 2014–2025.
- 2002JA5932 R. J. Keaton, L. A. Koterwas, J. C. Fettinger, L. R. Sita, *J. Am. Chem. Soc.* **2002**, *124*, 5932–5933.
- 2002JCS(D)1401 J.-F. Li, L.-H. Weng, X.-H. Wei, D.-S. Liu, *J. Chem. Soc., Dalton Trans.* **2002**, 1401–1405.
- 2002JCS(D)3454 J. A. R. Schmidt, J. Arnold, *J. Chem. Soc., Dalton Trans.* **2002**, 3454–3461.
- 2002JCS(D)3919 H. A. Jenkins, D. Abeyekera, D. A. Dickie, J. A. C. Clyburne, *J. Chem. Soc., Dalton Trans.* **2002**, 3919–3922.
- 2002JCS(D)4175 C. L. Boyd, A. E. Guiducci, S. R. Dubberley, B. R. Tyrrel, P. Mountford, *J. Chem. Soc., Dalton Trans.* **2002**, 4175–4184.
- 2002JCS(P1)2520 J. M. Khurana, G. Kukreja, G. Bansal, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2520–2524.
- 2002JHC309 R. A. Ahmed, M. M. Kandeel, M. S. Abbady, M. S. K. Youssef, *J. Heterocycl. Chem.* **2002**, *39*, 309–314.
- 2002JHC845 C. H. Lee, K.-J. Lee, *J. Heterocycl. Chem.* **2002**, *39*, 845–847.
- 2002JMC944 A. Renodon-Corniere, S. Dijols, C. Perollier, D. Lefevre-Groboillot, J.-L. Boucher, R. Attias, M.-A. Sari, D. Stuehr, D. Mansuy, *J. Med. Chem.* **2002**, *45*, 944–954.
- 2002JMC2942 J. L. Romine, S. W. Martin, V. K. Gribkoff, C. G. Boissard, S. I. Dworetzky, J. Natale, Y. Li, Q. Gao, N. A. Meanwell, J. E. Starrett Jr., *J. Med. Chem.* **2002**, *45*, 2942–2952.
- 2002JOC2619 H. Bibas, D. W. J. Moloney, R. Neumann, M. Shtaiwi, P. V. Bernhardt, C. Wentrup, *J. Org. Chem.* **2002**, *67*, 2619–2631.
- 2002JOC4298 K. Sung, S.-W. Wu, R.-R. Wu, S.-Y. Sun, *J. Org. Chem.* **2002**, *67*, 4298–4303.
- 2002JOC8558 M. Shtaiwi, C. Wentrup, *J. Org. Chem.* **2002**, *67*, 8558–8565.
- 2002JOM(662)144 L. Tunjie, Y. Yao, Q. Shen, J. Sun, L. Weng, *J. Organomet. Chem.* **2002**, *662*, 144–149.
- 2002JOM(662)178 J. Grundy, M. P. Coles, P. B. Hitchcock, *J. Organomet. Chem.* **2002**, *662*, 178–187.
- 2002JOM(663)78 C. C. Romao, B. Royo, *J. Organomet. Chem.* **2002**, *663*, 78–82.
- 2002MI1097 A. Mishra, H. Mohabey, *Asian J. Chem.* **2002**, *14*, 1097–1098. (*Chem. Abstr.* **2002**, *137*, 216736).
- 2002OM1420 J. Zhang, R. Ruan, Z. Shao, R. Cai, L. Weng, X. Zhou, *Organometallics* **2002**, *21*, 1420–1424.
- 2002OM2145 J. T. Patton, M. M. Bokota, *Organometallics* **2002**, *21*, 2145–2148.
- 2002OM2306 J. A. R. Schmidt, J. Arnold, *Organometallics* **2002**, *21*, 2306–2313.
- 2002OM4315 R. J. Keaton, L. R. Sita, *Organometallics* **2002**, *21*, 4315–4317.
- 2002OPP545 A. L. Silva, A. Covarrubias-Zuniga, L. A. Maldonado, *Org. Prep. Proced. Int.* **2002**, *34*, 545–549.
- 2002T3499 A. Kraft, L. Peters, H. R. Powell, *Tetrahedron* **2002**, *58*, 3499–3505.
- 2002T10437 M.-H. Shih, *Tetrahedron* **2002**, *58*, 10437–10445.
- 2002TL4221 M. Anbazhagan, C. E. Stephens, D. W. Boykin, *Tetrahedron Lett.* **2002**, *43*, 4221–4224.
- 2002TL8925 L. El Kaim, L. Grimaud, N. K. Jana, F. Mettetal, C. Tirla, *Tetrahedron Lett.* **2002**, *43*, 8925–8927.
- 2002USP0013464 Dunn, P.J.; Dunne, C. U.S. Patent 0013464 (**2002**) (*Chem. Abstr.* **2002**, *136*, 69817).
- 2002WOP50076 Nowakowski, M.; Gehring, R.; Heilmann, W.; Wahl, K.-H. World Patent 50076 (**2002**) (*Chem. Abstr.* **2002**, *137*, 47233).
- 2003IC301 A. V. Makarycheva-Mikhailova, N. A. Bokach, V. Y. Kukushkin, P. F. Kelly, L. M. Gilby, M. L. Kuznetsov, K. E. Holmes, M. Haukka, J. Parr, J. M. Stonehouse, M. R. J. Elsegood, A. J. L. Pombeiro, *Inorg. Chem.* **2003**, *42*, 301–311.
- 2003JOC3 T. D. Owens, A. J. Souers, J. A. Ellman, *J. Org. Chem.* **2003**, *68*, 3–10.
- 2003JPC3287 C. N. Sanrame, C. P. Suhrada, H. Dang, M. A. Garcia-Garibay, *J. Phys. Chem. A* **2003**, *107*, 3287–3294.
- 2003OM21 Y. Zhang, D. A. Kissounko, J. C. Fettinger, L. R. Sita, *Organometallics* **2003**, *22*, 21–23.
- 2003OM609 J. R. Hagadorn, M. J. McNevin, *Organometallics* **2003**, *22*, 609–611.

Biographical sketch

Peter Dunn was born in Birmingham. He worked for Robinson Brothers Ltd. (1977–1984), during which time he obtained a part time B.Sc. Ph.D. in 1987 from Imperial College, London under the direction of Professor C. W. Rees. Following postdoctoral research with Professor A. Eschenmoser (ETH, Zurich, with a Royal Society Fellowship Award) and Professor H. Rapoport (UC Berkeley) he has worked for Pfizer since 1989 and is a Director in Chemical Research and Development at Sandwich in Kent. His scientific interests include heterocyclic chemistry, organic synthesis and scale-up, crystallization, and green chemistry.

5.20

Iminoacyl Functions Linked to Any Heteroatom Other Than Halogen, Chalcogen, or Nitrogen

M. CASEY

University College Dublin, Dublin, Republic of Ireland

5.20.1	IMIDOYLPHOSPHORUS, -ARSENIC, -ANTIMONY, AND -BISMUTH FUNCTIONS— $R^1C(NR^2)PR_3^3$, etc.	702
5.20.1.1	Dicoordinate Phosphorus Derivatives	702
5.20.1.2	Tricoordinate Phosphorus Derivatives (Phospha-amidines)	702
5.20.1.2.1	From imidoyl chlorides	702
5.20.1.2.2	From cyanophosphanes	702
5.20.1.2.3	From phosphaaalkenes	703
5.20.1.3	Tetracoordinate Phosphorus Derivatives	703
5.20.1.3.1	From imidoyl halides	703
5.20.1.3.2	From α -aminophosphorus derivatives	704
5.20.1.3.3	From imines	705
5.20.1.3.4	From phosphorus-substituted oxime and hydrazone derivatives	705
5.20.1.3.5	From acylphosphorus derivatives	706
5.20.1.3.6	From nitrosobenzene	707
5.20.1.4	Higher-coordinate Phosphorus Derivatives	707
5.20.1.5	Imidoylarsenic Derivatives	707
5.20.1.6	Imidoylantimony Derivatives and Imidoylbismuth Derivatives	707
5.20.2	IMIDOYL METALLOID FUNCTIONS— $R^1C(NR^2)SiR_3^3$, $R^1C(NR^2)GeR_3^3$, $R^1C(NR^2)BR_2^3$	707
5.20.2.1	Tetracoordinate Silicon Derivatives	707
5.20.2.1.1	From isocyanides	707
5.20.2.1.2	From imidoyllithiums	708
5.20.2.1.3	From imidoyl chlorides	708
5.20.2.1.4	From cyanohydrins	708
5.20.2.1.5	From acylsilanes	709
5.20.2.1.6	From imines	709
5.20.2.2	Tetracoordinate Germanium Derivatives	709
5.20.2.3	Tricoordinate Boron Derivatives	710
5.20.2.4	Imidoyl Borate Derivatives	710
5.20.3	IMIDOYL METAL FUNCTIONS— $R^1C(NR^2)METAL$	710
5.20.3.1	Imidoyl Derivatives of Group 1 Metals—Li, Na, K, Rb, and Cs	710
5.20.3.1.1	From isocyanides	710
5.20.3.1.2	From imidoylstannanes	711
5.20.3.1.3	From imidoyl halides	711
5.20.3.2	Imidoyl Derivatives of Group 2 Metals—Be, Mg, Ca, Sr, and Ba	711
5.20.3.3	Imidoyl Derivatives of Transition Metals	711
5.20.3.3.1	Imidoyl transition metal derivatives from isocyanide insertion reactions	712
5.20.3.3.2	Imidoyl-Ti, -Zr, and -Hf derivatives	714
5.20.3.3.3	Imidoyl-V, -Nb, and -Ta derivatives	715
5.20.3.3.4	Imidoyl-Cr, -Mo, and -W derivatives	715
5.20.3.3.5	Imidoyl-Mn and -Re derivatives	716

5.20.3.3.6	Imidoyl-Fe, -Ru, and -Os derivatives	717
5.20.3.3.7	Imidoyl-Co, -Rh, and -Ir derivatives	717
5.20.3.3.8	Imidoyl-Ni, -Pd, and -Pt derivatives	717
5.20.3.3.9	Imidoyl-Zn, -Cd, and -Hg derivatives	718
5.20.3.4	Imidoyl Derivatives of Group 13 and Group 14 Metals—Al, Ga, In, Tl, Sn, and Pb	718
5.20.3.4.1	Imidoyl-Al and -Ga derivatives	718
5.20.3.4.2	Imidoyl-Sn derivatives	718
5.20.3.5	Imidoyl Derivatives of Lanthanides and Actinides	719

5.20.1 IMIDOYLPHOSPHORUS, -ARSENIC, -ANTIMONY, AND -BISMUTH FUNCTIONS— $R^1C(NR^2)PR_3^3$, etc.

5.20.1.1 Dicoordinate Phosphorus Derivatives

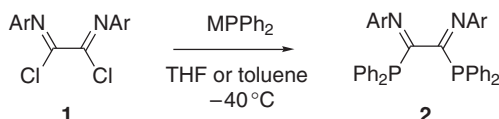
No reports of this structural class have been made since the publication of COFGT (1995).

5.20.1.2 Tricoordinate Phosphorus Derivatives (Phospha-amidines)

As detailed in chapter 5.20.1 in <1995COFGT(5)783>, the four principal methods for the formation of imidoylphosphorus(III) derivatives are: (i) nucleophilic substitution of imidoyl halides and ethers by phosphorus nucleophiles; (ii) nucleophilic addition to activated nitriles by phosphorus nucleophiles; (iii) addition of phosphanes to isocyanides; and (iv) reaction of imines with PCl_3 . Further examples of the first of these methods have been reported, along with two new synthetic methods: (i) by additions to cyanophosphanes and (ii) by additions of isocyanides to phosphaaalkenes.

5.20.1.2.1 From imidoyl chlorides

Treatment of oxalimidoyl chlorides **1** with sodium and potassium diphenylphosphide furnished bis(imidoylphosphanes) **2** (Equation (1)), which are novel ligands <2003IC625>. $Pd(OAc)_2$ was used as a catalyst for the coupling in one case.



(1)

Ar	Yield (%)
4-MeC ₆ H ₄	45
4-Bu ^t -C ₆ H ₄	56
2,4,6-Me ₃ C ₆ H ₂	80

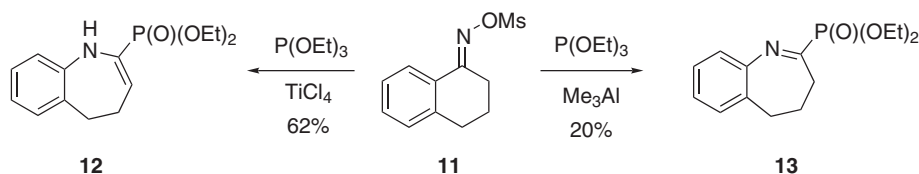
A simpler phospha-amidine was prepared in a similar way, also for use as a ligand <2003WOP2003076450>.

5.20.1.2.2 From cyanophosphanes

Hydrozirconation of a dicyanophosphane **3** followed by reaction of the zirconium amide intermediate **4** with phosphorus chlorides and an iminium chloride gave formimidoylphosphanes **5** <2003EJO385> (Scheme 1).

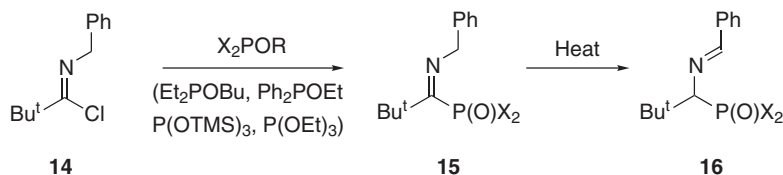
Reaction of a diphenylzirconium complex with cyanophosphanes **6** in refluxing toluene gave coupling products **7**, which furnished imidoylphosphanes **8** after protonolysis (Scheme 2) <2001CEJ221>.

reactions in which the imidoyl electrophile was generated by Beckmann rearrangement (Scheme 3) <1997H111>. Thus, rearrangement of an oxime mesylate **11** by using TiCl_4 , in the presence of triethyl phosphite, gave a phosphinyl enamine **12**. However, when the rearrangement was conducted using trimethylalane, the imine tautomer **13** was obtained, albeit in low yield.



Scheme 3

When the *N*-substituent contains α -hydrogens, thermal or base-catalyzed tautomerism may result in migration of the azomethine bond <1995ZOB1961, 1996ZOB936, 1994ZOB1744>. For example, an *N*-benzylimidoyl chloride **14** reacted with alkoxyphosphanes to give imidoylphosphoryl products **15**, which rearranged on heating to give the benzylidene tautomers **16** (Scheme 4) <1995ZOB1961>. The situation was further complicated by the observation of thermal and acid-catalyzed phosphorotropic shifts in the products.

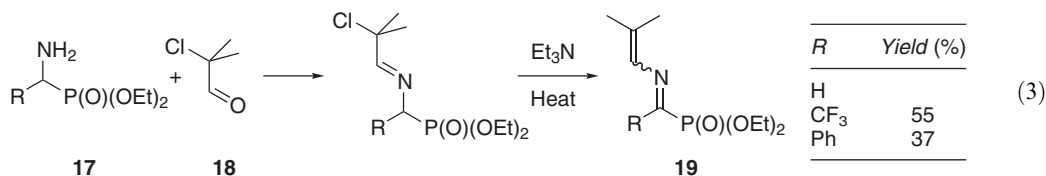


Scheme 4

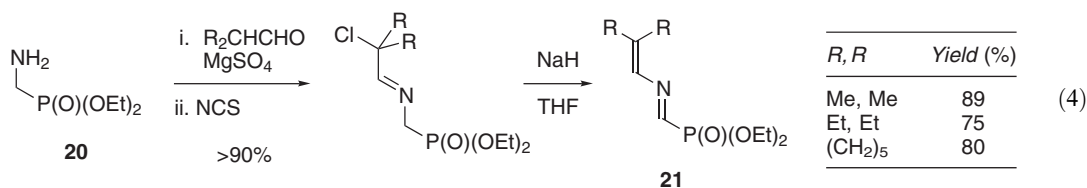
Use of an imidoyl chloride derived from enantiopure 1-phenylethylamine resulted in an asymmetric synthesis of an α -aminophosphonate derivative by this method <2000HAC536>.

5.20.1.3.2 From α -aminophosphorus derivatives

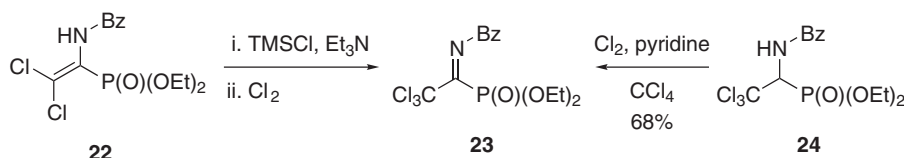
Condensation of α -aminophosphonates **17** with an α -chloroaldehyde **18**, followed by treatment with Et_3N to bring about 1,4-elimination of HCl , gave imidoyl phosphonates **19** (Equation (3)) <1998JGU536>.



In an improvement on this strategy, chlorination was carried out after condensation with the α -aminophosphonate **20**, and dehydrochlorination was accomplished with NaH to give the products **21** in high yields (Equation (4)) <1999TL3457>.

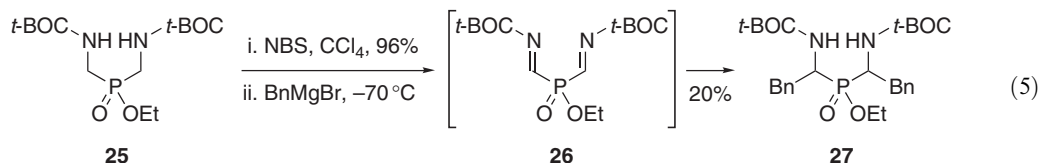


Further examples of oxidation of α -aminophosphonates by halogenation followed by 1,2-elimination have also appeared. Chlorination of α -benzamidophosphonate **24** in pyridine gave *N*-benzoylimidoylphosphonate **23** in good yield (Scheme 5) <1998MI2044>. The same product **23** was also obtained by chlorination of a silyl derivative of the phosphonyl enamide **22**.



Scheme 5

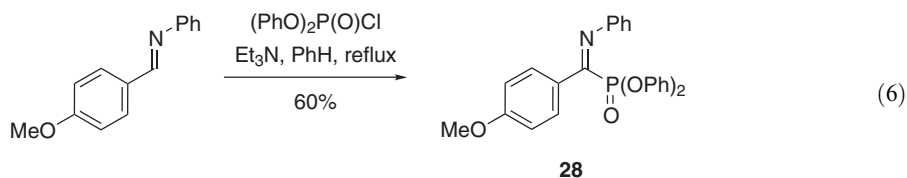
Similarly, α -bromination of protected bis(α -amino)phosphinate **25**, followed by treatment with Grignard reagents, gave imidoyl phosphinate intermediate **26**, which underwent nucleophilic attack *in situ* to give moderate yields of adducts such as **27** (Equation (5)) <1993AG(E)1720>. Some of the products were effective inhibitors of HIV protease.



Condensation of α -aminophosphonates with acyl phosphonates yields imidoyl phosphonates (see Section 5.20.1.3.5).

5.20.1.3.3 From imines

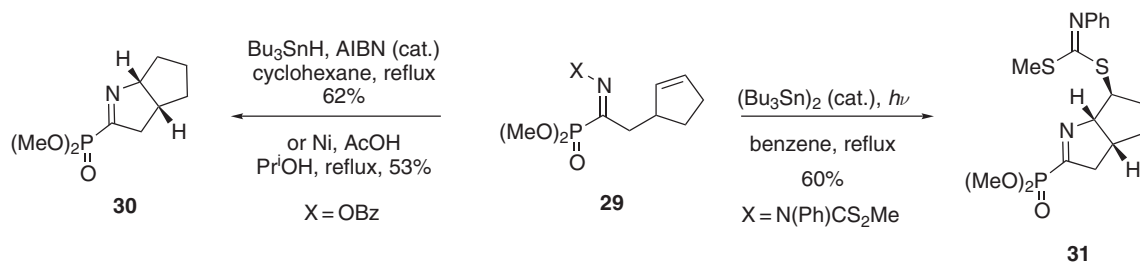
The addition of diphenyl chlorophosphate to imines in the presence of Et₃N provided a series of imidoyl phosphonates of type **28** in moderate-to-good yields (Equation (6)) <1997PS(126)243>. The example shown is typical of this convenient method. All the imines were benzylidene derivatives bearing electron-donating substituents in the 4-position.



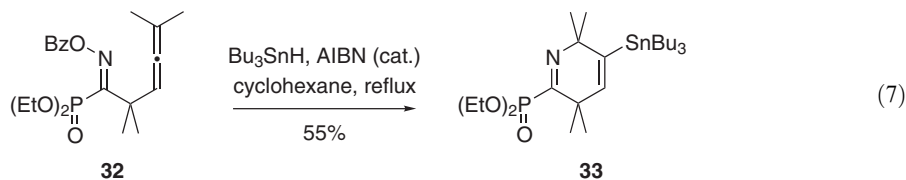
5.20.1.3.4 From phosphorus-substituted oxime and hydrazone derivatives

Condensation of acyl phosphonates with hydroxylamine or hydrazines, followed by *O*- or *N*-derivatization, provides ready access to P(IV)-substituted oximes and hydrazones. Reduction of one such derivative **29** under radical conditions led to generation of an iminyl radical that underwent cyclization to give an imidoyl phosphonate **30** (Scheme 6) <1995T6517>. More environmentally benign conditions for this transformation, using Ni and AcOH, were later developed, although the yield was slightly diminished <1999TL4531>. A more complex radical chain process, catalyzed by stannyl radicals, gave rise to a functionalized bicyclic product **31** <1997TL2463>.

Radical cyclization of another phosphonyl oxime derivative **32** led to imidoyl phosphonate **33**, although the mechanism in this case probably involved addition of a carbon-centered radical onto the azomethine, followed by loss of a benzoyloxy radical (Equation (7)) <2000EJO275>.

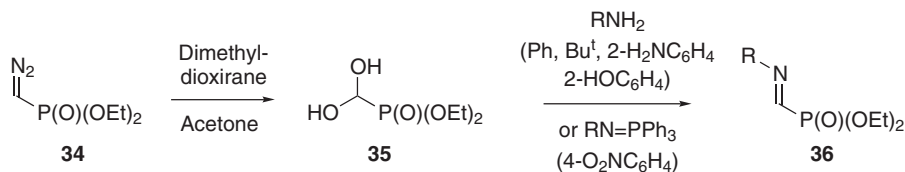


Scheme 6



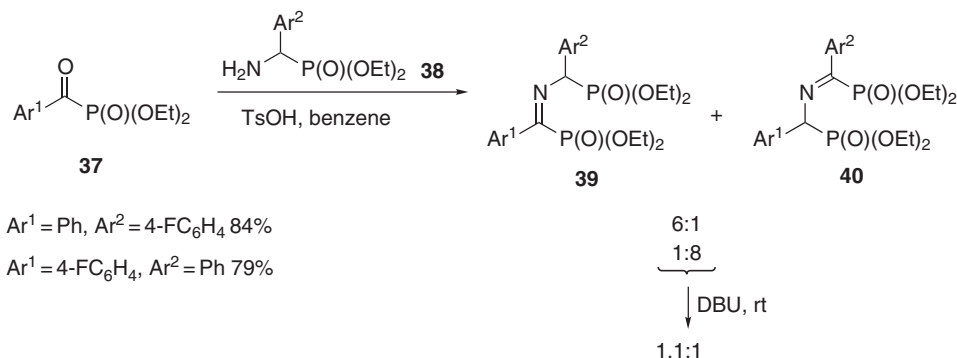
5.20.1.3.5 From acylphosphorus derivatives

Several formimidoyl phosphonates **36** were prepared by the addition of amines, and iminophosphoranes, to the corresponding formyl compound as its hydrate **35**, which was obtained by oxidation of the diazo derivative **34** (Scheme 7) <1994CC37, 1999PS(146)385>.



Scheme 7

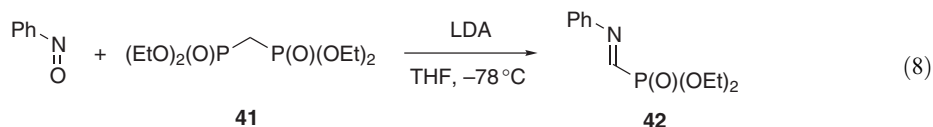
Acid-catalyzed condensation of α -aminophosphonates **38** with benzoyl phosphonates **37** gave mixtures of tautomeric imidoyl derivatives, **39** and **40**, that underwent equilibration on treatment with DBU (Scheme 8) <1994ZOB396>.



Scheme 8

5.20.1.3.6 From nitrosobenzene

One example of a Wittig-type reaction of nitrosobenzene with a diphosphonate **41** has been reported (Equation (8)); the yield of the imidoyl phosphonate **42** was not recorded <1994CC37>.



5.20.1.4 Higher-coordinate Phosphorus Derivatives

No reports of this structural class have been made since the publication of COFGT (1995).

5.20.1.5 Imidoarsenic Derivatives

No developments have been reported since the publication of chapter 5.20.1.5 in <1995COFGT(5)783>.

5.20.1.6 Imidoantimony Derivatives and Imidothallium Derivatives

No developments have been reported since the publication of chapter 5.20.1.6 in <1995COFGT(5)783>.

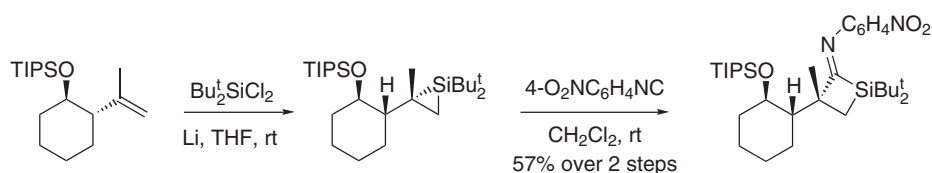
5.20.2 IMIDOYL METALLOID FUNCTIONS— $\text{R}^1\text{C}(\text{NR}^2)\text{SiR}_3^3$, $\text{R}^1\text{C}(\text{NR}^2)\text{GeR}_3^3$, $\text{R}^1\text{C}(\text{NR}^2)\text{BR}_2^3$

5.20.2.1 Tetracoordinate Silicon Derivatives

A considerable number of new imidoysilanes have been reported in the 1990s, and some have found use as synthetic intermediates. As summarized in chapter 5.20.2 in <1995COFGT(5)783>, the four principal methods for the formation of imidoysilicon derivatives were: (i) addition of silanes to isocyanides, (ii) silylation of imidoyllithiums, (iii) reaction of silicon nucleophiles with imidoyl halides, and (iv) reductive silylation of cyanohydrins. New variations on these methods have been reported, along with new routes from acylsilanes and from imines.

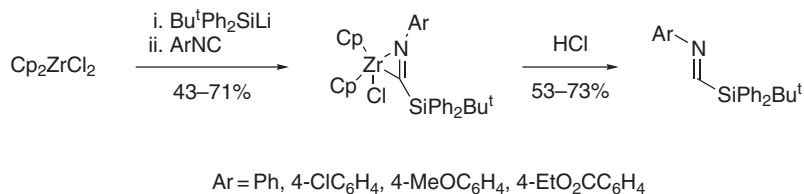
5.20.2.1.1 From isocyanides

No further reports of the addition of Si—H bonds to isocyanides have appeared, but the first examples of additions of Si—C and Si—metal bonds have been recorded. The highly activated Si—C bonds of siliranes add to isocyanides to give silacyclobutanamines <1996TL3675>. The insertions are regioselective for the more substituted Si—C bond of the silacyclopropane, and occur with complete retention of configuration <1999JOC1843>. The selectivity of silirane formation, and of the isocyanide insertion, are illustrated by the example in Scheme 9 <2002JA6524>. The strained imidoysilane products are potentially useful intermediates for the stereoselective synthesis of highly oxygenated products <2002JA6524>.



Scheme 9

Insertion of isocyanides into Si—metal bonds, followed by protonolysis of the imidoymetal intermediates, yields formimidoylsilanes. This method is not as direct as the addition of R_3SiH to isocyanides, and its discovery was a by-product of studies on the reactivity of silyl-containing metal complexes. Several examples involving Zr (Scheme 10) <1995OM1548>, and one involving Sc <1993OM2584>, have been reported.



Scheme 10

5.20.2.1.2 From imidoyllithiums

Silylation of imidoyllithiums (see Section 5.20.3.1) provides imidoysilanes. Few examples have been reported recently (Equation (9), Table 1), but the scope of the method is probably quite wide.

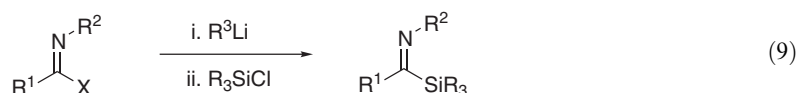


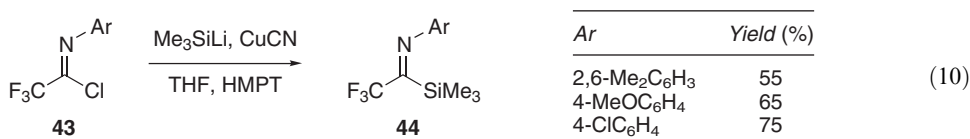
Table 1 Formation of imidoysilanes via imidoyllithiums (Equation (9))

R^1	R^2	X	$R^3\text{Li}$	Electrophile	Yield	References
Et	Bu	SnBu ₃	BuLi	Bu ^t Me ₂ SiCl	25%	<1993S981>
Ph	2,6-Me ₂ C ₆ H ₃	SnMe ₃	MeLi	Me ₃ SiCl	High	<1994JCS(P1)2283>
CF ₃	2,6-Me ₂ C ₆ H ₃	I	BuLi	Me ₃ SiCl	84%	<1994JOC758>

More complex examples, in which the imidoyllithiums are silylated by intramolecular silyl transfer, have also been studied <2001JCS(D)2409, 2000OM5431>. Imidoysilanes were assumed to be intermediates in the reaction of trifluoroacetimidoyl chlorides with Mg in the presence of TMSiCl <2003OL4297>, which yielded 1-trimethylsilyl-2,2-difluoroenamines. The product enamines reacted with carbonyl compounds and imines to give heavily substituted imidoysilanes in good yields.

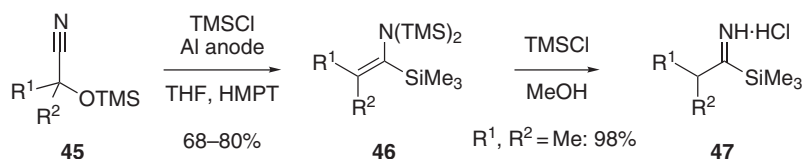
5.20.2.1.3 From imidoyl chlorides

A series of trifluoroacetimidoyl chlorides **43** underwent substitution by trimethylsilylmetals to afford imidoysilanes **44** (Equation (10)) <1996JOC6055>. Of the metallated silanes that were tested, only TMSLi in combination with CuCN gave good results.



5.20.2.1.4 From cyanohydrins

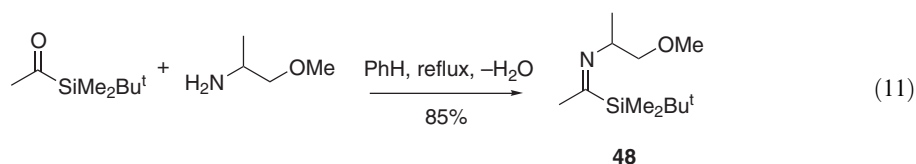
The reduction/silylation of cyanohydrin silyl ethers **45** to afford α -silylenamines **46** in good yields was accomplished electrochemically, and protodesilylation of the products gave protonated imidoysilanes **47**, which were not usually isolated, but reduced to afford α -silylamines (Scheme 11) <1996OM1604>.



Scheme 11

5.20.2.1.5 From acylsilanes

There appears to be just one example of the synthesis of an imidoysilane by condensation of an acylsilane with an amine (Equation (11)) <1996JA8765, 1997TL5771>. The azaenolate derived from the product **48** was used as a building block in several natural product total syntheses.



5.20.2.1.6 From imines

In the course of a study of the transition metal-catalyzed hydrosilylation of imines, it was discovered that imidoysilanes **49** were formed as side products in two instances <2002CHE46> (Equation (12) and Table 2). It is possible that good yields of imidoysilanes might be obtained with further catalyst screening and process development.

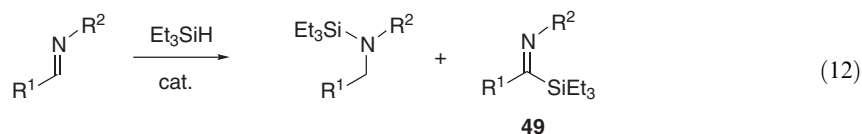
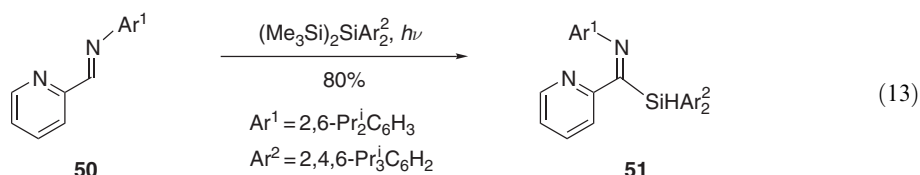


Table 2 Hydrosilylation of imines (Equation (12))

R ¹	R ²	Catalyst	Amine	Imine 49
5-Methyl-2-furyl	3-CF ₃ C ₆ H ₄	[Rh(COD)Cl] ₂	69%	19%
2-Thienyl	Ph	[Pd(allyl)Cl] ₂	52%	39%

Insertion of silylenes into the C—H bond of imines such as **50** gives imidoysilanes **51** (Equation (13)) <1994OM3990>. Good yields were only obtained when very hindered silylenes and very hindered imines were used.

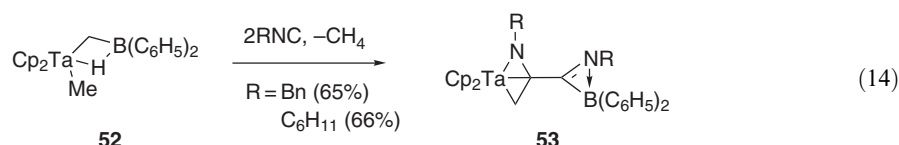


5.20.2.2 Tetracoordinate Germanium Derivatives

No new reports of imidoylgermanium derivatives have appeared since the publication of COFGT (1995) <1995COFGT(5)783>, but a method analogous to the formation of formimidoysilanes (Scheme 10), involving insertion of an isocyanide into a Ge—Zr bond, followed by protonolysis, should be noted <1992OM2198>.

5.20.2.3 Tricoordinate Boron Derivatives

The only routes to imidoylboron derivatives recorded previously (chapter 5.20.2 in <1995COFGT(5)783>), involving reaction of imidoyllithiums with boron halides, and reaction of nucleophiles with *N*-alkylated cyanoboranes, have not been further utilized. However, several examples of the preparation of imidoylboron derivatives by isocyanide insertions have been reported. Additions of isocyanides to iminoboranes <1995CB1037>, to azadiboriridines <1995CB1029>, and to a boraalkene <1993CB1551> all gave heterocycles incorporating imidoylboron moieties. Double insertion of isocyanides into a tantalocene borataalkene complex **52** gave imidoylboranes **53** in moderate yields (Equation (14)) <2002OM2422>.

**5.20.2.4 Imidoyl Borate Derivatives**

No developments have been reported since the publication of chapter 5.20.2.4 in <1995COFGT(5)783>.

5.20.3 IMIDOYL METAL FUNCTIONS—R¹C(NR²)METAL**5.20.3.1 Imidoyl Derivatives of Group 1 Metals—Li, Na, K, Rb, and Cs**

Imidoyllithium reagents are useful intermediates for the synthesis of other imidoyl derivatives and of imines. They can be prepared by (i) addition of organolithiums to isocyanides, (ii) tin–lithium exchange, or (iii) lithium–halogen exchange. Imidoyl derivatives of the other metals of group 1 appear not to have been reported. “Naked” imidoyl anions, with tetrabutylammonium counterions, have been formed by the treatment of imidoysilanes with TBAF, and they were found to be significantly more thermally stable than the corresponding imidoyllithiums <1996JOC6055>.

5.20.3.1.1 From isocyanides

As described in chapter 5.20.3 in <1995COFGT(5)783>, the addition of organolithiums to isocyanides is the most popular method for preparing imidoyllithiums. Generally, the addition is thermodynamically favorable only when alkylolithiums are used, but more stable organolithiums may be used provided that the adducts are efficiently trapped, for example, by intramolecular silyl transfer <2001JCS(D)2409, 2000OM5431>. Two other restrictions are that (i) if an alkyl isocyanide is used, it must not have α -hydrogens; and (ii) if an aryl isocyanide is used, it must not have *o*-hydrogens. Despite these limitations, the addition of alkylolithiums to isocyanides, followed by reaction with electrophiles, remains a widely used synthetic method (Equation (15) and Table 3).

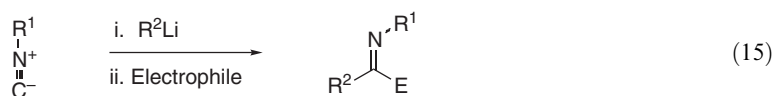


Table 3 Addition of organolithiums to isocyanides (Equation (15))

R^1	R^2	Electrophile (s)	Yield (%)	References
Bu ^t	Bu ^t	Metal carbonyls	51–83	<1996OM5254>
Bu ^t	Bu ^t	None		<1995CB1051>
Bu ^t , TMB ^a	Bu ⁿ , Bu ^t	Cyclobutenediones	12–91	<1994JOC6856>
TMB ^a	Bu ⁿ , Bu ⁱ , Pr ⁱ	Chlorostannanes	73–80	<1993JOM(443)C1>
Xy ^b	Me, Bu ⁿ	XyNC	95, 98	<1996CL7>
2,6-dialkylphenyl	Bu ^t	CO/MeI	42–44	<1994JOC477>
		RCN/CO/MeI	44–49	

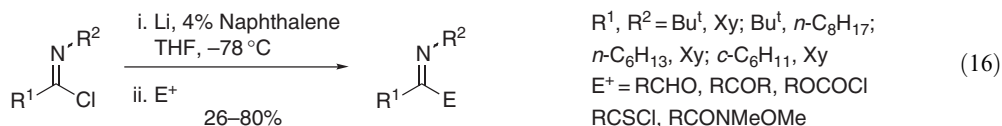
^a 1,1,3,3-Tetramethylbutyl; ^b 2,6-Dimethylphenyl.

5.20.3.1.2 From imidoystannanes

Tin–lithium exchange occurred on treatment of a benzimidoylstannane with MeLi, and the imidoyllithium reacted with a variety of electrophiles to give the products in high yields <1994JCS(P1)2283>. When the same procedure was applied to a propanimidoyl chloride, the yields were very poor because of competing α -deprotonation <1994JCS(P1)2283, 1993S981>.

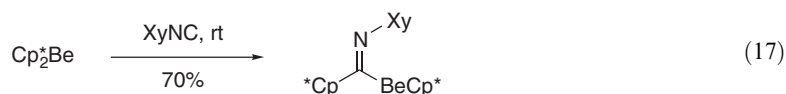
5.20.3.1.3 From imidoyl halides

The first example of the use of halogen–lithium exchange involved highly activated substrates, trifluoroacetimidoyl iodides <1994JOC758>. The best conditions involved the use of BuⁿLi in Et₂O at -78°C , and the most stable of the imidoyllithiums was found to be the *N*-2,6-dimethylphenyl derivative. This was trapped with a wide variety of electrophiles to give moderate-to-good yields of products. Perhaps a more general procedure relies on chlorine–lithium exchange using lithium metal, catalyzed by naphthalene, which gives good yields of products even when there are α -hydrogens present (Equation (16)) <1998T12007>.



5.20.3.2 Imidoyl Derivatives of Group 2 Metals—Be, Mg, Ca, Sr, and Ba

There are a few reports of imidoylberyllium and imidoylmagnesium compounds, but the Ca, Sr, and Ba analogs have not been studied. Several beryllocenes, in which the substituted cyclopentadienyl rings were thought to exchange between η^5 - and η^1 -binding modes, reacted with 2,6-dimethylphenyl isocyanide (XyNC) to give imidoylberyllium derivatives <2003CEJ4462>. One example is shown in Equation (17). Cp^{*}BeMe, which contains stronger Be–C bonds, did not undergo this insertion reaction.



Imidoylmagnesium species were probably involved in the reductive silylation of trifluoroacetimidoyl chlorides using Mg and TMSCl <2003OL4297>.

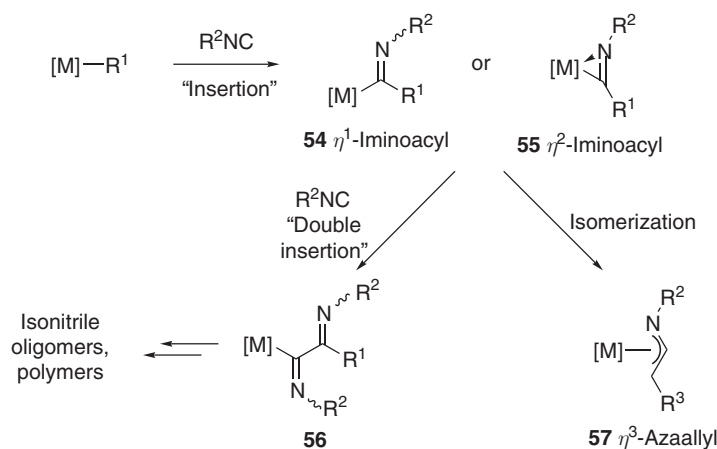
5.20.3.3 Imidoyl Derivatives of Transition Metals

The synthesis of imidoyl derivatives of transition metals is dominated by one reaction, the insertion of isocyanides into metal–carbon bonds. Because of the very large number of applications of this method, which include examples involving most of the transition metals, the main features will be discussed separately below (Section 5.20.3.3.1), rather than in the subsections devoted to the individual groups. Aspects of isocyanide insertions of particular interest will be

described in the subsections, but the main discussions therein will concentrate on other methods for the formation of imidoyl-transition metal derivatives. These other methods include preparation from imidoyl chlorides, from imines, from keteneimines, and from amines. While the great majority of the reported imidoyl-transition metal compounds were formed in the course of investigations on the reactivity of organometallic complexes, rather than out of a specific desire to prepare these species, interest in their synthetic potential is beginning to develop, and they are likely to attract increasing attention in the future. No further developments in the chemistry of imidoyl derivatives of the Sc group metals and the Cu group metals have occurred since the earlier review in chapter 5.20.3 in reference <1995COFGT(5)783>.

5.20.3.3.1 Imido transition metal derivatives from isocyanide insertion reactions

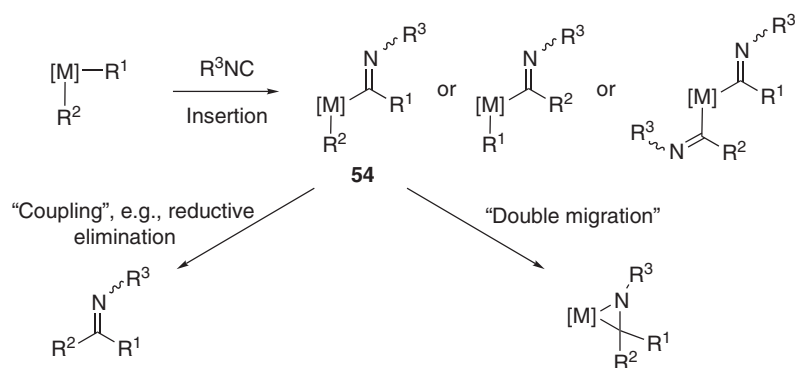
The reaction of organometallic compounds with isocyanides to give imido transition metal products (Scheme 12) has a very wide scope. Most transition metals, and many of the main group metals, undergo this reaction, and a wide variety of organic ligands and isocyanides can be incorporated into imido groups in this way. Main group chemists often refer to this reaction as an “addition” and to the products as “imido transition metal complexes,” but transition metal chemists more commonly use the terms “insertion” and “iminoacyl complexes,” and these terms will be adopted here. The iminoacyl ligand may be coordinated to the metal only through the carbon (η^1 -iminoacyl **54**), or through both carbon and nitrogen (η^2 -iminoacyl **55**). The former is the norm for late transition elements, but the latter form predominates for the early transition metals. Stereochemical complexities in the products will not be discussed here.



Scheme 12

The reaction is not entirely straightforward, and for example a second insertion of isocyanide may occur to give an α -diimino derivative **56**, and if further insertions ensue, isocyanide oligomers or even polymers may result. The tendency toward multiple insertion of the isocyanide appears to be especially pronounced for Ni and Pd. Another common secondary reaction is isomerization of the iminoacyl complex to an η^3 -azaallyl complex **57**, which can occur if the migrating group (R^1) contains α -hydrogens. Additional complications can arise when the starting organometallic complex contains two or more organic ligands (Scheme 13). Clearly, isocyanide insertion into just one metal-carbon bond, or into two, or more, can occur, and if the organic ligands are not all the same, issues of selectivity arise. However, with two, or more, organic ligands, other kinds of secondary reaction of the initially formed iminoacyl complex **54** or **55** can also intervene. A common competing pathway is migration of both organic groups onto the same carbon (“double migration”), and another possibility is some coupling reaction of the initially formed iminoacyl group with another organic ligand, for example, by reductive elimination.

Whether a single isocyanide insertion, or one of the other processes shown above, occurs depends on several factors. The metal (M), the other ligands on the metal, the migrating groups (R^1 , R^2), the group on the isocyanide (R^3), and the conditions of the reaction have all been shown to strongly influence the selectivity. However, these influences are not well understood and the outcome of reactions involving novel organometallic substrates generally cannot be predicted.



Scheme 13

The scope of the isocyanide insertion method is indicated by the large number of examples collected in Table 4. The reactions are listed according to the metal, in order of group number. Because of the large amount of published data, only representative examples are provided, and they are mostly reactions that gave the iminoacyl product arising from single insertion, in good yield (>60%). Only the most relevant aspects of the reaction, i.e., the identity of the metal, the type of migrating group, and the isocyanide are tabulated, and details of the conditions and the other ligands on the metal are not included.

Table 4 Formation of imidoacyl-transition metal derivatives **54** or **55** by isocyanide insertions (Scheme 12)

<i>M</i>	<i>R</i> ¹	<i>R</i> ^{2a}	References
Ti	Alkyl	Bu ^t , Xy	<2003OM4218, 1999OM606, 1999OM4442, 1998OM5836>
Ti	Alkynyl	Bu ^t	<1998JOM(571)83>
Ti	Benzyl	Xy	<2001JCS(D)181>
Zr	Allyl	Bu ^t	<1996CEJ919>
Zr	Alkenyl	Bu ^t	<2000JOM(611)304>
Zr	Alkyl	Bu ^t , <i>c</i> -C ₆ H ₁₁ , CH ₂ SiMe ₃ , Xy, Me	<2003JA8746, 2003EJI2626, 2002OM1, 2000OM1406, 1998OM5836, 1997JA9709, 1997JOM(542)247, 1997OM3548, 1995JA8083, 1994TL1445, 1993JOC5595>
Zr	Alkynyl	Bu ^t	<1998JOM(571)83>
Zr	Aryl	Bu ^t	<2000JA9880, 2001OM4080, 1997JA9709>
Zr	Benzyl	Bu ^t , <i>c</i> -C ₆ H ₁₁ , Xy	<2003EJI2626, 2002JCS(D)3398, 1998ICA(270)527>
Zr	H	Bu ^t	<1995OM4816>
Hf	Allyl	Bu ^t	<1996CEJ919>
Hf	Alkyl	Bu ^t	<1998OM5836>
Hf	Alkynyl	Bu ^t , Xy	<1998JOM(571)83>
V	Alkyl	Bu ^t	<1999OM606>
V	Aryl	Bu ^t	<1999OM606, 1998OM2328>
V	Benzyl	Bu ^t	<1998OM2328>
Nb	Alkyl	Bu ⁿ , Bu ^t , Xy	<2003EJI2438, 2002OM293, 2000JOM(595)36>
Nb	Allyl	Xy	<2003EJI2438>
Nb	Benzyl	Xy	<2002OM293, 2000JOM(595)36>
Ta	Alkyl	Bu ^t , Xy	<2000EJI2047, 2000JOM(595)36, 2000OM2243, 1998JOM(563)15, 1997OM3993>
Ta	Aryl	Bu ^t , Xy	<2000JOM(595)36, 1997OM3993>
Ta	Benzyl	Xy	<2000EJI2047, 2000JOM(595)36>
Cr	Alkyl	Bu ^t , Xy	<1999OM1994, 1998POL675, 1995JCS(D)2111>
Cr	Benzyl	Bu ^t , Xy	<1995JCS(D)2111>

Continued

Table 4 (continued)

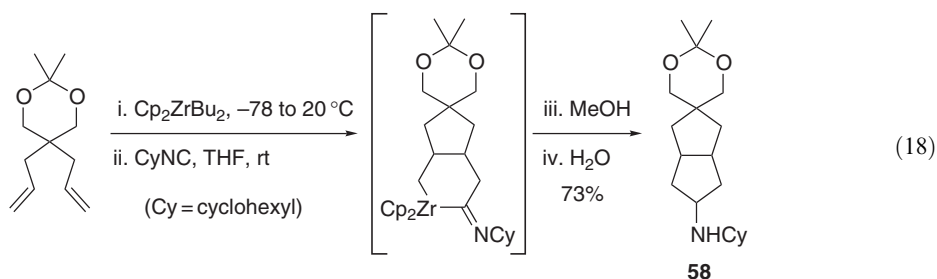
<i>M</i>	<i>R</i> ¹	<i>R</i> ^{2a}	References
Mo	Acyl	Bu ^t	<1999CC491>
Mo	Alkyl	<i>p</i> -An, Bn, Bu ^t , <i>c</i> -C ₆ H ₁₁ , Et, Me, Pr ⁱ , Xy	<1997JCS(D)3145, 1997OM2263, 1996JCS(D)3687>
Mo	Aryl	Bu ^t	<1995OM2145>
W	Acyl	Bu ^t	<1999CC491>
W	Alkyl	Bu ^t , Et, Me, Pr ⁱ	<1997JCS(D)3145, 1997OM2263, 1997OM1779>
Mn	Benzyl	<i>p</i> -An, <i>p</i> -Tol	<2002ICA(334)419, 1999OM5594>
Fe	Alkyl	Xy	<2000JOM(593-4)119, 1999ICA(286)233>
Fe	Aryl	Bu ^t	<1994JA9123>
Ru	Alkyl	Aryl	<1994OM385>
Ru	Aryl	<i>p</i> -Tol, 4-ClC ₆ H ₄	<1996JOM(510)267>
Os	Aryl	<i>p</i> -Tol, 4-ClC ₆ H ₄	<1996JOM(510)267>
Co	Alkyl	Bn, Bu ^t , Me, Ph	<1998JCS(D)775, 1997CB871>
Co	Aryl	Bu ^t	<1998JCS(D)775>
Co	H	Bu ^t	<1994OM4720>
Rh	H	Xy	<1993OM3410>
Ni	Alkyl	Xy	<1993JA9101>
Ni	Aryl	Bu ^t	<2003OM2817>
Pd	Acyl	Bn	<1997BCJ917>
Pd	Alkyl	Bn, Bu ^t , Xy	<2002OM4799, 2002OM581, 1998OM4335, 1997BCJ917, 1997JOM(549)167, 1997OM2948, 1995JOM(491)159>
Pd	Alkynyl	Aryl	<2000CEJ983, 1998OM4335>
Pd	Aryl	Bu ^t , <i>c</i> -C ₆ H ₁₁ , Xy, CH ₂ CO ₂ Me	<2003OM1967, 2002OL3215, 2000AG(E)4156, 1999JOM(588)268, 1997BCJ917, 1996MI663>
Pd	Benzyl	Bu ^t	<1999OM5225, 1997JOM(549)167>
Pt	Aryl	Aryl	<1995JOM(490)117>
Zn	Alkyl	Xy	<1993JOM(443)C1>

^a Xy = 2,6-Me₂C₆H₃, *p*-An = 4-MeOC₆H₄.

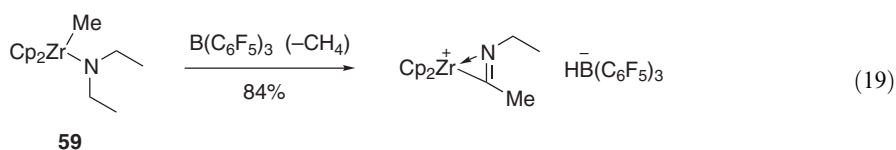
Because the factors that determine the success of the reaction are so poorly understood, and because many types of substrate have not yet been studied, it is premature to make generalizations regarding the scope of the reaction. However, a few brief comments are appropriate. It will be apparent from Table 4 that most attention has been devoted to the Ti, V, Cr, and Ni groups. The Fe and Co groups are relatively poorly represented, and the Sc, Mn, Cu, and Zn groups have attracted almost no interest. A wide range of organic groups (allyl, alkyl, alkenyl, alkynyl, aryl, and benzyl), and hydrogen, has been observed to undergo migration onto isocyanides. The alkyl groups used generally do not contain β -hydrogens, in order to suppress β -elimination, but this is by no means a strict requirement. As regards the isocyanides, a few commercially available ones (*t*-butyl and 2,6-dimethylphenyl especially), are very heavily utilized, but several others, including unhindered examples, have also been used successfully. The few reports that included studies of the scope of the process are described in the relevant subsections below.

5.20.3.3.2 Imidoyl-Ti, -Zr, and -Hf derivatives

A large number of imidoyl-Ti and -Zr derivatives and a few imidoyl-Hf compounds have been prepared by isocyanide insertion reactions (see Table 4). Of particular interest is the demonstration that a secondary alkyl group migrated from Zr with complete retention of configuration <2003JA8746>. This is a key result if asymmetric hydrozirconation processes are to be developed in the future. The synthetic potential of iminoacylzirconium complexes is exemplified by reactions involving: (i) intermolecular coupling with alkenes and alkynes, followed by protonolysis to give ketones <1993JOC5595>, and (ii) intramolecular coupling with alkyl groups to give various cyclic amines, e.g., compound **58** (Equation (18)) <1994TL1445>.

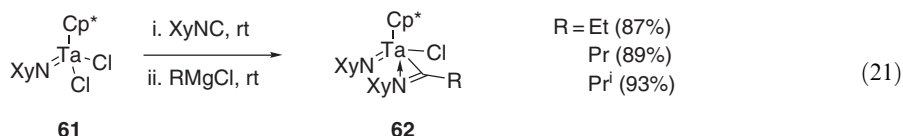
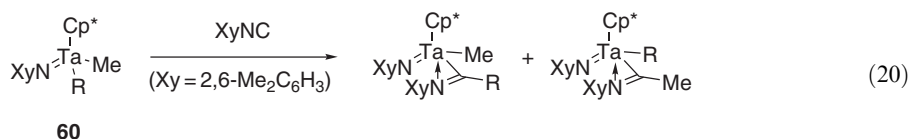


The only other method reported for the preparation of imidozirconium compounds is from amido complex **59**, and the analogous piperidine complex, by treatment with a Lewis acid which abstracts a methyl group, and then a hydride (Equation (19)) <1995JOM(488)177>.

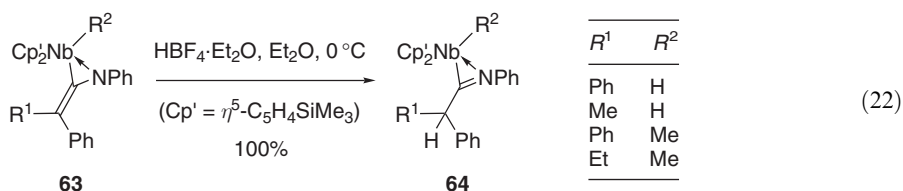


5.20.3.3 Imidozirconium, -Nb, and -Ta derivatives

A considerable number of imidozirconium, -Nb, and -Ta complexes have been obtained by isocyanide insertions (Table 4). Two studies are of particular interest. In one series of Ta complexes **60**, the relative migratory aptitudes in reactions with 2,6-dimethylphenyl isocyanide were found to be $\text{Ph} > \text{Me} > \text{CH}_2\text{SiMe}_3 > \text{Bn}$, with NMe_2 having a higher tendency to migrate than any of these organic groups (Equation (20)) <2000JOM(595)36>. Treatment of the related tantalum dichloride **61** with alkylmagnesium chlorides, in the presence of 2,6-dimethylphenyl isocyanide, gave the iminoacyl complexes **62** in high yields, showing that in this case insertion is faster than β -elimination from the intermediate alkyltantalum species (Equation (21)) <1998JOM(563)15>.



A method for the formation of iminoacyl-Nb complexes is by protonation of keteneimines complexes **63**, which occurs at the β -carbon in quantitative yield (Equation (22)) <1997JOM(533)87>. The overall transformation is equivalent to the addition of an Nb-H bond to the keteneimines to give iminoacyls **64**.

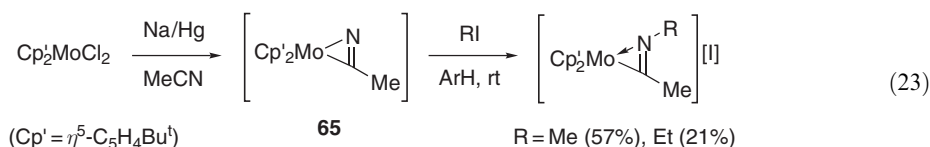


5.20.3.3.4 Imidozirconium, -Mo, and -W derivatives

Representative references to the formation of imidozirconium, -Mo, and -W complexes by isocyanide insertion reactions are listed in Table 4. These include many smooth insertions, but also some in which equilibration of the product iminoacyls with the isomeric azaallyl complexes was

observed <1997JCS(D)3145, 1997OM2263>. One report is of interest in which the precursors were acyl complexes, rather than alkyl complexes <1996JCS(D)3687>. Formation of iminoacyl products arising from alkyl migration occurred via isocyanide coordination, extrusion of CO, and insertion of the isocyanides. This is a convincing demonstration of the potential reversibility of such insertion reactions. Another notable observation was the formation of an imine, arising from reductive elimination of an aryl and an iminoacyl group, as the major product in one instance involving Mo <1995OM2145>.

One alternative route to imidoyl complexes has been reported, which relied on *N*-alkylation of a molybdenocene η^2 -nitrile complex **65**, formed by the reduction of the corresponding molybdenocene dichloride in acetonitrile (Equation (23)) <2001JCS(D)1732>.

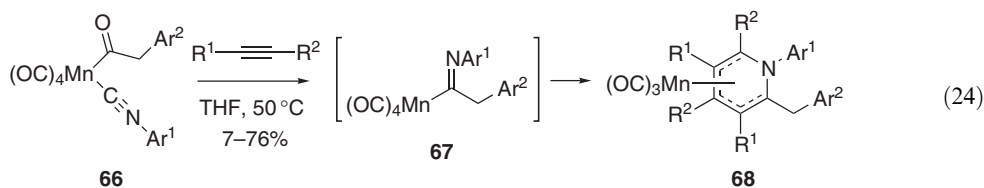


5.20.3.3.5 Imidoyl-Mn and -Re derivatives

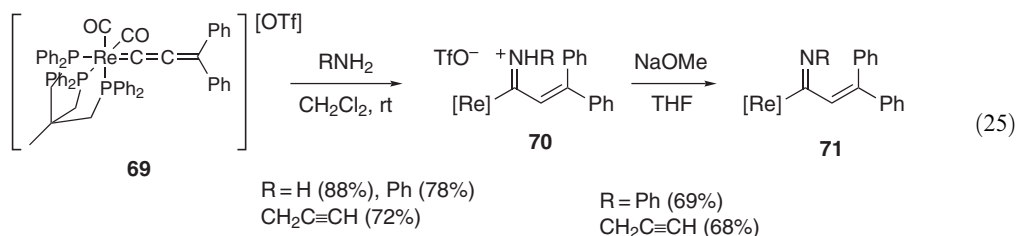
Very few examples of these derivatives, and none of the Tc analogs have been reported. Just two studies of the isocyanide insertion route have appeared. In the first study, reaction of 2,6-dimethylphenyl isocyanide with benzylmanganese pentacarbonyls afforded mixtures of products arising from double and triple insertion of the isocyanide <1999OM5594>. In the second study, reaction of acylmanganese complexes **66** with alkynes gave coupling products **68**, presumably via iminoacyl intermediates **67** (Equation (24)) (Table 5) <2002ICA(334)419>.

Table 5 Formation of manganese complexes **68** via iminoacyl manganese derivatives **67** (Equation (24))

Ar^1	Ar^2	R^1	R^2	Yield (%)
4-ClC ₆ H ₄	4-MeC ₆ H ₄	Ph	Ph	46
C ₆ H ₅	4-MeOC ₆ H ₄	Ph	Ph	7
4-ClC ₆ H ₄	4-MeC ₆ H ₄	H	Ph	76
4-ClC ₆ H ₄	4-MeOC ₆ H ₄	H	Ph	13
4-ClC ₆ H ₄	4-MeC ₆ H ₄	Me	CO ₂ Me	12



The only synthetic route that does not rely on isocyanides utilized addition of amines to allenylidene rhenium complexes **69** to give intermediates **70**, which were deprotonated to give imidoyl-Re derivatives **71** (Equation (25)) <2002OM2382>.



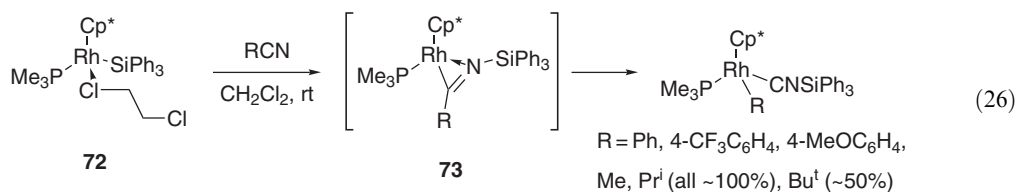
5.20.3.3.6 Imidoyl-Fe, -Ru, and -Os derivatives

There are relatively a few examples of the use of isocyanide insertions to prepare imidoyl-Fe and -Ru complexes, and Os analogs are very rare (Table 4). The mechanism of insertion into an Fe—Me bond has been studied in detail <2000JOM(593–594)119>. Another reaction whose mechanism has been elucidated is an Ru-catalyzed indole synthesis, in which the key step is intramolecular insertion of an isocyanide into an Ru—benzyl bond <1994OM385>. There is also a rare example of a photochemical reaction, which results in double insertion <1999ICA(286)233>.

A number of other preparative methods have been developed. Reaction of anionic Fe₂-complexes with imidoyl chlorides gives the imidoyliron complexes in poor yields <1999JOM(585)63>. Addition of amines to allenylidene—Ru <2003OM162> and alkenylidene—Ru complexes <1999OM2376>, followed by the treatment with a base, affords α,β -unsaturated imidoyl-Ru and phenylacetimidoyl-Ru derivatives, respectively, in a similar manner to the Re analogs shown in Equation (25). Insertion of a thiocyanate into an Fe₂-complex containing a bridging hydride, followed by thermal extrusion of sulfur, resulted in the formation of a formimidoyl—Fe complex in moderate overall yield <1995OM2325>. Finally, reactions of Fe₂(CO)₉ with an imine <1999JOM(579)211>, of Ru₃(CO)₁₂ with piperidine <1993JOM(458)211>, and of Os₃(CO)₁₀(MeCN)₂ with piperidine <1994MI481>, all afforded poor yields of imidoyl complexes of metal clusters via C—H bond activation.

5.20.3.3.7 Imidoyl-Co, -Rh, and -Ir derivatives

A small number of imidoyl complexes of Co and Rh have been prepared by isocyanide insertions (Table 4). No Ir analogs have been recorded. Imidoyl-Rh complexes **73** are intermediates in a remarkable process in which an Rh complex **72** cleaves the C—CN bond of nitriles (Equation (26)) <2003JA9808>.

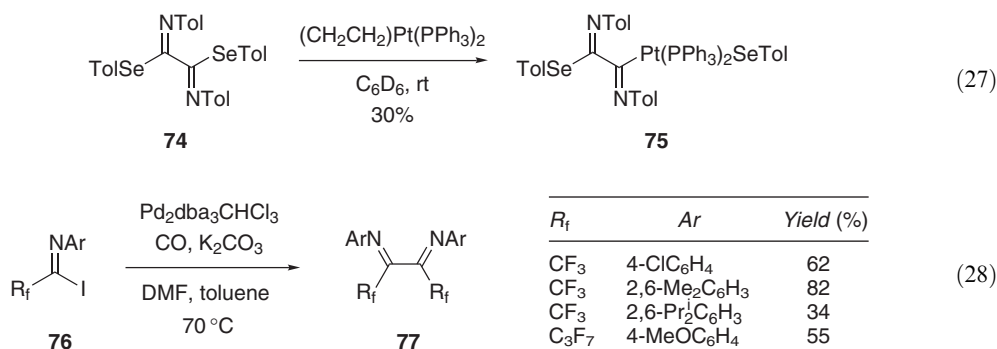


5.20.3.3.8 Imidoyl-Ni, -Pd, and -Pt derivatives

Insertions of isocyanides into Ni—C, Pd—C, and Pt—C bonds is a facile process and many examples have been described (Table 4). Multiple insertions are often observed, and Pd and Ni complexes can be used to initiate oligomerization and polymerization of isocyanides <2000CEJ983, 1993JA9101>. The influence of the isocyanide structure on the ease of insertion has been studied. 2,6-Dimethylphenyl isocyanide is more reactive than Bu^tNC <2002OM4799>, and more electron-deficient isocyanides are more reactive <1997OM2948>. Ligand effects are also very pronounced, for example, in one series of Pd diphosphane complexes, the dppe complexes were most reactive, dppf analogs were next, and dppp complexes were much less prone to insertion <2002OM4799>. Much effort has been devoted to studying further coupling reactions of the iminoacyl derivatives, partly with a view to discovering co-polymerizations of isocyanides with other monomers, an objective that has not yet been achieved. Interesting intramolecular coupling processes have been developed <2003OM1967, 2002OM581, 1998OM4335> and an elegant Pd-catalyzed cyclization has been designed and applied to alkaloid total synthesis <2002OL3215>. Efforts to carry out intermolecular coupling reactions have also been successful <2002OM4799, 1997BCJ917, 1997OM4150>, and imidoyl-Pd derivatives are almost certainly intermediates in a useful catalytic coupling of Bu^tNC with aryl bromides and amines to give amidines <2000AG(E)4156>.

Surprisingly, only one other synthetic method has been used, that being oxidative addition of M(0) complexes to imidoyl iodides and selenides. There is just one example of the use of the latter type of substrate <1998OM908>. A Pt(0) complex reacted with oxalimidoyl selenide **74** to give a poor yield of imidoylplatinum derivative **75** (Equation (27)). An even lower yield of an unstable Pd analog was obtained using Pd(PPh₃)₄. In contrast, moderate-to-good yields were obtained in the

Pd-catalyzed synthesis of α -diimines **77** by reductive coupling of imidoyl iodides **76** (Equation (28)) <2003CC1752>. The products are potentially interesting electron-deficient ligands. Pd-catalyzed alkoxy carbonylation of trifluoroacetimidoyl iodides has been achieved in excellent yields <2003OL4297>.



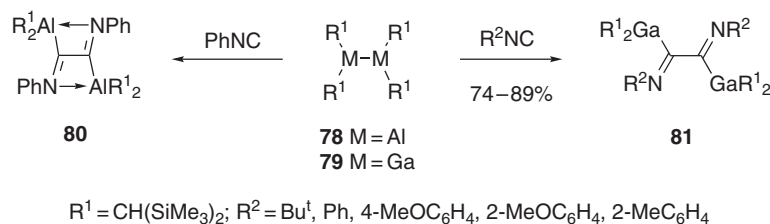
5.20.3.3.9 Imidoyl-Zn, -Cd, and -Hg derivatives

The only recent report of an imidoylzinc involved the addition of diethylzinc to an isocyanide <1993JOM(443)C1>. Trapping of the intermediate with TMSCl furnished an imidoylstannane. No reference has been made to the preparation of imidoyl-Cd or -Hg derivatives.

5.20.3.4 Imidoyl Derivatives of Group 13 and Group 14 Metals—Al, Ga, In, Tl, Sn, and Pb

5.20.3.4.1 Imidoyl-Al and -Ga derivatives

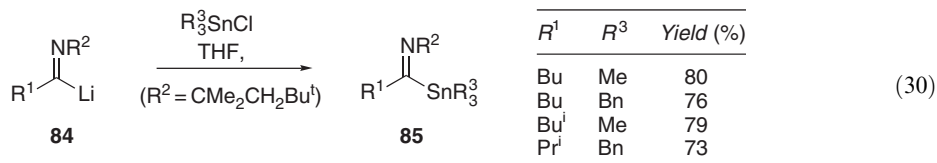
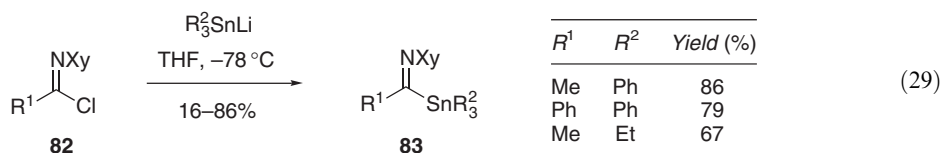
Only two reports of imidoyl-Al and -Ga species have appeared. Reaction of a dialuminum compound **78** with an excess of phenyl isocyanide gave the double insertion product **80** (Scheme 14) <1994CB1587>. The digallium analog **79** reacted with a series of isocyanides to give the corresponding insertion products **81**, which, in contrast to the aluminum derivatives, showed only weak Ga—N interactions <1996CB897>. In contrast, InMe₃ did not react with isocyanides to give insertion products <2001JOM(626)11>.



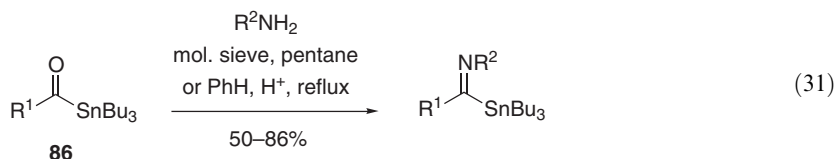
Scheme 14

5.20.3.4.2 Imidoyl-Sn derivatives

The preparation of imidoylstannanes **83** by the reaction of imidoyl chlorides with stannylolithiums was improved by the use of *N*-xylylimidoyl chlorides **82**, and by conducting the reactions at -78°C (Equation (29)) <1994JCS(P1)2283>. The reaction of imidoyllithiums **84** with chlorostannanes, i.e., the electronic converse of the first method, is also a versatile route to imidoylstannanes **85** (Equation (30)) <1993JOM(443)C1, 1994JOC758>. An imidoylzinc was also used in this transformation <1993JOM(443)C1>.



A third route to imidoystannanes is the condensation of acylstannanes **86** with primary aliphatic and aromatic amines (Equation (31)) <1993S981>. The scope of this reaction is very wide (R^1 and R^2 can be 1° alkyl, 2° alkyl, or phenyl) and it only fails when R^1 or R^2 is *t*-alkyl.



5.20.3.5 Imidoyl Derivatives of Lanthanides and Actinides

There has been little recent interest in imidoyl derivatives of the lanthanides and actinides. The use of imidoysamarium compounds as acyl anion equivalents has been reviewed <1994JOM(473)93>, but it has not been adopted by others. More recently, it was shown that the addition of organyllithiums and diorganylmagnesiums to mixtures of xyllyl isocyanide and CeCl_3 gave the imidoylcerium intermediates that reacted with electrophiles in high yields, whereas LaCl_3 and SmX_3 gave products derived from multiple insertions <1996BCJ25>. These imidoylceriums show promise as acyl anion equivalents. The reductive coupling of trifluoroacetimidoyl iodides using SmI_2 may proceed via imidoysamarium intermediates <2003TL8073>.

REFERENCES

- 1992OM2198 H. G. Woo, W. P. Freeman, T. D. Tilley, *Organometallics* **1992**, *11*, 2198–2205.
 1993AG(E)1720 A. Peyman, K. H. Budt, J. Spanig, D. Ruppert, *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1720–1722.
 1993CB1551 E. P. Mayer, H. Nöth, *Chem. Ber.* **1993**, *126*, 1551–1557.
 1993JA9101 T. J. Deming, B. M. Novak, *J. Am. Chem. Soc.* **1993**, *115*, 9101–9111.
 1993JOC5595 A. S. Guram, R. F. Jordan, *J. Org. Chem.* **1993**, *58*, 5595–5597.
 1993JOM(443)C1 B. Jousseau, M. Pereyre, N. Petit, J.-B. Verlhac, A. Ricci, *J. Organomet. Chem.* **1993**, *443*, C1–C2.
 1993JOM(458)211 M. P. Cifuentes, M. G. Humphrey, B. W. Skelton, A. H. White, *J. Organomet. Chem.* **1993**, *458*, 211–218.
 1993OM2584 B. K. Campion, R. H. Heyn, T. D. Tilley, *Organometallics* **1993**, *12*, 2584–2590.
 1993OM3410 G. Poszmik, P. J. Carroll, B. B. Wayland, *Organometallics* **1993**, *12*, 3410–3417.
 1993OM4653 L. Weber, A. Ruehlicke, H. G. Stammler, B. Neumann, *Organometallics* **1993**, *12*, 4653–4656.
 1993S981 H. Ahlbrecht, V. Baumann, *Synthesis* **1993**, 981–984.
 1994CB1587 W. Uhl, U. Schütz, W. Hiller, M. Heckel, *Chem. Ber.* **1994**, *127*, 1587–1592.
 1994CC37 R. Hamilton, M. A. McKervery, M. D. Rafferty, B. J. Walker, *J. Chem. Soc., Chem. Commun.* **1994**, 37–38.
 1994JA9123 A. Klose, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, N. Re, *J. Am. Chem. Soc.* **1994**, *116*, 9123–9135.
 1994JCS(P1)2283 B. Jousseau, N. Vilcot, A. Ricci, E. R. T. Tiekink, *J. Chem. Soc., Perkin Trans. 1* **1994**, 2283–2288.
 1994JOC477 A. Orita, M. Fukudome, K. Ohe, S. Murai, *J. Org. Chem.* **1994**, *59*, 477–481.
 1994JOC6856 L. J. Sun, L. S. Liebeskind, *J. Org. Chem.* **1994**, *59*, 6856–6858.
 1994JOC758 H. Watanabe, F. Yan, T. Sakai, K. Uneyama, *J. Org. Chem.* **1994**, *59*, 758–761.
 1994JOM(473)93 M. Murakami, Y. Ito, *J. Organomet. Chem.* **1994**, *473*, 93–99.
 1994MI481 S. E. Kabir, E. Rosenberg, M. Day, K. I. Hardcastle, M. Irving, *J. Cluster Sci.* **1994**, *5*, 481–503.
 1994OM385 G. C. Hsu, W. P. Kosar, W. D. Jones, *Organometallics* **1994**, *13*, 385–396.

- 1994OM3990 M. Weidenbruch, H. Piel, K. Peters, H. G. von Schnering, *Organometallics* **1994**, *13*, 3990–3994.
1994OM4720 C. P. Casey, R. A. Widenhoefer, S. L. Hallenbeck, R. K. Hayashi, J. A. J. Gavney, *Organometallics* **1994**, *13*, 4720–4731.
- 1994TL1445 J. M. Davis, R. J. Whitby, A. Jaxa-Chamiec, *Tetrahedron Lett.* **1994**, *35*, 1445–1448.
1994ZOB1744 P. P. Onys'ko, T. V. Kim, E. I. Kiseleva, V. P. Prokopenko, A. D. Sinitsa, *Zh. Obshch. Khim.* **1994**, *64*, 1744–1745.
- 1994ZOB396 P. P. Onys'ko, T. V. Kolodka, N. V. Kolotilo, A. A. Kudryavtsev, A. D. Sinitsa, *Zh. Obshch. Khim.* **1994**, *64*, 396–402.
- 1995CB1029 S. Luckert, E. Eversheim, M. Müller, B. Redenz-Stormanns, U. Englert, P. Paetzold, *Chem. Ber.* **1995**, *128*, 1029–1035.
1995CB1037 C. Klöforn, M. Schmidt, T. Spaniol, T. Wagner, O. Costisor, P. Paetzold, *Chem. Ber.* **1995**, *128*, 1037–1043.
- 1995CB1051 M. Tacke, *Chem. Ber.* **1995**, *128*, 1051–1053.
1995COFGT(5)783 M. Butters, *Comprehensive Organic Functional Group Transformations*, Pergamon, Oxford, **1995**.
1995JA8083 M. Zablocka, A. Igau, N. Cenac, B. Donnadieu, F. Dahan, J. P. Majoral, M. K. Pietrusiewicz, *J. Am. Chem. Soc.* **1995**, *117*, 8083–8089.
- 1995JCS(D)2111 A. A. Danopoulos, G. Wilkinson, T. K. N. Sweet, M. B. Hursthouse, *J. Chem. Soc., Dalton Trans.* **1995**, 2111–2123.
- 1995JOM(488)177 B. Temme, G. Erker, *J. Organomet. Chem.* **1995**, *488*, 177–182.
1995JOM(490)117 K. Onitsuka, K. Murakami, K. Matsukawa, K. Sonogashira, T. Adachi, T. Yoshida, *J. Organomet. Chem.* **1995**, *490*, 117–123.
- 1995JOM(491)159 D. L. Reger, J. E. Collins, *J. Organomet. Chem.* **1995**, *491*, 159–167.
1995OM1548 T. Honda, S. Satoh, M. Mori, *Organometallics* **1995**, *14*, 1548–1550.
1995OM2145 R. Laie, O. Desbois, F. Zamkotsian, R. Faure, J. Feneau-Dupont, J.-P. Declercq, *Organometallics* **1995**, *14*, 2145–2147.
- 1995OM2325 G. Hogarth, M. H. Lavender, K. Shukri, *Organometallics* **1995**, *14*, 2325–2341.
1995OM4816 D. Jacoby, S. Isoz, C. Floriani, K. Schenk, A. Chiesi-Villa, C. Rizzoli, *Organometallics* **1995**, *14*, 4816–4824.
- 1995PS(107)21 W. Huang, Y. Zhang, C. Yuan, *Phosphorus Sulfur Silicon* **1995**, *107*, 21–26.
1995T6517 J. Boivin, A.-C. Callier-Dublanchet, B. Quiclet-Sire, A.-M. Schiano, S. Z. Zard, *Tetrahedron* **1995**, *51*, 6517–6528.
- 1995ZOB1961 P. P. Onys'ko, T. V. Kim, E. I. Kiseleva, A. D. Sinitsa, *Zh. Obshch. Khim.* **1995**, *65*, 1961–1971.
1996BCJ25 M. Murakami, H. Ito, Y. Ito, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 25–30.
1996CB897 W. Uhl, I. Hahn, U. Schütz, S. Pohl, W. Saak, J. Martens, J. Manikowski, *Chem. Ber.* **1996**, *129*, 897–901.
- 1996CEJ919 B. Temme, J. Karl, G. Erker, *Chem. Eur. J.* **1996**, *2*, 919–924.
1996CL7 M. Murakami, H. Ito, Y. Ito, *Chem. Lett.* **1996**, 7–8.
1996JA8765 E. J. Corey, S. Lin, *J. Am. Chem. Soc.* **1996**, *118*, 8765–8766.
1996JCS(D)3687 M. d. M. Conejo, A. Pizzano, L. J. Sanchez, E. Carmona, *J. Chem. Soc., Dalton Trans.* **1996**, 3687–3691.
- 1996JOC6055 K. Uneyama, C. Noritake, K. Sadamune, *J. Org. Chem.* **1996**, *61*, 6055–6057.
1996JOM(510)267 S. M. Maddock, C. E. F. Rickard, W. R. Roper, L. J. Wright, *J. Organomet. Chem.* **1996**, *510*, 267–279.
- 1996MI663 Y.-J. Kim, J.-Y. Lee, D.-H. Kim, S.-W. Lee, *Bull. Korean Chem. Soc.* **1996**, *17*, 663–666.
1996OM1604 T. Constantieux, J.-P. Picard, *Organometallics* **1996**, *15*, 1604–1609.
1996OM5254 J.-J. Brunet, A. Capperucci, R. Chauvin, *Organometallics* **1996**, *15*, 5254–5255.
1996TL3675 E. Kroke, S. Willms, M. Weidenbruch, W. Saak, S. Pohl, H. Marsmann, *Tetrahedron Lett.* **1996**, *37*, 3675–3678.
- 1996ZOB936 P. P. Onys'ko, T. V. Kim, E. I. Kiseleva, A. D. Sinitsa, *Zh. Obshch. Khim.* **1996**, *66*, 936–941.
1997BCJ917 Y. Kayaki, I. Shimizu, A. Yamamoto, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 917–927.
1997CB871 H. Werner, L. Xiaolan, K. Peters, H. G. Von Schnering, *Chem. Ber./Recueil* **1997**, *130*, 871–877.
1997H111 T. Yokomatsu, T. Minowa, Y. Yoshida, S. Shibuya, *Heterocycles* **1997**, *44*, 111–116.
1997JA9709 L. Giannini, A. Caselli, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, N. Re, A. Sgamellotti, *J. Am. Chem. Soc.* **1997**, *119*, 9709–9719.
- 1997JCS(D)3145 U. Amador, P. J. Daff, M. L. Poveda, C. Ruiz, E. Carmona, *J. Chem. Soc., Dalton Trans.* **1997**, 3145–3151.
- 1997JOM(533)87 A. Antinolo, A. Otero, M. Fajardo, R. Gil-Sanz, M. Jose Herranz, C. Lopez-Mardomingo, A. Martin, P. Gomez-Sal, *J. Organomet. Chem.* **1997**, *533*, 87–96.
1997JOM(542)247 A. M. Barriola, A. M. Cano, T. Cuenca, F. J. Fernandez, P. Gomez-Sal, A. Manzanero, P. Royo, *J. Organomet. Chem.* **1997**, *542*, 247–253.
1997JOM(549)167 E. Gutierrez, M. C. Nicasio, M. Paneque, C. Ruiz, V. Salazar, *J. Organomet. Chem.* **1997**, *549*, 167–176.
- 1997OM1779 R. L. Huff, S.-Y. S. Wang, K. A. Abboud, J. M. Boncella, *Organometallics* **1997**, *16*, 1779–1785.
1997OM2263 P. J. Daff, A. Monge, P. Palma, M. L. Poveda, C. Ruiz, P. Valerga, E. Carmona, *Organometallics* **1997**, *16*, 2263–2275.
- 1997OM2948 J. G. P. Delis, P. G. Aubel, K. Vrieze, P. W. N. M. van Leeuwen, N. Veldman, A. L. Spek, F. J. R. van Neer, *Organometallics* **1997**, *16*, 2948–2957.
1997OM3548 L. Kloppenburg, J. L. Petersen, *Organometallics* **1997**, *16*, 3548–3556.
1997OM3993 E. Boring, M. Sabat, M. G. Finn, R. N. Grimes, *Organometallics* **1997**, *16*, 3993–4000.
1997OM4150 J. G. P. Delis, P. G. Aubel, K. Vrieze, P. W. N. M. van Leeuwen, N. Veldman, A. L. Spek, *Organometallics* **1997**, *16*, 4150–4160.
- 1997PS(126)243 A. N. El-Khazandar, *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *126*, 243–255.

- 1997TL2463 A.-C. Callier-Dublanche, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1997**, 38, 2463–2466.
1997TL5771 E. J. Corey, S. Lin, G. Luo, *Tetrahedron Lett.* **1997**, 38, 5771–5774.
1998HAC139 C. Yuan, Y. Zhang, W. Luo, Z. Yao, *Heteroatom Chem.* **1998**, 9, 139–146.
1998ICA(270)527 D. P. Steinhuebel, P. Fuhrmann, S. J. Lippard, *Inorg. Chim. Acta* **1998**, 270, 527–536.
1998JCS(D)775 J. E. Davies, M. J. Mays, P. R. Raithby, V. Sarveswaran, G. P. Shields, *J. Chem. Soc., Dalton Trans.* **1998**, 775–779.
1998JGU536 P. P. Onys'ko, N. K. Maidanovich, T. V. Kim, E. I. Kiseleva, A. D. Sinitsa, *Russ. J. Gen. Chem.* **1998**, 68, 536–538.
1998JGU753 A. V. Rogoza, G. G. Furin, *Russ. J. Gen. Chem.* **1998**, 68, 753–760.
1998JOM(563)15 P. Royo, J. Sanchez-Nieves, M. A. Pellinghelli, A. Tiripicchio, *J. Organomet. Chem.* **1998**, 563, 15–21.
1998JOM(571)83 W. Ahlers, G. Erker, R. Fröhlich, *J. Organomet. Chem.* **1998**, 571, 83–89.
1998MI2044 N. V. Kolotilo, A. A. Sinitsa, P. P. Onys'ko, *Russ. Chem. Bull.* **1998**, 47, 2044–2046.
1998OM2328 B. Castellano, E. Solari, C. Floriani, N. Re, A. Chiesi-Villa, C. Rizzoli, *Organometallics* **1998**, 17, 2328–2336.
1998OM4335 K. Onitsuka, M. Segawa, S. Takahashi, *Organometallics* **1998**, 17, 4335–4337.
1998OM5836 F. Amor, A. Butt, K. E. du Plooy, T. P. Spaniol, J. Okuda, *Organometallics* **1998**, 17, 5836–5849.
1998OM908 H. Kuniyasu, A. Maruyama, H. Kurosawa, *Organometallics* **1998**, 17, 908–913.
1998POL675 A. L. Odom, C. C. Cummins, *Polyhedron* **1998**, 17, 675–688.
1998T12007 E. Alonso, D. J. Ramon, M. Yus, *Tetrahedron* **1998**, 54, 12007–12028.
1999CC491 H. Adams, R. J. Cubbon, M. J. Sarsfield, M. J. Winter, *J. Chem. Soc., Chem. Commun.* **1999**, 491–492.
1999ICA(286)233 Y. Yamamoto, M. Tsuji, T. Igoshi, *Inorg. Chim. Acta* **1999**, 286, 233–236.
1999JOC1843 P. T. Nguyen, W. S. Palmer, K. A. Woerpel, *J. Org. Chem.* **1999**, 64, 1843–1848.
1999JOM(579)211 D.-L. Wang, W.-S. Hwang, L. Lee, M. Y. Chiang, *J. Organomet. Chem.* **1999**, 579, 211–216.
1999JOM(585)63 C.-G. Yan, J. Sun, *J. Organomet. Chem.* **1999**, 585, 63–67.
1999JOM(588)268 Y.-J. Kim, S.-C. Lee, M. H. Cho, S.-W. Lee, *J. Organomet. Chem.* **1999**, 588, 268–277.
1999OM1994 E. W. Jandci, J. Kuzelka, P. Legzdins, S. J. Rettig, K. M. Smith, *Organometallics* **1999**, 18, 1994–2004.
1999OM2376 C. Bianchini, D. Masi, A. Romerosa, F. Zanobini, M. Peruzzini, *Organometallics* **1999**, 18, 2376–2386.
1999OM4442 M. G. Thorn, P. E. Fanwick, I. P. Rothwell, *Organometallics* **1999**, 18, 4442–4447.
1999OM5225 J. Campora, S. A. Hudson, P. Massiot, C. M. Maya, P. Palma, E. Carmona, L. A. Martinez-Cruz, A. Vegas, *Organometallics* **1999**, 18, 5225–5237.
1999OM5594 T. M. Becker, J. J. Alexander, J. A. K. Bauer, J. L. Nauss, F. C. Wireko, *Organometallics* **1999**, 18, 5594–5605.
1999OM606 R. Crescenzi, E. Solari, C. Floriani, N. Re, A. Chiesi-Villa, C. Rizzoli, *Organometallics* **1999**, 18, 606–618.
1999PS(146)385 J. Cairns, C. Dunne, T. S. Franczyk, R. Hamilton, C. Hardacre, M. K. Stern, A. Treacy, B. J. Walker, *Phosphorus Sulfur Silicon* **1999**, 146, 385–388.
1999TL3457 C. Stevens, M. Gallant, N. De Kimpe, *Tetrahedron Lett.* **1999**, 40, 3457–3460.
1999TL4531 J. Boivin, A.-M. Schiano, S. Z. Zard, H. Zhang, *Tetrahedron Lett.* **1999**, 40, 4531–4534.
2000AG(E)4156 C. G. Saluste, R. J. Whitby, M. Furber, *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 4156–4158.
2000CEJ983 F. Takei, K. Yanai, K. Onitsuka, S. Takahashi, *Chem. Eur. J.* **2000**, 6, 983–993.
2000EJI2047 A. Castro, M. V. Galakhov, M. Gomez, P. Gomez-Sal, A. Martin, F. Sanchez, P. Velasco, *Eur. J. Inorg. Chem.* **2000**, 2047–2054.
2000EJO275 M. Depature, J. Diewok, J. Grimaldi, J. Hatem, *Eur. J. Org. Chem.* **2000**, 275–280.
2000HAC536 J. Xiao, X. Zhang, C. Yuan, *Heteroatom Chem.* **2000**, 11, 536–540.
2000JA9880 P. R. Sharp, *J. Am. Chem. Soc.* **2000**, 122, 9880–9881.
2000JOM(593–594)119 G. Bellachioma, G. Cardaci, A. Macchioni, C. Zuccaccia, *J. Organomet. Chem.* **2000**, 593–594, 119–126.
2000JOM(595)36 A. Castro, M. V. Galakhov, M. Gomez, P. Gomez-Sal, A. Martin, F. Sanchez, *J. Organomet. Chem.* **2000**, 595, 36–53.
2000JOM(611)304 S. Kuroda, Y. Sato, M. Mori, *J. Organomet. Chem.* **2000**, 611, 304–307.
2000OM1406 S. J. Skoog, C. Mateo, G. G. Lavoie, F. J. Hollander, R. G. Bergman, *Organometallics* **2000**, 19, 1406–1421.
2000OM2243 K. S. Cook, W. E. Piers, S. J. Rettig, R. McDonald, *Organometallics* **2000**, 19, 2243–2245.
2000OM5431 W.-P. Leung, H. Cheng, H. L. Hou, Q.-C. Yang, Q.-G. Wang, T. C. W. Mak, *Organometallics* **2000**, 19, 5431–5439.
2000SL1031 S. N. Osipov, O. I. Artyushin, A. F. Kolomiets, C. Bruneau, P. H. Dixneuf, *Synlett* **2000**, 1031–1033.
2001CEJ221 V. Cadierno, M. Zabolocka, B. Donnadieu, A. Igau, J.-P. Majoral, A. Skowronska, *Chem. Eur. J.* **2001**, 7, 221–229.
2001JCS(D)1732 J. H. Shin, W. Savage, V. J. Murphy, J. B. Bonanno, D. G. Churchill, G. Parkin, *J. Chem. Soc., Dalton Trans.* **2001**, 1732–1753.
2001JCS(D)181 P. N. Riley, P. E. Fanwick, I. P. Rothwell, *J. Chem. Soc., Dalton Trans.* **2001**, 181–186.
2001JCS(D)2409 P. B. Hitchcock, M. F. Lappert, M. Layh, *J. Chem. Soc., Dalton Trans.* **2001**, 2409–2416.
2001JFC(111)27 J. Ding, P. Zhong, C. Yuan, *J. Fluorine Chem.* **2001**, 111, 27–28.
2001JOM(626)11 R. Bertani, L. Crociani, G. D'arcangelo, G. Rossetto, P. Traldi, P. Zanella, *J. Organomet. Chem.* **2001**, 626, 11–15.
2001OM4080 T. J. Woodman, M. Thornton-Pett, D. L. Hughes, M. Bochmann, *Organometallics* **2001**, 20, 4080–4091.

- 2002CHE46 I. Iovel, L. Golomba, J. Popelis, E. Lukevics, *Chem. Heterocycl. Cmpd.* **2002**, 38, 46–53.
- 2002ICA(334)419 C. L. Homrighausen, J. J. Alexander, J. A. K. Bauer, *Inorg. Chim. Acta* **2002**, 334, 419–436.
- 2002JA6524 T. G. Driver, A. K. Franz, K. A. Woerpel, *J. Am. Chem. Soc.* **2002**, 124, 6524–6525.
- 2002JCS(D)3398 M. G. Thorn, J. Lee, P. E. Fanwick, I. P. Rothwell, *J. Chem. Soc., Dalton Trans.* **2002**, 3398–3405.
- 2002JFC(117)107 Y. V. Rassukana, K. O. Davydova, P. P. Onys'ko, A. D. Sinitsa, *J. Fluorine Chem.* **2002**, 117, 107–113.
- 2002JGU1695 Yu. V. Rassukanaya, Ya. A. Sizonenko, A. A. Sinitsa, V. I. Boiko, A. A. Podoprigrorina, P. P. Onys'ko, *Russ. J. Gen. Chem.* **2002**, 72, 1695–1698.
- 2002OL3215 D. P. Curran, W. Du, *Org. Lett.* **2002**, 4, 3215–3218.
- 2002OM1 T.-G. Ong, D. Wood, G. P. A. Yap, D. S. Richeson, *Organometallics* **2002**, 21, 1–3.
- 2002OM2382 N. Mantovani, L. Marvelli, R. Rossi, V. Bertolasi, C. Bianchini, I. de Rios, M. Peruzzini, *Organometallics* **2002**, 21, 2382–2394.
- 2002OM2422 K. S. Cook, W. E. Piers, P. G. Hayes, M. Parvez, *Organometallics* **2002**, 21, 2422–2425.
- 2002OM293 A. Galindo, M. Gomez, P. Gomez-Sal, A. Martin, D. Del Rio, F. Sanchez, *Organometallics* **2002**, 21, 293–304.
- 2002OM4799 G. R. Owen, R. Vilar, A. J. P. White, D. J. Williams, *Organometallics* **2002**, 21, 4799–4807.
- 2002OM581 K. Onitsuka, M. Yamamoto, S. Suzuki, S. Takahashi, *Organometallics* **2002**, 21, 581–583.
- 2003CC1752 H. Amii, M. Kohda, M. Seo, K. Uneyama, *J. Chem. Soc., Chem. Commun.* **2003**, 1752–1753.
- 2003CEJ4462 M. D. Conejo, R. Fernandez, E. Carmona, R. A. Andersen, E. Gutierrez-Puebla, M. A. Monge, *Chem. Eur. J.* **2003**, 9, 4462–4471.
- 2003EJI2438 I. Del Hierro, R. Fernandez-Galan, S. Prashar, A. Antinolo, M. Fajardo, A. M. Rodriguez, A. Otero, *Eur. J. Inorg. Chem.* **2003**, 2438–2445.
- 2003EJI2626 A. Antinolo, R. Fernandez-Galan, B. Gallego, A. Otero, S. Prashar, A. M. Rodriguez, *Eur. J. Inorg. Chem.* **2003**, 2626–2632.
- 2003EJO385 A. Maraval, A. Igau, B. Donnadiou, J.-P. Majoral, *Eur. J. Org. Chem.* **2003**, 385–394.
- 2003IC625 D. Walther, S. Liesicke, L. Boettcher, R. Fischer, H. Goerls, G. Vaughan, *Inorg. Chem.* **2003**, 42, 625–632.
- 2003JA8746 Y. Zhang, R. J. Keaton, L. R. Sita, *J. Am. Chem. Soc.* **2003**, 125, 8746–8747.
- 2003JA9808 F. L. Taw, A. H. Mueller, R. G. Bergman, M. Brookhart, *J. Am. Chem. Soc.* **2003**, 125, 9808–9813.
- 2003OL4297 T. Kobayashi, T. Nakagawa, H. Amii, K. Uneyama, *Org. Lett.* **2003**, 5, 4297–4300.
- 2003OM162 M. L. Buil, M. A. Esteruelas, A. M. Lopez, E. Onate, *Organometallics* **2003**, 22, 162–171.
- 2003OM1967 J. Vicente, J.-A. Abad, E. Martinez-Viviente, P. G. Jones, *Organometallics* **2003**, 22, 1967–1978.
- 2003OM2817 H. Hou, P. K. Gantzel, C. P. Kubiak, *Organometallics* **2003**, 22, 2817–2819.
- 2003OM4218 A. M. Martins, J. R. Ascenso, C. G. de Azevedo, A. R. Dias, M. T. Duarte, J. F. da Silva, L. F. Veiros, S. S. Rodrigues, *Organometallics* **2003**, 22, 4218–4228.
- 2003TL8073 J. P. Sadighi, L. M. Henling, J. A. Labinger, J. E. Bercaw, *Tetrahedron Lett.* **2003**, 44, 8073–8076.
- 2003WOP2003076450 M. Brookhart, O. Daugulis, WO Patent 2003076450 (2003).

Biographical sketch

Mike Casey was born in Cork, and studied at University College Cork, where he obtained a B.Sc. in 1979, and at Imperial College where he obtained his Ph.D. in 1982 under the supervision of Professor Charles Rees and Dr. Chris Moody. He spent two very enjoyable years as a postdoc with Professor Gilbert Stork at Columbia University working on alkaloid total synthesis, and was then appointed to a lectureship at the University of Salford. He returned to Ireland in 1992 to his present position as lecturer in chemistry at University College Dublin. His research interests focus on the development of new methods in asymmetric catalysis and the synthetic potential of sulfoxides and their application to natural product synthesis.

5.21

N-Heterosubstituted Iminoacyl Functions

B. DIETRICH

University of East Anglia, Norwich, UK

5.21.1	HALOIMIDIC DERIVATIVES	726
5.21.1.1	Haloimidic Halides	727
5.21.1.1.1	From nitriles	727
5.21.1.1.2	Other methods	727
5.21.1.2	Other N-Haloimidic Derivatives	727
5.21.1.2.1	N-Haloimidic acids and salts	727
5.21.1.2.2	N-Haloimidic esters (N-haloimidates)	728
5.21.1.2.3	N-Haloamidines	728
5.21.2	OXYIMIDIC DERIVATIVES	729
5.21.2.1	Oxyimidic Halides	729
5.21.2.1.1	From nitrile oxides	729
5.21.2.1.2	From aci-nitro compounds and nitro alkenes	729
5.21.2.1.3	From aldoximes	733
5.21.2.1.4	From α -amino acid derivatives	735
5.21.2.1.5	From nitro compounds	736
5.21.2.1.6	From carbonyl compounds	736
5.21.2.1.7	From N-alkoxyamides	737
5.21.2.1.8	From oxyimidic amides	738
5.21.2.1.9	From sulfonium salts	738
5.21.2.1.10	Other methods	738
5.21.2.1.11	Transhalogenation	739
5.21.2.1.12	Isomerization	739
5.21.2.2	Oxyimidic Esters and Related Structures	740
5.21.2.2.1	From oxyimidic halides	740
5.21.2.2.2	From nitrile oxides	741
5.21.2.2.3	From thiocarboxylic O-esters	742
5.21.2.2.4	From carboxylic acid alkoxy amides and acyloxy amides	742
5.21.2.2.5	From oximes and related structures	745
5.21.2.2.6	From carboxylic esters	745
5.21.2.2.7	From hydroxyimidic esters	745
5.21.2.3	Oxyimidic Sulfur Derivatives	745
5.21.2.3.1	From oxyimidic halides	746
5.21.2.3.2	From nitro compounds	746
5.21.2.3.3	From carbonyl compounds	747
5.21.2.3.4	From oxyimidic thioacids and esters	747
5.21.2.3.5	From γ -keto-bis-(alkylthio)alkenes	748
5.21.2.3.6	Other methods	748
5.21.2.4	Oxyimidic Selenium, Silicon, and Tellurium Derivatives	748
5.21.2.5	Oxyimidic Amides and Related Structures	749
5.21.2.5.1	From nitriles	749
5.21.2.5.2	From amides and thioamides	750
5.21.2.5.3	From oxyimidic halides	750
5.21.2.5.4	From oxyimidic and imidic esters	751
5.21.2.5.5	From amidines and hydroxyamidines	751

5.21.2.5.6	<i>From aliphatic nitro compounds</i>	752
5.21.2.5.7	<i>Other methods</i>	752
5.21.2.5.8	<i>Nitrolic acids</i>	753
5.21.2.6	Oxyimidic Phosphorus Derivatives	753
5.21.2.6.1	<i>From phosphonic acid esters</i>	753
5.21.2.6.2	<i>From phosphites</i>	754
5.21.2.6.3	<i>From phosphanes</i>	755
5.21.3	THIOIMIDIC DERIVATIVES	755
5.21.3.1	Thioimidic Halides and Related Structures	755
5.21.3.2	Thioimidic Esters and Related Structures	756
5.21.3.3	Thioimidic Thioesters and Related Structures	758
5.21.3.4	Thioimidic Amides and Related Structures	758
5.21.3.5	Thioimidic Silicon and Selenium Derivatives	759
5.21.4	HYDRAZONOYL DERIVATIVES	760
5.21.4.1	Hydrazonoyl Halides	760
5.21.4.1.1	<i>From hydrazones</i>	760
5.21.4.1.2	<i>From hydrazides</i>	762
5.21.4.1.3	<i>From 2-halo-1,3-dicarbonyl compounds</i>	762
5.21.4.1.4	<i>From diazenes and related compounds</i>	763
5.21.4.1.5	<i>From diazonium salts and related compounds</i>	763
5.21.4.1.6	<i>Other methods</i>	764
5.21.4.1.7	<i>Transhalogenation</i>	764
5.21.4.2	Hydrazonic Acid Derivatives	765
5.21.4.2.1	<i>From hydrazides</i>	765
5.21.4.2.2	<i>From hydrazones</i>	767
5.21.4.2.3	<i>Other methods</i>	767
5.21.4.3	Thio- and Selenohydrazonic Acid Derivatives	767
5.21.4.3.1	<i>From thioamides, thioureas, thiocarbonyl hydrazides, and derivatives</i>	767
5.21.4.3.2	<i>Other methods</i>	769
5.21.4.4	Hydrazonic Derivatives of Phosphorus and Silicon	771
5.21.4.5	Hydrazonamides and Related Structures	773
5.21.4.5.1	<i>From nitriles</i>	773
5.21.4.5.2	<i>From carbonyl compounds</i>	774
5.21.4.5.3	<i>From amines and hydrazine derivatives</i>	774
5.21.4.5.4	<i>From imidic esters</i>	775
5.21.4.5.5	<i>From thioimidic esters</i>	776
5.21.4.5.6	<i>From imidoyl halides</i>	776
5.21.4.5.7	<i>From amidines</i>	776
5.21.4.5.8	<i>From amides and related structures</i>	777
5.21.4.5.9	<i>From thioamides</i>	778
5.21.4.5.10	<i>From thiocarbazides and related structures</i>	778
5.21.4.5.11	<i>From hydrazones</i>	779
5.21.4.5.12	<i>From hydrazonic esters and thioesters</i>	780
5.21.4.5.13	<i>From hydrazonoyl halides</i>	780
5.21.4.5.14	<i>From 1-nitroaldehyde hydrazones</i>	780
5.21.4.5.15	<i>From heterocyclic precursors</i>	781
5.21.4.5.16	<i>From hydrazonamides</i>	781
5.21.4.5.17	<i>Other methods</i>	782
5.21.5	IMIDOYL DERIVATIVES WITH AN N-PHOSPHORUS BOND	782
5.21.5.1	Imidophosphorane Chlorides	782
5.21.5.2	Imidophosphorane Esters	782
5.21.5.3	Imidophosphorane Thioesters	783
5.21.5.4	Imidophosphorane Amides	784
5.21.5.5	Phosphorane Derivates of Hydrazonamides	784
5.21.5.6	Other Imidoyl Derivatives of Phosphorus	784
5.21.6	IMIDOYL DERIVATIVES WITH AN N-METALLOID BOND	785
5.21.6.1	N-Silylimidoyl Derivatives	785
5.21.6.2	N-Selenylimidoyl Derivatives	786
5.21.6.3	N-Borylimidoyl Derivatives	787

5.21.1 HALOIMIDIC DERIVATIVES

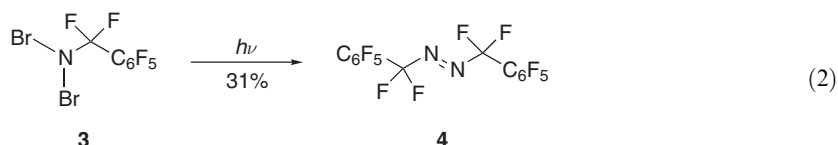
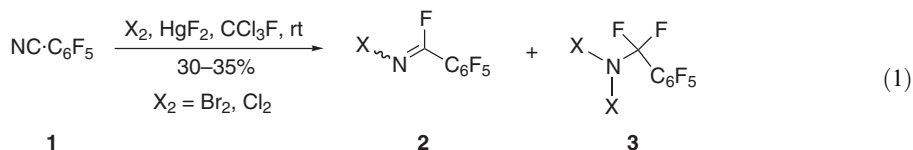
Caution: Many *N*-halo compounds are known to be powerful explosives. Reactions should be carried out on a small scale to minimize laboratory-handling hazards of the products. Adequate protective equipment should be used during all phases of the work, including the manipulations during spectroscopic and elemental analysis. For quantities greater than 1 g, remote handling is recommended. Liquid samples confined in metal containers are even more hazardous. (It should be noted that substantial work, on the synthesis of *N*-heterosubstituted iminoacyl derivatives, was

carried out before 1995. This chapter covers recent works only and therefore, COFGT (1995) (chapter 5.21) should also be consulted for synthetic methods not mentioned in this article.)

5.21.1.1 Haloimidic Halides

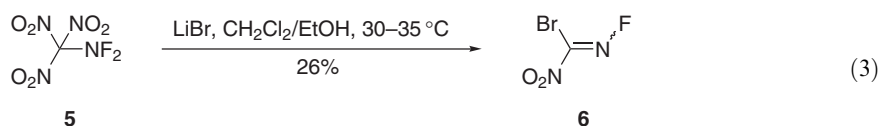
5.21.1.1.1 From nitriles

The synthesis of perfluoro-*N*-chloroimidic fluorides and *N*-bromoimidic fluorides is exemplified by the reaction of perfluoronitriles with chlorine or bromine in the presence of metal fluorides. *N*-Chloro- and *N*-bromo-1-fluoro-1-pentafluorophenylmethaneimines **2** are obtained by the reaction of perfluorobenzonitrile **1** with chlorine and bromine in the presence of mercury(II) fluoride (Equation (1)) <1994ZN(B)233>. Dihalogenated perfluorobenzylamines **3** are formed as by-products, which yield diazenes **4** under UV irradiation (Equation (2)).



5.21.1.1.2 Other methods

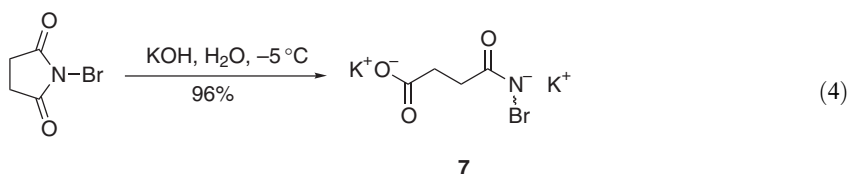
Bromonitro(fluoroimino)methane **6** has been obtained in the reaction of lithium bromide with difluoroaminotrinitromethane **5** in dichloromethane/ethanol (Equation (3)) <2001IZV706>. *N*-Haloimidic halides have been synthesized from a variety of precursors. The reader is referred to COFGT (1995) for more information.

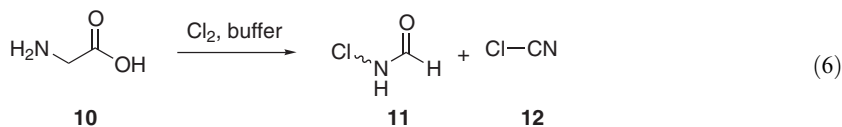
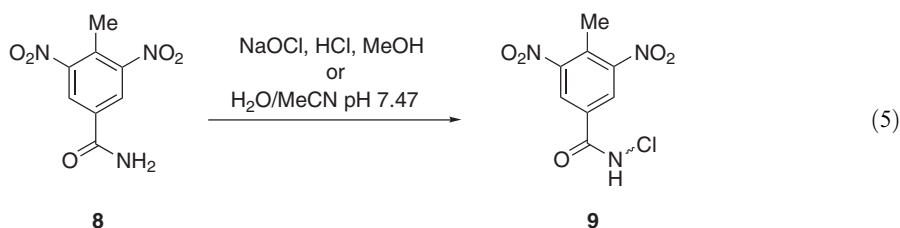


5.21.1.2 Other *N*-Haloimidic Derivatives

5.21.1.2.1 *N*-Haloimidic acids and salts

N-Haloamides are the tautomeric forms of *N*-haloimides and will have a brief mention here. The dipotassium salt of *N*-bromosuccinamic acid **7** has been obtained by base hydrolysis of *N*-bromosuccinimide <1996H821> (Equation (4)). Hypochlorite or chlorine oxidation is commonly used in the preparation of *N*-haloamides. *N*-Chloro-4-methyl-3,5-dinitrobenzamide **9** was obtained by the reaction of hypochlorous acid solution with 4-methyl-3,5-dinitrobenzamide **8** <1998MI615> (Equation (5)), and *N*-chloroformamide **11**, although not isolated, was formed in the direct chlorination of glycine **10** in aqueous phosphate buffer (Equation (6)). Cyanogen chloride **12** was amongst the by-products identified in this reaction <2000MI1721>.

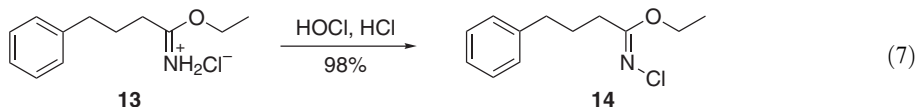




5.21.1.2.2 N-Haloimidic esters (N-haloimidates)

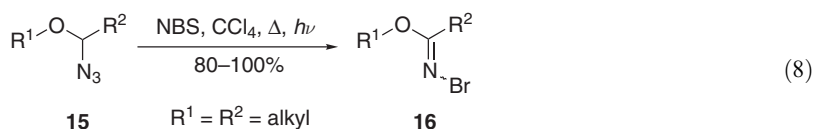
(i) From imidic esters

N-Haloimidates are prepared from the corresponding imidic esters by hypochlorite oxidation. Thus, ethyl *N*-chloro-4-phenylbutylimidate **14** has been obtained in excellent yield in the reaction between 4-phenylbutyrimidic acid ethyl ester hydrochloride **13** and hypochlorous acid or sodium hypochlorite (Equation (7)) <1998MI29, 2003TL2363>.



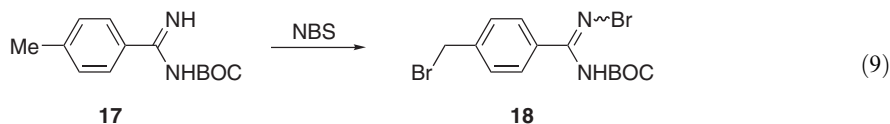
(ii) From azides

N-Haloimidates **16** are prepared in good-to-excellent yields by the treatment of azides **15** with *N*-bromosuccinimide in carbon tetrachloride under light irradiation (Equation (8)) <1995T1697>.



5.21.1.2.3 N-Haloamidines

N-Bromination of the amidine function has been effected with *N*-bromosuccinimide. Thus, *N*-bromoamidine **18** was obtained in the reaction of *p*-*N*-BOC-amidinotoluene **17** with NBS. It is interesting to note that the NBS-mediated bromination of **17** occurs preferentially at the amidine imine nitrogen. Bromination of the benzylic carbon occurs only after the addition of a second equivalent of NBS (Equation (9)) <1998BMCL1531>.



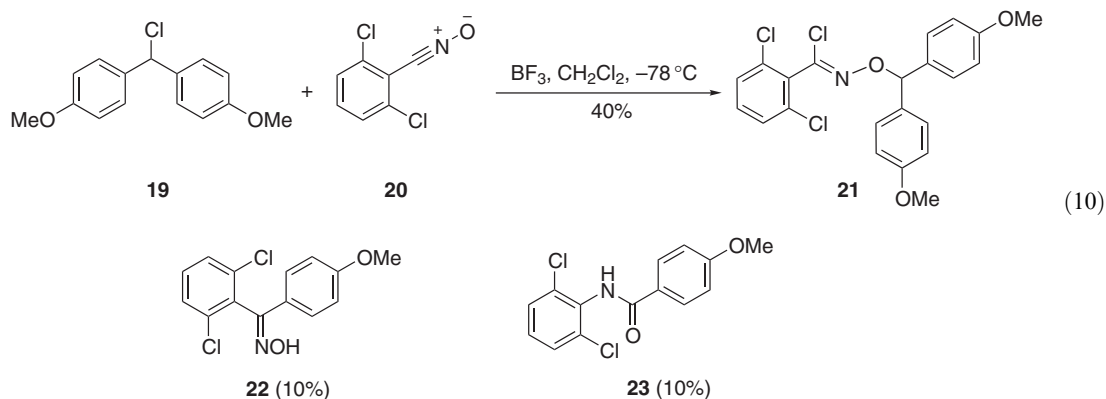
N-Haloamidines have been prepared by a variety of methods and from a variety of precursors, including the halogenation of amidines with hypochlorites, hydrohalic acids, or the free halogens, and from *N*-haloimidic halides, and *N*-haloimines. The reader is referred to COFGT (1995) for further information.

5.21.2 OXYIMIDIC DERIVATIVES

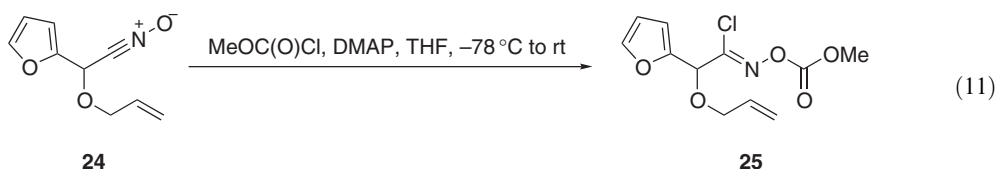
5.21.2.1 Oxyimidic Halides

5.21.2.1.1 From nitrile oxides

Oxyimidic chloride **21** was obtained from the addition of bis(4-methoxyphenyl)chloromethane **19** to 2,6-dichlorobenzonitrile oxide **20** in the presence of boron trifluoride. Two by-products, oxime **22** and amide **23**, were formed in 10% yield each (Equation (10)) <2002EJO2411>.

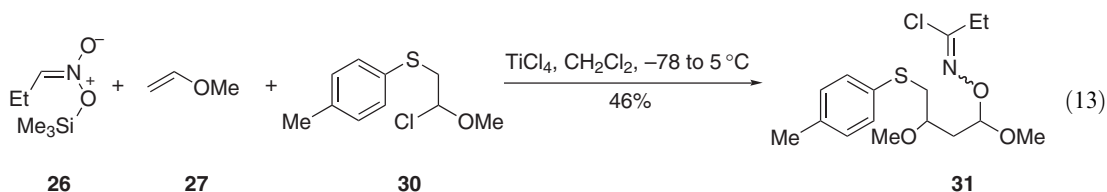
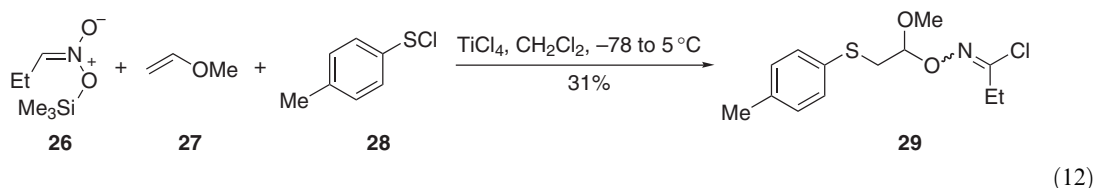


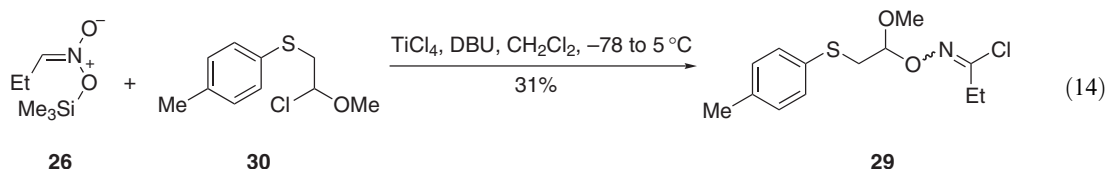
Oxyimidic chloride **25** was formed when nitrile oxide **24** was treated with methyl chloroformate in THF in the presence of DMAP <1999T12493> (Equation (11)).



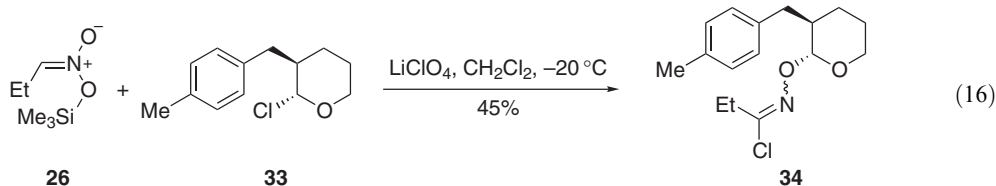
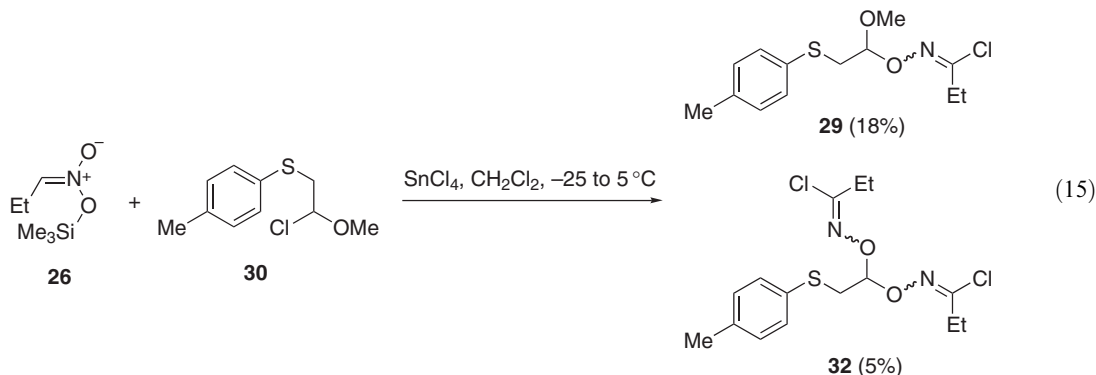
5.21.2.1.2 From aci-nitro compounds and nitro alkenes

Treatment of *aci*-nitropropane trimethylsilyl ester **26** with methyl vinyl ether **27** and sulfides **28** and **30** in the presence of a Lewis acid leads to the formation of oxyimidic chlorides **29** and **31**, respectively (Equations (12) and (13)). When ester **26** and sulfide **30** are reacted in the presence of TiCl_4 and 1,5-diazabicyclo[5.4.0]undec-5-ene, oxyimidic chloride **29** is obtained (Equation (14)) <1999IZV492>.

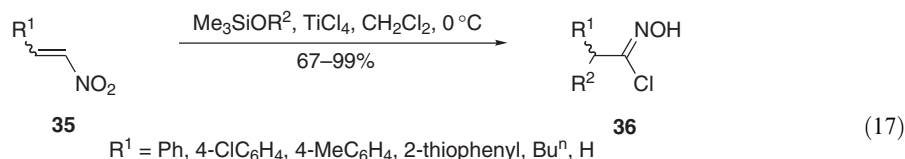




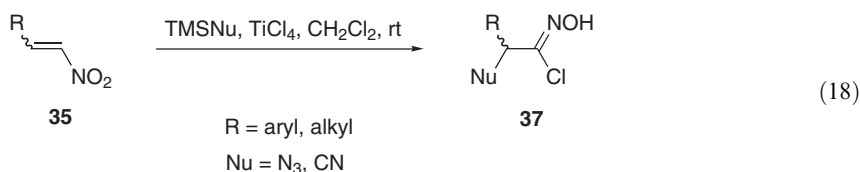
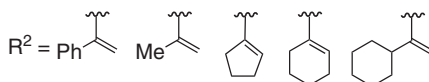
When the same *aci*-nitropropane trimethylsilyl ester **26** is reacted with sulfide **30** in the presence of tin(IV) chloride, a mixture of [2-methoxy-2-(1-chloropropylideneamino)oxyethyl] 4-tolyl sulfide **29** and {2,2-bis-[(1-chloropropylideneamino)oxy]ethyl} 4-tolyl sulfide **32** is obtained (Equation (15)). Reaction with chloropyran **33** in the presence of lithium perchlorate leads to the formation of hydroximoyl chloride **34** (Equation (16)) <1999IZV492>.



Hydroximoyl chlorides **36** have been obtained in high yields in the reaction between conjugated nitro compounds **35** and silyl enol ethers in the presence of titanium tetrachloride at 0 °C (Equation (17)) <2002TL7991>. In a variant of this reaction, the trimethylsilyl group was used to deliver the azide and cyanide nucleophiles in the preparation of β -azido and β -cyanohydroximoyl chlorides **37** (Equation (18)) <1997JOC1516>.

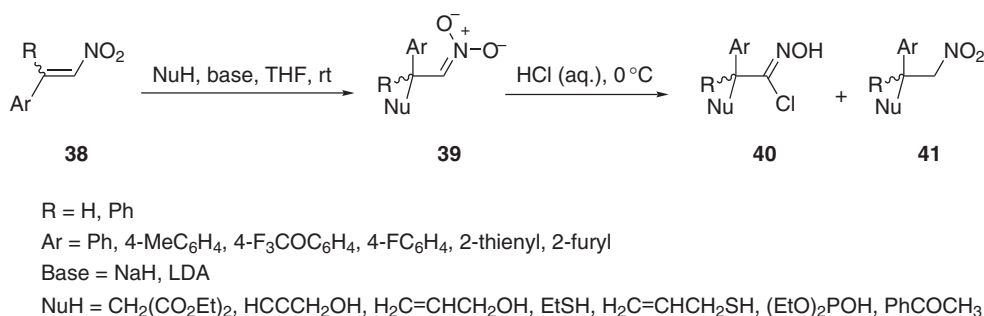


$\text{R}^1 = \text{Ph}, 4\text{-ClC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 2\text{-thiophenyl}, \text{Bu}^n, \text{H}$



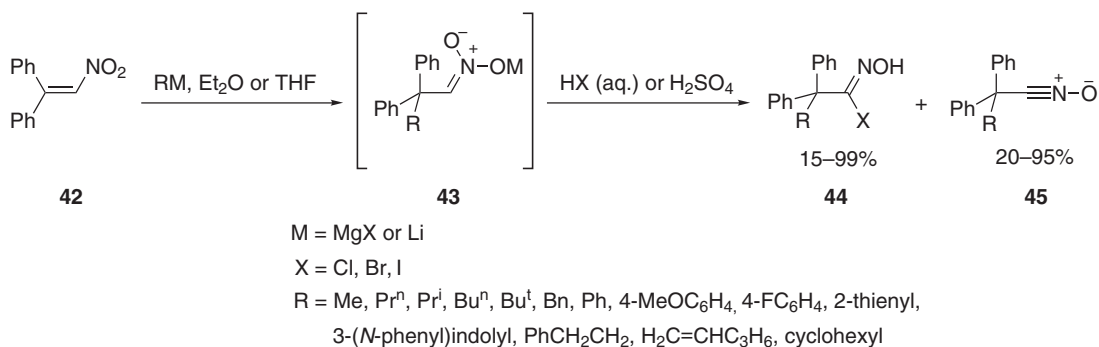
The reaction of β -nitrostyrenes **38** with carbon, oxygen, sulfur, phosphorus, and enolate nucleophiles yields nitronates **39**, which, upon treatment with aqueous hydrochloric acid, form hydroximoyl chlorides **40** in good-to-excellent yields. Saturated nitro compounds **41** are obtained

as side products in minor yields (Scheme 1) <1997TL6419, 1998T13997>. Monoarylacetoxyimoyl chlorides are also available from β -nitrostyrenes by treatment with titanium tetrachloride in the presence of triethylsilane. The reaction is carried out in dichloromethane at room temperature and yields range between 52% and 84% for various aryl groups <1997JOC1516>.



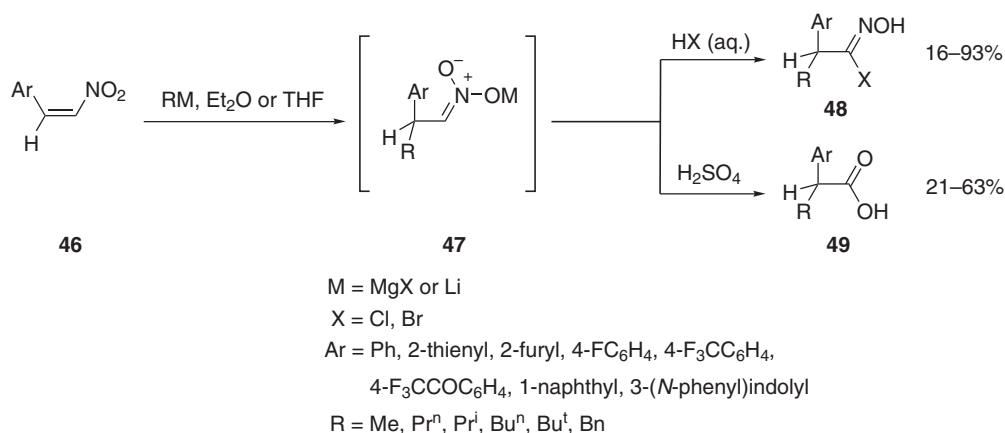
Scheme 1

Organometallic nucleophiles are versatile reagents for the synthesis of functionalized hydroximoyl halides from conjugated nitro compounds. The intermediates in this process are nitronate salts. For example, reaction of Grignard or lithium reagents with 2,2-diarylnitroethenes 42 in diethyl ether or tetrahydrofuran at low temperature (-78 or -20 °C) leads to the formation of nitronates 43 which, upon quenching with concentrated aqueous hydrohalic or 85% sulfuric acid, yield hydroximoyl halides 44 and/or nitrile oxides 45 (Scheme 2). In addition, nitronates generated from 2-monoarylnitroethenes (β -nitrostyrenes) 46 yield hydroximoyl halides upon quenching with concentrated hydrohalic acid, but quenching with 85% sulfuric acid results in hydrolysis to carboxylic acids 49 (Scheme 3). Concentrated hydrohalic acid must be employed to maximize yields of hydroximoyl halides: quenching of the nitronates with dilute hydrohalic acid results in poor yields of hydroximoyl halides, and a mixture of products, containing varying proportions of saturated nitro alkanes and/or oximes <1996TL6339, 1998T791, 1999T7115>.

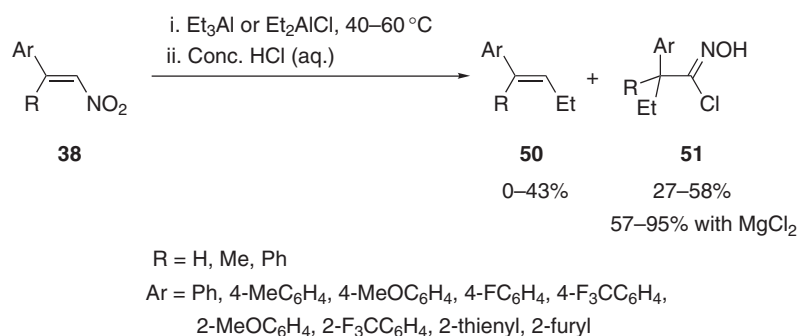


Scheme 2

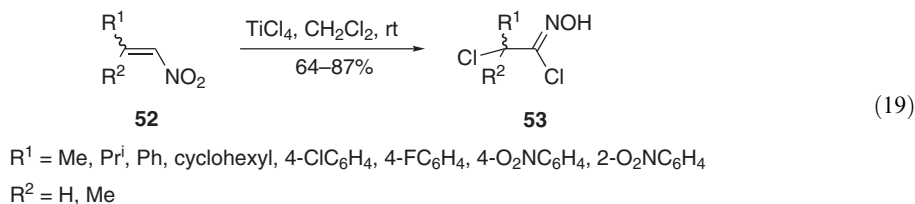
Aluminum alkyls are a further class of organometallic reagents used in the synthesis of hydroximoyl halides. Both β -unsubstituted and β -substituted nitrostyrenes 38 have been converted into the corresponding hydroximoyl chlorides 51 by treatment with triethylaluminum chloride or diethylaluminum chloride in diethyl ether to generate the corresponding nitronate, followed by hydrolysis by concentrated aqueous hydrochloric acid (Scheme 4). Triethylaluminum has in all cases been found to be more reactive than diethylaluminum chloride. Unsaturated alkenes 50 are a by-product in this reaction and are often obtained in significant yields, depending on the nature of the starting material. The presence of magnesium chloride in the reaction medium has been found to increase the yield of hydroximoyl chlorides <1999JCS(P1)47>. α -Chlorohydroximoyl chlorides 53 have been obtained from β -mono- or disubstituted nitroethenes 52 via the reaction with titanium tetrachloride in dichloromethane at room temperature. Medium-to-good yields were achieved with both aryl and alkyl substituents (Equation (19)) <1997JOC1516>.



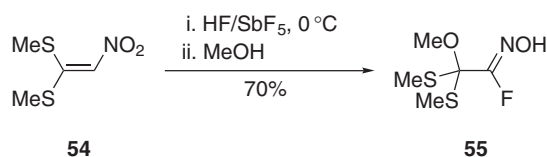
Scheme 3



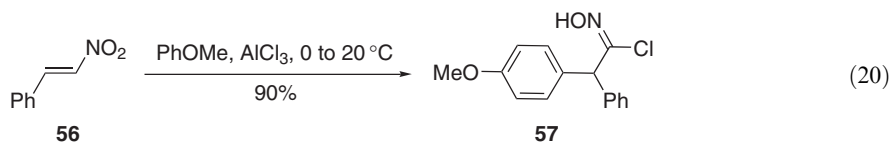
Scheme 4



1,1-Bismethylsulfanyl-2-nitroethene **54** was converted into trimethyl-(*Z*)- α -fluoro- α -hydroxyimino orthodithioacetate **55** by treatment with hydrogen hexafluoroantimonate followed by methanol at 0 °C (Scheme 5) <1995T10929>. The reaction of 2-nitrovinylbenzene **56** and anisole in the presence of aluminum trichloride afforded 1-(4-methoxyphenyl)-1-phenylacetohydroximoyl chloride **57** (Equation (20)) <1997JCR(M)2459>.

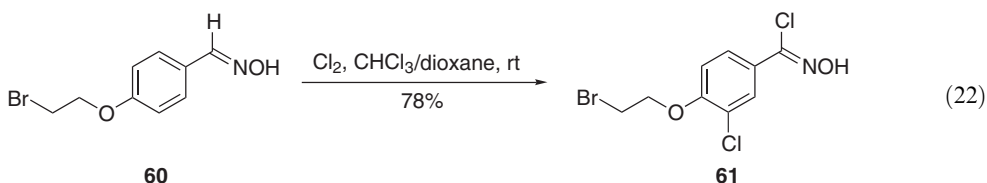
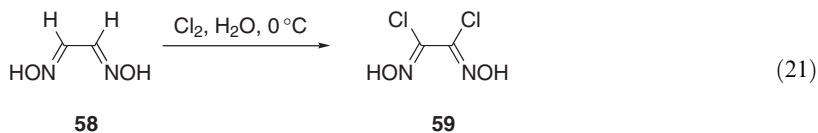


Scheme 5

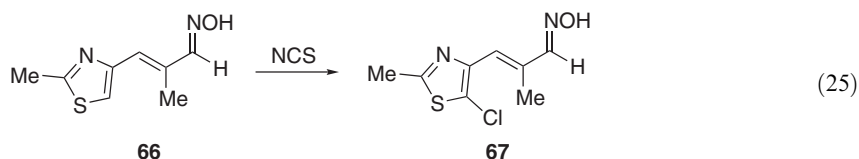
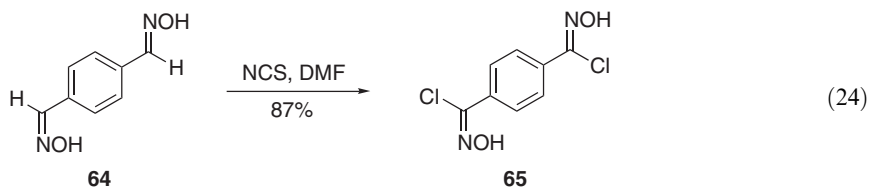
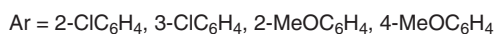
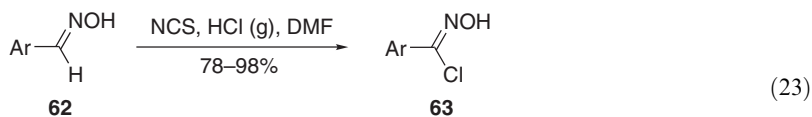


5.21.2.1.3 From aldoximes

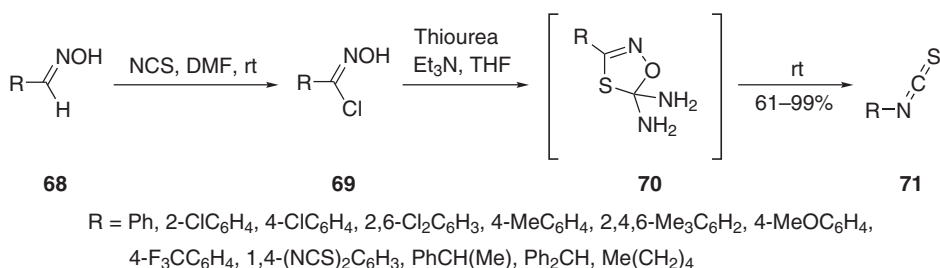
Chlorination or bromination of aldoximes with chlorine or bromine leads to the corresponding chlorides and bromides [\[1996ZOB512, 1997IZV2232, 1997JHC345, 1997JCS\(P1\)629, 2001ZOR455\]](#). Dichloroglyoxime **59** has been prepared from glyoxime **58** and chlorine in aqueous solution at 0 °C (Equation (21)) [\[1996TL4137\]](#). Care has to be exercised using this method as undesired chlorination may occur on aromatic rings of certain substrates (Equation (22)) [\[2002MI71\]](#).



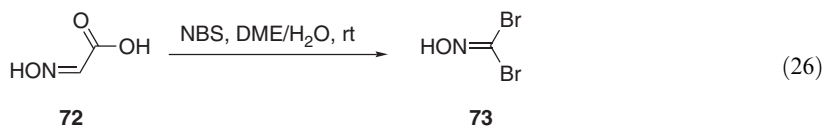
The reaction of aldoximes with *N*-chlorosuccinimide or *N*-bromosuccinimide is a frequently employed procedure for the synthesis of hydroximoyl chlorides and bromides, and is especially useful for substrates, which may undergo aromatic ring halogenation if chlorine or bromine is used. The procedure is generally carried out in DMF between 0 °C and room temperature, although other solvents, such as acetonitrile [\[2000JOC4289\]](#) or chloroform [\[2003OL391\]](#), have been reported. The yields range from good-to-excellent and a variety of aldoxime substrates have been employed (Equations (23) and (24)) [\[1999JCS\(P1\)2713, 2003JMC87\]](#). Although a milder oxidant than chlorine, *N*-chlorosuccinimide has been known to react with some reactive groups in preference to the aldoxime moiety (Equation (25)) [\[2001JOC6410\]](#).



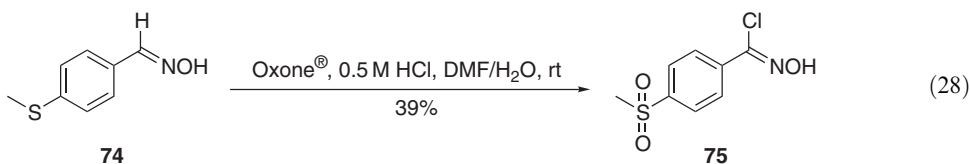
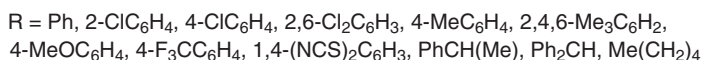
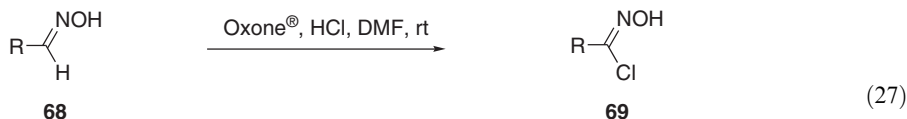
Hydroximoyl chlorides **69** obtained by *N*-chlorosuccinimide oxidation of the corresponding aldoximes **68** have been employed in the synthesis of isothiocyanates **71** in good-to-excellent yields (Scheme 6) [\[1997TL1597\]](#). Similarly, *N*-bromosuccinimide has been employed in the synthesis of dibromoformaldoxime **73** from acid **72** (Equation (26)) [\[1995MI619, 1997JHC345\]](#). Dibromoformaldoxime **73** was also formed in 45% yield in the bromination of acid **72** with bromine [\[1997JHC345, 1999JCS\(P1\)2713\]](#).



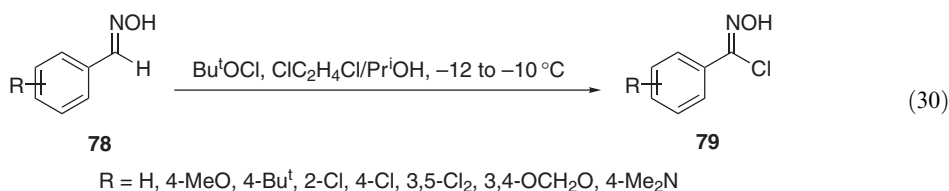
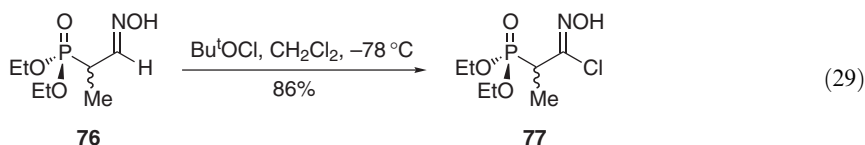
Scheme 6

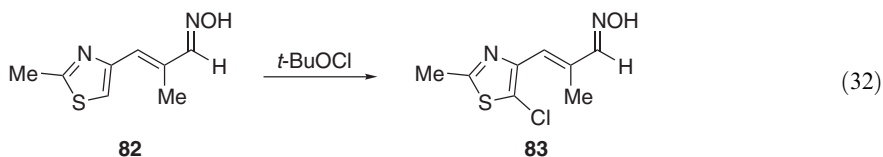
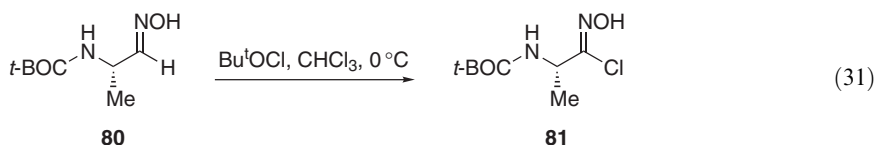


Oxone[®] (potassium monopersulfate triple salt, registered trademark of E. I. Dupont de Nemours & Co., Inc., $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) has been used in the oxidation of aldoximes **68** to hydroximoyl chlorides **69** (Equation (27)) <1997TL1597>. Care should be exercised when using this method however, as some sensitive groups may undergo oxidation as well, e.g., sulfides **74** to sulfones **75** (Equation (28)) <2003MI157>.

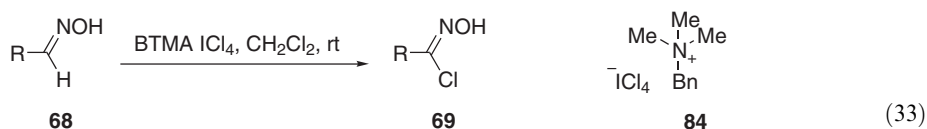


The mild oxidizing agent *t*-butyl hypochlorite has been used in the conversion of aldoximes (**76**, **78**, and **80**) to the corresponding hydroximoyl chlorides (**77**, **79**, and **81**) (Equations (29)–(31)) <1999SC3863, 2000SC1563, 2000TA3273, 2001JOC6410>. As with *N*-chlorosuccinimide, care is advised since some reactive groups may undergo chlorination in preference over the oxime moiety (Equation (32)) <2001JOC6410>.



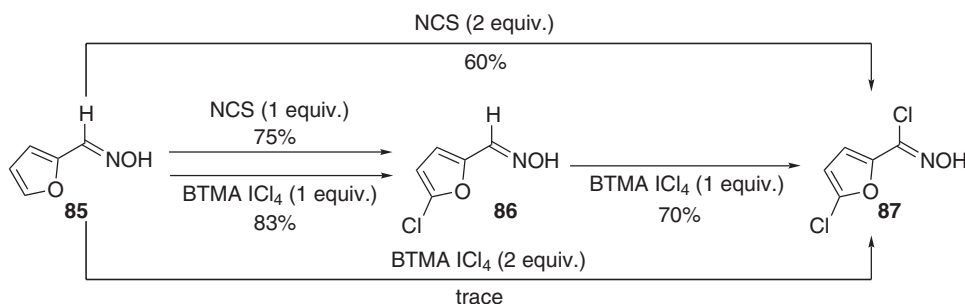


Benzyltrimethylammonium tetrachloroiodate (BTMA ICl₄) **84** deserves a separate mention here. BTMA ICl₄ is a convenient reagent for the preparation of hydroximoyl chlorides from the corresponding aldoximes by a simple procedure. When an aldoxime is treated with BTMA ICl₄ in dichloromethane, the suspension of BTMA ICl₄ shortly disappears as the reaction proceeds. Because the resulting BTMA ICl₂ is hardly soluble in diethyl ether, it can be precipitated out by the addition of this solvent. Not only stable aromatic and heteroaromatic hydroximoyl chlorides can be isolated by this method, but also rather unstable aliphatic hydroximoyl chlorides can be generated *in situ*. A variety of hydroximoyl chlorides **69** have been synthesized from the corresponding aldoximes **68** by this procedure (Equation (33)) <2000T1057>.



R = 4-MeC₆H₄, 4-MeOC₆H₄, 4-O₂NC₆H₄, 2-pyridyl,
3-pyridyl, 4-pyridyl, Bn, Prⁿ, Prⁱ, Bu^t, Bz

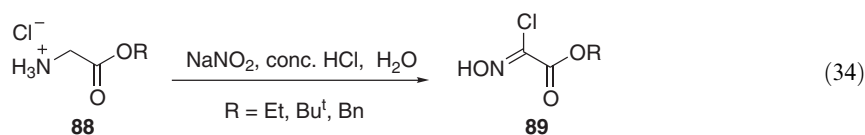
Nucleophilic heterocycles such as furan or thiophene readily undergo ring chlorination when treated with BTMA ICl₄. The reaction of 2-furancarbaldehyde oxime **85** with one molar equivalent of BTMA ICl₄ produced 5-chloro-2-furancarbaldehyde oxime **86** in 83% yield, as compared to 75% when the NCS method was employed. The reaction of **86** with a further equivalent of BTMA ICl₄ proceeded extremely sluggishly to yield the hydroximoyl chloride **87**. When aldoxime **85** was treated with two molar equivalents of BTMA ICl₄ however, only trace amounts of the corresponding hydroximoyl chloride **87** were found. In contrast, treatment of aldoxime **85** with two molar equivalents of *N*-chlorosuccinimide produced the ring-chlorinated hydroximoyl chloride **87**. Thus, the NCS method may be more suitable for the oxime chlorination of substrates similar to **85** (Scheme 7) <2000T1057>.



Scheme 7

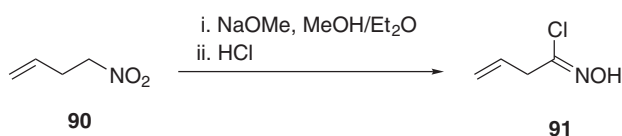
5.21.2.1.4 From α -amino acid derivatives

Hydroximoyl chlorides **89** have been obtained from the corresponding α -amino acid esters **88** by nitrosative deamination <1996MI1845, 1999JCS(P1)2713, 2001T8039> (Equation (34)).

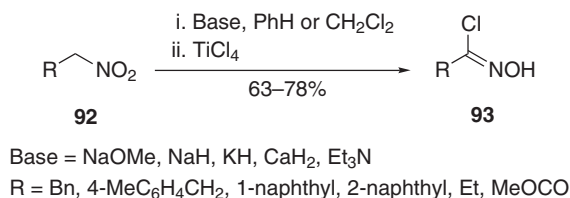


5.21.2.1.5 From nitro compounds

4-Nitrobutene **90** has been converted into hydroximoyl chloride **91** by reaction with sodium methoxide, followed by hydrogen chloride <1996MI109> (Scheme 8). The initial deprotonation α to the nitro group has also been effected using bases such as sodium, potassium or calcium hydride, or triethylamine. The chlorination of the resulting nitronate may be accomplished by reaction with titanium tetrachloride. In this manner, a variety of aliphatic and aromatic nitro compounds **92** have been converted into the corresponding hydroximoyl chlorides **93** in good yields <1996TL6407, 1997JOC1516> (Scheme 9).



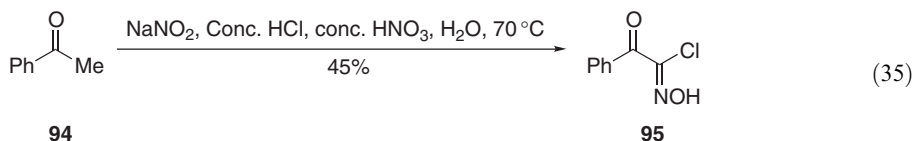
Scheme 8



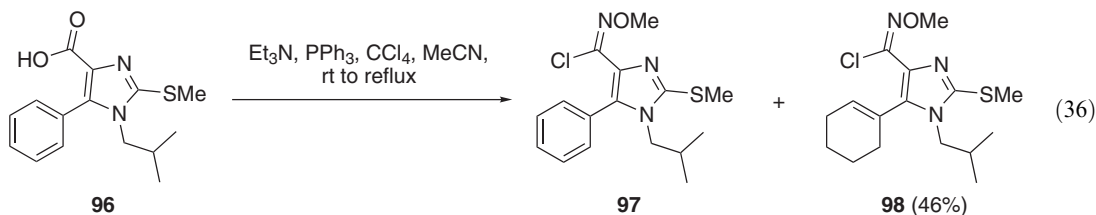
Scheme 9

5.21.2.1.6 From carbonyl compounds

Ketones have been used as substrates in the preparation of hydroximoyl chlorides. Thus, acetophenone **94** has been converted into (*Z*)-*N*-hydroxy-2-oxophenylacetimidoyl chloride **95** by oxidation with nitrous/nitric acid <1999HCA1289> (Equation (35)).

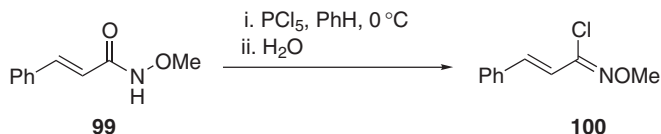


Carboxylic acid **96** was converted into the corresponding *N*-methoximoyl chloride **97** in the reaction with triphenylphosphine, triethylamine, and carbon tetrachloride under reflux conditions. Partial reduction of the benzene ring occurred during this process, and cyclohexene derivative **98** was isolated in a significant yield <1996CPB709> (Equation (36)).

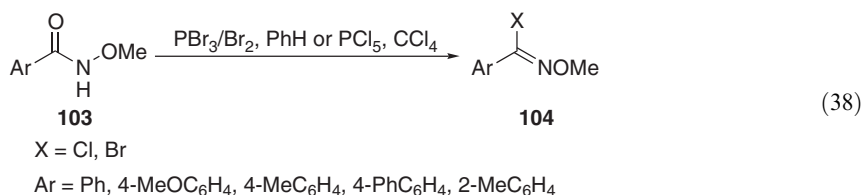
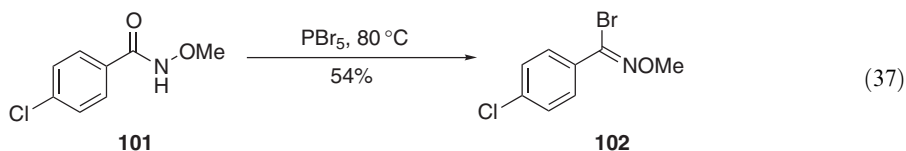


5.21.2.1.7 From N-alkoxyamides

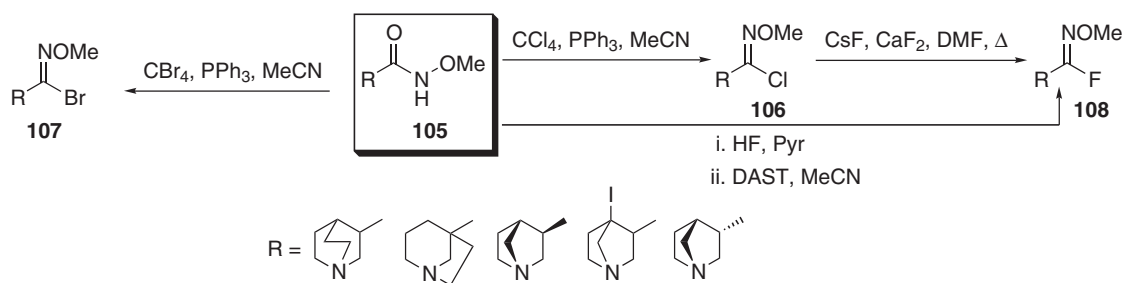
N-Methoxyamides (**99**, **101**, and **103**) are converted into the corresponding methoximoyl chlorides **100** or bromides (**102** and **104**) by reaction with phosphorus trichloride, phosphorus pentachloride, bromine, or phosphorus pentabromide <1996JOC45, 1999AJC807, 2000JOC6922> (Scheme 10, Equations (37) and (38)).



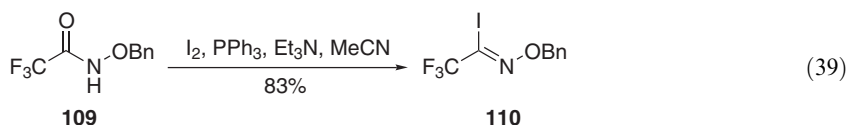
Scheme 10



N-Alkoxy-substituted imidoacyl halides have also been prepared by the reaction of the amide precursors with triphenylphosphine and carbon tetrachloride, carbon tetrabromide, or iodine. Thus, chlorides and bromides (**106** and **107**) have been obtained from N-methoxy amide **105** by reaction with carbon tetrachloride and -bromide, respectively <1997JMC4265>. Fluoride **108** was obtained from N-methoxy amide **105** by initial treatment with hydrogen fluoride in pyridine, followed by diethylaminosulfur trifluoride (DAST) in acetonitrile, or from the intermediate chloride **106** by reaction with caesium fluoride/calcium fluoride in N,N-dimethyl formamide at elevated temperature <1996T233> (Scheme 11). N-Benzyloximoyl iodide **110** was prepared from starting amide **109** by reaction with iodine, triphenylphosphine, and triethylamine <1996T233> (Equation (39)).

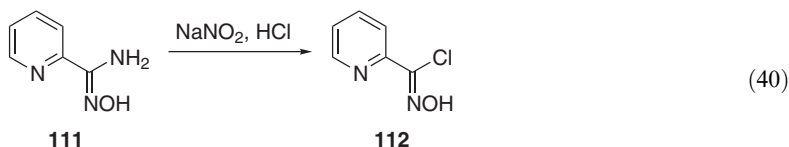


Scheme 11



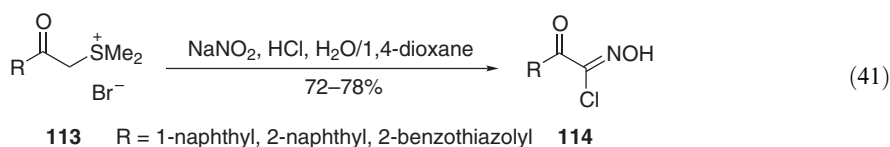
5.21.2.1.8 From oxyimidic amides

Some oxyimidic amides can serve as precursors to imidic halides. For example, 2-pyridylhydroximoyl chloride **112** has been obtained from oxyimidic amide **111** by nitrosative deamination <1995TL327> (Equation (40)).



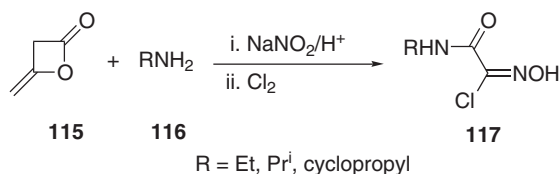
5.21.2.1.9 From sulfonium salts

Dimethylsulfonium salts are good substrates for the synthesis of hydroximoyl halides. Bromide salts **113** are converted into hydroximoyl chlorides **114** in good yields by treatment with sodium nitrite and aqueous hydrochloric acid <1995MI83, 1997T17461> (Equation (41)).



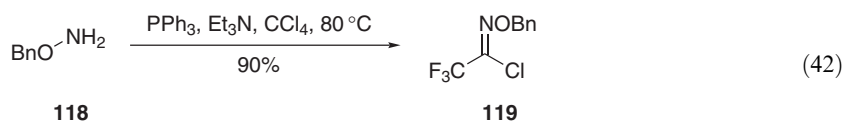
5.21.2.1.10 Other methods

Various other methods have been applied in the synthesis of hydroximoyl halide derivatives. Diazotization of amines **116** followed by treatment with diketene **115** and chlorine afforded hydroximoyl chlorides **117** <1995MI21> (Scheme 12).

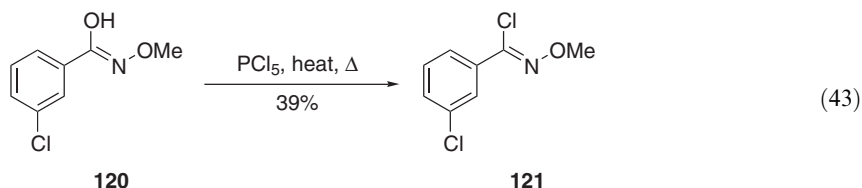


Scheme 12

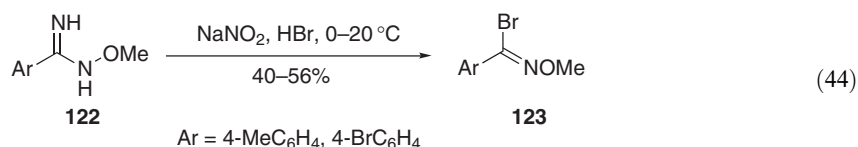
When benzyloxyamine **118** is reacted with trifluoroacetic acid and carbon tetrachloride in the presence of triphenylphosphine, *O*-benzylhydroximoyl chloride **119** is obtained in high yield <2002TL7189> (Equation (42)).



(*Z*)-*O*-Methyl-3-chlorobenzohydroximoyl chloride **121** was obtained in modest yield by the treatment of methyl 3-chlorobenzohydroxamate **120** with phosphorus pentachloride <1995JPO344> (Equation (43)).



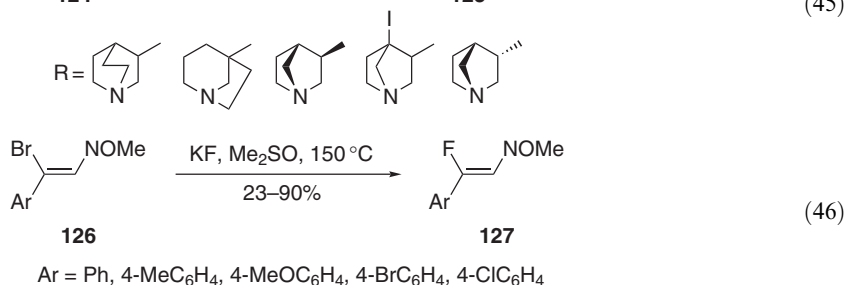
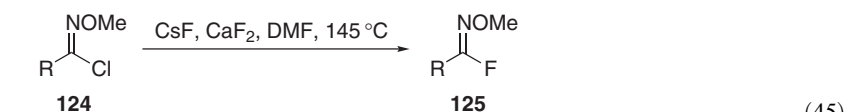
N-Methoxyamidines **122** are converted into *N*-methoxyhydroximoyl bromides **123** in moderate yields by treatment with sodium nitrite in aqueous hydrobromic acid at reduced temperature <1999AJC807> (Equation (44)).



Oxyimidic halides have also been prepared from activated alkenes, hydroxy compounds, and oxaziridines. The reader is referred to COFGT (1995) for more information on these transformations.

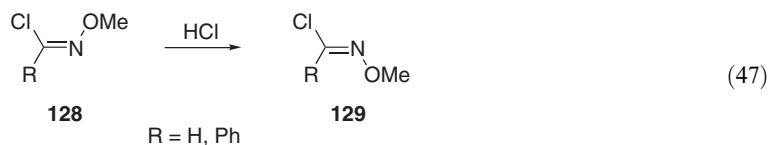
5.21.2.1.11 Transhalogenation

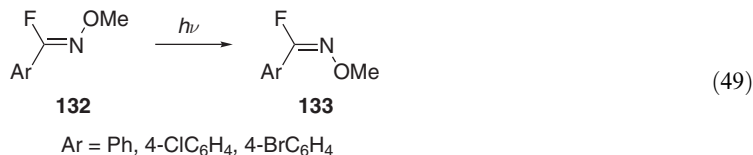
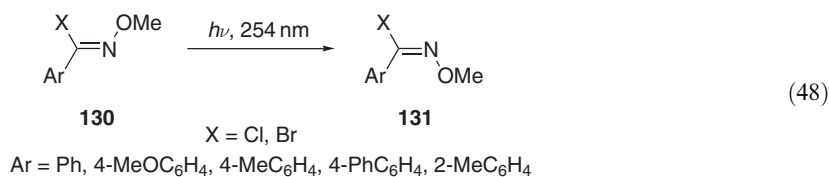
Hydroximoyl fluoride derivatives can be obtained from the corresponding chlorides or bromides under forcing conditions <1997JMC4265, 1999AJC807> (Equations (45) and (46)). Yields range from poor to excellent.



5.21.2.1.12 Isomerization

Hydroximoyl halide derivatives are usually obtained in the (*Z*)-isomer form. Isomerization to the corresponding (*E*)-structure can be achieved by the action of acid <2001JOC7979> (Equation (47)) or UV irradiation <1996JOC45, 1999AJC807> (Equations (48) and (49)). A nucleophilic counter-ion has been found to be necessary in the acid-mediated isomerization of (*Z*)-chloride **128** into its (*E*)-counterpart **129**: the process proceeded when hydrochloric acid was used, but not when tetrafluoroboric or trifluoromethanesulfonic acids were employed <2001JOC7979>.



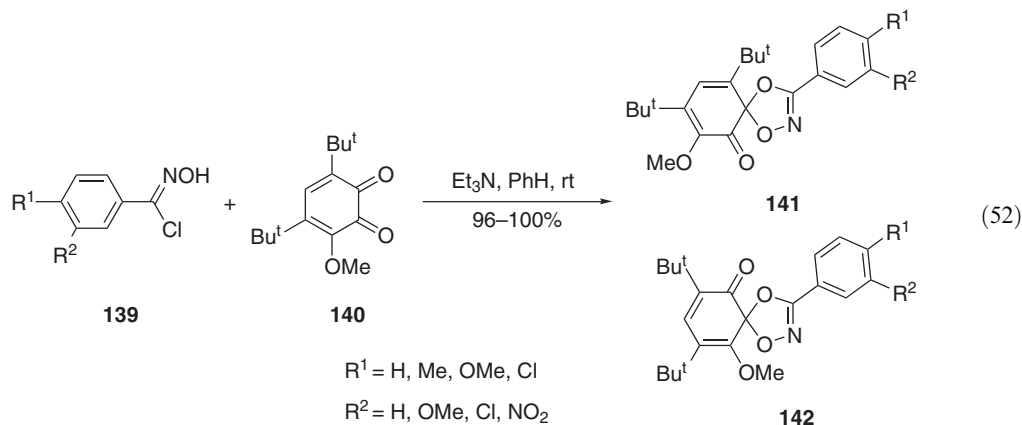
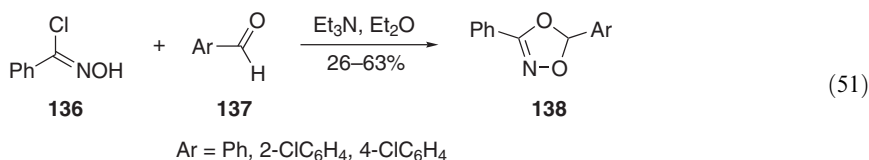
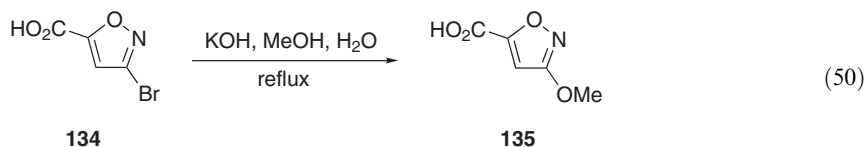


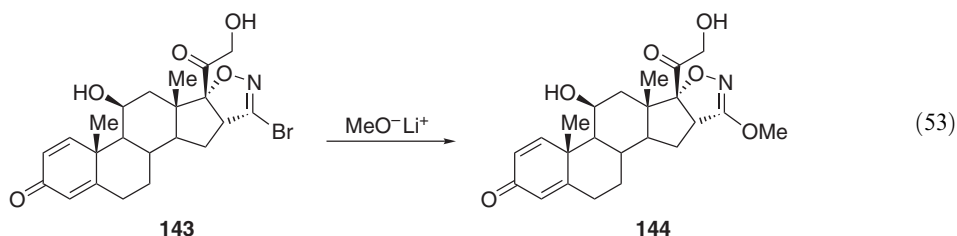
5.21.2.2 Oxyimide Esters and Related Structures

Numerous cyclic structures such as oxazoles and dioxazoles formally contain the oxyimide ester structural unit. For completeness, they will be treated alongside linear oxyimide derivatives.

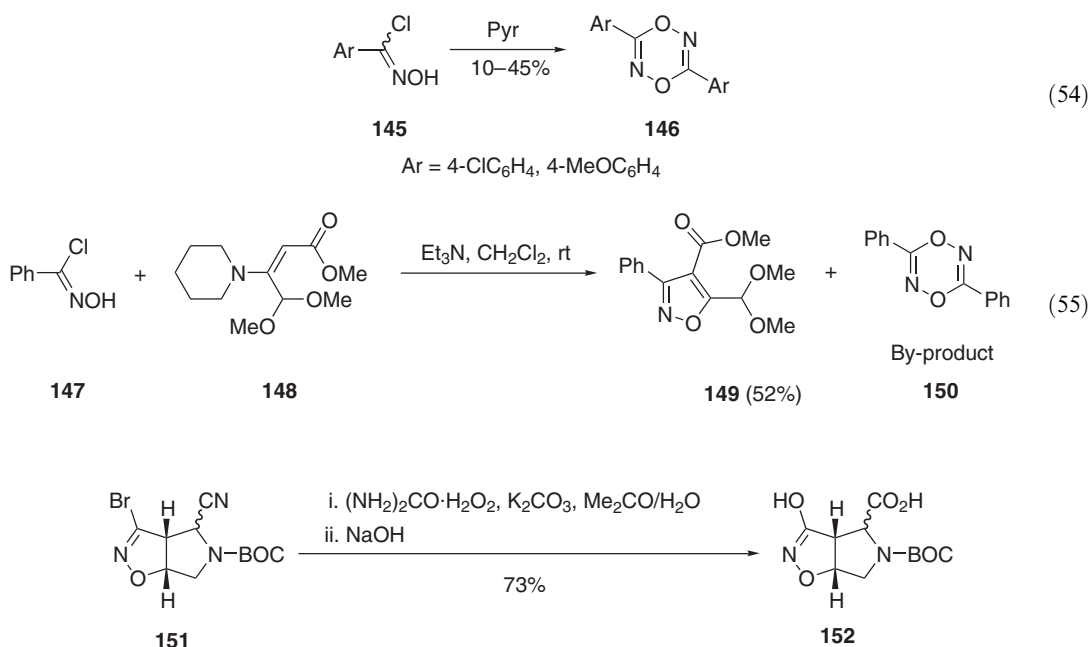
5.21.2.2.1 From oxyimide halides

Halogenated isoxazoles **134** react with alkanols under basic conditions to give the corresponding oxyimide esters **135** <1996JMC2232, 1996S1177> (Equation (50)). The reaction of aldehydes **137** and benzoquinones **140** with *N*-hydroxyimide halides (**136** and **139**) provides [1,4,2]-dioxazoles in moderate-to-excellent yields (Equations (51) and (52)), although in the case of **140**, both isomers (**141** and **142**) are obtained in approximately equal ratios (Equation (52)) <1996JCS(P1)747, 1999T14199>. Oxyimide esters **144** have also been obtained by substitution of the halide atom in *O*-alkyloxymide halides **143** using alkanoate salts (Equation (53)) <1997T14317>.





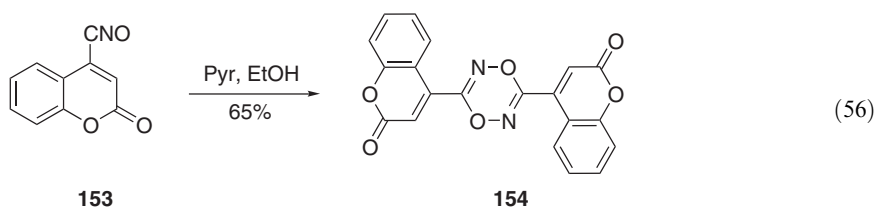
The dimerization of *N*-hydroxyimidic chlorides **145** in the presence of pyridine leads to the formation of [1,4,2,5]-dioxadiazines **146** in poor-to-modest yields (Equation (54)) <2001MI510>. The reaction of *N*-hydroxyimidic chloride **147** with *N*-substituted piperidine **148** in the presence of triethylamine yields the dimeric 3,6-diphenyl-[1,4,2,5]-dioxadiazine **150** as a by-product only, the main product being isoxazole **149** (Equation (55)) <1995H285>. Pyrrolidine-fused 4,5-dihydroisoxazol-3-ol **152** was obtained in good yield in the reaction of substrate **151** with urea–hydrogen peroxide adduct followed by treatment with sodium hydroxide. It should be noted that the nitrile group on **151** was hydrolyzed to the carboxylic acid **152** in this process (Scheme 13) <1999T5623>.



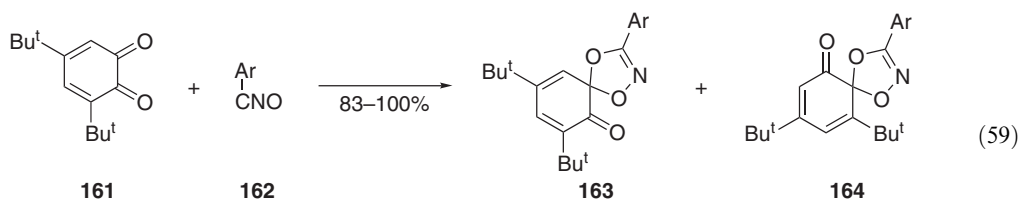
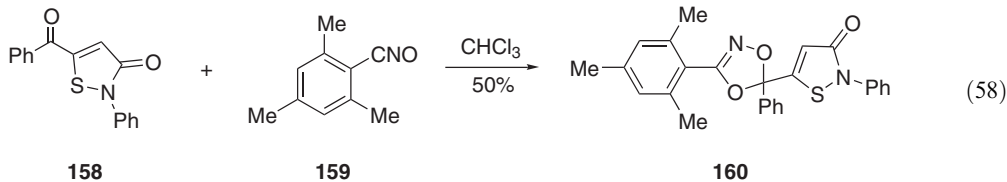
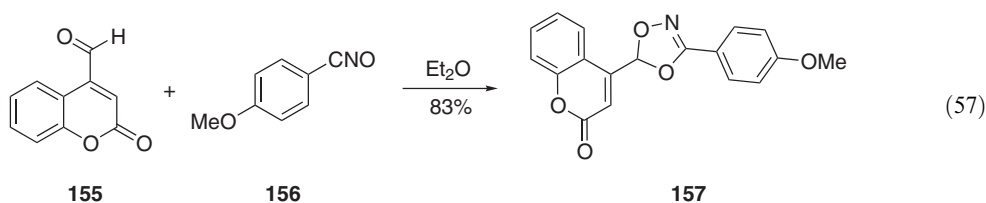
Scheme 13

5.21.2.2.2 From nitrile oxides

Nitrile oxides **153** dimerize to [1,4,2,5]-dioxadiazines **154** in the presence of a base (Equation (56)) <1997OPP594>.

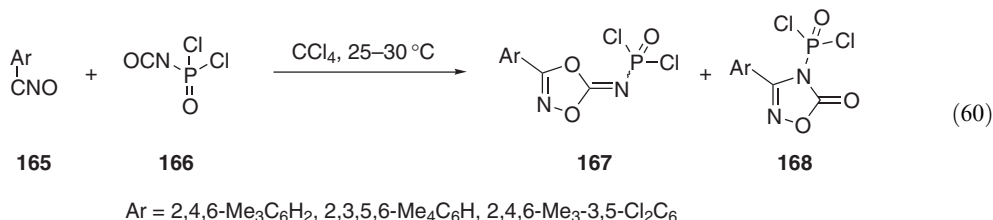


The reaction of aldehydes **155**, ketones **158**, or benzoquinones **161** with nitrile oxides (**156**, **159**, and **162**) leads, via a 1,3-dipolar cycloaddition, to the formation of dioxazoles (**157**, **160**, **163**, and **164**) (Equations (57)–(59)) <1996JHC731, 1996TL5623, 1997OPP594, 1999T14199>.



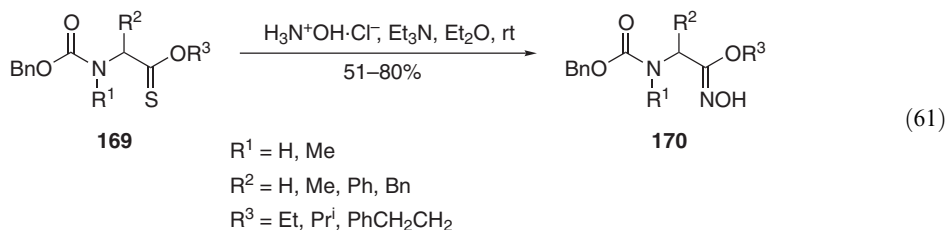
Ar = Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 3,4-(MeO)₂C₆H₃, 3-ClC₆H₄, 4-ClC₆H₄

Both [1,4,2]-dioxazole **167** and [1,2,4]-oxadiazolone **168** were obtained by the treatment of nitrile oxides **165** with isocyanide **166** in carbon tetrachloride (Equation (60)) <1998ZOR120>.



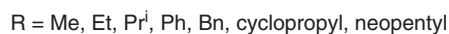
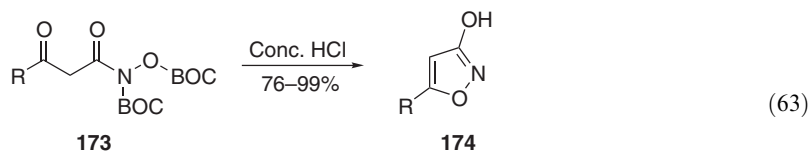
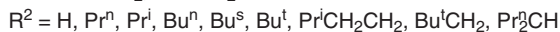
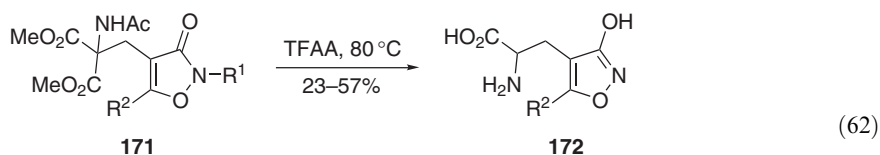
5.21.2.2.3 From thiocarboxylic O-esters

Thiocarboxylic acid O-esters **169** react with hydroxylamine to yield oxyimide esters **170** in moderate-to-good yields (Equation (61)) <2001ZN(B)547, 1996HCA319>.

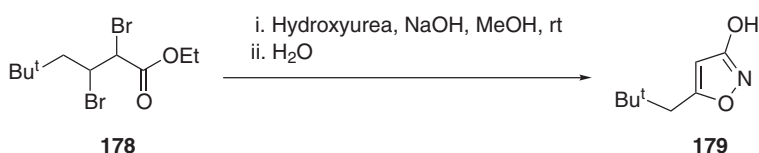
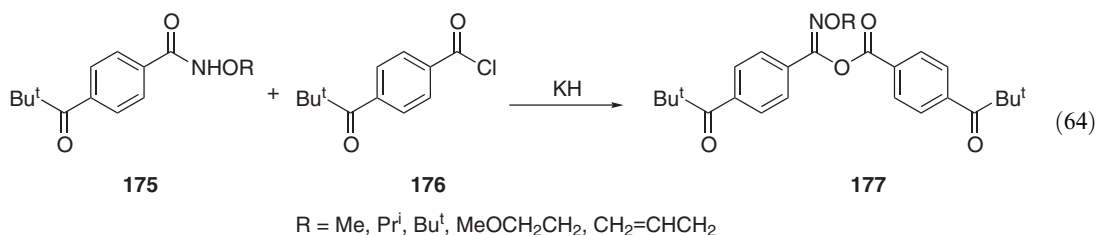


5.21.2.2.4 From carboxylic acid alkoxy amides and acyloxy amides

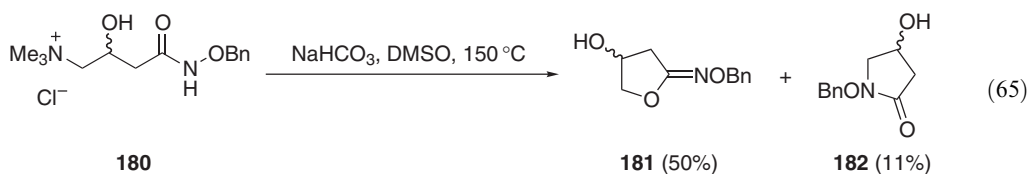
Treatment of isoxazol-3-ones **171** with trifluoroacetic anhydride at elevated temperatures yields isoxazol-3-ol α-amino acids **172** in modest-to-good yields (Equation (62)) <1997MI329>. 5-Substituted isoxazols **174** are also accessible from acyloxyamide derivative **173** in good-to-excellent yields by treatment with concentrated hydrochloric acid (Equation (63)). This procedure is superior to using β-keto esters and hydroxylamines as no 5-isoxazolone by-products are formed <2000JOC1003>.



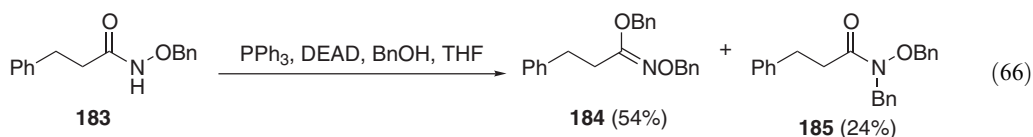
Treatment of alkoxy amide **175** with potassium hydride and 4-pivaloylbenzoyl chloride **176** yields oxyimidic derivative **177** (Equation (64)) <1999JMC153>. Isoxazol-3-ol **179** was obtained from α,β -dibromo ester **178** via reaction with sodium hydroxide and hydroxyurea followed by aqueous hydrolysis (Scheme 14) <1997MI329>. The synthesis of furan-derivative **181** from *N*-benzyloxy amide **180** required more forcing conditions (Equation (65)) <1997SL71>. A small amount of pyrrolidinone **182** was obtained as a by-product.

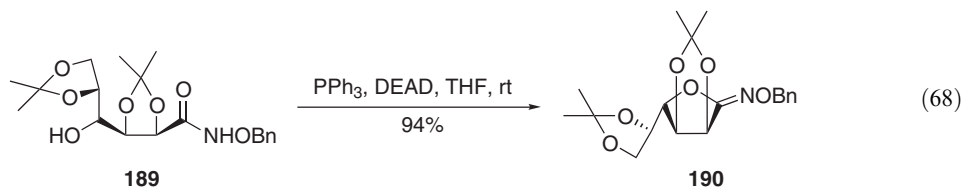
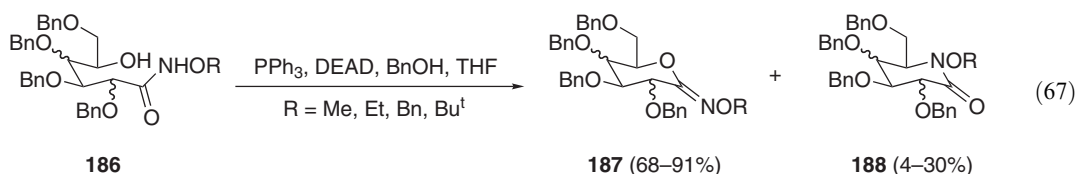


Scheme 14

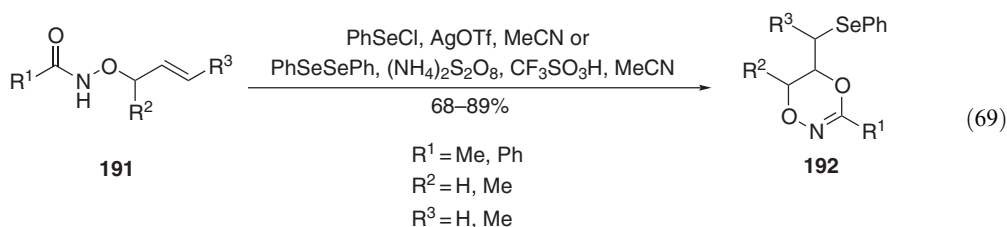


Alkoxy amides (**183**, **186**, and **189**) have been transformed into the corresponding oxyimidic esters (**184**, **187**, and **190**) under Mitsunobu conditions in varying yields (Equations (66)–(68)) <2000JA2995, 2002OL2401>. Minor amounts of *N*-alkyl-*N*-alkoxyamides (**185** and **188**), may be obtained as by-products (Equations (66) and (67)).

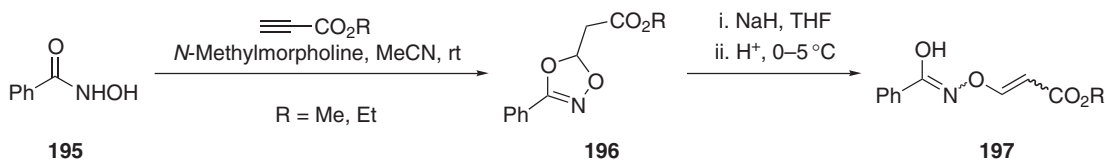
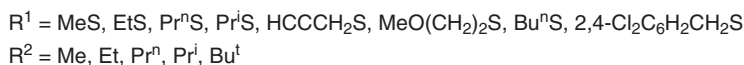
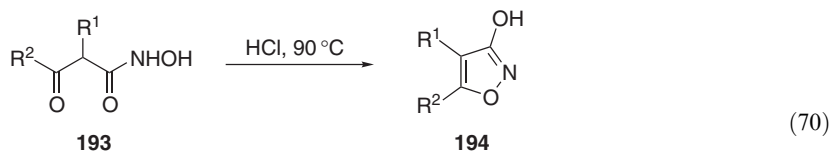




Various selenium derivatives of 5,6-dihydro-[1,4,2]-dioxazines **192** have been obtained from *N*-alkoxyamides **191** in high yields by reaction with silver triflate and phenylselenenyl chloride or ammonium persulfate, trifluoromethylsulfonic acid, and diphenyl diselenide (Equation (69)) <1995CC237>.



Besides *N*-alkoxyamides, *N*-hydroxyamides (**193** and **195**) have found use in the synthesis of isoxazol-3-ols **194** (Equation (70)) <2000CPB509> and [1,4,2]-dioxazoles **196**. Further treatment of dioxazoles **196** with sodium hydride followed by acid leads to hydroxamic acid derivatives **197** (Scheme 15) <2000T7433>.

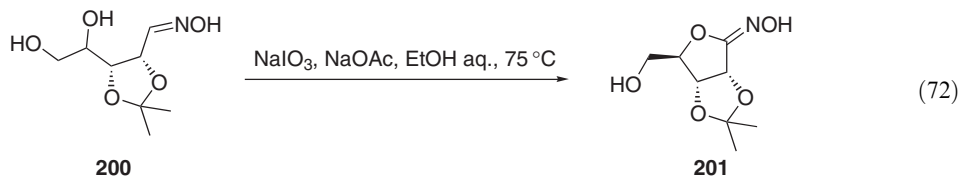
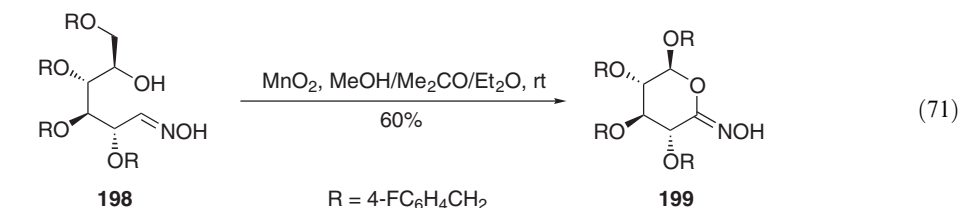


Scheme 15

Further examples of the use of *N*-hydroxyamides in the synthesis of oxymidic ester related linear and cyclic structures are found in <2002H143> (from thioketones, isonitriles, and isothionitriles) <1996ZOB1847> (oxidation/cyclization using bromine or selenium dioxide) <2001JOC2246> (reaction with diazomethane), <2002JOC4833> (cyclization with diethoxypropane), and <2000TL155> (via epoxidation using *m*-chloroperoxybenzoic acid). Examples of *N*-silyloxyimidic silyl ester formation from *N*-hydroxyamides are described in <1996JCS(P1)883, 1999MRC427, 2000MRC795>.

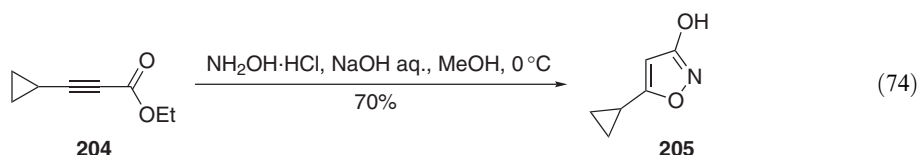
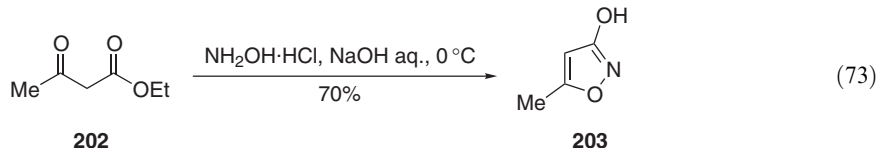
5.21.2.2.5 From oximes and related structures

The oxidation of δ - or γ -hydroxy oximes (**198** and **200**) using manganese dioxide (Equation (71)) or sodium iodate (Equation (72)) leads to cyclic N-hydroxyimidic esters (**199** and **201**) <1998JOC885, 1998HCA1359, 2000S1719>.



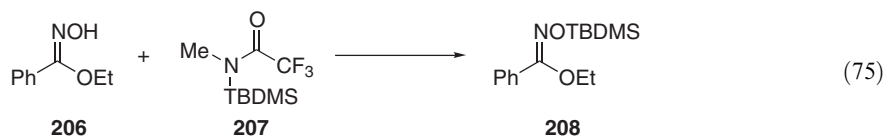
5.21.2.2.6 From carboxylic esters

A common route to isoxazoles is from hydroxylamine and β -keto esters or similarly activated esters. 5-Methylisoxazol-3-ol **203** was obtained from 3-oxobutyric acid ethyl ester **202** by reaction with hydroxylamine (Equation (73)) <2002MI1651>. In a similar fashion, 5-cyclopropylisoxazol-3-ol **205** was prepared from cyclopropylpropynoic acid ethyl ester **204** (Equation (74)) <1995JCS(P1)221>. Further literature examples of similar transformations exist <1995JMC617, 1996JMC3188, 1998BMC119, 2000TA4955>.



5.21.2.2.7 From hydroxyimidic esters

Hydroxyimidic esters **206** can be silylated with 2,2,2-trifluoroacetamide derivative **207** to yield **208** (Equation (75)) <1999MRC427>.

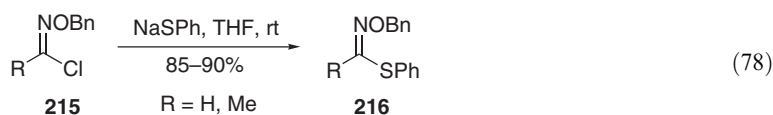
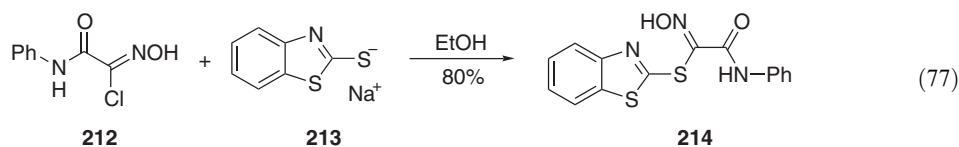
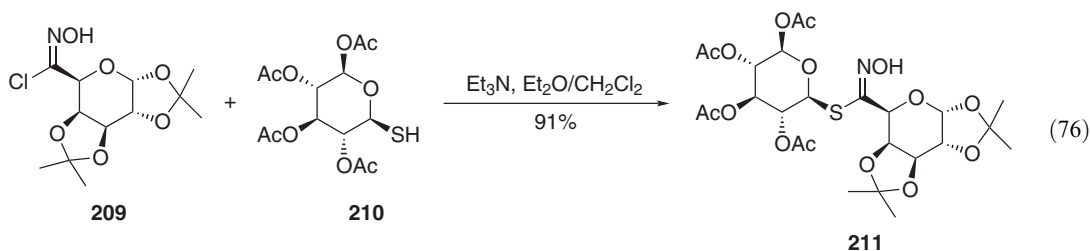


5.21.2.3 Oxyimidic Sulfur Derivatives

Numerous cyclic structures such as thioxazoles derivatives formally contain the oxyimidic sulfur derivative structural unit. Due to their importance in contemporary chemistry, they will be discussed alongside their linear counterparts.

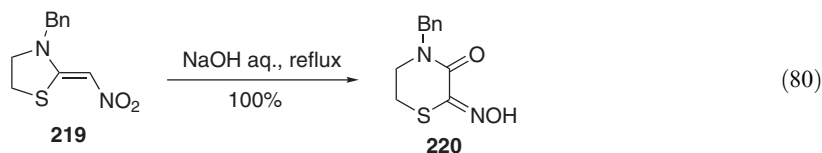
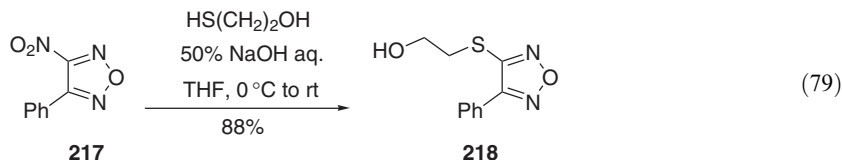
5.21.2.3.1 From oxymidic halides

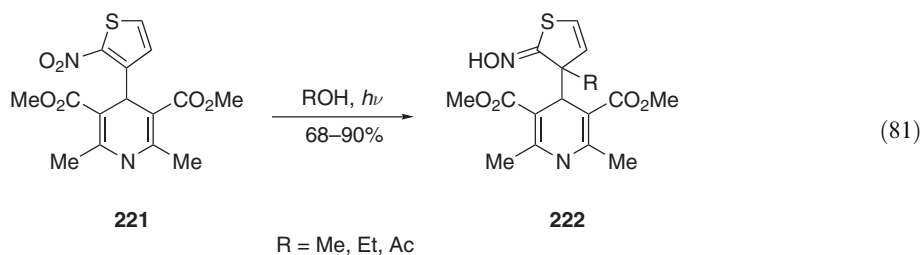
A common approach to oxymidic thioesters is by substitution of the halide in oxymidic halides by sulfur nucleophiles. The reactions are straightforward and generally proceed in good yields. Pyran **209** has been coupled with thioacetal **210** in the presence of triethylamine to give hydroxyimidic thioester **211** (Equation (76)) <1995CAR321, 1995CAR257, 1996MI109>. Anionic nucleophiles have been used with equal success in the synthesis of oxymidic thioesters (**214** and **216**) from the corresponding halides (**212** and **215**) (Equations (77) and (78)) <1996JA5138, 2002IZV1387>. A number of other literature examples exist: <1995MI83, 1996JHC327, 1996JHC1927, 1997CAR127, 1997JOC4672, 1999JOC1099, 2000JCR(S)84, 2001SL937>.



5.21.2.3.2 From nitro compounds

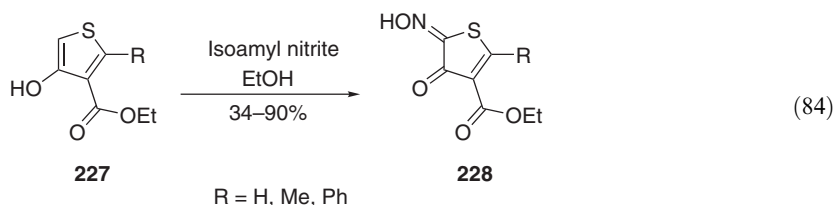
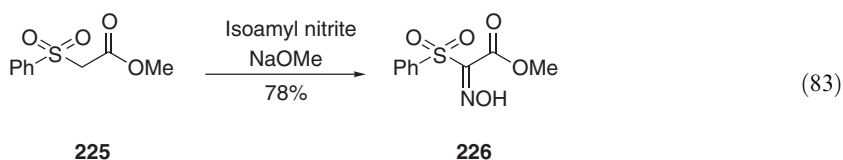
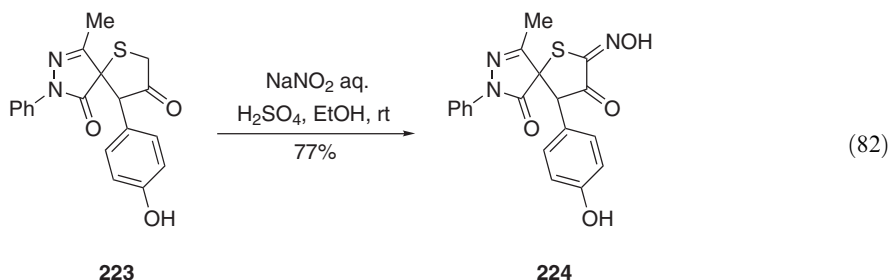
Furazan thiol derivative **218** has been obtained from nitrofurazan **217** by treatment with 2-mercaptoethanol and aqueous alkali in tetrahydrofuran (Equation (79)) <2001JCS(P1)1751>. Treatment of 3-benzyl-2-nitromethylenethiazolidine **219** with aqueous alkali under reflux conditions afforded the ring-expanded 4-benzylthiomorpholine-2,3-dione-2-oxime **220** in quantitative yield (Equation (80)) <1998JCS(P1)2833>. Irradiation by light has been found to transform certain nitrothiophene-derived compounds into their hydroxyiminothienyl derivatives. When 2,6-dimethyl-4-(2-nitrothien-3-yl)-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester **221** was irradiated in different solvents, the corresponding hydroxyimino dihydrothienyl derivatives **222** were obtained in good-to-excellent yields (Equation (81)) <1996PHA392>. When acetone was used as the solvent, a product identical to that obtained from acetic acid ($\text{R} = \text{Ac}$) was formed, albeit in a low (27%) yield.





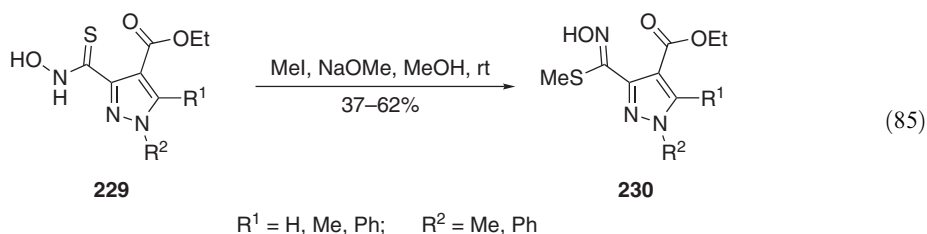
5.21.2.3.3 From carbonyl compounds

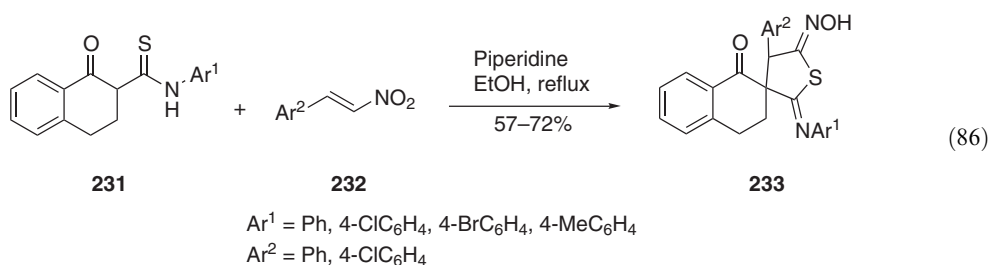
β -Keto sulfides **223** and β -keto sulfones **225** are oxidized to the corresponding oximes (**224** and **226**) in high yields by treatment with sodium nitrite or isoamyl nitrite (Equations (82) and (83)) <2003MI681, 1997SL475>. Isoamyl nitrite has also been employed in the synthesis of 2-substituted 5-hydroxyimino-4-oxo-4,5-dihydrothiophene-3-carboxylic acid ethyl esters **228** from the corresponding 4-hydroxythiophene-3-carboxylic acid ethyl esters **227** (Equation (84)) <1997JHC413>.



5.21.2.3.4 From oxyimidic thioacids and esters

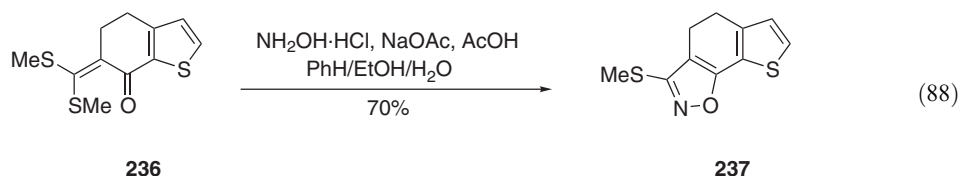
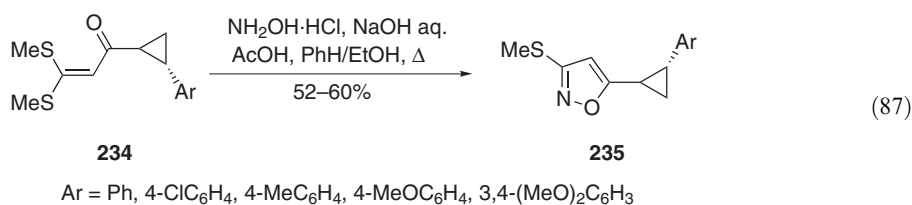
Oxyimidic thiones **229** are converted into oxyimidic thioesters **230** by reaction with alkylating agents (e.g., methyl iodide) in the presence of a base (sodium methoxide) (Equation (85)) <1997JHC413>. Spirocyclization of thioester **231** with nitrostyrene **232** in the presence of piperidine affords structures **233** in moderate-to-good yields (Equation (86)) <2001JOC7205>.





5.21.2.3.5 From γ -keto-bis-(alkylthio)alkenes

The reaction of γ -keto-bis-alkylthioalkenes such as **234** or **236** with hydroxylamine leads to cyclization and formation of isoxazoles **235** or **237** (Equations (87) and (88)) <1997JCS(P1)3673, 1999JCR(S)398>.

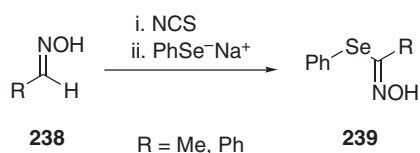


5.21.2.3.6 Other methods

Oxyimide sulfur derivatives have been obtained from nitrile oxides, from alkylthioimides and by oxidation/reduction of oxyimide thioacid derivatives. The reader is referred to COFGT (1995) for more information on these transformations.

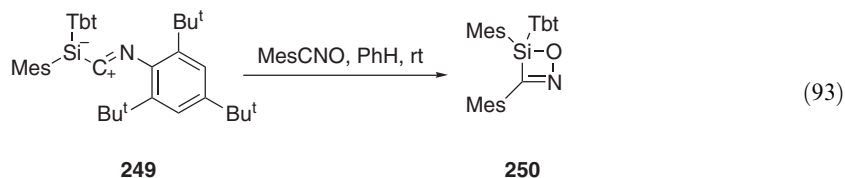
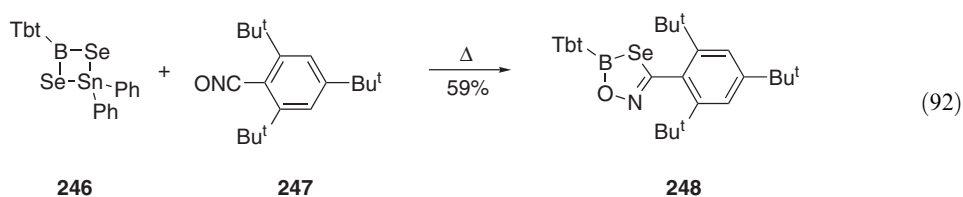
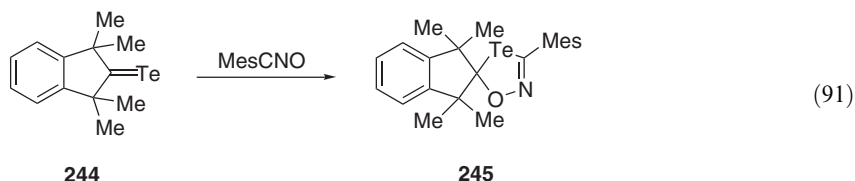
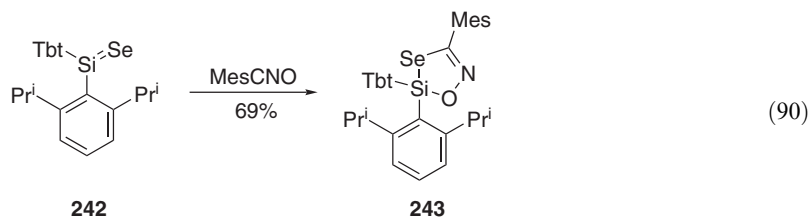
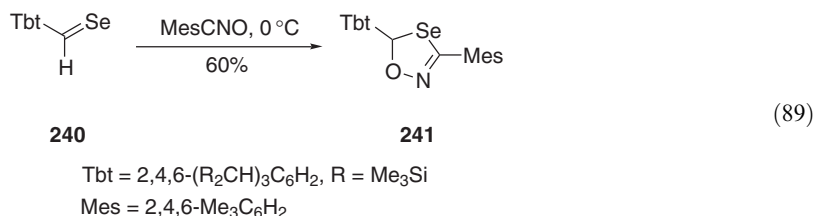
5.21.2.4 Oxyimide Selenium, Silicon, and Tellurium Derivatives

The reaction of oxyimide chlorides (produced *in situ* from the corresponding oximes **238** and *N*-chlorosuccinimide) with sodium benzeneselenoate yields the corresponding selenoesters **239** (Scheme 16) <1997SL950>. The cycloaddition of selenoaldehydes to mesitronitrile oxide leads to selenium heterocycles. Both [1,4,2]-oxaselenazole **241** and [1,3,5,2]-oxaselenazasilole **243** have been obtained from the corresponding selenoaldehydes (**240** and **242**) by reaction with mesitronitrile oxide (Equations (89) and (90)) <1996AG714, 1997T12167, 1998MI633, 2002CL34>. Similarly, condensation of 1,1,3,3-tetramethylindan-2-tellone **244** with mesitronitrile oxide yielded



Scheme 16

[1,4,2]-oxatellurazole **245** (Equation (91)) <1998MI549>. The reaction of [1,3,2,4]-diselenastannaboretane **246** with nitrile oxide **247** affords [1,3,5,2]-oxaselenazaborole **248** in good yield (Equation (92)) <2001MI41>, while oxazasilete **250** has been obtained from compound **249** by reaction with mesitonitrile oxide (Equation (93)) <2000CL244>.

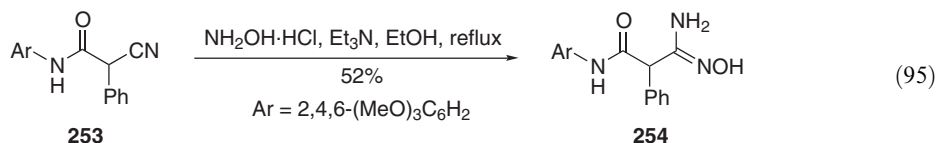
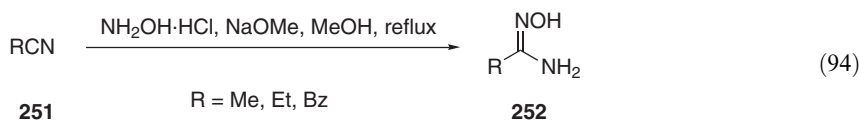


5.21.2.5 Oxyimidic Amides and Related Structures

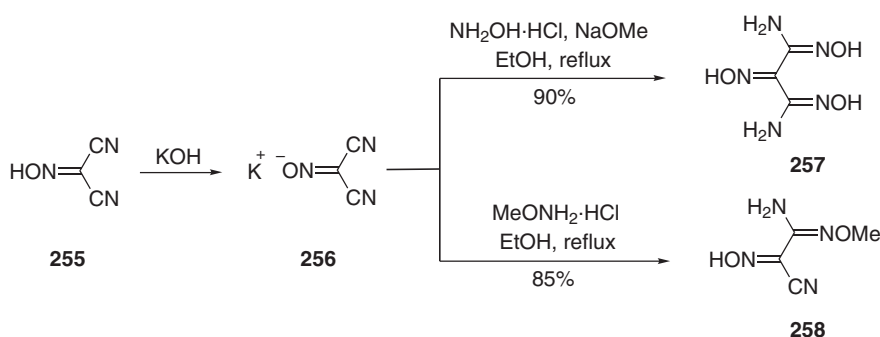
Oxyimidic amides are also known as amidoximes or oxamidines. According to *Chemical Abstracts* they are named hydroxyamidines. Review articles have been published; the reader is referred to COFGT (1995).

5.21.2.5.1 From nitriles

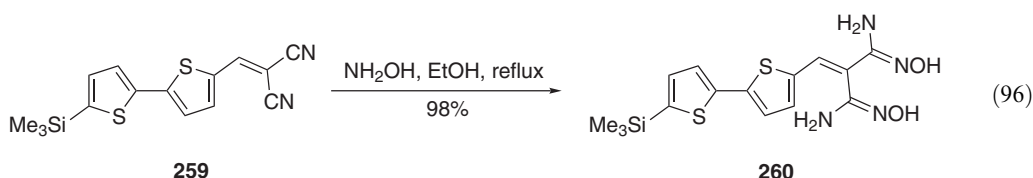
This class of compounds is most commonly obtained from nitriles (**251** and **253**). Nitriles react with hydroxylamine in the presence of a base (e.g., sodium or potassium carbonate, sodium ethoxide, triethylamine), usually at elevated temperature, to yield hydroxyamidines (**252** and **254**), (Equations (94) and (95)) <1996JMC237, 1996JMC3908, 1996BMCL111, 1999JCS(P1)2725, 2000S1148, 2000BMCL1431, 2000BMC1559, 2001BMCL2385, 2001TL1441, 2002BMCL3595>.



α,α -Dinitriles such as 2-hydroxyiminomalononitrile **255** (obtained from malononitrile and nitrous acid) or 2,2'-bithienyl derivative **259** are transformed into the respective bis-hydroxyamides (**257** and **260**) in the reaction with hydroxylamine (Scheme 17, Equation (96)) <2000JOC1139, 2001JOM26>. Methoxyamidine **258** is obtained when the salt **256** is reacted with *O*-methylhydroxylamine (Scheme 17) <2000JOC1139>.

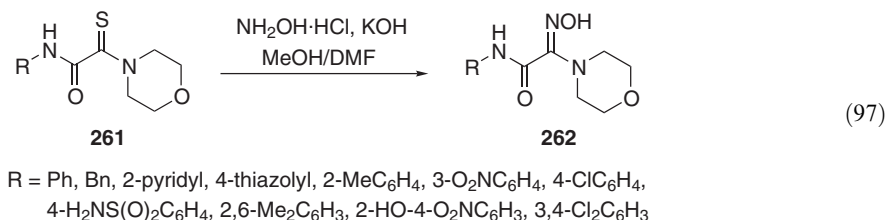


Scheme 17



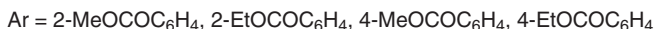
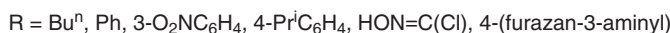
5.21.2.5.2 From amides and thioamides

Whilst amides are generally unreactive toward hydroxylamine, thioamides **261** condense with hydroxylamine to form the corresponding hydroxyamidines **262** (Equation (97)) <1998IZV2002>.



5.21.2.5.3 From oxyimide halides

Oxyimide halides readily react with amines to yield the corresponding oxyimide amides. The reactions are generally carried out in ethanolic solution in the presence of a mild base such as sodium hydrogencarbonate. Thus, *N,N'*-dihydroxyoxalodiimide acid dichloride **263** and

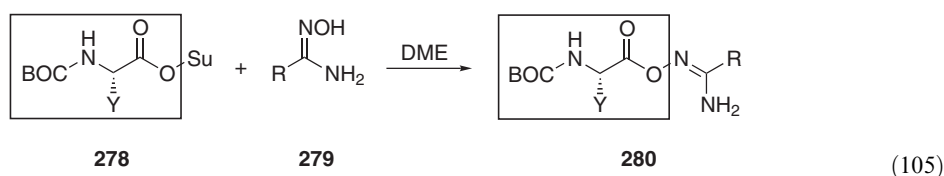
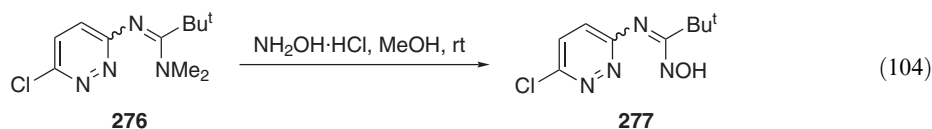
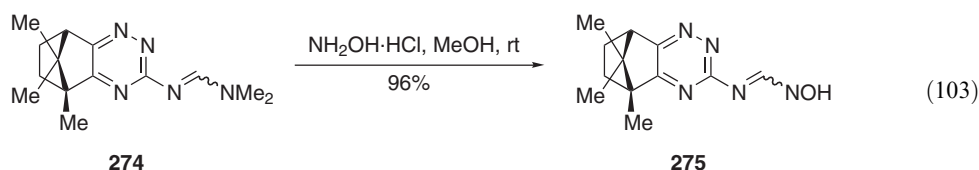
$$\text{Cl}-\text{C}(\text{NOH})=\text{C}(\text{NOH})-\text{Cl} \xrightarrow[\text{50-75\%}]{\text{ArNH}_2, \text{NaHCO}_3, \text{EtOH, rt}} \text{Ar}-\text{NH}-\text{C}(\text{NOH})=\text{C}(\text{NOH})-\text{NH}-\text{Ar} \quad (98)$$

$$\text{R}-\text{C}(\text{NOH})=\text{Cl} \xrightarrow[\text{57-97\%}]{\text{NaN}_3, \text{EtOH or DMF, rt}} \text{R}-\text{C}(\text{NOH})=\text{N}_3 \quad (100)$$


N-Hydroxyamidines **271** are accessible from oxyimide esters **270** by reaction with amines **269** (Equation (101)) <2000BMCL1077>. The reactions are usually carried out in alcoholic solution and under reflux conditions. Alkoxyamidines **273** have been obtained in good-to-excellent yields from imide esters **272** by reaction with alkoxyamines (Equation (102)) <1998CPB69, 1999JCS(P1)1853>.



The reaction of amidines (**274** and **276**) with hydroxylamine in methanolic solution yields hydroxyamidines (**275** and **277**) (Equations (103) and (104)) [<1998JHC293, 1999JCR\(M\)548, 2003CPB122>](#). *N*-Oximidic amides **280** have also been generated from hydroxyamidines **279**

and activated α -amino acid derivatives (**278**, amino acid residue is boxed) (Equation (105)) <1999JMC4088>.



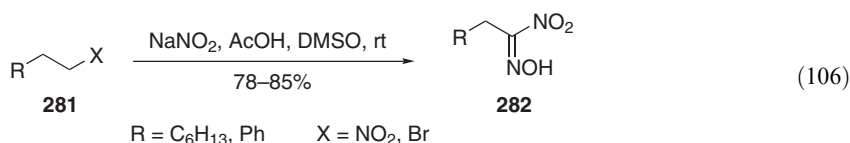
Y = amino acid-specific side chain

Su = *N*-succinimidyl

R = Bn, 3-ClC₆H₄, 4-MeC₆H₄CH₂, 4-PrⁱC₆H₄CH₂, 4-ClC₆H₄CH₂, 2,4-Cl₂C₆H₃CH₂, 3,4-Cl₂C₆H₃CH₂, 2,2,4-Cl₃C₆H₂CH₂, 1-naphthyl-CH₂, 2-naphthyl-CH₂

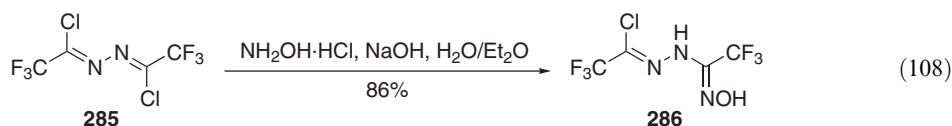
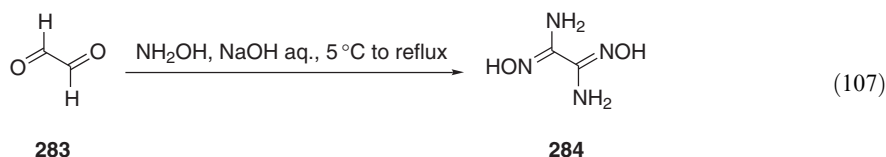
5.21.2.5.6 From aliphatic nitro compounds

Aliphatic nitro compounds **281** (X = NO₂) are transformed into nitrolic acids **282** by the action of sodium nitrite and acetic acid in DMSO (Equation (106)) <1997JOC234, 2000TL1191>. The same products are obtained from bromides **281** (X = Br). Nitrolic acids have also been obtained from aliphatic nitro compounds by reaction with sodium nitrite and sodium hydroxide in methanol at 0 °C <1996TL7791>.



5.21.2.5.7 Other methods

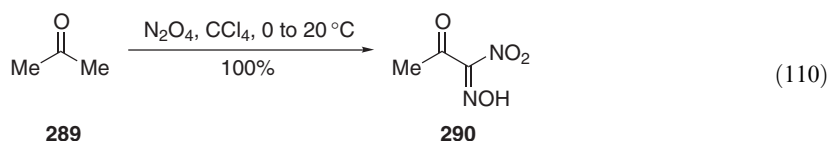
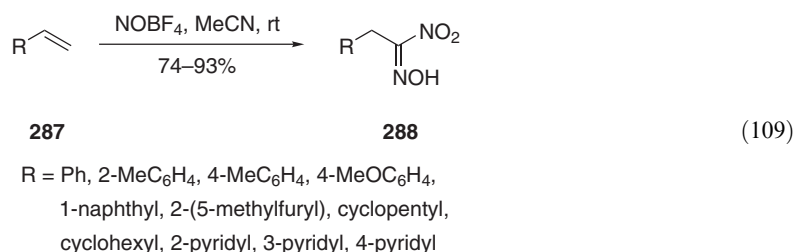
Glyoxal **283** has been used as a precursor to hydroxyamidine **284** by treatment with hydroxylamine and aqueous sodium hydroxide (Equation (107)) <2002TL4741>. *N,N'*-Di(1-chloro-2-trifluoroethylidene)hydrazine **285** was converted into **286** under similar conditions (Equation (108)) <1995JFC95>.



Oxyimidic amide derivatives have also been generated from nitrile oxides, oxime derivatives, oxyamide oximes, and nitrosolic and nitrolic acids. The reader is referred to COFGT (1995) for information on these transformations.

5.21.2.5.8 Nitrolic acids

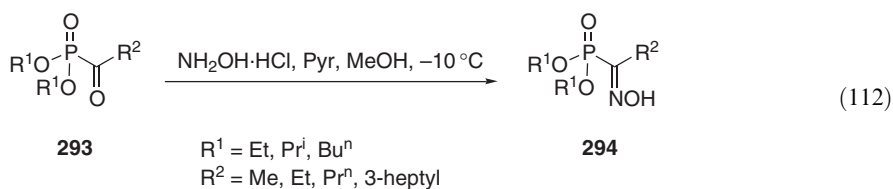
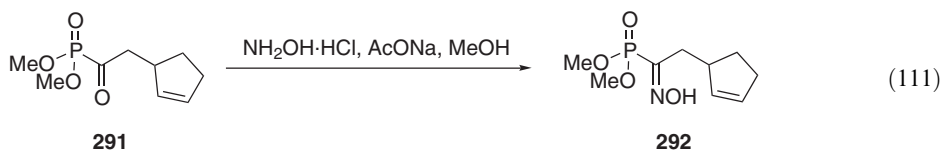
Nitrolic acids are generally synthesized from nitro compounds by reaction with nitrous acid in DMSO (see Section 5.21.2.5.6) <1996TL7791, 1997JOC234, 2000TL1191>. Compounds **288** are also available in good yields from terminal alkenes **287** by reaction with nitrosyl tetrafluoroborate in acetonitrile (Equation (109)) <1996TL7791>. Quantitative yield of nitrolic acid **290** has been obtained from acetone **289** by reaction with dinitrogen tetroxide in carbon tetrachloride (Equation (110)) <1995IZV722>.

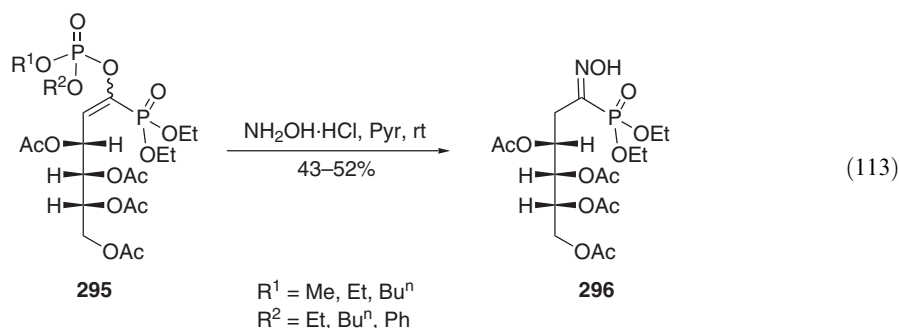


5.21.2.6 Oxyimidic Phosphorus Derivatives

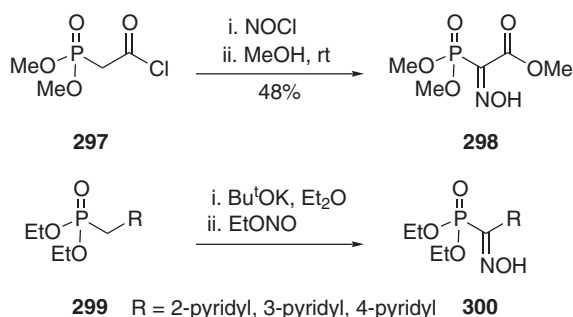
5.21.2.6.1 From phosphonic acid esters

Acylphosphonic acid dialkyl esters (**291** and **293**) react with hydroxylamine to yield 1-hydroxyimino alkylphosphonic acid esters (**292** and **294**) (Equations (111) and (112)) <1995T6517, 1996MI441, 1996MI179, 2000JCS(D)2587, 2000EJO275>. The treatment of alkylphosphates **295** with hydroxylamine results in the loss of one phosphate moiety and formation of hydroxyimino compounds **296** (Equation (113)) <1998ZOB691>.



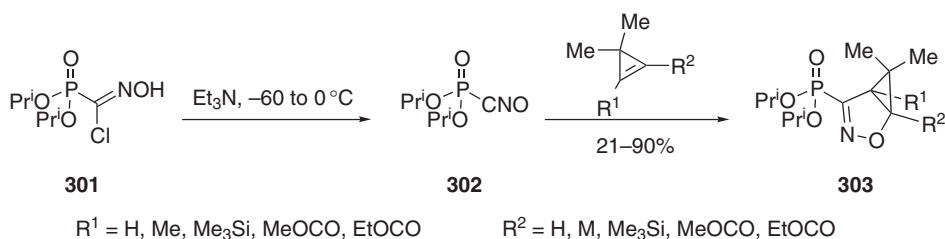


1-Hydroxyimino alkylphosphonic acid esters (**298** and **300**) are also available from alkylphosphonic acid esters (**297** and **299**) by treatment with nitrosating agents such as nitrosyl chloride or ethyl nitrite (Scheme 18) <1995TL9437, 1995MI45>.



Scheme 18

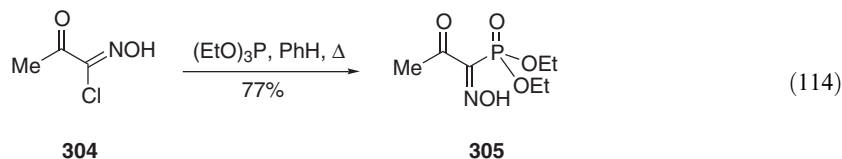
Phosphoryl nitrile oxides **302**, which are available from phosphorylhydroxyimidic chlorides **301** by treatment with a base, undergo a dipolar cycloaddition with functionalized cyclopropenes to yield bicyclic adducts **303** (Scheme 19) <1995DOK203, 1996T8877>. Yields vary from low to excellent.

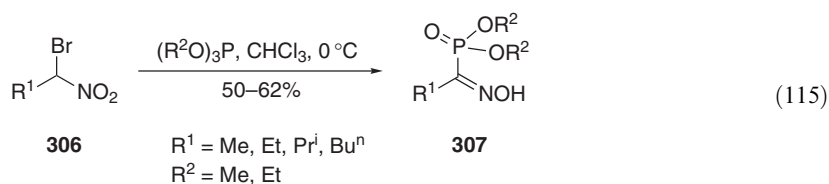


Scheme 19

5.21.2.6.2 From phosphites

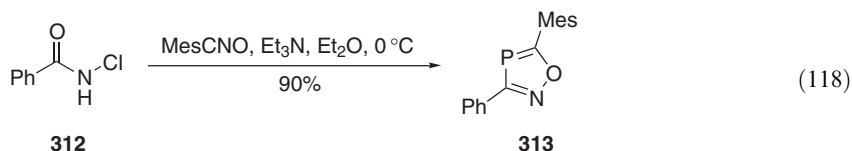
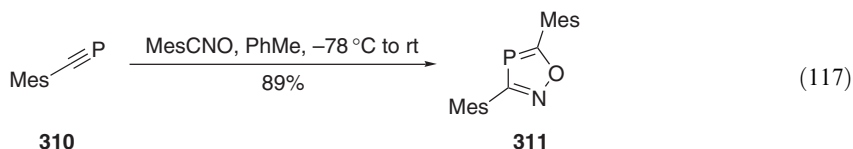
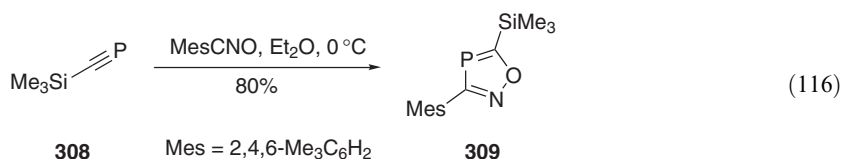
The treatment of hydroxyimidic chloride **304** with triethyl phosphite leads to displacement of the chloride, oxidation of the phosphorus center, and formation of oxyimidic phosphorus derivative **305** (Equation (114)) <2000ZOB1931>. α -Bromonitro alkanes **306** yield compounds **307** in modest yields on treatment with trialkyl phosphites (Equation (115)) <1999JOC9272>.



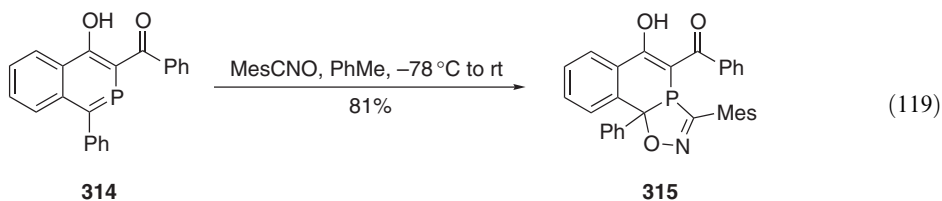


5.21.2.6.3 From phosphanes

The reaction of phosphanes (**308** and **310**) with mesitronitrile oxide yields [1,2,4]-oxazaphospholes (**309** and **311**) in high yields (Equations (116) and (117)) <1997BSB455, 1998S1305>. An analogous product **313** is obtained in the reaction of *N*-chlorobenzamide **312** with mesitronitrile oxide (Equation (118)) <1998S1305>.



Isophosphinoline **314** reacts with mesitronitrile oxide at low temperature to yield tricyclic structure **315** in high yield (Equation (119)) <2000T6259>.

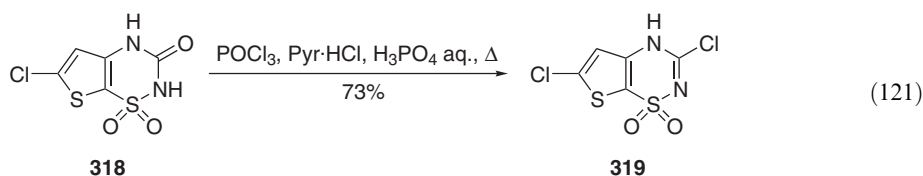
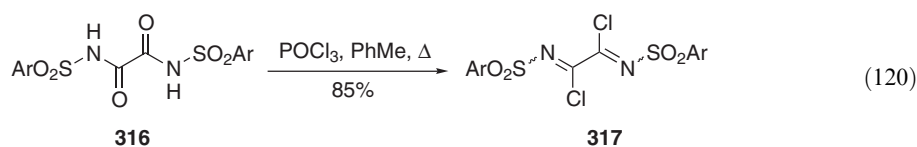


5.21.3 THIOIMIDIC DERIVATIVES

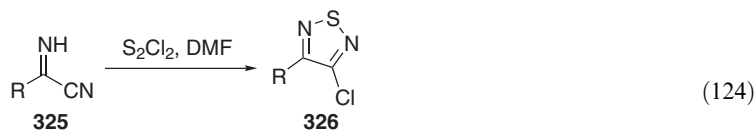
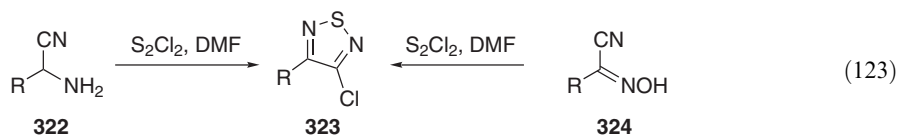
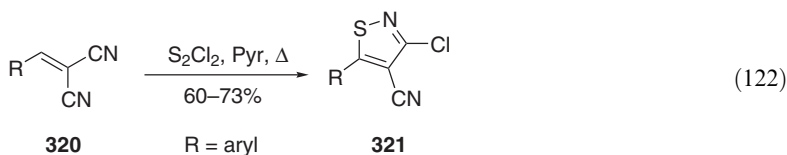
Numerous cyclic structures (e.g., thiadiazoles, thioxazoles, dithioxazines, etc.) formally contain the thioimidic structural unit. For completeness, they will be treated alongside their linear counterparts.

5.21.3.1 Thioimidic Halides and Related Structures

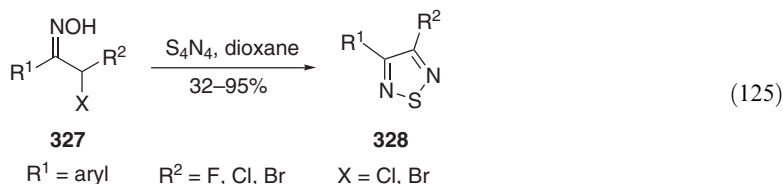
Thioimidic halide derivatives (**317** and **319**) are generated from *N*-sulfanyl- or *N*-sulfonyl amides **316** (Equation (120)) <1995JPR143> or urea derivatives **318** (Equation (121)) <2002JMC4171> by reaction with phosphoryl chloride, phosphoryl bromide, phosphorus pentachloride, or phosphorus pentabromide <1996H2435, 1996JMC4044, 1996MI269, 1997IZV1887, 1997SL1355, 2000JOC8439, 2001S1228, 2001EJO1225, 2002JCS(P2)1950, 2002JCR(S)299>. *N*-Sulfonylamides are also converted into the respective sulfonylimidic chlorides by reaction with trichloromethyl chloroformate in *N,N*-dimethyl formamide and tetrachloroethylene <2001S1228>.



Sulfur monochloride reacts with malononitrile derivatives **320** <1998BMC2271>, aminonitriles **322**, imidic cyanides **325** <1995JMC2038, 1996MI221, 1997JMC538, 1998JMC4378, 1998JMC109, 1998H2111, 1999JMC1999, 1999CPB876, 2000AP113, 2003AP230>, and oxyimide cyanides **324** <1998JMC379> to yield isothiazole **321** and thiadiazole derivatives (**323**, **326**, and **328**), respectively (Equations (122)–(124)). Oximes **327** are converted into thiadiazoles **328** by tetrasulfur tetranitride in dioxane (Equation (125)) <1998JCS(P1)109>. Thioimide fluorides can be prepared from the corresponding chlorides by heating with potassium fluoride <2001MI6258> or caesium fluoride in dimethyl sulfoxide <2002JMC4171>.

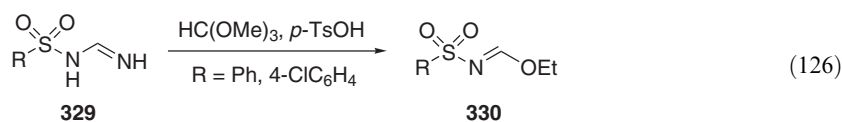


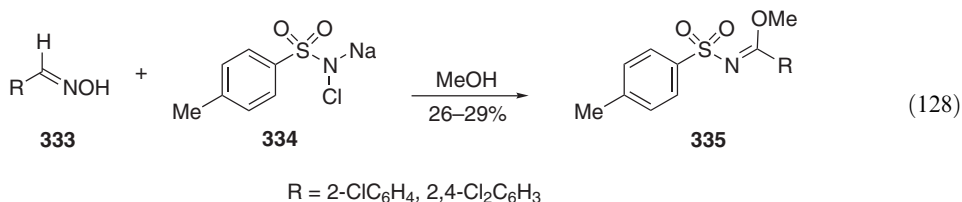
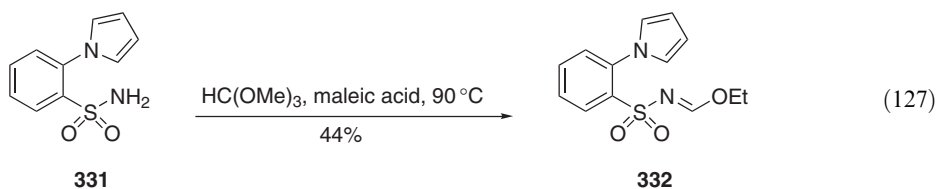
R = PrⁿO, BuⁿO, C₅H₁₁O, C₆H₁₃O, EtS, PrⁿS



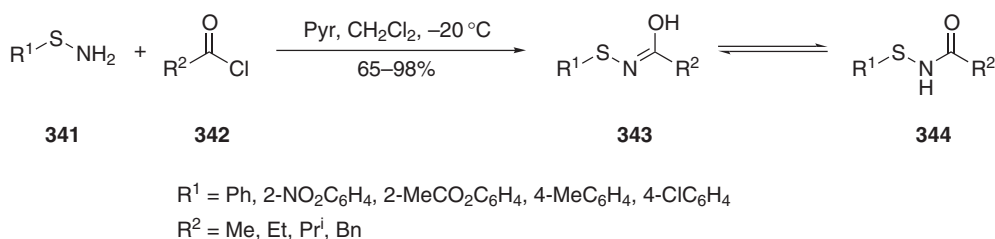
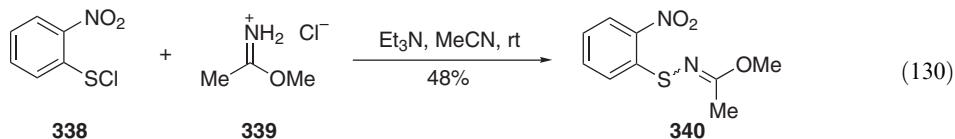
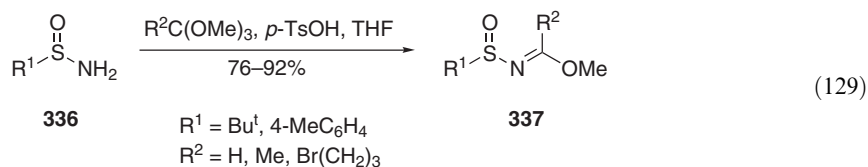
5.21.3.2 Thioimide Esters and Related Structures

A common route to sulfonyl derivatives of imidic esters (**330** and **332**) is by treatment of a sulfonamide (**329** and **331**) with an orthoester (Equations (126) and (127)) <1997AF431, 1997FES375>. Sulfonyl imidates **335** have also been obtained in the reaction of chloramine-T **334** with oximes **333**, albeit in low yields (Equation (128)) <2003JOC1567>.



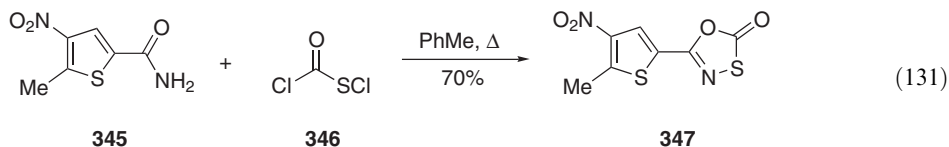


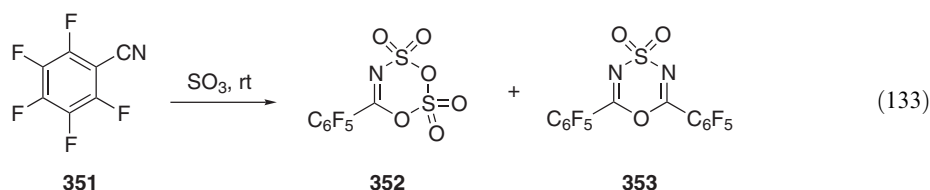
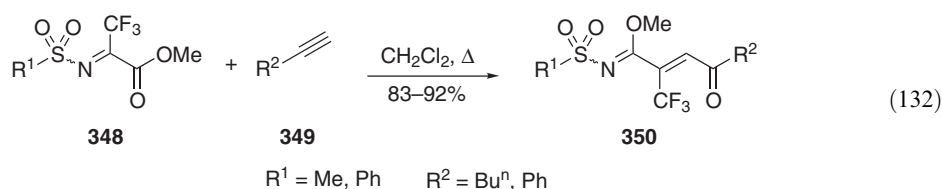
Sulfinamides **336** as well as sulfonyl chlorides **338** and amides **341** have been employed in the synthesis of the corresponding imide derivatives. Thus, sulfinyl derivatives **337** have been obtained in good yields by reaction with orthoesters (Equation (129)) <2001JA1539, 2003JOC3>. Sulfonyl imide **340** has been prepared from the chloride **338** and methyl acetimidate hydrochloride **339** (Equation (130)), and derivatives **343** were formed in the reaction of sulfonylamides **341** with acid chlorides **342** (Scheme 20) <2003T303>. Sulfonyl imides **343** have been shown to exist in tautomeric equilibrium with their sulfonylamide counterparts **344**.



Scheme 20

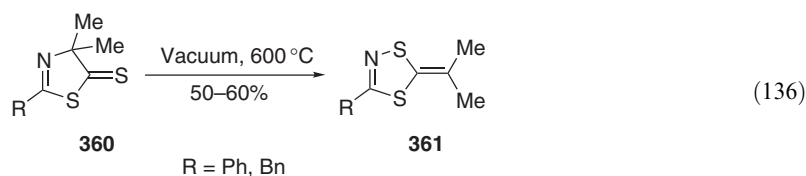
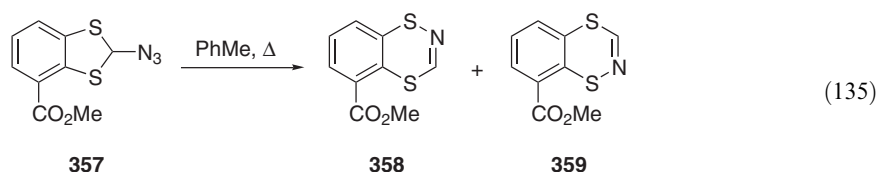
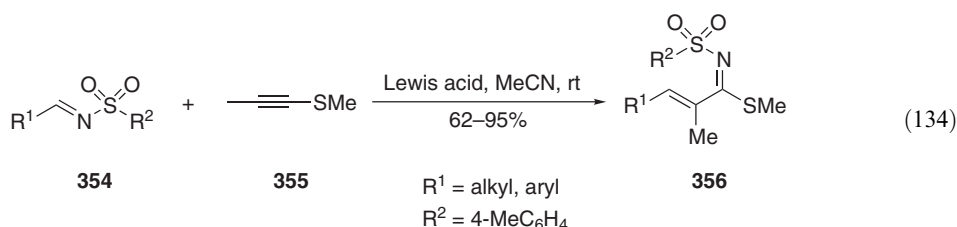
Sulfur derivatives of imides have been obtained from various other precursors, including amides **345** and carbonochloridic hypochlorous thioanhydride **346** (Equation (131)) <1995CJC212, 1997IZV118>, sulfonyl imides **348** and alkynes **349** (Equation (132)) <2001IZV1265>, and perfluoronitriles **351** and sulfur trioxide (Equation (133)) <2002ZOR931>.





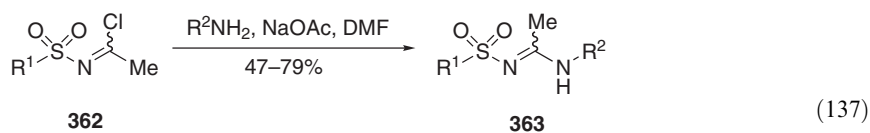
5.21.3.3 Thioimidic Thioesters and Related Structures

Sulfonimines **354** react with 1-methylsulfanylpropyne **355** in the presence of Lewis acids such as scandium triflate, ytterbium triflate, or boron trifluoride diethyl etherate to yield sulfonyl imidic thioesters **356** in moderate-to-excellent yields (Equation (134)) <1996JOC1902>. Benzodithiazines (**358** and **359**) are available from azides **357** via the Schmidt reaction (Equation (135)) <2000JHC955>. Although hardly a practical synthetic method, vacuum flash pyrolysis of thiazole thiones **360** affords dithiazoles **361** in moderate yields (Equation (136)) <1998PJC1915>.



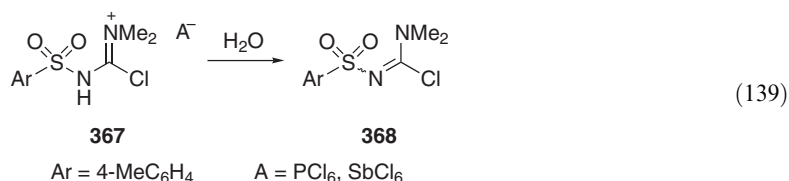
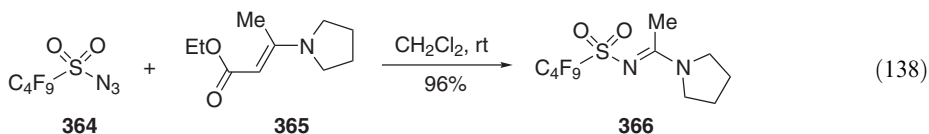
5.21.3.4 Thioimidic Amides and Related Structures

Thioimidic amide derivatives (**363** and **366**) are prepared from the corresponding chlorides **362** and amines (Equation (137)) <2001ZOR1043> or from α,β -unsaturated esters **365** and sulfonyl azides **364** (Equation (138)) <2000JFC195>. They **368** have also been obtained by hydrolysis of imidic salts **367** (Equation (139)) <1998JPR346>.

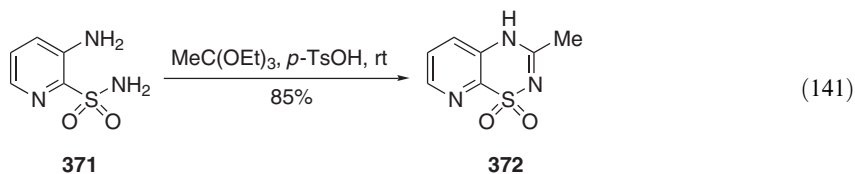
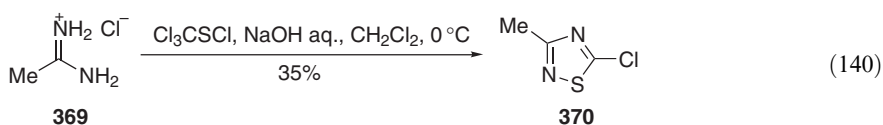


$\text{R}^1 = 4\text{-MeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4$

$\text{R}^2 = 2,6\text{-Me}_2\text{-4-HO-C}_6\text{H}_2, 3,5\text{-Me}_2\text{-4-HO-C}_6\text{H}_2, 3,5\text{-Cl}_2\text{-4-HO-C}_6\text{H}_2$

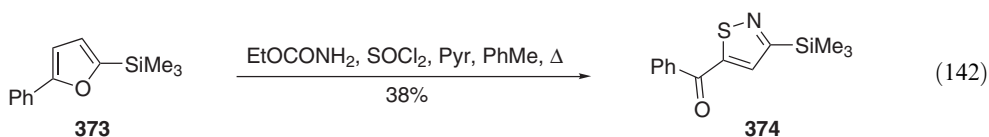


Various substituted [1,2,4]-thiadiazoles **370** are accessible from amidines **369** and trichloromethanesulfonyl chloride (Equation (140)) <2002JMC1887, 2002BMCL589, 2002JHC237>. Aminopyridine sulfonamides **371** react with acid anhydrides <1995T3221, 1996JMC937, 2000JMC1456> or orthoesters <1995T3221, 1998T13645> in the presence of catalytic amounts of acid to yield pyridothiadiazine dioxides **372** (Equation (141)).

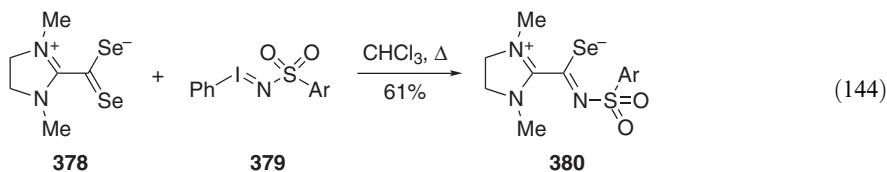
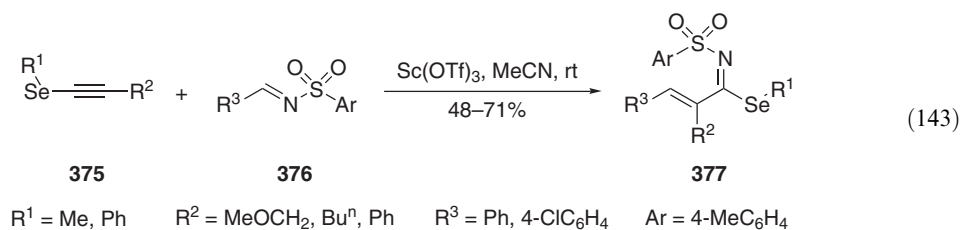


5.21.3.5 Thioimidic Silicon and Selenium Derivatives

The reaction of furan **373** with thionyl chloride, ethyl carbamate, and pyridine afforded substituted thiazole **374** in 38% yield (Equation (142)) <2001JCS(P1)1304>.



Sulfonimidic selenium derivatives **377** are obtained in moderate-to-good yields in the reaction of selanyl alkynes **375** with sulfonimines **376** in the presence of a Lewis acid (Equation (143)) <2000TL945>. Zwitterionic structure **380** was recovered when compound **378** was reacted with [*N*-(*p*-tolylsulfonyl)imino]phenyliodine **379** (Equation (144)) <2000JA9120>.



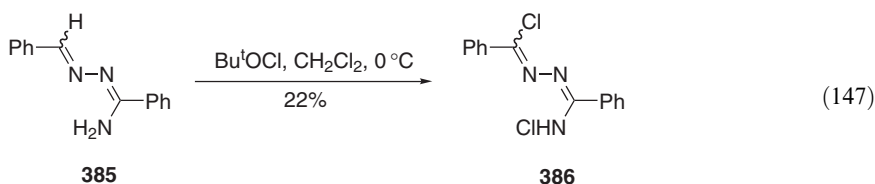
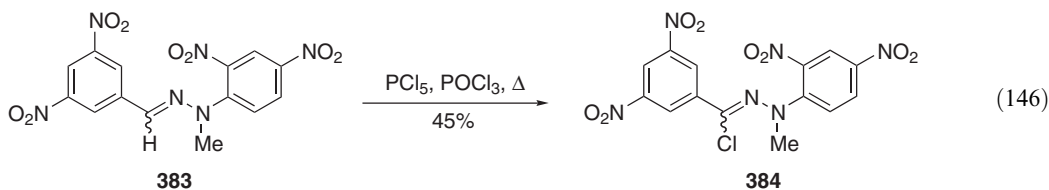
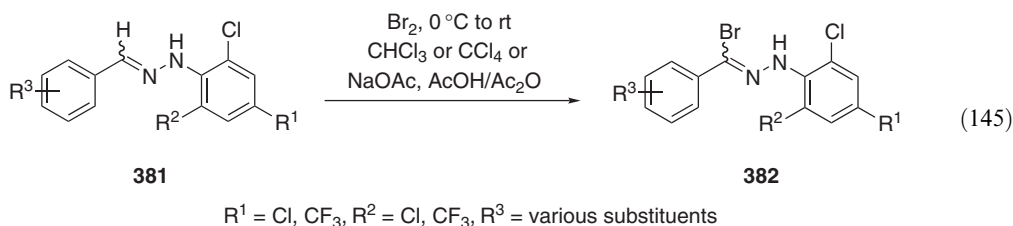
5.21.4 HYDRAZONOYL DERIVATIVES

5.21.4.1 Hydrazonoyl Halides

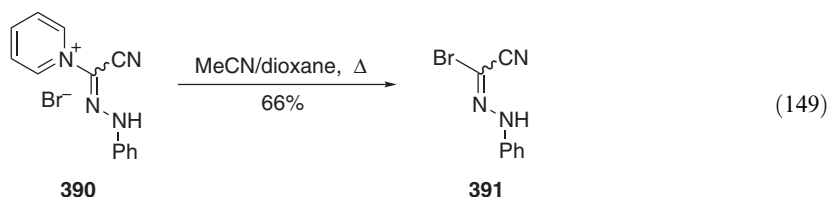
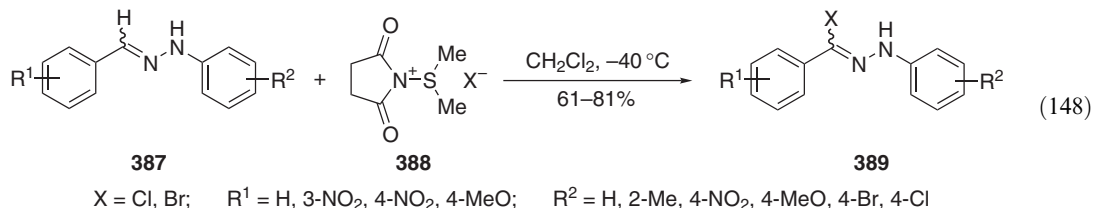
Numerous cyclic structures, such as halogenated pyrazoles, formally contain the hydrazonoyl halide structural unit. They will be included here alongside their acyclic counterparts.

5.21.4.1.1 From hydrazones

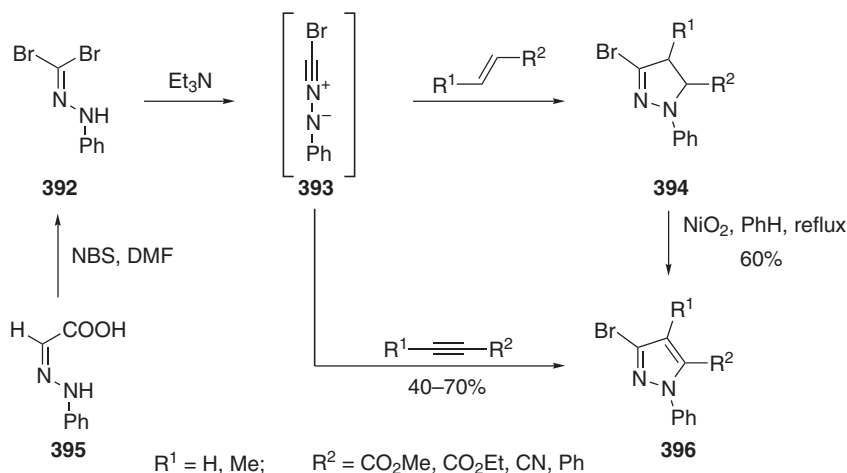
Hydrazones **381** are readily transformed into hydrazonoyl halides by means of a variety of halogenating agents. Bromine in chloroform, tetrachloromethane, or acetic acid at low temperature yields hydrazonoyl bromides **382** (Equation (145)) <1996AJC463, 1996S1076, 1996OPP699, 1998OPP177, 2002JMC2123>. The chlorination of hydrazone **383** was effected by treatment with phosphorus pentachloride and phosphoryl chloride to yield hydrazonoyl chloride **384** in modest yield (Equation (146)) <1997AJC849>. *t*-Butyl hypochlorite was used in the conversion of amidrazones **385** to dichlorinated species **386**, although the conversion proceeded in low yield (Equation (147)) <2000JOC931>.



Hydrazones **387** are chlorinated and brominated to their respective chlorides or bromides **389** in high yields by action of the Corey–Kim reagent **388**, which is conveniently made *in situ* from dimethyl sulfide and *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) at 0 °C respectively (Equation (148)) <1996T661, 1998TA3359, 2000T8071>. The reaction of hydrazones with NCS or NBS alone also yields the corresponding hydrazoneyl halides; the yields however, suffer markedly. Hydrazoneyl halides **391** are also accessible by elimination from their halide salts, e.g., pyridinium salt **390** (Equation (149)) <2000S1166>.

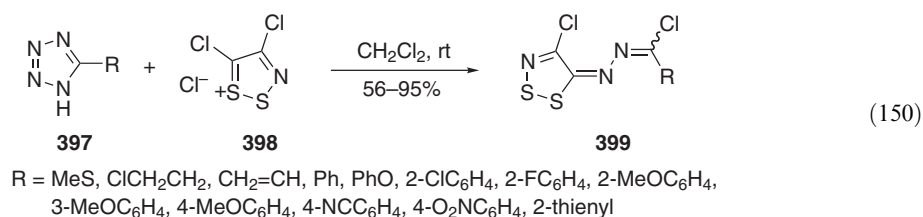


Hydrazones **395** yield dibromo-derivatives **392** upon treatment with NBS in *N,N*-dimethylformamide which, in turn, afford nitrilimines **393** by deprotonation with a base such as triethylamine. Nitrilimines undergo 1,3-dipolar cycloaddition reactions with alkenes or alkynes to yield the corresponding bromodihydropyrazoles **394** or bromopyrazoles **396** in good yields. Dihydropyrazoles **394** are oxidized to the corresponding pyrazoles **396** by heating at reflux with nickel peroxide (Scheme 21) <1999TL2605>.



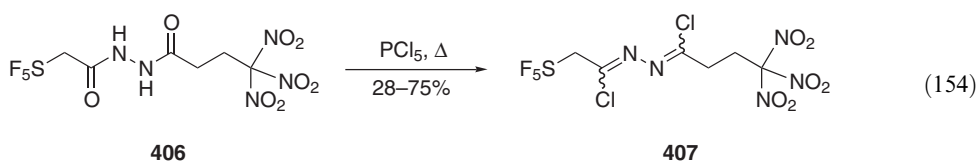
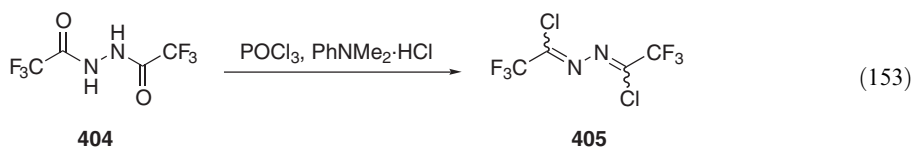
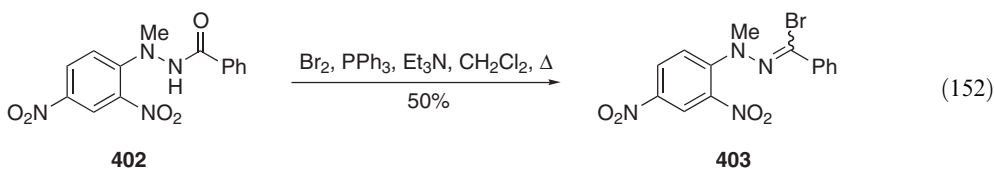
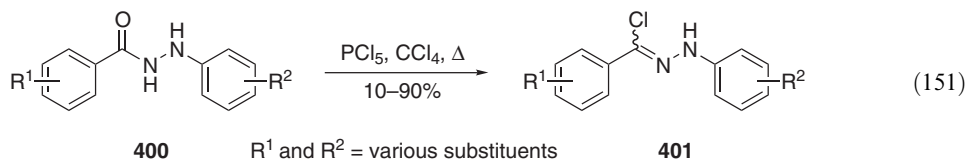
Scheme 21

The reaction of substituted tetrazoles **397** with Appel salt **398** leads to an opening of the tetrazole ring and the formation of structures **399** in moderate-to-excellent yields (Equation (150)) <2000TL9407, 2002JCS(P1)1535, 2002JCS(P1)1543>.



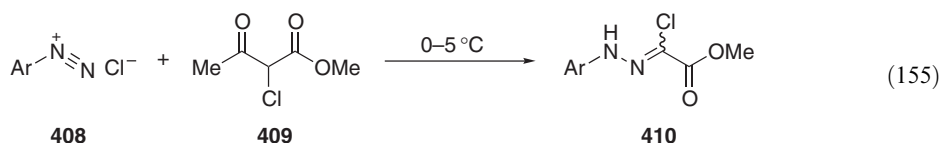
5.21.4.1.2 From hydrazides

Hydrazonoyl halides are prepared from monoacyl- and diacylhydrazines for both the aliphatic and aromatic series by the use of several halogenating agents. Yields are variable and range from poor through to excellent. Aromatic hydrazonoyl chlorides **401** have been obtained from their corresponding hydrazides **400** by treatment with phosphorus pentachloride in tetrachloromethane at elevated temperature (Equation (151)) <1999BMCL1727, 2000T4213, 2000BMCL601, 2001HAC557>, whilst the reaction of hydrazide **402** with bromine in the presence of triphenylphosphine and triethylamine afforded hydrazonoyl bromide **403** (Equation (152)) <1995AJC2041, 1999AJC807>. In the aliphatic series, both phosphoryl chloride and phosphorus pentachloride in solvents such as 1,2-dichloroethane, 1,2-dichlorobenzene, or xylene have been employed to convert hydrazides (**404** and **406**) to their respective hydrazonoyl chlorides (**405** and **407**) (Equations (153) and (154)) <1995JFC95, 1995JFC31, 2001MI191, 2001MI969>.

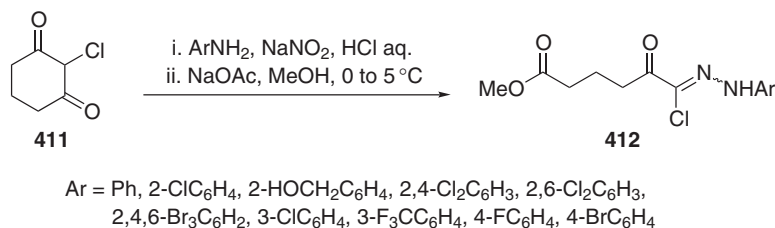


5.21.4.1.3 From 2-halo-1,3-dicarbonyl compounds

Probably the most common approach to hydrazonoyl halides is via the Japp-Klingemann reaction. Diazonium salts **408** (made by diazotization of the corresponding amines, most commonly using NaNO_2 and concentrated aqueous HCl ($\text{H}_2\text{SO}_4/\text{NaBF}_4$ or H_3PO_4 have also found use <2000JMC3824, 2001JMC3157>)) react with 2-chloro- (or bromo) 1,3-dicarbonyl compounds **409** to yield the corresponding hydrazonoyl halides **410**. The yields generally range from medium-to-high (Equation (155)). Literature examples for this transformation abound: <1995IJC(B)736, 1995JCR(M)2389, 1995JCR(S)276, 1998T2843, 1998JCS(P1)4103, 1998JCR(S)40, 1999TA3873, 1999TA487, 2000JCS(P1)1685, 2000TA1975, 2000H1737, 2001SC2649, 2002EJO1654, 2002MI487>.



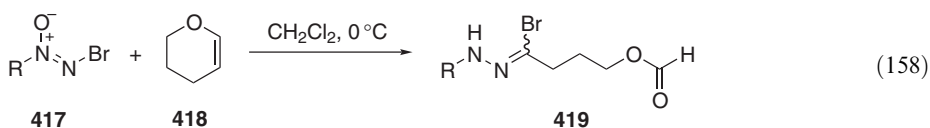
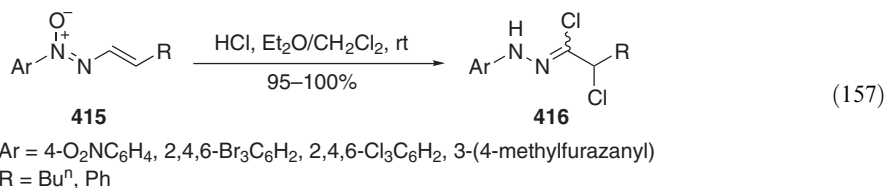
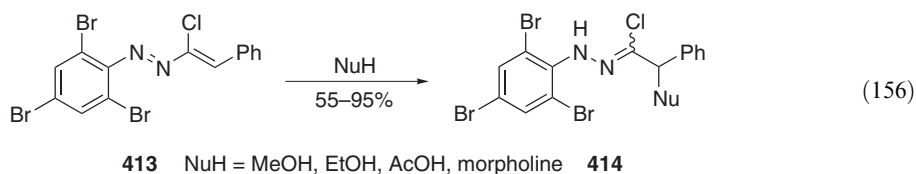
Cyclic 2-halo-1,3-dicarbonyl compounds **411** undergo ring cleavage to aliphatic hydrazonoyl halides **412** when reacted with aryldiazonium species (Scheme 22) <1995AP505, 1997H1183>.



Scheme 22

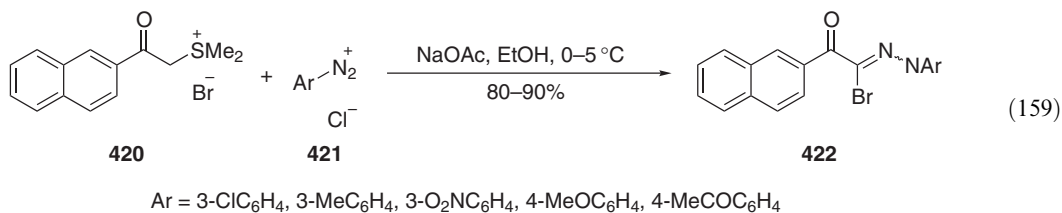
5.21.4.1.4 From diazenes and related compounds

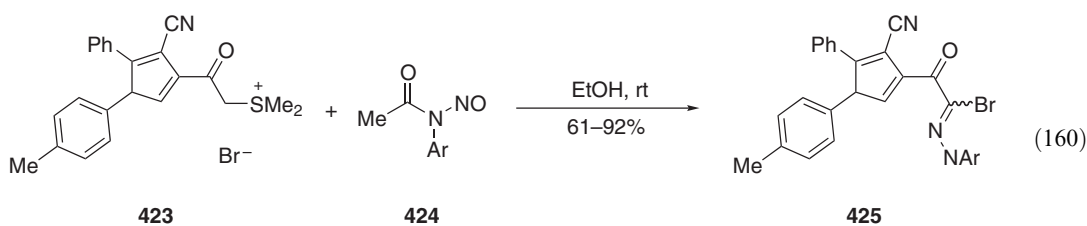
α,β -Unsaturated α -halo diazenes such as **413** react with nucleophiles to yield hydrazoneyl halides **414** (Equation (156)) <1995IZV928>. α,β -Unsaturated diazene *N*-oxides **415** are converted into dichlorohydrazoneyl derivatives **416** by hydrogen chloride in diethyl ether/dichloromethane (Equation (157)) <1995IZV928>. *N*-Alkyl-*N'*-bromodiazenes *N*-oxides **417** ring-open dihydropyran **418** to yield hydrazoneyl bromides **419** (Equation (158)) <1995IZV917>.



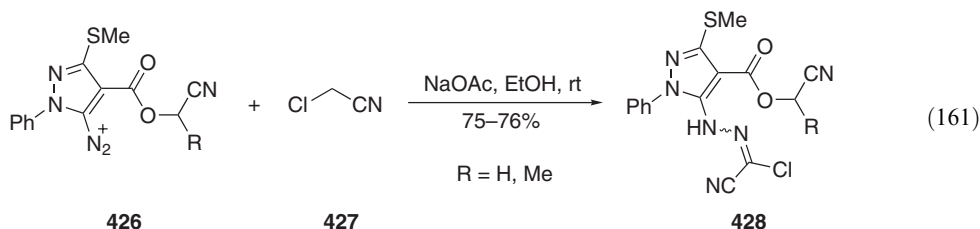
5.21.4.1.5 From diazonium salts and related compounds

Compounds such as dimethylsulfonium bromides (**420** and **423**) condense readily with diazonium salts (**421** or *N*-nitrosamides **424** with the formation of the corresponding hydrazoneyl halides (**422** and **425**) in moderate-to-high yields (Equations (159) and (160)) <1995JCR(M)3036, 2000MI35, 2001MI65, 2001SC1647>. Condensation is also observed between diazonium salts (**426** and **429**), and chloroacetonitrile **427** and bromoacetophenone **430**. These reactions yield chloro- and bromohydrazoneyl derivatives **428** and **431**, respectively, in good yields (Equations (161) and (162)) <2000MI933, 2000MI161>.

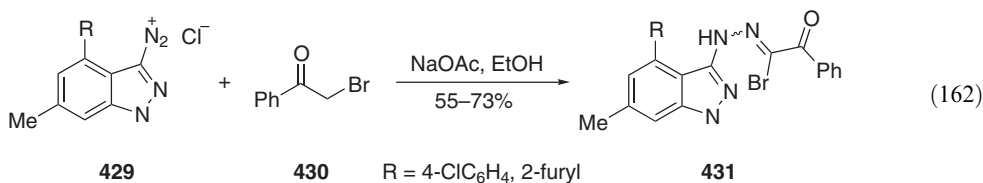




Ar = Ph, 4-ClC₆H₄, 4-MeC₆H₄



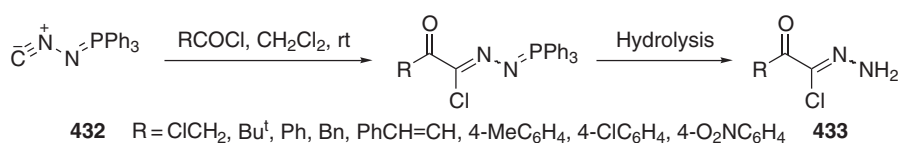
R = H, Me



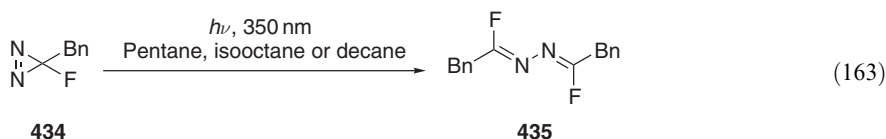
R = 4-ClC₆H₄, 2-furyl

5.21.4.1.6 Other methods

Hydrazonoyl chlorides **433** are obtained from isonitrileimine triphenylphosphoranes **432** by initial addition of acid chloride followed by hydrolysis (Scheme 23) <2000SL526>. Benzylfluorodiazirine **434** undergoes photolytic cleavage and dimerization to yield hydrazonoyl fluoride derivative **435** (Equation (163)). The yield of **435** is only 20–38% at 25 °C but rises to 77% when the reaction is carried out at –55 °C <1997TL7049>. Benzylchlorodiazirine undergoes a similar process <1998JOC3010, 1999JA5940>.



Scheme 23

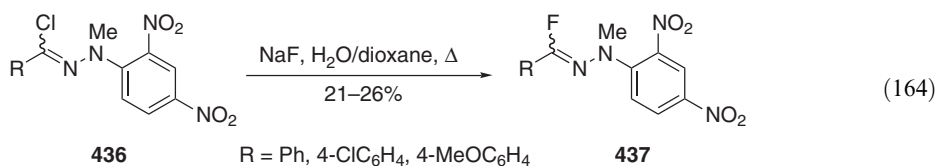


Hydrazonoyl halides have also been prepared from fluoroalkenes and aliphatic diazo compounds. The reader is referred to COFGT (1995) for information on these transformations.

5.21.4.1.7 Transhalogenation

Hydrazonoyl chlorides **436** are converted into the analogous fluorides **437** by heating in an aqueous solution of sodium fluoride and dioxane (Equation (164)). The yields obtained in this

procedure can be increased to around 65% by using calcium fluoride/potassium fluoride in acetonitrile <1995AJC2041, 1999AJC807>.

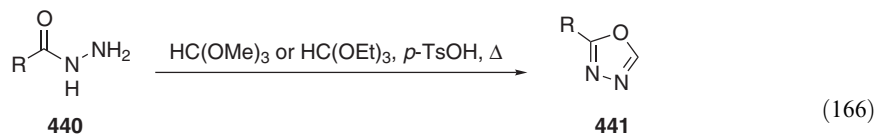
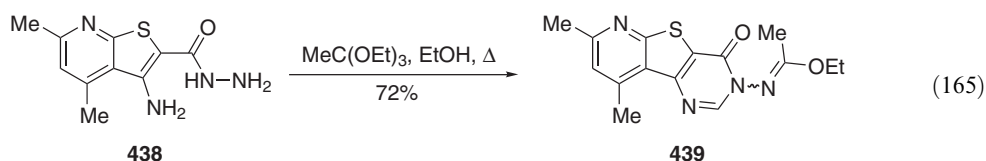


5.21.4.2 Hydrazoneic Acid Derivatives

Numerous cyclic structures such as oxadiazoles or thiadiazoles formally contain the hydrazoneic structural element. For completeness, they will be included here alongside their acyclic counterparts.

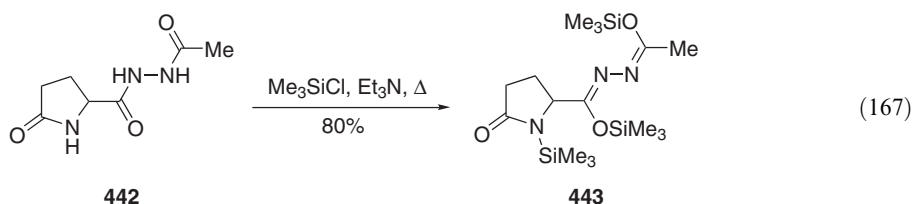
5.21.4.2.1 From hydrazides

Hydrazonates **439** can be prepared from acylhydrazines (hydrazides) **438** and orthoesters (Equation (165)) <2001MI1163>. [1,3,4]-Oxadiazoles **441** are obtained in a similar fashion, from orthoesters, acylhydrazines **440**, and an acid catalyst. Yields generally vary from medium to high (Equation (166)) <2000CPB1702, 2001JMC1268>.



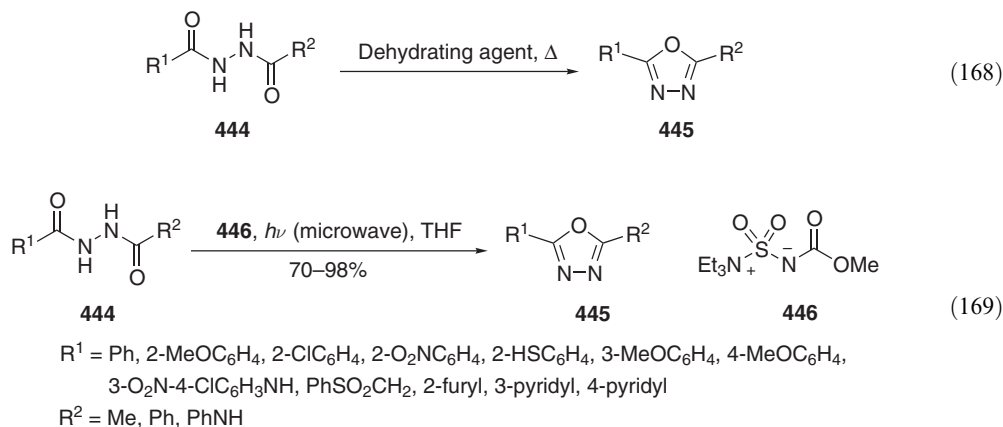
R = Me, Prⁱ, Buⁿ, Bu^t, cyclopropylmethyl, Ph, Bn, PhC(Me)₂, 3-MeC₆H₄CH₂,
3-MeC₆H₄C(Me)₂, 3,4-(OCH₂O)C₆H₃C(Me)₂, 4-MeOC₆H₄, 3-pyridyl

Hydrazoneic silyl ester derivatives **443** are available by deprotonation of diacylhydrazines **442** and by trapping of the resulting anion with trimethylchlorosilane (Equation (167)) <1996JHC1073>.

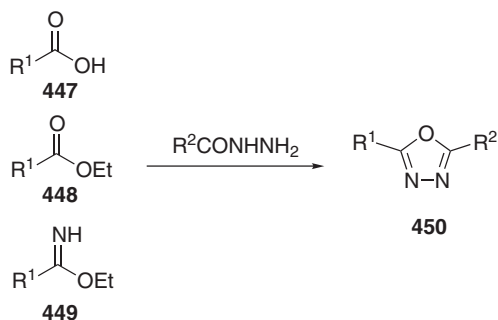


Heating of diacylhydrazines **444** with dehydrating agents such as phosphoryl chloride <1995KGS238, 1997KGS816, 1997MI2755, 2000KGS249>, phosphorus pentoxide <2002BMC1905>, phosphorus pentachloride <2000IZV1583>, polyphosphoric acid <2001MI913>, thionyl chloride <1995SC1451>, or trifluoromethanesulfonic anhydride <2000SC437> leads to disubstituted oxadiazoles **445** in generally good yields (Equation (168)). Oxadiazoles are also obtained when cyclization of diacylhydrazines is induced by triphenylphosphine and triethylamine in tetrachloromethane <1997PJC77>, hexamethyldisilazane, and tetra-*n*-butylammonium fluoride in THF <1996JHC1951> or tetrakis-triphenylphosphinopalladium(0)

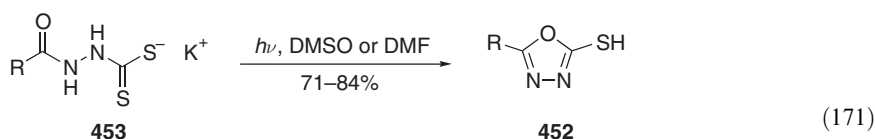
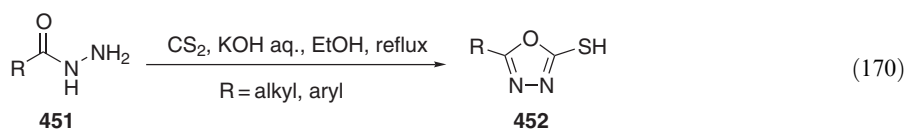
<1999SC111>. High-to-excellent yields of oxadiazoles **445** are obtained when diacylhydrazines **444** are irradiated with microwave energy in the presence of Burgess' reagent **446** (Equation (169)) <1999TL3275>.



Monoacylhydrazines yield oxadiazoles **450** when coupled with carboxylic acids **447** or esters **448** in the presence of phosphoryl chloride or polyphosphoric acid <1996JMC2753, 2000MI57>, triphenylphosphoranylidene-ethenone ($\text{Ph}_3\text{P}=\text{C}=\text{CO}$) in THF or xylene <1997SL283> or imidic esters **449** <1995KGS238, 1998JMC2390, 1998JHC377> (Scheme 24). 3*H*-[1,3,4]-Oxadiazol-2-ones are formed when monoacylhydrazines are treated with alkyl chloroformates <1997JHC1603>. Oxadiazole-2-thiols **452** are accessible from monoacylhydrazines by reaction with carbon disulfide in refluxing aqueous potassium hydroxide (Equation (170)) <1996BMCL2693, 2001MI1671>. Cyclization of acylhydrazine carbodithioic acid salts **453** induced by UV irradiation affords oxadiazole-2-thiols **452** in high yields (Equation (171)) <2002SC111>.



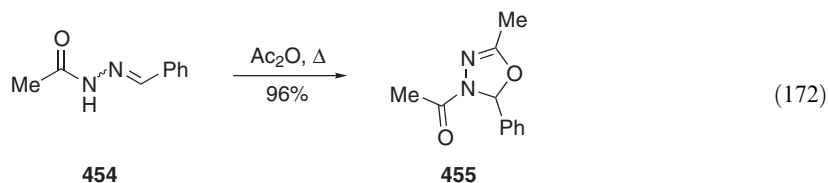
Scheme 24



$\text{R} = \text{Ph}, \text{Bn}, 2\text{-ClC}_6\text{H}_4, 3\text{-MeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4,$
 $4\text{-MeOC}_6\text{H}_4, 4\text{-HOC}_6\text{H}_4, 4\text{-pyridyl}$

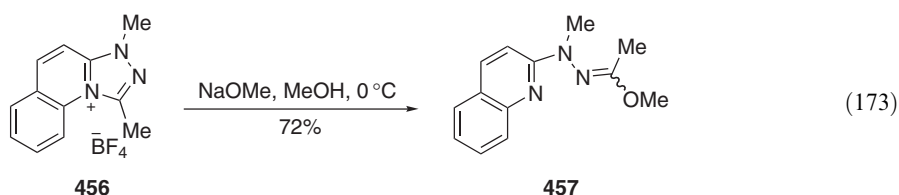
5.21.4.2.2 From hydrazones

The cyclization of hydrazone **454** to yield dihydrooxadiazole **455** was accomplished in near-quantitative yield by heating with acetic anhydride (Equation (172)) <1995JHC1647>.



5.21.4.2.3 Other methods

Hydrazone **457** has been obtained in good yield from azolinium salt **456** by treatment with sodium methoxide in methanol at low temperature (Equation (173)) <1996T1399>.



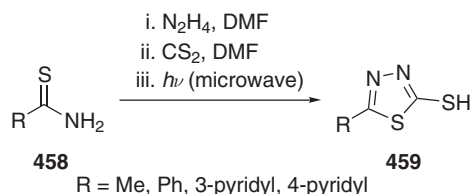
Hydrazone esters have also been obtained from hydrazoneyl halides, nitrene precursors, and ketene acetals. The reader is referred to COFGT (1995) for information on these methods.

5.21.4.3 Thio- and Selenohydrazone Acid Derivatives

Review articles have been published. The reader is referred to COFGT (1995) for more information.

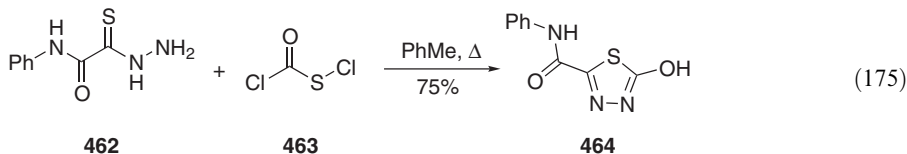
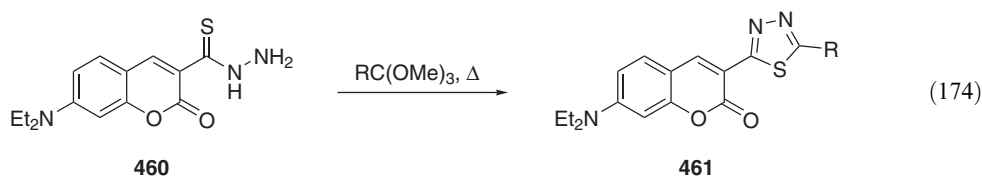
5.21.4.3.1 From thioamides, thioureas, thiocarbonyl hydrazides, and derivatives

Thioamides **458** are converted into thiadiazole thiols **459** by treatment with hydrazine and carbon disulfide followed by microwave irradiation. Reaction times are measured in minutes (Scheme 25) <1998IJC(B)427>.

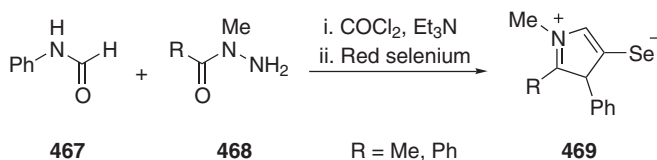
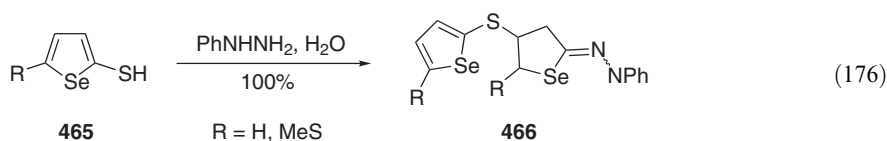


Scheme 25

Thiocarbonylhydrazides **460** cyclize to thiadiazoles **461** when treated with orthoesters (Equation (174)) <2000CPB1702>. Cyclization of thiohydrazides **462** into thiadiazoles **464** is also effected with (chlorothio)formyl chloride **463** (Equation (175)) <2003MI1283>.

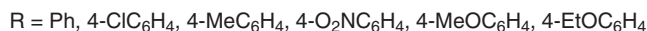
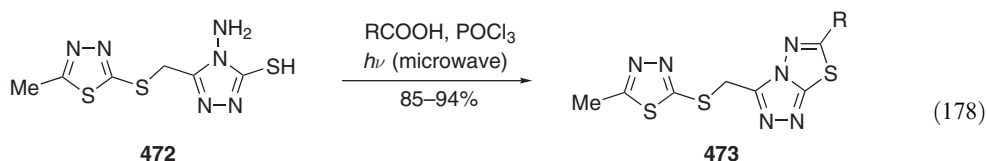
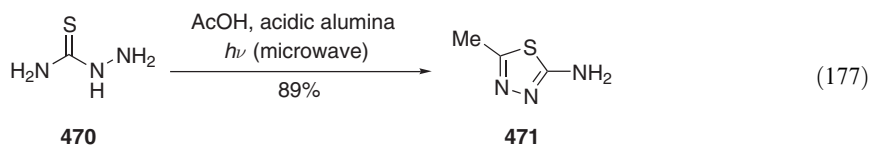


Selenohydrazonic and -amidrazonic derivatives **466** and **469** have been obtained by condensation of arylhydrazines with selenophene-2-thiols **465** (Equation (176)) <1997KGS500> and by reaction of amide **467** and acylhydrazide **468** with red selenium, respectively (Scheme 26) <1995PJC85>.

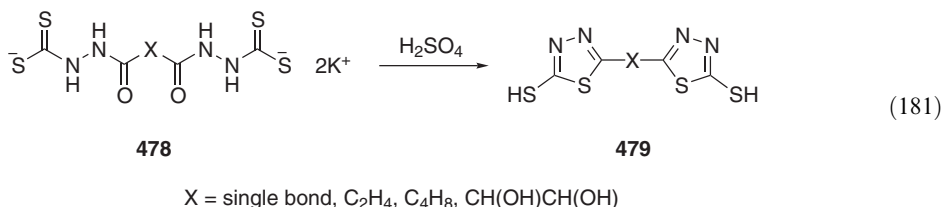
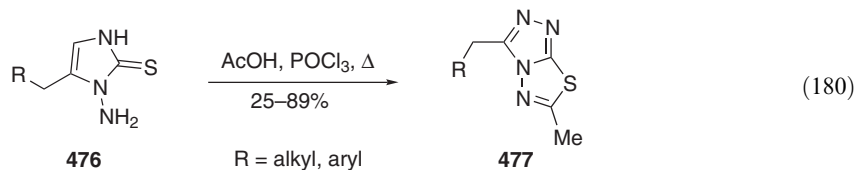
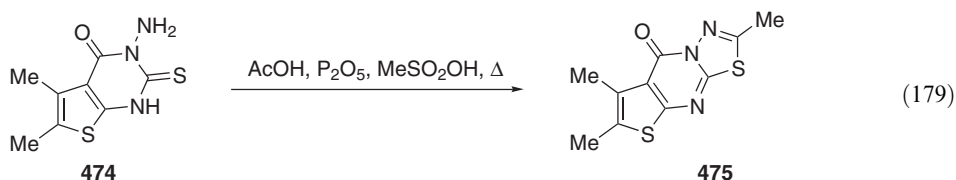


Scheme 26

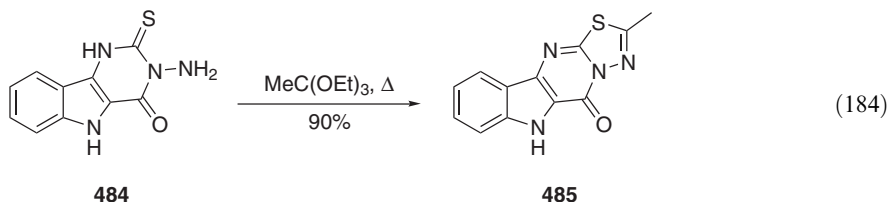
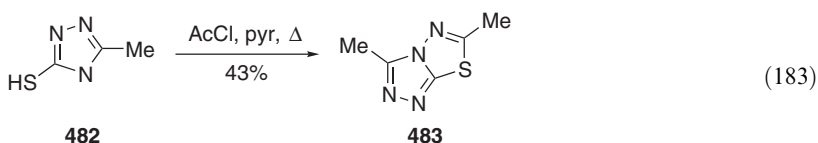
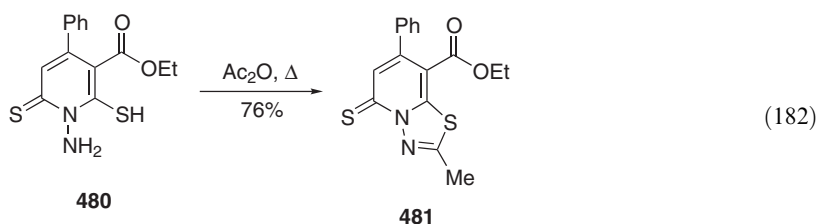
Thiosemicarbazide **470** and thiocarbazine-derived structures **472** undergo cyclocondensation with carboxylic acids under microwave irradiation to yield the corresponding thiadiazole **471** or fused compounds **473**. Yields in the microwave-assisted procedures are generally high and reaction times short (Equations (177) and (178)) <1996JCR(S)254, 2000SC3031>.



The cyclocondensation of thiocarbazine-like structures with carboxylic acids can also be induced by heating with dehydrating agents such as phosphorus pentoxide <1995MI605, 1999JCR(M)460, 2000PHA737, 2002MI1323>, phosphoryl chloride <1995IJC(B)707, 1997PHA844, 1997JHC1255, 1998MI48, 2000PHA500, 2001IJC(B)828, 2002MI253> (Equations (179) and (180)), or mineral acids such as sulfuric acid <1998MI1609, 2000MI199> (Equation (181)). The yields in those procedures are generally moderate but can approach 90% in some cases.

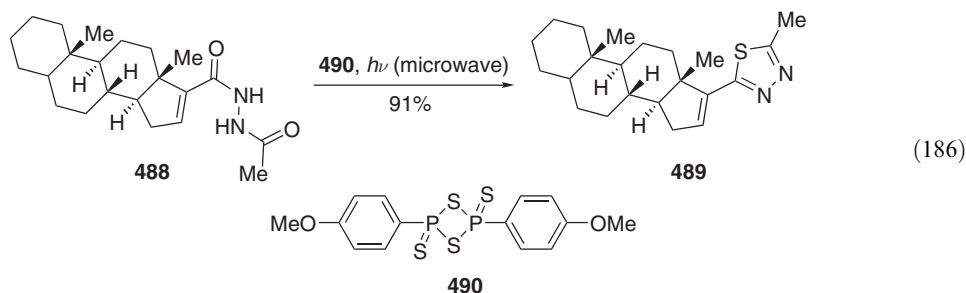
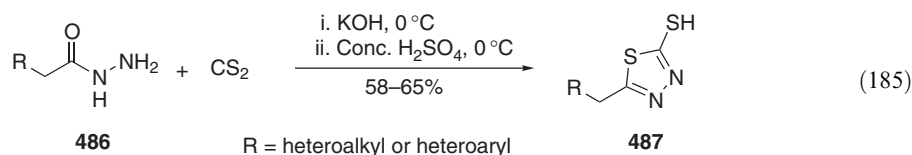


Apart from carboxylic acids, acid anhydrides (Equation (182)) <1995MI721, 1996JPR516, 1998MI48, 1998CAR9, 1999MI557>, acid chlorides in conjunction with a base (Equation (183)) <2000MI211> as well as orthoesters (Equation (184)) <1997MI973> have been employed in the cyclocondensation process forming nitrogen and sulfur heterocycles. Intramolecular cyclocondensations of thiosemicarbazides have been carried out in refluxing aqueous ferric ammonium sulfate <2003JMC427> or carbon disulfide in *N,N*-dimethyl formamide <2001IJC(B)636>.

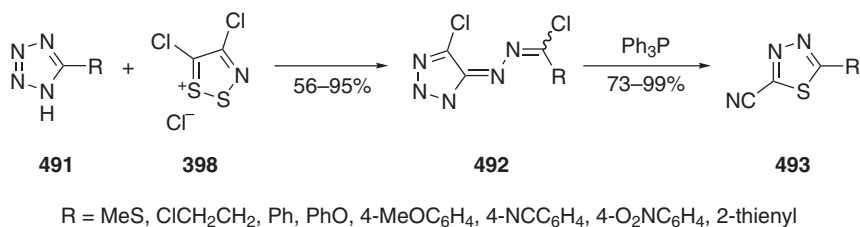


5.21.4.3.2 Other methods

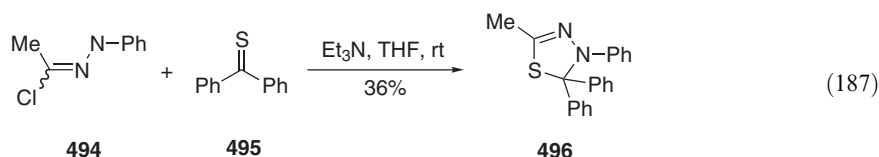
The treatment of monoacylhydrazines **486** with carbon disulfide in cold aqueous potassium hydroxide, followed by sulfuric acid, leads to thiadiazoles **487** in moderate yields (Equation (185)) <1997MI291, 1999IJC(B)993>. Diacylhydrazines **488** cyclize to thiadiazoles **489** when irradiated with microwave energy in the presence of Lawesson's reagent **490** (Equation (186)) <2002MI581> or heated with phosphorus pentasulfide <2001MI913>.



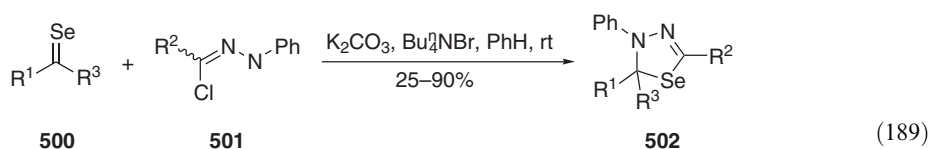
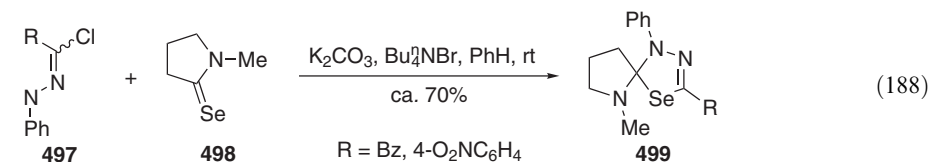
Dihydrothiazoles **493** are obtained in good yields from tetrazoles **491** via structures **492**, by reaction with Appel salt **398** followed by triphenylphosphine (Scheme 27) <2000TL9407, 2002JCS(P1)1543>. The reaction of hydrazonoyl chloride **494** with thioketone **495** also provides dihydrothiadiazole **496**, although in a much lower yield (Equation (187)) <1998AJC499>.



Scheme 27



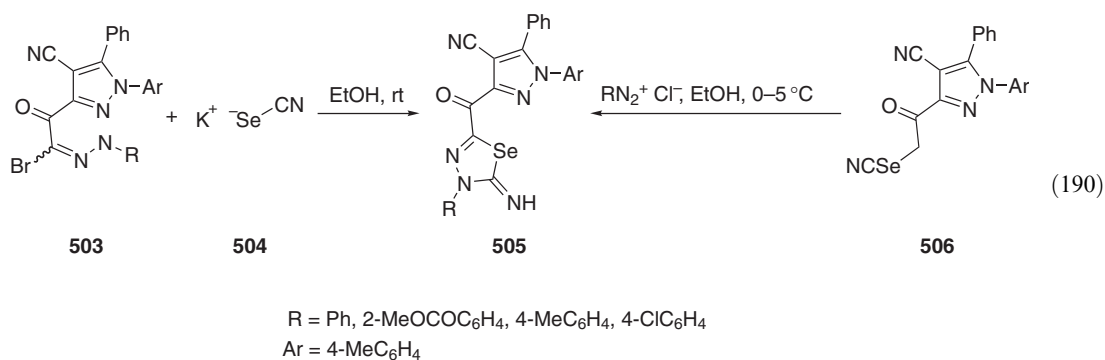
Hydrazonoyl halides (**497**, **501**, and **503**) are commonly used precursors to selenohydrazonic and -amidrazonic structures (**499**, **502**, and **505**). *N*-Methylpyrrolidine-2-selone **498** (Equation (188)), selenoamides **500** (Equation (189)) <1998MI331>, and selenocyanate salts **504** (Equation (190)) react with hydrazonoyl halides to yield selenohydrazonic or -amidrazonic derivatives. Compounds **505** are also available from selenocyanates **506** and aryldiazonium salts (Equation (190)) <1996MI493, 1997MI43, 1997MI37, 2001HAC468>.



R¹ = Me, Bu^tCH₂, Bn, 4-MeC₆H₄CH₂, 4-MeOC₆H₄CH₂, 4-ClC₆H₄CH₂

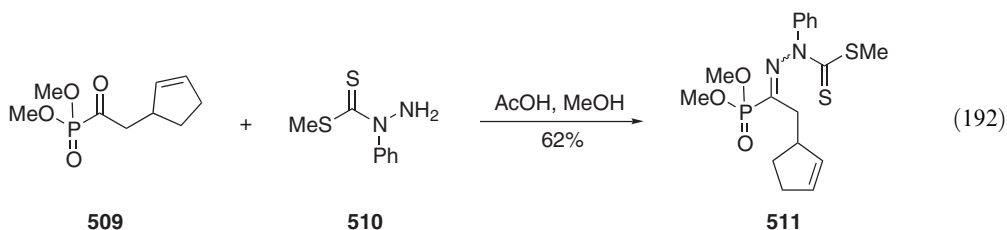
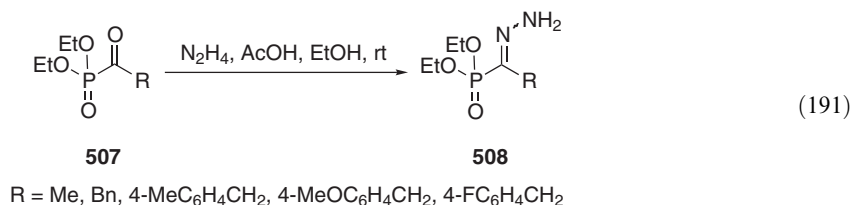
R² = MeCO, EtOCO, Ph, 4-O₂NC₆H₄

R³ = Et₂N, *N*-morpholinyl, *N*-piperidinyl

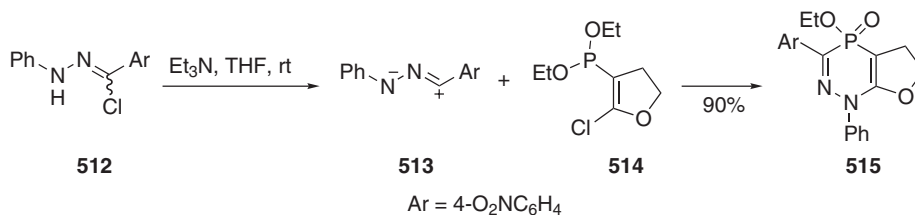


5.21.4.4 Hydrazoneic Derivatives of Phosphorus and Silicon

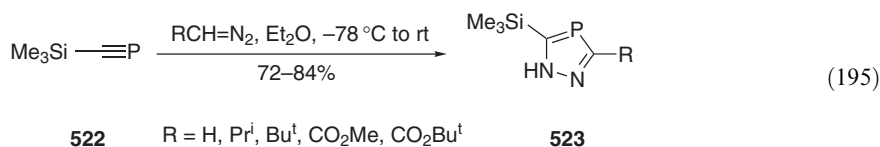
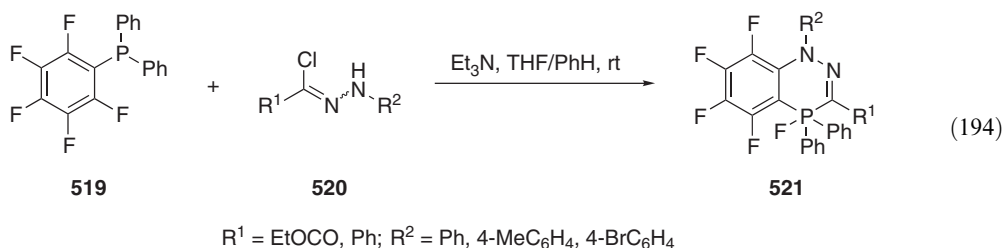
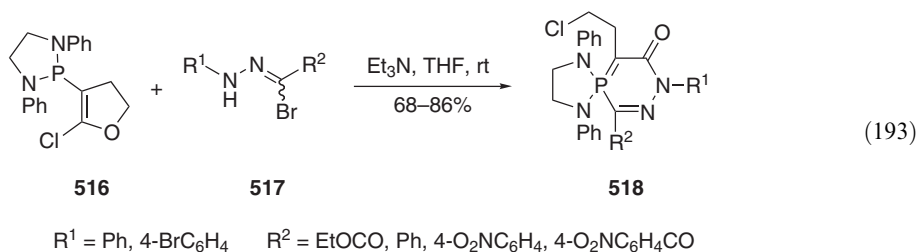
A simple route to hydrazoneic derivatives of phosphorus is by condensation of hydrazines with acylphosphoranes (**507** and **509**). Both unsubstituted <1995MI115, 1999AG(E)2201, 1999MI85> and substituted **510** <1997TL2463> hydrazine derivatives have been employed in the synthesis of hydrazoneoyl derivatives (**508** and **511**) (Equations (191) and (192)).



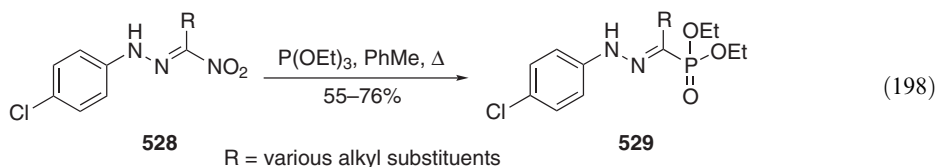
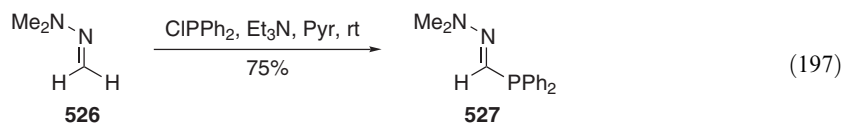
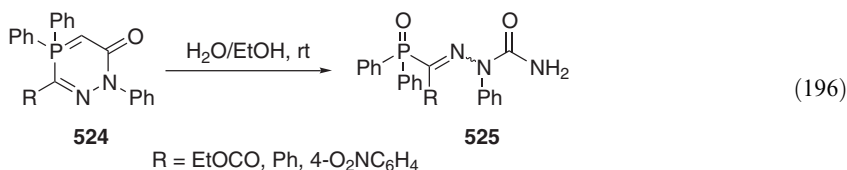
Another common method for the generation of hydrazoneic phosphorus derivatives **515** is by the treatment of hydrazoneoyl halides (**512**, **517**, and **520**) with a base and the subsequent cyclization of intermediate **513** with a suitable halovinylphosphine derivative **514** (Scheme 28) <1997ZOB1923, 1998ZOB1398, 1999ZOB767>. Diazaphosphinine derivative **515** is formed with loss of ethyl chloride and oxidation of the phosphorus center. If the phosphine does not bear substituents likely to fragment as a result of the oxidation of the phosphorus center (**516** and **519**), the halide anion may induce a ring cleavage to yield **518** (Equation (193)) <2002IZV960>, or halide transfer to phosphorus may occur by S_NAr mechanism to yield **521** (Equation (194)) <2001ZOB508>. Diazaphospholes **523** are also available in good yields via cycloaddition of phosphane **522** to diazo compounds (Equation (195)) <1997BSB455, 1998S1305>.



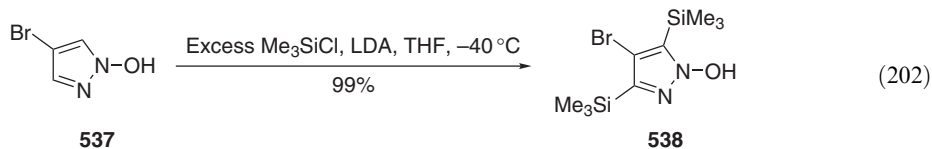
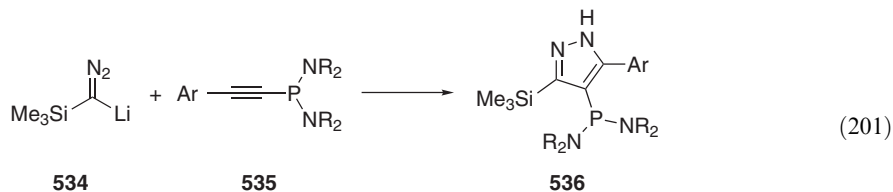
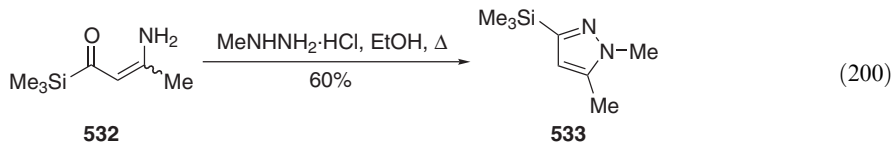
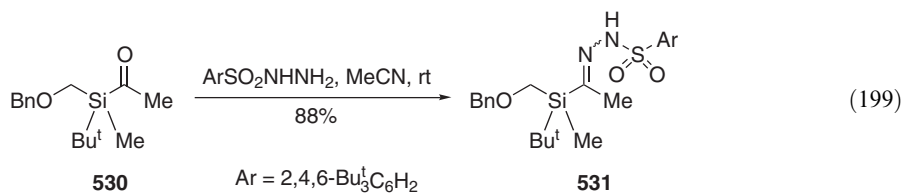
Scheme 28



Hydrazone phosphorus derivatives (**525**, **527**, and **529**) have also been obtained by hydrolysis of triazaphosphinine derivatives **524** (Equation (196)) <1996ZOB572, 1996ZOB1463>, by substitution from hydrazine **526** and chlorodiphenylphosphine (Equation (197)) <1998IZV1797>, or by Arbuzov-type reaction of 1-nitroaldehyde hydrazones **528** with trialkyl phosphite (Equation (198)) <2002TL2037>.



A simple route to hydrazone silicon derivatives is by condensation of hydrazines with carbonyl compounds (**530** and **532**). Both linear **531** <1996CSC1045, 2000HCA1611> and cyclic **533** <2000TL9791, 2001TL8981> hydrazone silicon derivatives are accessible in this manner (Equations (199) and (200)). Silyl diazo compounds **534** undergo cycloaddition with alkenes <1997T7045, 1999EJO2751> and alkynes **535** (Equation (201)) <1999TL883> to yield the corresponding hydrazone silicon derivatives **536**. Treatment of compounds **537** with lithium diisopropylamide and excess trimethylchlorosilane leads to the formation of silicon derivatives **538** (Equation (202)) <1999JOC5366>.

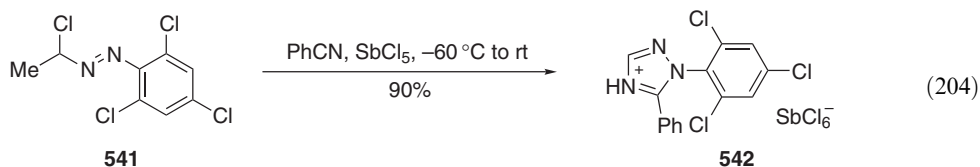
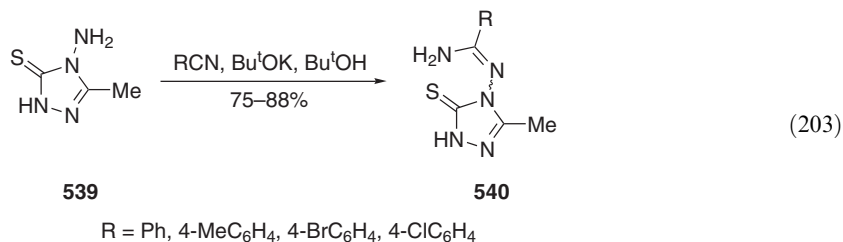


5.21.4.5 Hydrazonamides and Related Structures

Several reviews have been published on this type of compound. The reader is referred to COFGT (1995) for more information. Numerous cyclic structures such as triazoles and tetrazoles formally contain the hydrazonamidic structural element. In view of their importance, they will be included here alongside their acyclic counterparts.

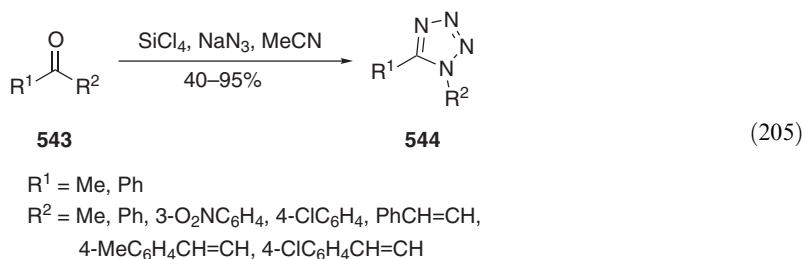
5.21.4.5.1 From nitriles

Nucleophilic attack of *N*-mono- or disubstituted hydrazines and derived structures **539** on nitriles results in the formation of hydrazonamides **540** (Equation (203)) <2002MI2923>. The cycloaddition of nitriles to diazenes **541** in the presence of antimony(V) chloride at low temperatures affords triazoles **542** (Equation (204)) <1996S274>, while tetrazoles are obtained from the cycloaddition of nitriles to azides <1996JHC1307>.



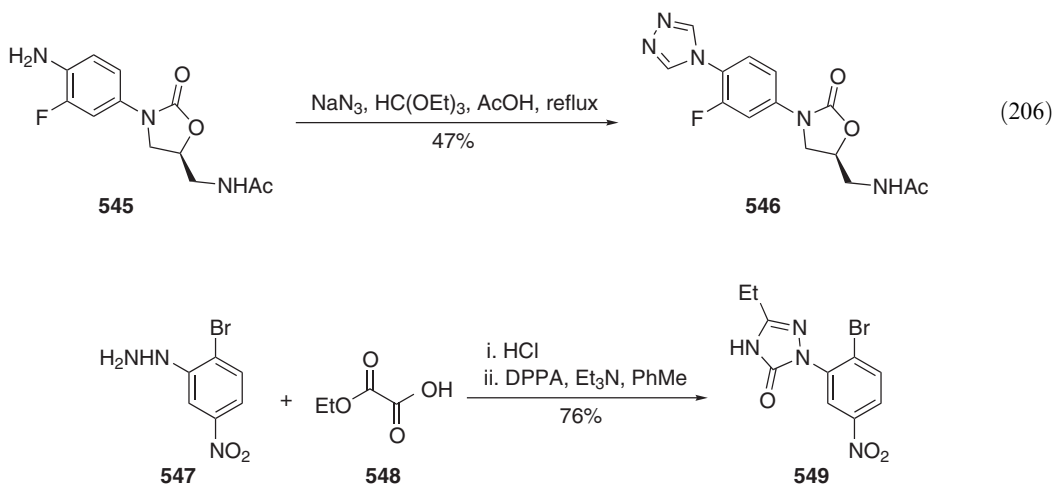
5.21.4.5.2 From carbonyl compounds

Saturated and α,β -unsaturated ketones **543** react with triazidochlorosilane to form tetrazoles **544** in modest-to-excellent yields. Triazidochlorosilane is conveniently prepared from tetrachlorosilane and sodium azide *in situ* (Equation (205)) <1995TL7337>.



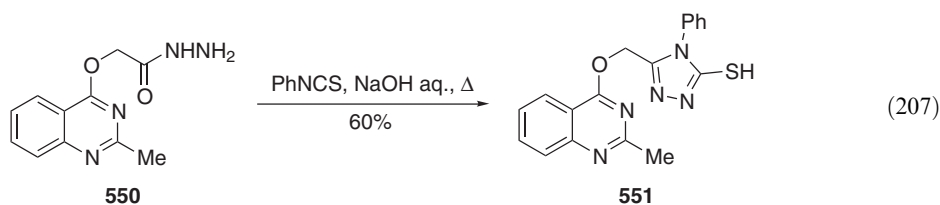
5.21.4.5.3 From amines and hydrazine derivatives

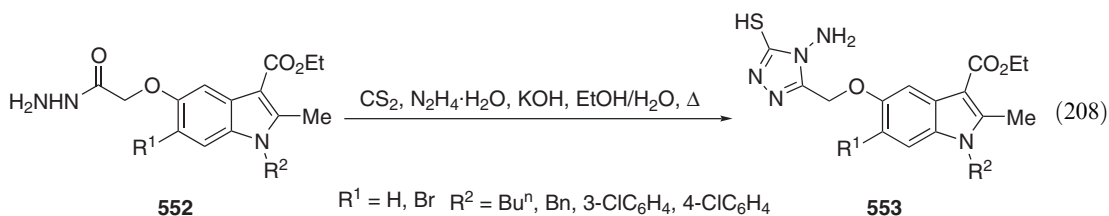
The reaction of amine **545** with sodium azide and triethoxymethane in refluxing acetic acid yields tetrazole **546** (Equation (206)) <2000JMC953>. Triazolone **549** was obtained when (2-bromo-5-nitrophenyl)hydrazine **547** was treated with monoethyl oxalate **548** and diphenyl phosphorazidate (DPPA, $\text{O}=\text{P}(\text{N}_3)(\text{OPh})_2$) (Scheme 29) <1995JMC3741>.



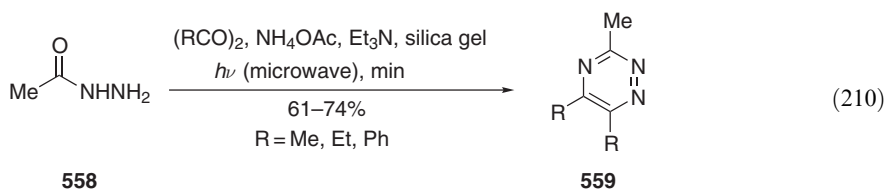
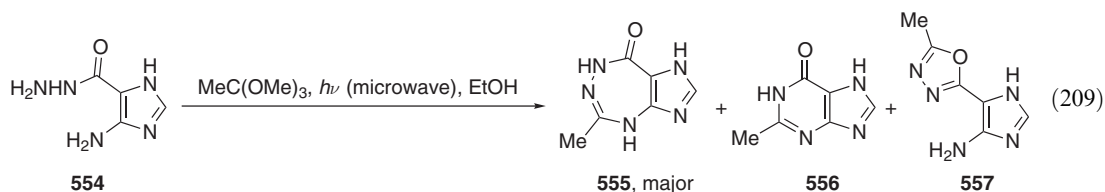
Scheme 29

Hydrazides **550** undergo a cyclocondensation reaction with isothiocyanates to yield triazole thiols **551** (Equation (207)) <1995IJC(B)537, 1998MI1609, 1998JCR(M)2056, 1999MI800, 2000SC3423, 2000MI11>. Isothiocyanate salts may be used in place of organic isothiocyanates. Triazole thiols **553** are also available from acylhydrazines **552** by treatment with carbon disulfide and hydrazine (Equation (208)) <1995RRC475, 2001IJC(B)640>, from dithiocarbamic acid salts and hydrazine <1995RRC475, 1995IJC(B)1059, 1996IJC(B)688, 1996MI659, 1996IJC(B)980, 1996MI31, 1998IJC(B)461, 1998IJC(B)127, 2000AF55, 2000MI541, 2001SC81, 2002IJC(B)1953> or monoacylhydrazines <1999JIC461, 2000JIC302, 2001JPP267, 2002AF572, 2002JIC381>.



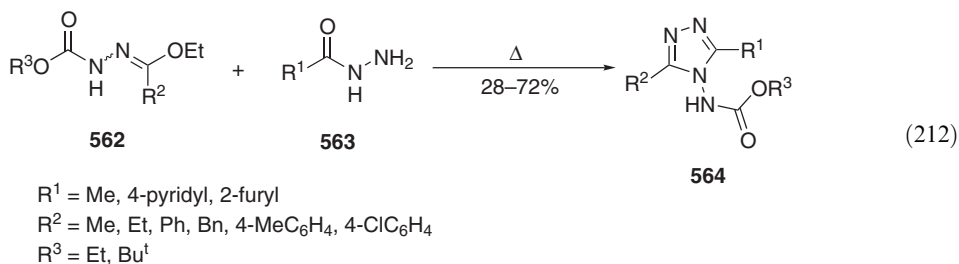
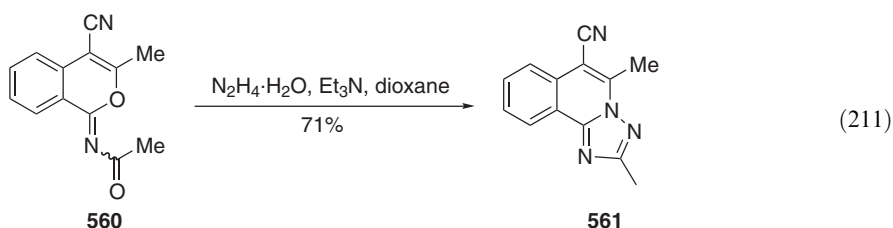


Cyclocondensation of orthoesters with various acylhydrazines **554** provides “triazine” <1995CCC709> or triazepine-derivatives **555** (Equation (209)) <2002SL519>. Although several by-products (**556** and **557**) are formed in the latter case, triazepinones **555** are the major product. A procedure for the facile one-pot preparation of [1,2,4]-triazines **559** from monoacylhydrazines **558** and 1,2-dicarbonyl compounds has been reported (Equation (210)) <2002SC1899>.



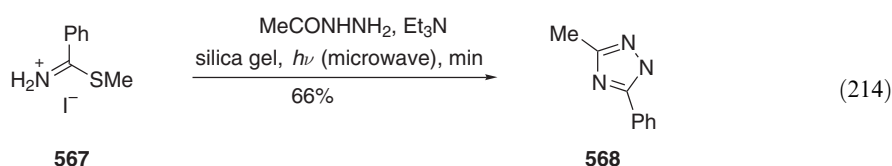
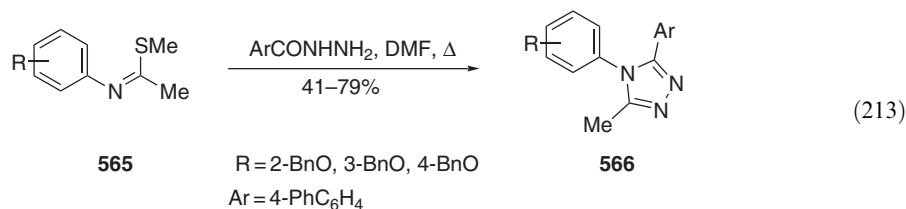
5.21.4.5.4 From imidic esters

Acylimidic esters **560** are generally more reactive than nitriles and react with hydrazine to form the corresponding hydrazone-amide-related compounds **561** (Equation (211)) <1996AJC485>. The reaction of acylhydrazines **563** with imidic esters **562** provides amidrazonamide-derived structures **564** (Equation (212)) <1996PJC1114, 1996JHC1765>.



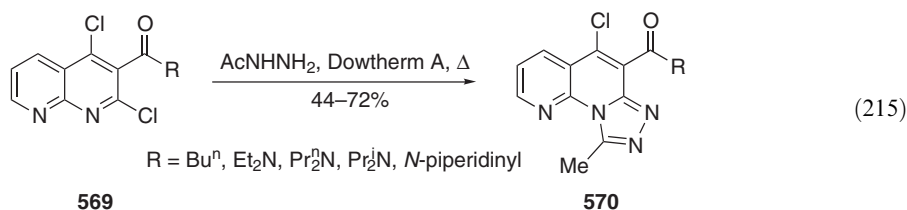
5.21.4.5.5 From thioimidic esters

Heating of aromatic acylhydrazines with thioimidic esters **565** in solvents such as *n*-butanol or *N,N*-dimethyl formamide yields cyclic amidrazonamides (triazoles) **566** (Equation (213)) <1995SC1027, 1995SC3287, 1997JHC921, 1998JMC1299, 2002JMC2589>. The reaction time for the formation of triazoles **568** from hydrazines and thioimidic esters or their salts **567** is reduced to minutes when the substrates are adsorbed on silica gel and irradiated with microwave energy (Equation (214)) <2003SC113>.



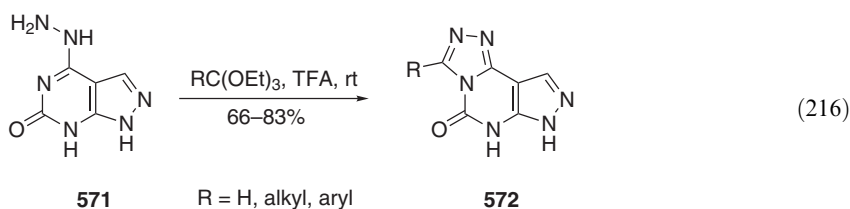
5.21.4.5.6 From imidoyl halides

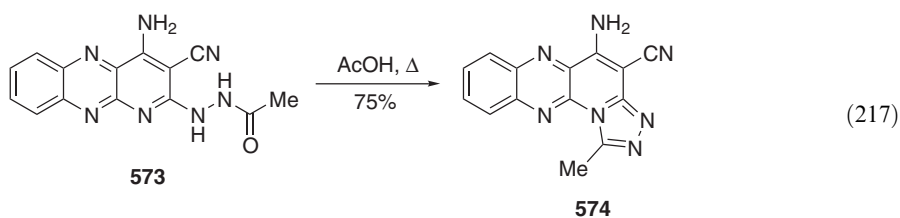
Substrates containing the imidoyl halide subunit, e.g., chloronaphthyridine **569**, undergo cyclocondensation with acylhydrazines to yield triazoles **570** (Equation (215)) <1997MI49>.



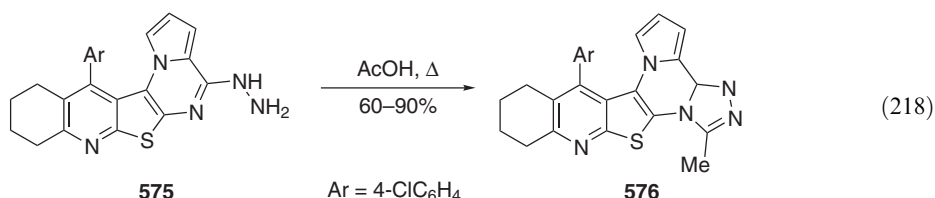
5.21.4.5.7 From amidines

A common route to triazoles **572** is by the reaction of pyrimidine-derivatives **571** with orthoesters (Equation (216)) in the presence of hydrochloric acid <1997JMC2053, 2002JHC213>, formic or acetic acid <1995JMC3524>, trifluoroacetic or nitric acid <1998BMCL3153, 1999JCS(P1)3117, 1999CC1461, 1999CJC216, 1999JHC1119, 1999CC1461, 2000JCS(P1)33, 2001JHC973, 2002H631>, or diethyl azodicarboxylate <1999CC1461, 2000JCS(P1)33>. The intramolecular cyclization of compound **573** to yield fused triazole-derivative **574** has been reported (Equation (217)) <2000PHA896, 2001ZN(B)826>.

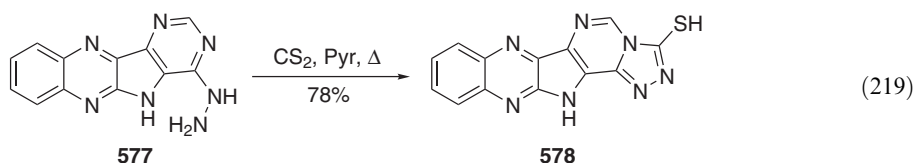




The conversion of structures **575** to yield cyclic amidrazone derivatives **576** is also possible using carboxylic acids under elevated temperatures (Equation (218)). Numerous examples of similar transformations can be found in the literature: <1995MI143, 1995JIC181, 1996SC3733, 1996IJC(B)106, 1996IJC(B)915, 1997PHA189, 1997JIC21, 1997IJC(B)566, 1999JHC1327, 2000MI1, 2000MI835, 2000MI171, 2001ZN(B)826, 2001SC2447, 2001JHC973, 2002PHA442, 2003JCR(M)236>. Apart from carboxylic acids, acid anhydrides <1995JCR(S)322, 1997JIC21, 1997PHA436, 1997JCR(M)2771, 1998M523, 1999KGS564, 1999JHC1327, 1999ZN(B)788, 2000MI835, 2000JHC1521, 2000MI149, 2000MI171, 2001SC2447, 2003JCR(M)236>, and acid chlorides <1995JCR(S)100, 1997JCR(M)2039, 2001MI519> have been successfully employed in similar cyclocondensation reactions. Examples of intramolecular cyclocondensations employing phosphoryl chloride <1996T1399, 1998AP163, 1999IJC(B)18>, lead(IV) acetate <1999S655>, or Dowtherm[®] <1999JHC1195, 2002JHC885> have been published. Yields were consistently between 60% and 90%.

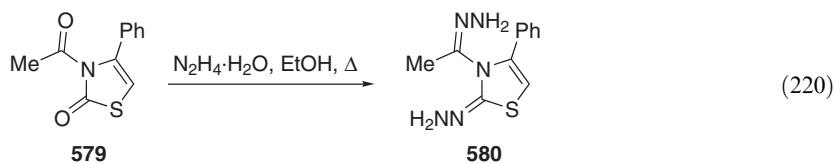


Similarly, triazole thiols **578** are available from compounds **577** by treatment with carbon disulfide in the presence of a base such as pyridine (heat) or sodium hydroxide (in ethanol) (Equation (219)) <1996M1263, 1997PHA500, 1997PHA436, 1999JHC1119, 2000MI1, 2000JHC1521>.

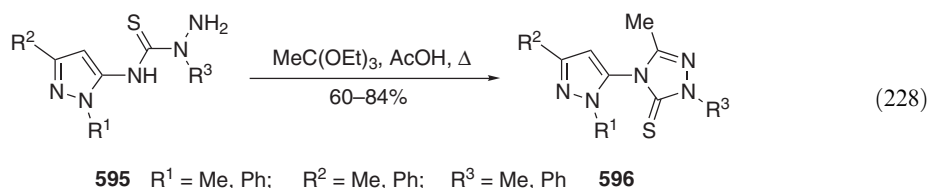
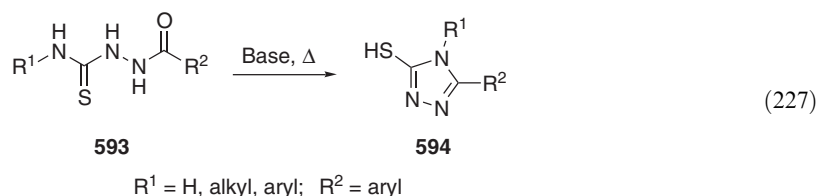


5.21.4.5.8 From amides and related structures

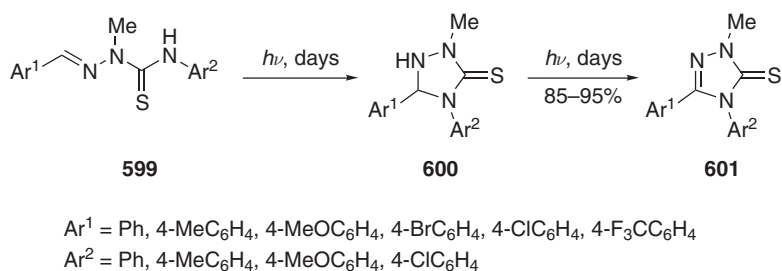
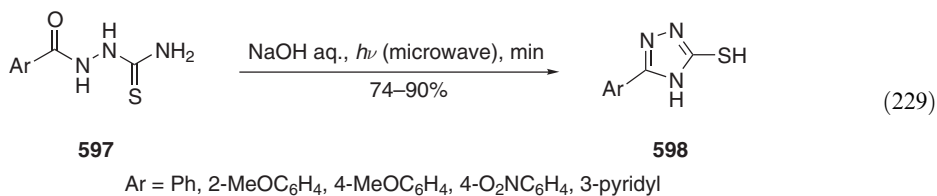
Hydrazonamides **580** are prepared by simple condensation of amides **579** with hydrazine (Equation (220)) <1999ZN(B)923>. Triazole thiols **582** are obtained by heating dithiocarbamic acids **581** with hydrazine (Equation (221)) <2001AF569, 2002IJC(B)1257>. Albeit in low yields, cyclic amidrazonamides (tetrazoles) **584** are available from amides **583** by treatment with azides in the presence of trifluoromethanesulfonic anhydride (Equation (222)) <1996BMCL1015>. Higher yields are obtained when the reaction is performed in the presence of silicon tetrachloride in acetonitrile (Equation (223)) <2002ZOR1422>.



thiols **594** thus formed are obtained in medium-to-high yields. Triazole thiols or thiones **596** are also obtained from thiocarbazides and semithiocarbazides by reaction with orthoesters in the presence of acid (Equation (228)) <1997BMCL1607, 1998JHC29>, acid anhydrides or acid halides <1997IJC(B)943, 1997BMCL1607, 1997JHC1255, 1998JST61, 1998MI574, 1998MI467>.



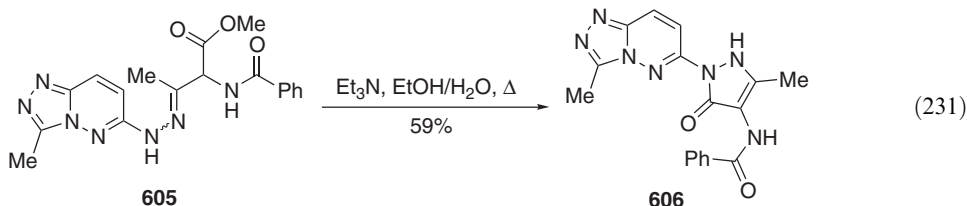
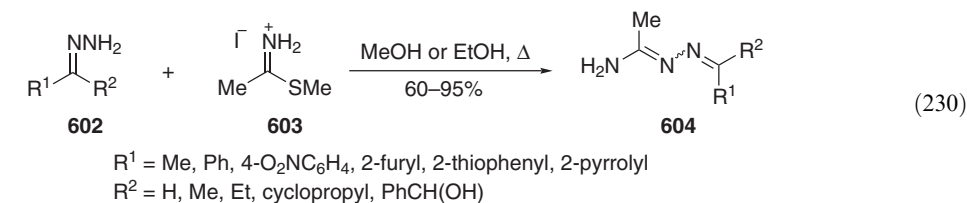
In the generation of triazole thiols from thiocarbazide-related structures in the presence of a base, reaction times are shortened dramatically by irradiation of the reaction mixture with microwave energy. Thus, 5-aryl-4*H*-[1,2,4]-triazole-3-thiols **598** have been obtained from thiosemicarbazides **597** by reaction with aqueous sodium hydroxide under microwave irradiation (Equation (229)) <2001SC2841>. The cyclization of thiosemicarbazides **599**, via the stable intermediates **600**, into dihydrothiazole thiones **601** is also induced by UV irradiation and proceeds in high yields, although reaction times tend to be long (Scheme 30) <2000T999>.



Scheme 30

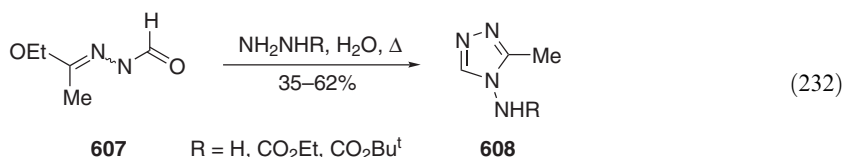
5.21.4.5.11 From hydrazones

Hydrazones **602** react with thioacetimidates **603** to yield amidrazones **604** in good-to-excellent yields (Equation (230)) <1996JHC1877, 1997JHC71, 1999JHC1235, 2000JCR(S)226>. The intramolecular cyclocondensation of hydrazone **605** to yield compound **606** is induced by heating in the presence of a base (Equation (231)) <1998JHC1281>. Similar condensations have been described which employed iron(III) chloride in ethanol <1997IJC(B)288, 2001ZN(B)826>.



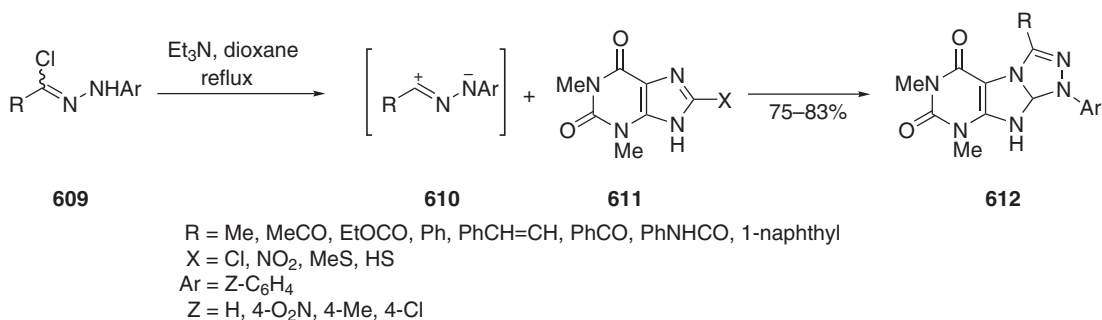
5.21.4.5.12 From hydrazone esters and thioesters

Triazoles **608** are formed in the reaction of hydrazone esters **607** with either hydrazine or hydrazine carboxylic acid esters (Equation (232)) <1998JHC377>.



5.21.4.5.13 From hydrazoneyl halides

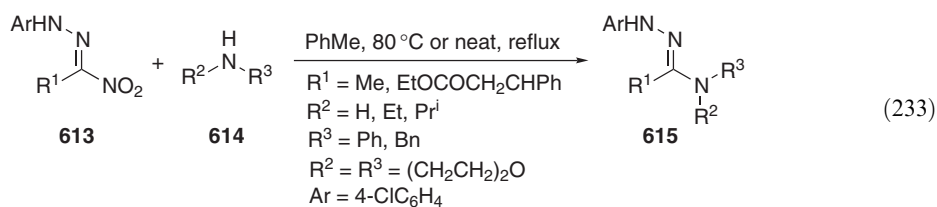
The deprotonation of hydrazoneyl chlorides **609** and subsequent reaction of the intermediate **610** with purines **611** leads to hydrazoneamide derivatives **612** in high yields (Scheme 31) <2001JOC4055>. Besides purines, triazinones have also been employed as substrates for cyclocondensation with hydrazoneyl halides <2000JPR96, 2001M959, 2002JHC45>.



Scheme 31

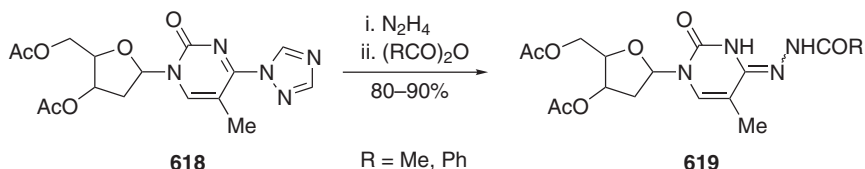
5.21.4.5.14 From 1-nitroaldehyde hydrazones

1-Nitroaldehyde hydrazones **613** react with amines **614** to yield hydrazoneamides **615**. When toluene is used as the solvent, yields remain modest (50–63%) and triazoles are formed as by-products. The yield of hydrazoneamides, however, rises to nearly quantitative when the reaction is performed neat (Equation (233)) <2002TL8925>.

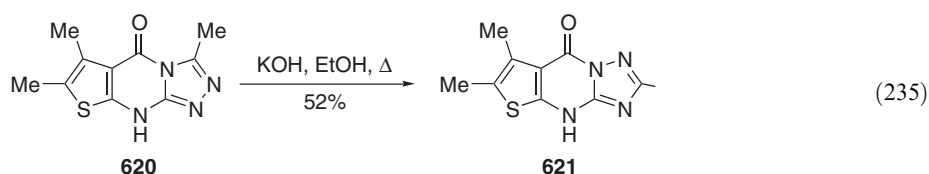


5.21.4.5.15 From heterocyclic precursors

The reaction of oxadiazoles **616** with nitrogen nucleophiles affords triazoles **617** (Equation (234)). The nucleophile may be an amine ($\text{R} = \text{alkyl, heteroaryl}$) <2000MI67, 2000SC3031>, a hydrazine ($\text{R} = \text{NR}^1_2$), or hydroxylamine ($\text{R} = \text{OH}$) <1995IJC(B)1007, 1996MI629, 1996IJC(B)106, 1996M549, 1999IJC(B)237>. Triazoles **618** are ring-opened to yield hydrazonamides **619** by treatment with hydrazine followed by acid anhydride (Scheme 32) <1999JCS(P1)1339>. Amidrazonic structures **620** undergo a Dimroth rearrangement to **621** when heated in alkaline solution (Equation (235)) <2001ZN(B)826>.

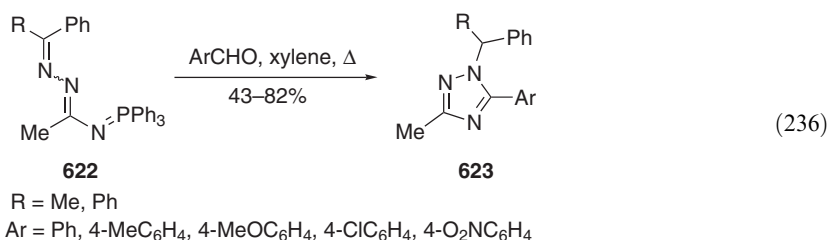


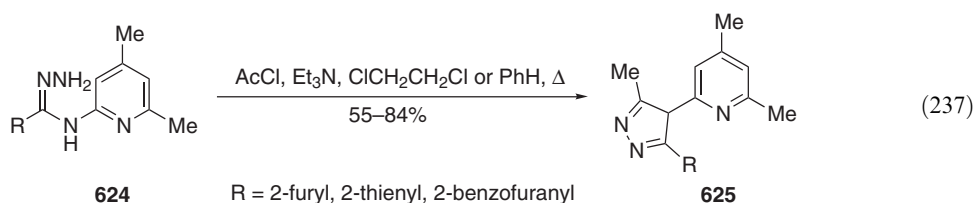
Scheme 32



5.21.4.5.16 From hydrazonamides

Triazoles **623** are available from triphenylphosphanylidene hydrazones **622** via a condensation reaction (Equation (236)) <1995TL2815, 1996JHC1877, 1997JHC71, 2002JHC845> or via cyclocondensation from the corresponding hydrazonamide derivatives. Cyclocondensation reagents include acid chlorides (Equation (237)) <1996MI431, 1997AF635, 2000JCR(S)164>, orthoesters <1995CCCC709>, and aldehydes <1996JPS326>.





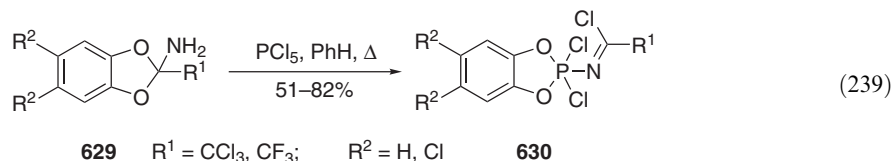
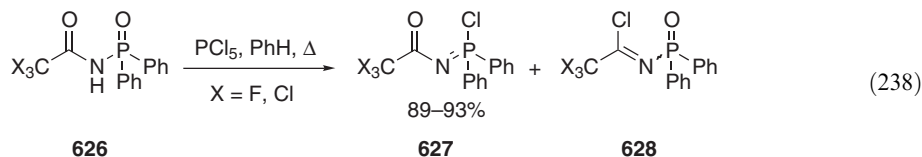
5.21.4.5.17 Other methods

Hydrazonamide-related structures have been obtained from carbodiimides, acylaminomalonates, and by reduction of nitrazones. The reader is referred to COFGT (1995) for more information on those reactions.

5.21.5 IMIDOYL DERIVATIVES WITH AN N-PHOSPHORUS BOND

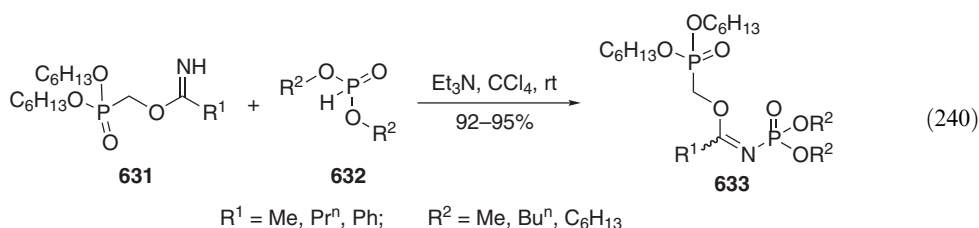
5.21.5.1 Imidophosphorane Chlorides

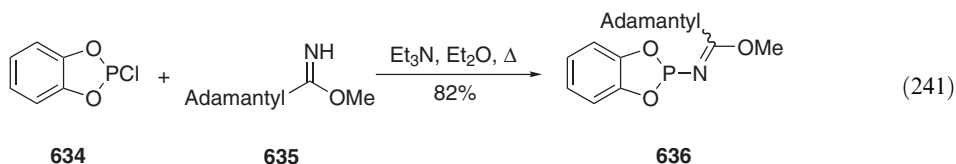
Phosphoryltrihaloiminoacetic acid chlorides **628** are obtained as side products in the formation of chlorophosphinimines **627** from phosphoramides **626** and phosphorus pentachloride (Equation (238)) <1997ZOB160>. Greater yields of phosphoryltrihaloiminoacetic acid chlorides **630** are obtained from benzodioxoles **629** (Equation (239)) <1996ZOB1715>.



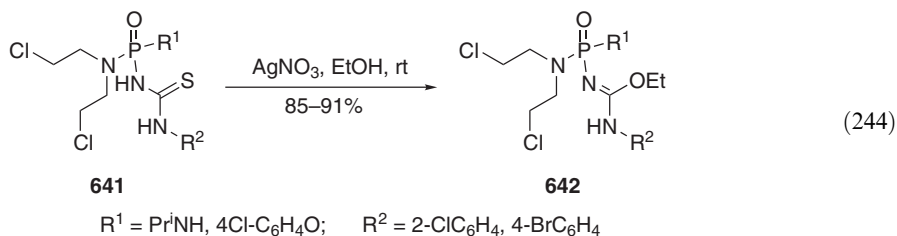
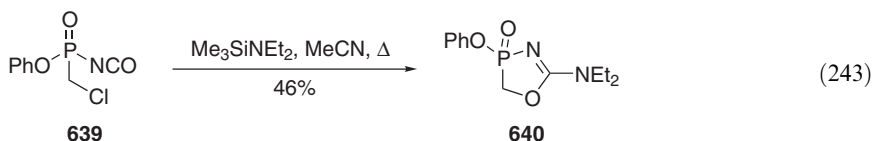
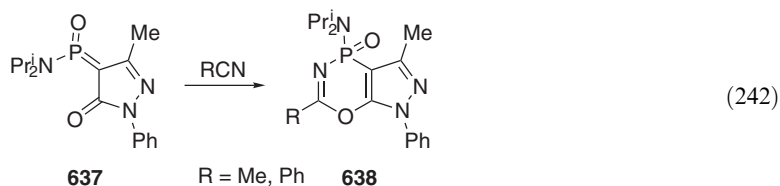
5.21.5.2 Imidophosphorane Esters

Some imidophosphorane esters **633** are obtained by the reaction of the corresponding phosphonic acid esters **632** with imidates **631** (Equation (240)) <1997ZOB168>. Chlorodioxaphosphole **634** reacts with imidate **635** under similar conditions to yield phospholimidic ester **636** (Equation (241)) <2000ZOB702>.



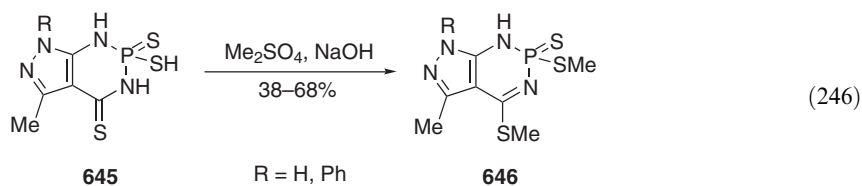
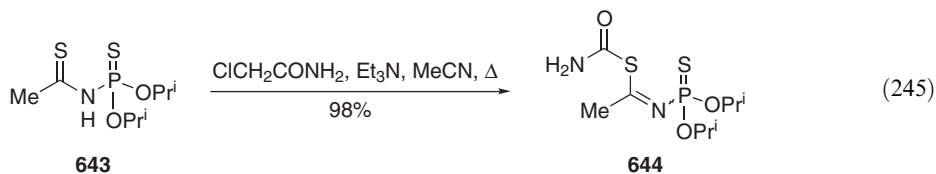


Phosphorus-containing heterocycles **638** are available by cycloaddition of nitriles with phosphoranes **637** (Equation (242)) <1996MI477>. Chloromethylphosphorylisonitrile oxide **639** undergoes substitution with diethylaminotrimethylsilane to yield [1,3,4]-oxazaphosphole **640** in modest yield (Equation (243)) <1996IZV1857, 1996ZOB360>. Compounds **642** have been generated from phosphorylthioureas **641** by reaction with silver nitrate (Equation (244)) <1998JCR(S)254>.



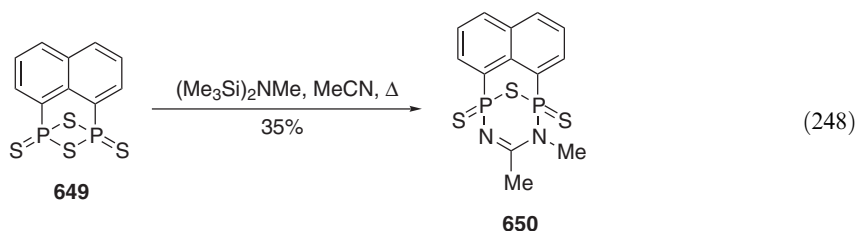
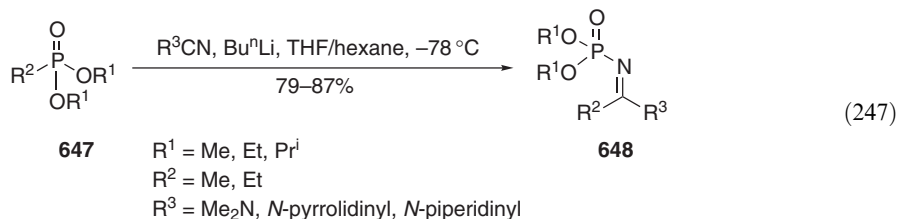
5.21.5.3 Imidophosphorane Thioesters

Imidophosphorane thioesters **644** are available from thiophosphorylthioamides **643** in near quantitative yields by reaction with chloroacetamide in the presence of a base (Equation (245)) <1998ZOB1100>. Cyclic structures **646** have been prepared from **645** by alkylation in the presence of a base (Equation (246)) <1998KFZ16, 2002IJC(B)1964>.



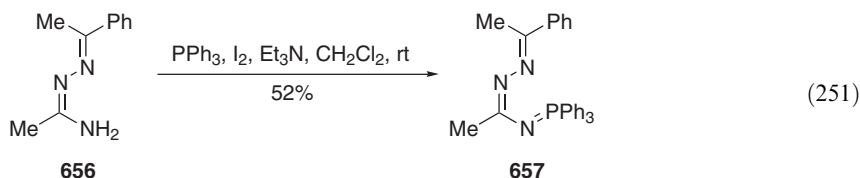
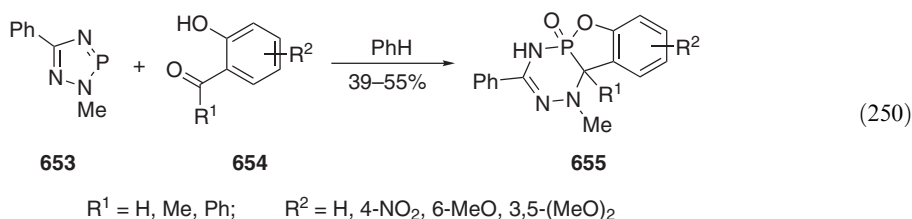
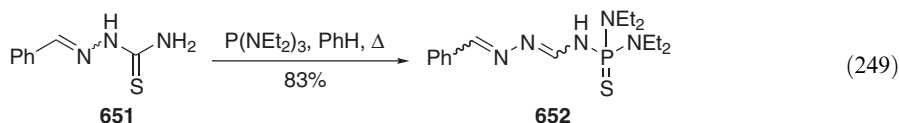
5.21.5.4 Imidophosphorane Amides

Imidophosphorane amides **648** are prepared in good yields from methylphosphonic acid esters **647** and amino-*N*-carbonitriles at low temperature (Equation (247)) <1998CC609>. Compound **650** is available from **649** by reaction with bis(trimethylsilyl)methylamine and acetonitrile (Equation (248)) <1999JCS(D)2231>.



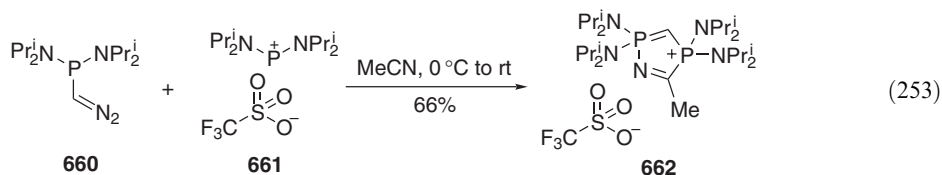
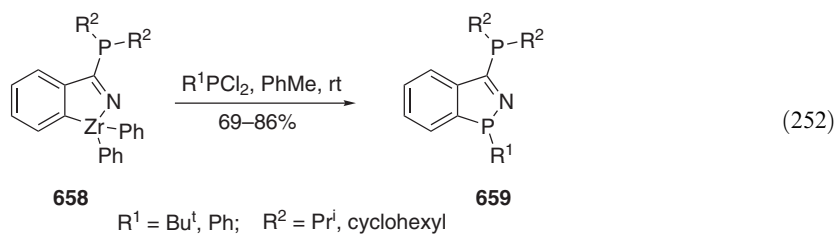
5.21.5.5 Phosphorane Derivates of Hydrazonamides

Hydrazonimidophosphoranes **652** can be prepared from hydrazonoyl derivatives **651** and phosphines (Equation (249)) <1997MI307>, while phosphaindenes **655** are available in modest yields from triazaphospholes **653** and various 2-carboxyphenols **654** (Equation (250)) <1996CB1493>. Amidrazone derivative **657** has been prepared by the reaction of triphenylphosphine with amidrazone **656** (Equation (251)) <2002JHC845>.



5.21.5.6 Other Imidoyl Derivatives of Phosphorus

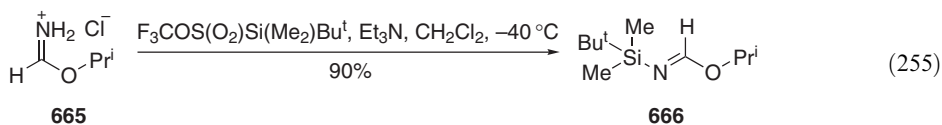
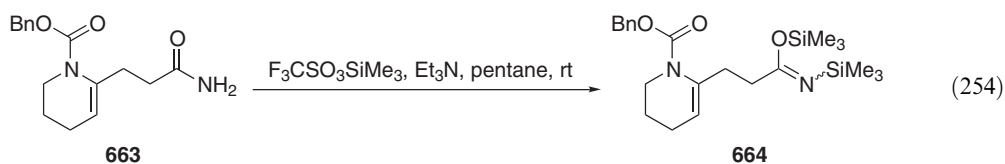
Phosphanyl-azaphosphole derivatives **659** have been obtained in good yields from compounds **658** by substitution with alkylidichlorophosphines (Equation (252)) <2000EJI417>, while the reaction of diazomethylphosphane **660** with phosphonium salt **661** afforded azadiphospholium salt **662** in good yield (Equation (253)) <2002JA2506>.



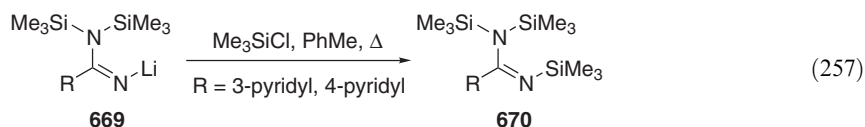
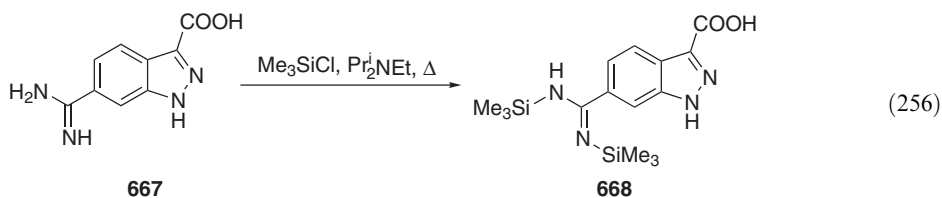
5.21.6 IMIDOYL DERIVATIVES WITH AN N-METALLOID BOND

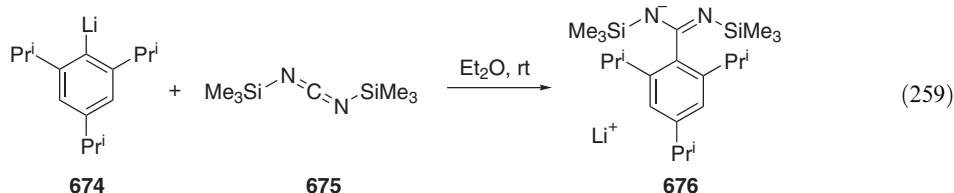
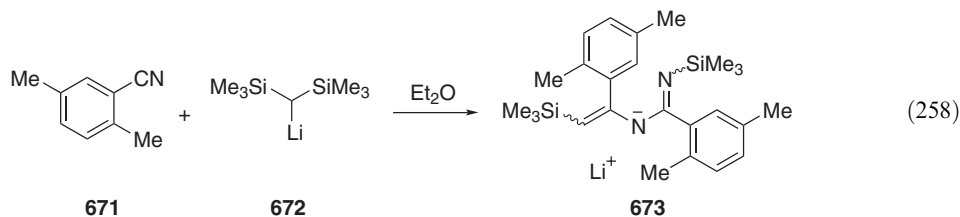
5.21.6.1 N-Silylimidoyl Derivatives

N-Silylimidoyl esters (**664** and **666**), are accessible from silyl triflates and amides **663** or imidic esters **665** (Equations (254) and (255)) <1998T12379, 1995T11021>.

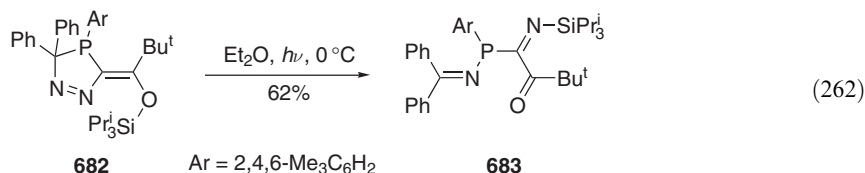
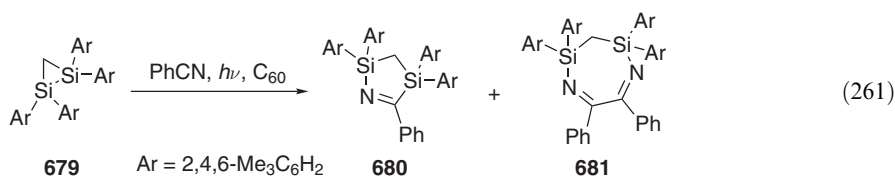
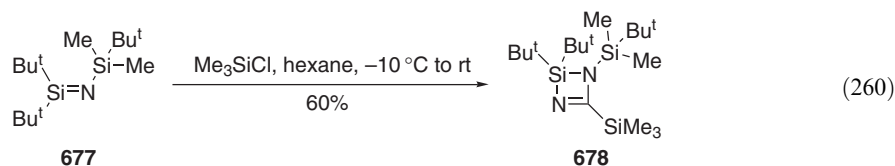


N-Silylimidoylamides (**668** and **670**) are obtained from amidines (**667** and **669**), and trimethylsilyl chloride in the presence of a base (Equations (256) and (257)) <1997JMC4308, 2000EJI1045>. Various N-silylimidoylamide salts (**673** and **676**), have been prepared, most commonly by the reaction of organolithium salts (**672** and **674**), with electrophiles such as nitrile **671** or carbodiimide **675** (Equations (258) and (259)) <1995JOM241, 1996JPR451, 1996T14607, 1997S696, 1998CJC85, 1998JCS(D)3113, 1999CC2269, 2000CC497, 2000JCS(D)967, 2001JCS(D)1692, 2002MI5305, 2002JHC1101, 2003JOM205, 2003JA2179>.



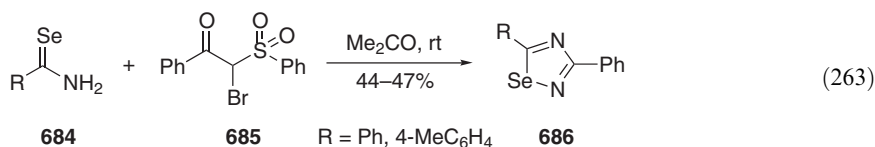


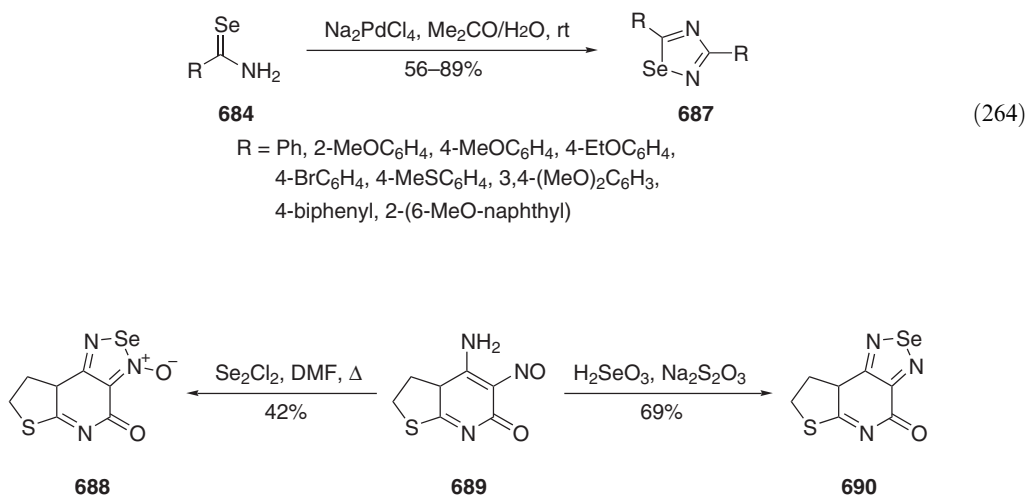
Several further, more unusual *N*-silylimidoyl derivatives have been described. Diazasilite **678** was obtained from compound **677** by reaction with trimethylsilyl cyanide (Equation (260)) <1998MI1>. Photolysis of disilirane **279** in the presence of benzonitrile and Buckminsterfullerene afforded a mixture of azadisilole **280** and diazadisilole **681** through cycloaddition of, respectively, one and two molecules of benzonitrile (Equation (261)) <2000JOM414, 2000CJC1469, 2001H777>. The photochemically induced generation of diazadisilene from a tetrazine has been reported <1996JOM355>. Photolysis of diazaphosphole derivative **682** afforded compound **683** in moderate yield (Equation (262)) <1998MI903>.



5.21.6.2 N-Selenylimidoyl Derivatives

Selenadiazoles **686** can be prepared from selenoamides **684** by reaction with ketosulfone **685** in acetone (Equation (263)) <1999JHC901>. Better yields however are achieved in the condensation/dimerization of selenoamides **684** induced by sodium tetrachloroplatinate(II) (Equation (264)) <2002JOM274>. 1,2-Nitroso amines **689** cyclize to selenadiazoles when reacted with selenium reagents: selenous acid in the presence of thiosulfate yields selenadiazoles **690** whilst selenadiazol-*N*-oxides **688** are obtained from selenium monochloride (Scheme 33) <1998KGS1130>.

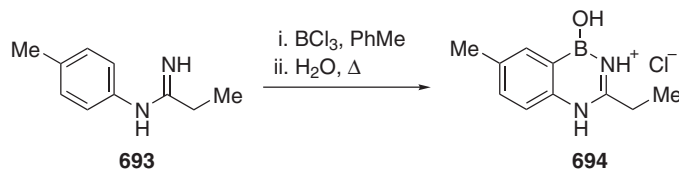
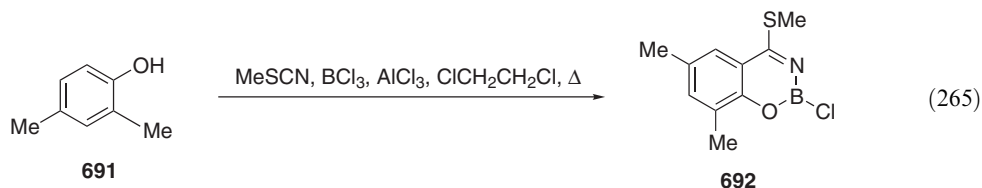




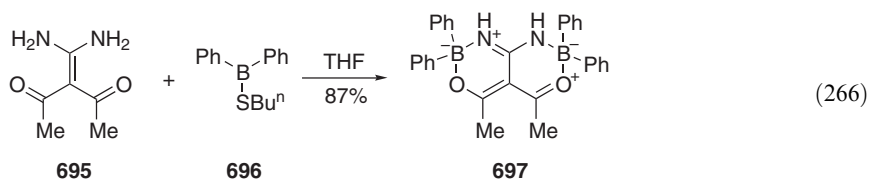
Scheme 33

5.21.6.3 N-Borylimidoyl Derivatives

Phenol **691** reacts with methyl thiocyanate in the presence of boron trichloride and aluminum(III) chloride to yield oxazaborinine **692** (Equation (265)) <2002HCA3773>, while diazaborinine derivatives **694** are easily synthesized from amidines **693** (made *in situ* from nitrile and amine in the presence of aluminum trichloride) and boron trichloride (Scheme 34) <2002TL3255>. Zwitterionic structure **697** has been obtained from borane **696** and 3-diaminomethylene pentane-2,4-dione **695** (Equation (266)) <1996IZV2733>.



Scheme 34



REFERENCES

- 1994ZN(B)233 G. Knitter, U. Behrens, E. Lork, R. Mews, *Z. Naturforsch. B* **1994**, 49, 233–237.
- 1995AJC2041 J. E. Rowe, D. A. Papanelopoulous, *Aust. J. Chem.* **1995**, 48, 2041–2046.
- 1995AP247 K. Goerlitzer, C. Wilpert, H. Ruebsamen-Waigmann, H. Suhartono, L. Wang, A. Immelmann, *Arch. Pharm. (Weinheim Ger.)* **1995**, 328, 247–256.
- 1995AP505 P. Froberg, C. Kupfer, P. Stenger, U. Baumeister, P. Nuhn, *Arch. Pharm. (Weinheim Ger.)* **1995**, 328, 505–516.
- 1995CAR257 H. Streicher, L. Latxague, T. Wiemann, P. Rollin, J. Thiem, *Carbohydr. Res.* **1995**, 278, 257–270.
- 1995CAR321 B. Joseph, P. Rollin, *Carbohydr. Res.* **1995**, 266, 321–326.
- 1995CC237 M. Tiecco, L. Testaferri, M. Tingoli, F. Marini, *J. Chem. Soc. Chem. Commun.* **1995**, 2, 237–238.
- 1995CCC709 V. Bobosik, A. Krustosikova, M. Dandarova, *Collect. Czech. Chem. Commun.* **1995**, 60, 709–714.
- 1995CCC903 A. A. Ikizler, K. Sancak, *Collect. Czech. Chem. Commun.* **1995**, 60, 903–909.
- 1995CJC212 J. N. Bridson, M. J. Schriver, S. Zhu, *Can. J. Chem.* **1995**, 73, 212–222.
- 1995DOK203 V. A. Pavlov, A. I. Kurdyukov, M. S. Baird, J. R. Al Dulayymi, G. A. Shamov, *Dokl. Akad. Nauk* **1995**, 344, 203–205.
- 1995H285 F. Farina, T. M. Fraile, R. M. Martin, V. M. Martin, A. M. de Guereny, *Heterocycles* **1995**, 40, 285–292.
- 1995IJC(B)70 S. B. Bhavsar, D. B. Shinde, M. S. Shingare, *Indian J. Chem. Sect. B* **1995**, 34, 70–74.
- 1995IJC(B)537 A. A. F. Wasfy, F. A. Yassin, A. M. F. Eissa, *Indian J. Chem. Sect. B* **1995**, 34, 537–539.
- 1995IJC(B)707 M. C. Hosur, M. B. Talawar, U. V. Laddi, R. S. Bennur, S. C. Bennur, *Indian J. Chem. Sect. B* **1995**, 34, 707–712.
- 1995IJC(B)736 H. H. Alnima, A. A. Ibrahim, W. F. Hammady, *Indian J. Chem. Sect. B* **1995**, 34, 736–739.
- 1995IJC(B)1007 M. H. Khan, S. Giri, *Indian J. Chem. Sect. B* **1995**, 34, 1007–1009.
- 1995IJC(B)1059 A. S. Shyadligeri, G. S. Gadaginamath, *Indian J. Chem. Sect. B* **1995**, 34, 1059–1065.
- 1995IZV722 I. V. Ovchinnikov, N. N. Makhova, L. I. Khmel'nitskii, *Izv. Akad. Nauk Ser. Khim.* **1995**, 4, 722–726.
- 1995IZV917 A. M. Churakov, A. Yu. Tyurin, E. L. Goncharova, S. L. Ioffe, Yu. A. Strelenko, V. A. Tartakovsky, *Izv. Akad. Nauk Ser. Khim.* **1995**, 5, 917–923.
- 1995IZV928 N. D. Tyurin, A. M. Churakov, E. L. Goncharova, S. L. Ioffe, Yu. A. Strelenko, V. A. Tartakovsky, *Izv. Akad. Nauk Ser. Khim.* **1995**, 5, 928–933.
- 1995JCR(M)2389 G. Broggini, L. Garanti, G. Molteni, G. Zecchi, *J. Chem. Res. Miniprint* **1995**, 10, 2389–2397.
- 1995JCR(M)3036 A. O. Abdelhamid, F. F. Abd-el-Mageid, N. M. Hassan, H. F. Zohdi, *J. Chem. Res. Miniprint* **1995**, 12, 3036–3053.
- 1995JCR(S)100 A. M. El-Agrody, S. M. Hassan, *J. Chem. Res. Synop.* **1995**, 3, 100–101.
- 1995JCR(S)276 L. Garanti, G. Molteni, G. Zecchi, *J. Chem. Res. Synop.* **1995**, 7, 276–277.
- 1995JCR(S)322 Y. A. Mohamed, M. A. Zahran, M. M. Ali, A. M. El-Agrody, U. H. El-Said, *J. Chem. Res. Synop.* **1995**, 8, 322–323.
- 1995JCS(P1)221 N. Skjaebaek, B. Ebert, E. Falch, L. Brehm, P. Krogsgaard-Larsen, *J. Chem. Soc. Perkin Trans. 1* **1995**, 3, 221–226.
- 1995JFC31 M. E. Sitzmann, *J. Fluorine Chem.* **1995**, 70, 31–38.
- 1995JFC95 M. M. Abdul-Ghani, A. E. Tipping, *J. Fluorine Chem.* **1995**, 72, 95–106.
- 1995JIC181 G. A. Ahmed, *J. Indian Chem. Soc.* **1995**, 72, 181–184.
- 1995JMC617 K. L. Kees, T. J. Caggiano, K. E. Steiner, J. J. Fitzgerald, M. J. Kates, T. E. Christos, J. M. Kulishoff, R. D. Moore, M. L. McCaleb, *J. Med. Chem.* **1995**, 38, 617–628.
- 1995JMC2038 Y. Hanasaki, H. Watanabe, K. Katsuura, H. Takayama, S. Shirakawa, K. Yamaguchi, S.-I. Sakai, K. Ijichi, M. Fujiwara, K. Konno, T. Yokota, S. Shigeta, M. Baba, *J. Med. Chem.* **1995**, 38, 2038–2040.
- 1995JMC3524 M. J. Fray, D. J. Bull, K. Cooper, M. J. Parry, M. H. Stefaniak, *J. Med. Chem.* **1995**, 38, 3524–3535.
- 1995JOM241 P. B. Hitchcock, M. F. Lappert, D.-S. Liu, *J. Organomet. Chem.* **1995**, 488, 241–248.
- 1995JPO344 J. E. Johnson, S. M. Dutton, D. D. Dolliver, S. L. Todd, M. Hotema, *J. Phys. Org. Chem.* **1995**, 8, 344–350.
- 1995JPR143 D. Lindauer, R. Beckert, M. Doering, P. Fehling, H. Goerls, *J. Prakt. Chem./Chem.-Ztg.* **1995**, 337, 143–152.
- 1995KGS238 R. A. Karakhanov, V. I. Kelarev, V. N. Koshelev, G. V. Morozova, A. Dibi, *Khim. Geterotsikl. Soedin.* **1995**, 2, 238–249.
- 1995MI1 Y. A. Ibrahim, A. H. M. Elwaha, A. A. Hashem, *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, 101, 1–8.
- 1995MI9 M. M. Ghorab, S. G. A. Hamide, *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, 106, 9–20.
- 1995MI21 P. Muenster, W. Freund, V. Maywald, T. Kuekenhoefer, M. Gerber, K. Grossmann, H. Walter, *Pestic. Sci.* **1995**, 44, 21–28.
- 1995MI45 M. P. Kaushik, R. Vaidyanathaswamy, *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, 102, 45–50.
- 1995MI83 A. O. Abdelhamid, A. A. Al-Hamidi, *J. Chin. Chem. Soc. (Taipei)* **1995**, 42, 83–88.
- 1995MI115 C. Yuan, S. Chen, R. Xie, H. Feng, L. Maier, *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, 106, 115–124.
- 1995MI143 E. A. Bakhite, A. A. Geies, A. M. K. El-Dean, H. S. El-Kashef, *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, 104, 143–150.
- 1995MI605 A. Santagati, M. Modica, M. Santagati, V. Cutuli, D. Amore, A. Caruso, *Farmaco* **1995**, 50, 605–610.
- 1995MI619 A. G. Griesbeck, J. Hirt, K. Peters, E.-M. Peters, H.-G. von Schnering, *Liebigs Ann. Org. Bioorg. Chem.* **1995**, 4, 619–624.
- 1995MI721 L. Somogyi, *Liebigs Ann. Org. Bioorg. Chem.* **1995**, 4, 721–724.
- 1995PJC85 W. Bocian, J. Jazwinski, L. Stefaniak, *Pol. J. Chem.* **1995**, 69, 85–89.
- 1995RRC475 G. S. Gadaginamath, R. G. Joshi, A. G. Kamat, *Rev. Roum. Chim.* **1995**, 40, 475–484.
- 1995SC1027 O. Cherkaoui, M. Z. Cherkaoui, E. M. Essassi, R. Zniber, *Synth. Commun.* **1995**, 25, 1027–1034.
- 1995SC1451 B. Oussaid, L. Moeini, B. Martin, D. Villemin, B. Garrigues, *Synth. Commun.* **1995**, 25, 1451–1460.
- 1995SC3287 O. Cherkaoui, M. Z. Cherkaoui, E. M. Essassi, R. Zniber, *Synth. Commun.* **1995**, 25, 3287–3292.

- 1995T1697 J.-P. Praly, D. Senni, R. Faure, G. Descotes, *Tetrahedron* **1995**, *51*, 1697–1708.
- 1995T3221 P. de Tullio, B. Pirotte, L. Dupont, B. Masereel, D. Laeckmann, T. Podona, O. Diouf, P. Lebrun, J. Delarge, *Tetrahedron* **1995**, *51*, 3221–3234.
- 1995T6517 J. Boivin, A.-C. Callier-Dublanche, B. Quiclet-Sire, A.-M. Schiano, S. Z. Zard, *Tetrahedron* **1995**, *51*, 6517–6528.
- 1995T10929 J.-M. Coustard, *Tetrahedron* **1995**, *51*, 10929–10940.
- 1995T11021 L. Ghosez, Ph. Bayard, P. Nshimyumukiza, V. Gouverneur, F. Sainte, R. Beaudegnies, M. Rivera, A.-M. Frisque-Hesbain, C. Wynants, *Tetrahedron* **1995**, *51*, 11021–11042.
- 1995TL327 B. M. Kelli-Basetti, I. Krodkiewska, W. H. F. Sasse, P. G. Savage, G. W. Simpson, *Tetrahedron Lett.* **1995**, *36*, 327–330.
- 1995TL2815 K.-J. Lee, S.-U. Kang, *Tetrahedron Lett.* **1995**, *36*, 2815–2816.
- 1995TL7337 A.-A. S. El-Ahl, S. S. Elmorsy, H. Soliman, F. A. Amer, *Tetrahedron Lett.* **1995**, *36*, 7337–7340.
- 1995TL9437 B. A. Kashemirov, M. Fujimoto, C. E. McKenna, *Tetrahedron Lett.* **1995**, *36*, 9437–9440.
- 1996AG714 N. Takeda, N. Tokitoh, R. Okazaki, *Angew. Chem.* **1996**, *108*, 714–716.
- 1996AJC463 D. J. Collins, T. C. Hughes, W. M. Johnson, *Aust. J. Chem.* **1996**, *49*, 463–468.
- 1996AJC485 L. W. Deady, P. M. Loria, N. H. Quazi, *Aust. J. Chem.* **1996**, *49*, 485–488.
- 1996BMCL111 P. L. Feldman, S. Chi, N. Sennequier, D. J. Stuehr, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 111–114.
- 1996BMCL1015 D. R. Armour, K. M. L. Chung, M. Congreve, B. Evans, S. Guntrip, T. Hubbard, C. Kay, D. Middlemiss, J. E. Mordaunt, N. A. Pegg, M. V. Vinader, P. Ward, S. P. Watson, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1015–1020.
- 1996BMCL2693 D. S. Dodd, S. Zhongqi, T. Nishi, N. Graber, D. Bealls, M. Fong, T. Ebert, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2693–2698.
- 1996CB1493 A. Schmidpeter, F. Steinmueller, H. Noeth, *Chem. Ber.* **1996**, *129*, 1493–1496.
- 1996CPB709 H. Yoshioka, Y. Matsuya, T. Choshi, E. Sugino, S. Hibino, *Chem. Pharm. Bull.* **1996**, *44*, 709–714.
- 1996CSC1045 S. Bratovanov, A. Linden, S. Bienz, *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **1996**, *52*, 1045–1047.
- 1996H821 C. H. Senanayake, L. E. Fredenburgh, R. A. Reamer, J. Liu, E. F. Roberts, G. Humphrey, A. S. Thompson, R. D. Larsen, T. R. Verhoeven, P. J. Reider, I. Shinkai, *Heterocycles* **1996**, *42*, 821–830.
- 1996H2435 Y. Hanasaki, *Heterocycles* **1996**, *43*, 2435–2442.
- 1996HCA319 A. Brunner, F. N. M. Kuehnle, D. Seebach, *Helv. Chim. Acta* **1996**, *79*, 319–345.
- 1996IJC(B)106 H. S. Rani, K. Mogilaiah, B. Sreenivasulu, *Indian J. Chem. Sect. B* **1996**, *35*, 106–110.
- 1996IJC(B)111 B. S. Vashi, D. S. Mehta, V. H. Shah, *Indian J. Chem. Sect. B* **1996**, *35*, 111–115.
- 1996IJC(B)339 G. R. Rao, K. Mogilaiah, B. Sreenivasulu, *Indian J. Chem. Sect. B* **1996**, *35*, 339–344.
- 1996IJC(B)688 N. Verma, B. S. Verma, V. Chawla, O. P. Malik, *Indian J. Chem. Sect. B* **1996**, *35*, 688–691.
- 1996IJC(B)915 M. R. Mahmoud, M. S. Abd-El-Halim, A. E. F. Ebrahim, A. M. Radwan, *Indian J. Chem. Sect. B* **1996**, *35*, 915–919.
- 1996IJC(B)980 H. Saad, *Indian J. Chem. Sect. B* **1996**, *35*, 980–984.
- 1996IZV1857 M. A. Pudovik, L. K. Kibardina, R. Kh. Al'myanova, R. M. Kamalov, A. N. Pudovik, *Izv. Akad. Nauk Ser. Khim.* **1996**, *7*, 1857–1859.
- 1996IZV2733 V. A. Dorokhov, L. G. Vorontsova, M. G. Kurella, L. I. Parfenova, *Izv. Akad. Nauk Ser. Khim.* **1996**, *11*, 2733–2735.
- 1996JA5138 S. Kim, I. Y. Lee, J.-Y. Yoon, D. H. Oh, *J. Amer. Chem. Soc.* **1996**, *118*, 5138–5139.
- 1996JCR(S)254 M. Kidwai, P. Kumar, *J. Chem. Res. Synop.* **1996**, *5*, 254–255.
- 1996JCS(P1)747 A. R. Aitken, S. V. Raut, *J. Chem. Soc. Perkin Trans. 1* **1996**, *7*, 747–752.
- 1996JCS(P1)883 P. A. Johnson, R. W. A. Luke, R. W. Steele, A. N. Boa, *J. Chem. Soc. Perkin Trans. 1* **1996**, *9*, 883–894.
- 1996JHC327 G. Sorba, G. Ermondi, R. Fruttero, U. Galli, A. Gasco, *J. Heterocycl. Chem.* **1996**, *33*, 327–334.
- 1996JHC731 E. Coutouli-Argyropoulou, C. Anastasopoulos, *J. Heterocycl. Chem.* **1996**, *33*, 731–734.
- 1996JHC1307 T. Boyer, L. Fournel, E. Nicolai, J. M. Teulon, *J. Heterocycl. Chem.* **1996**, *33*, 1307–1312.
- 1996JHC1765 A. Ikizler, N. Demirbas, A. A. Ikizler, *J. Heterocycl. Chem.* **1996**, *33*, 1765–1770.
- 1996JHC1877 K.-J. Lee, D.-H. Song, D.-J. Kim, S.-W. Park, *J. Heterocycl. Chem.* **1996**, *33*, 1877–1882.
- 1996JHC1927 A. R. Katritzky, I. Ghiviriga, D. C. Oniciu, F. Soti, *J. Heterocycl. Chem.* **1996**, *33*, 1927–1934.
- 1996JMC237 M. S. Malamas, R. P. Carlson, D. Grimes, R. Howell, K. Glaser, I. Gunawan, J. A. Nelson, M. Kanzelberger, U. Shah, D. A. Hartman, *J. Med. Chem.* **1996**, *39*, 237–245.
- 1996JMC937 P. de Tullio, B. Pirotte, P. Lebrun, J. Fontaine, L. Dupont, M.-H. Antoine, R. Ouedraogo, S. Khelili, C. Maggetto, B. Masereel, O. Diouf, T. Podona, J. Delarge, *J. Med. Chem.* **1996**, *39*, 937–948.
- 1996JMC2232 P. L. Ornstein, B. M. Arnold, N. K. Allen, T. Bleisch, P. S. Borromeo, C. W. Lugar, D. J. Leander, D. Lodge, D. D. Schoepp, *J. Med. Chem.* **1996**, *39*, 2232–2244.
- 1996JMC2753 P. Kotian, S. W. Mascarella, P. Abraham, A. H. Lewin, J. W. Boja, M. J. Kuhar, F. I. Carroll, *J. Med. Chem.* **1996**, *39*, 2753–2763.
- 1996JMC3188 H. Braeuner-Osborne, F. A. Sloek, N. Skjaerbaek, B. Ebert, N. Sekiyama, S. Nakanishi, P. Krosgaard-Larsen, *J. Med. Chem.* **1996**, *39*, 3188–3194.
- 1996JMC3908 A. D. White, C. F. Purchase, J. A. Picard, M. K. Anderson, S. B. Mueller, T. M. A. Bocan, R. F. Bousley, K. L. Hamelhele, B. R. Krause, P. Lee, R. L. Stanfield, J. F. Reindel, *J. Med. Chem.* **1996**, *39*, 3908–3919.
- 1996JMC4044 N. J. Hrib, J. G. Jurcak, D. E. Bregna, K. L. Burgher, H. B. Hartman, S. Kafka, L. L. Kerman, S. Kongsamut, J. E. Roehr, M. R. Szewczak, A. T. Woods-Kettelberger, R. Corbett, *J. Med. Chem.* **1996**, *39*, 4044–4057.
- 1996JOC45 J. E. Johnson, E. C. Riesgo, I. Jano, *J. Org. Chem.* **1996**, *61*, 45–50.
- 1996JOC1902 H. Ishitani, S. Nagayama, S. Kobayashi, *J. Org. Chem.* **1996**, *61*, 1902–1903.
- 1996JOM355 M. Weidenbruch, P. Will, K. Peters, H. G. von Schnering, H. Marsmann, *J. Organomet. Chem.* **1996**, *521*, 355–362.

- 1996JPR451 S. Brandl, R. Gompper, K. Polborn, *J. Prakt. Chem./Chem. -Ztg.* **1996**, 338, 451–459.
- 1996JPR516 M. Rehwald, H. Schaefer, K. Gewald, M. Gruner, *J. Prakt. Chem./Chem. -Ztg.* **1996**, 338, 516–522.
- 1996JPS326 T. Lessen, D.-C. (David) Zhao, *J. Pharm. Sci.* **1996**, 85, 326–329.
- 1996M549 M. M. Hamad, S. A. Said, Y. M. El-Ekyabi, *Monatsh. Chem.* **1996**, 127, 549–556.
- 1996M1263 A. A. Geies, A. M. K. El-Dean, O. S. Moustafa, *Monatsh. Chem.* **1996**, 127, 1263–1272.
- 1996M131 M. M. Ghorab, S. G. Abdel-Hamide, G. M. Ali, E.-S. H. Shaurub, *Pestic. Sci.* **1996**, 48, 31–36.
- 1996MI109 W. Abramski, M. Chmielewski, *Carbohydr. Chem.* **1996**, 15, 109–114.
- 1996MI179 D. St. C. Green, U. Gruss, G. Haegle, H. R. Hudson, L. Lindblom, M. Pianka, *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, 113, 179–208.
- 1996MI203 G. Grandolini, V. Ambrogi, L. Perioli, G. Giannaccini, A. Lucacchini, C. Martini, *Farmaco* **1996**, 51, 203–208.
- 1996MI221 P. H. Olesen, P. Sauerberg, S. Treppendahl, O. Larsson, M. J. Sheardown, *et al.*, *Eur. J. Med. Chem. Chim. Ther.* **1996**, 31, 221–230.
- 1996MI269 M. H. Norman, S. D. Gabriel, *J. Labelled Compd. Radiopharm.* **1996**, 38, 269–280.
- 1996MI301 R. Singh, C. Fiakupi, J. Galpin, J. Stewart, M. P. Singh, R. G. Micetich, *Eur. J. Med. Chem. Chim. Ther.* **1996**, 31, 301–310.
- 1996MI431 J. Lange, K. Wejroch, J. Karolak-Wojciechowska, J. Pleniewicz, M. Gniewosz, *et al.*, *Acta Pol. Pharm.* **1996**, 53, 431–436.
- 1996MI441 R. Hamilton, M. A. McKervey, D. M. Rafferty, B. J. Walker, *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, 109, 441–444.
- 1996MI477 A. M. Pinchuk, A. N. Tolmachev, A. N. Kostyuk, A. A. Yurchenko, A. I. Sviridon, *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, 109, 477–480.
- 1996MI493 N. M. Hassan, A. A. Fahmi, F. F. Abd-El-Mageid, A. O. Abdelhamid, *J. Chin. Chem. Soc. (Taipei)* **1996**, 43, 493–496.
- 1996MI629 U. Misra, A. Hitkari, A. K. Saxena, S. Gurtu, K. Shanker, *Eur. J. Med. Chem. Chim. Ther.* **1996**, 31, 629–634.
- 1996MI659 F. P. Invidiata, D. Simoni, F. Scintu, N. Pinna, *Farmaco* **1996**, 51, 659–664.
- 1996MI1845 H. Irngartinger, A. Weber, T. Escher, *Liebigs Ann. Org. Bioorg. Chem.* **1996**, 11, 1845–1850.
- 1996OPP699 G. Broggini, L. Garanti, G. Molteni, G. Zecchi, *Org. Prep. Proced. Int.* **1996**, 28, 699–701.
- 1996PHA392 K. Goerlitzer, P.-M. Dobberkau, P. G. Jones, *Pharmazie* **1996**, 51, 392–396.
- 1996PJC1114 A. Ikizler, N. Demibas, A. Demibas, A. A. Ikizler, *Pol. J. Chem.* **1996**, 70, 1114–1120.
- 1996S274 Y. Guo, Q. Wang, J. C. Jochims, *Synthesis* **1996**, 2, 274–280.
- 1996S1076 G. Broggini, L. Garanti, G. Molteni, G. Zecchi, *Synthesis* **1996**, 9, 1076–1078.
- 1996S1177 R. Amici, P. Pevarello, M. Colombo, M. Varasi, *Synthesis* **1996**, 10, 1177–1179.
- 1996SC3733 Z. A. Hozien, F. M. Atta, Kh. M. Hassan, A. A. Abdel-Wahab, S. A. Ahmed, *Synth. Commun.* **1996**, 26, 3733–3756.
- 1996T233 T. Sakai, F. Yan, S. Kashino, K. Uneyama, *Tetrahedron* **1996**, 52, 233–244.
- 1996T661 H. V. Patel, K. A. Vyas, S. P. Pandey, P. S. Fernandes, *Tetrahedron* **1996**, 52, 661–668.
- 1996T1399 A. Kotschy, G. Hajos, A. Messmer, G. Jones, *Tetrahedron* **1996**, 52, 1399–1410.
- 1996T8877 J. R. Al-Dulayymi, M. S. Baird, V. A. Pavlov, A. I. Kurdjukov, *Tetrahedron* **1996**, 52, 8877–8888.
- 1996T14607 R. Gompper, P. Walther, C. Braeuchle, S. Stadler, *Tetrahedron* **1996**, 52, 14607–14624.
- 1996TL4137 H. Irngartinger, A. Weber, *Tetrahedron Lett.* **1996**, 37, 4137–4140.
- 1996TL5623 V. Nair, K. V. Radhakrishnan, A. G. Nair, M. M. Bhadbhade, *Tetrahedron Lett.* **1996**, 37, 5623–5626.
- 1996TL6339 C.-F. Yao, W.-C. Chen, Y.-M. Lin, *Tetrahedron Lett.* **1996**, 37, 6339–6342.
- 1996TL6407 G. Kumaran, *Tetrahedron Lett.* **1996**, 37, 6407–6408.
- 1996TL7791 R. K. Chang, K. Kim, *Tetrahedron Lett.* **1996**, 37, 7791–7794.
- 1996ZOB360 M. A. Pudovik, N. E. Krepyshcheva, R. Kh. Al'myanova, R. M. Kamalov, A. N. Pudovik, *Zh. Obshch. Khim.* **1996**, 66, 360–363.
- 1996ZOB512 B. I. Buzykin, L. P. Sysoeva, *Zh. Obshch. Khim.* **1996**, 66, 512–513.
- 1996ZOB572 V. A. Galishev, Yu. T. Struchkov, T. S. Dolgushina, A. M. Shubnikov, K. A. Potekhin, *Zh. Obshch. Khim.* **1996**, 66, 572–577.
- 1996ZOB1463 A. M. Shubnikov, T. S. Dolgushina, V. K. Bel'skii, V. A. Galishev, *Zh. Obshch. Khim.* **1996**, 66, 1463–1472.
- 1996ZOB1715 V. I. Boiko, L. I. Samarai, N. V. Mel'nichenko, V. V. Pirozhenko, A. D. Gordeev, G. B. Soifer, *Zh. Obshch. Khim.* **1996**, 66, 1715–1719.
- 1996ZOB1847 Y. L. Zborovskii, V. F. Levon, V. I. Staninets, *Zh. Obshch. Khim.* **1996**, 66, 1847–1850.
- 1997AF431 L. Anglada, M. Raga, M. Marquez, A. Sacristan, J. M. Castello, J. A. Ortiz, *Arzneim. Forsch.* **1997**, 47, 431–434.
- 1997AF635 J.-M. Robert, O. Rideau, S. Robert-Piessard, M. Duflos, G. Le Baut, N. Grimaud, M. Juge, J. Y. Petit, *Arzneim. Forsch.* **1997**, 47, 635–642.
- 1997AJC849 J. E. Rowe, K. Lee, *Aust. J. Chem.* **1997**, 50, 849–852.
- 1997BMCL1607 Y. Ding, Y.-Y. Zhang, J. Zhang, Y.-Q. Chen, *Bioorg. Med. Chem. Lett.* **1997**, 7, 1607–1610.
- 1997BSB455 W. Fiedler, M. Regitz, G. Bertrand, *Bull. Soc. Chim. Belg.* **1997**, 106, 455–460.
- 1997CAR127 S. Cottaz, P. Rollin, H. Driguez, *Carbohydr. Res.* **1997**, 298, 127–130.
- 1997FES375 R. Di Santo, R. Costi, M. Artico, S. Massa, *Farmaco* **1997**, 52, 375–378.
- 1997H1183 P. Froberg, U. Baumeister, D. Stroehl, H. Danz, *Heterocycles* **1997**, 45, 1183–1190.
- 1997IJC(B)288 M. M. F. Ismail, N. A. M. M. Shmeiss, H. I. El-Diwani, M. S. Arbid, *Indian J. Chem. Sect. B* **1997**, 36, 288–292.
- 1997IJC(B)566 U. S. Pathak, I. S. Rathod, K. S. Jain, N. S. Laddha, K. S. Kolhe, *Indian J. Chem. Sect. B* **1997**, 36, 566–571.
- 1997IJC(B)943 B. S. Holla, R. Gonsalves, B. K. Sarojini, *Indian J. Chem. Sect. B* **1997**, 36, 943–946.

- 1997IZV118 V. N. Drozd, V. N. Knyazev, F. M. Stoyanovich, F. M. Dolgushin, A. I. Yanovsky, *Izv. Akad. Nauk Ser. Khim.* **1997**, 1, 118–126.
- 1997IZV1887 S. G. Zlotin, P. G. Kislitsin, O. A. Luk'yanov, *Izv. Akad. Nauk Ser. Khim.* **1997**, 10, 1887–1888.
- 1997IZV2232 M. A. Epishina, I. V. Ovchinnikov, N. N. Makhova, *Izv. Akad. Nauk Ser. Khim.* **1997**, 12, 2232–2235.
- 1997JCR(M)2039 A. M. El-Agrody, H. A. Emam, M. H. El-Hakim, M. S. Abd El-Iatif, A. H. Fakery, *J. Chem. Res. Miniprint* **1997**, 9, 2039–2048.
- 1997JCR(M)2459 S. Baskaran, C. Baskaran, G. K. Trivedi, *J. Chem. Res. Miniprint* **1997**, 11, 2459–2471.
- 1997JCR(M)2771 M. M. Basyouni, H. M. Hosni, K. A. M. El-Bayouki, *J. Chem. Res. Miniprint* **1997**, 12, 2771–2789.
- 1997JCS(P1)629 M. R. Paton, A. A. Young, *J. Chem. Soc. Perkin Trans. 1* **1997**, 5, 629–636.
- 1997JCS(P1)3673 S. S. Samanta, S. C. Ghosh, A. De, *J. Chem. Soc. Perkin Trans. 1* **1997**, 24, 3673–3678.
- 1997JHC71 K.-J. Lee, D.-H. Song, D.-J. Kim, S.-W. Park, *J. Heterocycl. Chem.* **1997**, 34, 71–76.
- 1997JHC345 R. N. Hanson, F. A. Mohamed, *J. Heterocycl. Chem.* **1997**, 34, 345–348.
- 1997JHC413 R. L. Robey, C. A. Alt, E. E. van Meter, *J. Heterocycl. Chem.* **1997**, 34, 413–428.
- 1997JHC921 H. Tanaka, T. Nakao, *J. Heterocycl. Chem.* **1997**, 34, 921–924.
- 1997JHC1255 F. P. Invidiata, G. Furno, I. Lampronti, D. Simoni, *J. Heterocycl. Chem.* **1997**, 34, 1255–1258.
- 1997JIC21 E. H. Eltamany, *J. Indian Chem. Soc.* **1997**, 74, 21–23.
- 1997JMC538 C. H. Mitch, T. J. Brown, F. P. Bymaster, D. O. Calligaro, D. Dieckman, L. Merrit, S. C. Peters, S. J. Quimby, H. E. Shannon, L. A. Shipley, J. S. Ward, K. Hansen, P. H. Olesen, P. Sauerberg, M. J. Sheardown, M. D. B. Swedberg, P. Suzdak, B. Greenwood, *J. Med. Chem.* **1997**, 40, 538–546.
- 1997JMC2053 J. Ohmori, M. Shimizu-Sasamata, M. Okada, S. Sakamoto, *J. Med. Chem.* **1997**, 40, 2053–2063.
- 1997JMC4265 S. M. Bromidge, F. Brown, F. Cassidy, M. S. G. Clark, S. Dabbs, M. S. Hadley, J. Hawkins, J. M. Loudon, C. B. Naylor, B. S. Orlek, G. J. Riley, *J. Med. Chem.* **1997**, 40, 4265–4280.
- 1997JMC4308 T. Su, M. A. H. Naughton, M. S. Smyth, J. W. Rose, A. E. Arfsten, J. R. McCowan, J. A. Jakubowski, V. L. Wyss, K. J. Ruterbories, D. J. Sall, R. M. Scarborough, *J. Med. Chem.* **1997**, 40, 4308–4318.
- 1997JOC234 C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1997**, 62, 234–235.
- 1997JOC1516 G. Kumaran, G. H. Kulkarni, *J. Org. Chem.* **1997**, 62, 1516–1520.
- 1997JOC4672 W.-S. Chung, T.-L. Tsai, C.-C. Ho, M. Y. N. Chiang, W. J. le Noble, *J. Org. Chem.* **1997**, 62, 4672–4676.
- 1997KGS500 V. Yu. Vvedenskii, E. D. Shtefan, R. N. Mayushenko, E. V. Shilkin, *Khim. Geterotsikl. Soedin.* **1997**, 4, 500–502.
- 1997KGS816 N. A. Popova, B. M. Krasovitskii, N. S. Pivnenko, Yu. N. Surov, *Khim. Geterotsikl. Soedin.* **1997**, 6, 816–821.
- 1997MI291 M. Kidwai, K. R. Bhushan, P. Kumar, R. Kumar, *Monatsh. Chem.* **1997**, 128, 1291–1296.
- 1997MI37 H. A. Emam, A. O. Abdelhamid, *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, 131, 37–48.
- 1997MI43 A. M. Farag, K. M. Dawood, Z. E. Kandeel, *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, 130, 43–52.
- 1997MI49 M. Di Braccio, G. Roma, G. Grossi, M. Ghia, F. Mattioli, *Farmaco* **1997**, 52, 49–54.
- 1997MI307 T.-B. Huang, L.-F. Liu, X.-M. Yu, W.-Q. Yang, X.-H. Qian, J.-L. Zhang, *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, 122, 307–312.
- 1997MI329 F. A. Sloek, B. Ebert, Y. Lang, P. Krogsgaard-Larsen, S. M. Lenz, U. Madsen, *Eur. J. Med. Chem. Chim. Ther.* **1997**, 32, 329–338.
- 1997MI617 H. F. Zohdi, T. A. Osman, A. O. Abdelhamid, *J. Chin. Chem. Soc. (Taipei)* **1997**, 44, 617–623.
- 1997MI973 A. Santagati, J. Longmore, S. Guccione, T. Langer, E. E. Tonnel, *et al.*, *Eur. J. Med. Chem. Chim. Ther.* **1997**, 32, 973–986.
- 1997MI2755 A.-L. Gustavsson, M. Tuveesson, M. C. Larsson, W. Wenqi, B. S. Hansson, T. Liljefors, *J. Chem. Ecol.* **1997**, 23, 2755–2776.
- 1997OPP594 E. Miyazawa, T. Sakamoto, Y. Kikugawa, *Org. Prep. Proced. Int.* **1997**, 29, 594–600.
- 1997PHA189 S. A. Shiba, A. A. El-Khamry, M. E. Shaban, K. S. Atia, *Pharmazie* **1997**, 52, 189–194.
- 1997PHA436 A. A. Geies, A. M. K. El-Dean, O. Sh. Moustafa, *Pharmazie* **1997**, 52, 436–441.
- 1997PHA500 A. A. Geies, *Pharmazie* **1997**, 52, 500–503.
- 1997PHA844 N. S. Habib, R. Soliman, F. A. Ashour, M. El-Taiebi, *Pharmazie* **1997**, 52, 844–847.
- 1997PJC77 R. Mazurkiewicz, M. Grymel, *Pol. J. Chem.* **1997**, 71, 77–82.
- 1997S696 R. Gompper, H.-J. Mair, K. Polborn, *Synthesis* **1997**, 6, 696–718.
- 1997SL71 G. Calvisi, R. Catini, W. Chiariotti, F. Giannessi, S. Muck, M. O. Tinti, F. DeAngelis, *Syn. Lett.* **1997**, 1, 71–74.
- 1997SL283 J. Loeffler, R. Schobert, *Syn. Lett.* **1997**, 3, 283–284.
- 1997SL475 S. Kim, J.-Y. Yoon, I. Y. Lee, *Syn. Lett.* **1997**, 5, 475–476.
- 1997SL950 S. Kim, T. A. Lee, *Syn. Lett.* **1997**, 8, 950–952.
- 1997SL1355 P. C. B. Page, D. Bethell, P. A. Stocks, J. P. Heer, A. E. Graham, H. Vahedi, M. Healy, E. W. Collington, D. M. Andrews, *Syn. Lett.* **1997**, 12, 1355–1358.
- 1997T7045 R. Saladino, L. Stasi, C. Crestini, R. Nicoletti, M. Botta, *Tetrahedron* **1997**, 53, 7045–7056.
- 1997T12167 N. Takeda, N. Takitoh, R. Okazaki, *Tetrahedron* **1997**, 53, 12167–12182.
- 1997T14317 E. Bacher, F. W. J. Demnitz, T. Hurni, *Tetrahedron* **1997**, 53, 14317–14326.
- 1997T17461 A. M. Farag, K. M. Dawood, A. O. Abdelhamid, *Tetrahedron* **1997**, 53, 17461–17468.
- 1997TL1597 J. N. Kim, K. S. Jung, H. J. Lee, J. S. Son, *Tetrahedron Lett.* **1997**, 38, 1597–1598.
- 1997TL2463 A.-C. Callier-Dublanche, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1997**, 38, 2463–2466.
- 1997TL6419 C.-F. Yao, C.-S. Yang, H.-Y. Fang, *Tetrahedron Lett.* **1997**, 38, 6419–6420.
- 1997TL7049 R. A. Moss, L. Maksimovic, D. C. Merrer, *Tetrahedron Lett.* **1997**, 38, 7049–7052.
- 1997ZOB160 N. V. Kolotilo, P. P. Onys'ko, A. A. Sinitsa, *Zh. Obshch. Khim.* **1997**, 67, 160–161.
- 1997ZOB168 V. E. Shishkin, E. V. Mednikov, E. V. Zubareva, B. I. No, *Zh. Obshch. Khim.* **1997**, 67, 168–168.
- 1997ZOB1923 V. I. Namestnikov, Yu. G. Trishin, *Zh. Obshch. Khim.* **1997**, 67, 1923–1924.
- 1998AJC499 J. B. F. Dunstan, G. M. Elsey, R. A. Russell, G. P. Savage, G. W. Simpson, E. R. T. Tiekink, *Aust. J. Chem.* **1998**, 51, 499–510.

- 1998AP163 B. Matuszczak, E. Pekala, C. E. Mueller, *Arch. Pharm. (Weinheim Ger.)* **1998**, 331, 163–169.
- 1998BMC119 N. Skjaerbaek, L. Brehm, T. N. Johansen, L. M. Hansen, B. Nielsen, B. Ebert, K. K. Søby, T. B. Stensbøl, E. Falch, P. Krogsgaard-Larsen, *Bioorg. Med. Chem.* **1998**, 6, 119–132.
- 1998BMC2271 C. C. C. Cutri, A. Garozzo, M. A. Siracusa, M. C. Sarva, G. Tempera, E. Geremia, M. R. Pinizzotto, F. Guerrero, *Bioorg. Med. Chem.* **1998**, 6, 2271–2280.
- 1998BMCL1531 J. H. van Maarseveen, J. A. J. den Hartog, K. Tipker, J.-H. Reinders, J. Brakkee, U. Schön, W. Kehrbach, C. G. Kruse, *Bioorg. Med. Chem. Lett.* **1998**, 8, 1531–1536.
- 1998BMCL3153 K. Ohsumi, T. Hatanaka, K. Fujita, R. Nakagawa, Y. Fukuda, Y. Nihei, Y. Suga, Y. Morinaga, Y. Akiyama, T. Tsuji, *Bioorg. Med. Chem. Lett.* **1998**, 8, 3153–3158.
- 1998CAR9 L. F. Awad, E. S. H. El Ashry, *Carbohydr. Res.* **1998**, 312, 9–22.
- 1998CC609 W. B. Jang, K. Lee, C.-W. Lee, D. Y. Oh, *Chem. Commun.* **1998**, 5, 609–610.
- 1998CJC85 R. A. Beekman, R. T. Boere, K. H. Moock, M. Parvez, *Can. J. Chem.* **1998**, 76, 85–93.
- 1998CPB69 T. Okazaki, A. Suga, T. Watanabe, K. Kikuchi, H. Kurihara, M. Shibasaki, A. Fujimori, O. Inagaki, I. Yanagisawa, *Chem. Pharm. Bull.* **1998**, 46, 69–78.
- 1998H2111 J. M. McGill, M. S. Miller, *Heterocycles* **1998**, 48, 2111–2124.
- 1998HCA1359 M. Weber, A. Vasella, M. Textor, N. D. Spencer, *Helv. Chim. Acta* **1998**, 81, 1359–1372.
- 1998IJC(B)127 X. Pengfei, Y. Xiping, W. Shaozu, Z. Ziyi, *Indian J. Chem. Sect. B* **1998**, 37, 127–131.
- 1998IJC(B)427 M. Kidwai, K. R. Bhushan, *Indian J. Chem. Sect. B* **1998**, 37, 427–428.
- 1998IJC(B)461 U. V. Laddi, S. R. Desai, Y. S. Somannavar, R. S. Bennur, S. C. Bennur, *Indian J. Chem. Sect. B* **1998**, 37, 461–467.
- 1998IZV1797 A. A. Tolmachev, A. S. Merkulov, A. A. Yurchenko, M. G. Semenova, A. M. Pinchuk, *Izv. Akad. Nauk Ser. Khim.* **1998**, 9, 1797–1801.
- 1998IZV2002 V. N. Yarovenko, S. A. Kosarev, I. V. Zavarzin, M. M. Krayushkin, *Izv. Akad. Nauk Ser. Khim.* **1998**, 10, 2002–2006.
- 1998JCR(M)2056 A. F. S. Ahmed, N. Aouf, M. G. Assy, *J. Chem. Res. Miniprint* **1998**, 9, 2056–2061.
- 1998JCR(S)40 G. Molteni, *J. Chem. Res. Synop.* **1998**, 1, 40–41.
- 1998JCR(S)254 J. Zhou, R.-Y. Chen, *J. Chem. Res. Synop.* **1998**, 5, 254–255.
- 1998JCS(D)3113 P. B. Hitchcock, M. F. Lappert, M. Layh, *J. Chem. Soc. Dalton Trans.* **1998**, 18, 3113–3118.
- 1998JCS(P1)109 S. C. Yoon, J. Cho, K. Kim, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1, 109–116.
- 1998JCS(P1)2833 I. Szabadkai, K. Harsanyi, M. Bihari, M. Renyei, G. Racz, *J. Chem. Soc. Perkin Trans. 1* **1998**, 17, 2833–2836.
- 1998JCS(P1)4103 G. Broggini, L. Garanti, G. Molteni, G. Zecchi, *J. Chem. Soc. Perkin Trans. 1* **1998**, 24, 4103–4106.
- 1998JHC29 C. B. Vicentini, M. Manfrini, A. C. Veronese, M. Guarneri, *J. Heterocycl. Chem.* **1998**, 35, 29–32.
- 1998JHC293 S.-I. Nagai, T. Ueda, M. Takamura, A. Nagatsu, N. Murakami, J. Sakakibara, *J. Heterocycl. Chem.* **1998**, 35, 293–296.
- 1998JHC377 A. A. Ikizler, N. Yildirim, *J. Heterocycl. Chem.* **1998**, 35, 377–380.
- 1998JHC1281 U. Bratusek, A. Hvala, B. Stanovnik, *J. Heterocycl. Chem.* **1998**, 35, 1281–1284.
- 1998JMC109 P. Sauerberg, P. H. Olesen, M. J. Sheardown, K. Rimvall, H. Thøgersen, H. E. Shannon, B. D. Sawyer, J. S. Ward, F. P. Bymaster, N. W. DeLapp, D. O. Calligaro, M. D. B. Swedberg, *J. Med. Chem.* **1998**, 41, 109–116.
- 1998JMC379 J. S. Ward, L. Merritt, D. O. Calligaro, F. P. Bymaster, H. E. Shannon, C. H. Mitch, C. Whitesitt, D. Brunsting, M. J. Sheardown, P. H. Olesen, M. D. B. Swedberg, L. Jeppesen, P. Sauerberg, *J. Med. Chem.* **1998**, 41, 379–392.
- 1998JMC1299 A. Link, C. Kunick, *J. Med. Chem.* **1998**, 41, 1299–1305.
- 1998JMC2390 A. Tanaka, T. Terasawa, H. Hagihara, Y. Sakuma, N. Ishibe, M. Sawada, H. Takasugi, H. Tanaka, *J. Med. Chem.* **1998**, 41, 2390–2410.
- 1998JMC4378 P. Sauerberg, L. Jeppesen, P. H. Olesen, T. Rasmussen, M. D. B. Swedberg, M. J. Sheardown, A. Fink-Jensen, C. Thomsen, H. Thøgersen, K. Rimvall, J. S. Ward, D. O. Calligaro, N. W. DeLapp, F. P. Bymaster, H. E. Shannon, *J. Med. Chem.* **1998**, 41, 4378–4384.
- 1998JOC885 D. Zhang, C. Sueling, M. J. Miller, *J. Org. Chem.* **1998**, 63, 885–888.
- 1998JOC3010 D. C. Merrer, R. A. Moss, M. T. H. Liu, J. T. Banks, K. U. Ingold, *J. Org. Chem.* **1998**, 63, 3010–3016.
- 1998JPR346 G. Kaupp, J. Boy, J. Schmeyer, *J. Prakt. Chem./Chem. -Ztg.* **1998**, 340, 346–355.
- 1998JST61 A. K. Sen, R. N. Singh, R. N. Handa, S. N. Dubey, P. J. Squattrito, *J. Mol. Struct.* **1998**, 470, 61–70.
- 1998KFZ16 D. B. Nilov, N. P. Solov'eva, I. S. Nikolaeva, V. V. Peters, L. Yu. Krylova, *et al.*, *Khim. Farm. Zh.* **1998**, 32, 16–19.
- 1998KGS1130 A. A. Yavolovskii, O. S. Timofeev, E. I. Ivanov, *Khim. Geterotsikl. Soedin.* **1998**, 8, 1130–1132.
- 1998M523 A. M. K. El-Dean, *Monatsh. Chem.* **1998**, 129, 523–534.
- 1998MI1 M. Jendras, U. Klingebiel, J. Niesmann, M. Noltemeyer, *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, 142, 1–26.
- 1998MI29 M. F. Oldfield, N. P. Botting, *J. Labelled Compd. Radiopharm.* **1998**, 41, 29–36.
- 1998MI48 M. M. Gineinah, A. M. Abdelal, H. I. El-Subbagh, I. A. Shenata, *Boll. Chim. Farm.* **1998**, 137, 48–54.
- 1998MI331 M. L. Petrov, M. A. Abramov, *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, 134, 331–344.
- 1998MI467 B. S. Holla, R. Gonsalves, *Boll. Chim. Farm.* **1998**, 137, 467–472.
- 1998MI549 M. Minoura, T. Kawashima, N. Tokitoh, R. Okazaki, *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, 136, 549–552.
- 1998MI574 B. S. Holla, R. Gonsalves, S. Shenoy, *Farmaco* **1998**, 53, 574–578.
- 1998MI615 R. J. Spanggord, L. A. Clizbe, *J. Labelled Compd. Radiopharm.* **1998**, 41, 615–622.
- 1998MI633 N. Takeda, N. Tokitoh, R. Okazaki, *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, 136, 633–636.
- 1998MI903 B. Manz, J. Kerth, G. Maas, *Chem. Europ. J* **1998**, 4, 903–913.
- 1998MI1609 A. K. Jaiswal, G. P. Rao, O. P. Pandey, S. K. Sengupta, *J. Agric. Food Chem.* **1998**, 46, 1609–1613.
- 1998OPP177 A. Kotali, M. Papapetrou, V. Dimos, *Org. Prep. Proced. Int.* **1998**, 30, 177–182.
- 1998PJC1915 S. Lesniak, G. Mloston, H. Heimgartner, *Pol. J. Chem.* **1998**, 72, 1915–1920.

- 1998S1305 A. Mack, E. Pierron, T. Allspach, U. Bergstraesser, M. Regitz, *Synthesis* **1998**, 9, 1305–1313.
- 1998T791 C.-F. Yao, K.-H. Kao, J.-T. Liu, C.-M. Chu, Y. Wang, W.-C. Chen, Y.-M. Lin, W.-W. Lin, M.-C. Yan, J.-Y. Liu, M.-C. Chuang, J.-L. Shiu, *Tetrahedron* **1998**, 54, 791–822.
- 1998T2843 G. Brogini, L. Garanti, G. Molteni, G. Zecchi, *Tetrahedron* **1998**, 54, 2843–2852.
- 1998T12379 M. J. Martin-Lopez, F. Bermejo, *Tetrahedron* **1998**, 54, 12379–12388.
- 1998T13645 C. G. Neill, P. N. Preston, R. H. Wightman, *Tetrahedron* **1998**, 54, 13645–13654.
- 1998T13997 K.-H. Kao, C.-S. Yang, J.-T. Liu, W.-W. Lin, H.-Y. Fang, C.-F. Yao, K. Chen, *Tetrahedron* **1998**, 54, 13997–14014.
- 1998TA3359 A. Agocs, A. Benyei, L. Somogyi, P. Herczegh, *Tetrahedron: Asymmetry* **1998**, 9, 3359–3364.
- 1998ZOB691 Z. I. Glebova, G. K. Kist'yan, A. A. Shvets, *Zh. Obshch. Khim.* **1998**, 68, 691–692.
- 1998ZOB1100 N. G. Zabiroy, F. D. Sokolov, R. A. Cherkasov, *Zh. Obshch. Khim.* **1998**, 68, 1100–1103.
- 1998ZOB1398 V. I. Namestnikov, Yu. G. Trishin, V. K. Bel'skii, *Zh. Obshch. Khim.* **1998**, 68, 1398–1399.
- 1998ZOR120 A. A. Esipenko, B. N. Kozhushko, V. V. Pirozhenko, *Zh. Org. Khim.* **1998**, 34, 120–122.
- 1999AG(E)2201 D. Amsallem, H. Gornitzka, A. Baceiredo, G. Bertrand, *Angew. Chem. Int. Ed.* **1999**, 38, 2201–2203.
- 1999AJC807 J. E. Rowe, K. Lee, D. D. Dolliver, J. E. Johnson, *Aust. J. Chem.* **1999**, 52, 807–812.
- 1999BMCL1727 B. H. Lee, F. E. Dutton, M. F. Clothier, J. W. Bowman, J. P. Davis, S. S. Johnson, E. M. Thomas, M. R. Zantello, E. W. Zinser, J. C. McGuire, D. P. Thompson, T. G. Geary, *Biorg. Med. Chem. Lett.* **1999**, 9, 1727–1732.
- 1999CC1461 T. Nagamatsu, T. Fujita, *Chem. Commun.* **1999**, 16, 1461–1462.
- 1999CC2269 T. M. Barclay, A. W. Cordes, N. A. George, R. C. Haddon, M. E. Itkis, R. T. Oakley, *Chem. Commun.* **1999**, 22, 2269–2270.
- 1999CJC216 O. A. Phillips, K. S. K. Murthy, C. Y. Fiakpui, E. E. Knaus, *Can. J. Chem.* **1999**, 77, 216–222.
- 1999CPB876 T. Suzuki, H. Uesaka, H. Hamajima, T. Ikami, *Chem. Pharm. Bull.* **1999**, 47, 876–879.
- 1999EJO2751 R. Saladino, L. Stasi, R. Nicoletti, C. Crestini, M. Botta, *Eur. J. Org. Chem.* **1999**, 11, 2751–2756.
- 1999HCA1289 Z. Hamersak, B. Peric, B. Kojic-Prodic, L. Cotarca, P. Delogu, V. Sunjic, *Helv. Chim. Acta* **1999**, 82i, 1289–1301.
- 1999IJC(B)18 V. A. Vardhan, V. R. Kumar, R. Rao, *Indian J. Chem. Sect. B* **1999**, 38, 18–23.
- 1999IJC(B)237 M. Amir, A. Oberoi, S. Alam, *Indian J. Chem. Sect. B* **1999**, 38, 237–239.
- 1999IJC(B)993 M. Kidwai, P. Misra, K. R. Bhushan, R. K. Saxena, R. Gupta, M. Singh, *Indian J. Chem. Sect. B* **1999**, 38, 993–997.
- 1999IZV492 I. M. Lyapkalo, M. I. Lazareva, A. D. Dil'man, S. L. Ioffe, W. A. Smit, *Izv. Akad. Nauk Ser. Khim.* **1999**, 48, 492–498.
- 1999JA5940 R. A. Moss, L. A. Johnson, D. C. Merrer, G. E. Lee, *J. Amer. Chem. Soc.* **1999**, 121, 5940–5944.
- 1999JCR(M)460 A. Santagati, M. Modica, L. M. Scolaro, M. Santagati, *J. Chem. Res. Miniprint* **1999**, 2, 460–470.
- 1999JCR(M)548 K. Sasaki, Y.-X. Zhang, H. Yamamoto, S. Kashino, T. Hirota, *J. Chem. Res. Miniprint* **1999**, 2, 548–558.
- 1999JCR(S)398 O. M. Singh, H. Junjappa, H. Ila, *J. Chem. Res. Synop.* **1999**, 6, 398–399.
- 1999JCS(D)2231 P. Kilian, J. Marek, R. Marek, J. Tousek, O. Humpa, A. M. Z. Slawin, J. Touzin, J. Novosad, J. D. Woollins, *J. Chem. Soc. Dalton Trans.* **1999**, 13, 2231–2236.
- 1999JCS(P1)47 C.-M. Chu, J.-T. Liu, W.-W. Lin, C.-F. Yao, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1, 47–52.
- 1999JCS(P1)1339 N. Abe, K. Odagiri, M. Otani, E. Fujinaga, H. Fujii, A. Kakehi, *J. Chem. Soc. Perkin Trans. 1* **1999**, 10, 1339–1346.
- 1999JCS(P1)1853 B. L. Booth, F. A. T. Costa, Z. Mahmood, R. G. Pritchard, M. F. Proenca, *J. Chem. Soc. Perkin Trans. 1* **1999**, 13, 1853–1858.
- 1999JCS(P1)2713 G. P. Moloney, G. R. Martin, N. Mathews, H. Hobbs, S. Dodsworth, P. Y. Sang, C. Knight, M. Maxwell, R. C. Glen, *J. Chem. Soc. Perkin Trans. 1* **1999**, 19, 2713–2724.
- 1999JCS(P1)2725 G. P. Moloney, G. R. Martin, N. Mathews, S. MacLennan, S. Dodsworth, P. Y. Sang, C. Knight, M. Maxwell, R. C. Glen, *J. Chem. Soc. Perkin Trans. 1* **1999**, 19, 2725–2734.
- 1999JCS(P1)3117 T. Nagamatsu, H. Yamasaki, T. Fujita, K. Endo, H. Machida, *J. Chem. Soc. Perkin Trans. 1* **1999**, 21, 3117–3126.
- 1999JHC901 A. Shafiee, M. A. Ebrahimzadeh, A. Maleki, *J. Heterocycl. Chem.* **1999**, 36, 901–904.
- 1999JHC1119 E. Kh. Ahmed, U. Sensfuss, W. D. Habicher, *J. Heterocycl. Chem.* **1999**, 36, 1119–1122.
- 1999JHC1195 G. Biagi, I. Giorgi, O. Livi, C. Manera, V. Scartoni, *J. Heterocycl. Chem.* **1999**, 36, 1195–1198.
- 1999JHC1235 K.-J. Lee, J.-L. Kim, M. K. Hong, J. Y. Lee, *J. Heterocycl. Chem.* **1999**, 36, 1235–1240.
- 1999JHC1327 W.-D. Pfeiffer, A. Hetzheim, P. Pazdera, A. Bodtke, J. Muecke, *J. Heterocycl. Chem.* **1999**, 36, 1327–1336.
- 1999JIC461 R. H. Udipi, A. Kushnoor, A. R. Bhat, *J. Indian Chem. Soc.* **1999**, 76, 461–462.
- 1999JMC153 T. D. Aicher, G. R. Bebernit, P. A. Bell, L. J. Brand, J. G. Dain, R. Deems, W. S. Fillers, J. E. Foley, D. C. Knorr, J. Nadelson, D. A. Otero, R. Simpson, R. J. Strohschein, D. A. Young, *J. Med. Chem.* **1999**, 42, 153–163.
- 1999JMC1999 L. Jeppesen, P. H. Olesen, L. Hansen, M. J. Sheardown, C. Thomsen, T. Rasmussen, A. Fink-Jensen, M. S. Christensen, K. Rimvall, J. S. Ward, C. Whitesitt, D. O. Calligaro, F. P. Bymaster, N. W. DeLapp, C. C. Felder, H. E. Shannon, P. Sauerberg, *J. Med. Chem.* **1999**, 42, 1999–2006.
- 1999JMC4088 C. B. Vu, E. G. Corpuz, T. J. Merry, S. G. Pradeepan, C. Bartlett, R. S. Bohacek, M. C. Botfield, C. J. Eyermann, B. A. Lynch, I. A. MacNeil, M. K. Ram, M. R. van Schravendijk, S. Violette, T. K. Sawyer, *J. Med. Chem.* **1999**, 42, 4088–4098.
- 1999JOC1099 T.-L. Tsai, W.-C. Chen, C.-H. Yu, W. J. le Noble, W.-S. Chung, *J. Org. Chem.* **1999**, 64, 1099–1107.
- 1999JOC5366 T. Balle, P. Vedsoe, M. Begtrup, *J. Org. Chem.* **1999**, 64, 5366–5370.
- 1999JOC9272 K. S. Kim, E. Y. Hurh, J. N. Youn, J. I. Park, *J. Org. Chem.* **1999**, 64, 9272–9274.
- 1999KGS564 I. B. Starchenkov, V. G. Andrianov, A. F. Mishnev, *Khim. Geterotsikl. Soedin.* **1999**, 4, 564–573.
- 1999MI85 H. Chen, D.-Q. Qian, G.-X. Xu, Y.-X. Liu, X.-D. Chen, X.-D. Shi, R.-Z. Cao, L.-Z. Liu, *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, 144, 85–88.

- 1999MI203 A. Chimirri, F. Bevacqua, R. Gitto, S. Quartarone, M. Zappala, A. De Sarro, L. Maciocco, G. Biggio, G. De Sarro, *Med. Chem. Res.* **1999**, 9, 203–212.
- 1999MI557 L. F. Awad, E. S. H. El Ashry, *Nucleosides Nucleotides* **1999**, 18, 557–558.
- 1999MI800 M. A. E. Shaban, A. Z. Nasr, A. E. A. Morgaan, *Farmaco* **1999**, 54, 800–809.
- 1999MRC427 J. Schraml, M. Kviclova, L. Soukupova, V. Blechta, *Magn. Reson. Chem.* **1999**, 37, 427–429.
- 1999S655 T. Nagamatsu, H. Yamasaki, T. Akiyama, S. Hara, K. Mori, H. Kusakabe, *Synthesis* **1999**, 4, 655–663.
- 1999SC111 S. Lutun, B. Hasiak, D. Couturier, *Synth. Commun.* **1999**, 29, 111–116.
- 1999SC3863 J.-A. Ma, Z.-H. Ma, H.-M. Ma, R.-Q. Huang, R.-L. Shao, *Synth. Commun.* **1999**, 29, 3863–3868.
- 1999T5623 P. Conti, C. Dallanoce, M. De Amici, C. De Micheli, R. Fruttero, *Tetrahedron* **1999**, 55, 5623–5634.
- 1999T7115 J.-T. Liu, W.-W. Lin, J.-J. Jang, J.-Y. Liu, M.-C. Yan, C. Hung, K.-H. Kao, Y. Wang, C.-F. Yao, *Tetrahedron* **1999**, 55, 7115–7128.
- 1999T12493 M.-C. Yan, J.-Y. Liu, W.-W. Lin, K.-H. Kao, J.-T. Liu, J.-J. Jang, C.-F. Yao, *Tetrahedron* **1999**, 55, 12493–12514.
- 1999T14199 V. Nair, K. V. Radhakrishnan, K. C. Sheela, N. P. Rath, *Tetrahedron* **1999**, 55, 14199–14210.
- 1999TA487 G. Brogini, L. Garanti, G. Molteni, G. Zecchi, *Tetrahedron: Asymmetry* **1999**, 10, 487–492.
- 1999TA3873 G. Molteni, T. Pilati, *Tetrahedron: Asymmetry* **1999**, 10, 3873–3876.
- 1999TL883 D. Bourissou, G. Bertrand, *Tetrahedron Lett.* **1999**, 40, 883–886.
- 1999TL2605 F. Foti, G. Grassi, F. Risitano, *Tetrahedron Lett.* **1999**, 40, 2605–2606.
- 1999TL3275 C. T. Brain, J. M. Paul, Y. Loong, P. J. Oakley, *Tetrahedron Lett.* **1999**, 40, 3275–3278.
- 1999ZN(B)788 F. A. Attaby, S. M. Eldin, *Z. Naturforsch. B* **1999**, 54, 788–798.
- 1999ZN(B)923 I. S. Abdel Hafiz, A. A. Hassanien, A. M. Hussein, *Z. Naturforsch. B* **1999**, 54, 923–928.
- 1999ZOB767 Yu. G. Trishin, V. I. Namestnikov, V. K. Bel'skii, *Zh. Obshch. Khim.* **1999**, 69, 767–775.
- 2000AF55 S. N. Pandeya, D. Sriram, G. Nath, E. de Clercq, *Arzneim. Forsch.* **2000**, 50, 55–59.
- 2000AP113 J.-G. Park, M.-J. Lee, J. Y. Kong, M. H. Jung, *Arch. Pharm. (Weinheim Ger.)* **2000**, 333, 113–117.
- 2000BMCL1559 S. Manfredini, I. Lampronti, S. Vertuani, N. Solaroli, M. Recanatini, D. Bryan, M. McKinney, *Bioorg. Med. Chem.* **2000**, 8, 1559–1566.
- 2000BMCL601 Z. Sui, J. Guan, M. P. Ferro, K. McCoy, M. P. Wachter, W. V. Murray, M. Singer, M. Steber, D. M. Ritchie, D. C. Argentieri, *Bioorg. Med. Chem. Lett.* **2000**, 10, 601–604.
- 2000BMCL1077 T. S. Maurer, J. Pan, B. P. Booth, T. I. Kalman, H.-L. Fung, *Bioorg. Med. Chem. Lett.* **2000**, 10, 1077–1080.
- 2000BMCL1431 T. Biftu, D. D. Feng, G.-B. Liang, H. Kuo, X. Qian, E. M. Naylor, V. J. Colandrea, M. R. Candelore, M. A. Cascieri, L. F. Colwell, M. J. Forrest, G. J. Hom, D. E. MacIntyre, R. A. Stearns, C. D. Strader, M. J. Wyvratt, M. H. Fisher, A. E. Weber, *Bioorg. Med. Chem. Lett.* **2000**, 10, 1431–1434.
- 2000CC497 E. A. C. Brussee, A. Meetsma, B. Hessen, J. H. Teuben, *Chem. Commun.* **2000**, 6, 497–498.
- 2000CJC1469 M. Weidenbruch, F. Meiners, W. Saak, *Can. J. Chem.* **2000**, 78, 1469–1473.
- 2000CL244 N. Takeda, N. Tokitoh, R. Okazaki, *Chem. Lett.* **2000**, 3, 244–245.
- 2000CPB509 N. Kudo, T. Yoneda, K. Sato, T. Honma, S. Sugai, *Chem. Pharm. Bull.* **2000**, 48, 509–515.
- 2000CPB1702 H. Takechi, Y. Oda, N. Nishizono, K. Oda, M. Machida, *Chem. Pharm. Bull.* **2000**, 48, 1702–1710.
- 2000EJI417 V. Cadierno, B. Donnadieu, A. Igau, J.-P. Majoral, *Eur. J. Inorg. Chem.* **2000**, 3, 417–422.
- 2000EJI1045 W.-K. Wong, C. Sun, W.-Y. Wong, D. W. J. Kwong, W.-T. Wong, *Eur. J. Inorg. Chem.* **2000**, 5, 1045–1054.
- 2000EJO275 M. Depature, J. Diewok, J. Grimaldi, J. Hatem, *Eur. J. Org. Chem.* **2000**, 2, 275–280.
- 2000H1737 A. S. Abushamleh, M. M. El-Abdelah, C. M. Moessmer, *Heterocycles* **2000**, 53, 1737–1744.
- 2000HCA1611 K. Schank, H. Beck, F. Werner, *Helv. Chim. Acta* **2000**, 83, 1611–1624.
- 2000JFC195 Y. Xu, Y. Wang, S. Zhu, *J. Fluorine Chem.* **2000**, 104, 195–200.
- 2000JMC953 M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, K. C. Grega, J. B. Hester, D. K. Hutchinson, J. Morris, R. J. Reischer, C. W. Ford, G. E. Zurenko, J. C. Hamel, R. D. Schaadt, D. Stapert, B. H. Yagi, *J. Med. Chem.* **2000**, 43, 953–970.
- 2000JMC1456 B. Pirotte, R. Ouedraogo, P. de Tullio, S. Khelili, F. Somers, S. Boverie, L. Dupont, J. Fontaine, J. Damas, P. Lebrun, *J. Med. Chem.* **2000**, 43, 1456–1466.
- 2000JMC3824 D. Catarzi, V. Colotta, F. Varano, L. Cecchi, G. Filacchioni, A. Galli, C. Costagli, V. Carla, *J. Med. Chem.* **2000**, 43, 3824–3826.
- 2000JA2995 H. Takahashi, Y. Hitomi, Y. Iwai, S. Ikegami, *J. Amer. Chem. Soc.* **2000**, 122, 2995–3000.
- 2000JA9120 J. Nakayama, T. Kitahara, Y. Sugihara, A. Sakamoto, A. Ishii, *J. Amer. Chem. Soc.* **2000**, 122, 9120–9126.
- 2000JCR(S)84 S. Dabak, V. Ahse, *J. Chem. Res. Synop.* **2000**, 2, 84–85.
- 2000JCR(S)164 A. Z. Sayed, N. A. El-Hady, A. M. El-Agrody, *J. Chem. Res. Synop.* **2000**, 4, 164–166.
- 2000JCR(S)226 S. Rostamizadeh, H. Keshavarz, *J. Chem. Res. Synop.* **2000**, 5, 226–227.
- 2000JCS(D)967 C.-T. Chen, L. H. Doerrer, V. C. Williams, M. L. H. Green, *J. Chem. Soc. Dalton Trans.* **2000**, 6, 967–974.
- 2000JCS(D)2587 A. S. W. Bligh, N. Choi, C. M. McGrath, M. McPartlin, T. M. Woodroffe, *J. Chem. Soc. Dalton Trans.* **2000**, 15, 2587–2594.
- 2000JCS(P1)33 T. Nagamatsu, T. Fujita, K. Endo, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1, 33–42.
- 2000JCS(P1)1685 G. Brogini, G. Molteni, *J. Chem. Soc. Perkin Trans. 1* **2000**, 11, 1685–1690.
- 2000JHC955 P. Stanetty, G. Hattinger, M. D. Mihovilovic, K. Mereiter, *J. Heterocycl. Chem.* **2000**, 37, 955–958.
- 2000JHC1521 H. S. El-Kashef, A. M. K. El-Dean, A. A. Geies, J. C. Lancelot, P. Dallemagne, S. Rault, *J. Heterocycl. Chem.* **2000**, 37, 1521–1526.
- 2000JIC302 R. H. Udupi, G. V. Suresh, S. R. Setty, A. R. Bhat, *J. Indian Chem. Soc.* **2000**, 77, 302–304.
- 2000JOC931 J. M. Farrar, M. K. Patel, P. Kaszynski, V. G. Young, *J. Org. Chem.* **2000**, 65, 931–940.
- 2000JOC1003 U. S. Soerensen, E. Falch, P. Krogsgaard-Larsen, *J. Org. Chem.* **2000**, 65, 1003–1007.
- 2000JOC1139 N. Arulsamy, D. S. Bohle, *J. Org. Chem.* **2000**, 65, 1139–1143.
- 2000JOC4289 T. D. Ros, M. Prato, V. Lucchini, *J. Org. Chem.* **2000**, 65, 4289–4297.

- 2000JOC6922 O. Miyata, A. Nishiguchi, I. Ninomiya, K. Aoe, K. Okamura, T. Naito, *J. Org. Chem.* **2000**, *65*, 6922–6931.
- 2000JOC8439 S. G. Ziotin, P. G. Kislitsin, A. I. Podgursky, A. V. Samet, V. V. Semenov, A. C. Buchanan, A. A. Gakh, *J. Org. Chem.* **2000**, *65*, 8439–8443.
- 2000JOM414 Y. Maeda, R. Sato, T. Wakahara, M. Okamura, T. Akasaka, M. Fujitsuka, O. Ito, K. Kobayashi, S. Nagase, M. Kako, Y. Nakadaira, E. Horn, *J. Organomet. Chem.* **2000**, *611*, 414–419.
- 2000JPR96 A. S. Shawali, A. A. Elghandour, S. M. El-Sheikh, *J. Prakt. Chem.* **2000**, *342*, 96–99.
- 2000KGS249 V. I. Kelarev, M. A. Silin, N. A. Grigor'eva, V. N. Koshelev, *Khim. Geterotsikl. Soedin.* **2000**, *36*, 249–255.
- 2000M175 E. Hamuryudan, Z. A. Bayir, O. Bekaroglu, *Monatsh. Chem.* **2000**, *131*, 175–180.
- 2000MI1 A. M. Abdel-Fattah, A. S. Aly, F. A. Gad, N. A. Hassan, A. B. A. El-Gazzar, *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *163*, 1–28.
- 2000MI11 H. M. Moustafa, *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *164*, 11–22.
- 2000MI35 A. O. Abdelhamid, N. M. Abed, F. M. Al-Fayez, *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *156*, 35–52.
- 2000MI57 Z. H. Khalil, A. S. Yanni, A. M. Gaber, Sh. A. Abdel-Mohsen, *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *166*, 57–70.
- 2000MI67 H. Foks, A. Czarnocka-Janowicz, W. Rudnicka, H. Trzeciak, *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *164*, 67–82.
- 2000MI149 A. E. Abdel-Rahman, E. A. Bakhite, O. S. Mohamed, E. A. Thabet, *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *166*, 149–172.
- 2000MI161 M. A. A. Elneairy, F. A. Attaby, M. S. Elsayed, *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *167*, 161–180.
- 2000MI171 E. A.-G. Bakhite, *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *159*, 171–194.
- 2000MI199 B. Modzelewska-Banachiewicz, E. Jagiello-Wojtowicz, E. Tokarzewska-Wielosz, *Acta Pol. Pharm.* **2000**, *57*, 199–204.
- 2000MI211 M. M. Heravi, M. Rahimizadeh, M. Seyf, A. Davoodnia, M. Ghassemzadeh, *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *167*, 211–218.
- 2000MI541 H.-S. Dong, K. Wei, Q.-L. Wang, B. Quan, *J. Chin. Chem. Soc. (Taipei)* **2000**, *47*, 541–546.
- 2000MI835 A. B. A. El-Gazzar, N. A. Hassan, *Molecules* **2000**, *5*, 835–850.
- 2000MI933 S. M. Sayed, *J. Chin. Chem. Soc. (Taipei)* **2000**, *47*, 933–936.
- 2000MI1721 C. Shang, W.-L. Gong, E. R. Blatchley, *Environ. Sci. Technol.* **2000**, *34*, 1721–1728.
- 2000MRC795 J. Schraml, M. Kvicalova, V. Blechta, L. Soukupova, O. Exner, H.-M. Boldhaus, F. Erdt, C. Bliefert, *Magn. Reson. Chem.* **2000**, *38*, 795–801.
- 2000PHA500 M. Modica, M. Santagati, A. Santagati, V. Cutuli, N. Mangano, A. Caruso, *Pharmazie* **2000**, *55*, 500–502.
- 2000PHA737 A. Santagati, M. Modica, M. Santagati, V. M. C. Cutuli, N. G. Mangano, A. Caruso, *Pharmazie* **2000**, *55*, 737–740.
- 2000PHA896 O. S. Moustafa, M. Z. A. Badr, E. M. Kamel, *Pharmazie* **2000**, *55*, 896–899.
- 2000S1148 S. A. Bakunov, A. V. Rukavishnikov, A. V. Tkachev, *Synthesis* **2000**, *8*, 1148–1159.
- 2000S1166 M. M. Abdel-Khalik, M. H. Elnagdi, S. M. Agamy, *Synthesis* **2000**, *8*, 1166–1169.
- 2000S1719 A. Defoin, M. Joubert, J.-M. Heuchel, C. Strehler, J. Streith, *Synthesis* **2000**, *12*, 1719–1726.
- 2000SC437 S. Liras, M. P. Allen, B. E. Segelstein, *Synth. Commun.* **2000**, *30*, 437–444.
- 2000SC1563 J.-A. Ma, Z.-H. Ma, H.-M. Ma, R.-Q. Huang, R.-L. Shao, *Synth. Commun.* **2000**, *30*, 1563–1568.
- 2000SC3031 M. Kidwai, P. Misra, K. R. Bhushan, B. Dave, *Synth. Commun.* **2000**, *30*, 3031–3040.
- 2000SC3423 A.-B. G. Ghattas, H. M. Moustafa, *Synth. Commun.* **2000**, *30*, 3423–3438.
- 2000SL526 E. Aller, P. Molina, A. Lorenzo, *Syn. Lett.* **2000**, *4*, 526–528.
- 2000T999 S. Buscemi, M. Gruttadauria, *Tetrahedron* **2000**, *56*, 999–1004.
- 2000T1057 S. Kanemasa, H. Matsuda, A. Kamimura, T. Kakinami, *Tetrahedron* **2000**, *56*, 1057–1064.
- 2000T4213 K.-P. Hartmann, M. Heuschmann, *Tetrahedron* **2000**, *56*, 4213–4218.
- 2000T6259 G. R. Ruf, J. Dietz, M. Regitz, *Tetrahedron* **2000**, *56*, 6259–6268.
- 2000T7433 M. P. Duarte, A. M. Lobo, S. Prabhakar, *Tetrahedron Lett.* **2000**, *41*, 7433–7436.
- 2000T8071 K. Paulvannan, T. Chen, R. Hale, *Tetrahedron* **2000**, *56*, 8071–8076.
- 2000TA1975 G. Brogini, G. Molteni, T. Pilati, *Tetrahedron: Asymmetry* **2000**, *11*, 1975–1984.
- 2000TA3273 R. C. F. Jones, S. J. Hollis, J. N. Iley, *Tetrahedron: Asymmetry* **2000**, *11*, 3273–3276.
- 2000TA4955 H. Pajouhes, M. Hosseini-Meresht, H. Pjoughesh, K. Curry, *Tetrahedron: Asymmetry* **2000**, *11*, 4955–4958.
- 2000TL155 S.-P. Hong, M. C. McIntosh, T. Barclay, W. Cordes, *Tetrahedron Lett.* **2000**, *41*, 155–160.
- 2000TL945 Y. Ma, C. Qian, *Tetrahedron Lett.* **2000**, *41*, 945–948.
- 2000TL1191 C. Matt, A. Gissot, A. Wagner, C. Mioskowski, *Tetrahedron Lett.* **2000**, *41*, 1191–1194.
- 2000TL9407 V.-D. Le, C. W. Rees, S. Sivasadan, *Tetrahedron Lett.* **2000**, *41*, 9407–9412.
- 2000TL9791 S. Gerard, R. Plantier-Royon, J.-M. Nuzillard, C. Portella, *Tetrahedron Lett.* **2000**, *41*, 9791–9796.
- 2000ZOB702 Yu. L. Zotov, E. V. Shishkin, D. S. Klimov, A. V. Gora, *Zh. Obshch. Khim.* **2000**, *70*, 702–702.
- 2000ZOB1931 S. K. Tukanova, V. Khagai, B. Zh. Dzhimbaev, *Zh. Obshch. Khim.* **2000**, *70*, 1931–1931.
- 2001AF569 A. A. Nadkarni, V. R. Kamat, B. G. Khadse, *Arzneim. Forsch.* **2001**, *51*, 569–573.
- 2001BMCL2385 K. G. Liu, J. S. Smith, A. H. Ayscue, B. R. Henke, M. H. Lambert, L. M. Leesnitzer, K. D. Plunket, T. M. Willson, D. D. Sternbach, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2385–2388.
- 2001EJO1225 L. M. Yagupolskii, S. V. Shelyazhenko, I. I. Maletina, V. N. Petrik, E. B. Rusanov, A. N. Chernega, *Eur. J. Org. Chem.* **2001**, *7*, 1225–1234.
- 2001H777 Y. Sasaki, M. Fujitsuka, O. Ito, Y. Maeda, T. Wakahara, T. Akasaka, K. Kobayashi, S. Nagase, M. Kako, Y. Nakadaira, *Heterocycles* **2001**, *54*, 777–788.
- 2001HAC468 A. O. Abdelhamid, M. M. M. Sallam, S. A. Amer, *Heteroat. Chem.* **2001**, *12*, 468–474.

- 2001HAC557 J. Xu, C. Wang, Q. Zhang, *Heteroat. Chem.* **2001**, 12, 557–560.
- 2001IJC(B)163 N. P. Shetgiri, S. V. Kokitkar, *Indian J. Chem. Sect. B* **2001**, 40, 163–166.
- 2001IJC(B)636 A. M. Dhiman, K. N. Wadodkar, S. D. Patil, *Indian J. Chem. Sect. B* **2001**, 40, 636–639.
- 2001IJC(B)640 A. M. Dhiman, K. N. Wadodkar, S. D. Patil, *Indian J. Chem. Sect. B* **2001**, 40, 640–643.
- 2001IJC(B)828 U. V. Laddi, M. B. Talawar, S. R. Desai, R. S. Bennur, S. C. Bennur, *Indian J. Chem. Sect. B* **2001**, 40, 828–833.
- 2001IZV706 G. Kh. Khisamutdinov, S. A. Shevelev, *Izv. Akad. Nauk Ser. Khim.* **2001**, 50, 706–707.
- 2001IZV1265 A. E. Kul'yanova, S. N. Osipov, A. F. Kolomiets, *Izv. Akad. Nauk Ser. Khim.* **2001**, 7, 1265–1267.
- 2001JA1539 T. D. Owens, F. J. Hollander, A. G. Oliver, J. A. Ellman, *J. Amer. Chem. Soc.* **2001**, 123, 1539–1540.
- 2001JCS(D)1692 A. Lisovskii, M. Botoshansky, M. S. Eisen, *J. Chem. Soc. Dalton Trans.* **2001**, 11, 1692–1698.
- 2001JCS(P1)1304 J. Guillard, C. Lamazzi, O. Meth-Cohn, C. W. Rees, A. J. P. White, D. J. Williams, *J. Chem. Soc. Perkin Trans. 1* **2001**, 11, 1304–1313.
- 2001JCS(P1)1751 D. Boschi, G. Sorba, M. Bertinaria, R. Fruttero, R. Calvino, A. Gasco, *J. Chem. Soc. Perkin Trans. 1* **2001**, 15, 1751–1757.
- 2001JHC929 Haijian Shi, Haoxin Shi, Z. Wang, *J. Heterocycl. Chem.* **2001**, 38, 929–932.
- 2001JHC973 M. Modica, M. Santagati, A. Santagati, *J. Heterocycl. Chem.* **2001**, 38, 973–978.
- 2001JMC1268 K. Ohmoto, T. Yamamoto, M. Okuma, T. Horiuchi, H. Imanishi, Y. Odagaki, K. Kawabata, T. Sekioka, Y. Hirota, S. Matsuoka, H. Nakai, M. Toda, *J. Med. Chem.* **2001**, 44, 1268–1285.
- 2001JMC3157 D. Catarzi, V. Colotta, F. Varano, G. Filacchioni, A. Galli, C. Costagli, V. Carla, *J. Med. Chem.* **2001**, 44, 3157–3165.
- 2001JOC2246 A. Leggio, A. Liguori, A. Napoli, C. Siciliano, G. Sindona, *J. Org. Chem.* **2001**, 66, 2246–2250.
- 2001JOC4055 A. S. Shawali, M. A. N. Mosselhi, N. M. Tawfik, *J. Org. Chem.* **2001**, 66, 4055–4057.
- 2001JOC6410 J. W. Bode, E. M. Carreira, *J. Org. Chem.* **2001**, 66, 6410–6424.
- 2001JOC7205 K. Bogdanowicz-Swed, J. Grochowski, A. Obara, B. Rys, P. Serda, *J. Org. Chem.* **2001**, 66, 7205–7208.
- 2001JOC7979 J. E. Johnson, N. M. Morales, A. M. Gorczyca, D. D. Dolliver, M. A. McAllister, *J. Org. Chem.* **2001**, 66, 7979–7985.
- 2001JOM26 E. Lukevics, G. Barbarella, P. Arsenyan, I. Shestakova, S. Belyakov, J. Popelis, O. Pudova, *J. Organomet. Chem.* **2001**, 636, 26–30.
- 2001JPP267 A. R. Bhat, G. V. Bhat, G. G. Shenoy, *J. Pharm. Pharmacol.* **2001**, 53, 267–272.
- 2001M753 A. El-Wareth, A. O. Sarhan, *Monatsh. Chem.* **2001**, 132, 753–764.
- 2001M959 M. A. Abdallah, *Monatsh. Chem.* **2001**, 132, 959–966.
- 2001MI41 R. Okazaki, *Phosphorus, Sulfur Silicon Relat. Elem.* **2001**, 168, 41–50.
- 2001MI65 A. S. Shawali, I. F. Zeid, M. H. Abdelkader, A. A. Elsherbini, F. M. A. Altalbawy, *J. Chin. Chem. Soc. (Taipei)* **2001**, 48, 65–72.
- 2001MI191 M. Boeger, D. Duerr, L. Gsell, R. G. Hall, F. Karrer, O. Kristiansen, P. Maienfisch, A. Pascual, A. Rindlisbacher, *Post Manage. Sci.* **2001**, 57, 191–202.
- 2001MI510 K. A. Kandeel, A. S. A. Youssef, *Molecules* **2001**, 6, 510–518.
- 2001MI519 A. M. El-Agrody, M. S. Abd El-Latif, N. A. El-Hady, A. H. Fakery, A. H. Bedair, *Molecules* **2001**, 6, 519–527.
- 2001MI685 G. Turan-Zitouni, M. Sivaci, F. S. Kilic, K. Erol, *Eur. J. Med. Chem. Chim. Ther.* **2001**, 36, 685–690.
- 2001MI913 M. A. Berghot, *J. Chin. Chem. Soc. (Taipei)* **2001**, 48, 913–920.
- 2001MI969 O. R. Gautun, P. H. J. Carlsen, *Molecules* **2001**, 6, 969–978.
- 2001MI1163 Y.-W. Ho, *J. Chin. Chem. Soc. (Taipei)* **2001**, 48, 1163–1174.
- 2001MI1671 R. Ahmad, R. Iqbal, H. Akhtar, Zia-ul-Haq, H. Duddeck, L. Stefaniak, J. Sitkowski, *Nucleosides Nucleotides* **2001**, 20, 1671–1682.
- 2001MI6258 T. Pasinszki, T. Karpati, N. P. C. Westwood, *J. Phys. Chem. A* **2001**, 105, 6258–6265.
- 2001S1228 D. Doepp, P. Lauterfeld, M. Schneider, D. Schneider, G. Henkel, Y. A. E.-S. Issac, I. Elghamry, *Synthesis* **2001**, 8, 1228–1235.
- 2001SC81 H.-S. Dong, K. Wei, Q.-L. Wang, B. Quan, *Synth. Commun.* **2001**, 31, 81–88.
- 2001SC1647 K. M. Dawood, *Synth. Commun.* **2001**, 31, 1647–1658.
- 2001SC2447 A.-B. A. G. Ghattas, H. M. Moustafa, O. A. Abd Allah, A. A. Amer, *Synth. Commun.* **2001**, 31, 2447–2456.
- 2001SC2649 G. Broggin, L. Garanti, G. Molteni, T. Pilati, *Synth. Commun.* **2001**, 31, 2649–2656.
- 2001SC2841 Z. Wang, Haoxin Shi, *Synth. Commun.* **2001**, 31, 2841–2848.
- 2001SL937 S. Kim, N. Kim, W.-J. Chung, C. H. Cho, *Syn. Lett.* **2001**, S937–S940.
- 2001T8039 D. J. Burkhart, P. Zhou, A. Blumenfeld, B. Twamley, N. R. Natale, *Tetrahedron* **2001**, 57, 8039–8046.
- 2001TL1441 A. R. Gangloff, J. Litvak, E. J. Shelton, D. Sperandio, V. R. Wang, K. D. Rice, *Tetrahedron Lett.* **2001**, 42, 1441–1444.
- 2001TL8981 L. A. Calvo, A. M. Gonzalez-Nogal, A. Gonzalez-Ortega, M. C. Sanudo, *Tetrahedron Lett.* **2001**, 42, 8981–8984.
- 2001ZN(B)547 W. Thimann, D. Geffken, *Z. Naturforsch. B* **2001**, 56, 547–553.
- 2001ZN(B)826 A. A. Hamed, H. F. Bader, E.-S. H. El-Ashry, *Z. Naturforsch. B* **2001**, 56, 826–836.
- 2001ZOB508 Yu. G. Trishin, V. I. Namestnikov, V. K. Bel'skii, *Zh. Obshch. Khim.* **2001**, 71, 508–512.
- 2001ZOR455 I. V. Tselinskii, S. F. Mel'nikova, T. V. Romanova, *Zh. Org. Khim.* **2001**, 37, 455–461.
- 2001ZOR1043 A. P. Avdeenko, V. V. Pirozhenko, L. M. Yagupol'skii, I. L. Marchenko, *Zh. Org. Khim.* **2001**, 37, 1043–1051.
- 2002AF572 P. Marakos, S. Papakonstantinou-Garoufalisa, E. Tani, P. N. Kourounakis, G. Athanaskiou, A. Chytyroglou-Lada, *Arzneim. Forsch.* **2002**, 52, 572–577.
- 2002BMCL589 J.-P. Bongartz, R. Stokbroekx, M. Van der Aa, M. Luyckx, M. Willems, M. Ceusters, L. Meerpoel, G. Smets, T. Jansen, W. Wouters, C. Bowden, L. Valletta, M. Herb, R. Tominovich, R. Tuman, *Bioorg. Med. Chem. Lett.* **2002**, 12, 589–592.

- 2002BMCL3595 H. K. Smith, R. P. Beckett, J. M. Clements, S. Doel, S. P. East, S. B. Launchbury, L. M. Pratt, Z. M. Spavold, W. Thomas, R. S. Todd, M. Whittaker, *Bioorg. Med. Chem. Lett.* **2002**, 12, 3595–3600.
- 2002CCC209 R. Gup, H. K. Alpoguz, A. D. Beduk, *Collect. Czech. Chem. Commun.* **2002**, 67, 209–218.
- 2002CL34 N. Tokitoh, T. Sadahiro, K. Hatano, T. Sasaki, N. Takeda, R. Okazaki, *Chem. Lett.* **2002**, 1, 34–35.
- 2002EJO1654 P. Froberg, G. Drutkowski, C. Wagner, *Eur. J. Org. Chem.* **2002**, 10, 1654–1664.
- 2002EJO2411 S. Auricchio, C. Magnani, A. M. Truscello, *Eur. J. Org. Chem.* **2002**, 14, 2411–2416.
- 2002H143 I. Shibuya, Y. Gama, M. Shimizu, M. Goto, *Heterocycles* **2002**, 57, 143–150.
- 2002H631 T. Nagamatsu, T. Fujita, *Heterocycles* **2002**, 57, 631–636.
- 2002HCA3773 C. S. Tomooka, E. M. Carreira, *Helv. Chim. Acta* **2002**, 85, 3773–3784.
- 2002IJC(B)1257 B. S. Holla, K. Shridhara, M. K. Shivananda, *Indian J. Chem. Sect. B* **2002**, 41, 1257–1262.
- 2002IJC(B)1953 H.-S. Dong, B. Quan, J.-D. Luo, *Indian J. Chem. Sect. B* **2002**, 41, 1953–1956.
- 2002IJC(B)1964 S. D. Sharma, A. Saluja, S. Bhaduri, S. Kanwar, *Indian J. Chem. Sect. B* **2002**, 41, 1964–1969.
- 2002IZV960 Yu. G. Trishin, V. L. Namestnikov, V. K. Belsky, *Izv. Akad. Nauk Ser. Khim.* **2002**, 6, 960–964.
- 2002IZV1387 V. N. Yarovenko, S. A. Kosarev, I. V. Zavarzin, M. M. Krayushkin, *Izv. Akad. Nauk Ser. Khim.* **2002**, 51, 1387–1391.
- 2002JA2506 T. Kato, H. Gornitzka, A. Baceiredo, W. W. Schoeller, G. Bertrand, *J. Amer. Chem. Soc.* **2002**, 124, 2506–2512.
- 2002JCR(S)299 A. F. Brigas, C. S. C. Fonseca, R. A. W. Johnstone, *J. Chem. Res. Synop.* **2002**, 6, 299–300.
- 2002JCS(P1)1535 C. W. Rees, S. Sivadasan, A. J. P. White, D. J. Williams, *J. Chem. Soc. Perkin Trans. 1* **2002**, 13, 1535–1542.
- 2002JCS(P1)1543 V.-D. Le, C. W. Rees, S. Sivadasan, *J. Chem. Soc. Perkin Trans. 1* **2002**, 13, 1543–1547.
- 2002JCS(P2)1950 L. M. Yagupolskii, V. N. Petrik, N. V. Kondratenko, L. Soovaeli, I. Kaljurand, I. Leito, I. A. Koppel, *J. Chem. Soc. Perkin Trans. 2* **2002**, 11, 1950–1955.
- 2002JHC45 A. S. Shawali, M. A. Abdallah, M. M. Zayed, *J. Heterocycl. Chem.* **2002**, 39, 45–50.
- 2002JHC213 A. Shafiee, M. Shekarchi, *J. Heterocycl. Chem.* **2002**, 39, 213–216.
- 2002JHC237 J. W. Pawlik, C. Changtong, S. Tantayanon, *J. Heterocycl. Chem.* **2002**, 39, 237–240.
- 2002JHC845 C. H. Lee, K.-J. Lee, *J. Heterocycl. Chem.* **2002**, 39, 845–848.
- 2002JHC885 G. Biagi, I. Giorgi, O. Livi, F. Pacchini, V. Scartoni, *J. Heterocycl. Chem.* **2002**, 39, 885–888.
- 2002JHC1101 U. Ghosh, J. A. Katzenellenbogen, *J. Heterocycl. Chem.* **2002**, 39, 1101–1104.
- 2002JIC381 R. H. Udupi, V. M. Kulkarni, P. Purushottamachar, N. Srinivasalu, *J. Indian Chem. Soc.* **2002**, 79, 381–382.
- 2002JMC1887 I. Collins, C. Moyes, W. B. Davey, M. Rowley, F. A. Bromidge, K. Quirk, J. R. Atack, R. M. McKernan, S.-A. Thompson, K. Wafford, G. R. Dawson, A. Pike, B. Sohal, N. N. Tsou, R. G. Ball, J. L. Castro, *J. Med. Chem.* **2002**, 45, 1887–1900.
- 2002JMC2123 D. M. Wilson, A. P. Termin, L. Mao, M. M. Ramirez-Weinhouse, V. Molteni, P. D. J. Grootenhuys, K. Miller, S. Keim, G. Wise, *J. Med. Chem.* **2002**, 45, 2123–2126.
- 2002JMC2589 A. Kakefuda, T. Suzuki, T. Tobe, J. Tsukada, A. Tahara, S. Sakamoto, S.-I. Tsukamoto, *J. Med. Chem.* **2002**, 45, 2589–2598.
- 2002JMC4171 F. E. Nielsen, T. B. Bodvarsdottir, A. Worsaae, P. MacKay, C. E. Stidsen, H. C. M. Boonen, L. Pridal, P. O. G. Arkhammar, P. Wahl, L. Ynddal, F. Junager, N. Dragsted, T. M. Tagmose, J. P. Mogensen, A. Koch, S. P. Treppendahl, J. B. Hansen, *J. Med. Chem.* **2002**, 45, 4171–4187.
- 2002JOC4833 M. Couturier, J. L. Tucker, C. Proulx, G. Boucher, P. Dube, B. M. Andresen, A. Ghosh, *J. Org. Chem.* **2002**, 67, 4833–4838.
- 2002JOM274 A. Z. Al-Rubaie, L. Z. Yousif, A. J. H. Al-Hamad, *J. Organomet. Chem.* **2002**, 656, 274–280.
- 2002MI71 M. J. Kohl, R. G. Lejeune, *Steroids* **2002**, 67, 71–76.
- 2002MI253 M. Kritsanida, A. Mouroutsou, P. Marakos, N. Pouli, S. Papakonstantinou-Garoufalias, C. Pannecoque, M. Witvrouw, E. De Clercq, *Pharmaco* **2002**, 57, 253–258.
- 2002MI487 M. A. N. Mosselhi, M. A. Abdallah, Y. F. Mohamed, A. S. Shawali, *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, 177, 487–496.
- 2002MI573 G. Turan-Zitouni, Z. A. Kaplancikli, A. Oezdemir, *Pharmaco* **2002**, 57, 573–576.
- 2002MI581 Z. Szarka, R. Skoda-Foeldes, J. Horvath, Z. Tuba, L. Kollar, *Steroids* **2002**, 67, 581–586.
- 2002MI1323 E. K. Ahmed, *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, 177, 1323–1336.
- 2002MI1651 H. He, M. Li, A. Lu, Z. Liu, *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, 177, 1651–1656.
- 2002MI1671 N. Yamada, D. Kusano, E. Kuwano, *Biosci. Biotechnol. Biochem.* **2002**, 66, 1671–1676.
- 2002MI2923 M. Rahimizadeh, A. Davoodnia, M. M. Heravi, M. Bakavoli, *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, 177, 2923–2930.
- 2002MI5305 D. Amsellem, S. Mazieres, V. Piquet-Faure, H. Gornitzka, A. Baceiredo, G. Bertrand, *Chem. Europ. J.* **2002**, 8, 5305–5311.
- 2002OL2401 H. Takahashi, Y. Iwai, Y. Hitomi, S. Ikegami, *Org. Lett.* **2002**, 4, 2401–2404.
- 2002PHA442 M. A. E. Shaban, A. Z. Nasr, A. E. A. Morgaan, *Pharmazie* **2002**, 57, 442–447.
- 2002PJC687 E. Canpolat, M. Kaya, A. O. Goerguelue, *Pol. J. Chem.* **2002**, 76, 687–694.
- 2002SC111 S. Joshi, A. V. Karnik, K. Sadeghi, *Synth. Commun.* **2002**, 32, 111–114.
- 2002SC1899 S. Rostamizadeh, K. Sadeghi, *Synth. Commun.* **2002**, 32, 1899–1902.
- 2002SL519 P. Raboisson, B. Norberg, J. R. Casimir, J.-J. Bourguignon, *Syn. Lett.* **2002**, 3, 519–521.
- 2002TL2037 L. El Kaim, L. Grimaud, N. K. Jana, C. Tirla, *Tetrahedron Lett.* **2002**, 43, 2037–2038.
- 2002TL3255 G. T. Lee, K. Prasad, O. Repic, *Tetrahedron Lett.* **2002**, 43, 3255–3258.
- 2002TL4741 E. Fernandez, S. Garcia-Ochoa, S. Huss, A. Mallo, J. M. Bueno, F. Micheli, A. Paio, E. Piga, P. Zarantonello, *Tetrahedron Lett.* **2002**, 43, 4741–4746.
- 2002TL7189 S. Kim, R. Kavali, *Tetrahedron Lett.* **2002**, 43, 7189–7192.
- 2002TL7991 M.-C. Yan, Z. Tu, C. Lin, C.-F. Yao, *Tetrahedron Lett.* **2002**, 43, 7991–7994.
- 2002TL8925 L. El Kaim, L. Grimaud, N. K. Jana, F. Mettetal, C. Tirla, *Tetrahedron Lett.* **2002**, 43, 8925–8928.
- 2002ZOR931 E. N. Utkina, A. A. Michurin, A. V. Shishulina, *Zh. Org. Khim.* **2002**, 38, 931–936.

- 2002ZOR1422 K. A. Esikov, S. E. Morozova, A. A. Malin, V. A. Ostrovskii, *Zh. Org. Khim.* **2002**, 38, 1422–1425.
2003AP230 M. H. Jung, J.-G. Park, W.-K. Park, *Arch. Pharm. (Weinheim Ger.)* **2003**, 336, 230–235.
2003CPB122 M. Gyoten, H. Nagaya, S. Fukuda, Y. Ashida, Y. Kawano, *Chem. Pharm. Bull.* **2003**, 51, 122–133.
2003JA2179 V. Volkis, E. Nelkenbaum, A. Lisovskii, G. Hasson, R. Semiat, M. Kapon, M. Botoshanky, Y. Eishen, M. S. Eisen, *J. Amer. Chem. Soc.* **2003**, 125, 2179–2194.
2003JCR(M)236 E. A. Bakhite, A. E. Abdel-Rahman, O. S. Mohamed, E. A. Thabet, *J. Chem. Res. Miniprint* **2003**, 2, 236–247.
2003JMC87 G. W. Zamponi, S. C. Stotz, R. J. Staples, T. M. Andro, J. K. Nelson, V. Hulubei, A. Blumenfeld, N. R. Natale, *J. Med. Chem.* **2003**, 46, 87–96.
2003JMC427 G. Chauviere, B. Bouteille, B. Enanga, C. de Albuquerque, S. L. Croft, M. Dumas, J. Perie, *J. Med. Chem.* **2003**, 46, 427–440.
2003JOC3 T. D. Owens, A. J. Souers, J. A. Ellman, *J. Org. Chem.* **2003**, 68, 3–10.
2003JOC1567 V. Padmavathi, K. V. Reddy, A. Padmaja, P. Venugopalan, *J. Org. Chem.* **2003**, 68, 1567–1570.
2003JOM205 Z.-X. Wang, D.-Q. Wang, J.-M. Dou, *J. Organomet. Chem.* **2003**, 665, 205–213.
2003MI157 A. Balsamo, I. Coletta, A. Guglielmotti, C. Landolfi, F. Mancini, A. Martinelli, C. Milanese, F. Minutolo, S. Nencetti, E. Orlandini, M. Pinza, *Eur. J. Med. Chem. Chim. Ther.* **2003**, 38, 157–168.
2003MI681 R. M. A. El-Aal, *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, 178, 681–692.
2003MI1283 V. N. Yarovenko, A. A. Es'kov, I. V. Zavarzin, E. I. Chernoburova, A. Yu. Martynkin, M. M. Krayuskin, N. D. Zelinsky, *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, 178, 1283–1288.
2003OL391 J. W. Bode, Y. Hachisu, T. Matsuura, K. Suzuki, *Org. Lett.* **2003**, 5, 391–394.
2003SC113 S. Rostamizadeh, H. Tajik, S. Yazdanfarahi, *Synth. Commun.* **2003**, 33, 113–118.
2003T303 M. Bao, M. Shimizu, S. Shimada, M. Tanaka, *Tetrahedron* **2003**, 59, 303–310.
2003TL2363 J. Volmajer, R. Toplak, S. Bittner, I. Leban, A. M. Le Marechal, *Tetrahedron Lett.* **2003**, 44, 2363–2366.

5.22

Diazo Functions with an α -Heteroatom (RC(X)N₂)

K. AFARINKIA

King's College London, London, UK

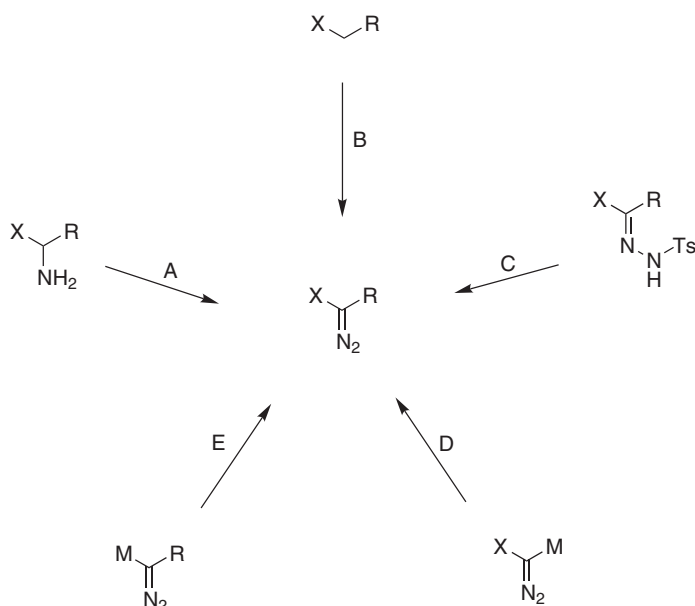
5.22.1 DIAZO FUNCTIONS WITH AN α -HETEROATOM	799
5.22.2 α -DIAZO HALO COMPOUNDS	800
5.22.3 α -DIAZO OXYGEN AND SULFUR COMPOUNDS	800
5.22.4 α -DIAZO NITROGEN COMPOUNDS	802
5.22.5 α -DIAZO PHOSPHORUS, ARSENIC, AND ANTIMONY COMPOUNDS	803
5.22.5.1 α -Diazo Phosphorus(V) Compounds	803
5.22.5.2 α -Diazo Phosphorus(III) Compounds	804
5.22.5.3 α -Diazo Arsenic and Antimony Compounds	806
5.22.6 α -DIAZO BORON, SILICON, AND GERMANIUM COMPOUNDS	806
5.22.6.1 α -Diazo Boron Compounds	806
5.22.6.2 α -Diazo Silicon Compounds	807
5.22.7 α -DIAZO METAL COMPOUNDS	809

5.22.1 DIAZO FUNCTIONS WITH AN α -HETEROATOM

The preparative chemistry of diazoalkyl compounds with an attached heteroatom has not significantly expanded since the publication of chapter 5.22 in COFGT (1995) <1995COFGT(5)865>. As was discussed then, the preparative routes to the molecules containing this function fall into one of five categories (Scheme 1). The significant extensions to these methods are the use of trifluoromethanesulfonyl azide as a superior diazo-transfer reagent (route A), further development of the application of lithiated and stannylated α -diazo compounds as nucleophiles in the preparation of other α -diazo phosphorus compounds (route D), and the use of iodonio α -diazo phosphorus compounds as electrophiles in the preparation of other α -diazo phosphorus compounds (route E).

In contrast, the synthetic applications of α -diazo compounds, in particular α -diazo phosphorus and silicon compounds, have continued to grow. It is clear from these investigations that the chemistry of the carbenes and metallocarbenoids generated from these diazo compounds is strongly influenced by the attached heteroatom.

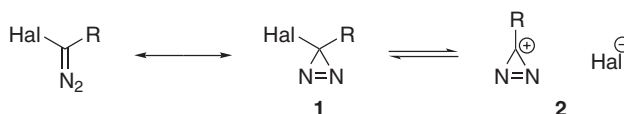
The insertion of carbenes generated from these α -diazo compounds into CH and XH (where X is a heteroatom such as oxygen, nitrogen, or sulfur) has continued to be an active area of research. Furthermore, the reaction of these α -diazo compounds with ketones and aldehydes has also proved to be synthetically useful with the Ohira-Bestmann protocol rapidly becoming a popular alternative to the Corey-Fuchs method <1972TL3769> for transformation of aldehydes to terminal alkynes.



Scheme 1

5.22.2 α -DIAZO HALO COMPOUNDS

Halogenated α -diazo compounds remain rare species. As discussed in <1995COFGT(5)865>, their chemistry can be understood in terms of a halodiazirine structure **1**, rather than an α -halodiazo structure **2** (Scheme 2). The halodiazirine structure is useful in rationalizing why these compounds undergo rapid S_N -type displacement reactions with nucleophiles <1987TL5801>. Interestingly however, arylodonio α -diazo compounds **3** and **4** have been prepared (Scheme 3) and compound **4** was shown to have the expected α -halodiazo structure <1994AG(E)1952>. The arylodonio ligand in these molecules can be easily displaced with a range of nucleophiles giving access to a diverse family of α -diazo compounds **5–9** (Scheme 3) <1998ZN(B)599, 1994AG(E)1952>.



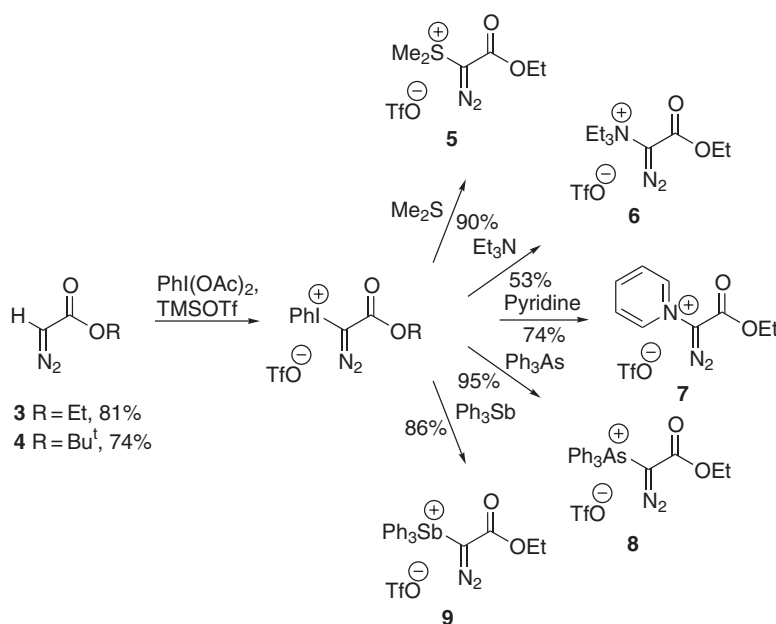
Scheme 2

The multiplicity of the α -halocarbenes generated from the corresponding α -halodiazo compounds has been investigated experimentally and computationally <2002JOC5578>.

5.22.3 α -DIAZO OXYGEN AND SULFUR COMPOUNDS

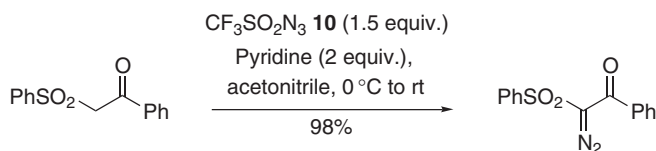
There have been no further examples of α -diazoalkane oxygen compounds reported since the publication of COFGT (1995) <1995COFGT(5)865>, although the scope of preparative routes to α -diazoalkane sulfur compounds has considerably expanded.

Traditionally, access to α -diazoalkane sulfur compounds has proven to be synthetically nontrivial. Since the diazo-function efficiently undergoes atom transfer reactions, a sulfoxide function was thought to be incompatible with it. However, the first example of an α -diazoalkane sulfoxide has recently been reported <1998TL2819>. The known examples of α -diazoalkane sulfone compounds have a further anion-stabilizing group at the β -position. Diazo-transfer is the most popular route for their synthesis, although with most reagents it is fairly inefficient <1999JCS(P1)593, 1993JOC21>. However, using trifluoromethanesulfonyl azide **10** as a diazo-transfer reagent

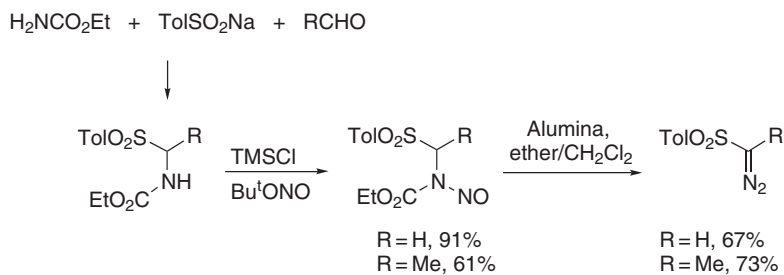


Scheme 3

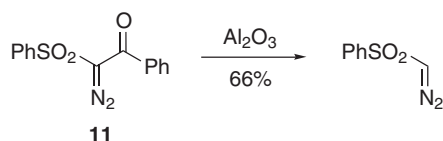
significantly improves the yields of the reaction (Scheme 4) <2003TL8845>. A direct route to toluenesulfonyldiazomethanes (Scheme 5) <2000TL5489> and a further example of the base-induced cleavage of the corresponding α -diazo- β -keto sulfone compounds such as **11** (Scheme 6) <1995S1248> have also been reported.



Scheme 4



Scheme 5

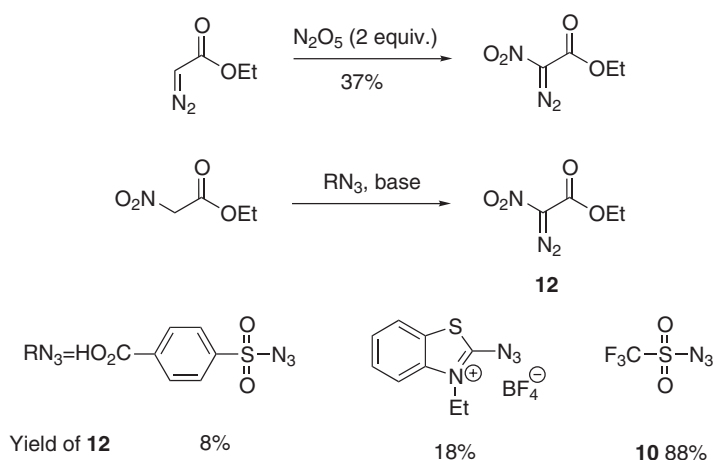


Scheme 6

Asymmetric insertion of carbenes from sulfonyldiazomethane into alkenes <2003TL9007, 2003JA2860> and C—H bonds <1999JOC8648, 1996T2489, 2003TL6405> has been widely reported. Finally, the reaction of Me_2S with diazo compound **3** affords an α -diazosulfonium salt **5** (Scheme 3) <1994AG(E)1952>.

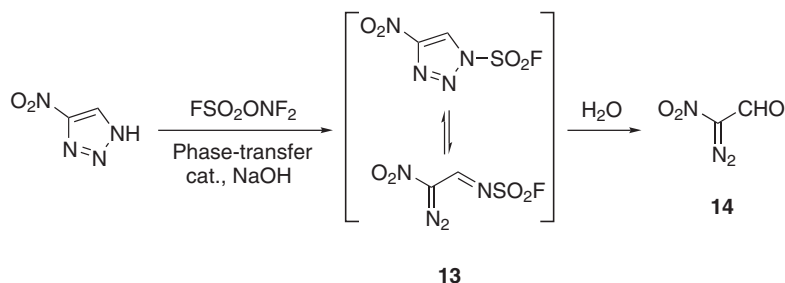
5.22.4 α -DIAZO NITROGEN COMPOUNDS

The preparation of α -nitrodiazo compounds was previously restricted to route E, using dinitrogen pentoxide as a nitrating agent, which was inefficient and gave impure products. However, it has now been shown that α -nitrodiazo compounds can be prepared cleanly and efficiently by a diazo-transfer reaction using trifluoromethanesulfonyl azide **10** as reagent (Scheme 7) <2002HCA4468, 2000JOC9252>. The crystal structure of **12** and a range of chemical reactions of α -nitrodiazo compounds, in particular cyclopropanation, have now been reported <2002HCA4468, 2003JMOC83>.



Scheme 7

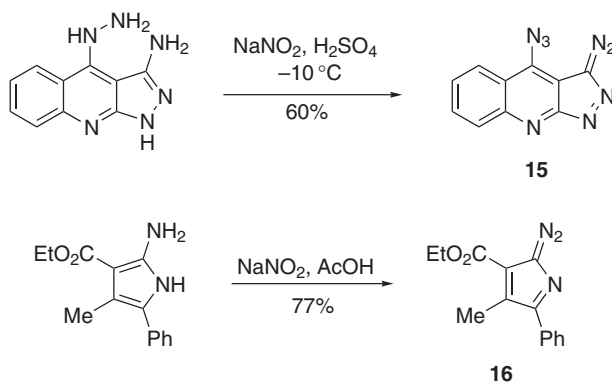
α -Nitrodiazo aldehyde **14** was isolated from the hydrolysis of fluorosulfonylated nitrotriazole **13** (Scheme 8) <1993MC14>.



Scheme 8

Heterocyclic amino compounds undergo a diazotization reaction when treated with nitrous acid. Usually, the products undergo further reactions but there are a number of examples of diazo-azoles, for example, **15** and **16**, in the literature (Scheme 9) <1995JCS(P1)2783, 2000JCS(P1)3085, 1999S2082, 2001SC1971, 1996FES275>.

Finally, as shown in Scheme 3, the reaction of Et_3N and pyridine with diazo compound **3** affords the α -diazammonium and α -diazopyridinium salts **6** and **7**, respectively <1994AG(E)1952>.



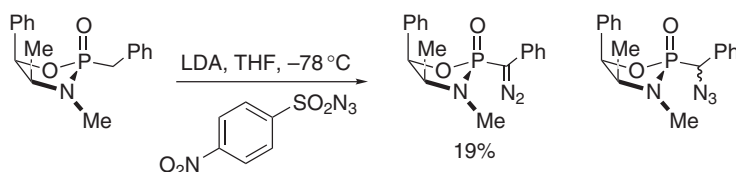
Scheme 9

5.22.5 α -DIAZO PHOSPHORUS, ARSENIC, AND ANTIMONY COMPOUNDS

5.22.5.1 α -Diazo Phosphorus(V) Compounds

Diazo-transfer (route B) remains the most popular route for the synthesis of α -diazo phosphorus(V) compounds. The method works best for β -keto phosphonates for two reasons. First, the initial step in the reaction requires deprotonation adjacent to the phosphorus atom and hence an anion-stabilizing group would facilitate the reaction with milder bases. Second, anion-stabilizing groups always confer stability to an adjacent diazo group making the compounds easier to handle and less likely to explode.

Many examples of the preparation of α -diazo- β -keto phosphonates have been reported [<2002CCC210, 1998JOC8894, 1996T6665, 1998T2257, 1995H175>](#). Reactions typically require an azide and an amine base although the use of caesium carbonate is reported to improve the yield [<1995SC1511>](#). Diazo-transfer can also be applied to the synthesis of α -diazo phosphonates without a further activating group at the β -position [<2001TA1657>](#), although this requires the use of stronger organometallic bases and more reactive azides (Scheme 10) and even so can be inefficient. Alternatively, Bamford–Stevens reaction (route C) has been used for the synthesis of such α -diazo phosphonates [<2003RCB1750>](#), although some azido compounds are formed as a by-product.

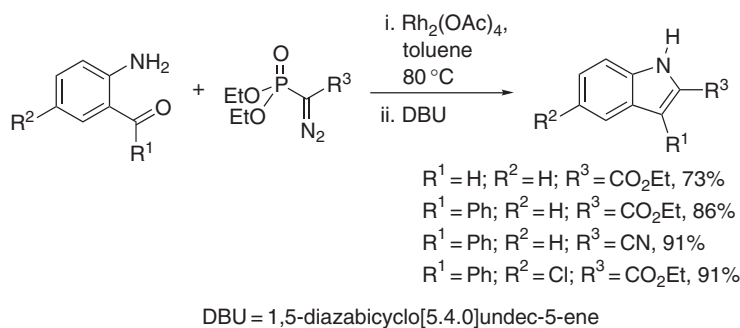


Scheme 10

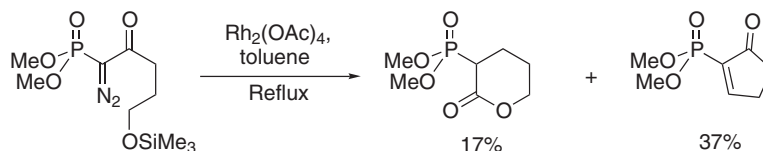
Under rhodium catalysis, α -diazo phosphonates initially afford metal carbenoids, which then insert into X—H (where X is a heteroatom such as oxygen, sulfur, or nitrogen), C—H, and C=C bonds. Insertion into an X—H bond has been used in the synthesis of heterocycles (Scheme 11) [<2002OL2317, 2002CC210>](#). An attempt at the asymmetric insertion into X—H bond has also been reported but with only modest stereoselectivity [<2001TA1657>](#). Diastereoselective insertion of carbenes generated from enantiopure α -diazo- β -keto phosphonates into a tethered alkene has been reported [<2003TA873>](#). Insertion into a fullerene has also been reported [<2003RCB1750>](#).

Wolff rearrangement competes with the insertion reactions and can afford unexpected or undesired products (Scheme 12) [<1995H175, 1995TL7859, 2001TL8455, 2002TL4131, 2003EJOC3798>](#). The reactions have also been reported in ionic liquid media [<2003TL6571>](#).

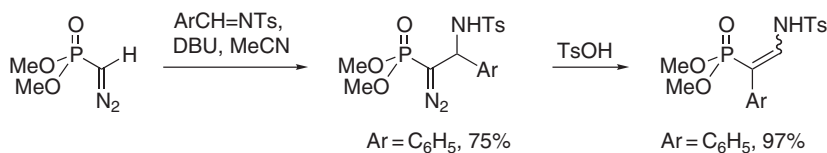
There has not been a great deal reported on derivatization of diazomethyl phosphorus compounds, although they have been shown to react with tosyl benzaldehydes in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) [<2003TL8339>](#). When the resulting β -amino- α -diazo phosphonate is decomposed in the presence of tosic acid, it undergoes a 1,2-aryl shift to afford an enamine (Scheme 13) [<2003TL8339>](#).



Scheme 11



Scheme 12



Scheme 13

Based on an initial observation by Ohira [\[1989SC561\]](#), Bestmann has shown that treatment of **17** with basic methanol affords dimethyl diazomethyl phosphonate **18** *in situ*, which reacts with aldehydes directly to give alkynes cleanly and efficiently (Scheme 13) [\[1996SL521\]](#). This has now been used a number of times in total synthesis [\[2001TL1941, 1994T11391, 2001OL503, 1996TL163, 2003T1719\]](#). An important feature of the Ohira–Bestmann protocol is that α,β -unsaturated aldehydes afford not an enyne but a propargylic methyl ether (Scheme 14).

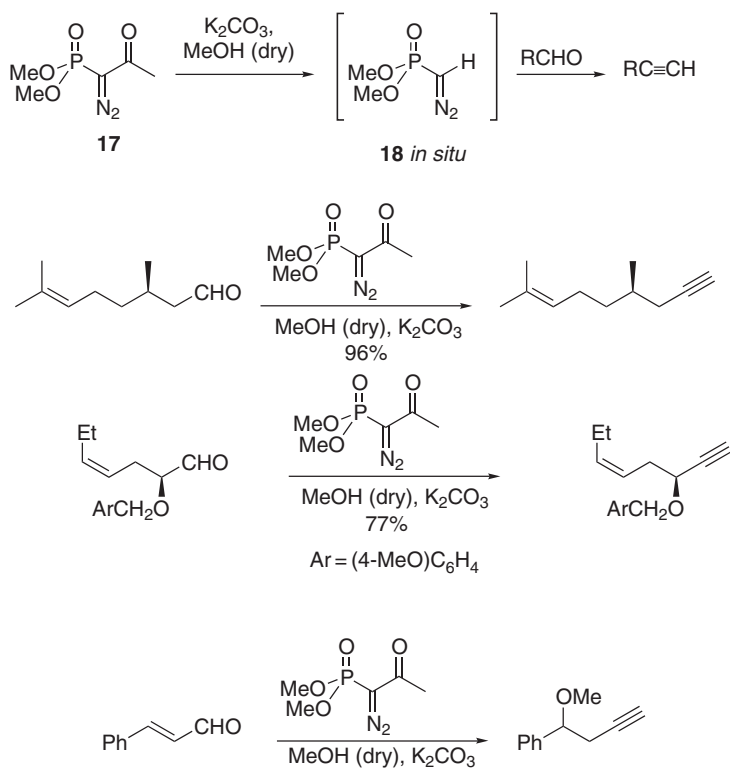
A rare example of the oxidation of an α -diazo phosphorus(III) compound to an α -diazo phosphorus(V) compound has also been reported. Using tetrachloro-*o*-quinone as an oxidant, compound **19** affords **20** [\[1993HAC525\]](#), although the silyl derivative **21** affords **22** (Scheme 15) [\[1995BSF1139\]](#). Similarly, treatment of **23** with aryl isocyanates gave, after atom transfer, triazolophosphonates such as **24**, which upon hydrolysis afford a β -amido- α -diazo phosphonate (Scheme 16) [\[1992BSF367\]](#).

5.22.5.2 α -Diazo Phosphorus(III) Compounds

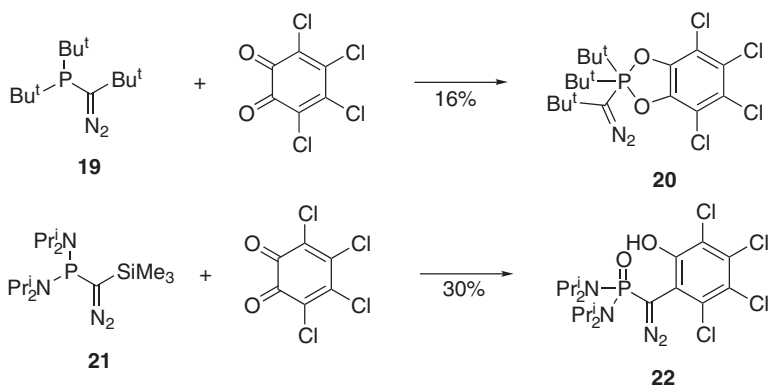
Routes D and E are the best methods for the synthesis of α -diazo phosphorus(III) compounds. Route E has been successfully applied to the synthesis of **25** (Scheme 17) [\[2002AG\(E\)2835, 2003JA124, 2000AG\(E\)3319\]](#). The carbenes generated in the cold from photochemical decomposition of these diazo compounds, for example **26**, are stable and have been isolated and their structure was confirmed from X-ray crystallography. These carbenes have a fascinating and expansive chemistry, which is beyond the scope of this review.

Route D is less common but nevertheless has been used to prepare methyl and trityl derivatives **27** and **28** (Scheme 18) [\[1992BSF367, 1991AG\(E\)1154\]](#).

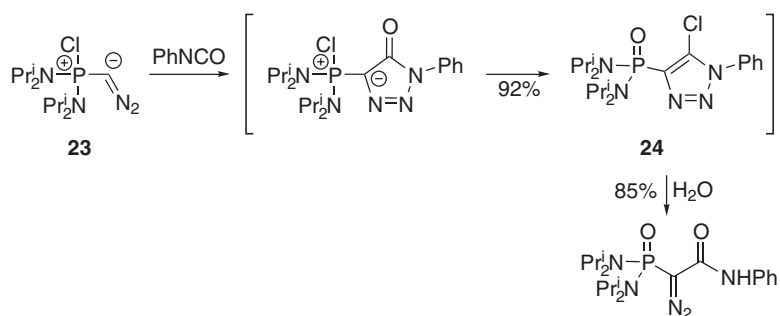
Recently, it has been shown that α -diazo phosphines can coordinate to metals through the phosphorus atom (Scheme 19) [\[2003OM1358\]](#).



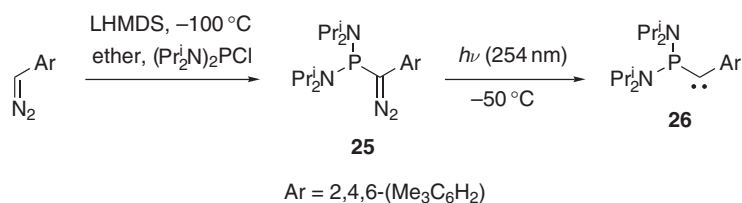
Scheme 14



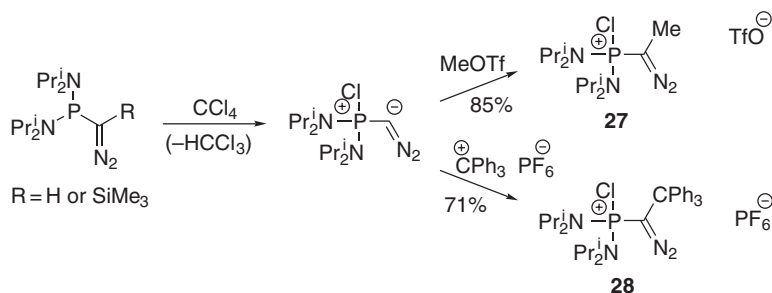
Scheme 15



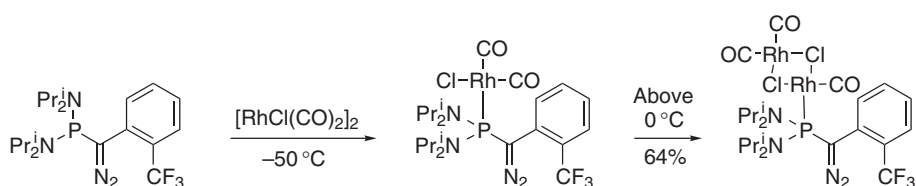
Scheme 16



Scheme 17



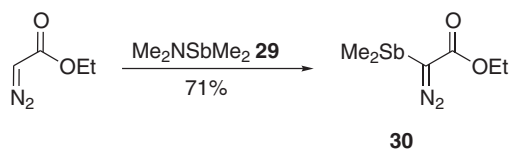
Scheme 18



Scheme 19

5.22.5.3 α -Diazo Arsenic and Antimony Compounds

Both the arsenium and antimony α -diazo compounds **8** and **9** have been prepared (Scheme 3) but as yet, little is known about their chemical properties and reactions. Antimony(III) derivative **30** has been prepared by treatment of ethyl diazoacetate with (dimethylamino)dimethylstibine **29** (Scheme 20) <1975JOM339> but as yet little is known about its chemistry.

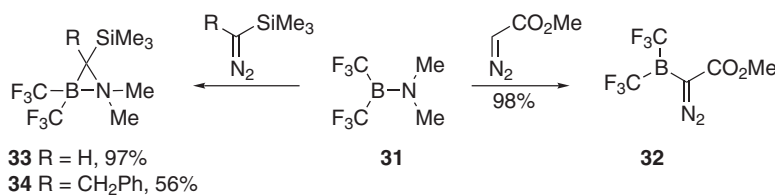


Scheme 20

5.22.6 α -DIAZO BORON, SILICON, AND GERMANIUM COMPOUNDS

5.22.6.1 α -Diazo Boron Compounds

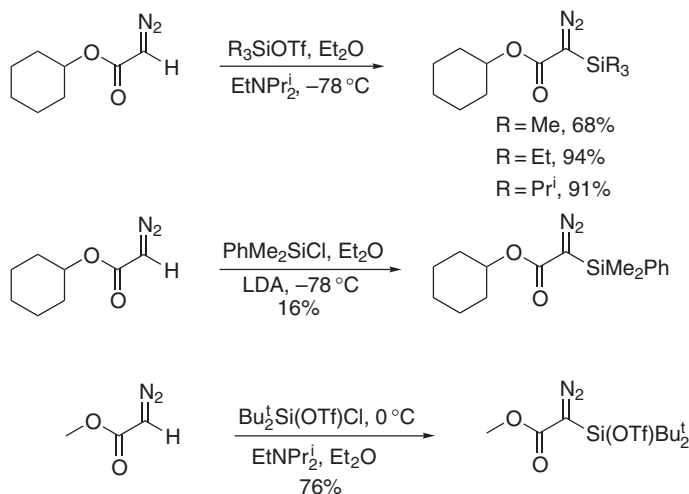
α -Diazo boron compounds are rare. However, it has been shown that methyl diazoacetate reacts with (dimethylamino)bis(trifluoromethyl)borane **31** to afford an α -diazo boron compound **32** (Scheme 21), the structure of which has been confirmed by X-ray crystallography. This is in contrast to the reactions of trimethylsilyldiazomethane, which affords azoniaboratocyclopropanes **33** and **34** (Scheme 21), the structures of which have also been confirmed by X-ray crystallography <1993AG(E)384>.



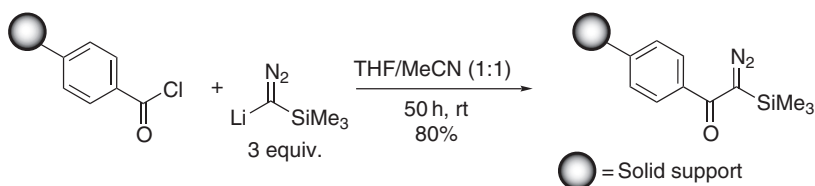
Scheme 21

5.22.6.2 α -Diazo Silicon Compounds

There has been a significant increase in the number and reactions of α -diazo silicon compounds reported since COFGT (1995). Diazo-transfer (route A) has not been used for the synthesis of α -diazo silicon compounds, although the reason for this may be more due to the lack of easy access to starting materials rather than inherent problems with the method. Routes D and E are by far the most popular methods of synthesis. Diazoacetate esters undergo a very facile silylation when treated with a nitrogen base and a chlorosilane or silyl trifluoromethanesulfonate [<1999S1175, 1992\(424\)JOM253, 1990\(398\)JOM229>](#), although with bulkier silanes use of amide bases may become necessary (Scheme 22) [<2003TA1503>](#). Similarly, lithiated diazomethane undergoes facile alkylation [<1993JA11775, 2001AG\(E\)1674, 1994CB191>](#) and acylation (Scheme 23) [<2000T5353, 2003SL2151>](#).



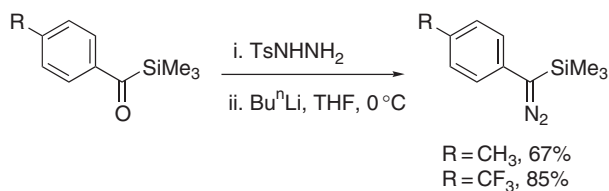
Scheme 22



Scheme 23

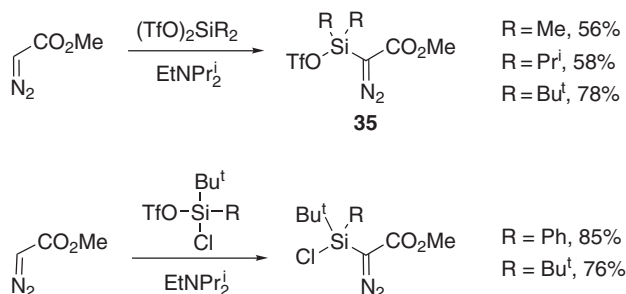
The nucleophilicity of α -diazo silicon compounds has been studied and it has been shown that the nucleophilicity of α -diazomethyl(trimethylsilane) is comparable to phenyl- α -diazomethane [<2003CEJ4068>](#). Insertion of α -diazomethyl(trimethylsilane) into alkenes has also been investigated [<2001\(630\)JOM57>](#).

Bamford-Stevens reaction (route C) has for the first time been used for the synthesis of an α -diazo silicon compound (Scheme 24) [<1999JCS\(P1\)1553, 1992TL6161>](#).

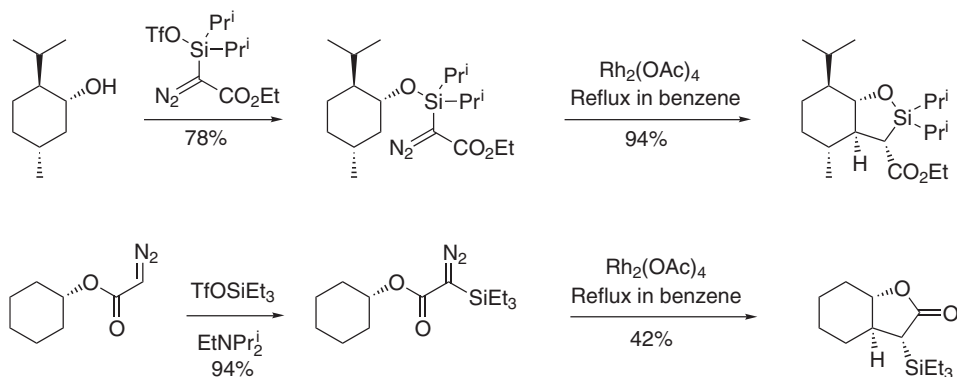


Scheme 24

Displacement of a second labile ligand on silyl bis(trifluoromethanesulfonate), for example, compound **35** allows a tether to be attached to the silicon atom (Scheme 25) <2001(617)JOM339, 1998TL5109, 1999EJOC1213>. Both insertion into a tethered C—H bond <1998TL5109> and insertion into a tethered alkene <1999EJOC1213> are reported (Scheme 26). Of course, α -diazo- α -silyl carboxylates can also be tethered through the ester function and the insertion into a C—H bond on the ester side chain is also known (Scheme 26) <1998TL6077, 2003TA1503>.



Scheme 25

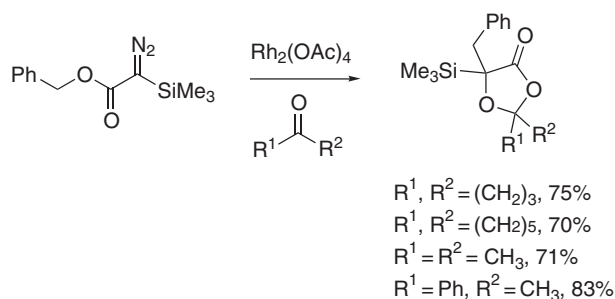


Scheme 26

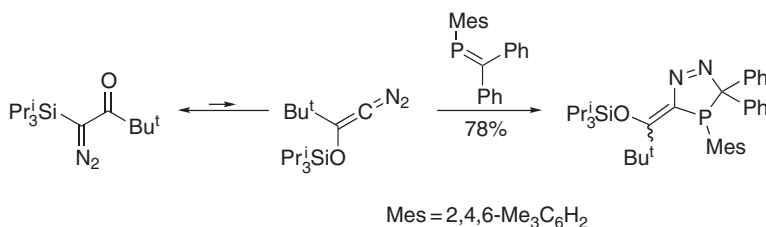
Reaction of benzyl α -silyl- α -diazoacetate with ketones is reported to afford dioxolanone (Scheme 27) <2002OL4631>. Finally it has been shown that (trimethylsilyl)diazomethane undergoes a highly *trans*-selective insertion reaction with styrene <2003TL9287>.

It has been reported that α -diazo- α -silyl ketones are in equilibrium with a small quantity of 1-diazo-2-silyloxy-1-alkene and that the latter form can be trapped in a dipolar cycloaddition with a phosphane (Scheme 28) <1996T10053, 1999EJOC2633>.

Finally, both the photochemical <2002OL2465, 1998JOC8380> and metal-catalyzed <1999CC1199> Wolff rearrangement of α -diazo- β -keto silanes have been shown to afford exceptionally stable silyl-substituted ketenes.



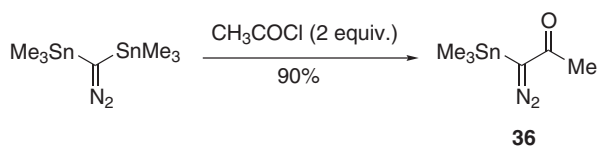
Scheme 27



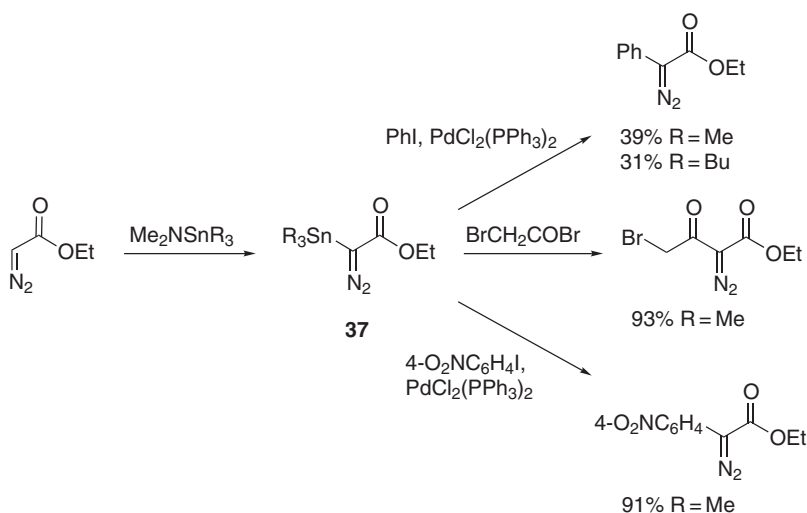
Scheme 28

5.22.7 α -DIAZO METAL COMPOUNDS

The lithiated diazomethanes are well known and used extensively in synthesis. More recently, the tin derivatives have also been used. Tin derivative **36** is prepared from the corresponding bis(tin) compound (Scheme 29) <1992JA6059> whereas tin diazoester **37** is prepared from ethyl diazoacetate (Scheme 30) <1997T2371>. These tin diazo compounds undergo a variety of reactions,

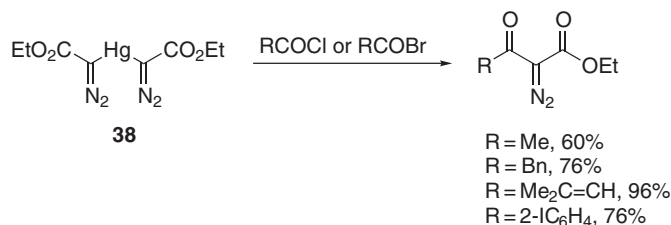


Scheme 29



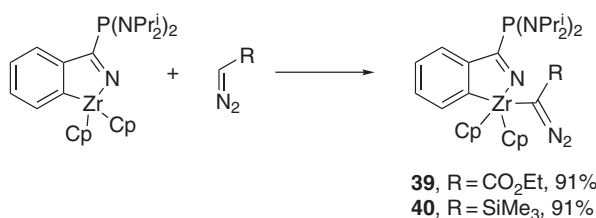
Scheme 30

most importantly C—C bond formation (Scheme 30) <1997T2371>. However, mercury diazo compound **38** also undergoes similar C—C bond-forming reactions (Scheme 31) <1997T2371>.



Scheme 31

The only known examples involving a transition metal are the zirconate derivatives **39** and **40** (Scheme 32) <2000AG(E)4524>.



Scheme 32

REFERENCES

- 1972TL3769 E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, 13, 3769–3772.
 1975JOM339 P. Krommes, J. Lorberth, *J. Organomet. Chem.* **1975**, 93, 339–351.
 1987TL5801 W. P. Dailey, *Tetrahedron Lett.* **1987**, 28, 5801–5804.
 1989SC561 S. Ohira, *Synth. Commun.* **1989**, 19, 561–564.
 1990(398)JOM229 G. Maas, A. Fronda, *J. Organomet. Chem.* **1990**, 398, 229–239.
 1991AG(E)1154 J.-M. Sotiropoulos, A. Baceiredo, K. Horchler Von Locquenghien, F. Dahan, G. Bertrand, *Angew. Chem., Int. Ed. Engl.* **1991**, 30, 1154–1156.
 1992BSF367 J. M. Sotiropoulos, A. Baceiredo, G. Bertrand, *Bull. Soc. Chim. Fr.* **1992**, 129, 367–375.
 1992(424)JOM253 A. Fronda, F. Krebs, B. Daucher, T. Werle, G. Maas, *J. Organomet. Chem.* **1992**, 424, 253–272.
 1992TL6161 F. Jin, Y. Xu, Y. Ma, *Tetrahedron Lett.* **1992**, 33, 6161–6164.
 1992JA6059 R. Reau, G. Veneziani, G. Bertrand, *J. Am. Chem. Soc.* **1992**, 114, 6059–6063.
 1993JOC21 A. Padwa, F. R. Kinder, *J. Org. Chem.* **1993**, 58, 21–28.
 1993JA11775 M. Trommer, W. Sander, A. Patyk, *J. Am. Chem. Soc.* **1993**, 115, 11775–11783.
 1993AG(E)384 A. Ansorge, D. J. Brauer, H. Buerger, T. Hagen, G. Pawelke, *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 384–385.
 1993MC14 S. A. Shevelev, V. M. Vinogradov, I. L. Dalinger, B. I. Ugrak, V. I. Filippov, *Mendeleev Communications* **1993**, 14–15.
 1993HAC525 H.-J. Nees, U. Bergstrasser, H. Heydt, M. Regitz, *Heteroatom Chem.* **1993**, 4, 525–530.
 1994T11391 D. A. Clark, F. De Riccardis, K. C. Nicolaou, *Tetrahedron* **1994**, 50, 11391–11426.
 1994CB191 G. Maier, R. Wolf, H.-O. Kalinowski, R. Boese, *Chem. Ber.* **1994**, 127, 191–200.
 1994AG(E)1952 R. Weiss, J. Seubert, F. Hampel, *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 1952–1953.
 1995COFGT(5)865 K. Afarinkia, M. V. Vinader, Diazo functions with an α -heteroatom ($RC(X)N_2$), in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 865–874.
 1995H175 Y. P. Chen, B. Chantegrel, C. Deshayes, *Heterocycles* **1995**, 41, 175–186.
 1995SC1511 J. C. Lee, J. Y. Yuk, *Synth. Commun.* **1995**, 25, 1511–1515.
 1995BSF1139 N. Dubau-Assibat, A. Baceiredo, F. Dahan, G. Bertrand, *Bull. Soc. Chim. Fr.* **1995**, 132, 1139–1143.
 1995TL7859 B. Chantegrel, C. Deshayes, R. Faure, *Tetrahedron Lett.* **1995**, 36, 7859–7862.
 1995S1248 S. Korneev, C. Richter, *Synthesis* **1995**, 1248–1250.
 1995JCS(P1)2783 Y. Wang, M. F. G. Stevens, W. T. Thomson, B. P. Shutts, *J. Chem. Soc., Perkin Trans. 1* **1995**, 2783–2787.
 1996T2489 S. Miah, A. M. Z. Slawin, C. J. Moody, S. M. Sheehan, J. P. Marino Jr., M. A. Semones, A. Padwa, I. C. Richards, *Tetrahedron* **1996**, 52, 2489–2514.
 1996FES275 G. Cirrincione, A. M. Almerico, P. Diana, S. Grimaudo, P. Barraja, G. Dattolo, E. Aiello, F. Mingoia, *Farmaco Ed. Sci.* **1996**, 51, 275–277.

- 1996SL521 S. Mueller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521–522.
1996T6665 D. Collomb, C. Deshayes, A. Doutheau, *Tetrahedron* **1996**, 52, 6665–6684.
1996T10053 B. Manz, G. Maas, *Tetrahedron* **1996**, 52, 10053–10072.
1996TL163 C. Mvondo Evina, G. Guillermin, *Tetrahedron Lett.* **1996**, 37, 163–166.
1997T2371 A. Padwa, M. M. Sa, M. D. Weingarten, *Tetrahedron* **1997**, 53, 2371–2386.
1998ZN(B)599 R. Weiss, M. Handke, S. Reichel, F. Hampel, *Z. Naturforsch., Teil B* **1998**, 53, 599–619.
1998TL2819 A. R. Maguire, P. G. Kelleher, G. Ferguson, J. F. Gallagher, *Tetrahedron Lett.* **1998**, 39, 2819–2822.
1998JOC8380 J. L. Loebach, D. M. Bennett, R. L. Danheiser, *J. Org. Chem.* **1998**, 63, 8380–8389.
1998TL6077 S. P. Marsden, W.-K. Pang, *Tetrahedron Lett.* **1998**, 39, 6077–6080.
1998TL5109 S. N. Kablean, S. P. Marsden, A. M. Craig, *Tetrahedron Lett.* **1998**, 39, 5109–5112.
1998T2257 C. J. Moody, D. J. Miller, *Tetrahedron* **1998**, 54, 2257–2268.
1998JOC8894 M. Mikolajczyk, R. Zurawinski, *J. Org. Chem.* **1998**, 63, 8894–8897.
1999EJOC1213 V. Gettwert, F. Krebs, G. Maas, *Eur. J. Org. Chem.* **1999**, 1213–1221.
1999EJOC2633 J. Kerth, G. Maas, *Eur. J. Org. Chem.* **1999**, 2633–2643.
1999S1175 G. Maas, S. Bender, *Synthesis* **1999**, 1175–1180.
1999JCS(P1)593 R. A. Aitken, J. M. Armstrong, M. J. Drysdale, F. C. Ross, B. M. Ryan, *J. Chem. Soc., Perkin Trans. 1* **1999**, 593–604.
1999JOC8648 A. Padwa, S. M. Sheehan, C. S. Straub, *J. Org. Chem.* **1999**, 64, 8648–8659.
1999S2082 P. Diana, P. Barraja, A. Lauria, A. M. Almerico, G. Dattolo, G. Cirrincione, *Synthesis* **1999**, 2082–2086.
1999JCS(P1)1553 S. Han, S. R. Kass, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1553–1558.
1999CC1199 S. P. Marsden, W.-K. Pang, *J. Chem. Soc., Chem. Commun.* **1999**, 1199–1200.
2000T5353 Y. Iso, H. Shindo, H. Hamana, *Tetrahedron* **2000**, 56, 5353–5361.
2000AG(E)4524 V. Cadierno, M. Zablocka, B. Donnadieu, A. Igau, J. P. Majoral, *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 4524–4526.
2000AG(E)3319 T. Kato, H. Gornitzka, A. Baceiredo, G. Bertrand, *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 3319–3321.
2000JOC9252 A. B. Charette, R. P. Wurz, T. Ollevier, *J. Org. Chem.* **2000**, 65, 9252–9254.
2000JCS(P1)3085 W. Stadlbauer, G. Hojas, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3085–3087.
2000TL5489 C. Plessis, D. Uguen, A. De Cian, J. Fischer, *Tetrahedron Lett.* **2000**, 41, 5489–5493.
2001TL1941 N. Murakami, T. Nakajima, M. Kobayashi, *Tetrahedron Lett.* **2001**, 42, 1941–1943.
2001OL503 D. A. Evans, J. D. Burch, *Org. Lett.* **2001**, 3, 503–505.
2001AG(E)1674 G. Maier, J. Neudert, O. Wolf, *Angew. Chem., Int. Ed. Engl.* **2001**, 40, 1674–1675.
2001(617)JOM339 G. Maas, D. Mayer, *J. Organomet. Chem.* **2001**, 617, 339–345.
2001TA1657 C. J. Moody, C. N. Morfitt, A. M. Z. Slawin, *Tetrahedron Asymmetry* **2001**, 12, 1657–1661.
2001TL8455 W. Dayoub, Y. Diab, A. Doutheau, *Tetrahedron Lett.* **2001**, 42, 8455–8457.
2001SC1971 R. A. Mekheimer, *Synth. Commun.* **2001**, 31, 1971–1982.
2001(630)JOM57 Y.-L. Lin, E. Turos, *J. Organomet. Chem.* **2001**, 630, 57–66.
2002JOC5578 T. Enyo, A. Nicolaidis, H. Tomioka, *J. Org. Chem.* **2002**, 67, 5578–5587.
2002HCA4468 A. B. Charette, R. P. Wurz, T. Ollevier, *Helv. Chim. Acta* **2002**, 85, 4468–4484.
2002OL2465 A. M. Dalton, Y. Zhang, C. P. Davie, R. L. Danheiser, *Org. Lett.* **2002**, 4, 2465–2468.
2002OL4631 C. Bolm, S. Saladin, A. Kasyan, *Org. Lett.* **2002**, 4, 4631–4633.
2002CC210 K. Yamazaki, Y. Kondo, *J. Chem. Soc., Chem. Commun.* **2002**, 210–211.
2002AG(E)2835 E. Despagne, H. Gornitzka, A. B. Rozhenko, W. W. Schoeller, D. Bourissou, G. Bertrand, *Angew. Chem., Int. Ed. Engl.* **2002**, 41, 2835–2837.
2002OL2317 Y. Nakamura, T. Ukita, *Org. Lett.* **2002**, 4, 2317–2320.
2002TL4131 W. Dayoub, Y. Diab, A. Doutheau, *Tetrahedron Lett.* **2002**, 43, 4131–4132.
2003TL9287 M. B. France, A. K. Milojevich, T. A. Stitt, A. J. Kim, *Tetrahedron Lett.* **2003**, 44, 9287–9290.
2003OM1358 E. Despagne-Ayoub, H. Gornitzka, J. Fawcett, P. W. Dyer, D. Bourissou, G. Bertrand, *Organometallics* **2003**, 22, 1358–1360.
2003TA1503 P. Muller, F. Lacrampe, G. Bernardinelli, *Tetrahedron Asymmetry* **2003**, 14, 1503–1510.
2003TL6405 S. Sengupta, S. Mondal, *Tetrahedron Lett.* **2003**, 44, 6405–6408.
2003TL9007 M. Honma, M. Nakada, *Tetrahedron Lett.* **2003**, 44, 9007–9011.
2003JA2860 M. Honma, T. Sawada, Y. Fujisawa, M. Utsugi, H. Watanabe, A. Umino, T. Matsumura, T. Hagihara, M. Takano, M. Nakada, *J. Am. Chem. Soc.* **2003**, 125, 2860–2861.
2003TL8845 R. P. Wurz, W. Lin, A. B. Charette, *Tetrahedron Lett.* **2003**, 44, 8845–8848.
2003SL2151 Y. Hari, S. Tanaka, Y. Takuma, T. Aoyama, *Synlett* **2003**, 2151–2154.
2003JMOC83 A. B. Charette, R. Wurz, *J. Mol. Catal.* **2003**, 196, 83–91.
2003TL6571 P. M. P. Gois, C. A. M. Afonso, *Tetrahedron Lett.* **2003**, 44, 6571–6573.
2003EJOC3798 P. M. P. Gois, C. A. M. Afonso, *Eur. J. Org. Chem.* **2003**, 3798–3810.
2003T1719 W. R. F. Goundry, J. E. Baldwin, V. Lee, *Tetrahedron* **2003**, 59, 1719–1729.
2003JA124 E. Despagne-Ayoub, S. Sole, H. Gornitzka, A. B. Rozhenko, W. W. Schoeller, D. Bourissou, G. Bertrand, *J. Am. Chem. Soc.* **2003**, 125, 124–130.
2003TL8339 Y. H. Zhao, N. Jiang, J. B. Wang, *Tetrahedron Lett.* **2003**, 44, 8339–8342.
2003RCB1750 I. P. Romanova, E. I. Musina, A. A. Nafikova, V. V. Zverev, D. G. Yakhvarov, O. G. Sinyashin, *Russ. Chem. Bull.* **2003**, 52, 1750–1757.
2003CEJ4068 T. Bug, M. Hartnagel, C. Schlierf, H. Mayr, *Chem. -Eur. J.* **2003**, 9, 4068–4076.
2003TA873 J. D. Moore, P. R. Hanson, *Tetrahedron Asymmetry* **2003**, 14, 873–880.

Biographical sketch



Dr. Kamyar Afarinkia was born in Tehran, Iran in 1963. After graduating from Imperial College, University of London, UK in 1987, he studied for a Ph.D. under the supervision of Prof Charles Rees, CBE FRS and Prof Sir John Cadogan, CBE FRS at the same institution. In 1990, he took up a postdoctoral position at Johns Hopkins University, Baltimore, USA, under supervision of Prof Gary H. Posner, working on the synthesis of vitamin D₃ analogs. In 1992, he returned to UK and was appointed as a Senior Scientist at Glaxo R&D in Ware, Hertfordshire where he worked as a medicinal chemist in projects on hypertension and diabetes. In 1995, he was appointed to his current position at King's College, University of London, UK. His area of research include application of asymmetric organophosphorus reagent in synthesis, chemistry of α -amino and α -hydroxy phosphonic acids, total synthesis of natural products, and the Diels–Alder cycloaddition of 2(*H*)-pyran-2-ones, 2(*H*)-pyridin-2-ones, and 2(*H*)-1,4-oxazon-2-ones.

5.23

Phosphoacyl Functions and Their As, Sb, and Bi Analogs

L. WEBER

University of Bielefeld, Bielefeld, Germany

5.23.1	DICOORDINATE PHOSPHORUS, ARSENIC, ANTIMONY, AND BISMUTH FUNCTIONS— $R^1C(PR^2)X$, $R^1C(AsR^2)X$, $R^1C(SbR^2)X$, AND $R^1C(BiR^2)X$	814
5.23.1.1	Dicoordinate Phosphorus Functions— $R^1C(PR^2)X$	814
5.23.1.1.1	Introduction	814
5.23.1.1.2	Halogen derivatives— $R^1C(PR^2)X$ ($X = F, Cl, Br, I$)	814
5.23.1.1.3	Chalcogen derivatives— $R^1C(PR^2)ER_n^3$ ($E = O, S, Se, Te$)	818
5.23.1.1.4	Nitrogen derivatives— $R^1C(PR^2)NR_n^3$	824
5.23.1.1.5	Group 15 element derivatives— $R^1C(PR^2)ER_n^3$ ($E = P, As, Sb, Bi$)	828
5.23.1.1.6	Metalloid derivatives— $R^1C(PR^2)ER_n^3$ ($E = Si, Ge, B$)	851
5.23.1.1.7	Metal derivatives— $R^1C(PR^2)M$	856
5.23.1.2	Dicoordinate Arsenic Functions— $R^1C(AsR^2)X$	860
5.23.1.2.1	Introduction	860
5.23.1.2.2	Halogen derivatives— $R^1C(AsR^2)X$ ($X = F, Cl, Br, I$)	860
5.23.1.2.3	Chalcogen derivatives— $R^1C(AsR^2)ER^3$ ($E = O, S, Se, Te$)	860
5.23.1.2.4	Nitrogen derivatives— $R^1C(AsR^2)NR_n^3$	861
5.23.1.2.5	Group 15 element derivatives— $R^1C(AsR^2)ER_n^3$ ($E = P, As, Sb, Bi$)	862
5.23.1.3	Dicoordinate Sb and Bi Functions— $R^1C(ER^2)X$ ($E = Sb, Bi$)	862
5.23.1.3.1	Chalcogen derivatives— $R^1C(SbR^2)ER^3$	862
5.23.2	TRICOORDINATE P, As, Sb, and Bi FUNCTIONS— $RC(PX^1Y)X^2$, $RC(AsX^1Y)X^2$, $RC(SbX^1Y)X^2$, and $RC(BiX^1Y)X^2$	863
5.23.2.1	Tricoordinate Phosphorus Functions— $RC(PX^1Y)X^2$	863
5.23.2.1.1	λ^3, σ^2 -Methylene phosphoranes	863
5.23.2.1.2	η^1 -Phosphaalkene complexes— $RC[PX^1(M)]X^2$	865
5.23.2.2	Tricoordinate As Functions— $RC(AsX^1Y)X^2$	869
5.23.2.3	Tricoordinate Sb and Bi Functions— $RC(EX^1Y)X^2$ ($E = Sb, Bi$)	869
5.23.3	TETRACOORDINATE P, As, Sb, AND Bi FUNCTIONS— $R^1C(PR_3^2)X$, $R^1C(AsR_3^2)X$, $R^1C(SbR_3^2)X$, AND $R^1C(BiR_3^2)X$	869
5.23.3.1	Tetracoordinate Phosphorus Functions— $R^1C(PR_3^2)X$	869
5.23.3.1.1	Introduction	869
5.23.3.1.2	Halogen derivatives— $R^1C(PR_3^2)X$ ($X = F, Cl, Br, I$)	870
5.23.3.1.3	Chalcogen derivatives— $R^1C(PR_3^2)ER_n^3$ ($E = O, S, Se, Te$)	872
5.23.3.1.4	Nitrogen derivatives— $R^1C(PR_3^2)NR_n^3$	875
5.23.3.1.5	Group 15 element derivatives— $R^1C(PR_3^2)ER_n^3$ ($E = P, As, Sb, Bi$)	878
5.23.3.1.6	Metalloid derivatives— $R^1C(PR_3^2)ER_n^3$ ($E = Si, Ge, B$)	894
5.23.3.1.7	Metal derivatives	895
5.23.3.2	Tetracoordinate Arsenic Functions— $R^1C(AsR_3^2)X$	896
5.23.3.2.1	Halogen derivatives— $R^1C(AsR_3^2)X$ ($X = F, Cl, Br, I$)	896
5.23.3.2.2	Chalcogen derivatives— $R^1C(AsR_3^2)ER_n^3$ ($E = O, S, Se, Te$)	896
5.23.3.2.3	Nitrogen derivatives— $R^1C(AsR_3^2)NR_n^3$	897
5.23.3.2.4	Group 15 element derivatives— $R^1C(AsR_3^2)ER_n^3$ ($E = P, As, Sb, Bi$)	897
5.23.3.3	Tetracoordinate Antimony Functions— $R^1C(SbR_3^2)X$	897
5.23.3.4	Tetracoordinate Bismuth Functions— $R^1C(BiR_3^2)X$	897

5.23.1 DICOORDINATE PHOSPHORUS, ARSENIC, ANTIMONY, AND BISMUTH FUNCTIONS— $R^1C(PR^2)X$, $R^1C(AsR^2)X$, $R^1C(SbR^2)X$, AND $R^1C(BiR^2)X$

5.23.1.1 Dicoordinate Phosphorus Functions— $R^1C(PR^2)X$

5.23.1.1.1 Introduction

Phosphoacyl compounds of the type $R^1C(=PR^2)X$ are more commonly addressed as methylene phosphanes or phosphalkenes, which express their close relationship to alkenes rather than to imines $R^1_2C(=NR^2)$. Accordingly, the formation of the $P=C$ double bond resembles, in many respects, well-known strategies of alkene syntheses.

This chapter is concerned with the preparation of isolable phosphalkenes featuring one heteroatom substituent at the tricoordinate carbon atom of the $P=C$ bond. In COFGT (1995) (chapter 5.23.1), species with halogen-, oxygen-, nitrogen-, phosphorus-, silicon-, and germanium-based substituents were discussed. *C*-Metallated phosphalkenes were confined to a few derivatives of Ti, Zr, Hg, and Sn. Prominent synthetic approaches to halogenated phosphalkenes made use of the base-assisted condensation of Mes^*PH_2 ($Mes^* = 2,4,6-Bu_3C_6H_2$) with haloforms. The halogen–lithium exchange at dihalomethylene phosphanes with subsequent protonation of the organolithium intermediate proved to be an additional useful approach to this target. Disilylated phosphanes react with carboxylic acid chlorides to afford acyl(silyl)phosphanes, which readily rearrange to oxygen-functionalized phosphalkenes. Nitrogen-functionalized phosphalkenes were mainly synthesized by condensing functionalized phosphanes or phosphides with carboxylic amides, imidoyl chlorides, and other amino-substituted electrophiles. Phosphalkenes with substituents based on the heavier group 15 elements are restricted to phosphorus up to early 1995.

The classical base-assisted dehydrohalogenation of suitable precursors such as of 1,3-dichloro-1,3-diphosphapropane derivatives constitutes a powerful method for such species.

Moreover, nucleophilic additions, cyclooligomerizations as well as cycloaddition reactions involving phosphalkynes were successfully utilized. The base-induced dehydrochlorination of α -trimethylsilyl-substituted chlorophosphanes has led to derivatives of the type $R^1C(PR^2)SiR^3_3$. A series of phosphalkenes with titanium and zirconium functions has been available from η^2 -phosphalkyne complexes and 3,3-dimethylcyclopropene, alkynes, and aldehydes by cycloaddition processes. Since the publication of COFGT (1995) the progress in phosphalkene chemistry has been documented in a number of reviews <1996AG(E)271, 1997AOC(41)1, B-1999MI523-01, 2000EJI2425, 2003TCC67> and also in a text book <B-1998MI523-02>.

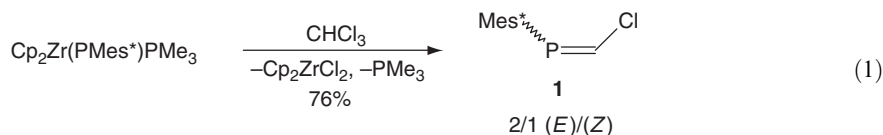
5.23.1.1.2 Halogen derivatives— $R^1C(PR^2)X$ ($X = F, Cl, Br, I$)

(i) Fluorine derivatives— $R^1C(PR^2)F$

Novel derivatives of the type $R^1C(PR^2)F$ have not been described in the literature.

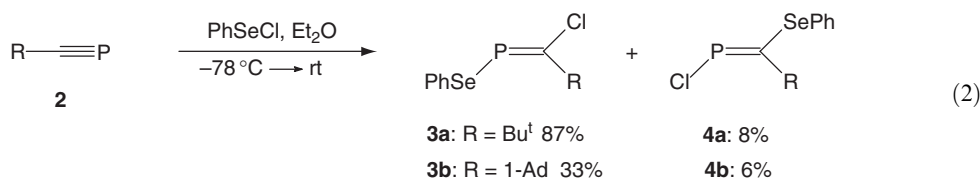
(ii) Chlorine derivatives

(a) *From phosphinidene complexes and chloroform.* The phosphinidene transfer reaction between phosphinidene complex $Cp_2Zr(PMes^*)PMe_3$ and 1 equiv. of chloroform afforded (Z)- and (E)-isomers of $Mes^*P=CHCl$ **1** (Equation (1)) <1995JA11914>.

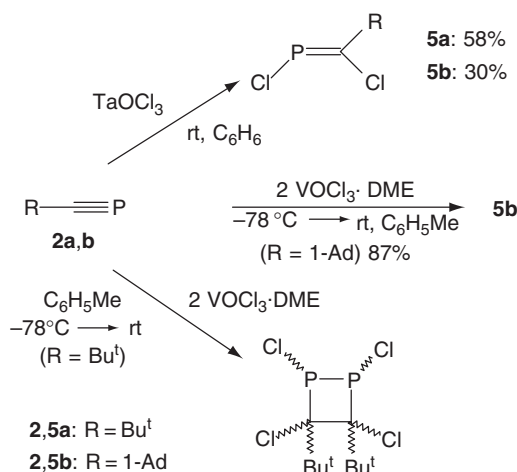


(b) *From phosphalkynes.* Addition of $PhSeCl$ to phosphalkynes $P\equiv CR$ **2** ($R = Bu^t$ (**a**), 1-Ad (1-adamantyl) (**b**)) at $-78^\circ C$ in diethyl ether or CH_2Cl_2 followed by slow warming to ambient temperature led to the formation of the *P*-seleno-*C*-chlorophosphalkenes **3**. In each reaction a

small amount of the *P*-chlorinated isomers **4** was found due to reverse addition. Obviously, the process is stereoselective and largely regioselective. The stereoselectivity is explained by invoking the intermediacy of a cyclic selenophosphirenylium cation (Equation (2)) <1997PS(130)23, 1997CC1641>.



Alternatively the heterogeneous reaction of TaOCl₃ with 2 equiv. of **2a** or **2b**, in benzene at 20 °C afforded chlorophosphaalkenes **5a** and **5b**, each as a single isomer. Improved yields of **5b** were obtained with VOCl₃·DME as the chlorinating agent in toluene at –78 °C. In contrast to this, **2a** and VOCl₃·DME gave rise to the formation of the cyclodimer of **5a** (Scheme 1) <2003ZN(B)44>.



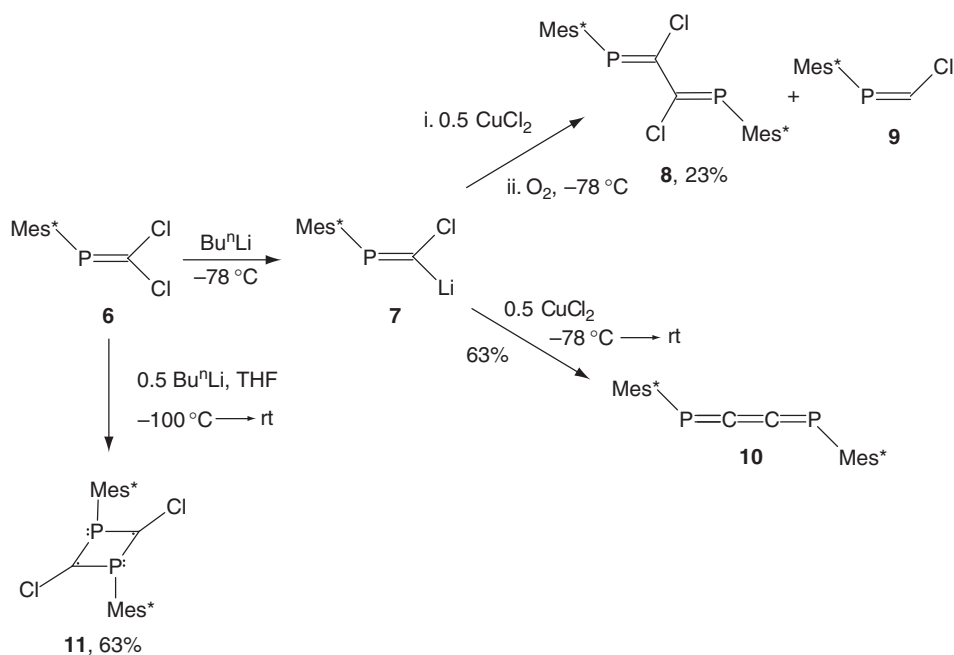
Scheme 1

(c) *From chloromethylene phosphanes.* A synthetic approach to 2,3-dichloro-1,4-diphospha-1,3-butadiene **8** made use of the lithiation of the dichloromethylene phosphane **6** by an equimolar amount of *n*-butyllithium in THF at –78 °C. The thermolabile lithium derivative **7** was quenched with 0.5 equiv. of CuCl₂ and gaseous oxygen at –78 °C to give product **8** in addition to (*Z*)-2-chloro-1-phosphaethene **9** (Scheme 2).

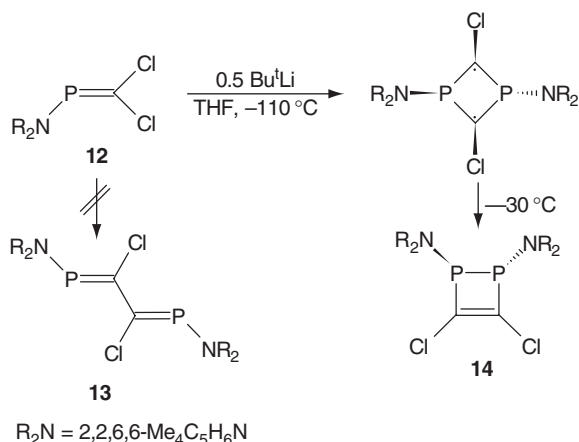
If, however, the reaction mixture of **7** and CuCl₂ was allowed to warm to ambient temperature in the absence of O₂ the 1,4-diphosphabutatriene **10** was obtained instead <1995CL747>. This result contrasts with the reaction of **6** and 0.5 equiv. of *n*-butyllithium in THF at –100 °C where the red crystalline heterocycle **11** was generated <1995AG(E)555>.

Metallation of **12** with Bu^tLi did not afford the expected 1,4-diphosphabutadiene derivative **13**, but resulted in the formation of **14** as a final product (Scheme 3) <1998AG(E)949>.

Compound **7**, although thermolabile at temperatures greater than –50 °C, proved to be a valuable synthon for the stereospecific functionalization of phosphaaalkenes at temperatures less than –50 °C as independently demonstrated by two research groups. Thus, carbenoid (*Z*)-**7**, which was quantitatively generated at –110 °C, was quenched with pivaloyl chloride, benzoyl chloride, or ethyl chloroformate to afford compounds **15**, **16**, and **17** as air stable crystalline compounds.



Scheme 2

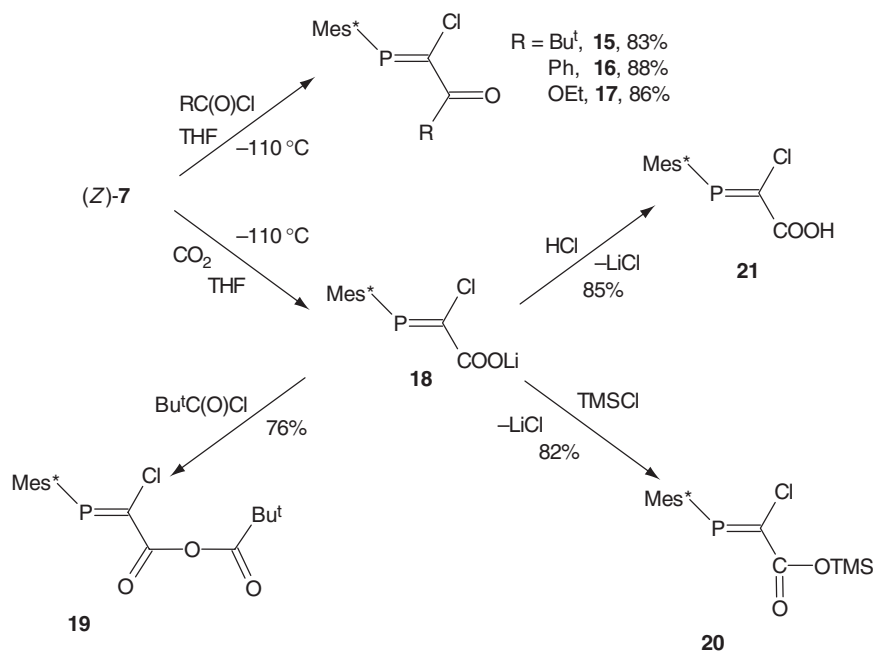


Scheme 3

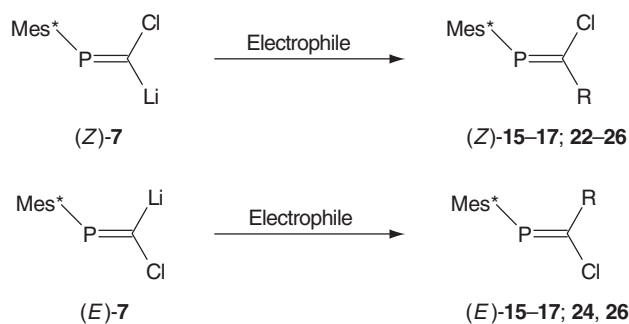
Sublimation of CO_2 into a solution of (*Z*)-**7** furnished the β -phosphaacrylate **18**. The latter compound was further derivatized by the addition of pivaloyl chloride or TMSCl to give anhydride **19** or silyl ester **20**. The corresponding carboxylic acid **21** was also prepared (Scheme 4) <1995CB465>.

In a similar way (*Z*)-**7** and (*E*)-**7** (obtained from (*E*)- $\text{Mes}^*\text{P}=\text{C}(\text{H})\text{Cl}$ and Bu^nLi in THF at -78°C) were converted into phosphalkenes **15–17** and **22–26** by treatment with a number of electrophiles (Scheme 5) (Tables 1 and 2) <1996OM174>. Thereby slow transformation of (*E*)-**7** and (*E*)-**24** into the (*Z*)-configured isomers occurred <1995BCJ1206>.

This synthetic route is limited by the protonation of the organolithium species **7** by means of CH -acidic compounds. This is particularly evident in the reaction of **7** with acetophenone or acetyl chloride. Proton abstraction from CH -acidic components by the organometallic component can be avoided if one replaces the lithiophosphaalkene by the corresponding Grignard reagent **27**. The latter was quantitatively formed from (*Z*)-**7** and MgCl_2 in THF at -110°C and was reacted with acetophenone or acetyl chloride in THF at -5°C to yield the expected products (*Z*)-**28** and (*Z*)-**29** (Scheme 6) <1996OM174>.



Scheme 4



Scheme 5

Table 1 Preparation of (Z)-2-chloro-1-phosphaalkenes from (Z)-7

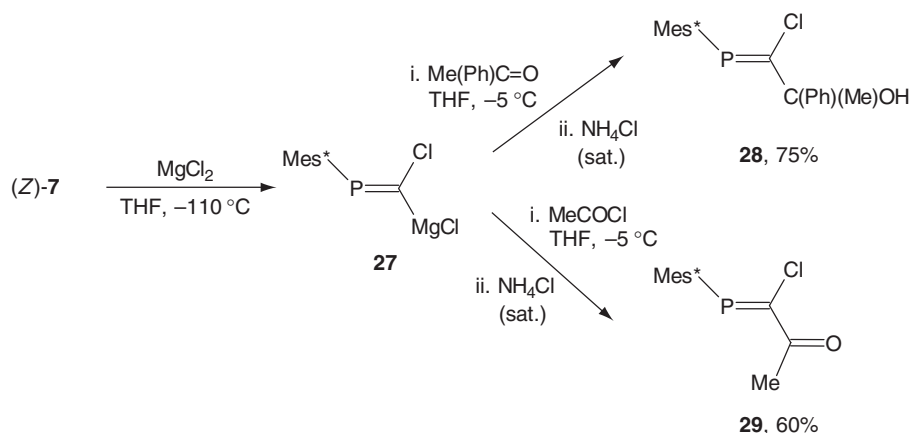
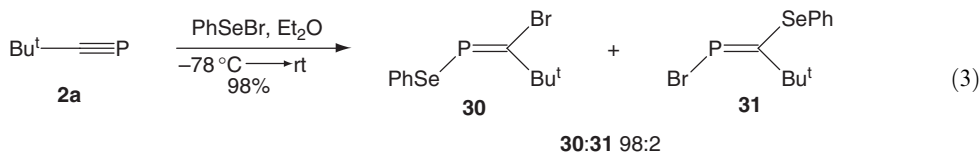
Entry	Substrate	Product	Yield (%)
1	PhCOCl	(Z)-Mes*P=C(Cl)C(O)Ph (Z)- 15	91
2	Bu ^t COCl	(Z)-Mes*P=C(Cl)C(O)Bu ^t (Z)- 16	74
3	ClCO ₂ Et	(Z)-Mes*P=C(Cl)CO ₂ Et (Z)- 17	86
4	PhCHO	(Z)-Mes*P=C(Cl)C(H)(OH)Ph (Z)- 22	94
5	(E)-MeCH=CHCHO	(Z)-Mes*P=C(Cl)C(H)(OH)CH=CHMe (Z)- 23	77
6	(CH ₂) ₅ CO	(Z)-Mes*P=C(Cl)C(OH)(CH ₂) ₅ (Z)- 24	29
7	Ph ₂ CO	(Z)-Mes*P=C(Cl)C(OH)Ph ₂ (Z)- 25	95
8	PhNCO	(Z)-Mes*P=C(Cl)C(O)NHPh (Z)- 26	81

(iii) Bromine derivatives— $R^1C(PR^2)Br$

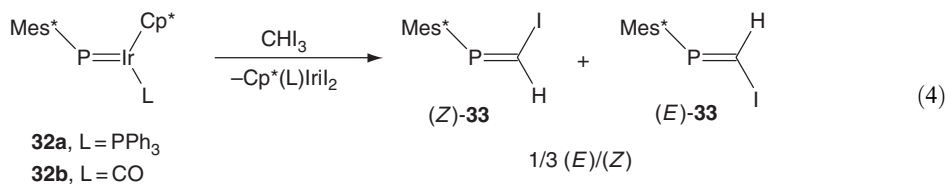
An analogous procedure as described for **3** was employed for the synthesis of the bromo-derivative **30** from **2a** and PhSeBr. The oily product was contaminated by the regioisomer **31** (Equation (3)) <1997PS(130)23>.

Table 2 Preparation of (*E*)-2-chloro-1-phosphaalkenes from (*E*)-**7**

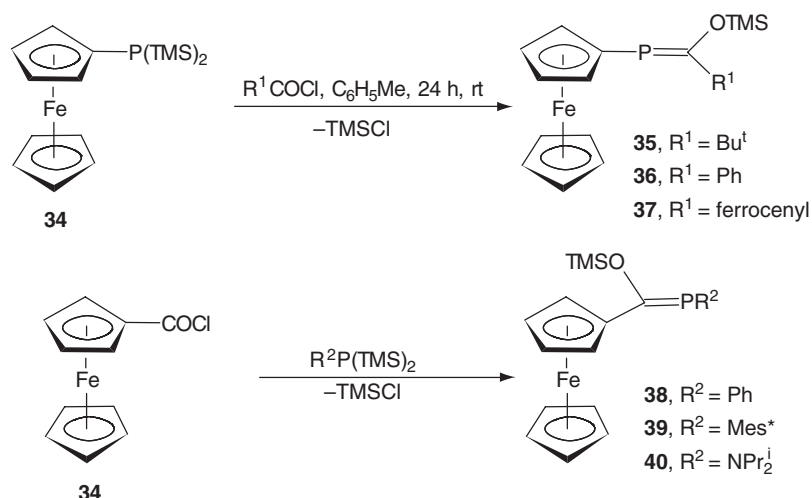
Entry	Substrate	Product	Yield (%)
1	PhCOCl	(<i>E</i>)-Mes*P=C(Cl)C(O)Ph (<i>E</i>)- 15	50
2	Bu ^t COCl	(<i>E</i>)-Mes*P=C(Cl)C(O)Bu ^t (<i>E</i>)- 16	70
3	ClCO ₂ Et	(<i>E</i>)-Mes*P=C(Cl)CO ₂ Et (<i>E</i>)- 17	78
4	(CH ₂) ₅ CO	(<i>E</i>)-Mes*P=C(Cl)—C(OH)(CH ₂) ₅ (<i>E</i>)- 24	24
5	PhNCO	(<i>E</i>)-Mes*P=C(Cl)—C(O)NHPh (<i>E</i>)- 26	16

**Scheme 6**(iv) Iodine derivatives— $R^1C(PR^2)I$

The synthesis of Mes*P=CHI **33** from CHI₃ and the phosphinidene complexes Cp*(PPh₃)Ir=PMes* **32a** and Cp*(CO)Ir=PMes* **32b** followed the principles described above for the chlorine analog **1**. Here complex **32b** appeared to be more reactive than **32a** presumably for steric reasons (Equation (4)) <2002OM3196>.

5.23.1.1.3 Chalcogen derivatives— $R^1C(PR^2)ER^3$ ($E = \text{O, S, Se, Te}$)(i) Oxygen derivatives— $R^1C(PR^2)OR^3$

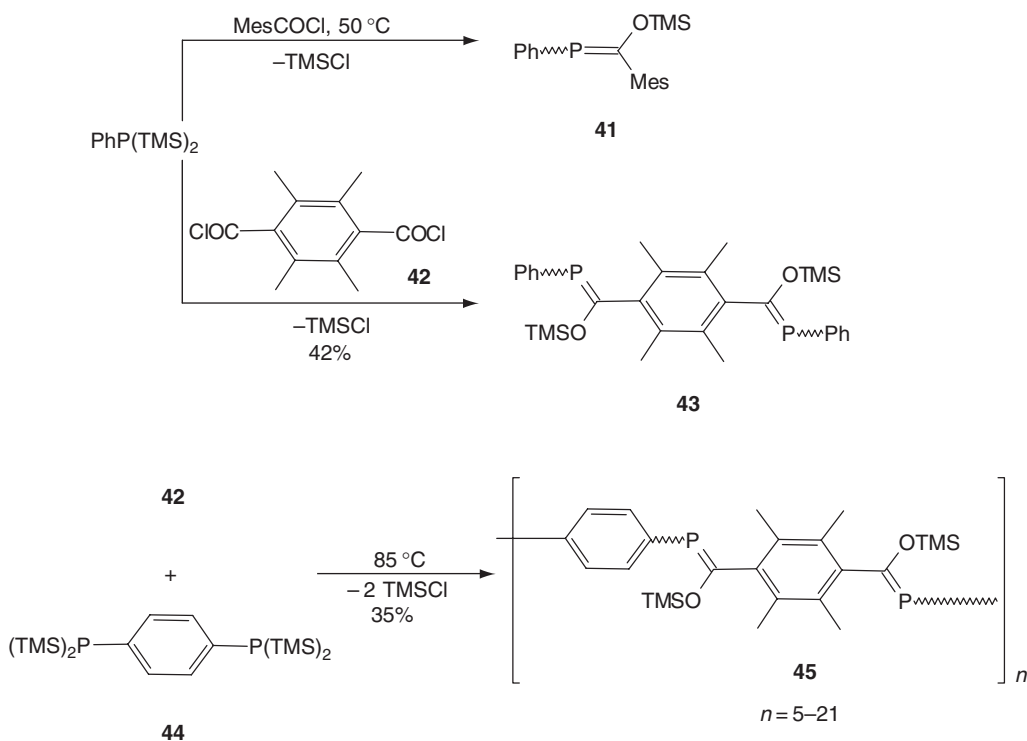
(a) From silylphosphanes and acid chlorides. In line with the classical route to oxygen-functionalized phosphoalkenes the *P*-ferrocenyl derivatives **35–37** were quantitatively synthesized from ferrocenylbis(trimethylsilyl)phosphane **34** and several acid chlorides in toluene (Scheme 7).



Scheme 7

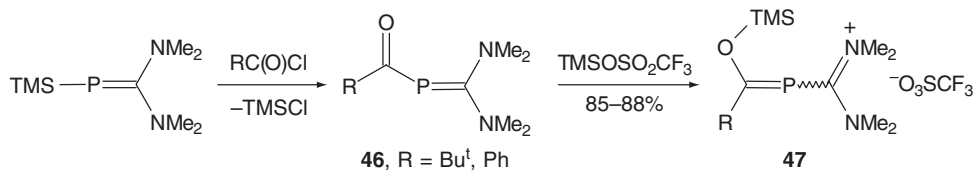
Analogously, the C-ferrocenyl-substituted phosphoalkenes **38–40** were obtained [<1997JOM\(529\)127>](#).

Compound **41** resulted from the reaction of mesitoyl chloride and PhP(TMS)₂ in the absence of solvent at 50 °C for several days. Heating a concentrated solution of 2 equiv. of PhP(TMS)₂ and **42** in a THF/hexane mixture at 85 °C for several days afforded the arylene bis(phosphoalkene) **43** as a colorless powder. Polycondensation of **42** and the silylated bisphosphane **44** occurred at 85 °C in a vacuum-sealed tube to yield a highly viscous yellow oil after 24 h. Purification of product **45** was effected by precipitation from a concentrated THF solution with hexanes at –30 °C affording a brittle yellow solid (Scheme 8) [<2002AG\(E\)2389>](#).



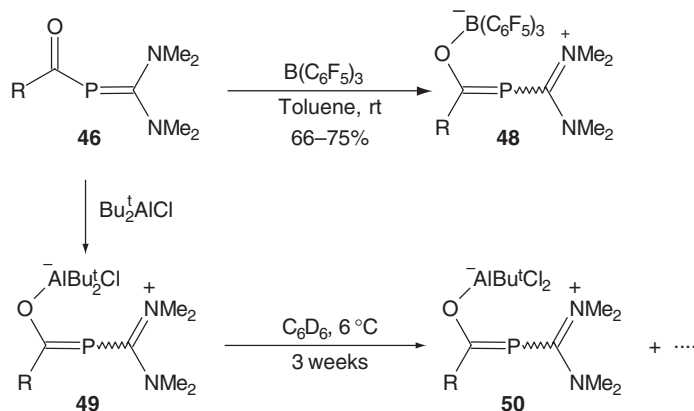
Scheme 8

(b) *From P-acylphosphaalkenes and Lewis acids.* The PC multiple bond in bis(aminomethylene)phosphanes of the type $\text{RP}=\text{C}(\text{NMe}_2)_2$ is polarized in the sense $\text{P}^{\delta-}-\text{C}^{\delta+}$. The negative charge on phosphorus is effectively stabilized by adjacent carbonyl groups via π -delocalization. According to the principle of hard and soft acids and bases (HSAB) the attack of hard electrophiles should occur at the hard carbonyl oxygen atom of $\text{RCOP}=\text{C}(\text{NMe}_2)_2$ whereas soft electrophiles should prefer addition to the soft phosphorus atom. The required precursors **46** were easily available from $\text{TMS}-\text{P}=\text{C}(\text{NMe}_2)_2$ and acid chlorides. The silylation of **46** with equimolar amounts of trimethylsilyl triflate in diethyl ether gave the extremely air- and moisture-sensitive salts **47**, which were isolated as viscous oils (Scheme 9) <1999EJI2369>.



Scheme 9

Boranes and alanes are isoelectronic to silyl cations and as hard Lewis acids they should prefer oxygen attack. In keeping with this, treatment of **46** ($\text{R} = \text{Bu}^t, \text{Ph}$) with tris(pentafluorophenyl)-borane in toluene solution at 20°C led to the adducts **48** as yellow solids (Scheme 10) <1999EJI2369>.

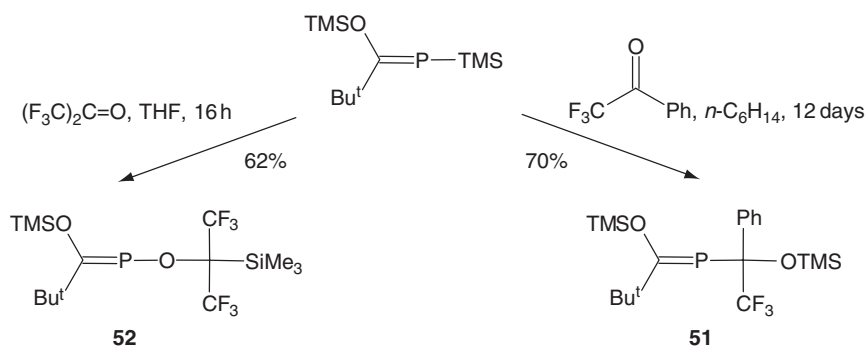


Scheme 10

Di-*t*-butylaluminum chloride smoothly reacted with equimolar amounts of **46** in toluene at -30°C to afford compounds **49** as extremely moisture-sensitive orange solids. Attempts to grow single crystals of **49** from saturated C_6D_6 solutions at 6°C led to dismutation. A few crystals of **50** were collected after 2–3 weeks and characterized by X-ray analysis. At this point, it should be noted that the reaction under discussion suffers from severe limitation. Whereas adduct formation of **46** with AlMe_3 gave products analogous to **49**, coordination of InMe_3 and the fragments $[\text{Ni}(\text{CO})_3]$, $[\text{Fe}(\text{CO})_4]$, and $[\text{Cr}(\text{CO})_5]$ was observed at the phosphorus atom. Moreover, protonation of **46** with ethereal HBF_4 or methylation with methyl triflate smoothly occurred at phosphorus to give heterocarbenium salts in high yields <1999EJI2369>.

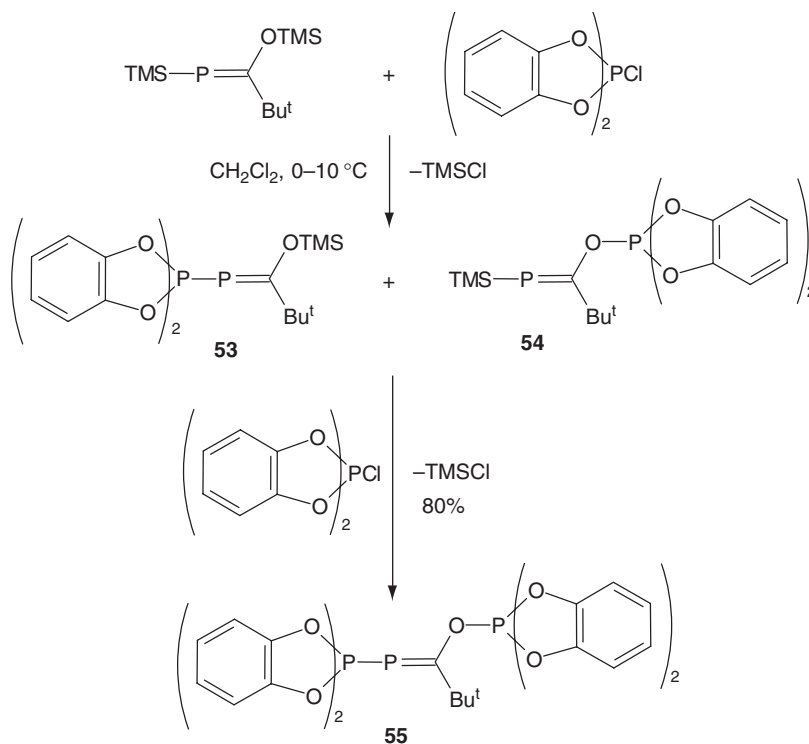
(c) *From peripheral reactions.* The silyl group at the phosphorus atom in $\text{TMS}-\text{P}=\text{C}(\text{Bu}^t)\text{OTMS}$ can be replaced by other functionalities leading to novel phosphoalkenes. Thus, combination with trifluoroacetophenone in *n*-hexane furnished insertion product **51** after 12 days of stirring at 20°C as a pale yellow viscous liquid (Scheme 11). Compound $\text{TMS}-\text{P}=\text{C}(\text{Bu}^t)\text{OTMS}$ was converted into the liquid phosphoalkene **52** by the reaction with hexafluoroacetone in THF <1995CB499>.

The treatment of an excess of bis(*o*-phenylenedioxy)chlorophosphorane with $\text{TMS}-\text{P}=\text{C}(\text{OTMS})(\text{Bu}^t)$ in CH_2Cl_2 led to P–Si and O–Si cleavage and the formation of crystalline **55**. The initial formation of an unseparable mixture of the phosphoalkenes **53** and **54**



Scheme 11

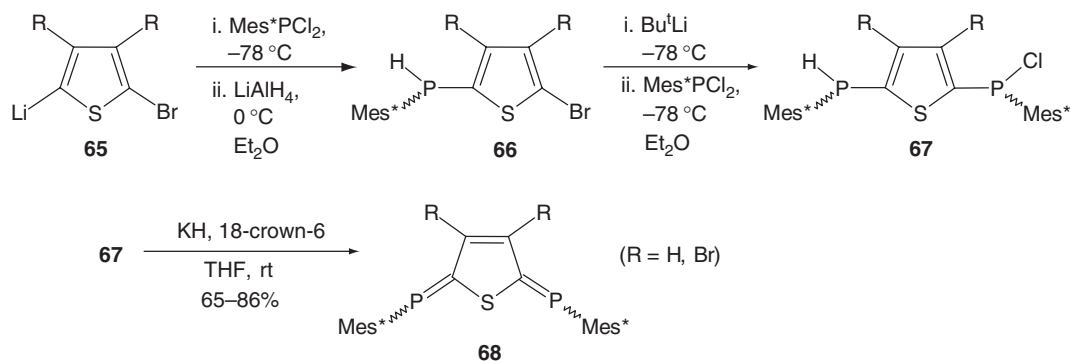
was evidenced by ^{31}P NMR spectroscopy (Scheme 12) <1999ZOB52>. As discussed before *P*-trimethylsilyl-4,5-dihydro-3-*H*-1,2,4-diazaphospholes were readily transformed into phosphaaalkenes by loss of N_2 and a 1,2-migration of the TMS group <1995COFGT(5)875>.



Scheme 12

This process was extended to the 5-alkylidene-4,5-dihydro-1,2,4-diazaphospholes **56**, which were produced from $\text{TMS}-\text{P}=\text{C}(\text{OTMS})\text{Bu}^t$ and $\text{R}(\text{Pr}^i_3\text{SiO})\text{C}=\text{C}=\text{N}_2$ in a dipolar $[3+2]$ -cycloaddition <1996T10053>. Thermolysis of **56** at 150°C in toluene in a sealed vessel was complete after 4 h, yielding a mixture of three products **57–59**. The isolation of the pure 2-phosphabutadiene derivative **57** was effected by twofold bulb-to-bulb distillation and subsequent crystallization from toluene at -78°C (Scheme 13). The success of this reaction is confined to precursors **56** with silyl substituents at the ring phosphorus atom <1997CB779>.

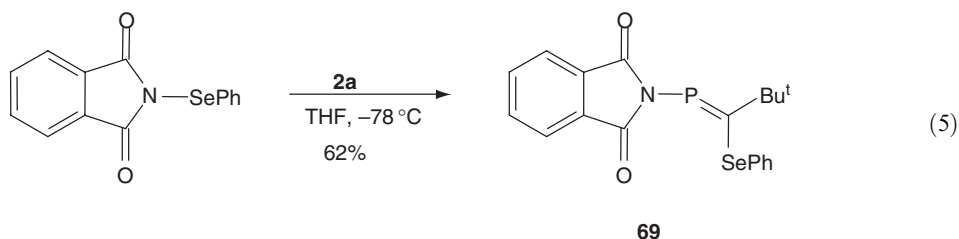
their synthesis is the elimination of HCl from precursor **67**. Compound **67** results from thienyllithium **65** via intermediate **66** by repeated treatment with Mes*PCl₂, LiAlH₄, and butyllithium, respectively. Thereby, compound **68** (R = H) was isolated as an inseparable 1:1 mixture of ((*E*),(*Z*))- and ((*Z*),(*Z*))-isomers. The exclusive formation of the ((*Z*),(*Z*))-isomer was achieved by increasing the steric bulk of the substituents in the 3- and 4-positions of the thiophene ring. Thus, HCl-elimination of the dibromothiophene **67** cleanly afforded ((*Z*),(*Z*))-product **68** as orange air-stable crystals (Scheme 15) <2002AG(E)2574>.



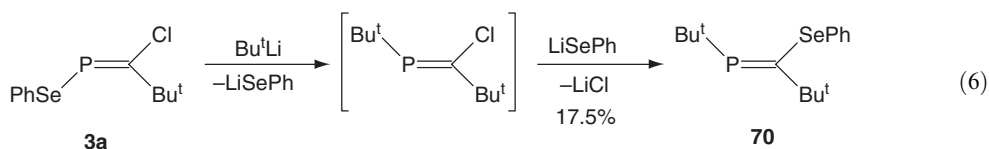
Scheme 15

(iii) Selenium derivatives— $R^1C(PR^2)SeR^3$

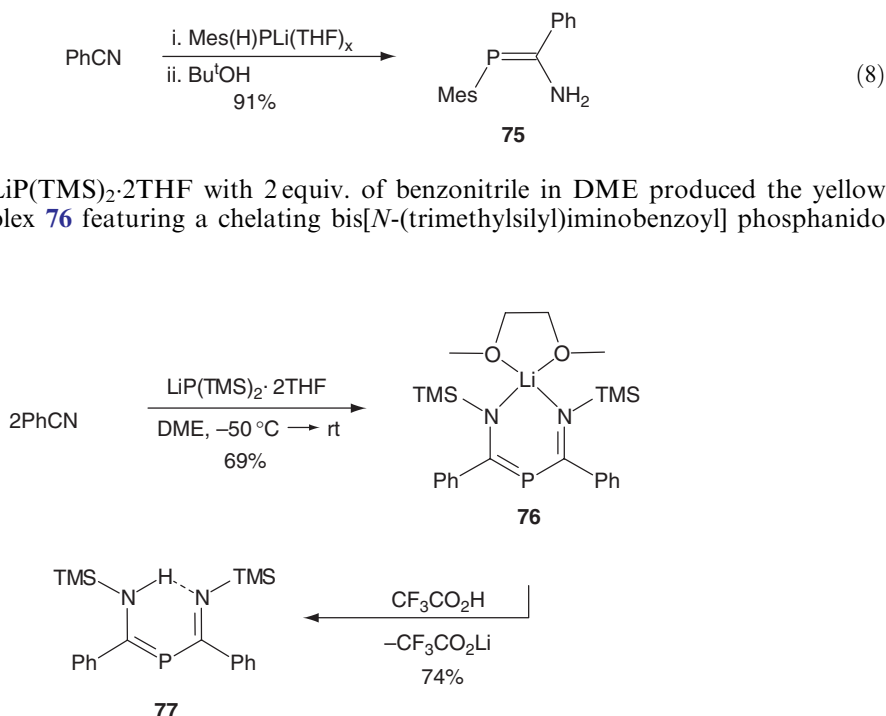
(a) *From phosphalkynes.* Reaction of diphenyl diselenide with phosphalkynes in the presence of XeF₂ led to unstable and nonisolable products of the diselenation of the PC triple bond <1997CC1641>. As discussed before small amounts of the phenylselenenyl-functionalized phosphalkenes **4a**, **4b**, and **31** were obtained from the stereoselective 1,2-addition of the respective phenylselenenyl halide to the triple bond of phosphalkynes **2a** and **2b** (Equations (2) and (3)) <1997PS(130)23>. To provide an improved regioselectivity in such processes the halide substituent in PhSeX was replaced by the bulky phthalimide function. As expected equimolar amounts of *N*-phenylselenenyl phthalimide and **2a** underwent a clean reaction in THF at $-78\text{ }^{\circ}\text{C}$ to give the phosphavinylselenium compound **69**, which was isolated as pale yellow crystals (Equation (5)) <2003JOM(665)127>.



Treatment of **3a** with *t*-butyllithium led to the formation of the C-selenated phosphalkene **70** as yellow crystals. As a rationale for this result the initial replacement of the PhSe-function at phosphorus was invoked. Substitution of chloride by the liberated phenylselenide gave product **70** (Equation (6)) <1997PS(130)23>.



Analogously, benzonitrile was converted into colorless, crystalline phosphalkene **75** by reaction with mesitylphosphanyl lithium in DME and the subsequent quench with *t*-butanol (Equation (8)) <1995AG(E)2369>.



Scheme 17

The same result was obtained with equimolar amounts of the reactants. The exchange of the solvent DME for diethyl ether led to a situation where the anticipated 1:1 adduct TMS—P=C(Ph)—N(TMS)Li could be detected by NMR spectroscopy. During the course of 3 days, however, complete transformation to **76** occurred. Conversion of the lithium chelate complex **76** into the corresponding acid **77** was accomplished by the addition of 1 equiv. of trifluoroacetic acid to a DME solution of the complex at -60 °C <1999ZAAC2008>.

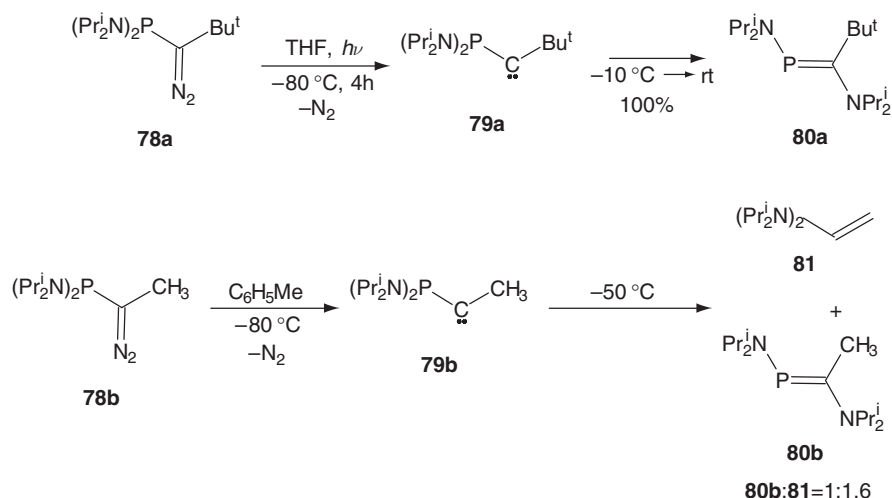
(iii) From phosphanyl diazoalkanes

Irradiation of the bis(diisopropylamino)phosphanyl diazoalkane **78a** in THF at -80 °C afforded the thermolabile phosphanyl carbene **79a**, which at -10 °C underwent a 1,2-migration of one diisopropylamino group to give phosphalkene **80a** as the final product. This type of reaction has some limitations. Thus the photolytically generated phosphanyl carbene **79b** rearranged not only to phosphalkene **80b**, but also to vinylphosphane **81** as a second major product (Scheme 18) <2002AG(E)2835>.

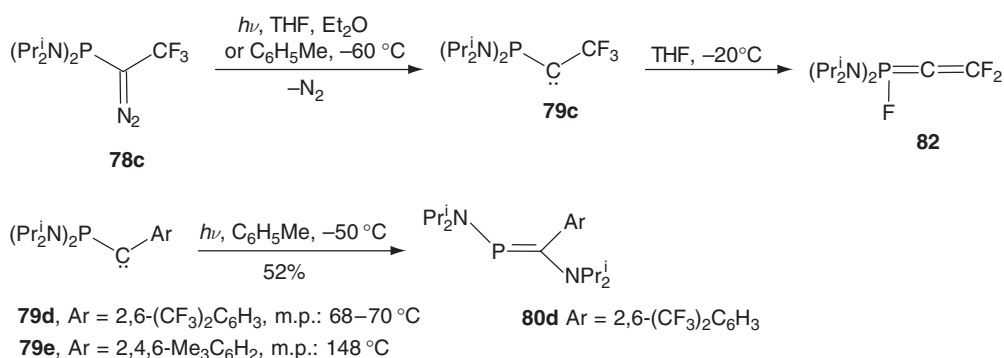
Solutions of phosphanyl(trifluoromethyl)carbene **79c**, which was generated analogously from diazoalkane **78c**, were stable up to -30 °C for weeks. When a THF solution of the carbene was warmed to -20 °C a clean rearrangement occurred affording the cumulene **82** as the result of two successive 1,2-F-migrations <2000SCI(288)834>. In contrast to this, arylated phosphanyl carbenes **79d** and **79e** are stable at room temperature both in solution and in the solid state <2000SCI(288)834, 2002AG(E)2835>. The conversion of **79d** into phosphalkene **80d** could, however, be achieved by irradiating a toluene solution of the carbene at -50 °C <2003EJO2039> (Scheme 19).

(iv) From phosphavinylidene carbenoids and isocyanates

As discussed before (Scheme 5) treatment of the (*Z*)-configured phosphavinylidene carbenoid (*Z*)-Mes*P=C(Cl)Li (*Z*)-**7** with phenyl isocyanate afforded phosphalkene (*Z*)-Mes*P=C(Cl)C(O)NHPh

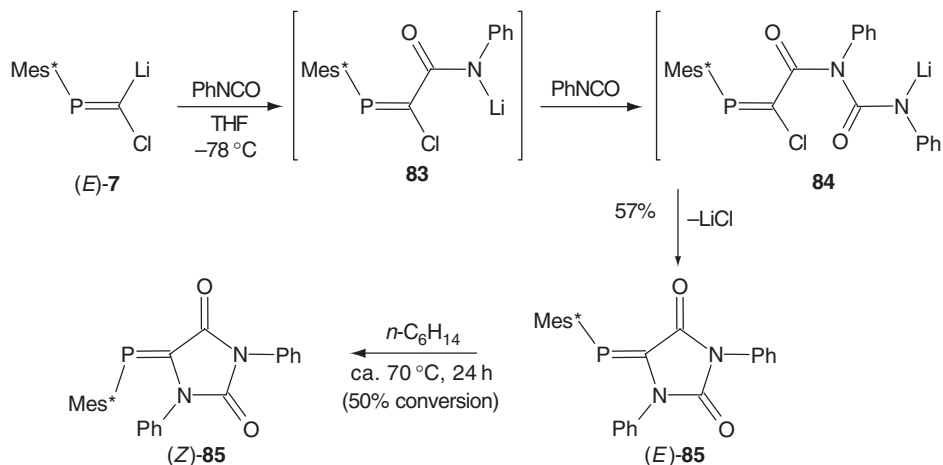


Scheme 18



Scheme 19

(*Z*)-**26** in 81%. The reaction of the corresponding (*E*)-configured compounds (*E*)-**7** gave (*E*)-**26** in only 16% yield. The main product was the yellow crystalline hydantoin derivative **85**, which implies the incorporation of 2 equiv. of isocyanate via transient **83** and **84** (Scheme 20) <1995BCJ1206>.

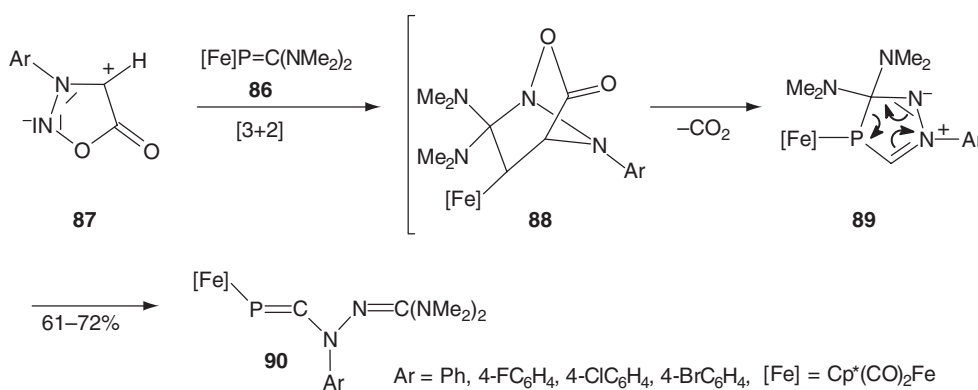


Scheme 20

Heating the *n*-hexane solution of (*E*)-**85** for 24 h under reflux caused a 50% conversion of (*E*)-**85** to (*Z*)-**85** and this ratio remained unchanged after 26 h. At room temperature compound (*Z*)-**85** crystallized from the solution in 30% yield. Heating pure samples of either (*E*)-**85** or (*Z*)-**85** in benzene in a sealed NMR tube for 24 h at 90 °C regenerated the 1:1 equilibrium mixture of isomers.

(v) *From phosphalkenes and sydnones*

The metallocphosphaalkene $\text{Cp}^*(\text{CO})_2\text{FeP}=\text{C}(\text{NMe}_2)_2$ **86** smoothly reacted with equimolar amounts of the *N*-aryl sydnones **87** (Ar = Ph, 4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄) to afford the red-brown microcrystalline ferriphosphaalkenes (*E*)- $\text{Cp}^*(\text{CO})_2\text{FeP}=\text{CHN}(\text{Aryl})-\text{N}=\text{C}(\text{NMe}_2)_2$ **90** (Scheme 21).

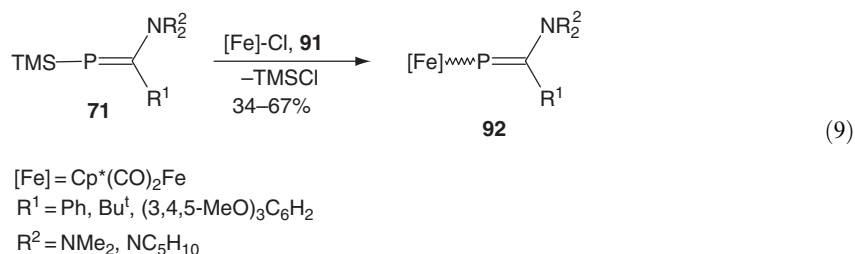


Scheme 21

In contrast to this, treatment of **86** with the more electron-rich 3-methyl- or 3-(4-methoxyphenyl)-sydnones led to decomposition. It is remarkable that the reaction of the phosphalkene with the chlorophenyl- and bromophenyl-substituted sydnones came to completion after 3 h, whereas for the two remaining candidates a reaction time of 24 h was required [<1997OM2958>](#). Possible intermediates such as **88** and **89** were not detected.

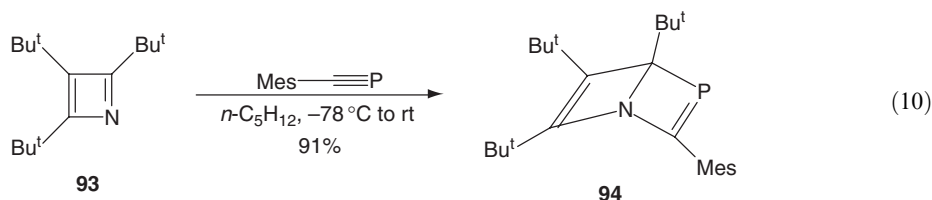
(vi) *Peripheral reaction at phosphalkenes*

The facile replacement of a TMS group in silylated phosphanes generally allows access to a wide variety of derivatives. Thus, upon combination of phosphalkenes **71** with 1 equiv. of Cp^{*}(CO)₂-FeCl **91**, reaction occurred at -75 to 25 °C to produce the red microcrystalline ferriphosphaalkenes **92** (Equation (9)) [<2000EJI1185>](#).



(vii) From phosphalkynes and azetes

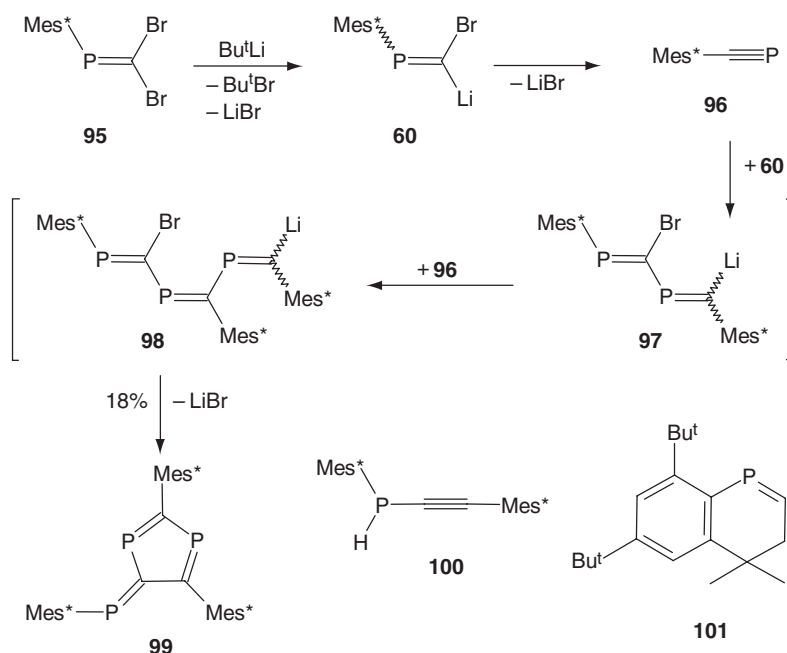
The Diels–Alder reaction of the phosphalkynes $\text{Bu}^t\text{CH}_2\text{—C}\equiv\text{P}$ and $\text{Bu}^t\text{—C}\equiv\text{P}$ with tri-*t*-butylazete **93** to give 1-Dewar-1,3-azaphosphinines was successfully extended to mesitylphosphaethyne, whereby product **94** was isolated as colorless crystals (Equation (10)) <1998S1305>.

5.23.1.1.5 Group 15 element derivatives— $\text{R}^1\text{C}(\text{PR}^2)\text{ER}_n^3$ ($\text{E} = \text{P}, \text{As}, \text{Sb}, \text{Bi}$)

Phosphaalkenes with substituents based on the heavier group 15 elements are restricted to phosphorus up to early 2003. The great majority of these compounds are synthesized from phosphalkynes by various types of cycloaddition and from heterocycles easily derived from phosphalkynes by either alkali metal reduction or oligomerization processes.

(i) Derivatives with dicoordinate phosphorus— $\text{R}^1\text{C}(\text{PR}^2)\text{PR}^3$

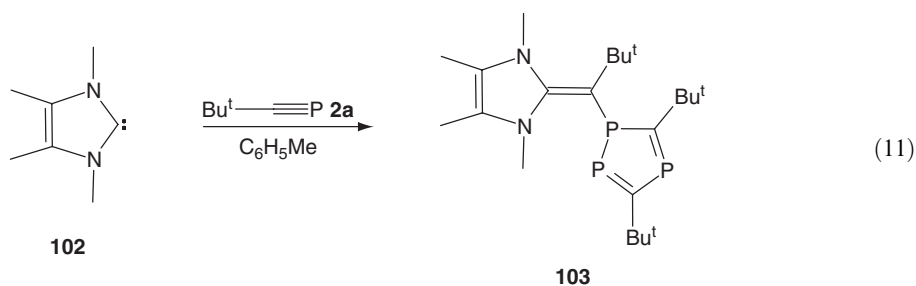
(a) From phosphavinylidene carbenoids. The reaction of dibromophosphaalkene $\text{Mes}^*\text{—P}=\text{CBr}_2$ **95** with 2 equiv. of *t*-butyllithium at -78 to 25°C and subsequent chromatography of the reaction residue on silica furnished 1,3,6-triphosphafulvene **99** as dark red crystals. Compounds **96**, **100**, and **101** were identified as impurities in the crude product (Scheme 22). Compound **99** can formally be regarded as a trimer of the hypothetical phosphanylidene carbene $\text{Mes}^*\text{P}=\text{C}$. According to Scheme 22 phosphalkyne **96** was initially formed from **60**. Addition



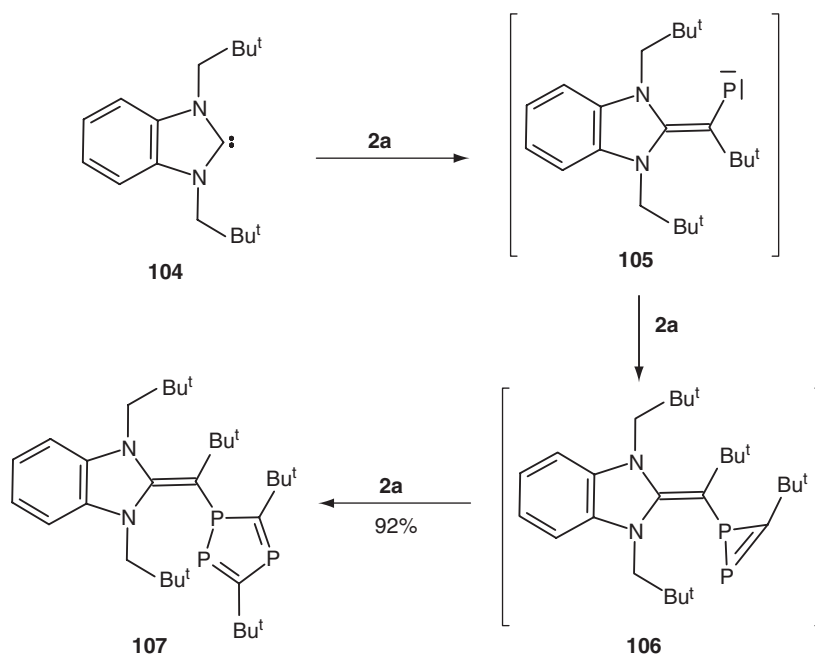
Scheme 22

of carbenoid **60** to the PC triple bond of **96** gave 1,3-diphosphabutadienyllithium **97**, which added a second molecule of $\text{Mes}^*\text{C}\equiv\text{P}$. Subsequently, cyclization of **98** to product **99** was effected with extrusion of LiBr <2000AG(E)2781>.

(b) *From phosphalkynes.* Combination of toluene solutions of phosphalkyne $\text{Bu}^t\text{C}\equiv\text{P}$ **2a** and the imidazolin-2-ylidene **102** afforded the red solid 1,2,4-triphosphole derivative **103** in 68% yield (Equation (11)) <2001AG(E)3144>. Triphosphole **103** has also been prepared quantitatively from 2,4,6-tri-*t*-butyl-1,3,5-triphosphenine and **102** <2000CC1305>. As the triphosphine has to be prepared from **2a** first, this reaction offers no advantages over that with **2a** as a precursor.

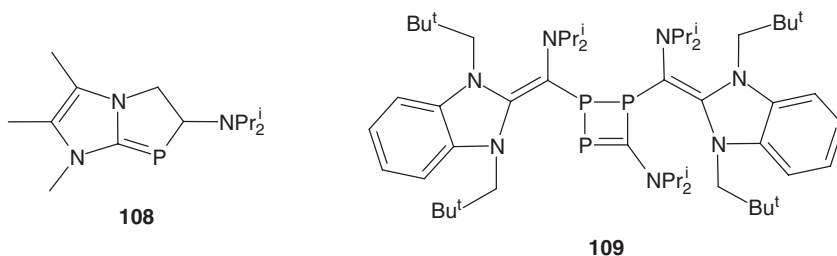


The reaction of benzimidazolin-2-ylidene **104** with **2a** in benzene proceeded analogously with the generation of red crystalline **107** (Scheme 23) <2000AG(E)2307>.

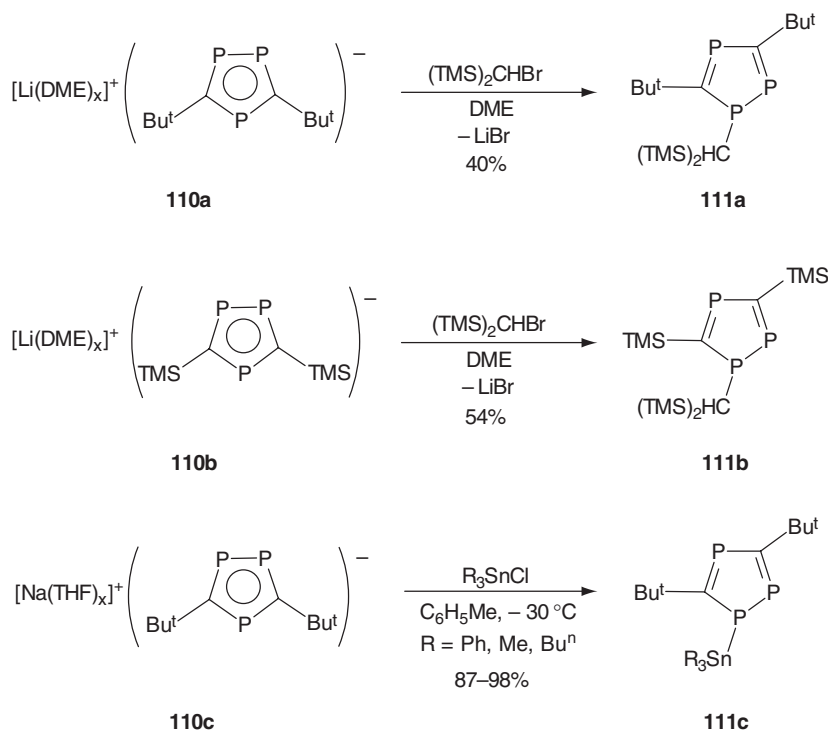


Scheme 23

The initial step of this process was the attack of the nucleophilic carbene at the carbon atom of the PC triple bond forming the highly reactive vinylphosphinidene **105**. The latter underwent a [2 + 1]-cycloaddition with **2a**, and the resulting diphosphirene **106** incorporated a third molecule of $\text{Bu}^t\text{C}\equiv\text{P}$ to give the final product. These transformations lack generality. If the phosphalkyne $\text{Bu}^t\text{C}\equiv\text{P}$ was replaced by diisopropylamino-phosphaethyne $\text{Pr}_2\text{N}-\text{C}\equiv\text{P}$ in the reaction with **102** formation of azaphosphole **108** was observed <2001AG(E)3144>. In contrast to this, carbene **104** and $\text{Pr}_2\text{N}-\text{C}\equiv\text{P}$ yielded the 1,2,3-triphosphetene derivative **109** <2000AG(E)2307>.



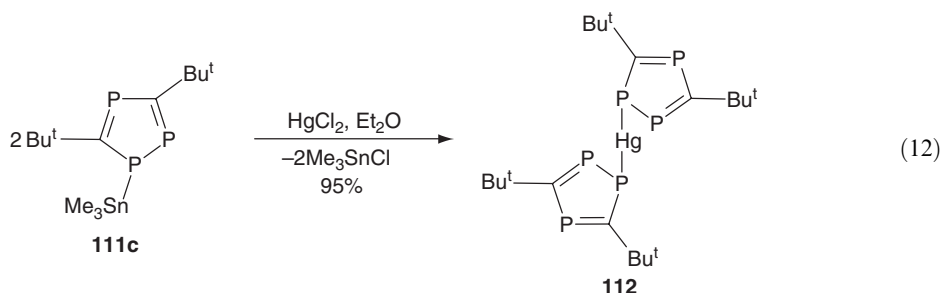
(c) *From 1,2,4-triphospholides.* The reaction of a DME solution of the lithium 1,2,4-triphospholide **110a** with $(\text{TMS})_2\text{CHBr}$ gave a yellow oil, which after purification by column chromatography afforded orange crystals of the 1,2,4-triphosphole **111a** (Scheme 24) <1995CC1661>. The tricoordinate phosphorus atom of the ring is nonplanar with a sum of angles of only 342° .



Scheme 24

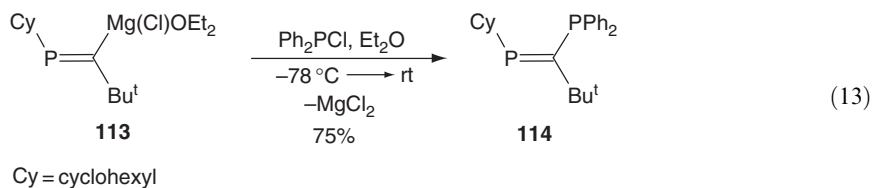
The replacement of the two *t*-butyl substituents in **111a** by TMS groups led to the completely planar yellow triphosphole **111b**, the synthesis of which was analogously conducted by alkylation of the corresponding 1,2,4-triphospholide **110b** <1998AG(E)1083>. The treatment of a toluene solution of the sodium triphospholide **110c** with R_3SnCl ($\text{R} = \text{Ph}, \text{Me}, \text{Bu}^n$) at -30°C afforded the 1-stannyl-3,5-di-*t*-butyl-1,2,4-triphospholes **111c** (Scheme 24). In order to obtain **111c** in more than 80% yield it was crucial to completely remove $\text{Na}[2,4,5\text{-tri}(t\text{-butyl})\text{-}1,3\text{-diphospholide}]$, which was generated as a by-product in the synthesis of **110c** from phosphaaalkyne **2a** <1999CEJ3143>.

Transmetalation of **111c** with HgCl_2 in the molar ratio of 2:1 resulted in the formation of **112** as a dark red amorphous solid. When brought into contact with *n*-hexane or toluene compound **112** decomposed rapidly with extrusion of metallic mercury (Equation (12)) <2002CEJ2622>.

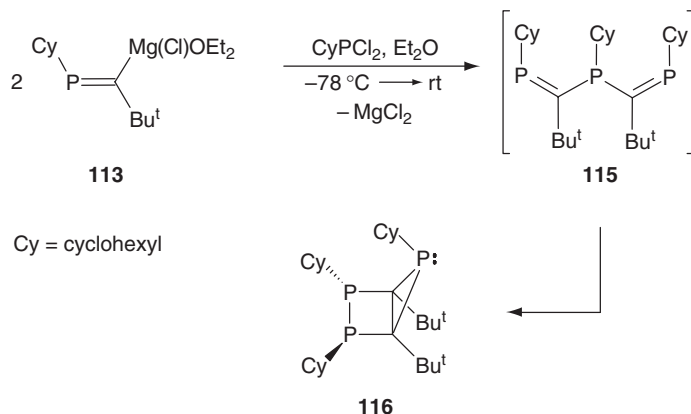


(ii) Derivatives with tricoordinate phosphorus— $R^1C(PR^2)PR_2^3$

(a) *The availability of phosphavinyl.* Grignard reagents open up a novel route to 1,3-diphosphapropenes $R^1C(PR^2)PR_2^3$. Accordingly, the reaction of Grignard compound **113** with Ph_2PCl cleanly afforded the expected product **114** as yellow prisms, whereby the stereochemistry of the phosphavinyl fragment was retained (Equation (13)) <2002NJC1209>.

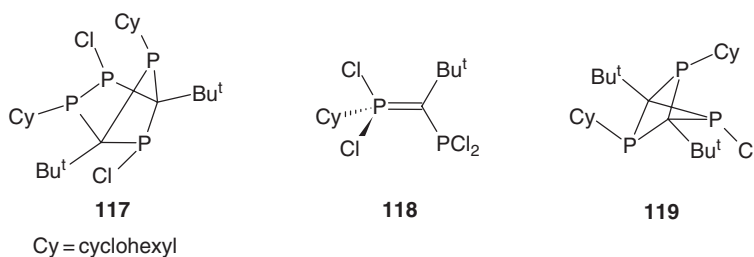


This type of transformation, however, lacks generality. Thus treatment of cyclohexylphosphorus dichloride with 2 equiv. of **113** did not give the desired 1,3,5-triphosphapentadiene **115** but afforded **116** instead as the result of an electrocyclicization (Scheme 25).



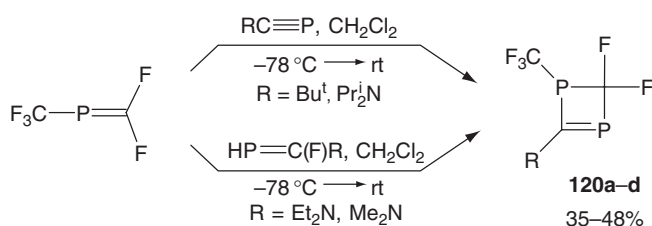
Scheme 25

Combination of **113** with PCl_3 in a 1:1 stoichiometry yields compounds **117** and **118** in poor yields. If the reaction between **113** and PCl_3 was conducted in 2:1 or 3:1 molar ratios, the triphosphabicyclo[1.1.1]pentane **119** was isolated in 36% yield <2002NJC1209>.



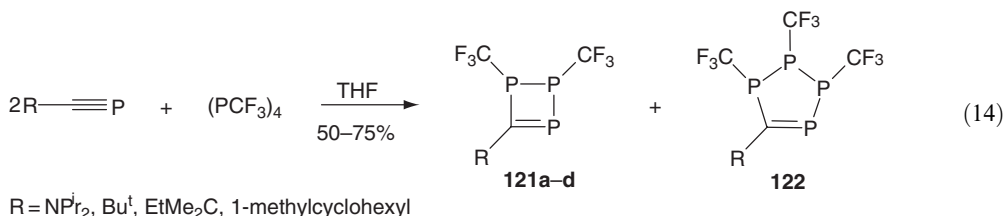
(b) *From phosphalkynes.* As already mentioned the ready availability of a number of kinetically stable phosphalkynes has opened the gateway to a plethora of molecules featuring $\text{P}=\text{C}$ multiple bonds which are substituted by tricoordinate phosphorus atoms. The transformation of the phosphalkyne precursor into the target compound may involve cycloaddition processes with unsaturated organic, organophosphorus, or inorganic species. In various cases, main group and transition metal compounds play an important role for the course of the transformation as well as for the product pattern.

When perfluoro-2-phosphapropane $\text{CF}_3\text{P}=\text{CF}_2$ was condensed into an equimolar amount of $\text{Pr}_2^i\text{NC}\equiv\text{P}$ in CH_2Cl_2 a rapid $[2+2]$ -cycloaddition occurred on warming, and pure 1,2-dihydro-1,3-diphosphetene **120c** was isolated as a colorless solid by sublimation. For the reaction of $\text{CF}_3\text{P}=\text{CF}_2$ with the nonisolable aminophosphalkynes $\text{Me}_2\text{NC}\equiv\text{P}$ and $\text{Et}_2\text{NC}\equiv\text{P}$ the easily accessible phosphalkenes $\text{HP}=\text{C}(\text{F})\text{NR}_2$ were used as synthetic equivalents. This allowed a simple preparation of the diphosphetenes **120a** and **120b**. Similarly, $\text{Bu}^t\text{C}\equiv\text{P}$ reacted at 25°C with $\text{CF}_3\text{P}=\text{CF}_2$ to give **120d**, albeit at a much lower rate. Completion of this transformation took 5 days (Scheme 26) <1997JOM(529)177>.



Scheme 26

The first 1,2,3-triphosphetenes **121a–d** were prepared from $(\text{PCF}_3)_4$ and 2 equiv. of $\text{Pr}_2^i\text{NC}\equiv\text{P}$, $\text{Bu}^t\text{C}\equiv\text{P}$, $\text{EtMe}_2\text{CC}\equiv\text{P}$, or 1-methylcyclohexylphosphaethyne (Equation (14)) <1996CEJ208>.



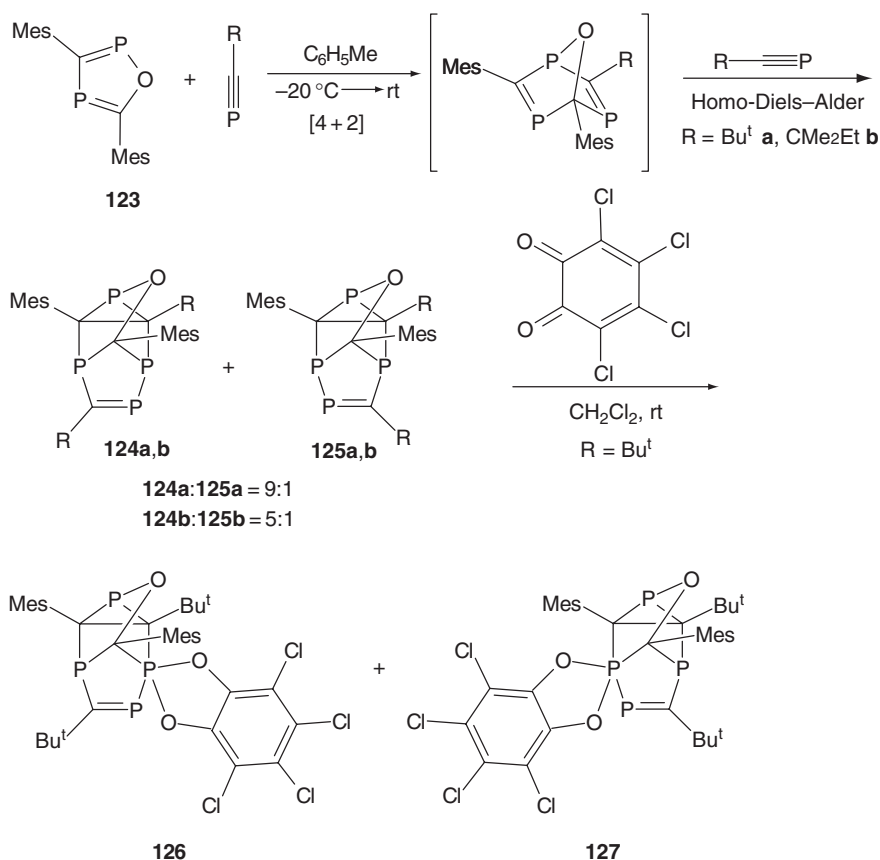
Small amounts of the five-membered rings **122** were also formed, although they could not be isolated. Unsaturated five-membered heterocycles such as 1,2,4-oxadiphospholes, 1,2,4-thiadiphospholes, 1,2,4-selenadiphospholes, or 1,2,4-triphospholes readily react as heterodienes toward phosphalkynes leading to a series of interesting bicyclic as well as cage compounds.

Even at low temperatures, the addition of 2 equiv. of phosphalkynes **2a** and $\text{EtMe}_2\text{CC}\equiv\text{P}$ to a toluene solution of the 1,2,4-oxadiphosphole **123** furnished the novel oxatetraphosphadeltacyclenes **124** and **125** in good yield. The separation of the regioisomers **124** and **125** by chromatography failed. However, isolation of the major isomers **124** was possible by crystallization from nonpolar solvents (Scheme 27).

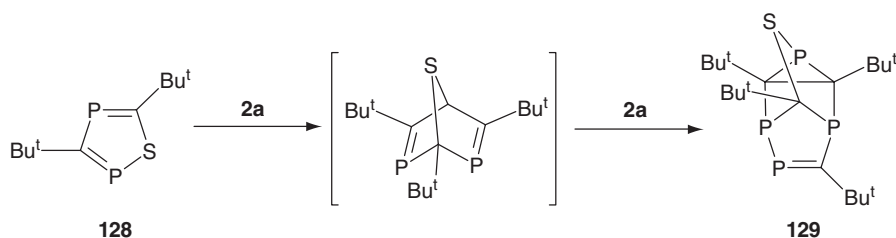
The reaction of the isomeric mixture of **124a** and **125a** with 1 equiv. of tetrachloro-*o*-benzoquinone specifically led to the new spirocyclic products **126** and **127**. The geometry of the major isomer **126** was unambiguously ascertained by X-ray crystallographic analysis <1999EJO587>.

Heating of a toluene solution of 1,2,4-thiadiphosphole **128** and 2 equiv. of $\text{Bu}^t\text{C}\equiv\text{P}$ at 80°C for 8 h furnished the tetracyclic product **129** (Scheme 28) <2002JOM(665)7>.

Analogously 2 equiv. of phosphalkynes $\text{RC}\equiv\text{P}$ ($\text{R} = \text{Bu}^t$, EtMe_2C , 1-adamantyl) underwent cycloaddition to the selenadiphospholes **130** through a $[4+2]/[2+2+2]$ -sequence to give the tetracyclic compound **131**. An alternative protocol for the synthesis of **131** was based on the



Scheme 27

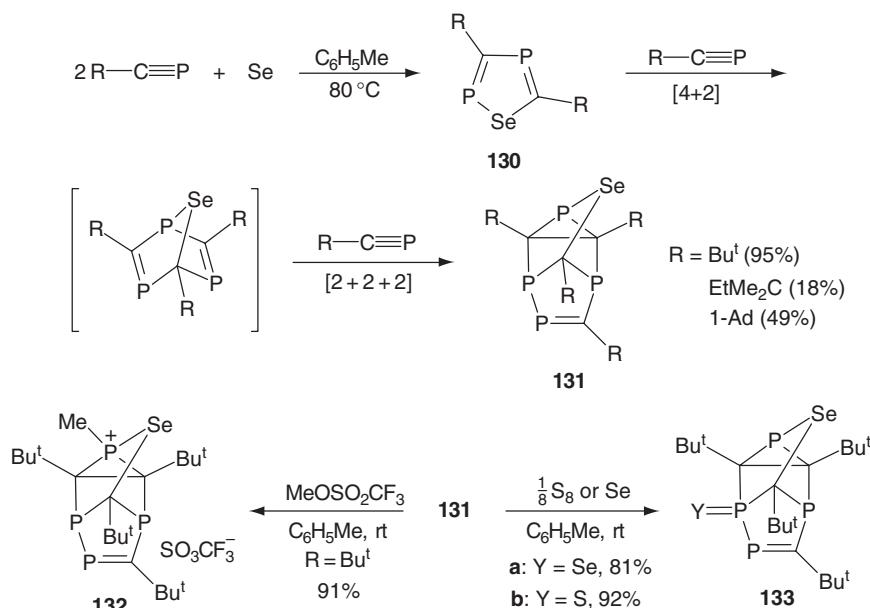


Scheme 28

reaction of gray selenium with a fourfold excess of the phosphoalkyne. Obviously, *in situ* generated selenadiphosphole was immediately intercepted to yield a transient triphosphaselenanorbornadiene derivative and finally **131** (Scheme 29) <1999S1642>.

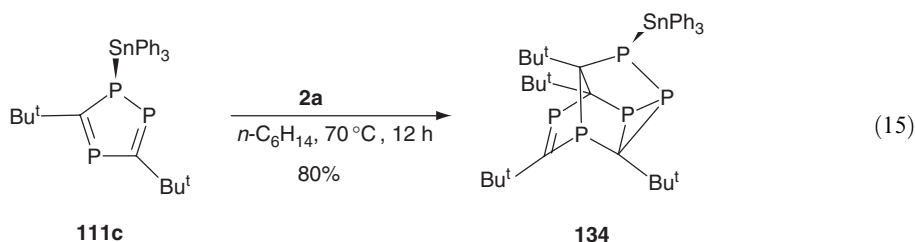
Selective methylation of **131** (R = Bu^t) to product **132** was effected by treatment with methyl trifluoromethanesulfonate in toluene at 25 °C. Grey selenium cleanly reacted with **131** in the presence of a catalytic amount of NEt₃ at room temperature to furnish cage **133a** (X = Se). Reaction of **131** with S₈ in the presence of 15 mol.% NEt₃ likewise afforded **133b** (X = S). A comparable reaction sequence with a related 1,2,4-telluradiphosphole was thwarted by the lability of this heterocycle (Scheme 29) <1999S1642>.

The stannylated 1,2,4-triphosphole **111c** also exhibits diene activity, and at elevated temperature, underwent a sequence of cycloadditions. Thus, heating an *n*-hexane solution of the



Scheme 29

compound in the presence of phosphalkyne **2a** led to the formation of yellow crystalline **134**. Despite the presence of seven stereogenic centers in the molecule only one pair of enantiomers was observed, both of which are present in the unit cell (Equation (15)) <1999CEJ3143>.

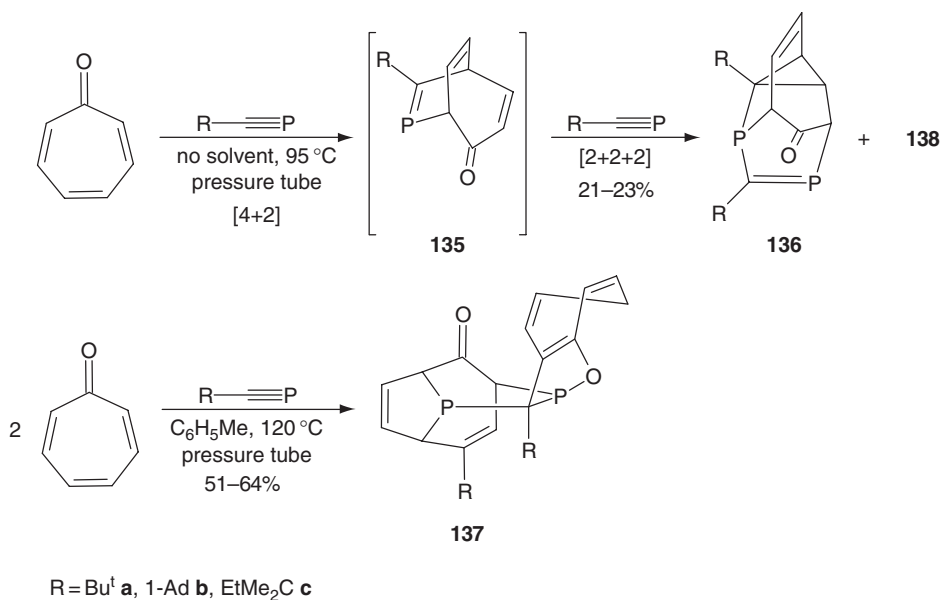


When tropone was subjected to thermolysis in the presence of an excess of the neat phosphalkynes **2a** or **2b** the homo-Diels–Alder adducts **136a** or **136b** were produced in 21% or 23% yield, respectively. Alternatively, heating tropone with equimolar amounts of **2a,b** or $EtMe_2CC\equiv P$ in toluene solution, afforded the pentacyclic compounds **137** as a result of an [8+2]-cycloaddition of tropone with the tetracyclic compounds **136** (Scheme 30) <1995JOC5884>.

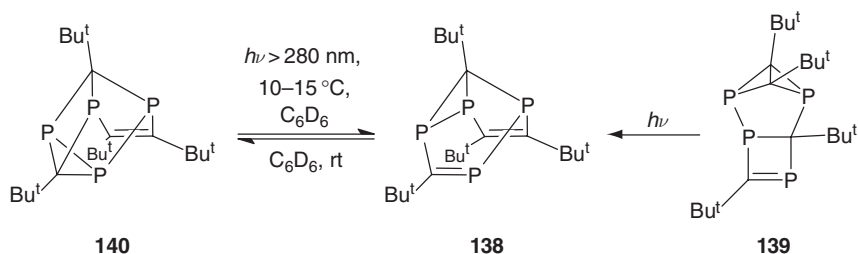
The formation of **136** ($R = Bu^t$) was accompanied by a cyclotetramerization process of **2a** which led to orange-red oily **138**. When neat **2a** was thermolyzed at 95 °C for 8 h a different product pattern was observed. Now the three cyclotetramers **139**, **138**, and **140** were formed in the ratio 55:25:20. In a careful study, it was shown that **138** was generated with 75% conversion, when **140** was photolyzed. The back-reaction of **138** to furnish **140** was slow at 25 °C (ca. 20% after 7 days). Moreover, exhaustive photolysis of **139** afforded an isomeric mixture of **138** and **140** in a ratio of 4:1. This was the first study where cyclotetramers of phosphalkynes took part in valence isomerization processes (Scheme 31) <1997AG(E)1337>.

In the following section the syntheses of rings and cages from phosphalkynes with the required $P=C-P$ motif by means of main group metal- or transition metal-compounds are discussed.

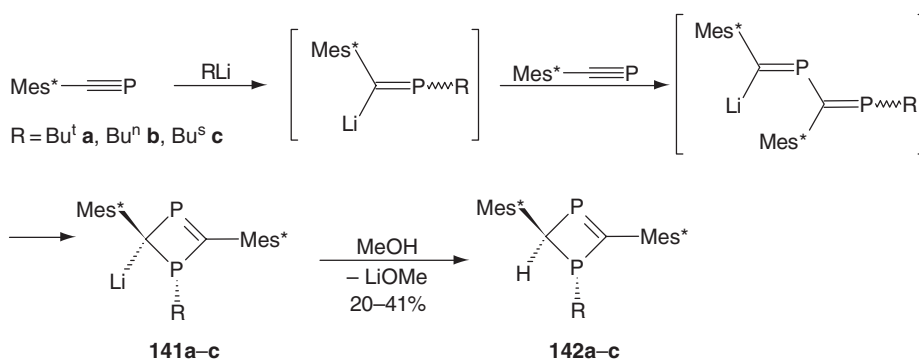
When phosphalkyne $Mes^*C\equiv P$ was allowed to react with 0.5 equiv. of *t*-butyllithium, *n*-butyllithium or *s*-butyllithium followed by quenching with methanol in THF at −78 °C the 1,3-diphosphacyclobutenes **142a–c** were generated as a single diastereomer (Scheme 32) <2002CC1744>. The initial step in the reaction sequence seems to be the 1,2-addition of the alkylolithium to the $P\equiv C$ bond of $Mes^*C\equiv P$ and the subsequent addition of the phosphavinyl-lithium to a second molecule of the phosphalkyne.



Scheme 30



Scheme 31

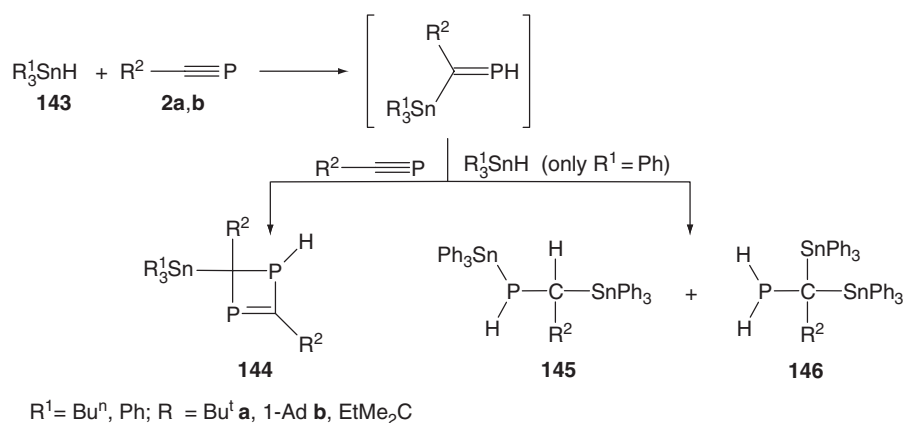


Scheme 32

The resulting 1,3-diphosphabutadienyllithium underwent cyclization to give the lithiated 1,3-diphosphacyclobutenes **141**. Compound **141a** (R = Bu^t) was observed by ³¹P NMR spectroscopy.

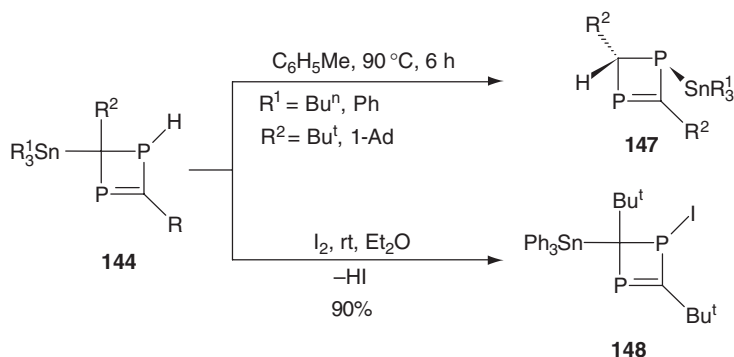
Quenching the latter with methanol afforded the final products. 1,3-Diphosphacyclobutenes were also available from phosphoalkynes and organotin hydrides. The reactions of the tin hydrides **143** with an excess of the phosphoalkynes **2a,b** and EtMe₂CC≡P in *n*-pentane at room temperature for 2 weeks gave rise to the formation of 2-stannyl-substituted-1,3-diphosphacyclobutenes **144**. The reaction of tributyltin hydride **143a** with 1-adamantylphosphoethyne **2b**

required heating at 60 °C for 4 h to reach completion. Increasing concentrations of the tin hydrides favored the formation of the stannylated phosphanes **145** and **146**. When Ph_3SnH was used in excess compounds **145** were formed in yields exceeding 75% while the isomeric phosphanes **146** were only observed in less than 5% yield. Phosphaalkenes of the type $\text{R}^2(\text{R}^1_3\text{Sn})\text{C}=\text{PH}$ may be postulated as reactive intermediates in these stoichiometry-dependent reactions. [2+2]-Cycloaddition to afford **144** was observed with an excess of phosphalkyne (Scheme 33) <1998EJI227>. The employment of diorganotin hydride also furnished 1,3-diphosphacyclobutenes, which, however, suffered from decomposition at 25 °C.



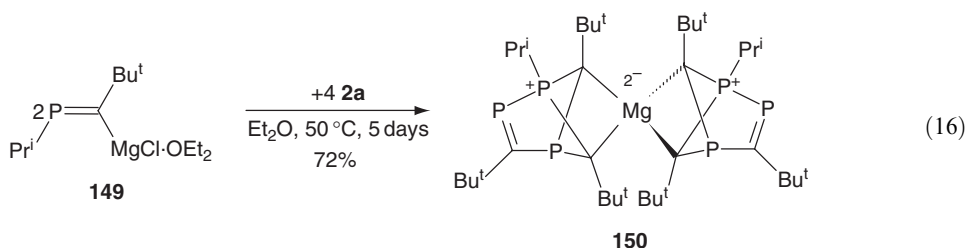
Scheme 33

Heterocycles **144** were subject to further transformations. After heating the compounds, quantitative isomerization of the original 2-stannyl-substituted 1,3-diphosphacyclobutenes into the 1-stannylated isomers **147** was observed (Scheme 34). Moreover, conversion of the PH function of one representative of **144** ($\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{Bu}^t$) into a PI function was effected by exposure to iodine. Product **148** was isolated as a yellow, nondistillable oil (Scheme 34) <1998EJI227>.



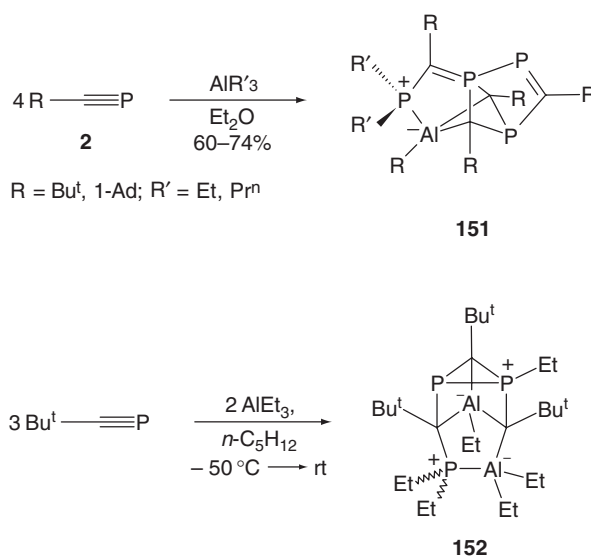
Scheme 34

An excess of **2a** was added to an ethereal solution of phosphavinyl Grignard reagent **149**, which was freshly prepared from *i*-propylmagnesium chloride and **2a**, and the mixture was heated in a pressure tube at 50 °C for 5 days. The novel magnesium complex **150** formed by the incorporation of 2 equiv. of **2a** was isolated as dark red crystals (Equation (16)) <2000EJI2337>.



The skeleton of the organophosphorus ligand in **150** was previously observed in a monomeric tantalum complex obtained from the reaction of TaCl_5 with 3 equiv. of **2a** <1987PS(30)349, 1985MI55>.

The reaction of the phosphoalkynes **2a** and **2b** with triethylaluminum and tri-*n*-propylaluminum led to a highly selective phosphoalkyne cyclotetramerization with incorporation of one organometallic unit to afford cages **151**. This process proved to be highly solvent-dependent. Thus, in *n*-pentane the reaction of **2a** and AlEt_3 followed a completely different course and furnished the tetracyclic cage compound **152** (Scheme 35) <1997JOM(539)61>.



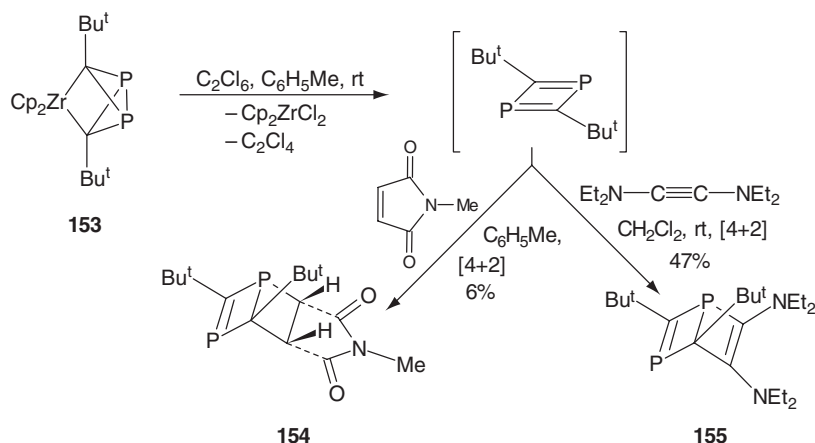
Scheme 35

Targeted generation and trapping reactions of 1,3-diphosphacyclobutadienes have become feasible via the dimerization of phosphoalkyne **2a** in the coordination sphere of a zirconocene complex. The resulting zirconium-containing cage compound **153** was chlorinated by hexachloroethane to liberate the highly reactive 2,4-di-*t*-butyl-1,3-diphosphabutadiene. If this process was performed in toluene in the presence of *N*-methylmaleimide the cycloadduct **154** formed regioselectively, albeit in poor yields.

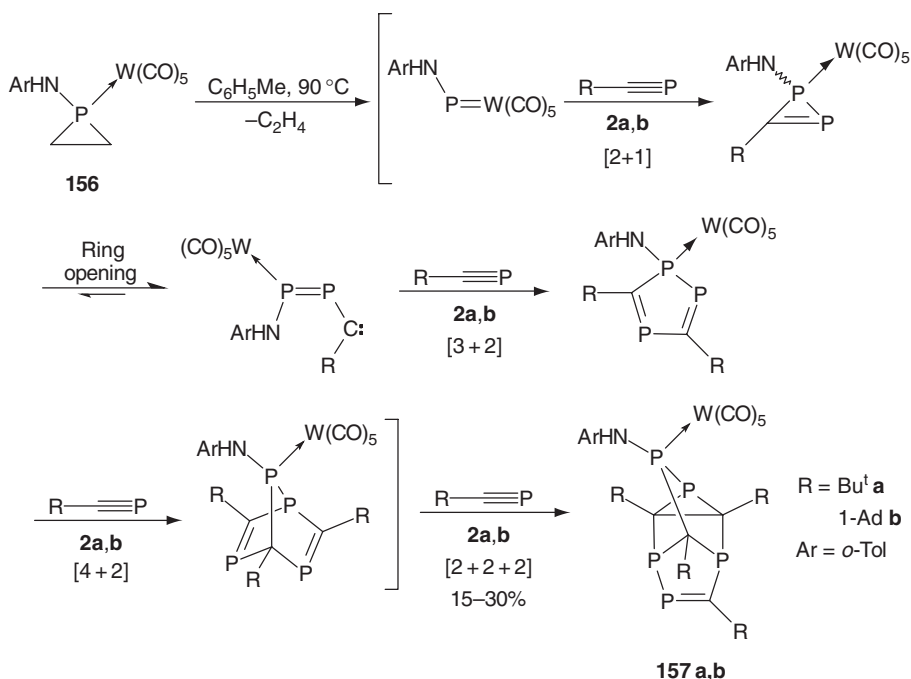
The trapping reaction of the transient 1,3-diphosphacyclobutadiene with the ynediamine $\text{Et}_2\text{N}-\text{C}\equiv\text{C}-\text{NEt}_2$ selectively afforded the first member of the new class of 1,3-diphosphadewar-benzenes **155** as a yellow oil after distillation (Scheme 36).

With bis(acceptor)-substituted acetylenes the reaction took a completely different course yielding diphosphabenzvalene derivatives <2002JOM(643-644)409>.

The syntheses of the complexed pentaphosphadeltacyclanes **157a** and **157b** were achieved by thermolysis of the phosphirane complex **156** in toluene at 50°C in the presence of a seven- to ten-fold excess of the phosphoalkynes **2a** or **2b**. The tetracyclic products, which were isolated as red crystals resulted from the repeated cycloaddition of four molecules of phosphoalkyne to the transiently generated phosphinidene complex $[o\text{-TolN(H)}-\text{P}=\text{W(CO)}_5]$ (Scheme 37) <1995CB991>.



Scheme 36

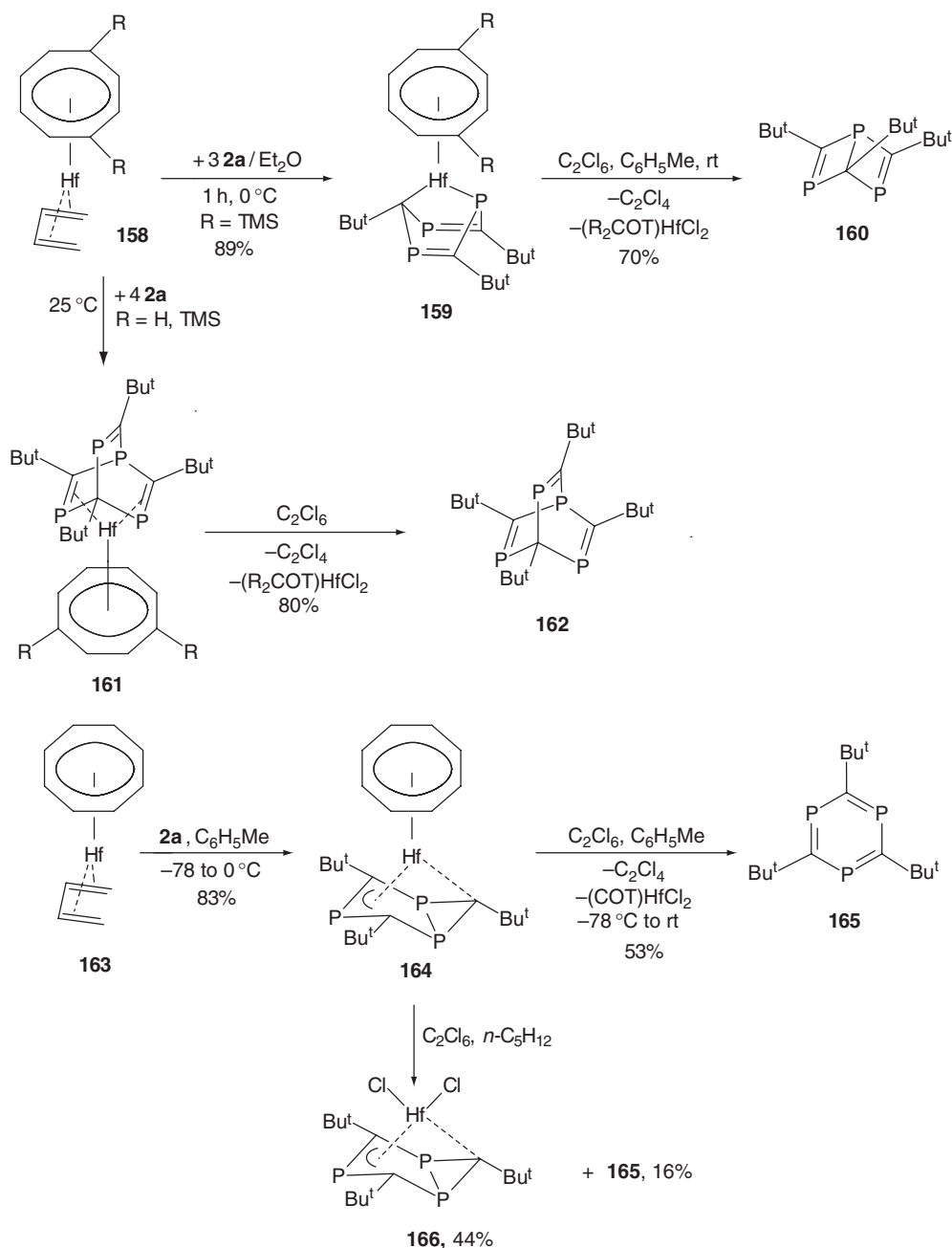


Scheme 37

The cyclotrimerization of $\text{Bu}^t\text{C}\equiv\text{P}$ **2a** in the presence of the cyclooctatetraene hafnium complex **158** ($\text{R} = \text{TMS}$) at 0 to 20°C afforded compound **159** as green crystals.

The orange crystalline ligand **160** was liberated from **159** by reaction with an equimolar amount of hexachloroethane in toluene. When the reaction of **158** with **2a** was conducted at 25°C cyclotetramerization to the 1,3,5,7-tetraphosphabarrelene complex **161** occurred, and again the organophosphorus ligand **162** was set free by treatment with C_2Cl_6 <1995AG(E)2227>. A similar result was obtained by reacting bicyclooctatetraene zirconium and $\text{Bu}^t\text{C}\equiv\text{P}$ <1995AG(E)81>. In contrast to this, combination of cyclooctatetraene complex **163** with the phosphoalkyne in toluene at -78 to 0°C furnished complex **164** as a green microcrystalline solid. Reaction of the complex with C_2Cl_6 in toluene in the temperature range of -78°C to room temperature yielded the first 1,3,5-triphosphinine **165** as a yellow solid (Scheme 38) <1995AG(E)2227>.

If, however, the chlorination of **164** with C_2Cl_6 was performed in *n*-pentane at room temperature for 12 h 1,3,5-triphosphinine **165** was produced in low yield, the main product being the red-violet crystalline complex **166**.

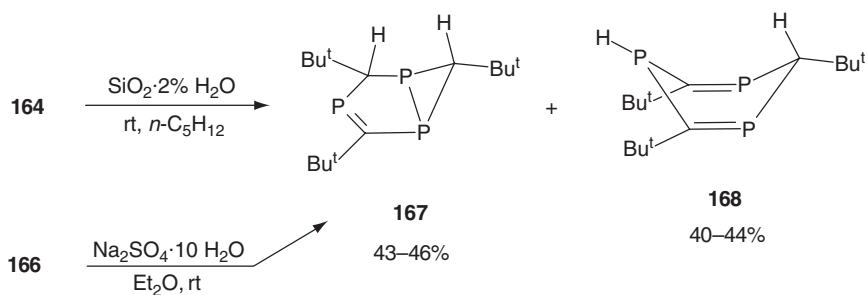


Scheme 38

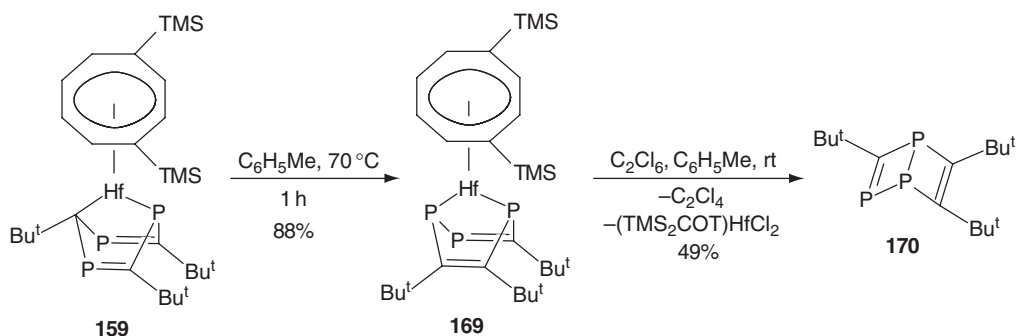
Hydrolysis of an *n*-pentane solution of **164** by means of hydrated silica gel spontaneously occurred at 20°C to give products **167** and **168**. The same compounds were obtained from the hydrolysis of hafnium complex **166** with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ in diethyl ether (Scheme 39) <1999EJI763>.

A more efficient synthesis of 1,3,5-triphosphinines is based on the action of phosphalkynes $\text{RC}\equiv\text{P}$ ($\text{R} = \text{Bu}^t$, CMe_2Et , $c\text{-C}(\text{Me})\text{C}_4\text{H}_8$, $c\text{-C}(\text{Me})\text{C}_5\text{H}_{11}$, 1-Ad) with stoichiometric amounts of $\text{Bu}^t\text{N}=\text{VCl}_3$ in toluene at -78 to 25°C <1998AG(E)1233, 2000CEJ455>.

Heating a toluene solution of complex **159** to 70°C for 1 h resulted in a rearrangement to the unsymmetrical 1,2,4-triphospha-7-hafnanorbornadiene **169**, which was isolated as reddish brown microcrystals. Hexachloroethane readily removed the Dewar-triphosphinine **170** from complex **169** as a pale-yellow powder (Scheme 40) <1997CB1491>.



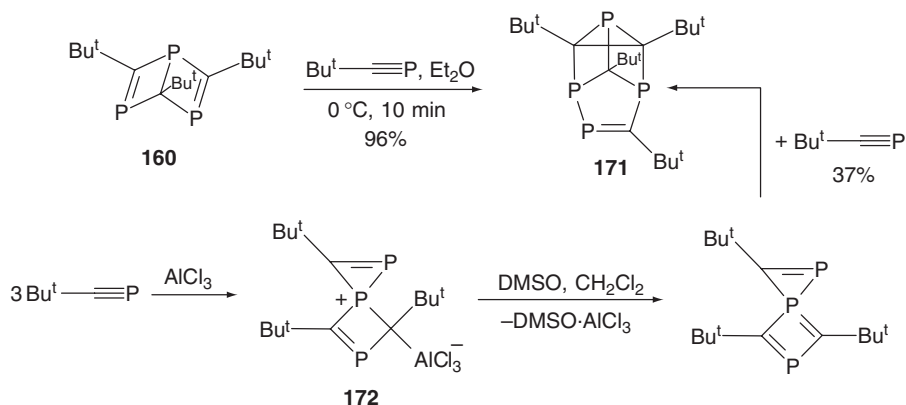
Scheme 39



Scheme 40

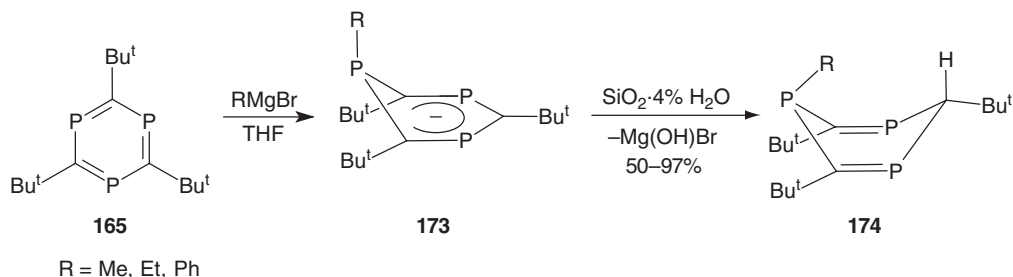
(c) *From 1,3,5-Dewar-triphosphinines.* Phosphaalkynes such as $\text{Bu}^t\text{C}\equiv\text{P}$ **2a** readily underwent [2 + 2 + 2]-cycloadditions with 1,3,5-Dewar-triphosphinine **160** to furnish the tetracyclic compound **171** <1997JOM(529)215>.

A less efficient approach to **171** made use of the cyclotrimerization of **2a** under the influence of AlCl_3 to give the spirocyclic species **172**. Removal of the Lewis acid from **172** by means of DMSO and addition of a further equivalent of **2a** to the transient spiro compound furnished **171** (Scheme 41) <1996CB489>.



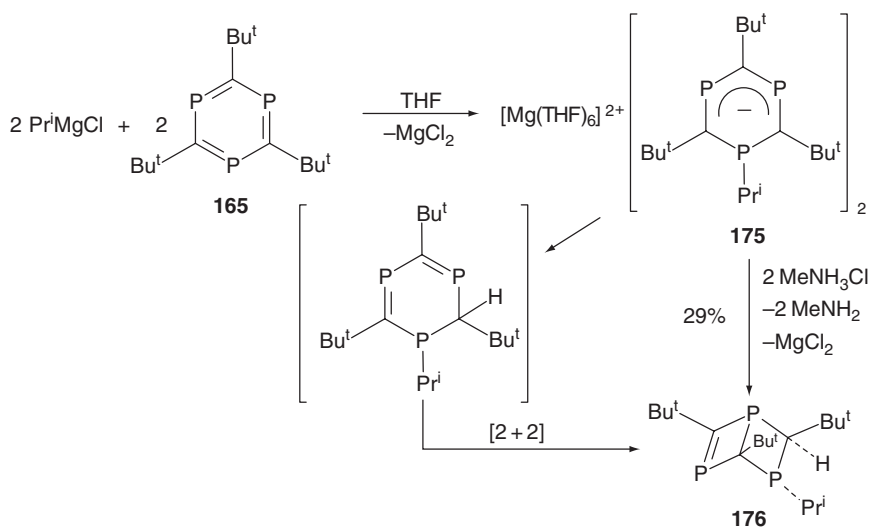
Scheme 41

(d) *From 1,3,5-triphosphinines.* The easily available 1,3,5-triphosphinines turned out to be valuable precursors for the synthesis of a number of compounds featuring PC double bonds with tricoordinate phosphorus substituents at the carbon atom. Compound **165** readily added 1 equiv. of a Grignard reagent at phosphorus to give anions **173**. Subsequent addition of hydrated silica gel to the THF solution of freshly prepared **173** caused protonation of the anion at C4 and the formation of 1,4-dihydrophosphinines **174** (Scheme 42) <B-2002MI523-03>.



Scheme 42

A completely different course of the hydrolysis reaction was encountered between the adduct **175** and methylammonium chloride in THF at room temperature. After 4 days the bicyclic compound **176** was isolated as yellow platelets (Scheme 43).



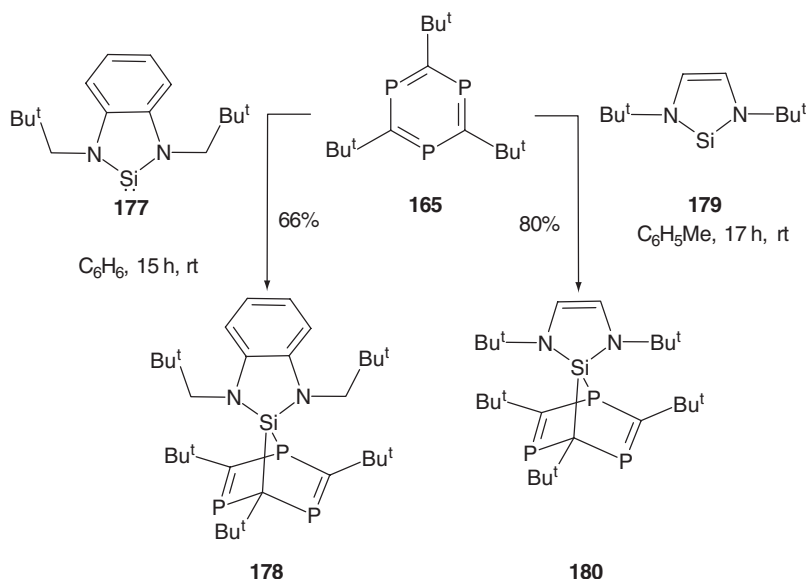
Scheme 43

This result was rationalized by protonation at the α -position of the tricoordinate P-atom of **175** and by an intramolecular [2 + 2]-cycloaddition of this intermediate <B-2002MI523-03>.

The stable bis(amino)silylene **177** underwent smooth [1 + 4]-cycloaddition with **165** in benzene to afford pale orange crystalline **178** <1999CC2451>. Similarly, addition of a colorless solution of silylene **179** to the yellow toluene solution of the triphosphinine gave cycloadduct **180** as dark purple crystals (Scheme 44).

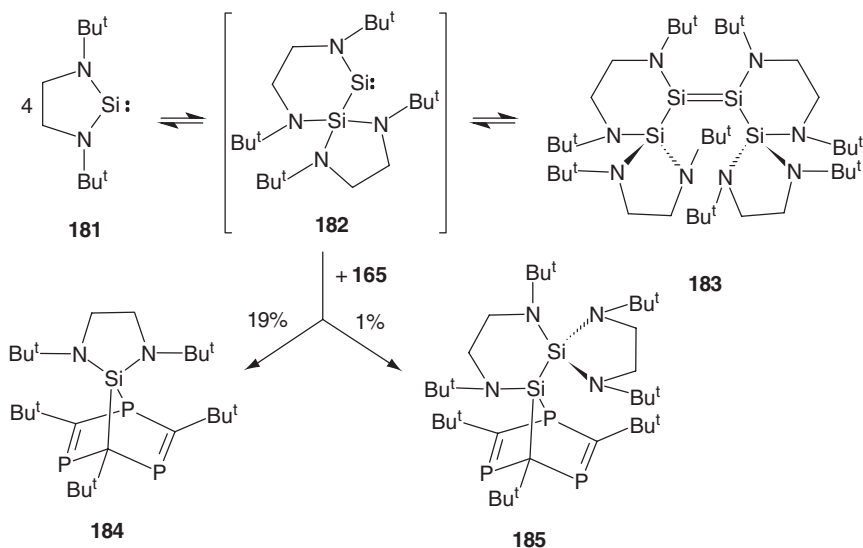
Despite the presence of two P=C double bonds in [1 + 4]-cycloadduct **178**, it failed to undergo any further reaction with excess **177** during heating the reaction mixture at 80 °C for 3 days <2002JCS(D)484>.

The reaction of the more reactive silylene **181** with triphosphinine **165** was complicated by oligomerization processes of the organosilicon species. Under an inert atmosphere colorless crystalline **181** slowly converted into the red powdery tetramer **183**. Dissolution of the latter in an inert solvent yielded a mixture of monomeric **181** and disilene **183**. Decreasing concentrations



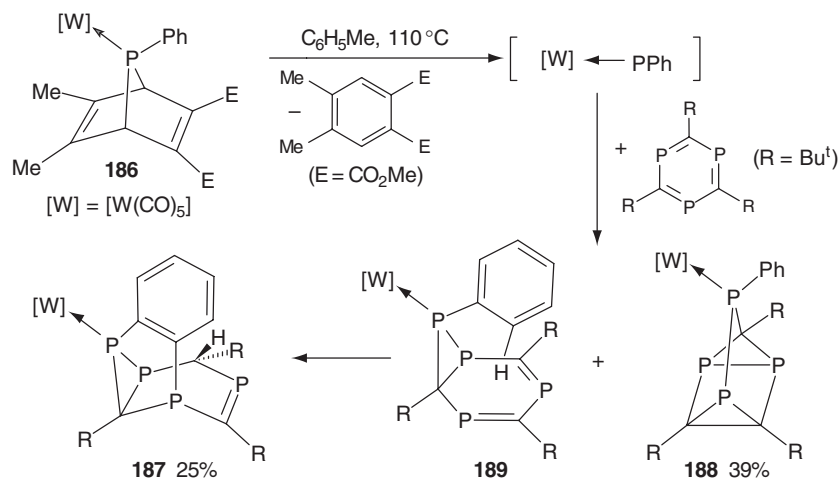
Scheme 44

avored the formation of silylene [\[1999JA9479\]](#). Evidence for intermediate **182** was limited to trapping reactions. Allowing the disilene **183** dissociate in a THF solution 48 h prior to the addition of **165** led to the preparation of [1 + 4]-cycloadduct **184** as an orange crystalline solid. If, however, a solid mixture of disilene **183** and triphosphinine **165** was combined with precooled toluene (-40°C) and the resulting reaction mixture then slowly warmed to ambient temperature compound **185**, the [1 + 4]-cycloadduct of **165** and transient **182** precipitated as a yellow fine powder but in only 1% yield (Scheme 45) [\[1999JA9479\]](#).



Scheme 45

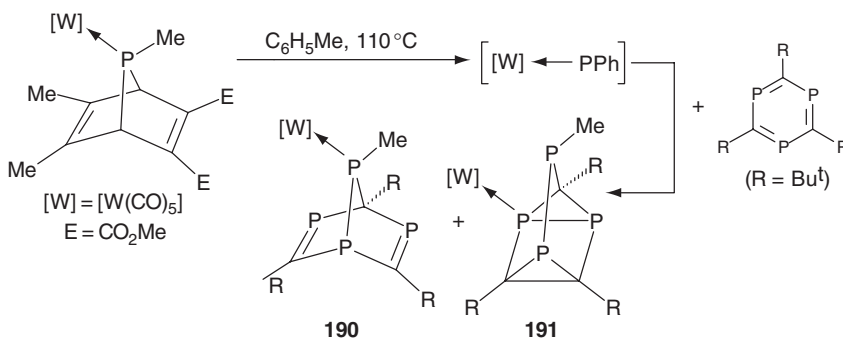
The chemical behavior of complexed phosphinidenes $[\text{RPW}(\text{CO})_5]$ toward triphosphinine **165** has also been investigated anticipating an analogous [1 + 4]-cycloaddition as was observed with the isolobal silylenes. Treatment of **165** with $[\text{PhPW}(\text{CO})_5]$ generated *in situ* by thermolysis of **186** in boiling toluene unexpectedly gave the compounds **187** and **188**, which were separated to afford yellow crystals of **187** and colorless crystalline **188** (Scheme 46).



Scheme 46

The formation of **187** is rationalized by invoking an initial 1,2-addition affording intermediate **189** and its subsequent rearrangement to the final product [<2001CEJ3545>](#).

Compound **188** most likely resulted from the intramolecular [2+2]-cycloaddition of a formal [1+4]-adduct as a precursor. This idea was underlined by quantum-mechanical calculations as well as by the reaction of **165** with *in situ* generated [MePW(CO)₅] where tetraphosphanorbornadiene **190** and tetraphosphaquadracyclane **191** were observed as products in a 1:8 ratio. Separation gave yellow crystalline **191** in addition to orange crystalline **190**. Heating the pure compounds in toluene at 110 °C returned the original 1:8 equilibrium mixture (Scheme 47) [<2001AG\(E\)4412>](#).



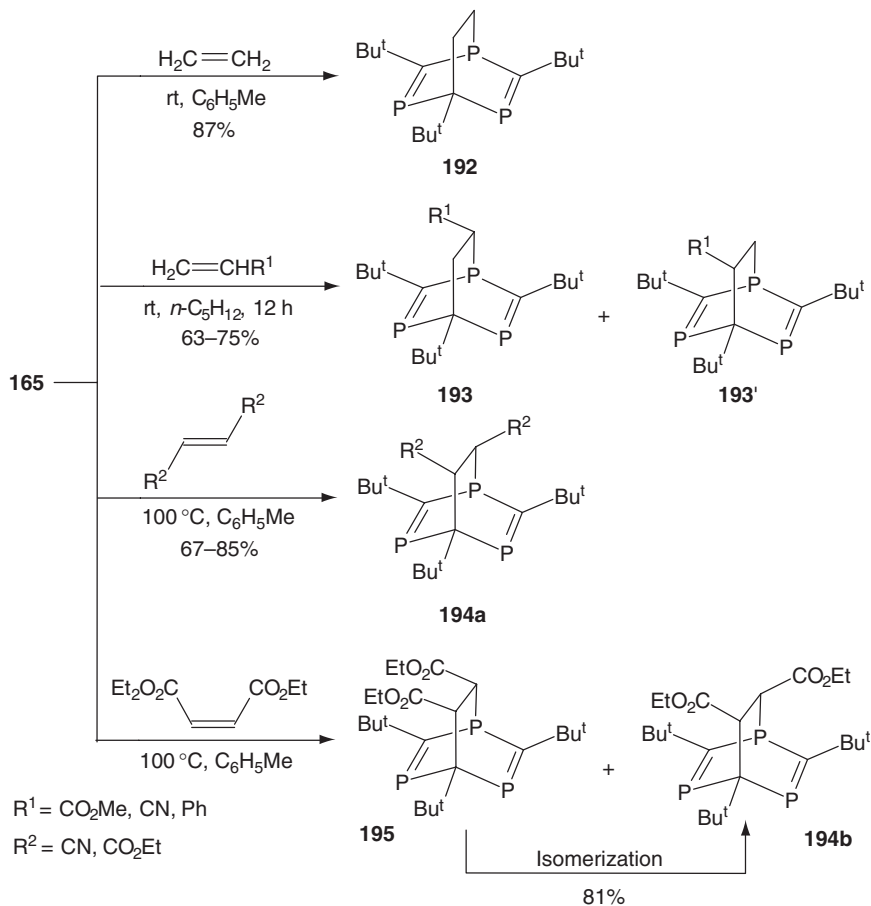
Scheme 47

When ethene was bubbled into a toluene solution of 1,3,5-triphosphinine **165** at 20 °C, a [4+2]-cycloaddition occurred to afford the pale yellow 7,8-dihydro-1,3,5-triphosphabarrelene **192** in 87% yield after recrystallization from *n*-pentane. Methyl acrylate and acrylonitrile also readily reacted with **165** in *n*-pentane to give the corresponding isomeric dihydrobarrelenes **193** and **193'**.

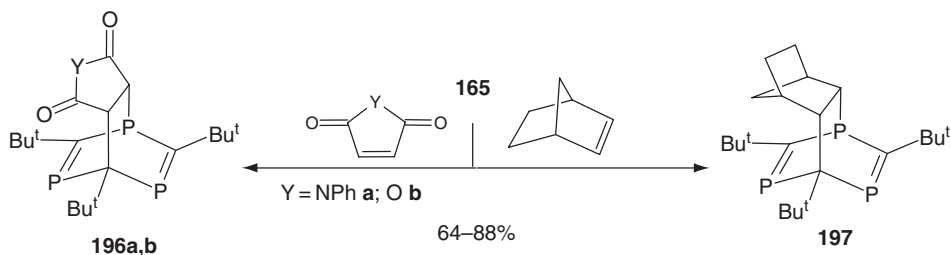
The ratio **193**:**193'** was determined to be 4:1 for R' = CO₂Me and 2:1 for R' = CN. A successful reaction of **165** with styrene to yield **193** and **193'** (R' = Ph) required a large excess of the alkene and heating at 65 °C in toluene for 2 days.

The transformation of **165** into the 7,8-dihydro-1,3,5-triphosphabarrelenes **194a** (R'' = CN) and **194b** (R'' = CO₂Et) by treatment with fumarc dinitrile or diethyl fumarate was accomplished by heating toluene solutions at 100 °C for 8–12 days. Interestingly, derivative **194b** also resulted from the treatment of **165** with diethyl maleate in toluene after 18 days at 100 °C. After 8 days the reaction mixture contained unchanged **165** and a 1:1 mixture of [4+2]-cycloadducts **195** and **194b**.

Obviously, upon prolonged heating the initially formed *cis*-cycloadduct **195** underwent complete isomerization to the *trans*-cycloadduct **194b**, which agrees with the reversibility of Diels–Alder reactions (Scheme 48) <2001EJO3425>. Cyclic disubstituted alkenes such as *N*-phenylmaleimide, maleic anhydride, and norbornene also readily underwent [4 + 2]-cycloaddition reactions with **165** to furnish the dihydrobarrelenes **196a,b** and **197** (Scheme 49).



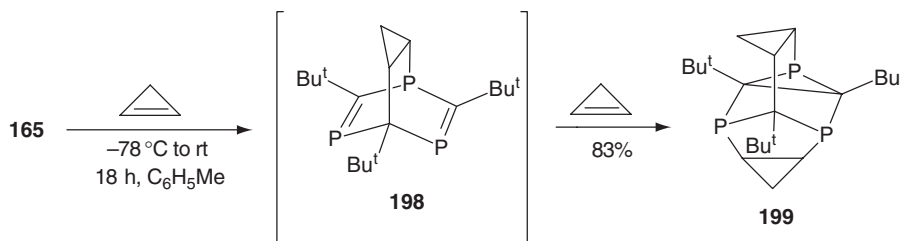
Scheme 48



Scheme 49

The cycloalkenes maleic anhydride and norbornene were also treated with 1,3,5-triphosphinines bearing sterically demanding groups other than *t*-butyl in the 2,4,6-positions. Thus, the tri-*t*-pentyl- or the tris(1-methylcyclohexyl)-derivatives were converted at 60°C into the [4 + 2]-cycloadducts analogous to **196a,b** and **197** in comparable yields whereas the 2,4,6-tris(1-adamantyl)-1,3,5-triphosphinine gave the corresponding thermolabile cycloadducts in only 4% yield, presumably due to steric hindrance <2001EJO3425>.

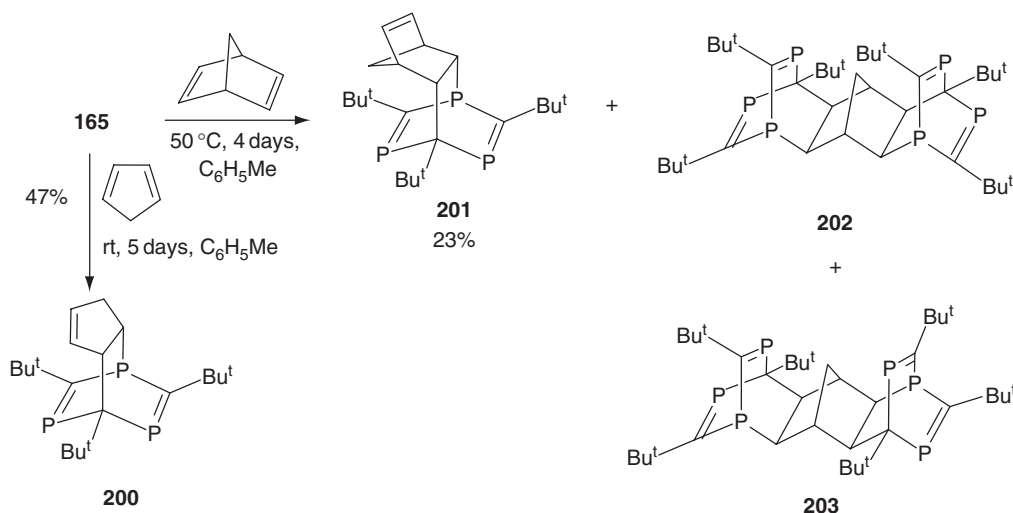
Cyclopropene reacted even at -78°C with **165**. However, 2 equiv. of the cycloalkene were required for a complete reaction. The initially formed [4+2]-cycloadduct **198** spontaneously added a second molecule of cyclopropene in a homo-Diels–Alder reaction to produce the cage compound **199**. The Diels–Alder adduct could not be isolated nor detected by spectroscopy (Scheme 50) <2001EJO3425>.



Scheme 50

This behavior paralleled the reactivity of alkynes toward **165** <2000S529>.

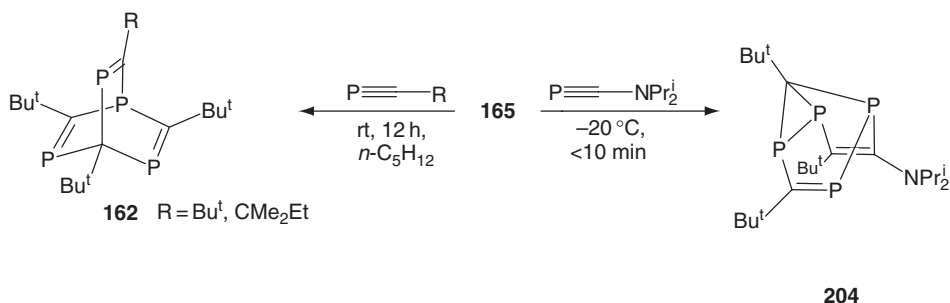
[4+2]-Cycloaddition processes of the 1,3,5-triphosphinine **165** with dienes have been studied with cyclopentadiene and norbornadiene. Thereby cyclopentadiene reacted exclusively as a dienophile and underwent regioselective addition to **165** at 25°C to afford the moisture-sensitive dihydrobarrelene **200** (Scheme 51).



Scheme 51

Equimolar amounts of **165** and norbornadiene, however, when heated in toluene for 4 days at 50°C , furnished the monoadduct **201** and a mixture of the bisadducts **202** and **203**. The latter products were also available from the reaction of **201** and **165**. According to NMR spectroscopy, the bisadducts **202** and **203** were formed in a ratio of 3:1 but they could not be separated on a preparative scale <2001EJO3425>.

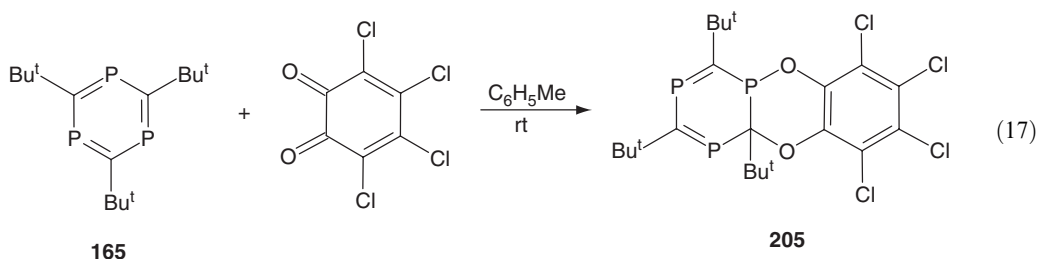
In contrast to alkynes, it has been possible to synthesize [4+2]-cycloadducts **162** from **165** and phosphalkynes $\text{RC}\equiv\text{P}$ ($\text{R} = \text{Bu}^t, \text{CMe}_2\text{Et}$). The tetraphosphabarrelenes **162** were formed quantitatively within 12 h by treating a pentane solution of **165** with the phosphalkynes at 25°C (Scheme 52). This result demonstrated that the addition of a further phosphalkyne molecule to **165** was possible even without being coordinated to a complex fragment as illustrated in Scheme 38.



Scheme 52

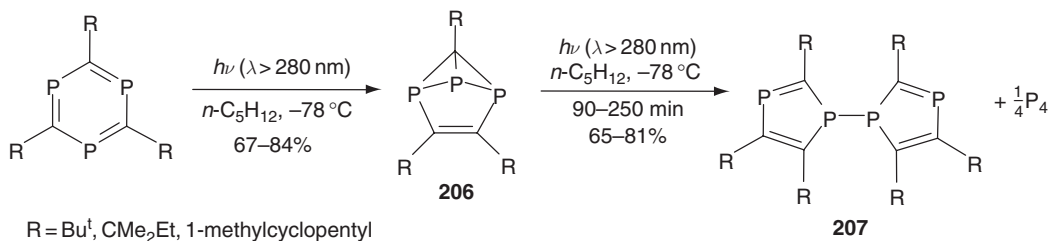
The analogous reaction of **165** with diisopropylaminophosphaethyne at -20°C unexpectedly led to the quantitative formation of the tetraphosphasemibullvalene derivative **204** (Scheme 52) <1998EJI2071>.

In almost all cycloadditions discussed above, the 1,3,5-triphosphinines behave as the diene component. From a formal point of view the transformation of **165** with tetrachloro-*o*-quinone to furnish the tricyclic orange compound **205** in 67% yield can be regarded as a hetero-Diels–Alder reaction with **165** acting as the dienophile (Equation (17)) <B-1997MI523-04>.



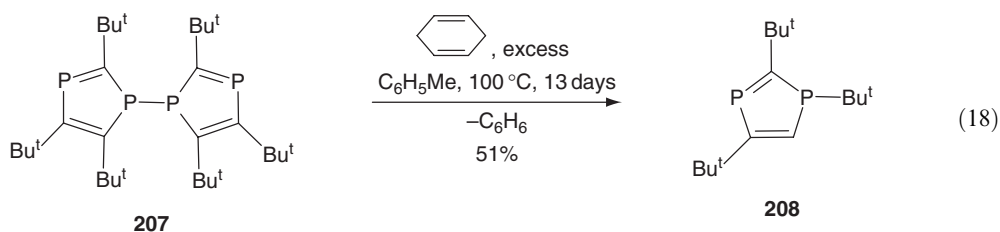
(e) From 1,2,5-triphosphabenzvalenes. Thermolabile and light-sensitive 1,2,5-triphosphabenzvalenes **206** are available in high yields by photolysis of 1,3,5-triphosphinines in *n*-pentane at -78°C . According to ^{31}P NMR spectroscopic monitoring, the isomerization was complete in 18–31 min. Compounds **206** are versatile precursors for a series of compounds featuring P–C double bonds with trivalent phosphorus substituents (Scheme 53) <B-2002MI523-05>. Irradiation of *n*-pentane solutions of **206** at -78°C selectively afforded the 3,3'-diphospha-1,1'-biphospholes **207** within 90–250 min.

Compound **207** ($\text{R} = \text{Bu}^t$) has previously been prepared by oxidative coupling of sodium 2,4,5-tri-*t*-butyl-1,3-diphospholide with $[(\text{COD})\text{RuCl}_2]$ <1993CC267> and by thermolysis of **165** <B-1997MI523-04>.

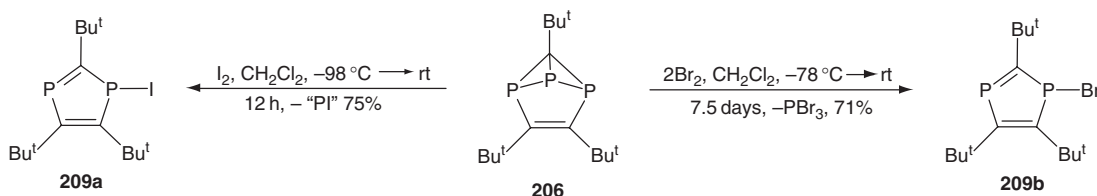


Scheme 53

Heating a toluene solution of **207** ($\text{R} = \text{Bu}^t$) in the presence of 1,4-cyclohexadiene as a hydrogen source at 100°C for 13 days selectively led to 1,3-diphosphole **208** as a yellow oil. The reaction was performed under an argon pressure of 4.5 bar to prevent the cyclohexadiene evaporating <B-2002MI523-05>. The generation of **208** from **207** involved homolysis of a P–P bond, hydrogen abstraction and a 1,5-shift of the *t*-butyl group from a carbon to a phosphorus atom (Equation (18)).

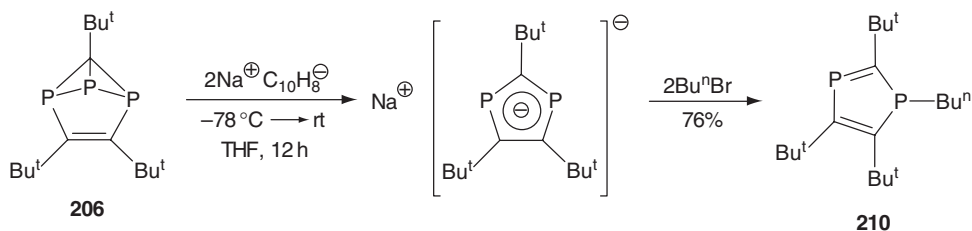


Reaction of **206** ($R = \text{Bu}^t$) with iodine or bromine in the dark and at low temperature was accompanied by the loss of a phosphorus atom and the formation of the halogenated 1*H*-1,3-diphospholes **209** (Scheme 54). The synthesis of the bromine derivative **209b** required 2 equiv. of bromine and prolonged stirring at 25 °C. Phosphorus tribromide was generated as a by-product (Scheme 54).



Scheme 54

A reductive degradation of 1,2,5-triphosphabenzvalene **206** was accomplished by treating a cold THF solution of the compound with 2 equiv. of sodium naphthalenide in the absence of light. The resulting 1,3-diphospholide anion was subsequently transformed into the 1*H*-1,3-diphosphole derivative **210** by treatment with *n*-butyl bromide (Scheme 55) <B-2002MI523-05>.



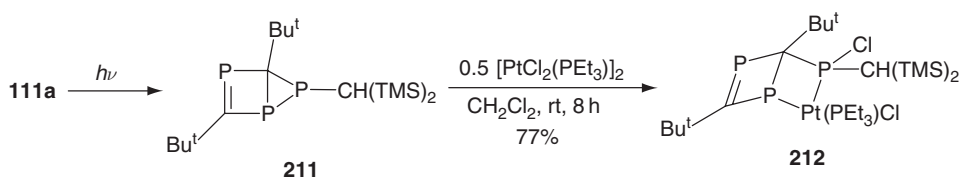
Scheme 55

(*f*) From 1,2,4-triphospholes. Some 1,2,4-triphospholes serve as valuable starting materials in chemical transformations leading to products featuring $\text{P}=\text{C}$ double bonds with the substitution pattern under discussion. The 1,2,4-triphosphole **111a** readily underwent a slow electrocyclization reaction on standing in sunlight at room temperature to afford the new isomeric 1,3,5-triphosphabicyclo[2.1.0]pent-2-ene **211**. The reaction which could be accelerated by irradiation with a tungsten lamp (100 W) was about 60% complete after one week.

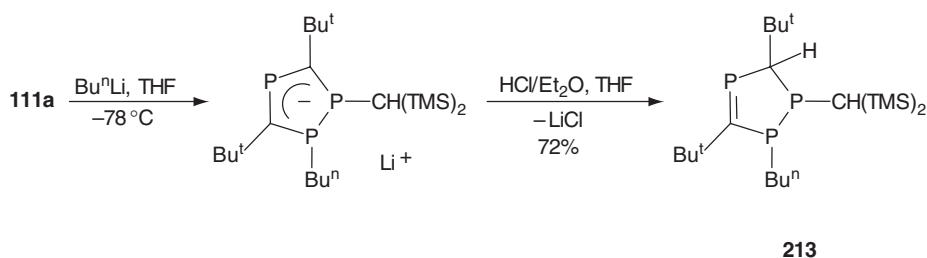
When solid $[\text{PtCl}_2(\text{PET}_3)]_2$ was reacted with **211** in chloroform and stirred for 8 h, complex **212** was produced as a yellow solid (Scheme 56). This complexation process involved insertion of the coordinatively unsaturated $\text{Pt}(\text{PET}_3)\text{Cl}_2$ fragment into the reactive $\text{P}-\text{P}$ bond of **211** and a chlorine migration from platinum onto the phosphorus <1998CC1537>.

The first 2,3-dihydro-1*H*-1,2,4-triphosphole was derived from compound **111a** by addition of 1 equiv. of *n*-butyllithium in THF at -78°C and the subsequent quenching of the formed organolithium species with ethereal HCl to afford **213** (Scheme 57).

A similar reaction sequence with methyllithium and HCl gave several uncharacterized compounds but no evidence for the generation of an analog of **213**. Presumably the presence of the larger butyl substituent in **213** is crucial for the stability of this ring system <2002JOM(650)198>.

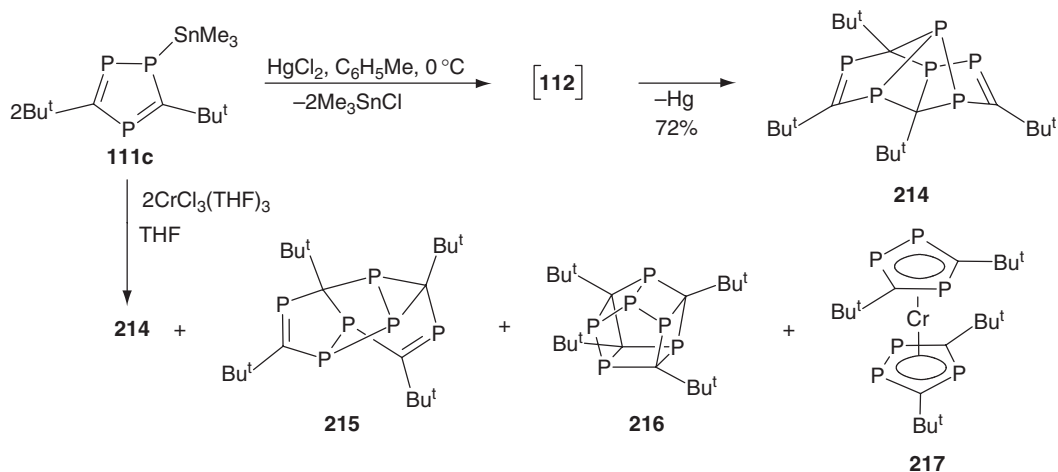


Scheme 56



Scheme 57

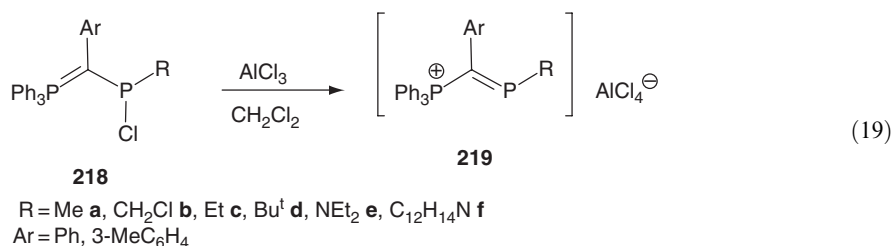
Several routes to cage compounds featuring the required structural motif $\text{P}=\text{C}-\text{PR}_2$ were based on stannylated 1,2,4-triphospholes. Thus, reaction of **111c** with HgCl_2 in toluene did not lead to isolable **112** as was described above in Equation (10), but furnished tetracyclic **214** with extrusion of metallic mercury [<2002CEJ2622>](#). Treatment of the trimethylstannyl triphosphole with an equimolar amount of $\text{CrCl}_3(\text{THF})_3$ afforded a mixture of several $\text{P}-\text{C}$ cage compounds **215** and **216** together with small amounts of the hexaphosphachromocene **217** depending on the reaction conditions. When the components were reacted for 2 h compound **214** was the main product, whereas longer reaction times favored the formation of **215** (Scheme 58).



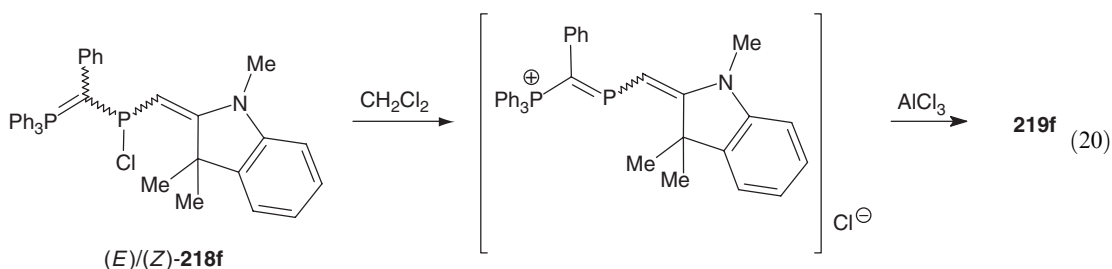
Scheme 58

(iii) Derivatives with tetracoordinate phosphorus— $\text{R}^1\text{C}(\text{PR}^2)\text{PR}_3^3$

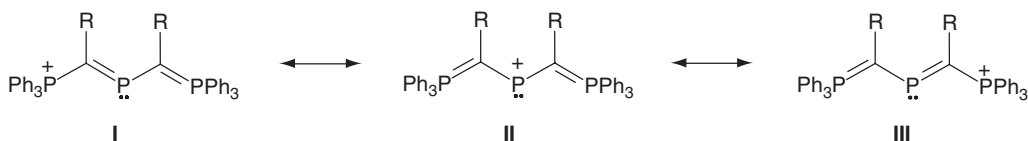
(a) From ylides. *C*-Phosphonio-substituted phosphalkenes **219** are very rare species. They were readily synthesized by the reaction of chlorophosphanyl functionalized phosphorus ylides **218** with Lewis acids such as AlCl_3 in dichloromethane (Equation (19)).



From ³¹P NMR spectroscopy it was evident that the multiple bond is mainly localized between the carbon atom and the dicoordinate phosphorus center. From the solvent dependence of the ³¹P NMR data for the chlorophosphane **218**, having an ylide and an enamine substituent it was concluded that the compound dissociates completely in dichloromethane solution. The spectra were not significantly changed upon the addition of AlCl₃ to give **219f**. A similar observation was made with the chlorophosphane Ph₃P=C(Ar)—P(Cl)—N=PPh₃ (Ar = 3-MeC₆H₄). (Equation (20)) <1996HAC239, 1995CB379>.



Bis(triphenylphosphoniumylidyl)halophosphines {Ph₃PC(R)}₂PX **220** enter a spontaneous dissociation to yield the ionic isomers [{Ph₃PC(R)}₂P]⁺X[−], which can be represented by three limiting structures **I–III**.

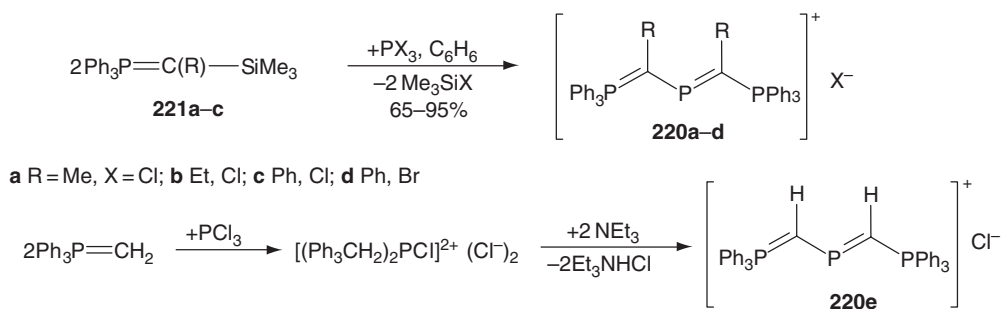


Although addressed by the authors as bis(ylidyl)phosphenium halides, emphasizing formula **II**, the X-ray analysis of the ion with R = Ph underlines the major contributions of resonance forms **I** and **III** since short PC bonds to the dicoordinate phosphorus atoms [1.714(7), 1.724(6) Å] and longer PC-distances to the tetracoordinate phosphorus atoms [1.746(6), 1.753(7) Å] were encountered. It is, however, admitted that the question as to whether cations **220** are phosphaaalkenes with tetravalent phosphorus substituents at the C-atom of the double bond or phosphorus ylides with a dicoordinate phosphorus substituent is rather a semantic one, and in this context scientifically not particularly meaningful. The synthesis of such salts involved the condensation of trimethylsilyl ylides **221** with phosphorus trihalide in a 2:1 molar ratio.

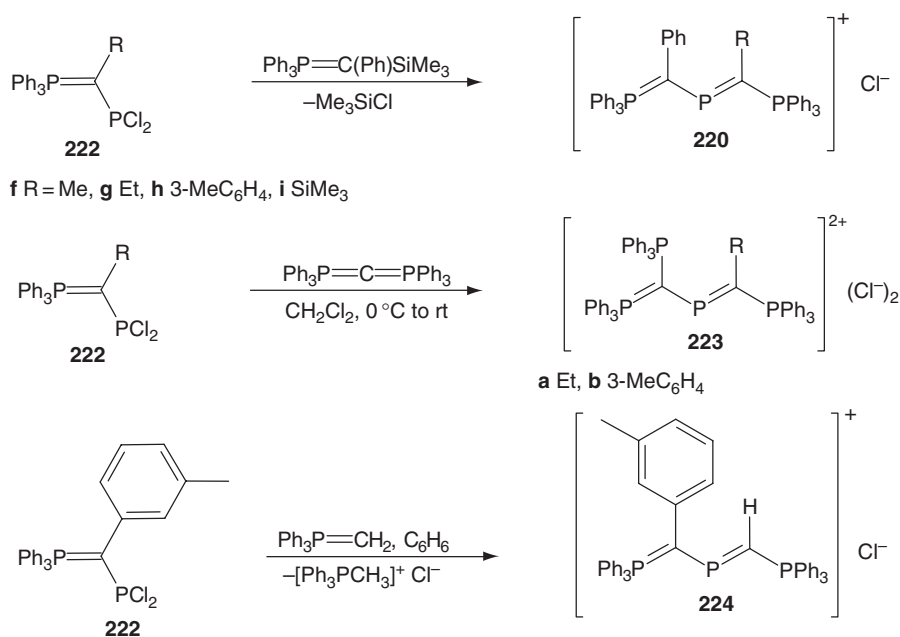
The C-unsubstituted compound **220e** (R = H) cannot be prepared in this manner owing to the unspecific reaction of Ph₃P=CH(SiMe₃) with PCl₃. A successful approach to **220e** made use of the treatment of Ph₃P=CH₂ with PCl₃ in a 2:1 molar ratio and the subsequent deprotonation of the resulting bisphosphonium salt by triethylamine. Such a synthetic strategy cannot be applied when derivatives **220** exhibit similar solubilities to the triethylammonium halides (Scheme 59) <1995CB379, 1997JOM(529)87>.

Nonsymmetrical bis(ylidyl)phosphenium chlorides **220f–i** and **223a,b** were obtained from ylidyl dichlorophosphines **222** and Ph₃P=C(Ph)SiMe₃ or hexaphenylcarbodiphosphorane (Scheme 60) <1997JOM(529)87>.

The bis(ylidyl)phosphenium chloride **224** with one P=CH—PPh₃-group was synthesized from **222** (R = 3-MeC₆H₄) and the Wittig ylide (1:2) by transylidation.

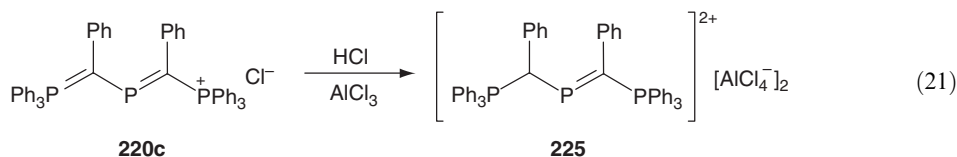


Scheme 59



Scheme 60

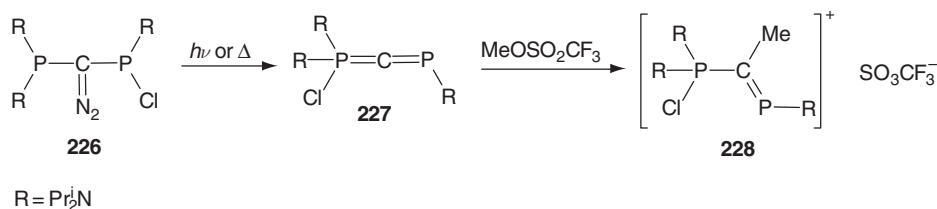
Protonation of **220c** (R = Ph) by HCl in the presence of AlCl₃ occurred at the ylidic carbon atom and left the central phosphorus atom in product **225** dicoordinate (Equation (21)) <1997JOM(529)87>.



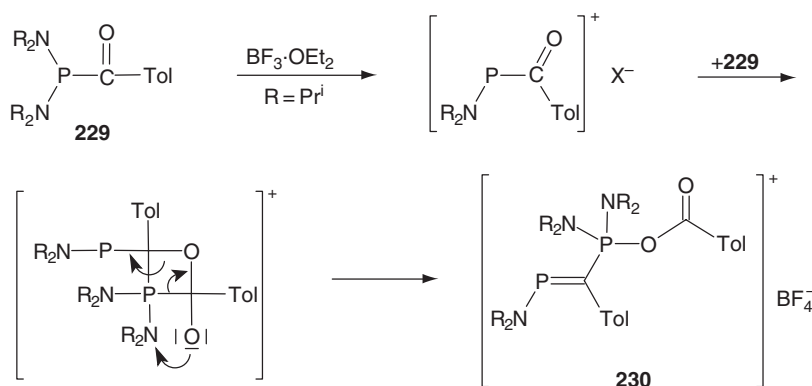
Photolysis (300 nm) or thermolysis (70 °C) of a solution of the diazo derivative **226** in toluene led to the formation of the cumulene **227**, the methylation of which by methyl triflate occurred at the ylidic carbon atom to afford the phosphonio-functionalized phosphaaalkene **228** (59%) (Scheme 61) <2000AG(E)3319>.

(b) *By miscellaneous methods.* One equivalent of BF₃·OEt₂ reacted in refluxing dichloromethane with bis(diisopropylamino)(toluoyl)phosphane **229** affording compound **230** in nearly quantitative yield. Formally phosphonio-phosphaaalkene **230** resulted from the reaction of an intermediate phosphonium salt with starting material **229**. The same product was obtained by protonation of **229** with trifluoromethanesulfonic acid at −78 °C (Scheme 62). The outcome of this process seems

to depend on the nature of the acyl group in the precursor. Thus, reaction of the corresponding pivaloylphosphane $(\text{Pr}^i\text{N})_2\text{P}-\text{C}(\text{O})\text{Bu}^t$ with $\text{CF}_3\text{SO}_3\text{H}$ or HBF_4 at -78°C afforded a phosphonium salt which eventually decomposed to a complicated mixture of products <1997PS(123)161>.



Scheme 61



Scheme 62

5.23.1.1.6 Metalloid derivatives— $\text{R}^1\text{C}(\text{PR}^2)\text{ER}_n^3$ ($\text{E} = \text{Si}, \text{Ge}, \text{B}$)

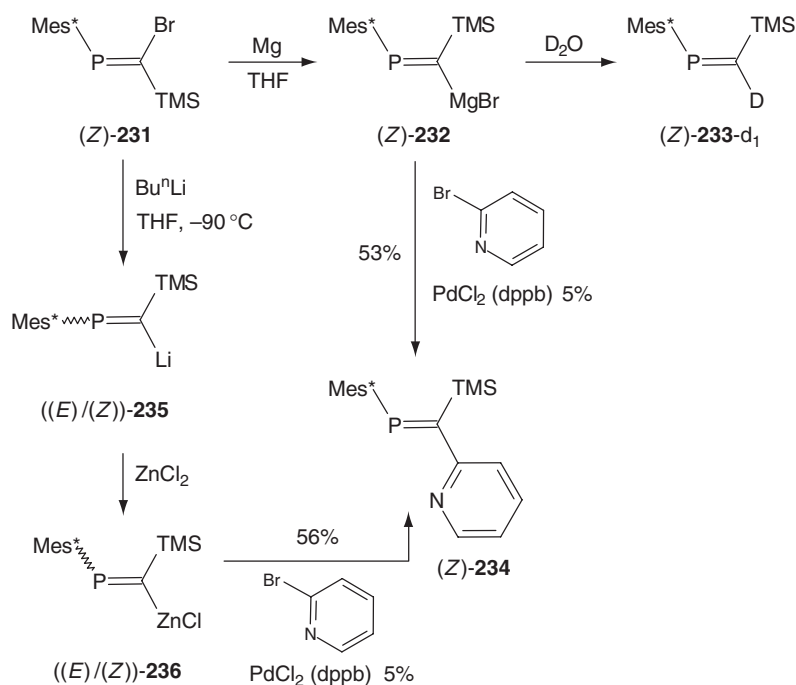
(i) Silicon derivatives— $\text{R}^1\text{C}(\text{PR}^2)\text{SiR}_3$

(a) *From C-halo-(C-silyl)phosphaalkenes.* C-Halogenated phosphaalkenes are useful precursors for the synthesis of silyl-functionalized phosphaalkenes.

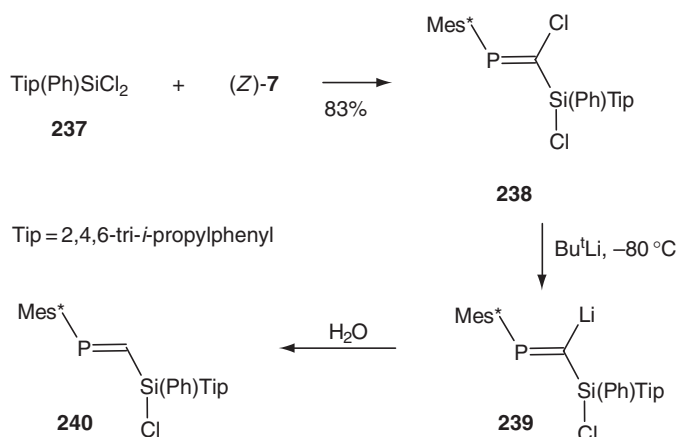
Grignard reagent (Z)-**232** was formed by stirring a THF solution of (Z)-**231** with magnesium metal. Deuterolysis of the reaction mixture afforded only the deuterolysis product (Z)-**233-d₁** and the protonated analog in a ratio of 87:13, corresponding to a 87% yield in Grignard reagent generation. The Grignard reagent (Z)-**232** was used for the Pd(II)-catalyzed coupling reaction with 2-bromopyridine by heating the reactants in boiling THF for 6 h in the presence of 5 mol.% of 1,4-bis(diphenylphosphino)butane-palladium dichloride ($\text{PdCl}_2(\text{dppb})$) to afford (Z)-**234** (Scheme 63).

Product (Z)-**234** was alternatively prepared via the phosphaalkenyl zinc derivative **236**, which was obtained from ((E)/(Z))-**235** by transmetalation (Scheme 63) <1997OM1144>. Here, however, (Z)-**233** was also formed in 35% yield. A THF solution of (Z)-**7** (-78°C) was combined with an equimolar amount of dichlorosilane **237**. After 2 h of stirring at -20°C it was warmed to 25°C and phosphaalkene **238** was isolated as a white powder. Addition of 1 equiv. of *t*-butyllithium to **238** in a toluene/ Et_2O mixture (90:10) at -80°C immediately afforded the lithio-derivative **239**. Quenching with water furnished phosphaalkene **240** (Scheme 64) <1999CEJ774>.

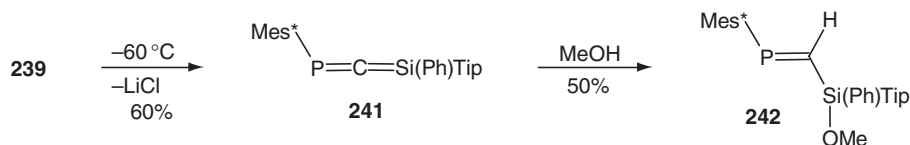
Gradually warming **239** to -60°C effected the elimination of LiCl with formation of the phosphasilaallene **241**. Addition of methanol to a solution of **241** at -60°C produced phosphaalkene **242** as colorless crystals (Scheme 65) <1999CEJ774>.



Scheme 63

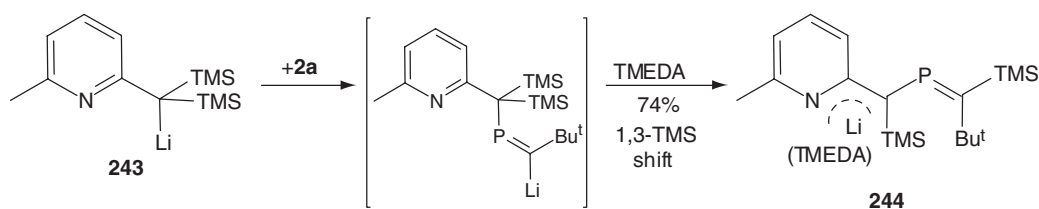


Scheme 64



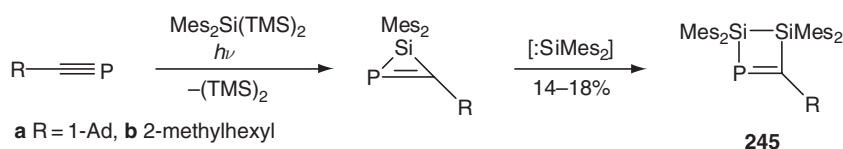
Scheme 65

(b) *From phosphalkynes.* Searching for a stable phosphavinyl lithium reagent compound **243** was reacted with 1 equiv. of **2a** in diethyl ether at -78 °C which afforded a deep green solution. Warming to room temperature was accompanied by a color change to purple. Work-up of the reaction mixture and treatment with an excess of tetramethylethylenediamine (TMEDA) gave the phosphalkenyl-functionalized η^3 -azaallyl complex **244**. It was assumed that this reaction was initiated by a 1,2-addition of **243** to the P≡C triple bond to furnish a thermolabile phosphavinyl lithium compound as an intermediate <2002JOM(645)256> (Scheme 66).



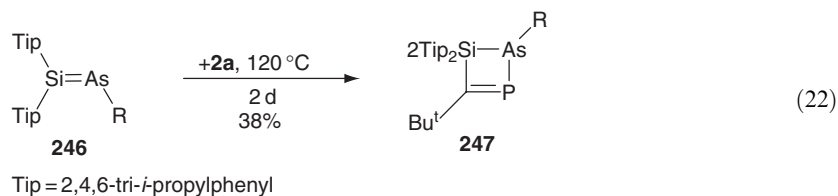
Scheme 66

The phosphoalkynes $\text{RC}\equiv\text{P}$ ($\text{R} = 1\text{-Ad}, 2\text{-methylcyclohexyl}$) reacted with dimesitylsilylene, generated photochemically from the trisilane $\text{Mes}_2\text{Si}(\text{TMS})_2$, to furnish the phosphadisisilacyclobutenes **245a** and **245b** as yellow crystals. This transformation presumably proceeded by an initial $[2+1]$ -cycloaddition to give phosphasilirenes. They subsequently incorporated a second silylene molecule with the formation of the four-membered heterocycles (Scheme 67) <1997CC1433>. As previously reported the three-membered rings were isolated when di-*t*-butylsilylene was employed in the reaction with phosphoalkenes **2a** and **2b**. Obviously the *t*-butyl groups effectively shield the phosphasilirene from further attack <1987AG(E)776>.



Scheme 67

Phosphoalkyne **2a** and arsilene **246** underwent a $[2+2]$ -cycloaddition to give yellow crystalline heterocycle **247**, when heated to 120°C for 2 days. (Equation (22)) <1996OM1845>. The corresponding phosphasilene did not react with **2a**.

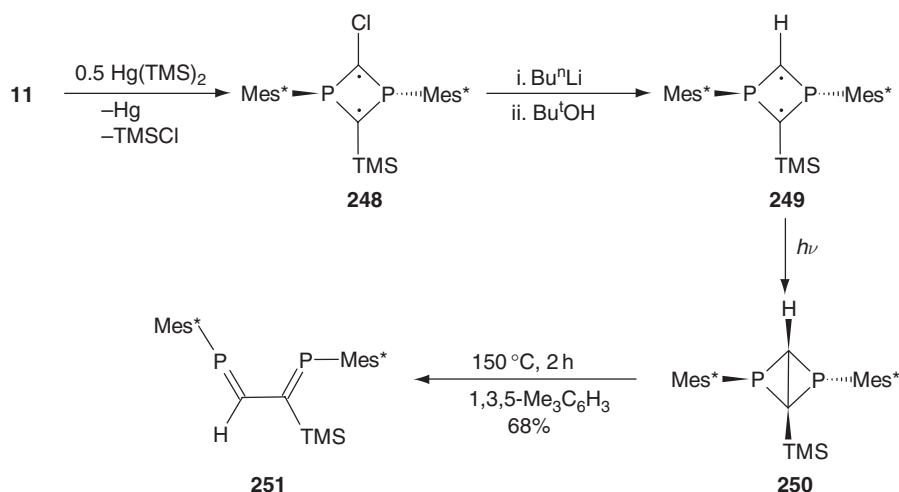


(c) *By miscellaneous methods.* The selective introduction of one trimethylsilyl group into ring **11** was achieved by reaction with 0.5 equiv. of $\text{Hg}(\text{TMS})_2$. The crystalline 1,3-diphosphacyclobutane-2,4-diyl **248** was converted into derivative **249** by a sequence of lithium/chlorine exchange and protonation. Upon irradiation in *n*-pentane at -30°C this red crystalline product underwent rearrangement into the yellow 1,3-diphosphabicyclo[1.1.0]-butane **250**. Heating a solution of **250** in mesitylene at 150°C for 2 h resulted in a cycloreversion with formation of the yellow crystalline 1,4-diphosphabutadiene **251** <1999AG(E)3028> (Scheme 68).

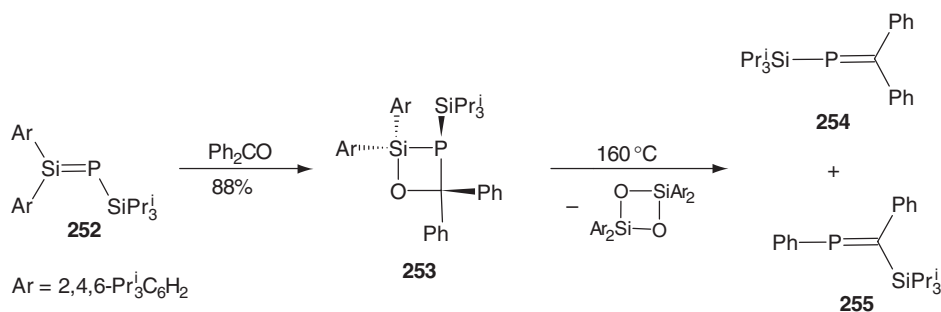
In a pseudo-Wittig reaction phosphasilene **252** and benzophenone yielded heterocycle **253**, which upon heating in toluene at 160°C for 2 days collapsed to the isomeric phosphoalkenes **254** and **255** as well as to a 1,3-dioxo-2,4-disiletane derivative (Scheme 69) <1996OM1845>.

(ii) Germanium derivatives

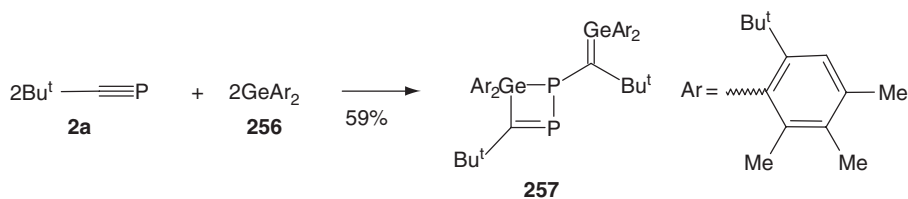
(a) *From phosphoalkynes.* From the reaction of the germylene **256** which exists as a dimer in the solid state, with phosphoalkyne **2a** compound **257** was isolated as orange crystals. The formation of **257** was without precedent in the chemistry of germylenes and phosphoalkynes. It was presumably initiated by a $[2+1]$ -cycloaddition of the germylene to the $\text{P}\equiv\text{C}$ bond and a dimerization of the transient phosphagermyrene <2001CC215> (Scheme 70).



Scheme 68



Scheme 69

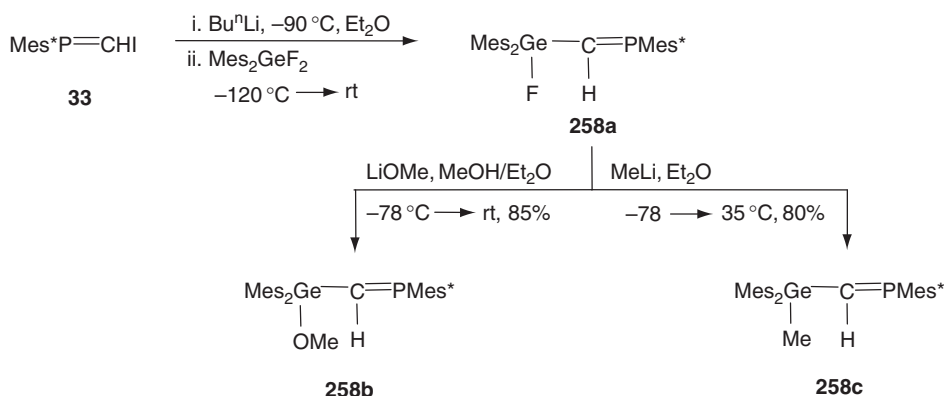


Scheme 70

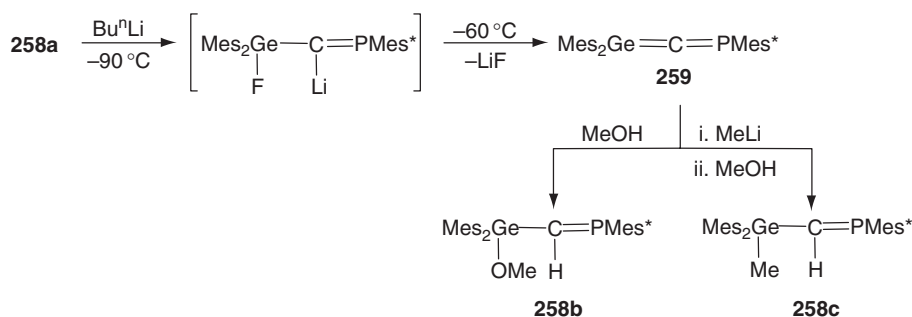
It is also conceivable that a phosphadigermacyclobutene analogous to compounds **245a,b** was initially formed. Subsequent ring opening to a 1,4-digerma-2-phospha-butadiene $\text{Ar}_2\text{Ge}=\text{P}-\text{C}(\text{Bu}^t)=\text{GeAr}_2$ and the $[2+2]$ -cycloaddition of the $\text{P}=\text{Ge}$ double bond to the $\text{P}\equiv\text{C}$ bond of a second molecule of **2a** would furnish **257**.

(b) *From iodomethylene phosphanes.* A phosphavinyl lithium reagent was prepared from $\text{Mes}^*\text{P}=\text{CHI}$ and n -butyllithium in diethyl ether at -80°C and then treated with Mes_2GeF_2 at -120°C . Warming to 25°C within 2 h gave an orange yellow slurry from which phosphalkene **258a** was isolated as yellow crystals. The product was converted into phosphalkenes **258b** and **258c** by reaction with LiOMe or methyllithium, respectively [\[1996OM3070\]](#) (Scheme 71).

Lithiation of **258a** with n -butyllithium at -90°C and warming to -60°C led to extrusion of LiF from the organolithium intermediate and to the formation of the thermolabile germaphosphaallene **259**. Reaction of the heteroallene with MeOH or methyllithium followed by methanolysis constituted an alternative pathway to **258b** and **258c** [\[1996OM3070\]](#), although here no analytically pure products could be obtained (Scheme 72).



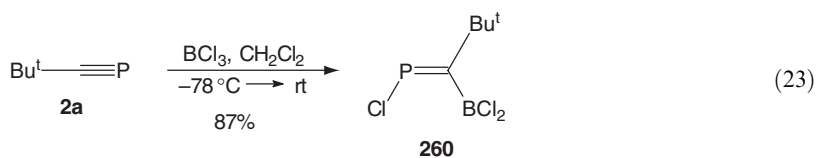
Scheme 71



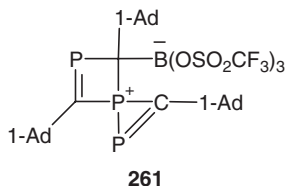
Scheme 72

(iii) Boron derivatives— $\text{R}^1\text{C}(\text{PR}^2)\text{BR}_2^3$

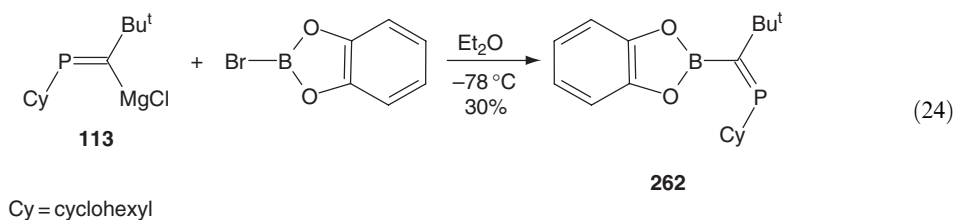
(a) *From phosphaaalkynes.* Addition of the phosphaaalkyne **2a** to a solution of boron trichloride in dichloromethane at -78°C followed by warming to ambient temperature delivered the boron-functionalized phosphaaalkene **260** as a highly moisture- and oxygen-sensitive pale yellow oil (Equation (23)).



The 1,2-addition of the boron compound is not a general route to borylated phosphaaalkenes as was documented in the reaction of **2b** with boron tris(triflate), which furnished a mixture of diastereoisomers of the spiro-cyclotrimer **261** instead of the expected phosphaaalkene $\text{F}_3\text{CO}_2\text{SOP}=\text{C}(\text{1-Ad})\text{B}(\text{OSO}_2\text{CF}_3)_2$ <1996CB489>.



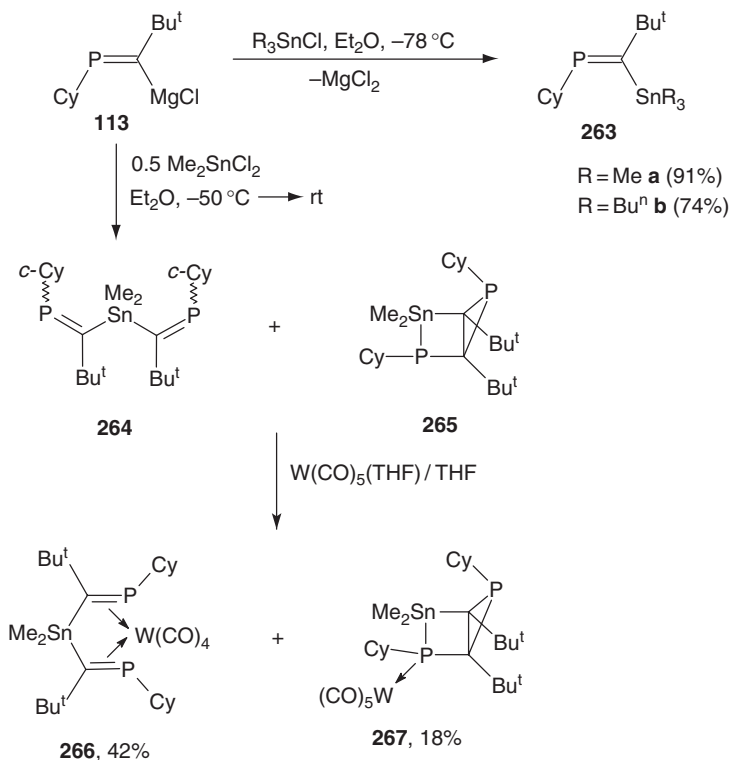
(b) *From phosphavinyl Grignard reagents.* The phosphavinylborane **262** was synthesized by combining an ethereal solution of bromocatecholborane with $\text{CyP}=\text{C}(\text{Bu}^t)\text{MgCl}$ **113** in diethyl ether at -78°C (Equation (24)) <2003JOM(665)127>.



5.23.1.1.7 Metal derivatives— $R^1C(PR^2)M$

(i) Derivatives with group 14 metals

The availability of phosphavinyl Grignard reagents has opened a promising and elegant gateway to metal-functionalized phosphalkenes as an alternative to elaborated methods with lithiated phosphalkenes. Combination of Grignard reagent **113** with Me_3SnCl or Bu^n_3SnCl in diethyl ether at -78°C gave rise to the formation of the stannylated derivatives **263a** and **263b** as colorless liquids (Scheme 73) <2003JOM(665)127>.

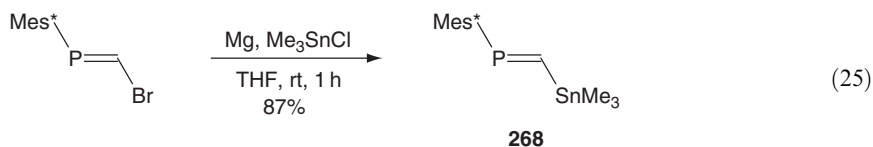


Scheme 73

Reaction of Me_2SnCl_2 with 2 equiv. of **113** in diethyl ether at -50°C and stirring the resulting mixture overnight at room temperature furnished an inseparable mixture of several products with compounds **264** and **265** being the major components. Separation of **264** and **265** was accomplished by chromatography of their thermally robust and air-stable carbonyltungsten complexes **266** and **267** (Scheme 73) <2000JCS(D)3233>.

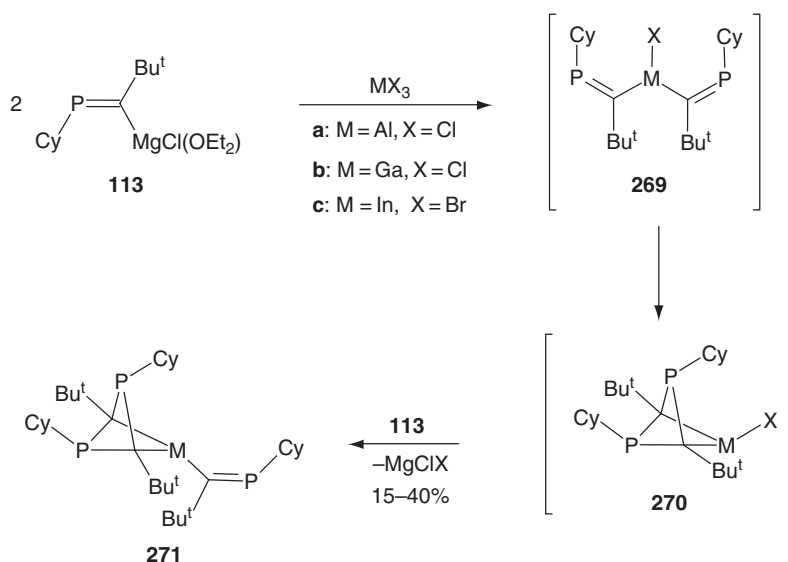
A variation of the stannylation procedure depicted in Scheme 73 was based on the reaction of (*E*)- $\text{Mes}^*\text{P}=\text{CHBr}$ with magnesium metal under Barbier conditions to furnish product **268** (Equation (25)). Lead derivatives are unknown as of early 2003. Instead reaction of PbCl_2 with

113 afforded the first example of an *endo:endo*-2,4-diphosphabicyclo[1.1.0]butane, $\text{Cy}_2\text{P}_2\text{C}_2\text{Bu}^t_2$ by oxidative coupling of two phosphavinyl units <2001CC663>.



(ii) Derivatives with group 13 metals

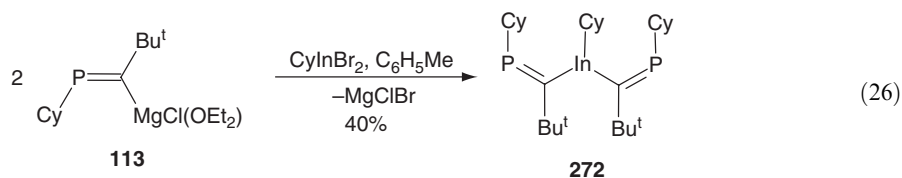
When slurries of the trihalides of aluminum, gallium, or indium in toluene at -78°C were treated with 3 equiv. of **113** and warmed to ambient temperature reaction occurred with the unexpected formation of the diphospha metallobicyclo[1.1.1]pentane derivatives **271a–c**, which contain terminal phosphavinyl ligands. The yellow crystalline products were isolated in low to moderate yields <2001JOM(629)109> (Scheme 74).



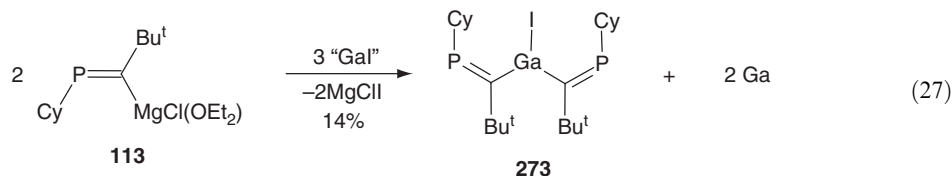
Scheme 74

It was assumed that the metal halide initially reacted with two molecules of **113** to give intermediate **269**. This then underwent a facile intramolecular electrocyclozation to afford **270**, which reacted with a third equivalent of **113** to afford the final products. The structural motif of **269** can be stabilized if cyclohexylindium dibromide instead of InBr_3 was allowed to react with the Grignard reagent.

Accordingly, 2 equiv. of **113** were combined with freshly prepared CyInBr_2 in toluene to give compound **272** as colorless crystals (Equation (26)) <2001JOM(629)109>. The reluctance of derivative **272** to undergo electrocyclozation and to provide an analog of **270** was rationalized by the extra steric demand of the cyclohexyl group.

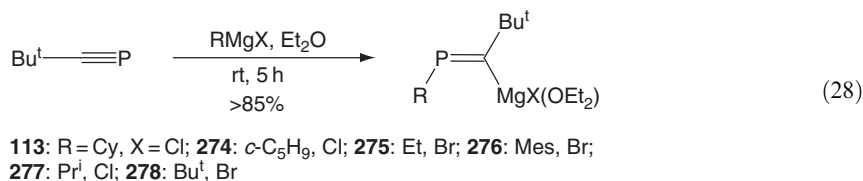


Surprisingly, the 1:1 reaction of **113** with “GaI,” which results from the sonication of gallium metal and 0.5 equiv. of I₂ in toluene, led to the precipitation of **273** (Equation (27)). The attempted preparation of [M{C(Bu^t)=PCy}] with M = Tl or In via combination of **113** with MCl resulted in metal deposition and the high yield formation of the known 2,4-diphosphabicyclobutane, Cy₂P₂C₂Bu₂^t, presumably by an oxidative coupling of two phosphavinyl fragments <2003JOM(665)127>.



(iii) Derivatives with group 2 metals

The only well-defined phosphalkenes featuring alkaline earth metals as substituents at the carbon atom of the P=C bond were derived from magnesium, and they are frequently regarded as phosphavinyl Grignard reagents. As already pointed out in this chapter, such species have been exceedingly useful in organophosphorus synthesis. A convenient synthetic route to a range of such species (**113**, **274–276**) with a variety of *P*-substituents is based upon the regio- and stereo-selective addition of several Grignard reagents across the P≡C bond of phosphalkyne Bu^tC≡P **2a** (Equation (28)) <1999JCS(D)3531>. Compounds **277** and **278** were made analogously in the temperature range of −78 to 25 °C <2000EJI2337>.



The dimeric structure of phosphavinyl Grignard compounds was authenticated by a single crystal X-ray diffraction analysis.

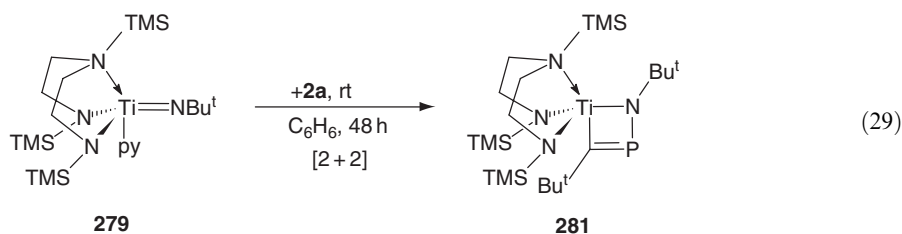
(iv) Derivatives with group 1 metals

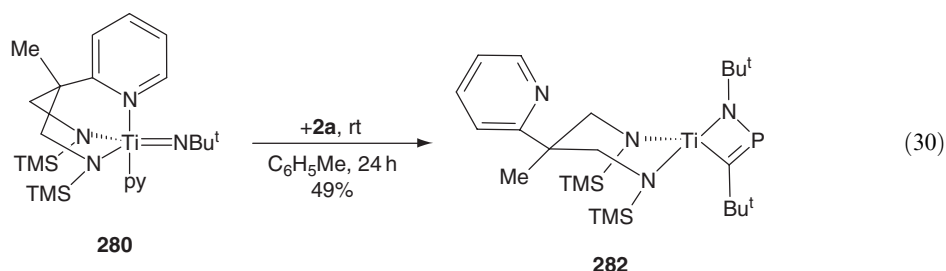
No isolable phosphalkenes that are functionalized by alkali metals have been described as of early 2003.

(v) Transition metal derivatives

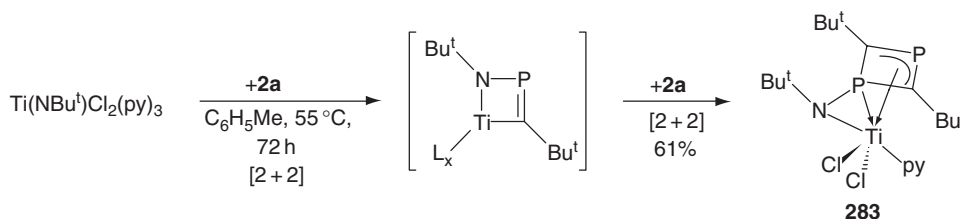
A few cyclic phosphalkenes with Ti, Zr, and V functions were synthesized from phosphalkyne **2a** and the respective metal imido complexes.

Treatment of titanium imides **279** and **280** with an excess of **2a** at 25 °C in toluene afforded oily orange **281** (Equation (29)) or orange crystalline **282** (Equation (30)) <1999CC6611, 2000OM3205>.



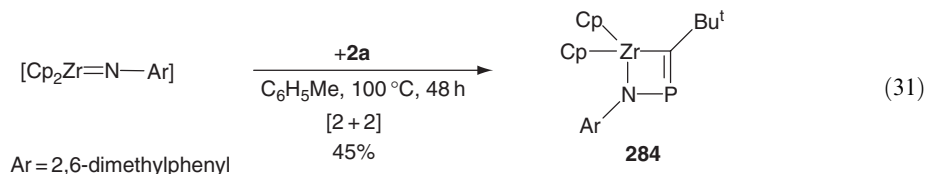


For the outcome of the reaction of titanium imides and **2a** the steric encumbrance about the metal was crucial. Thus, reaction of complex $\text{Ti}(\text{NBu}^t)\text{Cl}_2(\text{py})_3$ with an excess of the phosphalkyne in toluene at 55 °C for 72 h yielded the dark red crystalline complex **283**. This result may be interpreted as a [2 + 2]-cycloaddition of a second molecule of **2a** to the transient four-membered ring. Moreover, the course of the reaction under discussion is also affected by the nature of the imido *N*-substituent (Scheme 75) <1999CC661>.

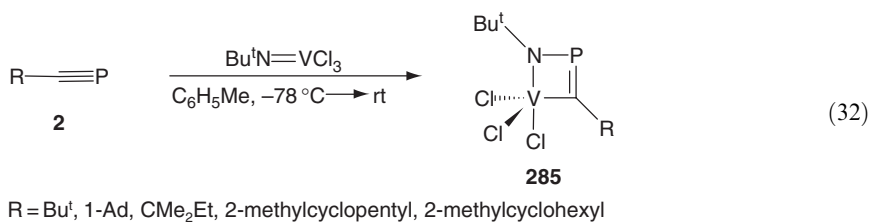


Scheme 75

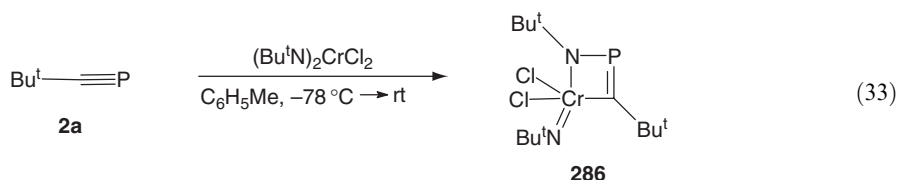
Treatment of the transient imide $\text{Cp}_2\text{Zr}=\text{N}-\text{Ar}$ (prepared by the thermolysis of $\text{Cp}_2\text{Zr}(\text{NHC}_6\text{H}_3\text{Me}_2-2,6)_2$) with an excess of **2a** in toluene at 100 °C for 48 h yielded the orange crystalline zirconophosphalkene **284**. An analogous compound was prepared from $\text{Cp}_2\text{Zr}=\text{NBu}^t$ and **2a** (Equation (31)) <1999CC661>.



Reaction of equimolar amounts of a phosphalkyne **2** with imidovanadium(V) trichloride proceeded through [2 + 2]-cycloaddition of the $\text{P}\equiv\text{C}$ bond to the metal–nitrogen multiple bond and quantitatively furnished the 1,2,4-azaphosphavanada(V)-cyclobutenes **285**, which are stable at 25 °C. Low temperatures and observation of the exact stoichiometry were essential for the success of the reaction (Equation (32)).



This type of cyclization reaction was also applied to the easily accessible bis(*t*-butylimido) chromium(VI) dichloride, and indeed combination of equimolar amounts of $\text{Bu}^t\text{C}\equiv\text{P}$ and $(\text{Bu}^t\text{N})_2\text{CrCl}_2$ in toluene under comparable conditions resulting in the quantitative formation of the metallocycle **286** (Equation (33)). A possible second addition of **2a** to the remaining metal–nitrogen multiple bond in **286** was not observed even in the presence of a large excess of $\text{Bu}^t\text{C}\equiv\text{P}$.



Changes in the alkyl group of the phosphaalkyne had no effect on the stability of compounds **285**, whereas replacement of the *t*-butyl group of the imido units in $\text{RN}=\text{VCl}_3$ could change the course of the reaction and the product pattern significantly. Thus, only the reactions of $\text{RN}=\text{VCl}_3$ with the bulky groups $\text{R} = \text{Bu}^t$, CPh_3 , 1-adamantyl, and TMS gave rise to stable and isolable vanadacycles, whereas with secondary and primary substituents on the ring nitrogen atoms compounds analogous to **285** were merely detected as intermediates in the reaction mixture. At 25°C they underwent quantitative conversion to 1*H*-1,2,4-azadiphospholes within 24 h.

Complex $\text{Bu}^t\text{N}=\text{VCl}_3$ assisted the formation of 1,3,5-triphosphinines, when exposed to an excess of the phosphaalkynes under otherwise comparable conditions <2000CEJ4558>.

5.23.1.2 Dicoordinate Arsenic Functions— $\text{R}^1\text{C}(\text{AsR}^2)\text{X}$

5.23.1.2.1 Introduction

Compounds of the type $\text{R}^1\text{C}(\text{AsR}^2)\text{X}$ are usually described as methylene arsanes or arsaalkenes. Their chemistry has been developed to a much lesser extent than that of the related phosphaalkenes. Synthetic pathways to such compounds mainly mirror those affording the phosphorus analogs. Thus, organodisilylarsanes, their lithium derivatives as well as lithium arsenide are commonly used in condensation and rearrangement processes. Moreover, dehydrohalogenations play an important role in the synthesis of carbon-substituted arsaalkenes. Based on these methods a few arsaalkenes with oxygen-, nitrogen-, and silicon-based substituents were presented in the literature up to early 1995 <1995COFGT(5)875>. There is one review article dedicated to the chemistry of the arsenic carbon multiple bond <1996CB367>.

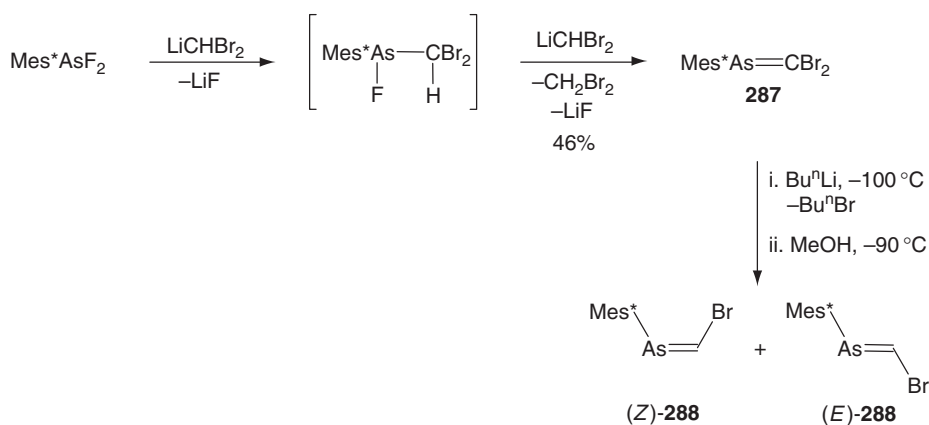
5.23.1.2.2 Halogen derivatives— $\text{R}^1\text{C}(\text{AsR}^2)\text{X}$ ($\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$)

The *C,C*-dibromoarsaalkene **287** was prepared in a one-pot reaction from 2 equiv. of LiCHBr_2 and 1 equiv. Mes^*AsF_2 . As already discussed in the synthesis of the related phosphaalkenes it was assumed that the carbenoid acts first as a nucleophile to afford transient $\text{Mes}^*\text{As}(\text{F})\text{C}(\text{H})\text{Br}_2$ and then as a base facilitating the dehydrofluorination. Addition of *n*-butyllithium to **287** at -100°C followed by methanolysis at -90°C afforded the new arsaalkenes (*Z*)-**288** and (*E*)-**288** in the ratio 95:5 (Scheme 76). The pure (*Z*)-isomer was obtained in 78% by crystallization <1996OM2683>. The syntheses of the related arsaalkenes $\text{Mes}^*\text{As}=\text{CCl}_2$ and $\text{Mes}^*\text{As}=\text{CBr}_2$ were also reported, but their conversion into the monohalogenated molecules, however, was not.

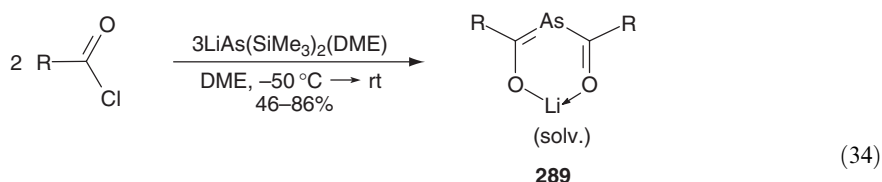
5.23.1.2.3 Chalcogen derivatives— $\text{R}^1\text{C}(\text{AsR}^2)\text{ER}^3$ ($\text{E} = \text{O}, \text{S}, \text{Se}, \text{Te}$)

(i) Oxygen derivatives

Compounds **289a–d** were prepared by the treatment of carboxylic acid chlorides with $\text{LiAs}(\text{SiMe}_3)_2(\text{DME})$ in a 2:3 ratio in DME at -50°C and slow warming of the mixture to 25°C . Derivatives **289b** and **289c** were recrystallized from diethyl ether (Equation (34)) <1996JCS(D)3277>.



Scheme 76

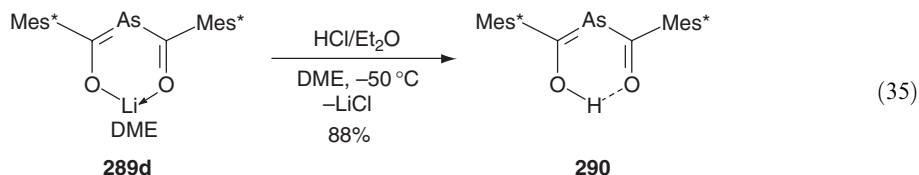


R = Bu^t, solv. = 0.5 DME **a** or Et₂O **b**

R = C₆H₂Pr₃ⁱ-2,4,6, solv. = Et₂O **c**

R = Mes*, solv. = DME **d**

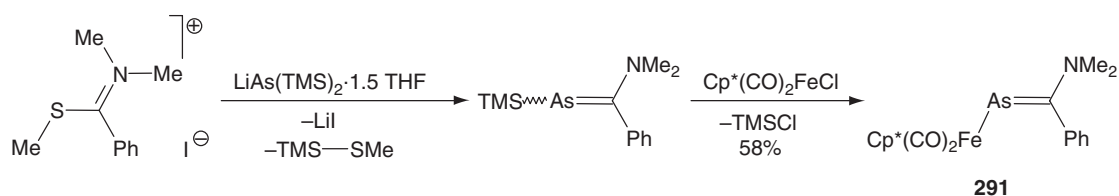
Protonation of **289d** was achieved by addition of an equimolar amount of ethereal HCl to the DME solution of the salt at -50°C . From the yellow solution bright yellow needles of **290** were isolated (Equation (35)). From an X-ray structure analysis it was obvious that in the crystalline state the diacylarsane was present in the enol form.



5.23.1.2.4 Nitrogen derivatives— $\text{R}^1\text{C}(\text{AsR}^2)\text{NR}_2^3$

(i) From lithium (silyl)arsenides and carbenium salts

Reaction of equimolar amounts of the carbenium iodide [Me₂N(Ph)CSMe]I and LiAs(TMS)₂·1.5 THF in a dimethoxyethane/*n*-pentane mixture at -78 to 25°C led to an orange-red solution. Because of the pronounced thermolability of the produced arsaalkene complex Cp*(CO)₂FeCl was added to the filtered solution. After 16 h of stirring at room temperature black crystalline arsaalkene **291** was isolated (Scheme 77) <2001ZAAC863>.

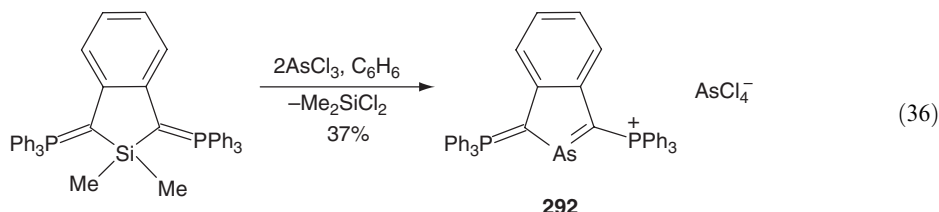


Scheme 77

5.23.1.2.5 Group 15 element derivatives— $R^1C(AsR^2)ER_n^3$ ($E = P, As, Sb, Bi$)

(i) Phosphorus derivatives

1,3-Bis(triphenylphosphonio)isoarsindolide tetrachloroarsenate(III) **292** was obtained from the reaction of equimolar amounts of a dimethyl-2-silaindene derivative and $AsCl_3$ in benzene at room temperature (Equation (36)) <2000CEJ3531>.

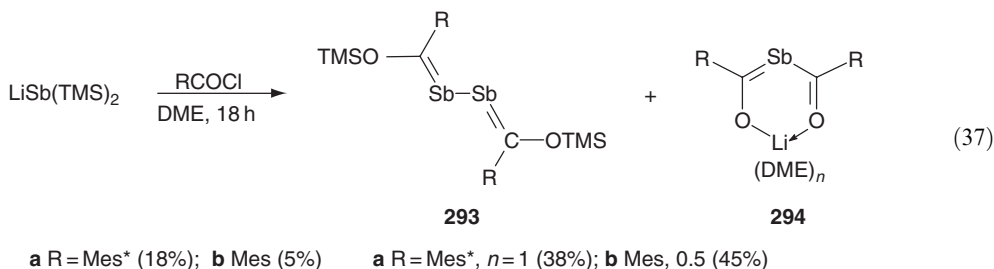


5.23.1.3 Dicoordinate Sb and Bi Functions— $R^1C(ER^2)X$ ($E = Sb, Bi$)

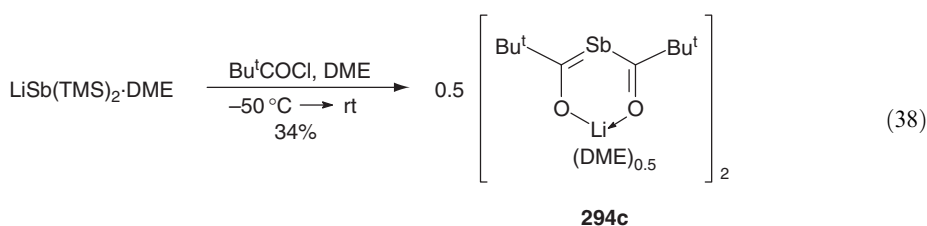
5.23.1.3.1 Chalcogen derivatives— $R^1C(SbR^2)ER^3$

(i) Oxygen derivatives— $R^1C(SbR^2)OR^3$

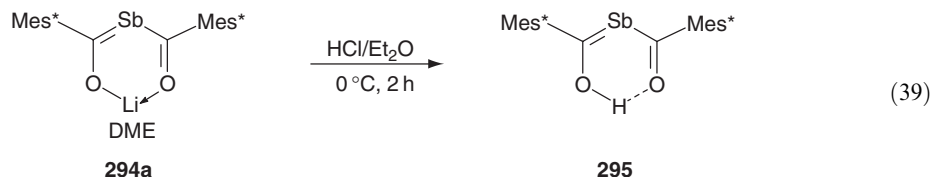
Not surprisingly the chemistry of compounds containing AsC multiple bonding was slower to develop and to date much less well explored than that of their phosphorus homologs. Compared with this, there is an even greater paucity of knowledge on analogous antimony compounds, which probably results from their inherent thermal instability. In fact to date there are just a handful of structurally characterized acyclic compounds featuring SbC multiple bonding. The product mixtures obtained from the treatment of $LiSb(TMS)_2$ with 1 equiv. of either Mes^*COCl or $MesCOCl$ in DME (−40 to 25 °C, 18 h) were extracted with hexane to afford the deep-red crystalline distibabutadienes **293a** and **293b**. Extraction of the hexane insoluble residues with diethyl ether furnished the 2-stiba-1,3-dionato lithium derivatives **294a** and **294b** (Equation (37)) <1999JCS(D)1541, 1995AG(E)492>.



If pivaloyl chloride was allowed to react with $LiSb(TMS)_2$ -DME under comparable conditions no product analogous to **293a,b** was observed. Instead orange blocks of the 2-stiba-1,3-dionato complex **294c** were isolated by crystallization from DME at −30 °C (Equation (38)) <1996JCS(D)3277>.



Treatment of a diethyl ether solution of **294a** with 1 equiv. of HCl in ether solution, followed by recrystallization from the same solvent gave red crystals of the light sensitive stiba-enol **295** (Equation (39)) <1999JCS(D)1541>.



Stable and isolable bismaalkenes have not been reported in the literature up to early 2003. Recent developments in low coordination organo-antimony and -bismuth chemistry are discussed in a review <2001CCR(215)151>.

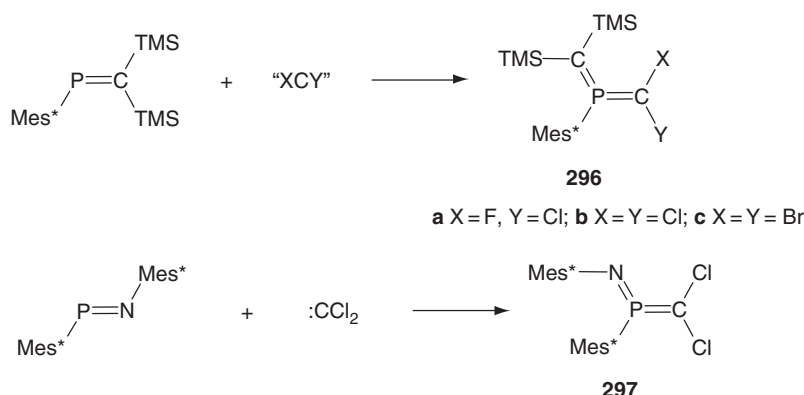
5.23.2 TRICOORDINATE P, As, Sb, and Bi FUNCTIONS—RC(PX¹Y)X², RC(AsX¹Y)X², RC(SbX¹Y)X², and RC(BiX¹Y)X²

5.23.2.1 Tricoordinate Phosphorus Functions—RC(PX¹Y)X²

Compounds of the above type are quite rare if simple metal coordination compounds of phosphaaalkenes are neglected. Basically, λ^3, σ^2 -bismethylene phosphoranes Mes*P] = C(TMS)₂(=CXH) or λ^3, σ^2 -iminomethylenephosphoranes Mes*P(=N Mes*)(=CXH) may be derived from the dihalomethylene precursor by lithium/halogen exchange and subsequent protolysis.

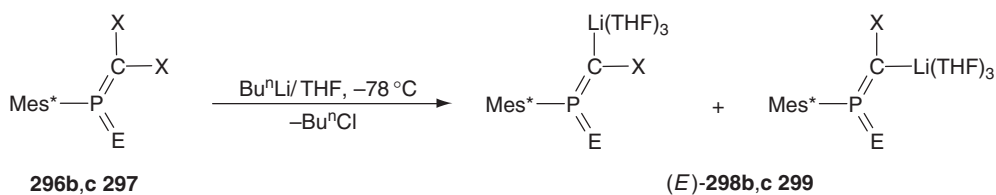
5.23.2.1.1 λ^3, σ^2 -Methylene phosphoranes

The dihalomethylene phosphoranes **296a–c** and **297**, which are suitable precursors for the corresponding halocarbenoids **298a–c** and **299**, and monohalomethylene phosphoranes **300a–c** and **301** were conveniently accessible via oxidation of the phosphaaalkene Mes*P=C(TMS)₂ or the iminophosphane Mes*P=N Mes* with dihalocarbenes (Scheme 78) <1995AG(E)1849, 1999JA5953>.

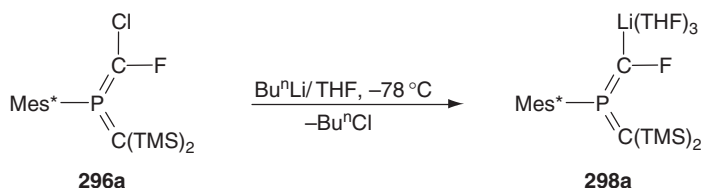


Scheme 78

Reaction of the bis(methylene)phosphoranes **296a–c** and **297** with 1 equiv. of *n*-butyllithium in THF at -78°C proceeded via X/Li exchange to yield a 6:1 mixture of the (*Z*)- and (*E*)-configured carbenoids **298b,c** and **299**. Metallation of the chlorofluoromethylene phosphorane **296a** occurred exclusively via Li/Cl exchange and gave the (*Z*)-configured compound **298a** (Scheme 79).

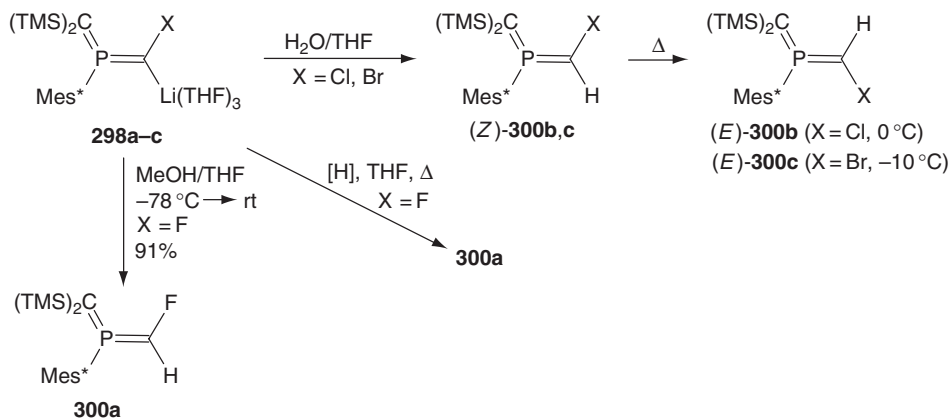


296b, 298b X = Cl, E = C(TMS)₂; **296c, 298c** X = Br, E = C(TMS)₂; **297, 299** X = Cl, E = NMe^{*}



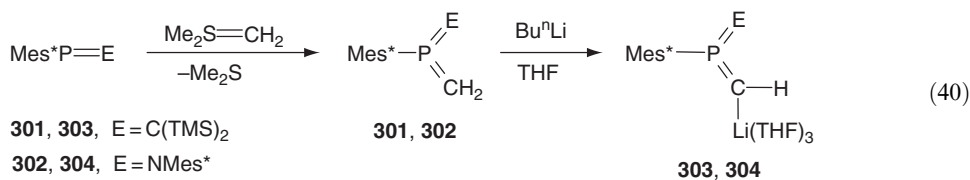
Scheme 79

Quenching the reaction mixture in THF with water at -50°C at low temperature led to (*E*)/(*Z*) mixtures of the monohalogenated bis(methylene)phosphoranes **300b,c**. Rearrangement to the thermodynamically more stable (*E*)-configured isomers was observed at 0°C (X = Cl) or at -10°C (X = Br). Products (*E*)-**300b,c** were isolated as yellow or orange crystals, respectively. Protonation of carbenoid **298a** afforded compound (*Z*)-**300a** as yellow crystals. Surprisingly **298a** did not decompose through loss of lithium fluoride upon warming to 25°C . Li/H exchange with the solvent THF yielded (*Z*)-**300a** instead (Scheme 80) <1995AG(E)1849, 2002OM4919>.



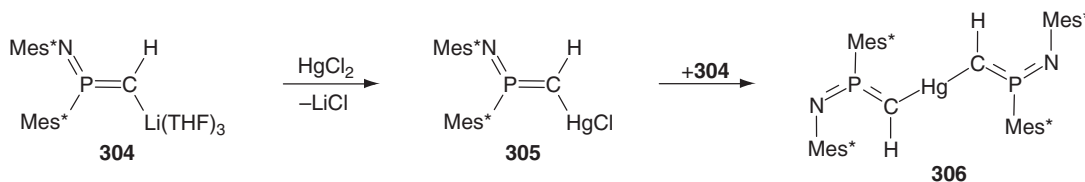
Scheme 80

Another interesting approach to λ^3, σ^2 -bis(methylene)phosphoranes and λ^3, σ^2 -iminomethylene-phosphoranes made use of the reaction of $\text{Mes}^*\text{P}=\text{E}$ (E = C(TMS)₂; NMe^{*}) with dimethylsulfonium methylene (Equation (40)) <1997JA12410>.



Metallation of **301** and **302** by *n*-butyllithium in THF at 0 °C gave the lithium derivatives **303** and **304**, which were isolated as highly air- and moisture-sensitive yellow crystals. The identity of both compounds was ascertained by single crystal X-ray diffractometry.

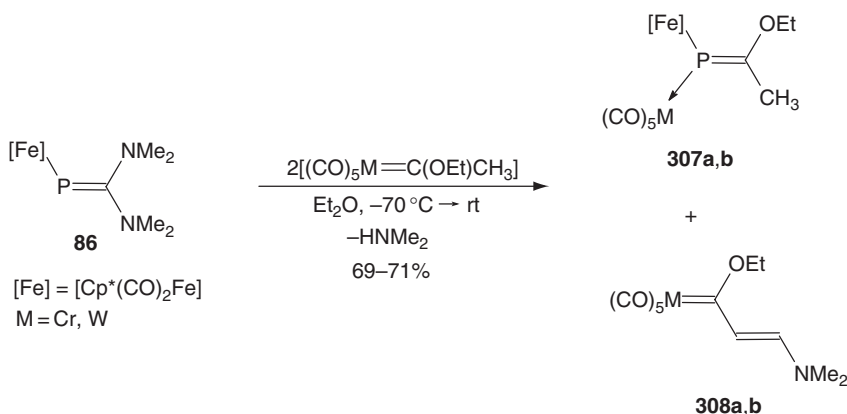
The lithium phosphoranylidene compounds **303** and **304** were easily converted into novel organometallics with retention of the low-coordinate phosphorus atom. Thus treatment of **304** with 1 equiv. of HgCl₂ produced **305**. Subsequent addition of another equivalent of **304** afforded the diorganomercury derivative **306** which was isolated as light yellow air- and moisture-sensitive crystals (Scheme 81) <1997JA12410>.



Scheme 81

5.23.2.1.2 η^1 -Phosphaalkene complexes— $RC[PX^I(M)]X^2$

Inversely polarized phosphaalkenes react as nucleophiles toward carbene complexes of the Fischer type. When metallophosphaalkene **86** was combined with 2 equiv. of ethoxy(methyl)carbene complexes in diethyl ether at −70 °C orange precipitates were formed. The isolation of these compounds, however, was thwarted by their decomposition. Upon warming to 25 °C, the precipitates dissolved and the novel red crystalline ferriphosphaalkene pentacarbonyl metal adducts **307a,b** were generated. The yellow (*E*)- β -aminoalkenyl(ethoxy)carbene complexes **308a,b** were formed as by-products in comparable yields and were separated by fractional crystallization (Scheme 82).

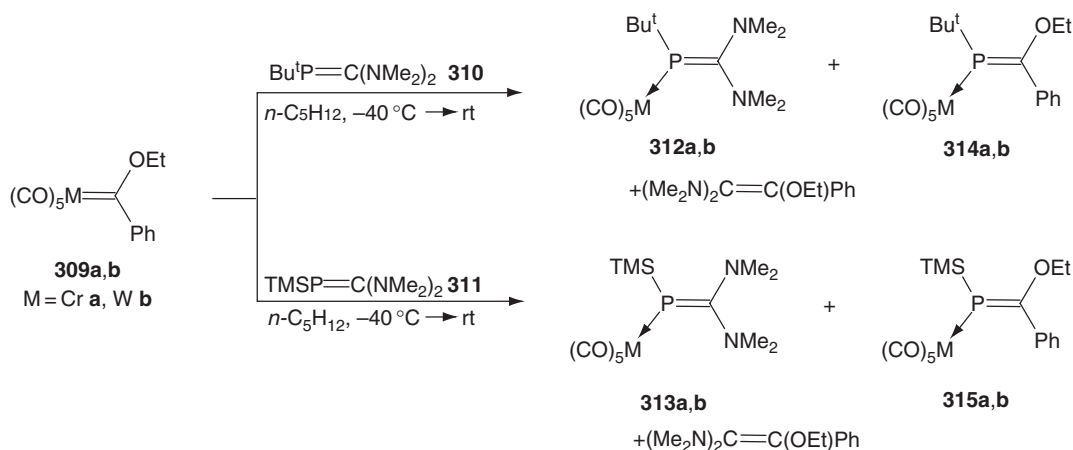


Scheme 82

The reaction of phenylcarbene complex (CO)₅Cr=C(Ph)OEt **309a** with **86** was complicated and gave [Fe(CO)₂Cp*]₂ as the main product (70% yield). Obviously this reaction was dominated by the cleavage of the Fe—P bond in **86** <1998CEJ469>.

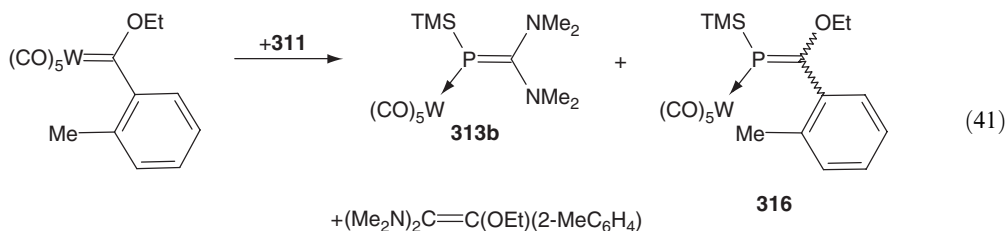
When phenylcarbene complexes **309a,b** were combined with the phosphaalkenes RP=C(NMe₂)₂ (**310**: R = Bu^t, **311**: TMS) in *n*-pentane at −40 °C and stirred for 2 h at 25 °C, the yellow η^1 -phosphaalkene complexes **312b** and **313b** (M = W) were isolated by fractional crystallization. The yellow η^1 -phosphaalkene complexes **314b** and **315b** (M = W) were also formed but they cannot be separated from alkene (Me₂N)₂C=C(OEt)Ph without decomposition (Scheme 83) <2001CEJ5401>.

It was assumed that an increase of steric bulk at the aryl ring would provide additional stability to the novel phosphaalkene complexes, in which the former carbene ligand is incorporated into the P=C unit.



Scheme 83

When sterically more demanding ethoxy(*o*-tolyl)carbene pentacarbonyl tungsten was subjected to reaction with **311** the yellow complex **313b** was formed in addition to the novel orange crystalline η^1 -phosphaalkene complex **316** and alkene (Me₂N)₂C=C(OEt)(2-MeC₆H₄). No reaction was observed between the carbene complex and phosphoalkene **310** (Equation (41)) <2001CEJ5401>.



The reaction of *o*-methoxyphenylcarbene tungsten complex with **310** under comparable conditions yielded the complex **312b** and the orange η^1 -phosphaalkene complex **317**, which were separated by fractional crystallization from *n*-pentane.

In addition, a mixture of small amounts of the alkenes [(*E*)/(*Z*)-2-MeOC₆H₄(OEt)C]₂ and (Me₂N)₂C=C(OEt)(2-MeOC₆H₄) was distilled from the mother liquors after crystallization.

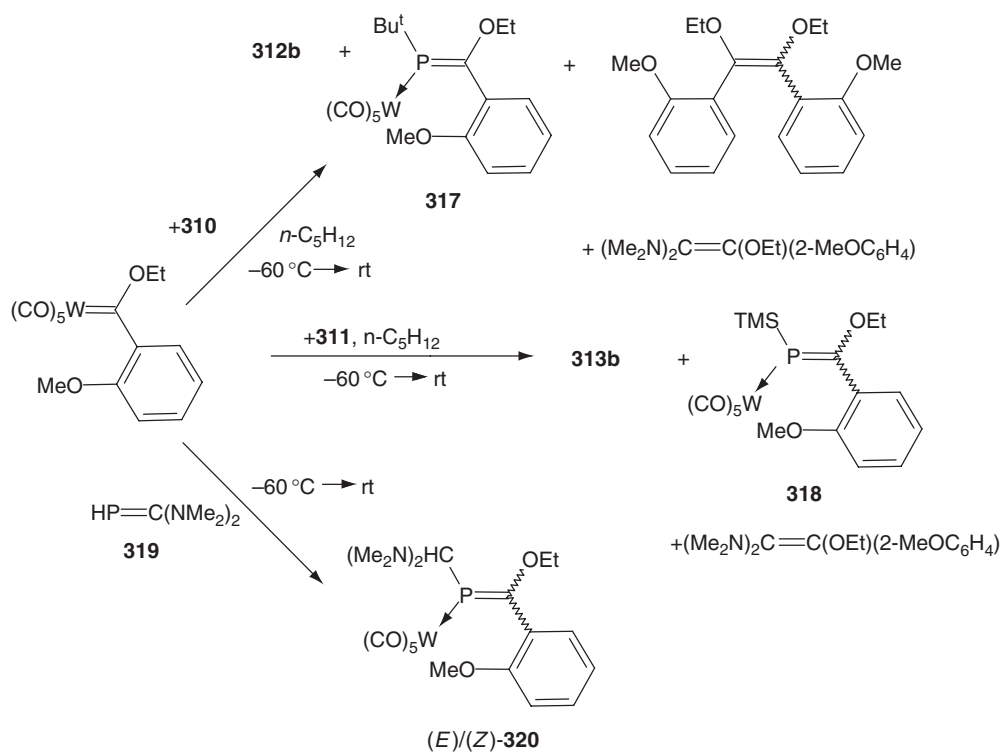
Similarly, combination of the carbene complex with **311** gave rise to the formation of **313b** and the metathesis product **318**, which was obtained as an orange solid. The reaction residue contained (Me₂N)₂C=C(OEt)(2-MeOC₆H₄) as the only alkene. The course of the reaction between the carbene complex and HP=C(NMe₂)₂ **319** was completely different. Here W(CO)₅ complexes of the two geometric isomers of the phosphoalkene (Me₂N)₂CHP=C(OEt)(2-MeOC₆H₄) ((*E*)/(*Z*))-**320** were isolated as orange crystals. An ((*E*)/(*Z*)) ratio of 1:2 was determined by NMR-spectroscopy (Scheme 84).

Deprotonation of benzyl(ethoxy)carbene pentacarbonyl complexes with *n*-butyllithium at -78 °C and subsequent addition of the phosphoalkene ClP=C(TMS)₂ cleanly afforded the complexes **321a,b** featuring a 2-phosphabutadiene ligand. Heating solutions of **321a,b** in toluene or *n*-hexane to 70 °C induced an electrocycization of the ligand with the formation of the η^1 -2,3-dihydrophosphete complexes **322a,b** (Scheme 85) <1997AG(E)1095>.

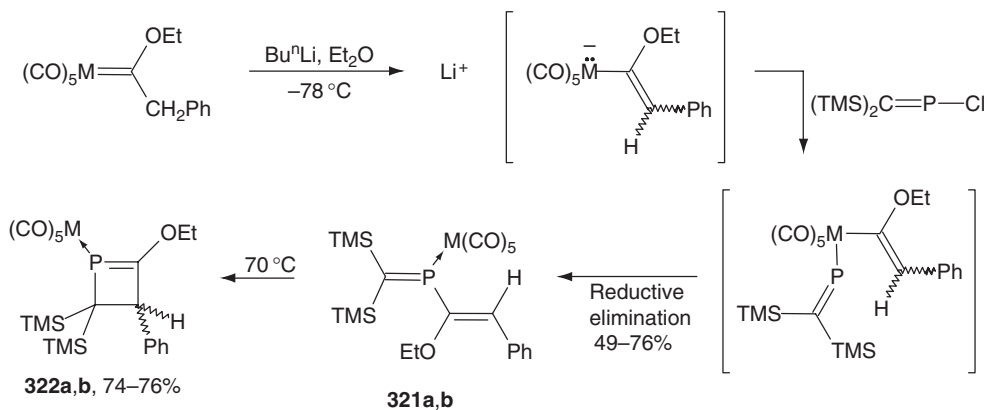
2-Phosphabutadiene formation was rationalized by an electrophilic attack of the chlorophosphoalkene at the metal center of the anionic alkenyl complex and a reductive elimination of the unsaturated ligands.

Treatment of the [bis(diisopropylamino)phosphanyl][2,6-bis(trifluoromethyl)(phenyl)] carbene **87** with 0.5 equiv. of [RhCl(CO)₂]₂ in toluene at -50 °C quantitatively afforded the corresponding carbene complex **323**, which at -10 °C quickly isomerized to the η^1 -phosphaalkene complex **324** (Scheme 86) <2002JA11834>.

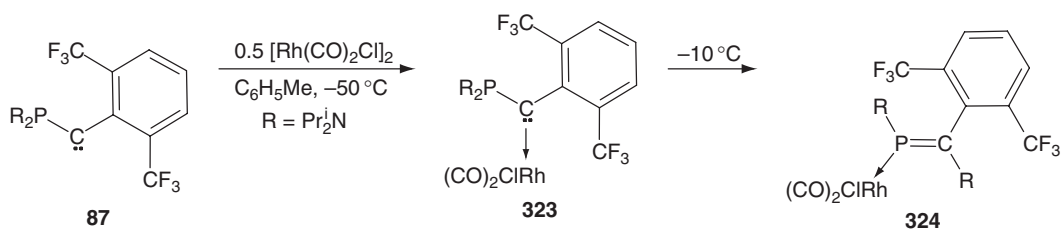
The reaction of equimolar amounts of (*Z*)-Cp*(CO)₂FeP=C(Bu^t)NMe₂ **95** and methyl or ethyl propiolate or dialkyl acetylenedicarboxylates afforded the five-membered metallo-heterocycles **325** or **326** in good yields (Scheme 87) <2002ZAAC803>.



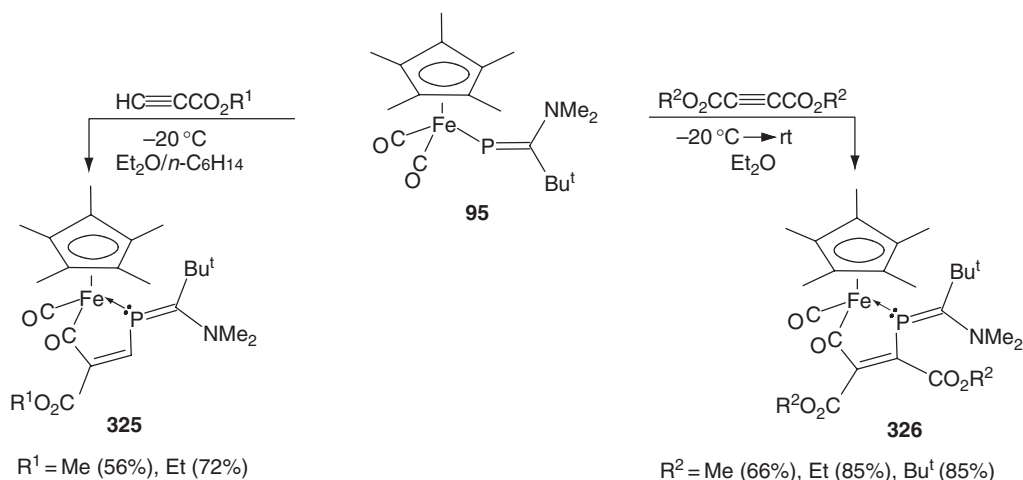
Scheme 84



Scheme 85

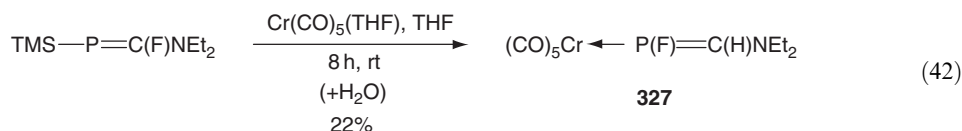


Scheme 86



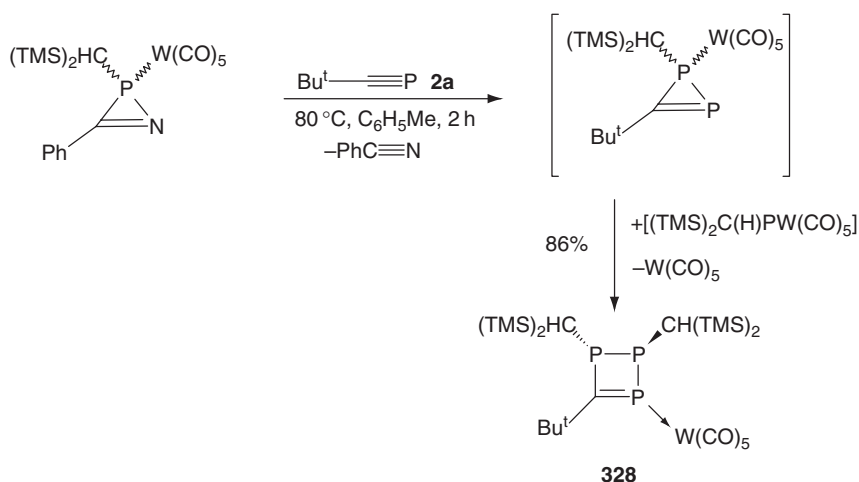
Scheme 87

Unexpectedly, the reaction of phosphalkene $\text{TMSP}=\text{C}(\text{F})\text{NEt}_2$ with $\text{Cr}(\text{CO})_5(\text{THF})$ in THF at 25°C did not furnish the corresponding pentacarbonyl complex, but instead the η^1 -fluorophosphalkene complex **327** was isolated as lemon-yellow microcrystals. It was assumed that the ligand $\text{FP}=\text{C}(\text{H})\text{NEt}_2$ of **327** resulted from hydrolysis of $\text{TMSP}=\text{C}(\text{F})\text{NEt}_2$ and rearrangement of initially formed $\text{HP}=\text{C}(\text{F})\text{NEt}_2$ in the coordination sphere of the metal (Equation (42)) <2000ZAAC1141>.



Phosphalkyne **2a** served as a source for the $\text{P}=\text{C}$ double bond in the first *trans*-1,2-dihydro-1,2,3-triphosphete tungsten complex.

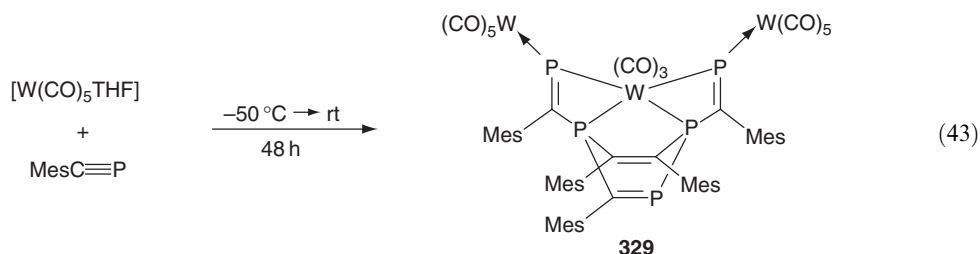
Thermolysis of a 2*H*-azaphosphirene complex in toluene at 80°C in the presence of **2a** produced complex **328** as yellow solid (Scheme 88).



Scheme 88

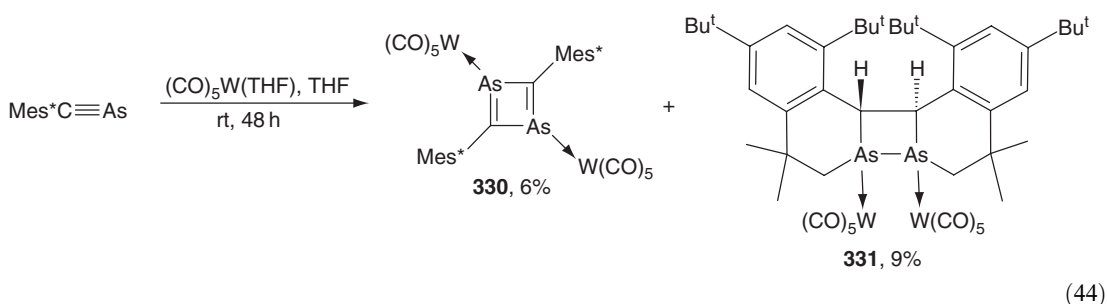
The transient 1*H*-diphosphirene complex could not be detected. Obviously rapid ring extension by a $[(\text{TMS})_2\text{C}(\text{H})\text{PW}(\text{CO})_5]$ unit and loss of $[\text{W}(\text{CO})_5]$ was responsible for the spontaneous formation of the observed product **328**. If, however, **2a** was replaced by aminophosphalkyne $\text{Pr}^i(\text{TMS})\text{NC}\equiv\text{P}$ the transformation stopped at the stage of corresponding 1*H*-diphosphirene complex <1995CC2113>.

Pentamerization of $\text{MesC}\equiv\text{P}$ was achieved by reacting the phosphalkyne with $\text{W}(\text{CO})_5\text{THF}$ in a THF/*n*-hexane mixture in the temperature range of -50 to 25°C . Product **329** was isolated from a complex mixture in low yield as an orange crystalline solid (Equation (43)) <1999AG(E)3183>.



5.23.2.2 Tricoordinate As Functions— $\text{RC}(\text{AsX}^1\text{Y})\text{X}^2$

The reaction of $\text{Mes}^*\text{C}\equiv\text{As}$ with $\text{W}(\text{CO})_5\text{THF}$ at room temperature over 48 h resulted in the low-yield formation of the red complex **330** and the yellow complex **331**. Most of the employed arsaalkyne was, however, recovered unaffected (Equation (44)) <1996CC631>.



5.23.2.3 Tricoordinate Sb and Bi Functions— $\text{RC}(\text{EX}^1\text{Y})\text{X}^2$ (E = Sb, Bi)

Representatives of such types of compounds are unknown as of early 2003.

5.23.3 TETRACOORDINATE P, As, Sb, AND Bi FUNCTIONS— $\text{R}^1\text{C}(\text{PR}_3^2)\text{X}$, $\text{R}^1\text{C}(\text{AsR}_3^2)\text{X}$, $\text{R}^1\text{C}(\text{SbR}_3^2)\text{X}$, AND $\text{R}^1\text{C}(\text{BiR}_3^2)\text{X}$

5.23.3.1 Tetracoordinate Phosphorus Functions— $\text{R}^1\text{C}(\text{PR}_3^2)\text{X}$

5.23.3.1.1 Introduction

Phosphorus ylides or methylene phosphoranones are accessible by several synthetic routes, the most prominent being the deprotonation of phosphonium salts. Phosphonium salts are frequently intermediates in the reactions of ylides with electrophiles, and in these cases are rapidly deprotonated by the parent ylide to afford novel functionalized ylides (transylation). The conversion of tertiary phosphanes into *P*-haloylides by carbon tetrahalides also involves the deprotonation of a transient phosphonium ion by the trihalomethanide anion. Since the first report on phosphorus ylides in COFGT (1995) <1995COFGT(5)875> a series of reviews and text books on ylide chemistry have appeared <1996CRV1641, 1996T1855, 1998JOM(557)37, 1999JCS(D)4111, B-1999MI523-06, 2001SL1065>.

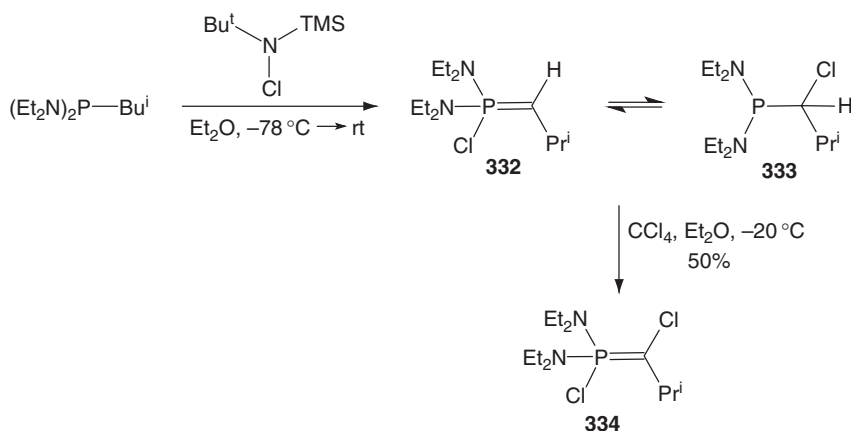
5.23.3.1.2 Halogen derivatives— $R^I C(PR_3^2)X$ ($X = F, Cl, Br, I$)

(i) Fluorine derivatives— $R^I C(PR_3^2)F$

In the literature on α -fluoroylides no isolable and well-characterized species with fluoromethylene functions are described. Instead the *in situ* generation of such species and their subsequent conversion into fluoroalkene derivatives by the Wittig reaction is the main research interest <1996CRV1641, 1997CJC1315, 2002SL1281>.

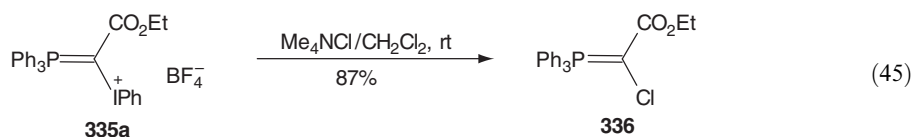
(ii) Chlorine derivatives— $R^I C(PR_3^2)Cl$

(a) *From ylides.* The reaction of $(Et_2N)_2P-Bu^i$ with the sterically hindered *N*-chloro-trimethylsilyl-*t*-butylamine occurred smoothly in diethyl ether at -70 to $20^\circ C$ to give the *P*-chloroylide **332**. Ylide **332** is stable in solution for several hours. On heating or distillation in vacuo it rearranged into the α -chloroalkylphosphane **333** until an equilibrium mixture **332**, **333** in the ratio 4:1 was reached. This mixture reacted with carbon tetrachloride to afford the *P,C*-dichlorinated ylide **334** as an oil (Scheme 89) <1995PS(102)133, 1998HAC219>.



Scheme 89

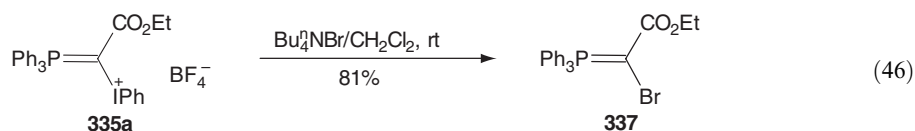
The polarity of the α -carbon in an ylide is reversed through introducing hypervalent iodine groups at this position and enables the ylides to react with nucleophiles. In keeping with this, reaction of **335a** with tetramethylammonium chloride cleanly led to the replacement of iodobenzene and the formation of the *C*-chloroylide **336** (Equation (45)).



If the same reaction was carried out in the presence of aldehydes, functionalized chloroalkenes were efficiently generated <2002JOC8261, 2002TL6823>. Moreover, *in situ* prepared α -chloroylides have also found application in the condensation with cyclic anhydrides <1997CJC1315>.

(iii) Bromine derivatives— $R^I C(PR_3^2)Br$

Analogous treatment of ylide **335a** with tetrabutylammonium bromide gave rise to the formation of the α -bromoylide **337** (Equation (46)). In the presence of aldehydes this substitution reaction was utilized to prepare for bromoalkenes <2002JOC8261, 2002TL6823>.

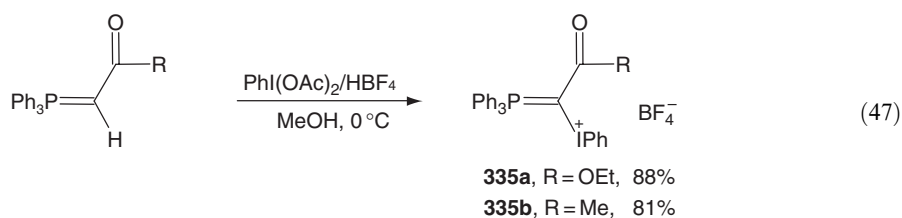


α -Bromoylides, prepared *in situ* from carbonyl-stabilized ylides, *N*-bromosuccinimide, and K_2CO_3 , were successfully converted into the corresponding alkenes, when treated with aldehydes or cyclic anhydrides <1997CJC1315>.

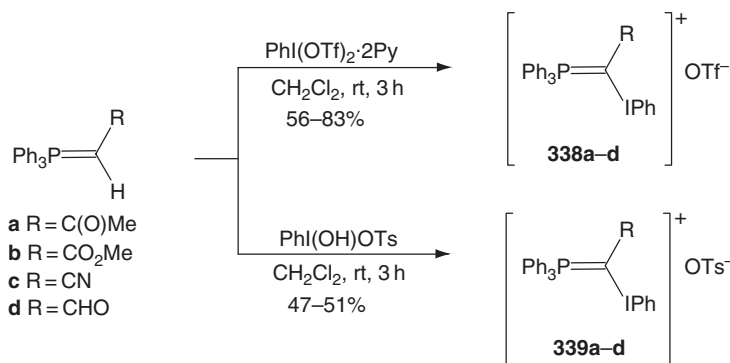
(iv) Iodine derivatives— $\text{R}^1\text{C}(\text{PR}_3)_2\text{I}$

Mirroring the chemistry of the corresponding α -bromoylides, the *in situ* preparation of α -iodoylide $\text{Ph}_3\text{P}=\text{C}(\text{I})\text{CO}_2\text{Bu}^t$ was effected by mixing $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Bu}^t$, *N*-iodosuccinimide, and K_2CO_3 in dichloromethane. The formed ylide was subsequently trapped by reaction with benzaldehyde or phthalic anhydride to give (*Z*)/(*E*) mixtures of iodoalkenes in 87% and 93% yield, respectively <1997CJC1315>.

Several stable phosphorus ylides **335** with α -aryliodonium substituents were previously synthesized by reacting an appropriate carbonyl-stabilized ylides with $\text{ArI}(\text{OAc})_2$ in the presence of HBF_4 <1984JA6082>. This transformation was further developed particularly because of the synthetic use of α -hypervalent iodine-functionalized ylides (Equation (47)) <2002JOC8261>.

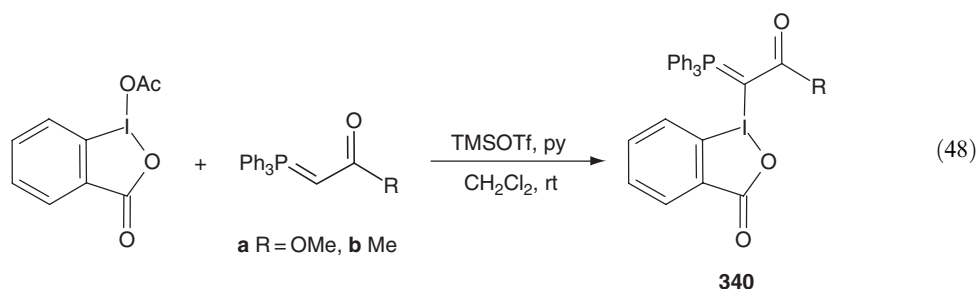


The iodonium triflates **338** were prepared as microcrystalline, off-white solids in good yield by the reaction of ylides $\text{Ph}_3\text{P}=\text{CHR}$ with the pyridine complex of iodobenzene ditriflate under mild conditions. The use of the pyridine/ $\text{PhI}(\text{OTf})_2$ adduct was crucial for the success of the reaction, as the alternative application of $\text{PhIO}/\text{Tf}_2\text{O}$ only led to the precipitation of a black tar due to the strongly acidic character of this reagent. The tosylates **339** were conveniently synthesized by treatment of $\text{Ph}_3\text{P}=\text{CHR}$ with $\text{PhI}(\text{OH})\text{OTs}$ (Koser's reagent) in CH_2Cl_2 (Scheme 90) <2002TL2359>.



Scheme 90

The series of reagents for ylide-iodation was successfully extended to acetoxybenziodoxole. Accordingly, compounds **340a,b** were obtained by the reaction of the corresponding ylide with acetoxybenziodoxole in the presence of trimethylsilyl triflate and pyridine. The products were isolated as stable white microcrystalline solids in moderate yields and authenticated by single X-ray analyses (Equation (48)) <2002JA11614>.



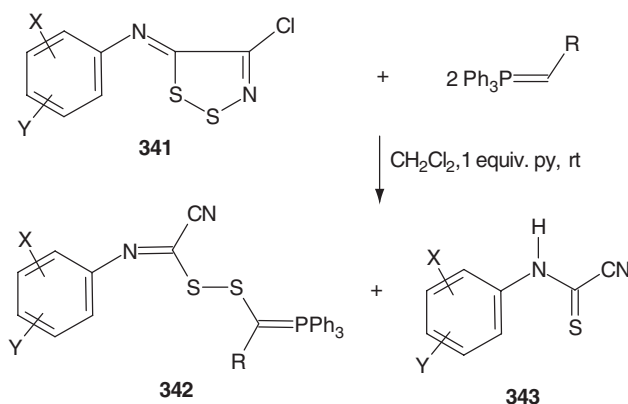
5.23.3.1.3 Chalcogen derivatives— $R^1C(PR_3^2)ER_n^3$ ($E = O, S, Se, Te$)

(i) Oxygen derivatives— $R^1C(PR_3^2)OR^3$

Generally, stable α -oxygen-functionalized ylides are rare, which is understandable if one considers the destabilizing effect of oxygen atoms at carbanionic centers due to the lack of π -acceptor qualities. Accordingly, no new acyclic derivatives $R^1C(PR_3^2)OR^3$ have been described recently.

(ii) Derivatives with dicoordinate sulfur— $R^1C(PR_3^2)SR^3$

(a) *From ylides.* In COFGT (1995) a variety of useful methods to functionalize phosphorus ylides with sulfur-containing groups were discussed <1995COFGT(5)875>. Previously 5-arylimino 4-chloro-5*H*-1,2,3-thiazoles **341** were employed for the introduction of a novel sulfur substituent at the α -carbon atom of carbonyl-functionalized ylides. Solutions of the heterocycles **341** in CH_2Cl_2 were treated with an equivalent amount of pyridine before 2 equiv. of the ylide were added to the solution. Chromatographic work-up after 3 h furnished the products **342** in moderate-to-good yields. It was demonstrated that pyridine was essential for a high yield of compounds **342**. In the absence of pyridine the yields of **343** increased at the expense of the desired product (Scheme 91, Table 3) <1996TL869>.

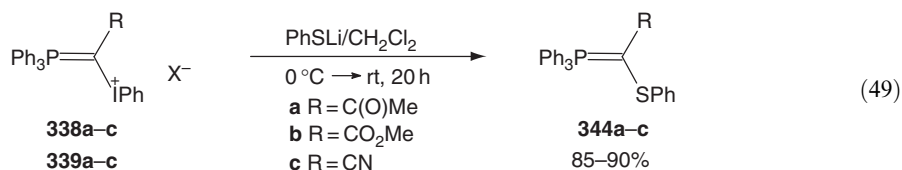


Scheme 91

The iodonium-functionalized ylides **338a–c** and **339a–c** are well-suited candidates for the introduction of a thiophenolate group into the α -position (Equation (49)) <2002TL2359>.

Table 3 Preparation of aryliminocyanomethyl dithiomethylenephosphoranes from 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles

342	X	Y	R	Yield (%)
a	4-MeO	H	CO ₂ Et	69
b	4-Me	H	CO ₂ Et	81
c	2-Cl	H	CO ₂ Et	41
d	4-Cl	H	CO ₂ Et	75
e	4-Br	H	CO ₂ Et	78
f	4-NO ₂	H	CO ₂ Et	70
g	2-Me	4-NO ₂	CO ₂ Et	74
h	4-MeO	H	COMe	79
i	4-Me	H	COMe	77
j	4-Cl	H	COMe	70
k	4-Br	H	COMe	80
l	2-CN	H	COMe	68
m	3-NO ₂	H	COMe	76
n	4-NO ₂	H	COMe	76
o	2-Me	4-NO ₂	COMe	64
p	2-Me	H	4-ClC ₆ H ₄ CO	48
q	2-Me	4-NO ₂	4-ClC ₆ H ₄ CO	63
r	4-MeO	H	CN	53
s	2-Me	H	CN	48
t	2-Me	4-NO ₂	CN	45

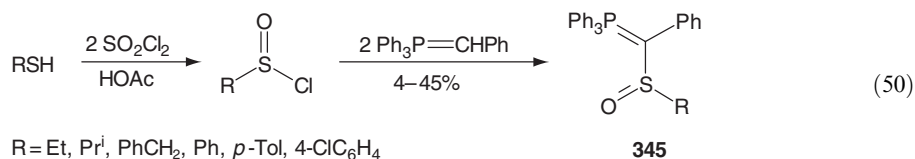


In the presence of benzaldehyde the *in situ* generated ylides **344a–c** underwent a Wittig-reaction to give the corresponding alkenyl(phenyl)sulfanes (40–50% yield).

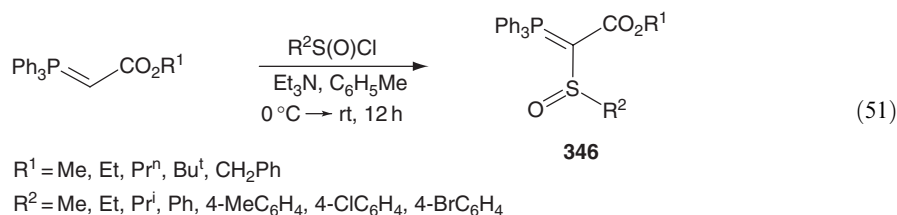
The nucleophilic substitution of iodobenzene from ylide **335a** was also accomplished with sodium thiophenolate or by reacting equimolar amounts of the ylide, thiophenol, and K₂CO₃ in acetonitrile (84% yield) <2002JOC8261, 2002TL6823>.

(iii) Derivatives with tricoordinate sulfur—R¹C(PR₃)SR³R⁴

A series of α-sulfinylylides **345** was prepared in low-to-moderate yields by reaction of 2 equiv. of Ph₃P=CHPh with sulfinyl chlorides RS(O)Cl. The required sulfinyl chlorides which are notoriously unstable and difficult to purify were used directly as obtained from the treatment of thiols RSH with 2 equiv. of SO₂Cl₂ and 1 equiv. of acetic acid (Equation (50)) <1998JCS(P1)3345>.



In an extension of a preliminary communication <1994CC805> full details for the syntheses of 18 carbonyl-stabilized α-sulfinyl phosphorus ylides were provided. They were readily formed as colorless or yellow crystals in low-to-moderate yields from alkoxycarbonylides and sulfinyl chlorides in the presence of triethylamine (Equation (51)) <1999JCS(P1)593>.



(iv) Derivatives with tetracoordinate sulfur— $\text{R}^1\text{C}(\text{PR}_3^2)\text{SO}_2\text{R}^3$

An efficient approach to α -sulfonylphosphonium ylides **347** involved the sulfonylation of ylides by arenesulfonyl fluorides in THF at 20 °C. The corresponding arenesulfonyl chlorides could not be employed in this transylation since this resulted in formation of α -chloroylides (Equation (52), Table 4) <1998JCS(P1)875>.

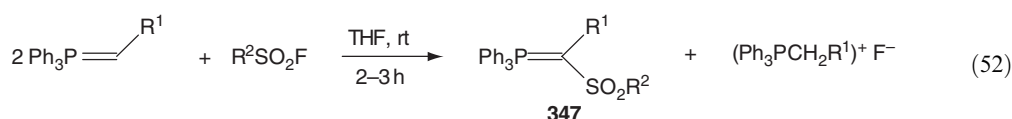
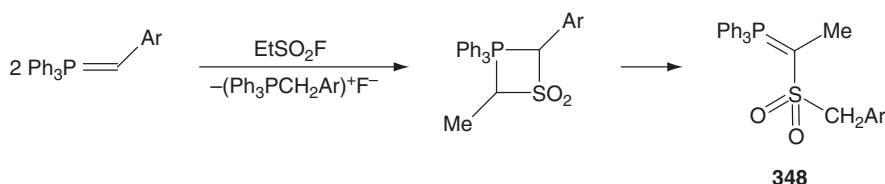


Table 4 Sulfonylation of ylides $\text{Ph}_3\text{P}=\text{CHR}^1$ by sulfonyl fluorides $\text{R}^2\text{SO}_2\text{F}$

347	R^1	R^2	Yield (%)
a	Me	Ph	71
b	Et	Ph	78
c	Me	<i>p</i> -Tol	79
d	Et	<i>p</i> -Tol	26
e	Pr^n	<i>p</i> -Tol	67
f	Ph	PhCH_2	82
g	<i>p</i> -Tol	PhCH_2	72
h	2-MeOC ₆ H ₄	PhCH_2	40
i	2-MeSC ₆ H ₄	PhCH_2	67

Rearranged products **348** were formed when ylides $\text{Ph}_3\text{P}=\text{CHAr}$ with bulky aryl groups like Ph, *o*-Tol, or 2-MeOC₆H₄ were submitted to reaction with ethanesulfonyl fluoride (Scheme 92).

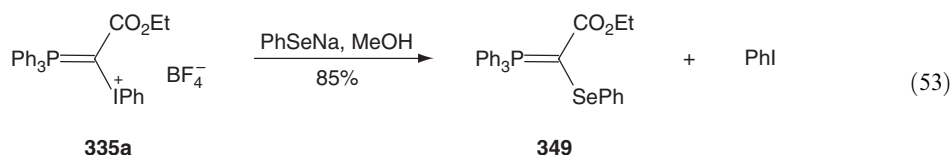


Scheme 92

This unexpected course of the reaction involved the [2+2]-cycloaddition between transient methylsulfene and the ylide. The ylides **347** and **348** were obtained as stable high-melting point solids <1998JCS(P1)875>.

(v) Derivatives with dicoordinate selenium— $\text{R}^1\text{C}(\text{PR}_3^2)\text{SeR}^3$

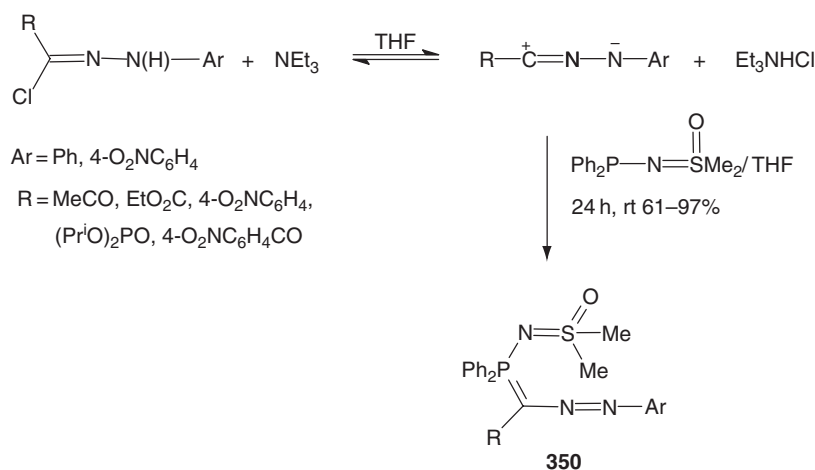
The preparation of the α -phenylselenenyl phosphonium ylide **349** from ylide **335a** and sodium phenylselenide in methanol at room temperature mirrors that of the corresponding sulfur derivative **344** (Equation (53)) <2002TL6823, 2002JOC8261>.



5.23.3.1.4 Nitrogen derivatives— $R^1C(PR_3^2)NR_n^3$

(i) Derivatives with dicoordinate nitrogen— $R^1C(PR_3^2)NR^3$

Crystalline ylides **350** resulted from the reaction of *N*-(diphenylphosphino)dimethyl-sulfoximide with *in situ* prepared nitrilimines in THF at 20 °C. The required nitrilimines were prepared by the dehydrohalogenation of the respective hydrazonoyl chlorides with triethylamine. For the success of this reaction, electron-withdrawing substituents R in the hydrazonoyl chlorides are required. The reaction of *C*-methyl-, *C*-phenyl-, *C*-4-bromophenyl-, and *C*-4-fluorophenyl-*N*-aryl-nitrilimines with $\text{Ph}_2\text{P}-\text{N}=\text{S}(\text{O})\text{Me}_2$ provided phosphonium salts which arose from the hydrochlorination of the initially formed ylides by triethylamine hydrochloride (Scheme 93) <1995ZOB1342>.

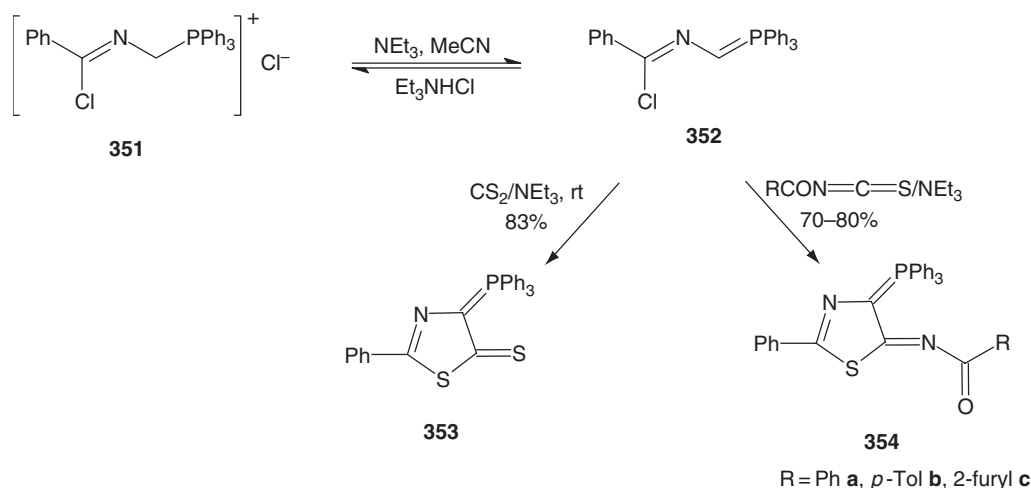


Scheme 93

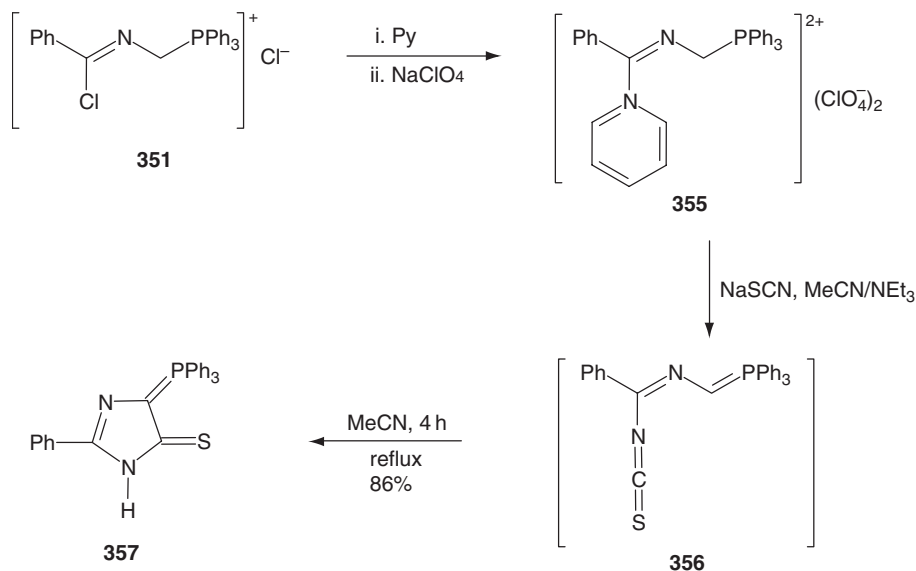
The imido-yl-functionalized ylide **352** was formed by dehydrochlorination of phosphonium salt **351** with triethylamine. From spectroscopic studies of the equilibrium mixture in acetonitrile solution it was evident, that ylide **352** is only present in small amounts. Despite the incomplete dehydrochlorination of **351** ylide **352** was found useful for the *in situ* cyclocondensation with carbon disulfide and acyl isothiocyanates to give the azole derivatives **353** and **354a–c** featuring the structural motif of α -*N*-functionalized phosphorus ylides (Scheme 94).

Treatment of salt **351** with pyridine and subsequent anion exchange with NaClO_4 furnished the dication **355**. Reaction of this salt with sodium thiocyanate and methylamine in anhydrous acetonitrile gave transient ylide **356**, which upon heating cyclized to afford ylide **357** (Scheme 95) <1999ZOB1652>.

Reaction of azomethine **358** with 2 equiv. of hexafluoroacetone in toluene at 20 °C afforded racemic 1,2- σ^5, λ^5 -oxaphosphetane **359** as a solid in 48% yield. The two postulated intermediates could not be detected. Chloroform solutions of compound **359** were unstable at room temperature, and upon stirring for 3 days the compound rearranged nearly quantitatively into ylide **360b**. A similar reaction between **358** and trifluoroacetophenone at 20 °C failed. Heating the mixture in toluene at 70 °C, however, led to the direct formation of **360a** (Scheme 96) <1998ZAAC650>.



Scheme 94

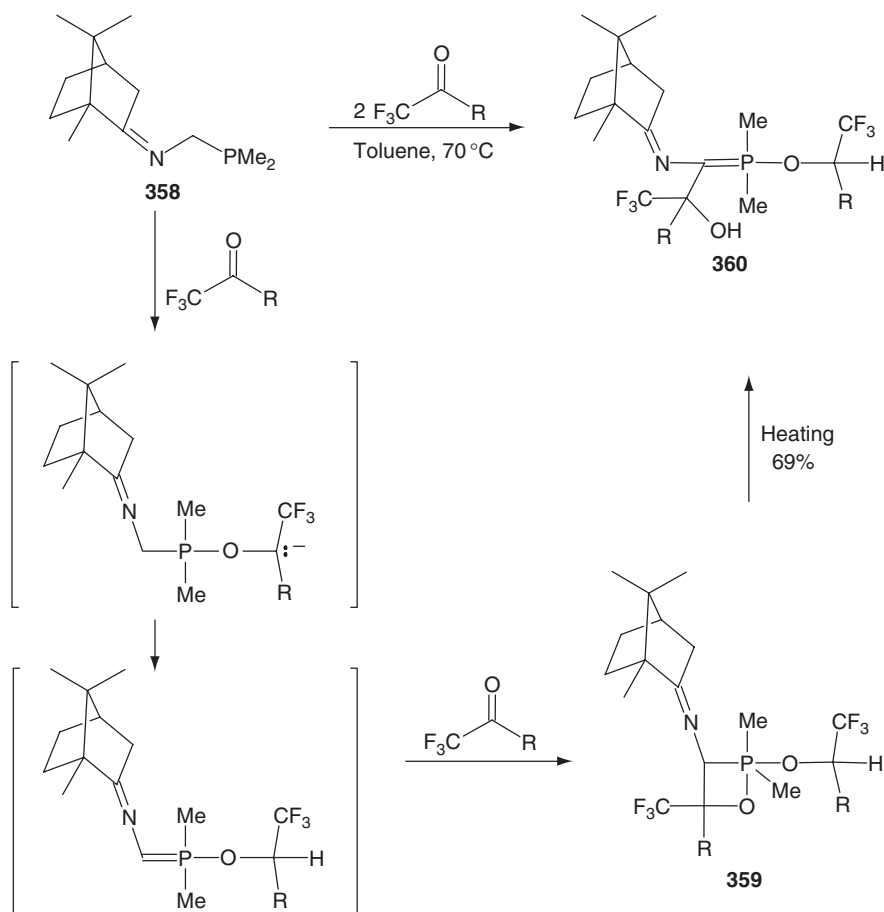


Scheme 95

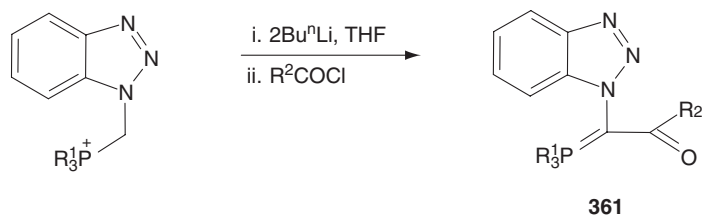
(ii) Derivatives with tricoordinate nitrogen— $\text{R}^1\text{C}(\text{PR}_3^2)\text{NR}_2^3$

Quantum-chemical calculations have shown that tricoordinate nitrogen substituents destabilize the ylide carbanion. *C*-Amino-functionalized phosphorus ylides are therefore only stable, when a second substituent at the α -carbon atom has electron-accepting properties to compensate the electron-releasing effect of the amino group. Attempts to synthesize nonstabilized α -amino ylides have failed <B-1999MI523-05>.

A total of 17 ylides **361** were readily prepared by treating the corresponding phosphonium salts ($\text{R}^1 = \text{Ph}, \text{Bu}^n$) with *n*-butyllithium followed by the appropriate acid chloride (0.5 equiv.) (Equation (54), Table 5) <1997JCS(P1)3107>.



Scheme 96



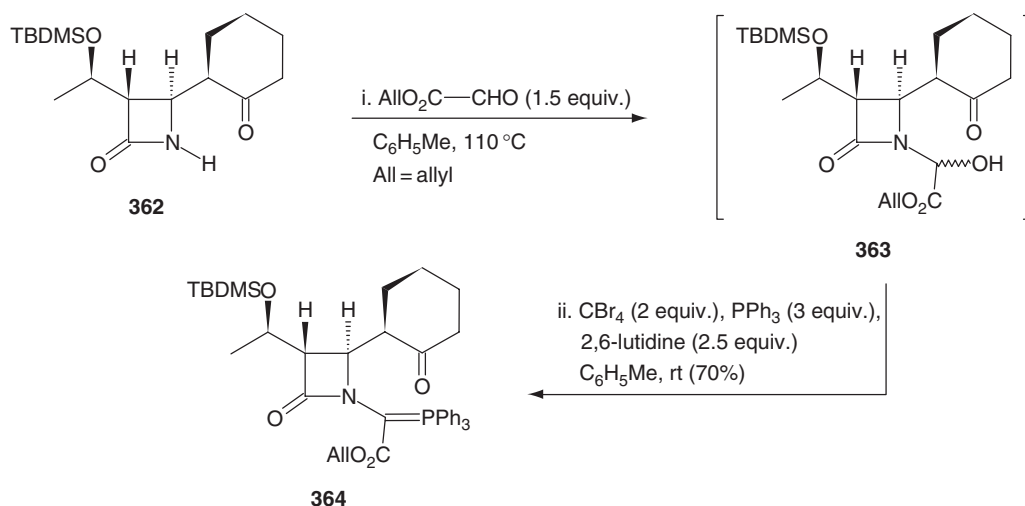
(54)

The key step in a synthesis of β -lactam antibiotics is the intramolecular Wittig-reaction of an ylide with an azetidinone substituent in the α -position. The standard method of generating phosphoranes such as **364** involves condensing azetidinone **362** with allyl glyoxylate under Dean and Stark conditions, chlorination of the resulting epimeric hemiaminals **363** with SOCl_2 and lutidine and then treating the crude product with PPh_3 and 2,6-lutidine. The intermediate chloro derivatives were quite moisture sensitive and unstable, necessitating their immediate conversion into ylides **364**. These inconveniences were avoided by a protocol, where hemiaminal **363** was treated with the $\text{CBr}_4/\text{PPh}_3$ system. Thereby the reactive bromide was directly converted into a phosphonium salt in the presence of an excess of the phosphane. Excess base present in the process facilitated for the formation of the ylide (Scheme 97) <1997TL3569>.

Several other azetidinone-functionalized ylides were produced analogously and were subsequently submitted to an intramolecular Wittig-reaction <1997BMCL2061, 2000CPB126, 1995TL4487>.

Table 5 Preparation of benzotriazol ylides **361**

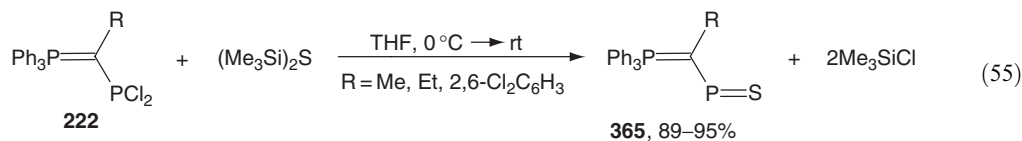
361	R^1	R^2	Yield (%)
a	Ph	Ph	20
b	Ph	Bu ^t	27
c	Ph	Me	83
d	Ph	4-MeOC ₆ H ₄	28
e	Ph	4-ClC ₆ H ₄	96
f	Ph	<i>p</i> -Tol	78
g	Ph	4-O ₂ NC ₆ H ₄	78
h	Ph	2-MeOC ₆ H ₄	50
i	Ph	2-MeSC ₆ H ₄	25
j	Bu ⁿ	Ph	57
k	Bu ⁿ	Bu ^t	56
l	Bu ⁿ	Me	69
m	Bu ⁿ	4-MeOC ₆ H ₄	89
n	Bu ⁿ	4-ClC ₆ H ₄	66
o	Bu ⁿ	<i>p</i> -Tol	77
p	Bu ⁿ	4-O ₂ NC ₆ H ₄	95
q	Bu ⁿ	Et	12

**Scheme 97**

5.23.3.1.5 Group 15 element derivatives— $R^1\text{C}(\text{PR}_3^2)\text{ER}_n^3$ ($E = \text{P, As, Sb, Bi}$)

(i) Derivatives with dicoordinate phosphorus— $R^1\text{C}(\text{PR}_3^2)\text{PR}^3$

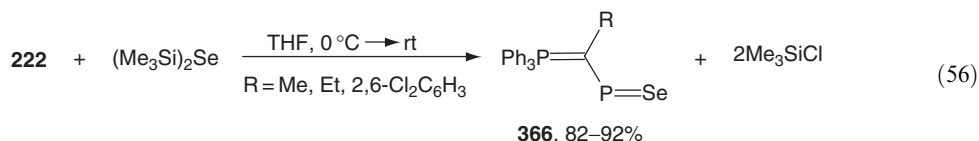
Orange crystalline ylides **365** with $\text{P}=\text{S}$ functions were isolated from the reaction of $\text{Ph}_3\text{P}=\text{C}(\text{R})\text{PCl}_2$ **222** with a disilyl sulfide in THF at $0-20^\circ\text{C}$ <1995CB1207> (Equation (55)).



Compounds **365** were previously prepared by thiolysis of the precursors with sodium sulfide in THF <1993AG(E)1089>.

In contrast to the straightforward formation of alkyl-substituted derivatives **365**, the aryl-substituted ylides ($\text{R} = \text{Ph, } n\text{-Tol}$) were unstable and rapidly decomposed to a complex mixture of products.

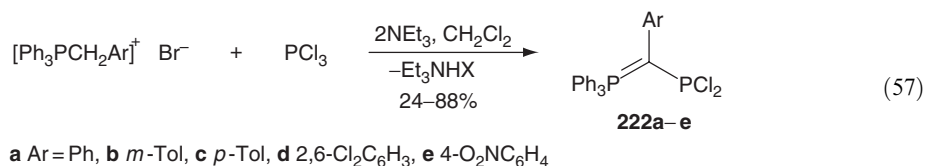
The red-to-violet crystalline selenoxophosphanes $\text{Ph}_3\text{P}=\text{C}(\text{R})\text{P}=\text{Se}$ **366** were prepared similarly from **222** and sodium selenide or alternatively $(\text{Me}_3\text{Si})_2\text{Se}$. The second route was preferred because of the absence of solid by-products (Equation (56)).



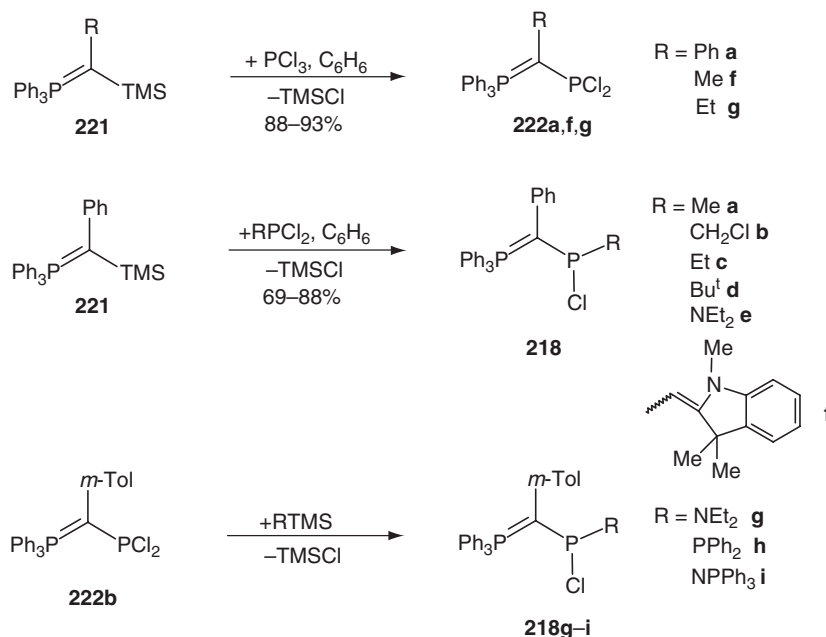
As with the thioxo derivative the success of this transformation is limited to alkyl-substituted ylides or to such arylated species where the *o*-positions of the ring are blocked by groups other than hydrogen atoms <1995CB1207>.

(ii) Derivatives with tricoordinate phosphorus— $\text{R}^1\text{C}(\text{PR}_3^2)\text{PR}_2^3$

(a) From phosphonium salts. The methylene group of benzyltriphenylphosphonium bromide is sufficiently acidic to react at room temperature with phosphorus trichloride and triethylamine as an auxiliary base to give the C-aryl-substituted ylidyl dichlorophosphanes **222a–e**. In the case of **222e** a reaction temperature of -78°C was recommended to avoid side reactions (Equation (57)) <1995CB379, 1997JOM(529)87>.



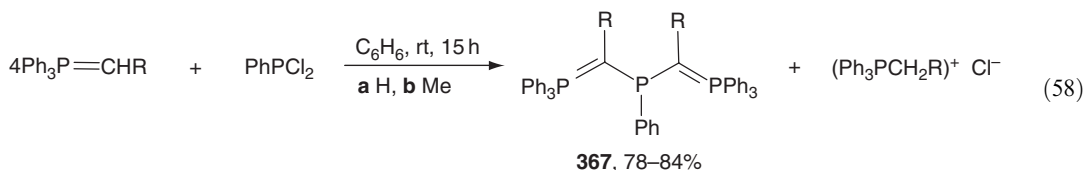
(b) From ylides. A more general route to phosphorus ylides which are functionalized in the α -position by a tricoordinate phosphorus atom makes use of the condensation of trimethylsilyl ylides $\text{Ph}_3\text{P}=\text{C}(\text{R})\text{TMS}$ with PCl_3 or organodichlorophosphanes RPCl_2 (Scheme 98).



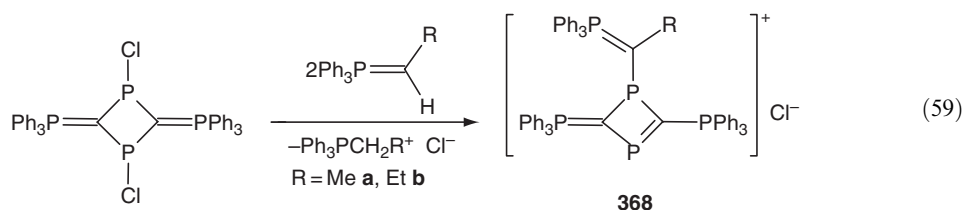
Scheme 98

In a different study, ylidyl dichlorophosphane **222b** served as a starting material and was reacted with trimethylsilyl-substituted amines, phosphanes, or iminophosphoranes (Scheme 98) <1996HC239>.

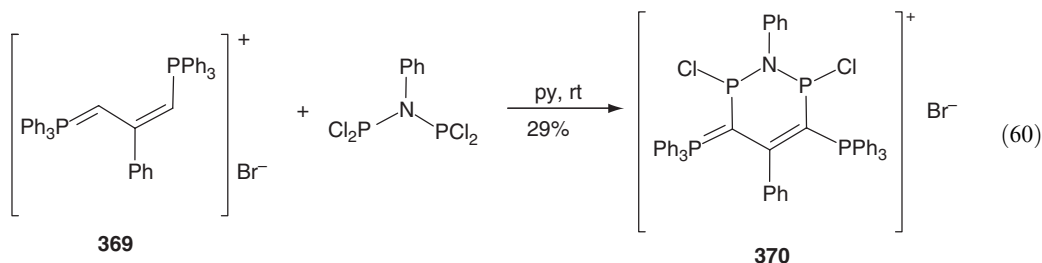
The reaction of highly nucleophilic ylides such as methylene- or ethylidene-triphenylphosphorane with phenyldichlorophosphane in a molar ratio 4:1 afforded the bis(ylidyl)phenylphosphanes **367a,b** (R = H, Me) as yellow-to-orange solids, respectively. This transformation proceeded via twofold transylidation (Equation (58)) <1996ZN(B)267>.



Reaction of a dichloro-substituted diphosphetane with 2 equiv. of ylides yielded the monosubstituted products **368a,b**. Due to negative hyperconjugation between the $\text{PCl}-\sigma^*$ -orbital and the occupied $2p_z$ -orbital at the ylidic carbon atoms the remaining chlorine substituent dissociated spontaneously from the four-membered ring (Equation (59)) <1997CB1519>.



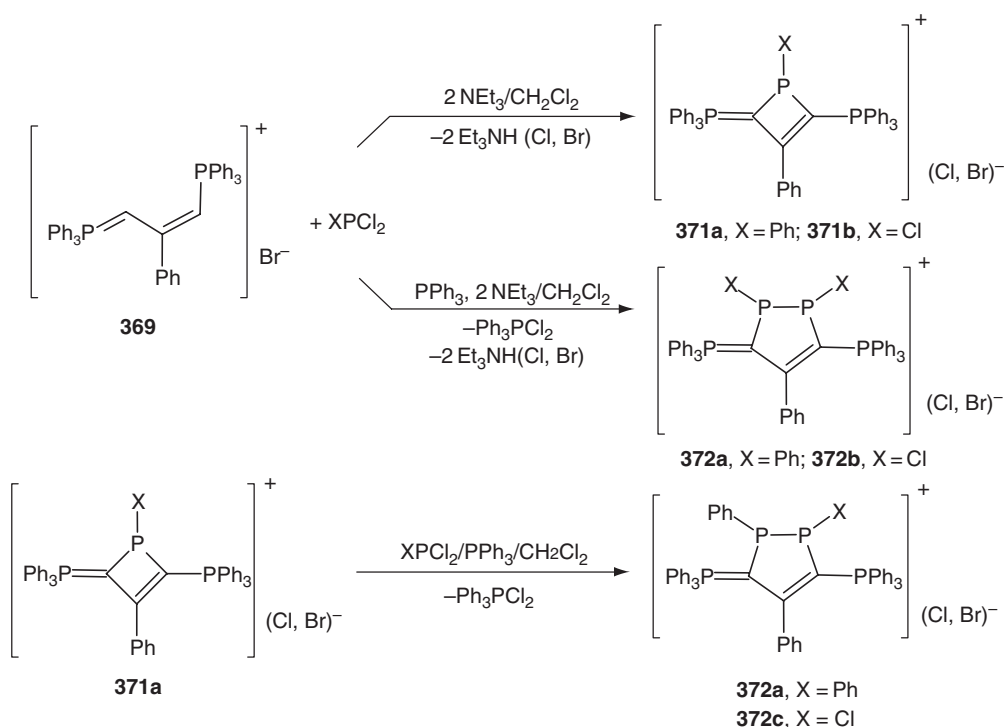
The smooth condensation of 2-phenyl-1,3-bis(triphenylphosphino)propenide bromide **369** with $(\text{Cl}_2\text{P})_2\text{NPh}$ in pyridine gave heterocycle **370**, which was separated from pyridinium halides by fractional crystallization (Equation (60)) <1996ZN(b)1761>.



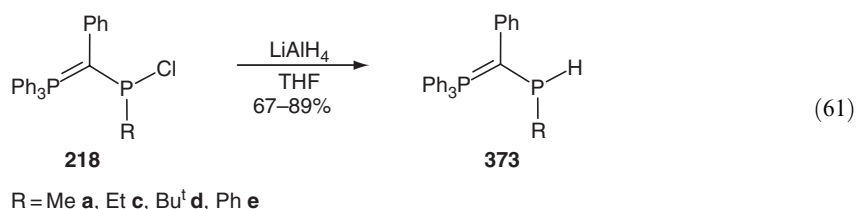
One equivalent of phenyldichlorophosphane or PCl_3 and 2 equiv. of triethylamine reacted with compound **369** yielding salts **371a,b** and minor amounts of compounds **372a,b** (**371a**:**372a** = 5:1). The by-products **372** were derived from the primary product **371** and a second molecule of the chlorophosphane by reductive P–P coupling and expansion of the four-membered ring, whereby **371** must serve as the reducing agent. Consequently, if starting material **369** was allowed to react with 2 equiv. of the dichlorophosphane XPCl_2 , 1 equiv. of PPh_3 as reducing agent and again 2 equiv. of NEt_3 the 3,5-bis(triphenylphosphonio)-4-phenyl-1,2-dihydro-1,2-diphospholide halides **372** became the main products in 80–90% yield (Scheme 99) <1996CEJ221>.

Compound **372a** was also formed when 1 equiv. each of PhPCl_2 and PPh_3 were added to a CH_2Cl_2 solution of **371a**. These results clearly reveal compounds **371** as intermediates in the reaction sequence leading from **369** to **372**.

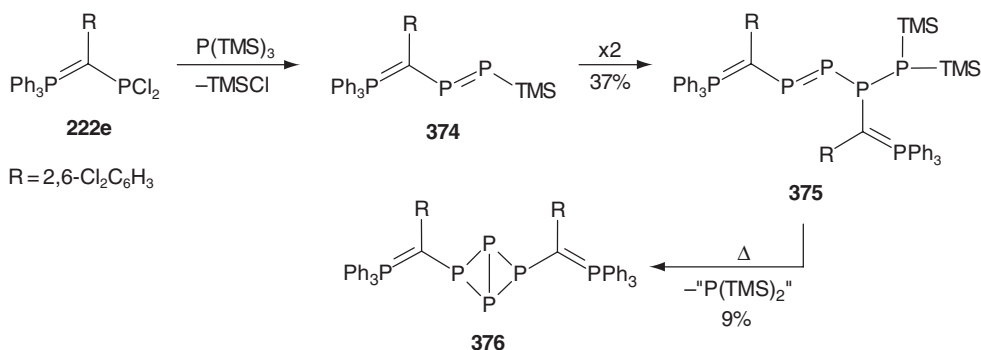
The chlorophosphanyl benzylidene phosphanes **218** were converted to the phosphanyl derivatives **373** by reduction with LiAlH_4 at -40°C in THF solution (Equation (61)) <1998EJI381>. This synthesis could not be extended, however, to ylide precursors with a methyl substituent at the ylidic carbon atom.



Scheme 99

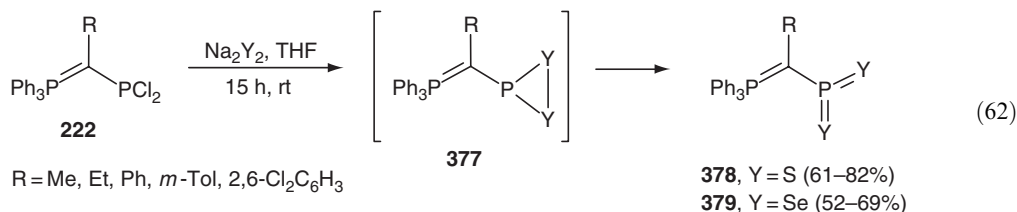


The reaction of ylidyldichlorophosphanes **222** with $\text{P}(\text{SiMe}_3)_3$ led to the known bis-(ylidyld)phosphonium chlorides $[\{\text{Ph}_3\text{P}=\text{C}(\text{R})\}_2\text{P}]^+ \text{Cl}^-$ **220** <1995CB379, 1997JOM(529)87>. However, for $\text{R} = 2,6\text{-Cl}_2\text{C}_6\text{H}_3$ the condensation in THF furnished thermolabile diphosphene **374**, which in solution dimerized within three days to orange **375** featuring a tetraphosphene structure. In an attempt to recrystallize a crude mixture of **374** (20%) and **375** (70%) from a warm mixture (50°C) of benzene and CH_2Cl_2 the bicyclo[1.1.0]tetraphosphene derivative **376** was obtained in low yield (Scheme 100) <1997CB1801>.



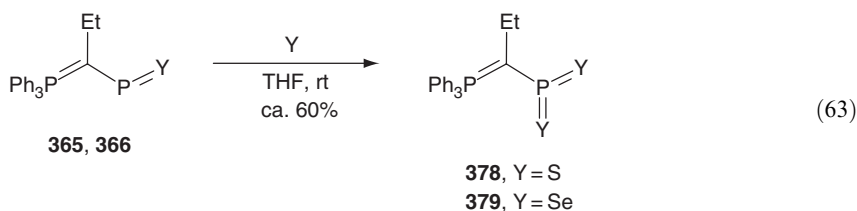
Scheme 100

The preparation of the ylidylthiophosphoranes **378** was based on a substitution reaction between **222** and sodium disulfide. Dithiaphosphirane **377** was postulated as an initial product, which was converted to the final product by scission of the S—S bond (Equation (62)) <1995CB1207>.



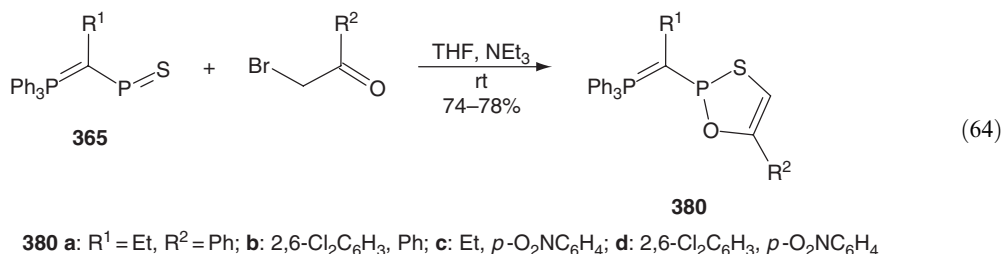
Analogously the corresponding diselenides **379** were obtained by reacting $\text{Ph}_3\text{P}=\text{C}(\text{R})\text{PCl}_2$ with sodium diselenide in THF (Equation (62)).

The monosulfide $\text{Ph}_3\text{P}=\text{C}(\text{Et})\text{P}=\text{S}$ **365** as well as the corresponding monoselenide **366** were smoothly oxidized to **378** or **369** by treatment with elemental sulfur or grey selenium, respectively (Equation (63)) <1995CB1207>.



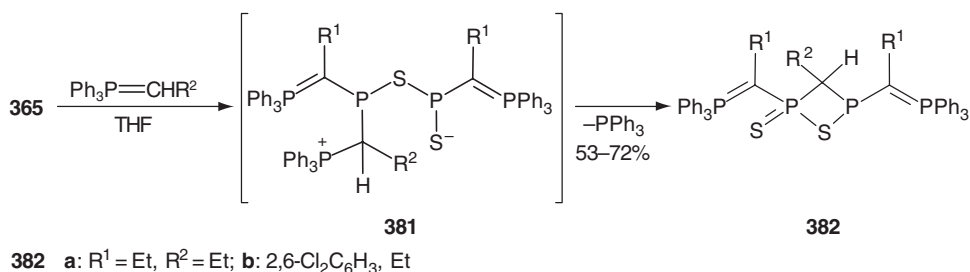
Ylidyl thioxophosphanes and ylidyl selenoxophosphanes are susceptible to electrophilic as well as nucleophilic attacks at the P=Y-moiety.

Thioxophosphanes **365** ($\text{R} = \text{Et, } 2,6\text{-Cl}_2\text{C}_6\text{H}_3$) were reacted with phenacyl bromides in the presence of an excess of NEt_3 to yield the 2-ylidyl-1,3,2-oxathiaphospholes **380** as yellow ($\text{R}^2 = \text{Ph}$) or red ($\text{R}^2 = p\text{-O}_2\text{NC}_6\text{H}_4$) crystals (Equation (64)) <1995ZN(B)1543>.



The corresponding 2-ylidyl-1,3,2-oxaselenaphospholes were also formed but could not be isolated due to rapid selenium transfer (see below).

When propylidene triphenylphosphorane was added to the thioxophosphanes **365** in a molar ratio of 1:2 in THF at room temperature or at -78°C the 1,3-bisylidyl functionalized 1,2,4-thiadiphosphetanes **382** were formed as two diastereoisomers (Scheme 101).



Scheme 101

The formation of **382** was probably initiated by the attack of the propylidene-phosphorane on the dicoordinate phosphorus of the thioxophosphane. The sulfur atom of the primary adduct then interacted in the same way with a second molecule of **365** to give intermediate **381**. The latter compound was eventually stabilized by ring closure and PPh_3 extrusion. The selenoxophosphane **366** ($\text{R} = \text{Et}$) reacted analogously. This reaction, however, was not straightforward, and the existence of a product analogous to **382** was supported only by ^{31}P NMR evidence <1995CB1015>.

(c) *From phosphalkenes*. As discussed previously bis(ylidyl)phosphenium cations **220** may also be addressed as phosphalkenes with a *P*-ylidyl- and a *C*-triphenylphosphonio-substituent. The cation **220a** exhibits sufficient electrophilicity at the dicoordinate phosphorus atom to add a variety of nucleophiles X^- with the result of bis(ylidyl)phosphanes **383** (Equation (65), Table 6) <1996ZN(B)267>. Moreover, the successful addition of LiBEt_3D , LiNHPH , $\text{NaN}(\text{SiMe}_3)_2$, KNC_4H_4 , NaOPPh_2 , and $\text{LiN}(\text{PPh}_2)_2$ was proven in an NMR experiment. This synthetic principle provides a route to compounds **383** where an alternative protocol would suffer from the non-existence of the required dichlorophosphanes XPCl_2 .

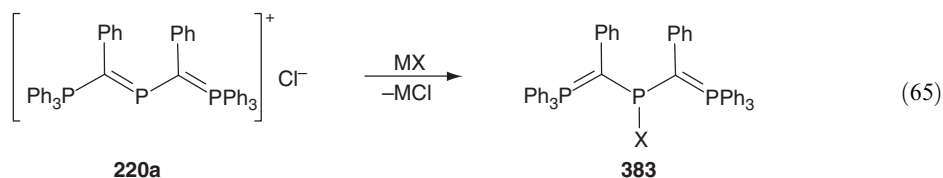
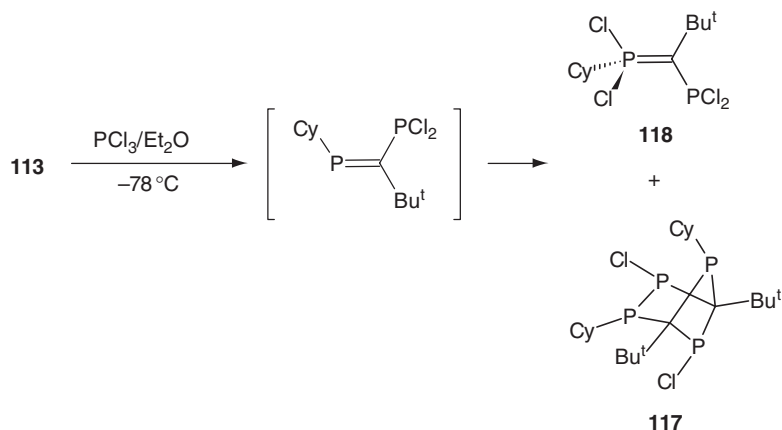


Table 6 Formation of bis(ylidyl)phosphanes **383**

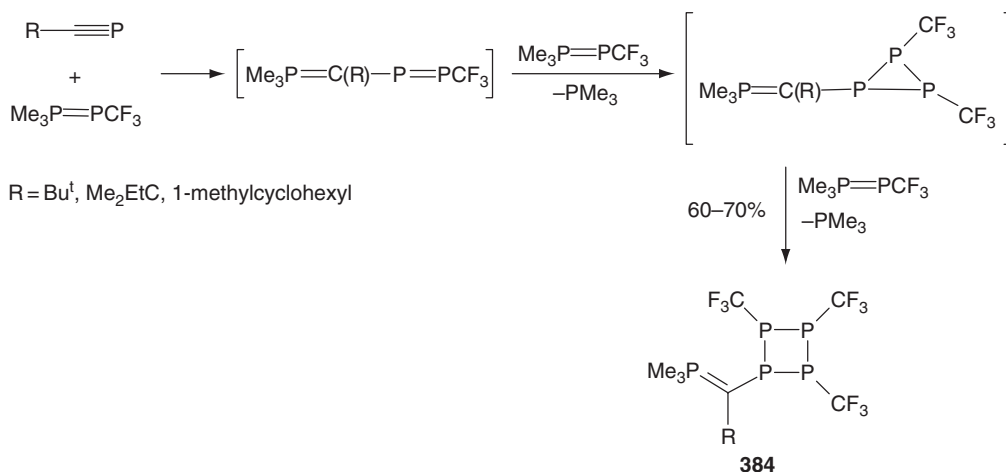
383	<i>MX</i>	<i>X</i>	<i>Yield (%)</i>
a	LiAlH_4	H	81
b	LiMe	Me	97
c	LiBu^n	Bu^n	99
d	LiPh	Ph	63
e	NaSnPh_3	SnPh_3	75
f	LiNPh_2	NPh_2	92
g	LiPPh_2	PPh_2	72

As already discussed in chapter 5.23.1.1.5 the reaction between phosphavinyl-Grignard reagent **113** and PCl_3 strongly depends on the stoichiometry employed. Treatment of **113** with 1 equiv. of PCl_3 at -78°C furnished compounds **117** (15% yield) and the ylide **118** in 5% yield. It was assumed that **118** resulted from a disproportionation process of the initially formed phosphalkene $\text{CyP}=\text{C}(\text{Bu}^t)\text{PCl}_2$. Accordingly, the reaction of **113** with PCl_3 at -78°C and subsequent addition of SO_2Cl_2 to the intermediate afforded ylide **118** as the sole phosphorus-containing product in 26% yield (Scheme 102) <2002NJC1209>.



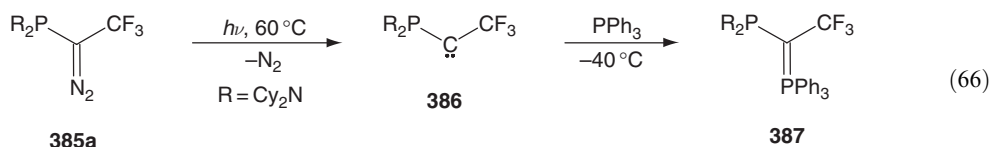
Scheme 102

(d) *From phosphalkynes.* As already discussed triphosphetene **121a** was quantitatively prepared by the treatment of phosphalkyne $\text{Pr}_2^i\text{N}-\text{C}\equiv\text{P}$ with $\text{Me}_3\text{P}=\text{PCF}_3$ in a molar ratio of 2:1. In contrast to this, the reaction of phosphalkynes $\text{RC}\equiv\text{P}$ ($\text{R} = \text{Bu}^t$, Me_2EtC , 1-methylcyclohexyl) with a threefold excess of $\text{Me}_3\text{P}=\text{PCF}_3$ in diethyl ether led to the yellow crystalline phosphorus ylides **384** as main products (Scheme 103) <1996CEJ208>.

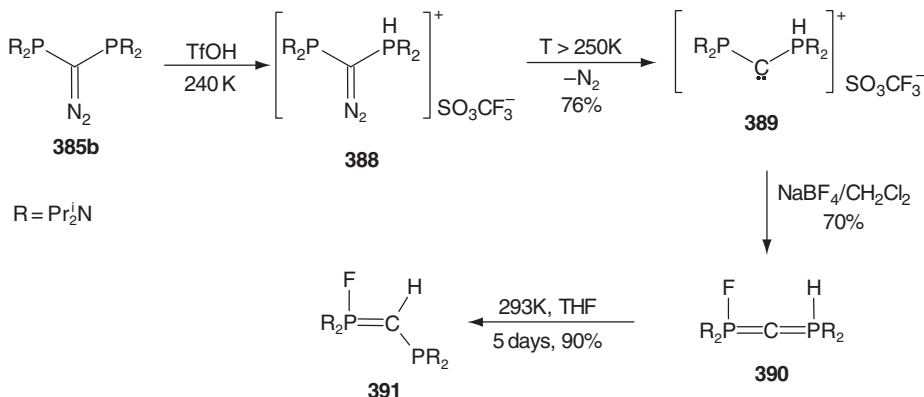


Scheme 103

(e) *From carbenes.* Photolysis of [bis(dicyclohexylamino)phosphanyl](trifluoromethyl)diazomethane **385a** in THF or diethyl ether at -60°C cleanly generated carbene **386**, which was trapped at -40°C with PPh_3 to quantitatively yield ylide **387** (Equation (66)) <2000SCI(288)834>.



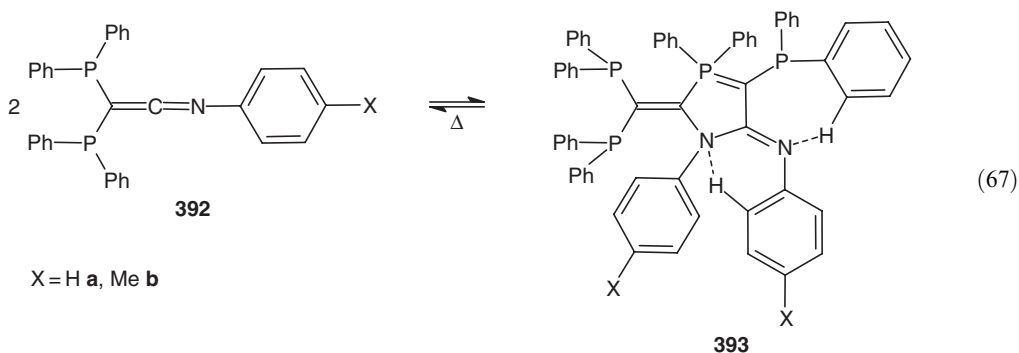
Diazomethane derivative $(\text{R}_2\text{P})_2\text{C}=\text{N}_2$ ($\text{R} = \text{Pr}_2^i\text{N}$) **385b** was protonated at 240 K by addition of triflic acid. The resulting cation **388** lost N_2 by warming to above 250 K to yield the stable cationic carbene **389**. Reaction of **389** with NaBF_4 in CH_2Cl_2 at room temperature afforded carbodiphosphorane **390**. Stirring a THF solution of **390** for 5 days at room temperature produced ylide **391** as a viscous oil (Scheme 104) <1996IC46>. Treatment of salt **389** with *t*-butyllithium in THF at -78°C led to the thermolabile carbodiphosphorane $\text{R}_2\text{P}(\text{H})=\text{C}=\text{P}(\text{H})\text{R}_2$ which at room temperature rearranged to $(\text{R}_2\text{P})_2\text{CH}_2$ via ylide $\text{R}_2\text{P}(\text{H})=\text{C}(\text{H})\text{PR}_2$ ($\text{R} = \text{Pr}_2^i\text{N}$).



Scheme 104

(f) *From diphosphanylketenimines.* Solutions of *N*-arylketenimines **392** (R = Ph, *p*-Tol) in different organic solvents are stable for weeks. However, when a hexane solution of **392** was very slowly concentrated to dryness under vacuum, and the process of adding and removing hexane was repeated at least three times, orange solids corresponding to the unsymmetrical dimer **393** with the structural feature of an ylide were formed. This dimerization is fully reversible.

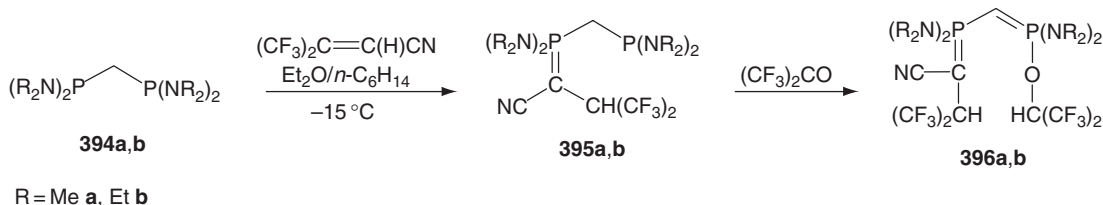
In contrast to this the analogous *N*-*o*-xylyl- or *N*-*t*-butyl-ketenimines did not dimerize at all (Equation (67)) <2000AG(E)1821>.



Intramolecular nonconventional CH to N hydrogen bonds seems to promote this novel type of [2 + 3]-cycloaddition.

(iii) *Derivatives with tetracoordinate phosphorus— $R^1C(PR_3^2)PR_3^3$*

(a) *From methylenediphosphanes.* Methylenediphosphanes **394a,b** rapidly add 1 equiv. of bis(trifluoromethyl)acrylonitrile in hexane solution at -15°C to give ylides **395a,b** almost quantitatively. These compounds were quantitatively converted into double ylides **396a,b** by treatment with hexafluoroacetone (Scheme 105) <2002EJI2985>.

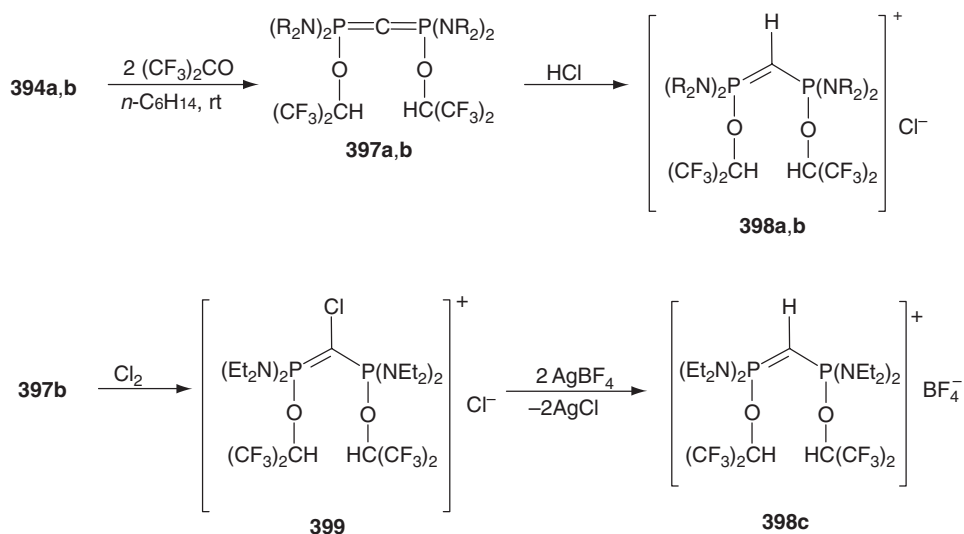


Scheme 105

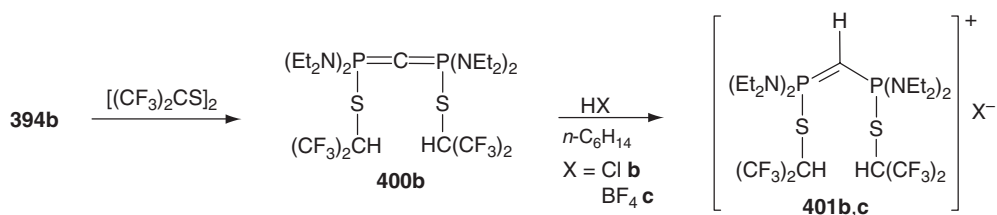
Slow bubbling of gaseous hexafluoroacetone through a hexane solution of **394a** or **394b** at 20°C afforded the thermolabile carbodiphosphoranes **397a,b**, which were converted by treatment with HCl into stable salts **398a,b** with the structural motif under discussion. By chlorination of **397b** and reaction of the resulting dichloride with 2 equiv. of AgBF_4 the corresponding tetrafluoroborate was obtained (Scheme 106) <1998CC1203, 1999EJI1665>.

Combination of compound **394b** and the dimer of hexafluorothioacetone in *n*-hexane at -40°C quantitatively gave the thermolabile carbodiphosphorane **400b**, which was protonated by HCl or HBF_4 in an ether/*n*-hexane mixture to the corresponding salts **401b,c**. However, the chloride decomposed in solution (toluene, CDCl_3). Derivative **401c** with the less nucleophilic BF_4^- ion was stable even in boiling CDCl_3 solution (Scheme 107) <2001EJI2377>.

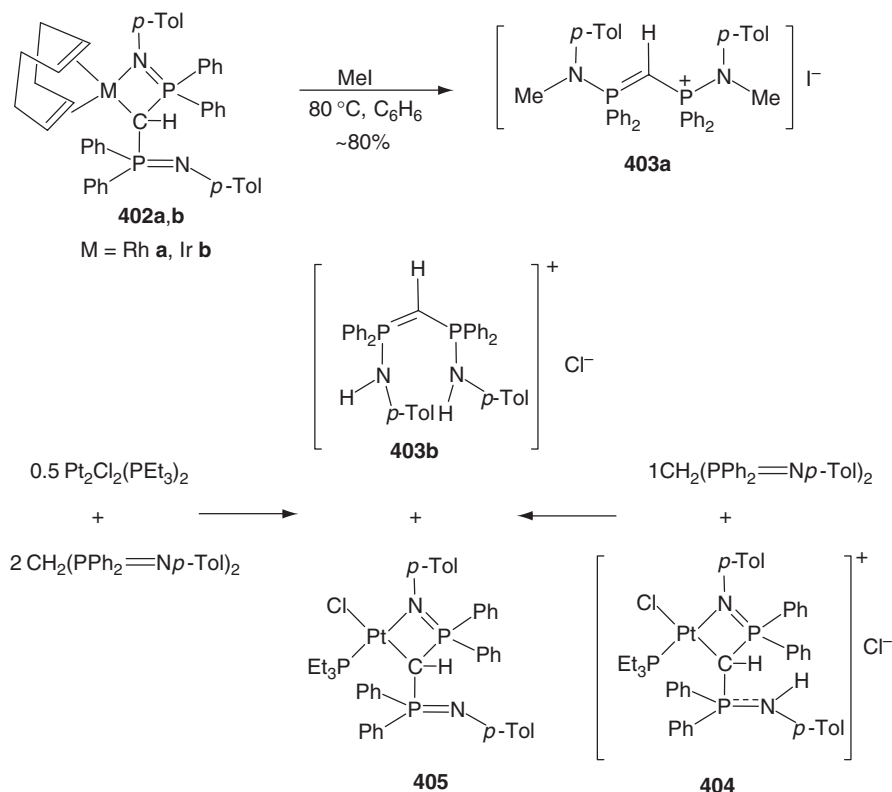
(b) *From bis(iminophosphoranyl)methanide complexes.* Refluxing complexes **402a** or **402b** with a tenfold excess of methyl iodide in benzene for 3 h yielded exclusively $[\text{MI}(\text{COD})_2]_2$ and the salt **403a** (Scheme 108) <1995ICA(235)77>.



Scheme 106



Scheme 107

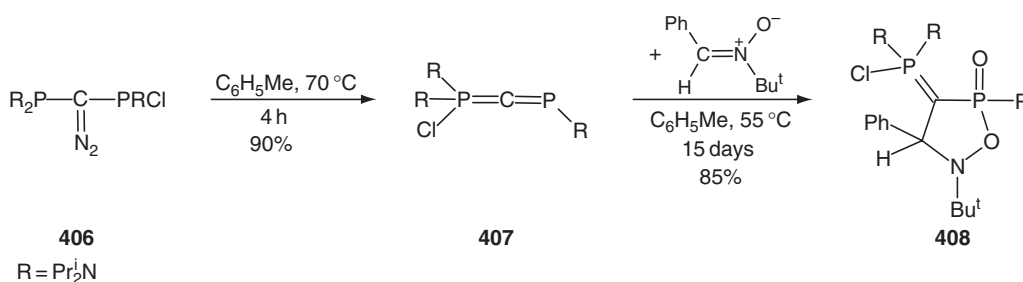


Scheme 108

When a toluene solution of complex **404** and 1 equiv. of the bis(iminophosphoranyl)methane was stirred at 20 °C, or alternatively the dimeric complex $\text{Pt}_2\text{Cl}_2(\text{PEt}_3)_2$ was allowed to react with a threefold excess of the ligand in the same solvent, neutral complex **405** was formed in addition to salt **403b**. The outcome of this reaction was enormously influenced by the metal-to-ligand ratio. Metal-to-ligand ratios of 1:1 or 2:1 invariably afforded the complex cation of **404** without the occurrence of **403b** (Scheme 108) <1995IC4092>.

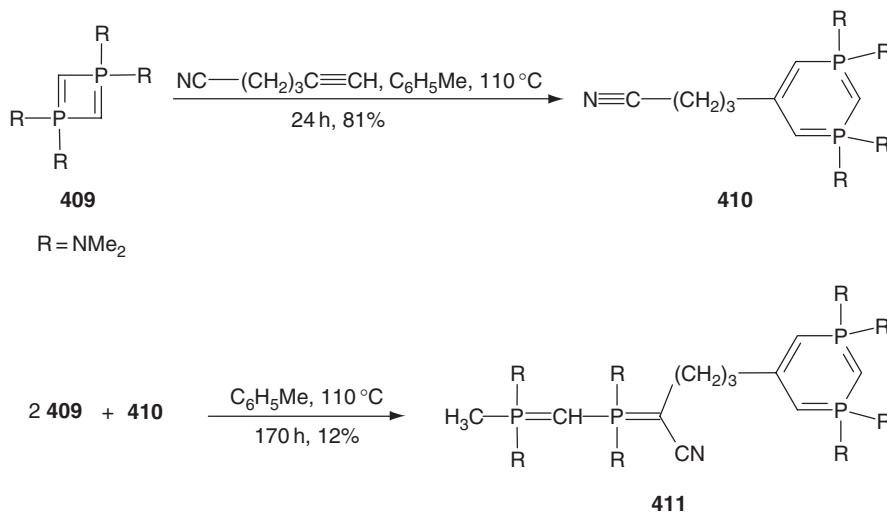
(c) *From phosphalkynes.* Compounds **151** formed from phosphalkynes **2** and triethyl- or tri-*n*-propylaluminum, respectively in diethyl ether (Scheme 35) also possess the structural features of a phosphorus ylide <1997JOM(539)61>.

(d) *From ylides.* $1\sigma^4,3\sigma^2$ -Diphosphaallenes $\text{R}_3\text{P}=\text{C}=\text{PR}^2$ **407** combine the structural features of an ylidic carbodiphosphorane $\text{R}_3\text{P}=\text{C}=\text{PR}_3^1$ with those of the heterocumulenic 1,3-diphosphaallenes $\text{R}^2\text{P}=\text{C}=\text{PR}^2$. Compound **407** was synthesized by heating or photolysis of the unsymmetrical bisphosphanilydiazomethane **406** in toluene. The phosphorus–carbon- π -bond behaved as an excellent dipolarophile in the reaction with a nitron. Heterocycle **408**, resulting from a diastereoselective [2 + 3]-cycloaddition, followed by an oxidation by the excess of nitron was isolated as colorless crystals (Scheme 109) <2000AG(E)3319>.



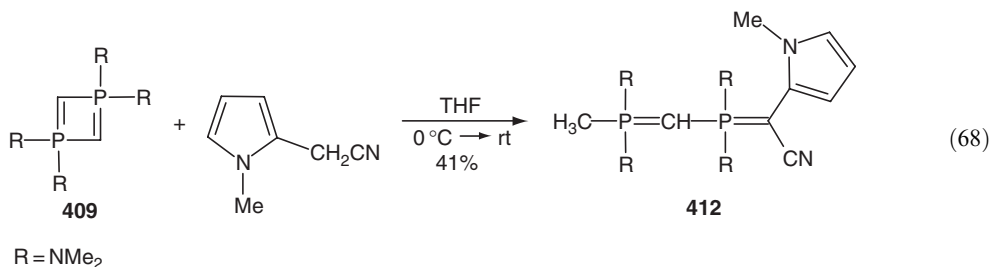
Scheme 109

5-Cyano-1-pentyne reacted with an equimolar amount of the ylide λ^5 -diphosphate **409** in boiling toluene to afford the insertion product **410** of the acetylenic function into a C–P bond of the heterocycle. When a twofold excess of the diphosphate was exposed to 5-cyano-1-pentyne in a sealed tube at 110 °C for 170 h yellow crystalline **411** was isolated. Obviously, the $\text{C}\equiv\text{N}$ -function was not incorporated into the heterocycle. Instead proton-transfer from the α -position of the nitrile and nucleophilic ring opening by the resulting carbanion occurred (Scheme 110) <2000ZAAC1739>.

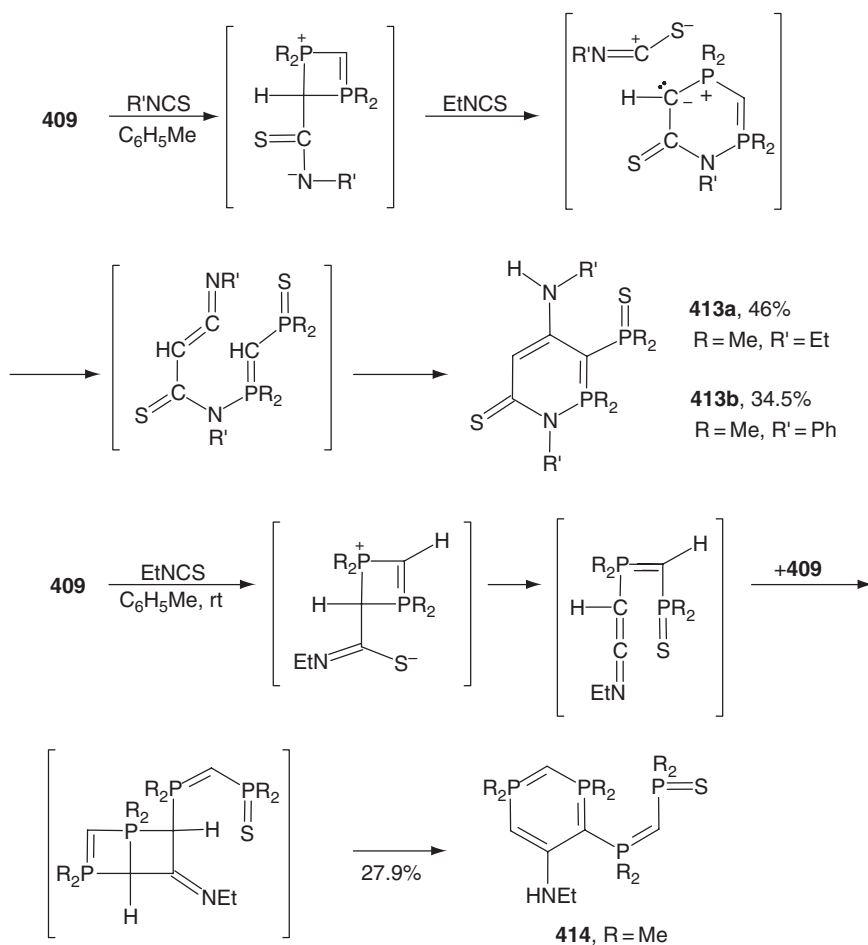


Scheme 110

A similar process took place in the reaction of 2-cyanomethyl-1-methylpyrrol with the diphosphate, where colorless crystals of ylide **412** were generated (Equation (68)) <2000ZAAC1739>.



Reaction of diphosphate **409** with the 2 equiv. of ethyl isothiocyanate or phenyl isothiocyanate in precooled toluene (−30 °C or −50 °C, respectively) and slow warming up to 20 °C led to the formation of compound **413a, b** as bright yellow crystals (Scheme 111).

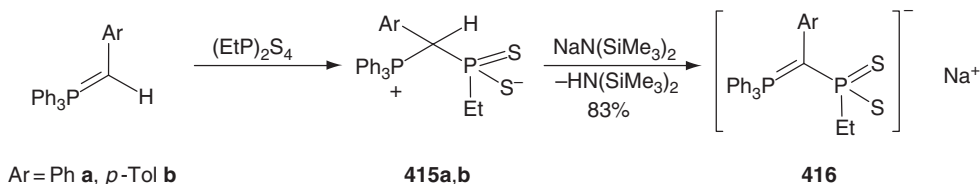


Scheme 111

If, however, the reaction between **409** and ethyl isothiocyanate was conducted in the molar ratio 2:1 in toluene at 20 °C, compound **414** was obtained instead (Scheme 111) <1995HAC355>.

The results were rationalized by a nucleophilic attack of the ylidic carbon atom of **409** at the dicoordinate C-atom of the isothiocyanate followed by a series of ring-opening and cyclization steps.

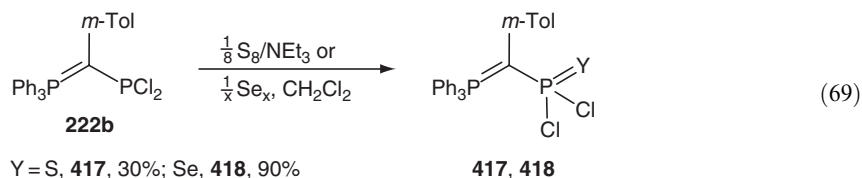
Zwitterionic adducts **415a,b** separated as white precipitate upon combination of ylides $\text{Ph}_3\text{P}=\text{C}(\text{Ar})\text{H}$ ($\text{Ar} = \text{Ph}, p\text{-Tol}$) with ethylperthiophosphonic anhydride in THF. Deprotonation of **415a** was effected by $\text{NaN}(\text{SiMe}_3)_2$ to afford salt **416** as a powder (Scheme 112) <1998HAC433>.



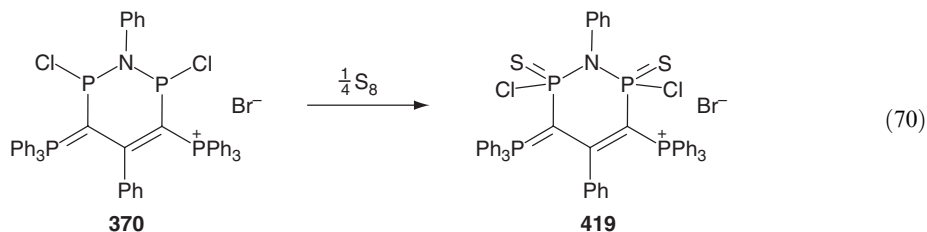
Scheme 112

The pronounced reactivity of tricoordinate phosphorus atoms toward sulfur and selenium was also observed in the systems under discussion.

Oxidation of ylidylchlorophosphane **222b** to the yellow products **417** and **418** was achieved with sulfur under the catalysis of triethylamine or with grey selenium in CH_2Cl_2 at 20°C (Equation (69)) <1995CB379>.

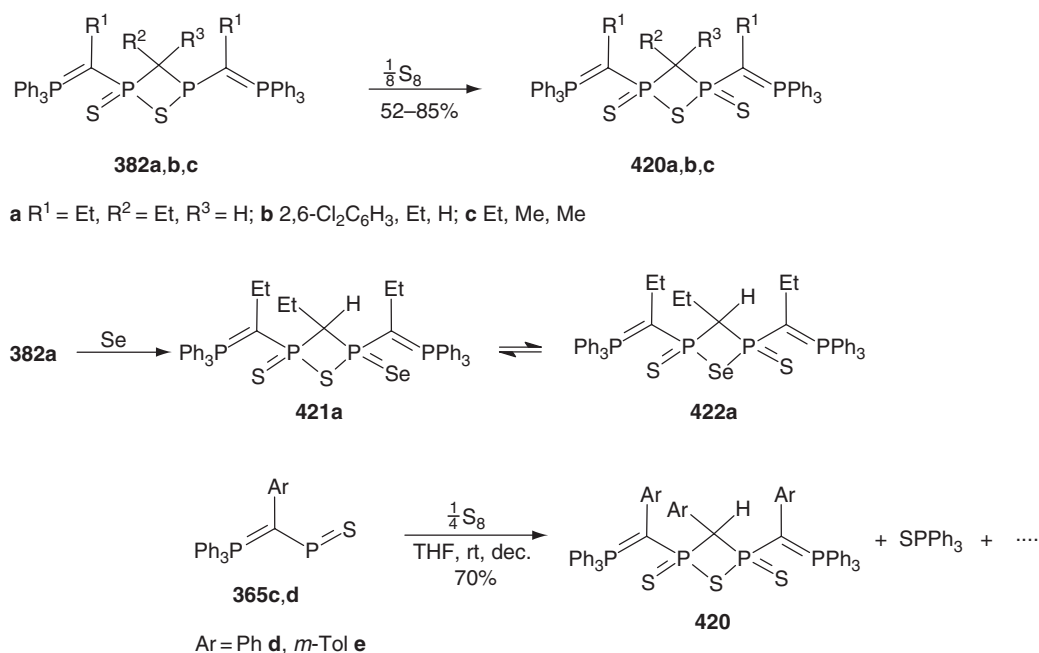


Similarly compound **370** was oxidized by sulfur in a mixture of benzene, pyridine, and CH_2Cl_2 to give the disulfide **419** as pale yellow crystals after 10 days (Equation (70)) <1996ZN(B)1761>.



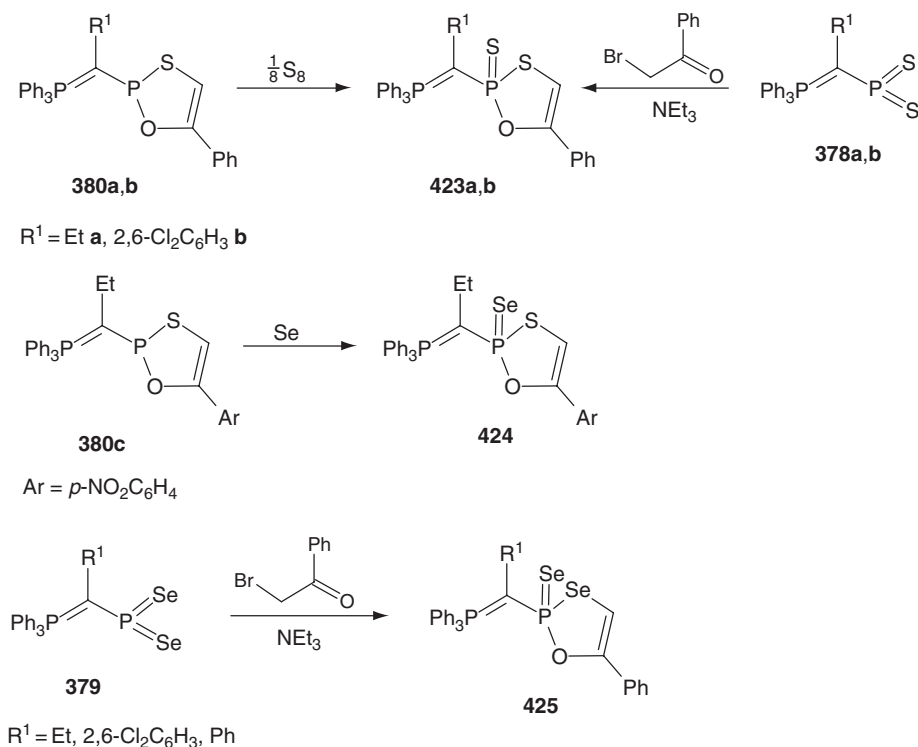
Oxidation of the 1,2,4-thiadiphosphetane derivatives **382a,b,c** with elemental sulfur yielded the corresponding yellow crystalline disulfides **420a,b,c** (52–85% yield). The selenation of **382a** in CH_2Cl_2 for 3 days afforded yellow crystals (51% yield), which were found to be a mixture of isomers **421a** and **422a**. When the C-arylated ylides **365c,d** ($\text{Ar} = \text{Ph}, m\text{-Tol}$) were produced from $\text{Ph}_3\text{P}=\text{C}(\text{Ph})\text{PCl}_2$ and Na_2S or by reduction of $\text{Ph}_3\text{P}=\text{C}(m\text{-Tol})\text{PS}_2$ with tri-*n*-butylphosphane and then left in solution for decomposition, disulfides **420d** and **420e** were isolated as the main products (Scheme 113) <1995CB1015>.

Ylidyl-oxathiaphospholes **380a,b** reacted with elemental sulfur to afford the sulfides **423a,b**, which were also available by treatment of dithiophosphoranes **378a,b** with phenacyl bromide in



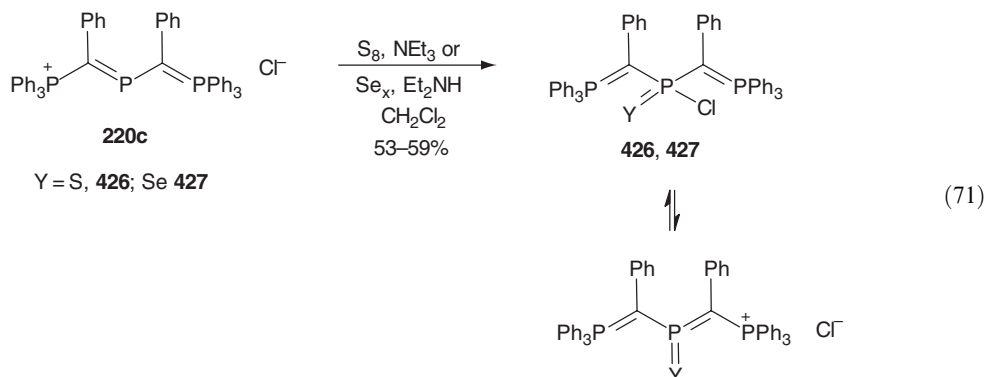
Scheme 113

the presence of NEt₃. With grey selenium the corresponding selenides were generated as illustrated by the transformation **380c** → **424**. Ylidyl-oxoselena phosphole selenides **425** were smoothly synthesized by combination of the diselenoxophosphorane **379** with phenacyl bromide and NEt₃ (Scheme 114) <1995ZN(B)1543>.

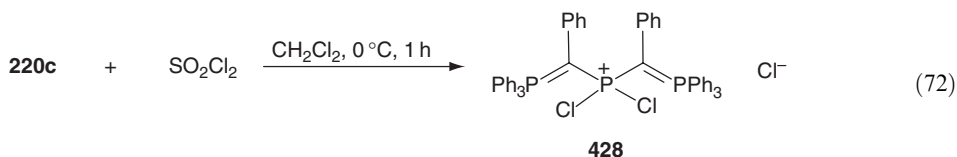


Scheme 114

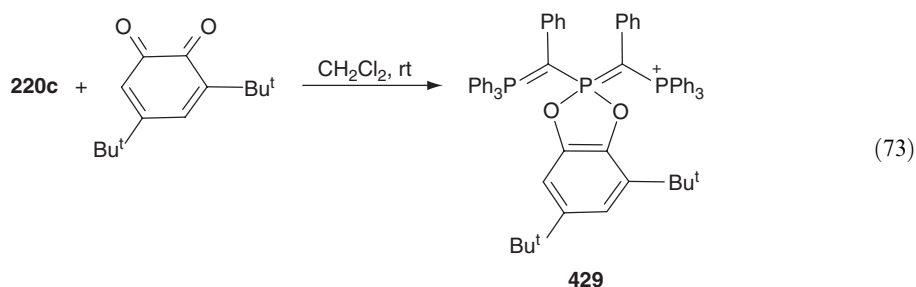
In a base-catalyzed reaction the dicoordinate phosphorus atom of bis(ylidyl)phosphenium chloride **220c** was oxidized by elemental sulfur or selenium. Yellow crystalline **426** and **427** were isolated (Equation (71)) <1997JOM(529)87>.



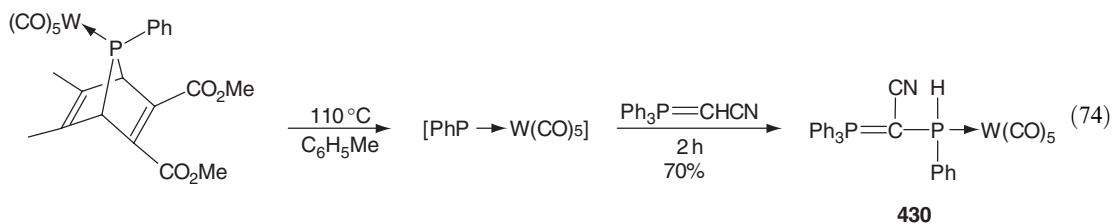
In polar solvents such as CH_2Cl_2 dissociation to ionic species with tricoordinate phosphorus was observed by ^{31}P NMR spectroscopy. Compound **220c** was quantitatively chlorinated by treatment with an equivalent of sulfuryl chloride in CH_2Cl_2 at 0°C to yield phosphonium salt **428** (Equation (72)).



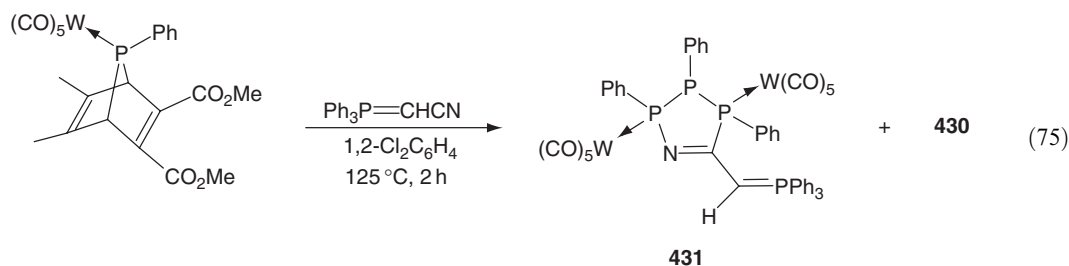
This product also resulted from reacting 2 equiv. of $\text{Ph}_3\text{P}=\text{C}(\text{Ph})\text{SiMe}_3$ with PCl_5 . A quantitative conversion to bis(ylidyl)1,3,2-dioxaphosphenium chloride **429** was achieved when **220c** was oxidized by 3,5-di-*t*-butyl-1,2-benzoquinone in CH_2Cl_2 solution at 20°C (Equation (73)).



The insertion of the thermally generated phosphinidene complex $[\text{PhP} \rightarrow \text{W}(\text{CO})_5]$ into the CH bond of $\text{Ph}_3\text{P}=\text{CHCN}$ led to a new ylide **430** (Equation (74)) <2002JOM(650)57>.

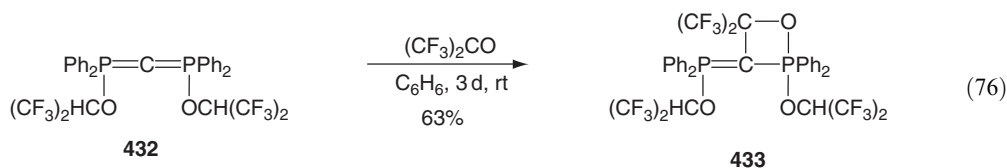


If the co-thermolysis of the 7-phosphanorbornadiene derivative and $\text{Ph}_3\text{P}=\text{CHCN}$ was performed in 1,2-dichlorobenzene at 125°C the 1,2,3,4-azatriphospholene complex **431** was generated in addition to **430** in a ratio of 3:5. It was assumed that **431** resulted from a 1,3-addition of the nitrilium phosphanylide intermediate $[\text{Ph}_3\text{P}=\text{CH}-\text{C}\equiv\text{N}^+-\text{P}^-(\text{Ph})\text{W}(\text{CO})_5]$ to the diphosphene complex $(\text{PhP}=\text{PPh})\text{W}(\text{CO})_5$ (Equation (75)) <2002CC454>.

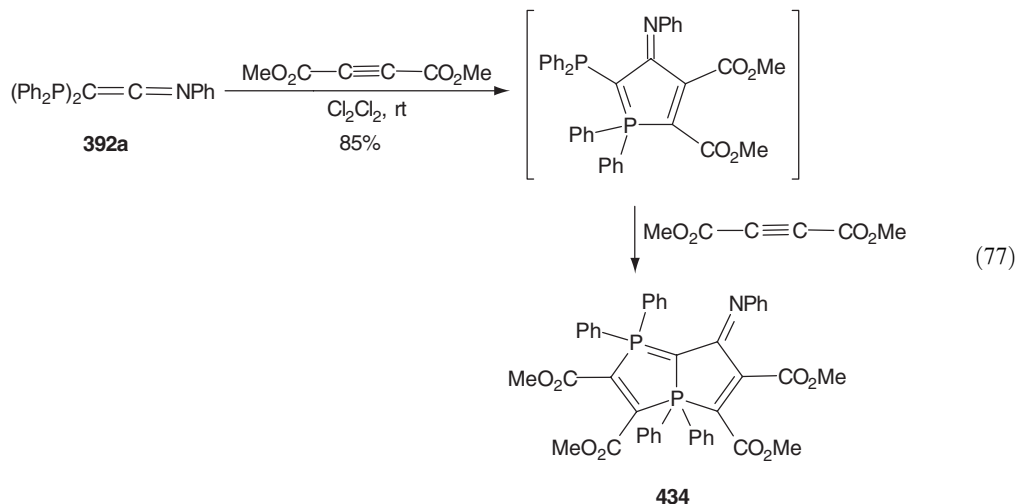


(iv) Derivatives with pentacoordinate phosphorus— $R^1C(PR_3^2)PR_4^3$

Carbodiphosphorane **432**, which was easily synthesized from $\text{Ph}_2\text{PCH}_2\text{PPh}_2$ and gaseous hexafluoroacetone in benzene smoothly added 1 equiv. of the ketone across one of the ylidic $\text{P}=\text{C}$ bonds when treated with an excess of hexafluoroacetone in benzene solution in a sealed vessel for 3 days. Crystalline **433** was isolated (Equation (76)) <2001EJI2377>.



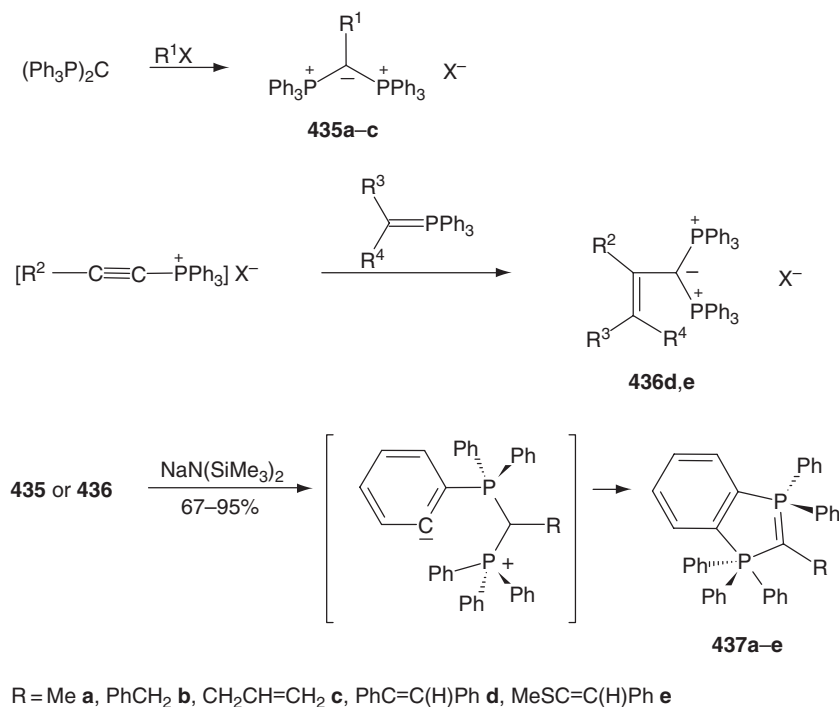
N-Phenylketenimine **392a** added 2 equiv. of dimethylacetylene dicarboxylate in CH_2Cl_2 at 20°C to give the bicyclic ylide **434** as red crystals (Equation (77)) <2000AG(E)1821>.



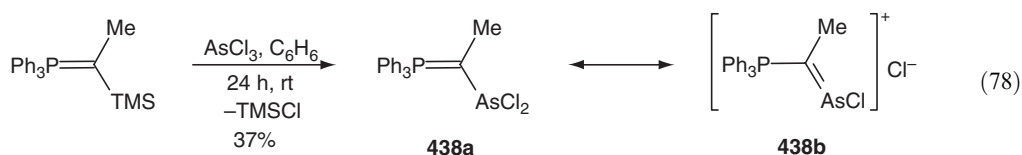
The bis(triphenylphosphonio)methanides (**435** ($\text{R}^1 = \text{Me}$ (a), CH_2Ph (b), $\text{CH}_2\text{CH}=\text{CH}_2$ (c)) resulted from alkylation of hexaphenylcarbodiphosphorane. The related cations (**436** were synthesized from alkynylphosphonium salts and phosphonium ylides (R^2 and $\text{R}^3 \neq \text{H}$). Deprotonation of these salts with sodium hexamethyldisilazide in benzene or pyridine afforded compounds **437**, which contain a pentacoordinate and a tetracoordinate phosphorus atom in the 1,3-positions of the five-membered ring. The carbon atom between the two phosphorus centers is ylidic (Scheme 115) <1995AG(E)2017>.

(v) Arsenic derivatives— $R^1C(PR_3^2)\text{AsR}_2^3$

Bright yellow crystalline triphenylphosphonium-dichlorarsanylmethanide **438** was prepared from $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{SiMe}_3$ and AsCl_3 (Equation (78)).



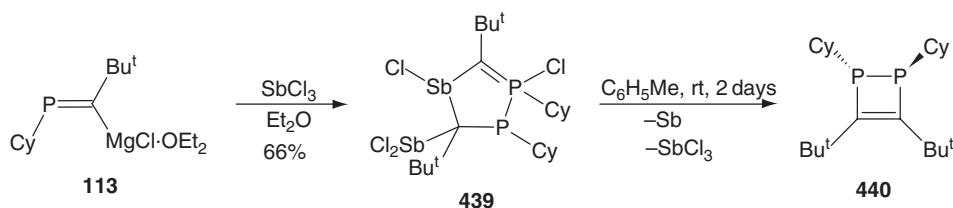
Scheme 115



One AsCl bond was found to be 15 pm longer (273 pm) than the second one. The remarkably short As—C bond (183.1 pm) points to a bonding situation which may be expressed by the limiting structures **438a** and **438b** <2000CEJ3531>.

(vi) Antimony derivatives— $\text{R}^1\text{C}(\text{PR}_3^2)\text{SbR}_2^3$

Compound **439** was synthesized from equimolar amounts of phosphavinyl Grignard reagent **113** and SbCl₃ in a straightforward reaction. Although moderately stable in the solid state, this unusual and unexpected compound quantitatively decomposed over 2 days in toluene solution to heterocycle **440**, liberating elemental antimony and presumably SbCl₃ (Scheme 116) <2002NJC1209>.



Scheme 116

5.23.3.1.6 Metalloid derivatives— $R^1C(PR_3^2)ER_n^3$ ($E = Si, Ge, B$)

(i) Silicon derivatives

(a) *From ylides.* A very efficient and widely applicable approach for the synthesis of silylated ylides is based upon the treatment of α -H-functionalized ylides with 0.5 equiv. of a triorganosilyl halide via transylidation. This classical approach was followed for the preparation of a series of silylated ylides with functional groups at the silicon centers (Equation (79), Table 7) <1997ZN(B)669>.

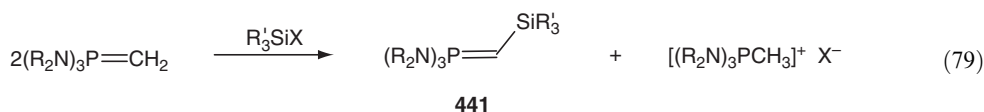
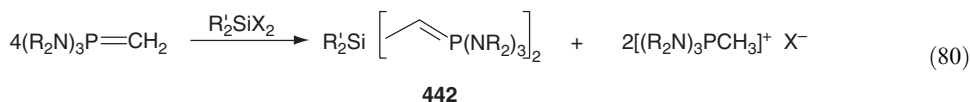


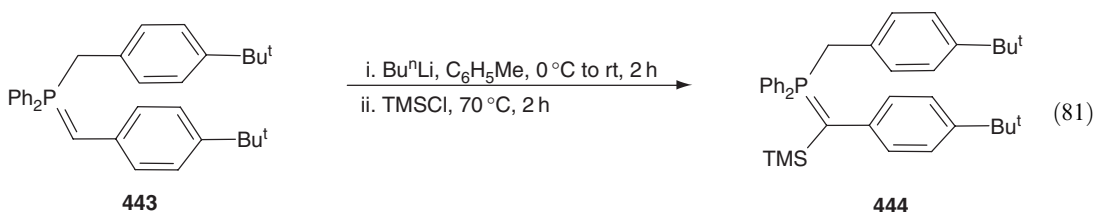
Table 7 Ylides **441** and **442** from $(R_2N)_3P=CH_2$ and R'_3SiX or R'_2SiX_2

R	SiR'_3 (SiR'_2)	X	Solvents and conditions	Yield (%)
Me	SiPhH ₂	Br	Et ₂ O, 0 to 20 °C, 3 days	67
Me	SiCl ₃	Cl	<i>n</i> -C ₅ H ₁₂ , 35, 1 h	27
Me	SiBr ₃	Br	<i>n</i> -C ₅ H ₁₂ , 35, 1 h	42
Me	Si(OMe) ₃	Cl	<i>n</i> -C ₅ H ₁₂ , 0 to 20 °C, 12 h	68
Me	Si(OPr ⁱ) ₃	Cl	<i>n</i> -C ₅ H ₁₂ , 0 to 20 °C, 12 h	78
Et	Si(OPr ⁱ) ₃	Cl	<i>n</i> -C ₅ H ₁₂ , 0 to 20 °C, 12 h	92
Me	Si(NMe ₂) ₃	OTf	Et ₂ O, 0 to 20 °C, 12 h	68
Me	SiMe ₂	Cl	<i>n</i> -C ₆ H ₁₄ , 69 °C, 2 h	88
Me	Si(OMe) ₂	OTf	<i>n</i> -C ₆ H ₁₄ , PhMe, 69 °C, 2 h	69
Et	Si(OEt) ₂	Cl	<i>n</i> -C ₆ H ₁₄ , PhMe	59
Me	Si(NMe ₂) ₂		Et ₂ O, 0 °C	58

Similarly, bis(ylidyl)silanes **442** were synthesized (Equation (80), Table 7).

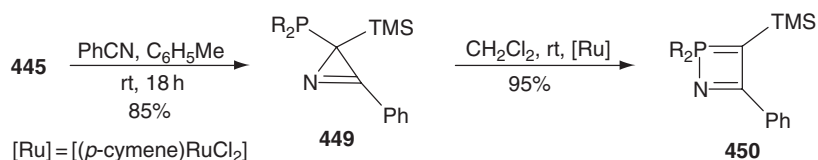
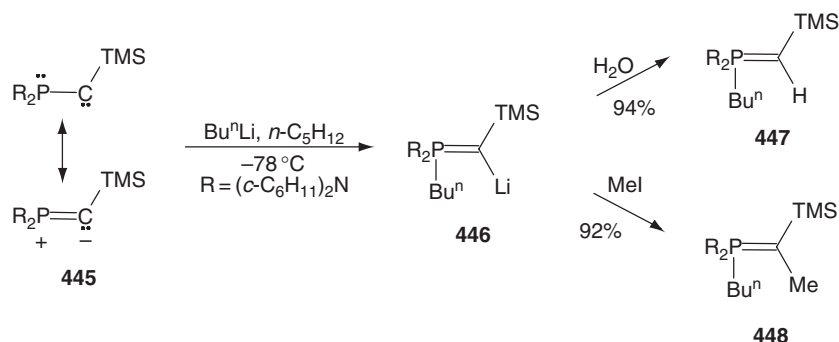


The synthetic pathway to ylide **444** involved the deprotonation of precursor **443** by *n*-butyllithium prior to the addition of an excess of trimethylchlorosilane and heating the mixture to 70 °C for ca. 3 h (Equation (81)) <2001OM5629>.

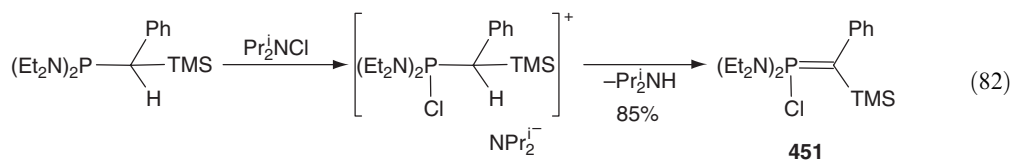


α -(Lithiomethylene)phosphorane **446** resulted quantitatively from the 1,2-addition of *n*-butyllithium across the P—C bond of the stable carbene **445** in *n*-pentane at -78 °C. The lithiated ylide is very moisture sensitive and easily transformed into ylide **447** or methylated to afford **448** (Scheme 117) <1999AG(E)678>.

Carbene **445** underwent a [1 + 2]-cycloaddition with benzonitrile in toluene to afford 2-*H*-azirine **449** (Scheme 118). Addition of a catalytic amount of dichloro(*p*-cymene)ruthenium(II) to a dichloromethane solution of **449** at room temperature effected a ring expansion to the 1,2- λ^5 -azaphosphete **450** (Scheme 118) <1995AG(E)1246>.



(b) From phosphanes. α -Silylated ylide **451** resulted from the oxidation of phosphane $(\text{Et}_2\text{N})_2\text{PCH}(\text{Ph})\text{TMS}$ by chlorodiisopropylamine and release of diisopropylamine from the initially formed phosphonium salt (Equation (82)) <1995ZOB341>.



5.23.3.1.7 Metal derivatives

(i) Lithium, sodium, potassium, rubidium, and caesium derivatives— $R^I\text{C}(\text{PR}_3^2)\text{M}$

No isolable and stable representatives of this class of compounds have been reported as of early 2003.

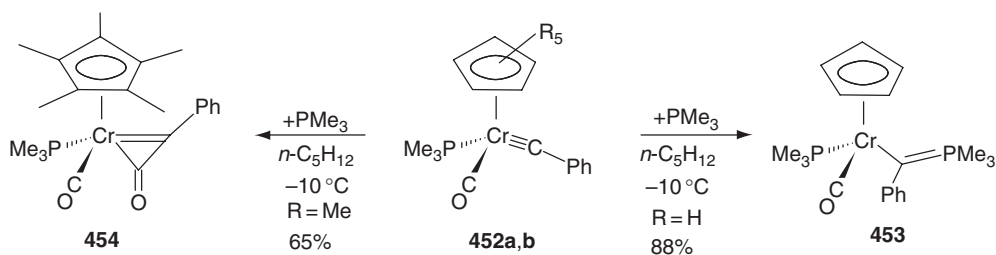
(ii) Beryllium, magnesium, calcium, strontium, and barium derivatives— $R^I\text{C}(\text{PR}_3^2)\text{MR}^3$

No compounds of this type have been reported as of early 2003.

(iii) Transition metal derivatives— $R^I\text{C}(\text{PR}_3^2)\text{ML}_n$

The chromium phenyl carbyne complex **452a** adds PMe_3 at the carbyne-carbon atom to give the chromium-substituted ylide **453**. This nucleophilic addition at the carbyne ligand of **452a** is surprising since Cp-substituted group VI metal carbyne complexes of the type $(\eta^5\text{-C}_5\text{R}_5)\text{-(CO)}_2\text{M}\equiv\text{CR}'$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$; $\text{R} = \text{H}, \text{Me}$; $\text{R}' = \text{alkyl, aryl, amino}$) have been so far shown to add only electrophiles at the carbyne-carbon atom. Nucleophilic addition of PMe_3 to this carbon atom has been observed, however, in cationic half-sandwich carbyne complexes of the type $[(\eta^6\text{-C}_6\text{H}_6)(\text{CO})_2\text{Cr}\equiv\text{CPh}]\text{BCl}_4$ and $[(\eta^5\text{-C}_5\text{H}_4\text{R})(\text{CO})_2\text{M}\equiv\text{CPh}]\text{BCl}_4$ ($\text{R} = \text{H}, \text{Me}$; $\text{M} = \text{Mn}, \text{Re}$).

In contrast to this, addition of PMe_3 to the phenylcarbyne complex **452b** induced coupling of the carbyne with one carbonyl ligand to give the η^2 -ketenyl complex **454** (Scheme 119) <1997JOM(541)333>.



Scheme 119

(iv) Group 13 derivatives

Such ylidic species have not been reported in the years 1995–2003.

(v) Group 14 derivatives

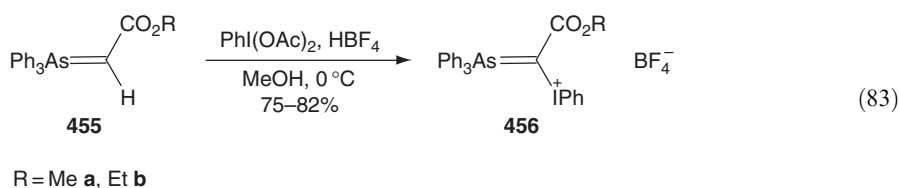
No such species were reported in the years 1995–2003.

5.23.3.2 Tetracoordinate Arsenic Functions— $\text{R}^1\text{C}(\text{AsR}_3^2)\text{X}$

5.23.3.2.1 Halogen derivatives— $\text{R}^1\text{C}(\text{AsR}_3^2)\text{X}$ ($\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$)

Generally, the synthesis of arsonium ylides or methylene arsoranes mirror those protocols successfully employed for the phosphorus analogs.

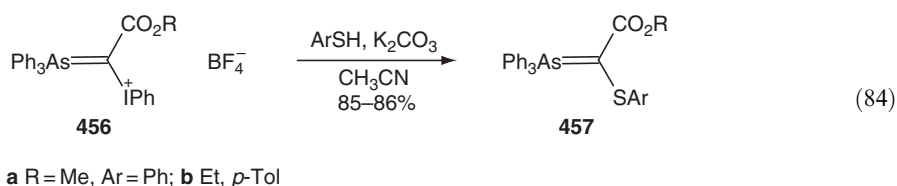
The only isolable and stable arsonium ylides containing one halogen atom at the α -carbon atom are derived from hypervalent iodocompounds. Ylides **456a,b** were synthesized from carbonyl-stabilized ylides **455a,b** and iodobenzene diacetate in the presence of HBF_4 in methanol solution (Equation (83)) <2002JOC8261, 2002TL6823>.



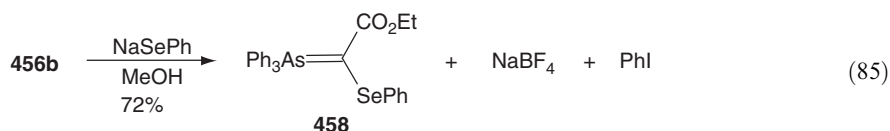
Comparable to the related phosphonium ylides the hypervalent iodo-substituent in **456** renders the ylidic α -carbon atom electrophilic in character and is thus susceptible to nucleophilic attack. Products of the treatment of **456** with Bu_4NBr and Et_4NI were not isolated. Instead the *in situ* preparation of $\text{Ph}_3\text{As}=\text{C}(\text{CO}_2\text{R})\text{X}$ ($\text{X} = \text{Br}, \text{I}$) and their subsequent conversion into halogenated alkenes by the Wittig reaction was the focus of interest <2002JOC8261, 2002TL6823>. The α -bromoarsonium ylides $\text{Ph}_3\text{As}=\text{C}(\text{Br})\text{CO}_2\text{R}$ were also obtained from **455** by reaction with bromine via transylidation. Here again the *in situ* generated compounds were immediately transformed into α -bromo- α,β -unsaturated esters <1996SC677>.

5.23.3.2.2 Chalcogen derivatives— $\text{R}^1\text{C}(\text{AsR}_3^2)\text{ER}_n^3$ ($\text{E} = \text{O}, \text{S}, \text{Se}, \text{Te}$)

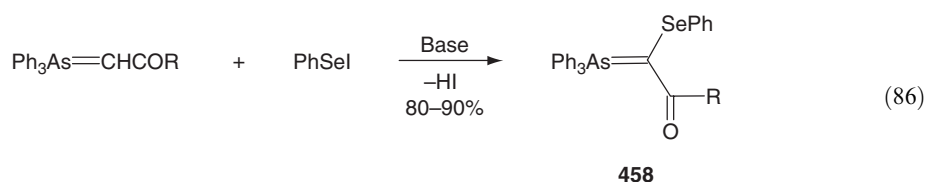
Combination of the iodonium-functionalized ylides **456** with thiophenol or *p*-tolylthiol in CH_3CN in the presence of K_2CO_3 efficiently afforded arsonium ylides with sulfur substituents **457** (Equation (84)).



Reaction of **456b** with sodium phenylselenolate in methanol led to the formation of the selenium-functionalized arsonium ylide **458** (Equation (85)).



Alternative syntheses of compound **457** and **458** were based on the treatment of the ylides **455** with PhSeI (100%) <1999JCR(S)144> or PhSeI in the molar ratio of 2:1 <1995TL425, 1995JCS(P1)95, 1995JOM(490)C23>. Due to transylidation half the amount of the ylide employed was converted to the corresponding arsonium salt. In an improved protocol α -selenoarsonium ylides were formed from equimolar amounts of $\text{Ph}_3\text{As}=\text{CHCOR}$ (R = OMe, Me, Ph, *p*-ClC₆H₄, *p*-BrC₆H₄) and PhSeI in the presence of bases such as sodium acetate, potassium carbonate, or triethylamine (Equation (86)) <2000MI293>.

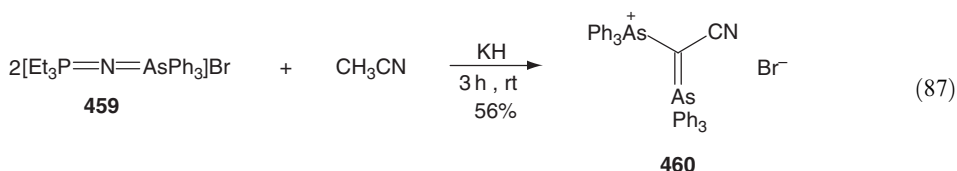


5.23.3.2.3 Nitrogen derivatives— $\text{R}^1\text{C}(\text{AsR}_3^2)\text{NR}_n^3$

No such compounds have been reported in the literature since 1995.

5.23.3.2.4 Group 15 element derivatives— $\text{R}^1\text{C}(\text{AsR}_3^2)\text{ER}_n^3$ (E = P, As, Sb, Bi)

Acetonitrile solutions of the nonsymmetrical iminium salts **459** reacted in the presence of potassium hydride with cleavage of the N—As bond and formation of an arsonium ylide **460**, which is substituted by tetracoordinate arsenic atom (Equation (87)) <1998ZAAC1341>.



No other stable arsonium ylides with the structural feature under discussion have been reported.

5.23.3.3 Tetracoordinate Antimony Functions— $\text{R}^1\text{C}(\text{SbR}_3^2)\text{X}$

No such compounds have been reported since 1995.

5.23.3.4 Tetracoordinate Bismuth Functions— $\text{R}^1\text{C}(\text{BiR}_3^2)\text{X}$

Such compounds are unknown.

REFERENCES

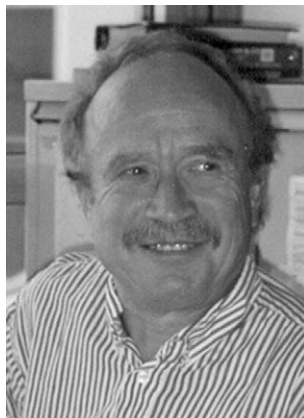
- 1984JA6082
1985MI55
- 1987AG(E)776
1987PS(30)349
- 1993AG(E)1089
1993CC267
- 1994CC805
1995AG(E)81
1995AG(E)492
1995AG(E)555
- 1995AG(E)1246
1995AG(E)1849
1995AG(E)2017
1995AG(E)2227
- 1995AG(E)2369
1995BCJ1206
1995CB379
- 1995CB465
1995CB499
1995CB991
- 1995CB1015
1995CB1207
- 1995CC1661
1995CC2113
1995CL747
1995COFGT(5)875
- 1995HAC355
1995ICA(235)77
- 1995IC4092
- 1995JA11914
1995JCS(P1)95
1995JOC5884
1995JOM(490)C23
1995PS(102)133
1995TL425
1995TL4487
1995ZN(B)1543
1995ZOB341
1995ZOB1342
1996AG(E)271
1996CB367
1996CB489
1996CC631
- 1996CEJ208
- 1996CEJ221
1996CRV1641
1996HAC239
1996IC46
1996JCS(D)3277
- 1996OM174
1996OM1845
1996OM2683
- R. M. Moriarty, I. Prakash, O. Prakash, W. A. Freeman, *J. Am. Chem. Soc.* **1984**, *106*, 6082–6084.
G. Becker, W. Becker, R. Knebel, H. Schmidt, U. Weber, W. Westerhausen, *Nova Acta Leopoldina(neue Folge)* **1985**, *59*, 55–67.
A. Schäfer, M. Weidenbruch, W. Saak, S. Pohl, *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 776–777.
G. Becker, W. Becker, R. Knebel, H. Schmidt, M. Mildtenbrand, W. Westerhausen, *Phosphorus, Sulfur and Silicon* **1987**, *30*, 349–352.
G. Jochem, H. Nöth, A. Schmidpeter, *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1089–1091.
S. S. Al-Juaid, P. B. Hitchcock, R. M. Matos, J. F. Nixon, *J. Chem. Soc., Chem. Commun.* **1993**, 267–269.
R. A. Aitken, M. J. Drysdale, B. M. Ryan, *J. Chem. Soc., Chem. Commun.* **1994**, 805–806.
P. Binger, G. Glaser, B. Gabor, R. Mynott, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 81–83.
P. B. Hitchcock, C. Jones, J. F. Nixon, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 492–493.
E. Niecke, A. Fuchs, F. Baumeister, M. Nieger, W. W. Schoeller, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 555–558.
G. Alcaraz, U. Wecker, A. Baceiredo, F. Dahan, G. Bertrand, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1246–1247.
E. Niecke, P. Becker, M. Nieger, D. Stalke, W. W. Schoeller, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1849–1852.
H. J. Bestmann, H. P. Oechsner, L. Kieselowski, C. Egerer-Sieber, F. Hampel, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2017–2020.
P. Binger, S. Leininger, J. Stannek, B. Gabor, R. Mynott, J. Bruckmann, C. Krüger, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2227–2230.
K. Paasch, M. Nieger, E. Niecke, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2369–2371.
M. Yoshifuji, S. Ito, K. Toyota, M. Yasunami, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1206–1212.
A. Schmidpeter, H. Nöth, G. Jochem, H.-P. Schrödel, K. Karaghiosoff, *Chem. Ber.* **1995**, *128*, 379–393.
M. van der Sluis, F. Bickelhaupt, N. Veldman, H. Kooijman, A. L. Spek, W. Eisefeld, M. Regitz, *Chem. Ber.* **1995**, *128*, 465–476.
C. Müller, R. Bartsch, A. Fischer, P. G. Jones, R. Schmutzler, *Chem. Ber.* **1995**, *128*, 499.
M. Julino, M. Slany, U. Bergsträßer, F. Mercier, F. Mathey, M. Regitz, *Chem. Ber.* **1995**, *128*, 991–997.
G. Jochem, A. Schmidpeter, F. Kulzer, S. Dick, *Chem. Ber.* **1995**, *128*, 1015–1020.
G. Jochem, K. Karaghiosoff, S. Planck, S. Dick, A. Schmidpeter, *Chem. Ber.* **1995**, *128*, 1207–1219.
V. Caliman, P. B. Hitchcock, J. F. Nixon, *J. Chem. Soc., Chem. Commun.* **1995**, 1661–1662.
R. Streubel, L. Ernst, J. Jeske, P. G. Jones, *J. Chem. Soc. Chem. Commun.* **1995**, 2113–2114.
S. Ito, K. Toyota, M. Yoshifuji, *Chem. Lett.* **1995**, 747–748.
L. Weber, Phosphoacyl functions and their As, Sb, and Bi analogs, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 875–922.
E. Fluck, F. Rosche, G. Heckmann, F. Weller, *Heteroatom. Chem.* **1995**, *6*, 355–363.
P. Imhoff, J. H. Gülpén, K. Vrieze, W. J. J. Smeets, A. L. Spek, C. J. Elsevier, *Inorg. Chim. Acta* **1995**, *235*, 77–88.
M. W. Avis, K. Vrieze, H. Kooijman, N. Veldman, A. L. Spek, C. J. Elsevier, *Inorg. Chem.* **1995**, *34*, 4092–4105.
T. L. Breen, D. W. Stephan, *J. Am. Chem. Soc.* **1995**, *117*, 11914–11921.
Z.-Z. Huang, X. Huang, Y.-Z. Huang, *J. Chem. Soc., Perkin Trans. 1* **1995**, 95–96.
M. Julino, U. Bergsträßer, M. Regitz, *J. Org. Chem.* **1995**, *60*, 5884–5890.
Z.-Z. Huang, X. Huang, Y.-Z. Huang, *J. Organomet.* **1995**, *490*, C23–C26.
O. I. Kolodiazny, O. R. Golovaty, *Phosphorus, Sulfur, Silicon* **1995**, *102*, 133–141.
Z.-Z. Huang, X. Huang, Y.-Z. Huang, *Tetrahedron Lett.* **1995**, *36*, 425–426.
N. Hussain, D. U. Morgan, *Tetrahedron Lett.* **1995**, *36*, 4487–4488.
A. Schmidpeter, S. Plank, K. Polborn, *Z. Naturforsch. Teil B* **1995**, *50*, 1543–1549.
O. I. Kolodiazny, O. R. Golovaty, *Zh. Obshch. Khim.* **1995**, *65*, 341–342.
V. I. Namestnikov, S. M. Senyukh, Yu. G. Trishin, *Zh. Obshch. Khim.* **1995**, *65*, 1342–1346.
L. Weber, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 271–288.
L. Weber, *Chem. Ber.* **1996**, *129*, 367–379.
B. Breit, M. Regitz, *Chem. Ber.* **1996**, *129*, 489–494.
M. Francis, D. E. Hibbs, M. B. Hursthouse, C. Jones, K. M. A. Malik, *J. Chem. Soc., Chem. Commun.* **1996**, 631–632.
H. Pucknat, J. Grobe, D. Le Van, B. Broschke, M. Hegemann, B. Krebs, M. Läge, *Chem. Eur. J.* **1996**, *2*, 208–213.
G. Jochem, A. Schmidpeter, H. Nöth, *Chem. Eur. J.* **1996**, *2*, 221–227.
D. J. Burton, Z.-Y. Yang, W. Qiu, *Chem. Rev.* **1996**, *96*, 1641–1715.
G. Jochem, F. Breitsameter, A. Schier, A. Schmidpeter, *Heteroatom. Chem.* **1996**, *7*, 239–247.
P. Dyer, A. Baceiredo, G. Bertrand, *Inorg. Chem.* **1996**, *46*, 50.
J. Durkin, D. E. Hibbs, P. B. Hitchcock, M. B. Hursthouse, C. Jones, J. Jones, K. M. A. Malik, J. A. Nixon, G. Parry, *J. Chem. Soc. Dalton Trans.* **1996**, 3277–3282.
M. van der Sluis, J. B. M. Wit, F. Bickelhaupt, *Organometallics* **1996**, *15*, 174–180.
M. Driess, H. Pritzkow, S. Rell, U. Winkler, *Organometallics* **1996**, *15*, 1845–1855.
H. Ramdane, H. Ranaivonjatovo, J. Escudié, N. Knouzi, *Organometallics* **1996**, *15*, 2683–2684.

- 1996OM3070 H. Ramdane, H. Ranaivonjatovo, J. Escudié, S. Mathieu, N. Knouzi, *Organometallics* **1996**, *15*, 3070–3075.
- 1996SC677 Z.-Z. Huang, L. L. Wu, L.-S. Zhu, X. Huang, *Synth. Commun.* **1996**, *26*, 677–682.
- 1996T1855 O. I. Kolodiazhnyi, *Tetrahedron* **1996**, *52*, 1855–1929.
- 1996T10053 B. Manz, G. Maas, *Tetrahedron* **1996**, *52*, 10053–10072.
- 1996TL869 H.-S. Lee, K. Kim, *Tetrahedron Lett.* **1996**, *37*, 869–872.
- 1996ZN(B)267 G. Jochem, A. Schmidpeter, H. Nöth, *Z. Naturforsch. Teil B* **1996**, *51*, 267–276.
- 1996ZN(B)1761 G. Jochem, M. Schmidt, H. Nöth, A. Schmidpeter, *Z. Naturforsch. Teil B* **1996**, *51*, 1761–1767.
- 1997AG(E)1095 R. Streubel, M. Hobbold, J. Jeske, P. G. Jones, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1095–1097.
- 1997AG(E)1337 A. Mack, B. Breit, T. Wettling, U. Bergsträßer, S. Leininger, M. Regitz, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1337–1339.
- 1997AOC(41)1 L. Weber, *Adv. Organomet. Chem.* **1997**, *41*, 1–69.
- 1997BMCL2061 S. Biondi, E. Piga, T. Rossi, G. Vigelli, *Biorg. Med. Chem. Lett.* **1997**, *7*, 2061–2066.
- 1997CB779 B. Manz, V. Bergsträßer, J. Kerth, G. Maas, *Chem. Ber./Recueil* **1997**, *130*, 779–788.
- 1997CB1491 P. Binger, S. Leininger, K. Günther, U. Bergsträßer, *Chem. Ber./Recueil* **1997**, *130*, 1491–1494.
- 1997CB1519 H.-P. Schrödel, A. Schmidpeter, *Chem. Ber./Recueil* **1997**, *130*, 1519–1527.
- 1997CB1801 H.-P. Schrödel, H. Nöth, M. Schmidt-Amelunxen, W. W. Schoeller, A. Schmidpeter, *Chem. Ber./Recueil* **1997**, *130*, 1801–1805.
- 1997CC1433 M. Weidenbruch, S. Olthoff, K. Peters, H. G. von Schnering, *J. Chem. Soc., Chem. Commun.* **1997**, 1433–1434.
- 1997CC1641 K. K. Laali, W. Fiedler, M. Regitz, *J. Chem. Soc., Chem. Commun.* **1997**, 1641–1642.
- 1997CJC1315 M. M. Kayser, J. Zhu, D. L. Hooper, *Can. J. Chem.* **1997**, *75*, 1315–1321.
- 1997JA12410 T. Baumgartner, B. Schinkels, D. Gudat, M. Nieger, E. Niecke, *J. Am. Chem. Soc.* **1997**, *119*, 12410–12411.
- 1997JCS(P1)3107 R. R. Aitken, I. M. Fairhurst, A. Ford, P. E. Y. Milne, D. W. Russell, M. Whittaker, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3107–3112.
- 1997JOM(529)127 R. Pietschnig, E. Niecke, M. Nieger, K. Airola, *J. Organomet. Chem.* **1997**, *529*, 127–133.
- 1997JOM(529)215 P. Binger, S. Leininger, M. Regitz, U. Bergsträßer, J. Bruckmann, C. Krüger, *J. Organomet. Chem.* **1997**, *529*, 215–221.
- 1997JOM(539)61 A. Hofmann, S. Leininger, M. Regitz, *J. Organomet. Chem.* **1997**, *539*, 61–66.
- 1997JOM(541)333 A. C. Filippou, D. Wössner, G. Kociok-Köhn, I. Hinz, *J. Organomet. Chem.* **1997**, *541*, 333–343.
- B-1997MI523-04 Stutzmann, S., Ph. D. Thesis, Universität Kaiserslautern, **1997**.
- 1997OM1144 M. van der Sluis, V. Beverwijk, A. Termaten, E. Gavrilova, F. Bickelhaupt, H. Kooijman, N. Veldman, A. L. Spek, *Organometallics* **1997**, *16*, 1144–1152.
- 1997OM2958 L. Weber, M. H. Scheffer, E. Beckmann, H.-G. Stammmler, B. Neumann, *Organometallics* **1997**, *16*, 2958–2062.
- 1997PS(130)23 M. D. Francis, C. Jones, P. C. Junk, J. L. Roberts, *Phosphorus, Sulfur and Silicon* **1997**, *130*, 23.
- 1997PS(123)161 M. Soleilhavoup, O. Guerret, J.-L. Faure, A. Baceiredo, G. Bertrand, *Phosphorus, Sulfur and Silicon* **1997**, *123*, 161–167.
- 1997TL3569 C. Ghiron, T. Rossi, R. J. Thomas, *Tetrahedron Lett.* **1997**, *38*, 3569–3572.
- 1997ZN(B)669 K.-H. Dreihäupl, H. Schmidbaur, *Z. Naturforsch. Teil B* **1997**, *52*, 669–673.
- 1998AG(E)949 O. Schmidt, A. Fuchs, D. Gudat, M. Nieger, W. Hofbauer, E. Niecke, W. W. Schoeller, *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 949–952.
- 1998AG(E)1083 F. G. N. Cloke, P. B. Hitchcock, P. Hunnab, J. F. Nixon, L. Nyulászi, E. Niecke, V. Thelen, *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1083–1086.
- 1998AG(E)1233 F. Tabellion, A. Nachbauer, S. Leininger, C. Peters, M. Regitz, F. Preuss, *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1233–1235.
- B-1998MI523-02 K. B. Dillon, F. Mathey, J. F. Nixon, Eds., *Phosphorus: The Carbon Copy*, Wiley, Chichester, **1998**, 88.
- 1998CC1203 I. Shevchenko, *J. Chem. Soc., Chem. Commun.* **1998**, 1203–1204.
- 1998CC1537 V. Caliman, P. Hitchcock, *J. Chem. Soc., Chem. Commun.* **1998**, 1537–1538.
- 1998CEJ469 L. Weber, B. Quasdorff, H.-G. Stammmler, B. Neumann, *Chem. Eur. J.* **1998**, *4*, 469–475.
- 1998CL651 S. Ito, M. Yoshifuji, *Chem. Lett.* **1998**, 651.
- 1998EJ1227 M. Schmitz, R. Göller, U. Bergsträßer, S. Leininger, M. Regitz, *Eur. J. Inorg. Chem.* **1998**, 227–235.
- 1998EJ1381 F. Breitsamer, A. Schmidpeter, A. Schier, *Eur. J. Inorg. Chem.* **1998**, 381–388.
- 1998EJ12071 P. Binger, S. Stutzmann, J. Bruckmann, C. Krüger, J. Grobe, D. Le Van, T. Pohlmeier, *Eur. J. Inorg. Chem.* **1998**, 2071–2074.
- 1998HAC219 O. I. Kolodiazhnyi, V. E. Grishkun, *Heteroatom. Chem.* **1998**, *9*, 219–228.
- 1998HAC433 F. Breitsamer, H.-P. Schrödel, A. Schmidpeter, *Heteroatom. Chem.* **1998**, *9*, 433–437.
- 1998JCS(P1)875 R. A. Aitken, M. J. Drysdale, G. Ferguson, A. J. Lough, *J. Chem. Soc., Perkin Trans. 1* **1998**, 875–880.
- 1998JCS(P1)3345 R. A. Aitken, M. J. Drysdale, B. M. Ryan, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3345–3348.
- 1998JOM(557)37 U. Belluco, R. A. Michelin, M. Mozzon, R. Bertani, G. Facchin, L. Zanutto, L. Pandolfo, *J. Organomet. Chem.* **1998**, *557*, 37–68.
- 1998S1305 A. Mack, E. Pierron, T. Allspach, U. Bergsträßer, M. Regitz, *Synthesis* **1998**, 1305–1313.
- 1998ZAAC650 F. Borkenhagen, I. Neda, H. Thönnessen, P. G. Jones, R. Schmutzler, *Z. Anorg. Allg. Chem.* **1998**, *624*, 650–654.
- 1998ZAAC1341 S. Chitsaz, B. Neumüller, K. Harms, K. Dehnicke, *Z. Anorg. Allg. Chem.* **1998**, *624*, 1341–1346.
- 1999AG(E)678 S. Goumri-Magnet, H. Gornitzka, A. Baceiredo, G. Bertrand, *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 678–680.
- 1999AG(E)3028 E. Niecke, A. Fuchs, M. Nieger, *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3028–3031.

- 1999AG(E)3183
B-1999MI523-01
B-1999MI523-06
1999CC661
1999CC2451
1999CEJ774
1999CEJ3143
1999EJI763
1999EJI665
1999EJI2369
1999EJO587
1999JA5953
1999JA9479
1999JCR(S)144
1999JCS(D)1541
1999JCS(D)3531
1999JCS(D)4111
1999JCS(P1)593
1999S1642
1999ZAAC2008
1999ZOB52
1999ZOB1652
2000AG(E)1821
2000AG(E)2307
2000AG(E)2781
2000AG(E)3319
2000CC1305
2000CEJ3531
2000CEJ4558
2000CL1390
2000CPB126
2000EJI1185
2000EJI2337
2000EJI2425
2000JCS(D)3233
2000MI293
2000OM3205
2000S529
2000SCI(288)834
2000ZAAC1141
2000ZAAC1739
2001AG(E)3144
2001AG(E)4412
2001CC215
2001CC663
2001CCR(215)151
2001CEJ3545
2001CEJ5401
P. Kramkowski, M. Scheer, *Angew. Chem., Int. Ed. Engl.* **1999**, 38, 3183–3186.
L. Weber, in *Advances in Strained and Interesting Organic Molecules*, K. K. Laali, Ed., Suppl.1, JAI Press, Inc, Stamford, **1999**, p. 269.
O. I. Kolodiaznyi, *Phosphorus Ylides*, Wiley-VCH, Weinheim, **1999**.
F. G. N. Cloke, P. B. Hitchcock, J. F. Nixon, D. J. Wilson, P. Mountford, *J. Chem. Soc., Chem. Commun.* **1999**, 661–662.
S. B. Clendenning, B. Gehrhus, P. B. Hitchcock, J. F. Nixon, *J. Chem. Soc., Chem. Commun.* **1999**, 2451–2452.
L. Rigon, H. Ranaivonjatovo, J. Escudié, A. Dubourg, J.-P. Delercq, *Chem. Eur. J.* **1999**, 5, 774–781.
A. Elvers, F. W. Heinemann, B. Wrackmeyer, U. Zenneck, *Chem. Eur. J.* **1999**, 5, 3143–3153.
P. Binger, S. Stutzmann, J. Stannek, K. Günther, P. Phillips, R. Mynott, J. Bruckmann, C. Krüger, *Eur. J. Inorg. Chem.* **1999**, 763–769.
I. Shevchenko, R. Mikolenko, S. Loss, H. Grützmacher, *Eur. J. Inorg. Chem.* **1999**, 1665–1671.
L. Weber, S. Uthmann, H.-G. Stammer, B. Neumann, W. W. Schoeller, R. Boese, D. Bläser, *Eur. J. Inorg. Chem.* **1999**, 2369–2381.
A. Mack, U. Bergsträßer, G. J. Reiß, M. Regitz, *Eur. J. Org. Chem.* **1999**, 587–595.
T. Baumgartner, D. Gudat, M. Nieger, E. Niecke, T. J. Schiffer, *J. Am. Chem. Soc.* **1999**, 121, 5953–5960.
T. A. Schmedake, M. Haaf, Y. Apeloig, T. Müller, S. Bukalov, R. West, *J. Am. Chem. Soc.* **1999**, 121, 9479–9480.
G.-S. Deng, Z.-Z. Huang, X.-C. Yu, X. Huang, *J. Chem. Res. (S)* **1999**, 144–145.
C. Jones, J. W. Steed, R. C. Thomas, *J. Chem. Soc. Dalton Trans.* **1999**, 1541–1542.
D. Hibbs, C. Jones, A. F. Richards, *J. Chem. Soc. Dalton Trans.* **1999**, 3531–3532.
R. Navarro, E. P. Urriolabeitia, *J. Chem. Soc., Dalton Trans.* **1999**, 4111–4122.
R. A. Aitken, J. M. Armstrong, M. J. Drysdale, F. C. Ross, B. M. Ryan, *J. Chem. Soc., Perkin Trans. 1* **1999**, 593–604.
S. M. F. Asmus, U. Bergsträßer, M. Regitz, *Synthesis* **1999**, 1642–1650.
G. Becker, J. R. Heck, U. Hübner, W. Schwarz, E.-U. Würthwein, *Z. Anorg. Allg. Chem.* **1999**, 625, 2008–2024.
E. V. Popova, V. F. Mironov, E. A. Ishmaeva, I. I. Patsanovskii, *Zh. Obshch. Khim.* **1999**, 69, 52–54.
O. B. Smolii, S. Ya. Panchishin, E. A. Romanenko, B. S. Drach, *Zh. Obshch. Khim.* **1999**, 69, 1652–1656.
J. Ruiz, F. Marquinez, V. Riera, M. Vivanco, S. Garcia-Granda, M. R. Diaz, *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 1821–1823.
F. G. Hahn, L. W. Heubecher, D. Le Van, R. Fröhlich, B. Wibbeling, *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 2307–2310.
S. Ito, H. Sugiyama, M. Yoshifuji, *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 2781–2783.
T. Kato, H. Gornitzka, A. Baceiredo, G. Bertrand, *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 3319–3321.
S. B. Clendenning, P. B. Hitchcock, J. F. Nixon, L. Nyulászi, *J. Chem. Soc., Chem. Commun.* **2000**, 1305–1306.
F. Breitsameter, A. Schmidpeter, H. Nöth, *Chem. Eur. J.* **2000**, 6, 3531–3539.
F. Tabellion, C. Peters, U. Fischbeck, M. Regitz, F. Preuss, *Chem. Eur. J.* **2000**, 6, 4558–4566.
S. Ito, M. Yoshifuji, *Chem. Lett.* **2000**, 1390–1391.
M. Mori, S. Oida, *Chem. Pharm. Bull.* **2000**, 48, 126–130.
L. Weber, S. Kleibekel, A. Rühlicke, H.-G. Stammer, B. Neumann, *Eur. J. Inorg. Chem.* **2000**, 1185–1191.
J. Renner, U. Bergsträßer, P. Binger, M. Regitz, *Eur. J. Inorg. Chem.* **2000**, 2337–2340.
L. Weber, *Eur. J. Inorg. Chem.* **2000**, 2425–2441.
C. Jones, A. F. Richards, *J. Chem. Soc. Dalton Trans.* **2000**, 3233–3234.
G. S. Deng, Z.-Z. Huang, X. Huang, *Chin. Chem. Lett.* **2000**, 11, 293–294.
S. M. Pugh, D. J. M. Trösch, D. J. Wilson, A. Bashall, F. G. N. Cloke, L. H. Gade, P. B. Hitchcock, M. Mc Partlin, J. F. Nixon, P. Mountford, *Organometallics* **2000**, 19, 3205–3210.
C. Peters, S. Stutzmann, H. Disteldorf, S. Werner, U. Bergsträßer, C. Krüger, P. Binger, M. Regitz, *Synthesis* **2000**, 529–536.
C. Buron, H. Gornitzka, V. Romanenko, G. Bertrand, *Science* **2000**, 288, 834–836.
J. Grobe, D. Le Van, A. H. Maulitz, B. Krebs, M. Läge, *Z. Anorg. Allg. Chem.* **2000**, 626, 1141–1147.
G. Heckmann, S. Plank, B. Neumüller, E. Fluck, *Z. Anorg. Allg. Chem.* **2000**, 626, 1739–1746.
F. E. Hahn, D. Le Van, M. C. Moyes, T. v. Fehren, R. Fröhlich, E.-U. Würthwein, *Angew. Chem., Int. Ed. Engl.* **2001**, 40, 3144–3147.
M. J. M. Vlaar, A. W. Ehlers, M. Schakel, S. B. Clendenning, J. F. Nixon, M. Lutz, A. L. Spek, K. Lammertsma, *Angew. Chem., Int. Ed. Engl.* **2001**, 40, 4412–4415.
F. Meiners, W. Saak, M. Weidenbruch, *J. Chem. Soc., Chem. Commun.* **2001**, 215–216.
C. Jones, J. A. Platts, A. F. Richards, *J. Chem. Soc., Chem. Commun.* **2001**, 663–664.
C. Jones, *Coord. Chem. Rev.* **2001**, 215, 151–169.
M. J. M. Vlaar, A. W. Ehlers, M. Schakel, S. B. Clendenning, J. F. Nixon, M. Lutz, A. L. Spek, K. Lammertsma, *Chem. Eur. J.* **2001**, 7, 3545–3550.
L. Weber, M. Meyer, H.-G. Stammer, B. Neumann, *Chem. Eur. J.* **2001**, 7, 5401–5408.

- 2001EJI2377 I. Shevchenko, R. N. Mikolenko, E. Lork, G.-V. Rösenthaller, *Eur. J. Inorg. Chem.* **2001**, 2377–2383.
- 2001EJO3425 C. Peters, H. Disteldorf, E. Fuchs, S. Werner, S. Stutzmann, J. Bruckmann, C. Krüger, P. Binger, H. Heydt, M. Regitz, *Eur. J. Org. Chem.* **2001**, 3425–3435.
- 2001JOM(629)109 C. Jones, A. F. Richards, *J. Organomet. Chem.* **2001**, 629, 109–113.
- 2001IOM5629 M. Said, M. Thonton-Pett, M. Bochmann, *Organometallics* **2001**, 20, 5629–5635.
- 2001SL1065 O. I. Kolodiaznyi, R. Schmutzler, *Synlett* **2001**, 1065–1078.
- 2001ZAAC863 L. Weber, S. Kleinebckel, P. Lönnecke, *Z. Anorg. Allg. Chem.* **2001**, 627, 863–868.
- 2002AG(E)2389 V. A. Wright, D. P. Gates, *Angew. Chem., Int. Ed. Engl.* **2002**, 41, 2389–2392.
- 2002AG(E)2574 F. Murakami, S. Sasaki, M. Yoshifuji, *Angew. Chem., Int. Ed. Engl.* **2002**, 41, 2574–2576.
- 2002AG(E)2835 E. Despagne, H. Gornitzka, A. B. Rozhenko, W. W. Schoeller, D. Bourissou, G. Bertrand, *Angew. Chem., Int. Ed. Engl.* **2002**, 41, 2835–2837.
- 2002CC454 N. Hofmann, C. Wismach, P. G. Jones, R. Streubel, N. H. T. Huy, F. Mathey, *J. Chem. Soc., Chem. Commun.* **2002**, 454–455.
- 2002CC1744 S. Ito, H. Sugiyama, M. Yoshifuji, *J. Chem. Soc., Chem. Commun.* **2002**, 1744–1745.
- 2002CEJ2622 M. M. Al-Ktaifani, W. Bauer, U. Bergsträßer, B. Breit, M. D. Francis, F. W. Heinemann, P. B. Hitchcock, A. Mack, J. F. Nixon, H. Pritzkow, M. Regitz, M. Zeller, U. Zenneck, *Chem. Eur. J.* **2002**, 8, 2622–2633.
- 2002EJI2985 I. Shevchenko, V. Andrushko, E. Lork, G.-V. Rösenthaller, *Eur. J. Inorg. Chem.* **2002**, 2985–2990.
- 2002JA11614 V. V. Zhdankin, O. Maydanovych, J. Herschbach, R. McDonald, R. R. Tykwinski, *J. Am. Chem. Soc.* **2002**, 124, 11614–11615.
- 2002JA11834 E. Despagne, K. Miqueu, H. Gornitzka, P. W. Dyer, D. Bourissou, G. Bertrand, *J. Am. Chem. Soc.* **2002**, 124, 11834–11835.
- 2002JCS(D)484 S. B. Clendenning, B. Gehrhus, P. B. Hitchcock, D. F. Moser, J. F. Nixon, R. West, *J. Chem. Soc. Dalton Trans.* **2002**, 484–490.
- 2002JOC8261 Z. Huang, X. Yu, X. Huang, *J. Org. Chem.* **2002**, 67, 8261–8264.
- 2002JOM(643-644)409 A. Mack, S. Danner, U. Bergsträßer, H. Heydt, M. Regitz, *J. Organomet. Chem.* **2002**, 643–644, 409–415.
- 2002JOM(645)256 C. Jones, A. F. Richards, *J. Organomet. Chem.* **2002**, 645, 256–261.
- 2002JOM(650)57 N. H. T. Huy, C. Compain, L. Ricard, F. Mathey, *J. Organomet. Chem.* **2002**, 650, 57–58.
- 2002JOM(665)7 S. E. d'Arbeloff-Wilson, P. B. Hitchcock, J. F. Nixon, L. Nyulászi, *J. Organomet. Chem.* **2002**, 655, 7–15.
- B-2002MI523-03 Renner, J., Ph. D. Thesis, **2002**, Universität Kaiserslautern.
- B-2002MI523-05 Weidner, S., Ph. D. Thesis, **2002**, Universität Kaiserslautern.
- 2002NJC1209 C. Jones, P. C. Junk, A. F. Richards, M. Waugh, *Nouv. J. Chim.* **2002**, 26, 1209–1215.
- 2002OM3196 A. T. Termaten, T. Nijbacker, M. Schakel, M. Lutz, A. L. Spek, K. Lammertsma, *Organometallics* **2002**, 21, 3196–3202.
- 2002OM4919 T. Baumgartner, P. Moors, M. Nieger, H. Hupfer, E. Niecke, *Organometallics* **2002**, 21, 4919–4926.
- 2002SL1281 Z.-Z. Huang, L. Wang, *Synlett* **2002**, 1281–1282.
- 2002TL2359 V. V. Zhdankin, O. Maydanovych, J. Herschbach, J. Bruno, E. D. Matveeva, N. S. Zefirov, *Tetrahedron Lett.* **2002**, 43, 2359–2361.
- 2002TL6823 Z.-Z. Huang, X.-C. Yu, X. Huang, *Tetrahedron Lett.* **2002**, 43, 6823–6825.
- 2002ZAAC803 L. Weber, S. Kleinebckel, P. Lönnecke, *Z. Anorg. Allg. Chem.* **2002**, 628, 803–809.
- 2003EJO2039 E. Despagne-Ayoub, H. Gornitzka, D. Bourissou, G. Bertrand, *Eur. J. Org. Chem.* **2003**, 2039–2042.
- 2003JOM(665)127 S. Aldridge, C. Jones, P. C. Junk, A. F. Richards, M. Waugh, *J. Organomet. Chem.* **2003**, 665, 127–134.
- 2003TCC67 M. Yoshifuji, S. Ito, *Top. Curr. Chem.* **2003**, 223, 67–89.
- 2003ZN(B)44 C. Peters, U. Fischbeck, F. Tabellion, M. Regitz, F. Preuss, *Z. Naturforsch. Teil B* **2003**, 58, 44–51.

Biographical sketch



Lothar Weber was born in 1944 in Langenöls in Schlesien. He studied at the Universität Marburg and received his doctorate there under the direction of Professor Günter Schmid in 1973. Thereafter he carried out postdoctoral studies with Professor Barry M. Trost at the University of Wisconsin in Madison, USA. On his return to Marburg, he began the experimental work leading to his habilitation, which was completed in 1982 at the Universität Essen. His work focuses on the coordination chemistry of sulfur ylides. In 1985, he became a C2 Professor and then joined the Fakultät für Chemie der Universität Bielefeld. His research interests include the chemistry of compounds with low-coordinate elements of the fifth main group, the synthesis of homo- and heterocycles with heavy elements, as well as new aspects in boron chemistry.

5.24

Doubly Bonded Metalloid Functions, $R^1C(X)=SiR_2^2$, $R^1C(X)=BR^2$, $R^1C(X)=GeR_2^2$

L. HAUGHTON and C. FLYNN

Eli Lilly and Company Ltd., Windlesham, UK

5.24.1	SILICON DERIVATIVES, $R^1C(X)=SiR_2^2$	903
5.24.1.1	Oxasilenes, $R_2^2Si=CR^1-OR^3$	903
5.24.1.1.1	From acyl silanes	903
5.24.1.2	Silasilenes, $R_2^2Si=CR^1-SiR_3^3$	907
5.24.1.3	Germasilenes, $R_2^2Si=CR^1-GeR_3^3$	907
5.24.2	GERMANIUM DERIVATIVES, $R^1C(X)=GeR_2^2$	907
5.24.3	BORON DERIVATIVES, $R^1C(X)=BR^2$	907

5.24.1 SILICON DERIVATIVES, $R^1C(X)=SiR_2^2$

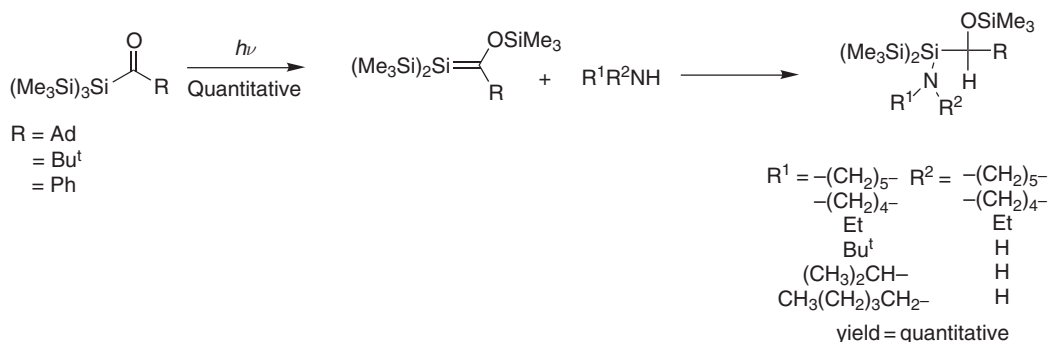
Silenes are generally reactive species that are not isolated but rather trapped *in situ*. Examples of the atom X (not including carbon) in the general structure $R^1C(X)=SiR_2^2$ were found in *Chemical Abstracts* for oxygen, silicon, and germanium. As the subject of silenes has become more widely understood, a number of reviews are now available including chapter 5.24 in COFGT (1995) <1995COFGT(5)923, 1998JCS(P1)2209, 1998CCR565>. A comprehensive review of silenes $Si=C$ entitled *The Chemistry of Silenes* <1996AOC71> has been published by Brook which covers the synthesis, physical properties, and chemical behavior of these species. The photochemistry <B-1998MI1233> of organosilicon compounds and kinetic studies of the reactions of $Si=C$ bonds <B-2001MI949, 1998JA9504> have also been recently reviewed.

5.24.1.1 Oxasilenes, $R_2^2Si=CR^1-OR^3$

5.24.1.1.1 From acyl silanes

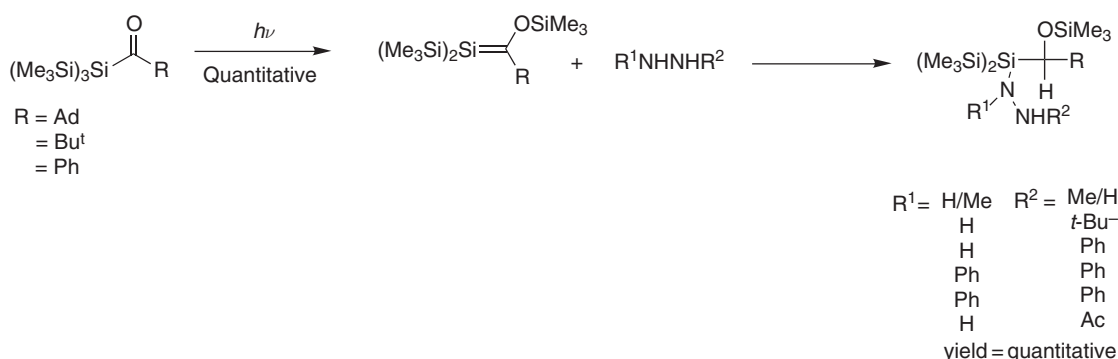
It has been widely demonstrated that oxasilenes can be readily generated by either thermal or photochemical 1,3-silyl rearrangement of acyl silanes (Scheme 1) <1995COFGT(5)923>. The [2+2]-addition reactions of silenes with a variety of reagents, including alcohols and ketones, have been described by a variety of groups and summarized in several reviews <1996AOC71,

[B-1998MI827](#)>. In 2000 the first examples of the addition of nitrogen nucleophiles to oxasilenes were reported [<2000OM1859>](#). It was found that both primary and secondary amines can add to silenes of the family $(\text{Me}_3\text{Si})_2\text{Si}=\text{C}(\text{OSiMe}_3)\text{R}$ in almost quantitative yields.



Scheme 1

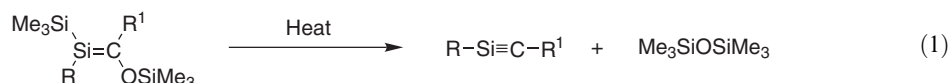
Using the same experimental conditions, hydrazines and ureas [<2003OM1314>](#) can also add to these oxasilenes in essentially quantitative yields (Scheme 2).



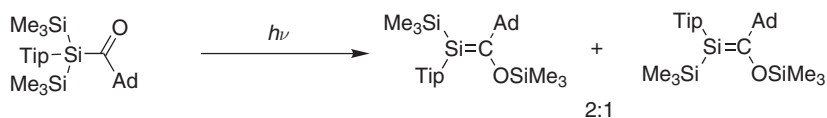
Scheme 2

Further exemplification of the reactions of oxasilenes with ketones [<1996OM3836>](#) and a review of their reactions with alcohols [<B-1998MI827>](#) have been published.

In the absence of trapping agents, oxasilenes undergo self-dimerization to produce head-to-head dimers and/or readily convert back to their parent acyl silanes. However, a stable oxasilene of the family $(\text{Me}_3\text{Si})\text{RSi}=\text{C}(\text{OSiMe}_3)\text{Ad}$ (Ad = adamantyl) has been isolated and characterized where $\text{R} = t\text{-Bu}$ [<1989OM693>](#). More recently, Brook and co-workers have studied the role of the R group in the reactivities of silene $(\text{Me}_3\text{Si})\text{RSi}=\text{C}(\text{OSiMe}_3)\text{Ad}$. They found that when $\text{R} = \text{mesityl}$, the silene was relatively stable and did not revert back to its parent acyl silane but slowly decomposed. Brook speculated that the silene decomposed to form a compound containing the hitherto unknown silicon-carbon triple bond via the elimination of hexamethyldisiloxane (Equation (1)) [<1992OM3088>](#).

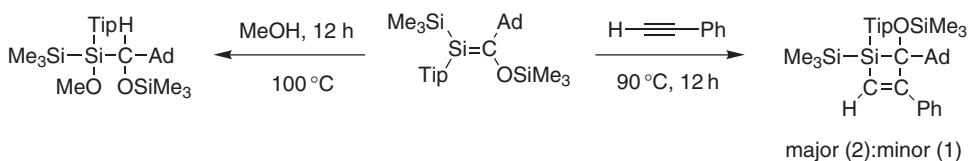


To understand this type of decomposition further, Brook and co-workers studied the reactivities of sterically hindered silenes such as $(\text{Me}_3\text{Si})\text{RSi}=\text{C}(\text{OSiMe}_3)\text{Ad}$ where $\text{R} = \text{Tip}$ (Tip = 2,4,6-triisopropylphenyl). The synthesis of the Tip-silene as a 2:1 mixture of geometric isomers was achieved through photolysis of its corresponding acylpolysilane (Scheme 3) [<1995OM4359>](#). With the Tip-silene in hand its reactivity was investigated.



Scheme 3

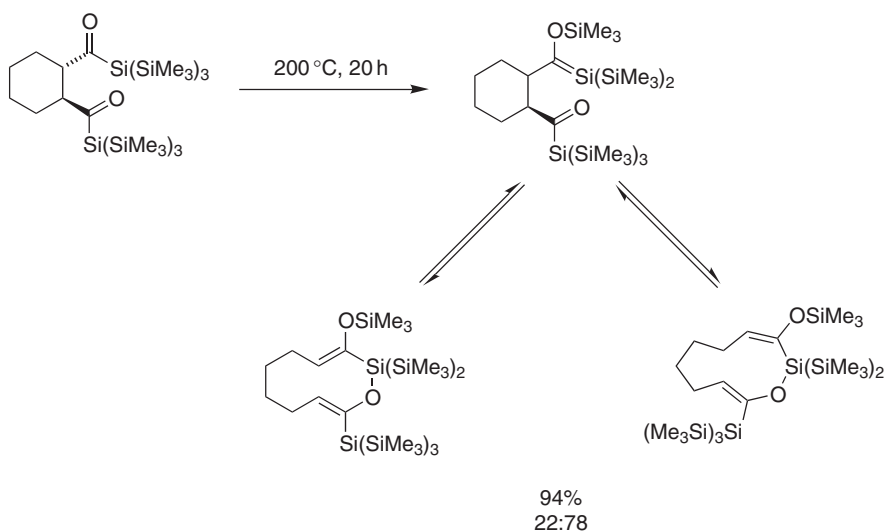
Thus when phenylacetylene was added to the Tip-silenes, a 2:1 mixture of the related 1-silacyclobut-2-enes was formed after the solution was heated to 90 °C for 12 h (Scheme 4). The reaction of methanol with a 2:1 mixture of the Tip-silenes did not immediately occur at 20 °C, but after 16 h the major silene isomer reacted exclusively to give a single methanol adduct, whereas the minor isomer remained unreacted. Reaction with methanol at 100 °C gave the methanol adducts of both isomers.



Scheme 4

It is worthy of note that generally the reactions of silenes with methanol have been observed to be nonstereospecific. It is thought that the bulkiness of the Tip group is why the reaction is stereospecific in this case <1995OM4359>.

To further explore the scope of the chemistry of acylpolysilanes, Oshita's group prepared the oxasilene from 1,2-bis[tris(trimethylsilyl)silylcarbonyl]cyclohexane and investigated its reaction under thermal conditions. Interestingly, the silenes generated underwent skeletal rearrangement to form one of two stereoisomeric silicon-containing macrocycles. This is the first reported example of an oxa-Cope type of rearrangement of silenes (Scheme 5) <2001JA8400>.

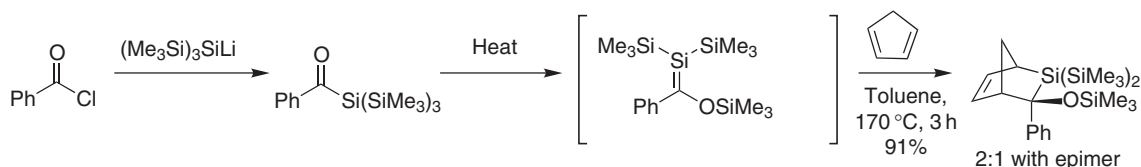


Scheme 5

The cycloaddition reactions of oxasilenes with nonsymmetrical dienes were first reported by Wiberg <1991CB1981>. Steele and co-workers <1996TL2491> have followed on from Wiberg's initial experimentation by investigating the diastereoselectivity in the Diels–Alder reactions of phenyl(trimethylsiloxy)silene with cyclopentadiene (Scheme 6).

To study the cycloaddition of phenyl(trimethylsiloxy)silene, the oxasilene precursor was prepared through the reaction of the appropriate acid chloride with tris(trimethylsilyl)silyllithium.

Photolysis of the acylsilane with cyclopentadiene produced the desired products, although the reaction times were lengthy and yields low. However, it was found that rearrangement to the silene and cycloaddition could simply and most efficiently be achieved through thermolysis. The reaction was repeated with a further three dienes (Table 1).

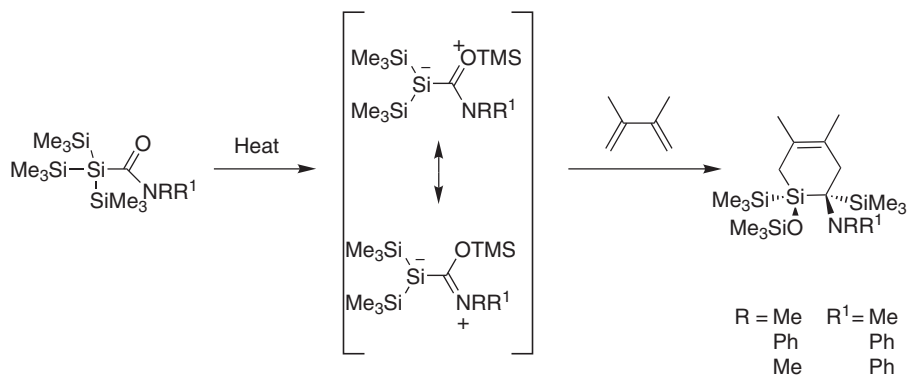


Scheme 6

Table 1 The Diels–Alder reactions of phenyl(trimethylsiloxy)silene

	Toluene, 180 °C, 2 h, 64%		75:25
	Toluene, 180 °C, 2 h, 57%		89:11
	Toluene, 175 °C, 2 h, 62%		85:15

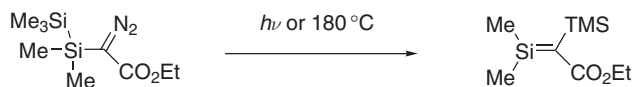
Furthermore, it has been reported that the thermal reaction of tris(trimethylsilyl)silylamides with 2,3-dimethyl-1,3-butadiene quantitatively yielded only one diastereoisomer of the functionalized cyclic allyl silane (Scheme 7) <2002OL1915>.



Scheme 7

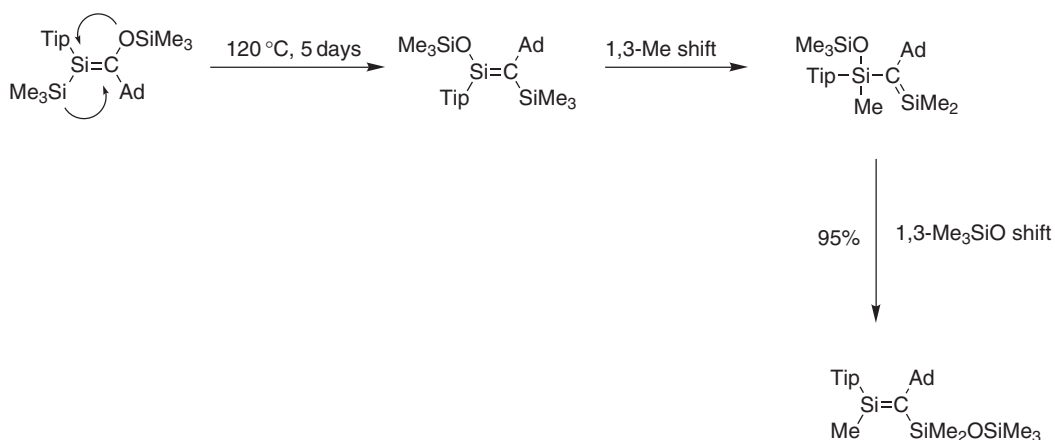
5.24.1.2 Silasilenes, $R_2Si=CR^1-SiR_3^3$

The photolysis or thermolysis of silyl-substituted diazo derivatives is a general route to silasilenes and usually proceeds in high yield. These reactions occur via an α -silylcarbene to give the corresponding silasilene <1981JA5573> (Scheme 8).



Scheme 8

More recently, Brook has reported the synthesis of a silasilene from an oxasilene. It was found that heating the Tip-silene neat at 120 °C for 5 days gave the silasilene product via a remarkable rearrangement. The reaction was followed by 1H and ^{29}Si NMR spectroscopy and gave a 95% yield of a single geometric isomer. A possible mechanism for the formation of the silasilene was proposed (Scheme 9) <1995OM4359>.



Scheme 9

5.24.1.3 Germasilenes, $R_2Si=CR^1-GeR_3^3$

There are no general synthetic methods for germasilenes and only one example is known in the literature <1980JA1584>, which has been outlined in the previous volume <1995COFGT(5)923>.

5.24.2 GERMANIUM DERIVATIVES, $R^1C(X)=GeR_2^2$

The literature describing germenes of the type $Ge=C-X$ relevant to this section is sparse with no new material being published since COFGT (1995).

5.24.3 BORON DERIVATIVES, $R^1C(X)=BR_2^2$

The literature describing boron derivatives of the type $R^1C(X)=BR_2^2$ relevant to this section is sparse with no new material being published since COFGT (1995).

REFERENCES

- 1980JA1584 T. J. Barton, *J. Am. Chem. Soc.* **1980**, *102*, 1584–1587.
 1981JA5573 W. Ando, A. T. Sekiguchi, T. Sato, *J. Am. Chem. Soc.* **1981**, *103*, 5573.
 1989OM693 K. M. Baines, A. G. Brook, R. R. Ford, P. D. Lickiss, A. K. Saxena, W. J. Chatterton, J. F. Sawyer, B. A. Behnem, *Organometallics* **1989**, *8*, 693–709.
 1991CB1981 N. Wiberg, S. Wagner, G. Fischer, *Chem. Ber.* **1991**, *124*, 1981–1983.
 1992OM3088 A. G. Brook, A. Baumegeger, A. Lough, *Organometallics* **1992**, *11*, 3088–3093.
 1995COFGT(5)923 B. P. Clark, Doubly bonded metalloid functions, $R^1C(X)=SiR_2^2$, $R^1C(X)=BR^2$, $R^1C(X)=GeR_2^2$, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 923–930.
 1995OM4359 P. Lassacher, A. G. Brook, A. J. Lough, *Organometallics* **1995**, *14*, 4359–4365.
 1996AOC71 A. G. Brook, M. A. Brook, *Adv. Organomet. Chem.* **1996**, 71–158.
 1996OM3836 M. Ishikawa, S. Matsui, A. Naka, J. Oshita, *Organometallics* **1996**, *15*, 3836–3843.
 1996TL2491 A. S. Batsanov, I. M. Clarkson, J. A. K. Howard, P. G. Steele, *Tetrahedron Lett.* **1996**, *37*, 2491–2494.
 B-1998MI827 Z. Rappoport, Y. Apeloig, Eds., in *The Chemistry of Organosilicon Compounds*, John Wiley and Sons Ltd., **1998**.
 B-1998MI1233 Z. Rappoport, Y. Apeloig, Eds., in *The Photochemistry of Organo-silicon Compounds*, John Wiley and Sons Ltd., **1998**.
 1998CCR565 J. Escudie, C. Couret, H. Ranaivonjato, *Coord. Chem. Rev.* **1998**, *178–180*, 565–592.
 1998JA9504 W. J. Leigh, R. Boukherroub, C. Kerst, *J. Am. Chem. Soc.* **1998**, *120*, 9504–9512.
 1998JCS(P1)2209 J. Hermanns, B. Schmidt, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2209–2230.
 2000OM1859 A. G. Brook, Z. Yu, *Organometallics* **2000**, *19*, 1859–1863.
 B-2001MI949 Z. Rappoport, Y. Apeloig, Eds., *Kinetic Studies of the Reaction of Si=C and Si=Si bonds*, John Wiley and Sons Ltd., **2001**.
 2001JA8400 J. Ohshita, K. Yoshimoto, T. Iida, A. Kunai, *J. Am. Chem. Soc.* **2001**, *123*, 8400–8401.
 2002OL1915 I. El-Sayed, T. Guliashvili, R. Hazell, A. Gogoll, H. Ottosson, *Org. Lett.* **2002**, *4*, 1915–1918.
 2003OM1314 D. Azarifar, *Organometallics* **2003**, *22*, 1314–1319.

Biographical sketch



Louise Haughton was born in the Lake District in 1973 and studied at Loughborough University, where she obtained a B.Sc. in 1996, working at Glaxo during her years of industrial placement. After spending 1997 in the laboratories of Professor Phillip Kocienski, University of Glasgow, she moved to University of Bath where she completed a Ph.D. entitled “Kinetic and Dynamic Kinetic Resolutions Using Enzymes in Organic Synthesis,” under the direction of Professor J. M. J. Williams. Currently she is working at Eli Lilly and Company as a Medicinal Chemist in the neuroscience therapeutic area.



Claire Flynn was born in Dundee, Scotland in 1974. She studied at Heriot-Watt University, where she obtained a B.Sc. in 1996. She moved to the University of Nottingham, where she completed a Ph.D. entitled “The Synthesis of Amino and Diamino-Sugars and the Evaluation of Sugar-Dye Conjugates,” under the direction of Dr. Mark Mascal, in collaboration with BASF. Currently she is working at Eli Lilly and Company as a Medicinal Chemist in the neuroscience therapeutic area.

5.25

Functions Doubly Bonded to a Metal

M. GÓMEZ-GALLEGO, M. J. MANCHEÑO, and M. A. SIERRA
Universidad Complutense, Madrid, Spain

5.25.1	INTRODUCTION	911
5.25.2	STRUCTURE AND BONDING	911
5.25.3	PREPARATION FROM NONCARBENE STARTING MATERIALS	912
5.25.3.1	The Fischer Reaction	912
5.25.3.1.1	From lithium salts	912
5.25.3.1.2	From “ate” complexes	917
5.25.3.1.3	From acyl complexes	918
5.25.3.2	Formation of the M=C Double Bond from Acid Derivatives	919
5.25.3.3	Alkyne-Vinylidene and Related Rearrangements	921
5.25.3.4	Miscellaneous Methods	923
5.25.4	FUNCTIONALIZATION OF PREFORMED CARBENE COMPLEXES WITH RETENTION OF THE CARBENE MOIETY	925
5.25.4.1	α -Carbanion Reactions	925
5.25.4.1.1	Alkylation and acylation	926
5.25.4.1.2	Aldol condensations and related processes	928
5.25.4.2	Conjugate Additions Involving Carbene Complexes	930
5.25.4.2.1	Carbene as a Michael acceptor	930
5.25.4.2.2	Carbene as a Michael donor	934
5.25.4.3	Cycloaddition Reactions	935
5.25.4.4	Miscellaneous Reactions	938

5.25.1 INTRODUCTION

The designed preparation of the first organometallic complex having an M=C double bond in 1964 by Fischer and Maasböl <1964AG(E)580> opened a new era in organometallic and organic chemistry. It soon became evident that the extremely high synthetic potential of these compounds with the applications of metal carbenes in organic synthesis was still growing <1995COMC-II(12)469, 1995COMC-II(12)549, 1996CRV271, 1997AOC163, 1997T4105, 1998MI551, 2000AG(E)3964, 2000CR3591, 2000T4597, 2001JOM(624)5>.

5.25.2 STRUCTURE AND BONDING

From a theoretical point of view <1994JP11406, 1995OM224, 1996IC775, 1996OM105, 1997JCS(D)1653, 1997JPC8887, 1997OM442, 1998CEJ1428, 1998OM1492, 1999EJI2037, 2001JOM(635)9, 2002OM4182>, Fischer carbene complexes may be regarded as derived from a singlet-state carbene. The electron density is donated to the metal from a filled “ sp^2 orbital” centered on the carbene carbon to an empty $4s4p3d$ hybrid on the metal forming the σ -bond. The π -bond is formed by back transfer from a filled degenerate d -orbital of the metal fragment to the vacant p -orbital centered on the carbene carbon (Figure 1).

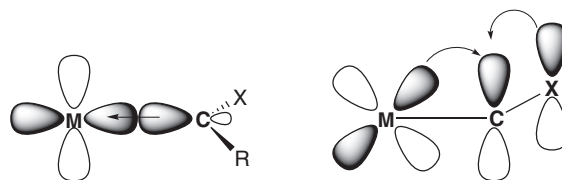


Figure 1

This simple model leads to two situations of bonding depending on the metal and the nature of the remaining ligands (Figure 2). To the first group belong those complexes having metals that are good π -back donors and good σ -acceptors resulting in strong $M=C$ bonds and, usually, in complexes having nucleophilic carbene carbons. Schrock-carbene complexes may be included in this group. A decrease in the carbene ability to accept electrons leads to longer $M=C$ bonds while maintaining the nucleophilicity of the carbene carbon. Grubbs's metathesis catalyst pertains to this group. The second situation is found in complexes with metals that are poor π -back donors but good σ -acceptors. This results in carbene complexes having electrophilic carbene carbons generically known as Fischer carbenes. Fischer carbene complexes have an additional stabilizing effect derived from the donation of the nonbonding electron pair of the heteroatom that is bonded to the carbene carbon. This donation results in a partial double bond character of the carbon–heteroatom bond and rotation around this bond is restricted. The efficiency of heteroatom donation follows the order $N > S > O$ and is reflected in the ^{13}C NMR shifts. Ylidenes having dipolar structures are the extreme situation of this type of complexes. These are in general highly reactive organometallic complexes that can be established by the combined donating ability of two heteroatoms joined to the carbene carbon.

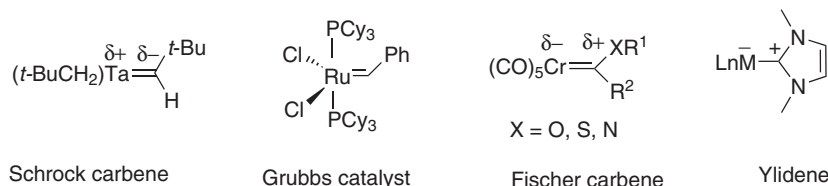


Figure 2

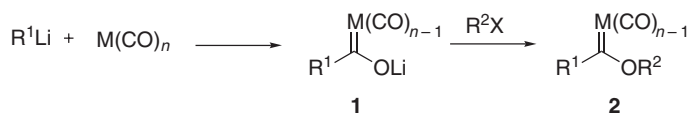
5.25.3 PREPARATION FROM NONCARBENE STARTING MATERIALS

Due to the evolution of the field since the publication of COFGT (1995) <1995COFGT(5)931>, the organization of this section has been rearranged according to the major routes of synthesis of metal–carbene complexes.

5.25.3.1 The Fischer Reaction

5.25.3.1.1 From lithium salts

The most common procedure for the synthesis of metal–carbene complexes is the Fischer synthesis, which involves coupling of an organolithium reagent with a metal carbonyl derivative. The intermediate anionic lithium acyl “ate” complex **1** is subsequently captured by a hard alkylating agent such as methyl triflate or trimethyloxonium salts, to produce the alkoxycarbene complex **2** in good yield (Scheme 1). The “ate” complexes can be isolated as the stable tetramethylammonium salts, which can be prepared on a large scale and stored for months without substantial decomposition. This simple method enables the preparation of alkyl (Figure 3) <1996JOC6121, 2002EJO39>, alkenyl (Equation (1)) <1995CB157, 2001EJO2501, 2002JA6512>, aryl (Equation (2)) <1999CC2385, 2001JOC1297>, and heteroaromatic carbene complexes (Equations (3)–(5)) <1997TL5587, 1997TL6787, 1999JOM(590)158, 2001T5199> and is general for a number of transition metals (e.g., Cr, Mo, W, Mn, Tc, Re, and Ni) (Equations (6) and (7)).



Scheme 1

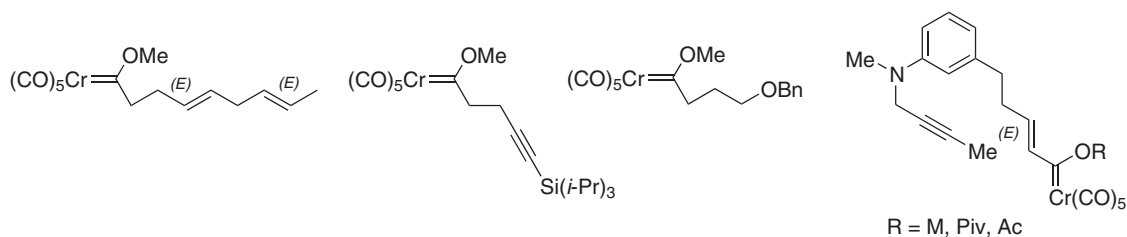
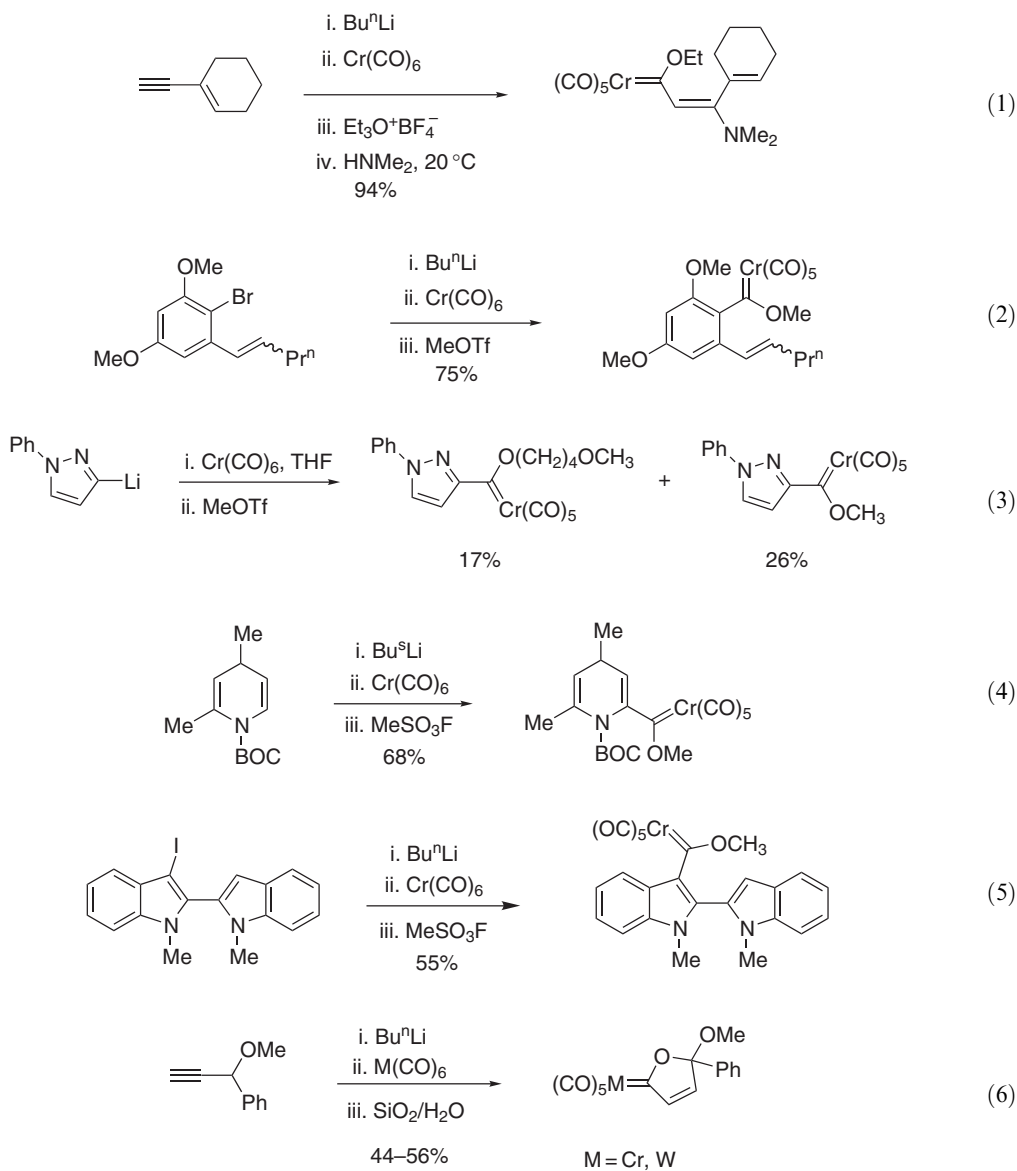
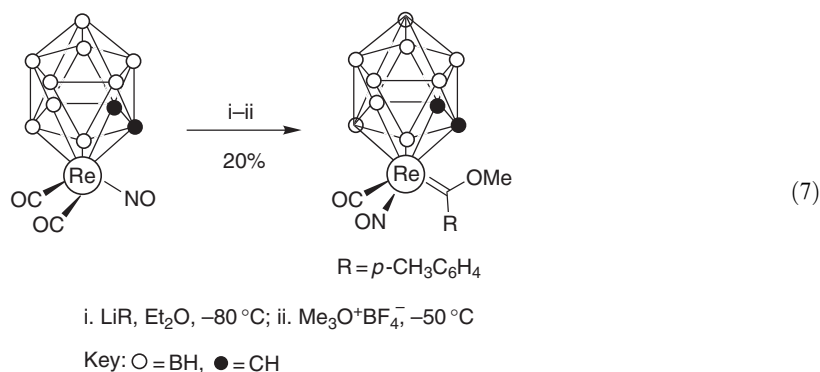
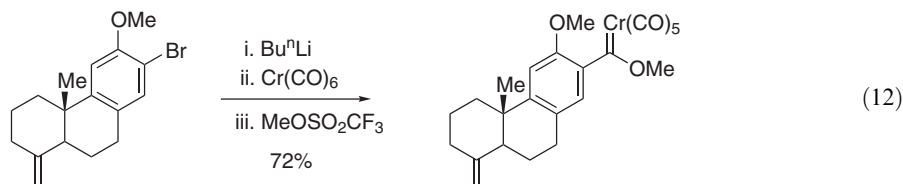
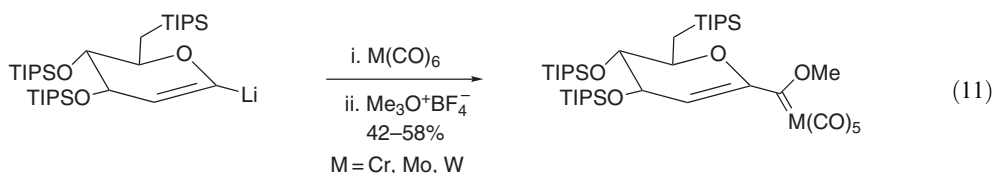
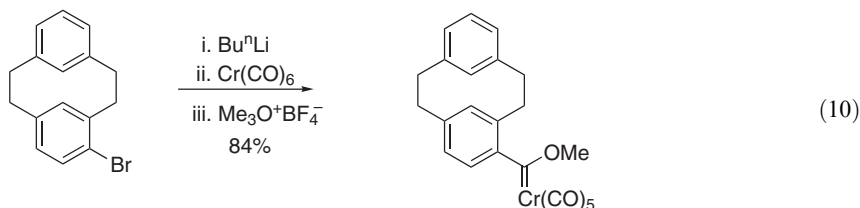
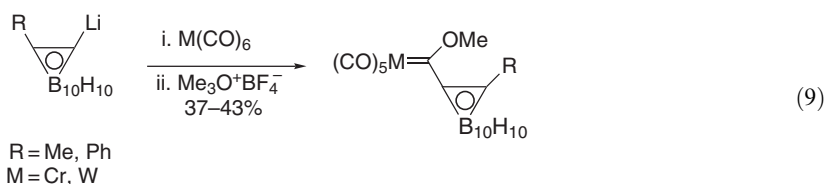
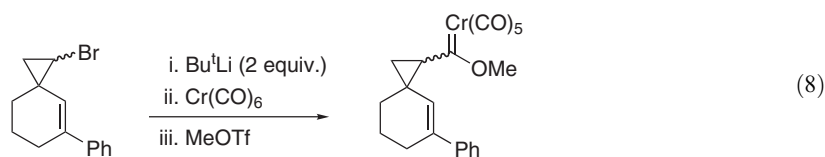


Figure 3

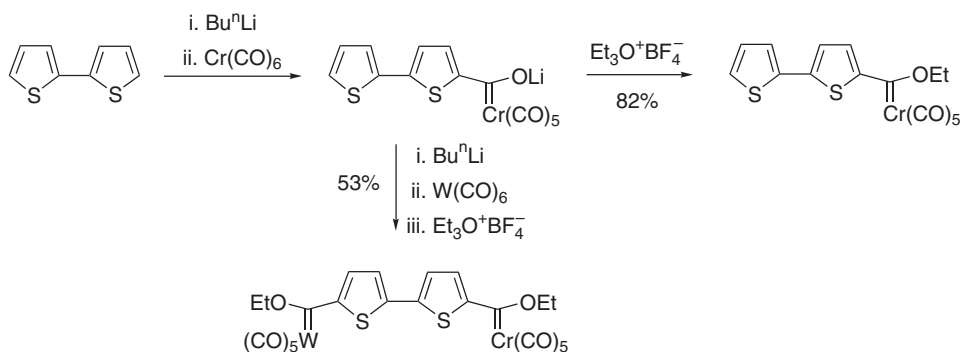
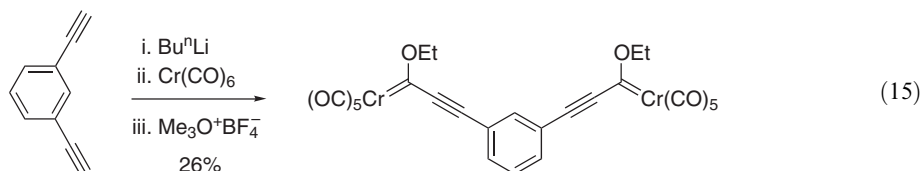
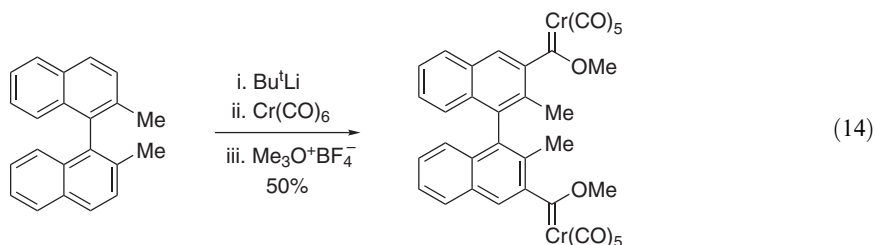
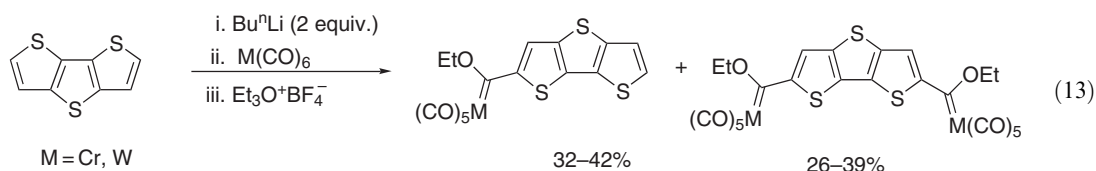




More complex structures can be obtained by the Fischer method. Thus, spiro (Equation (8)) <1996TL1359>, *o*-carboranyl (Equation (9)) <1997MI1061, 1998OM1109>, cyclophane (Equation (10)) <1997CB1105>, glycal carbene complexes (Equation (11)) <1997AG(E)2376>, and diterpenoid carbene derivatives (Equation (12)) <2001JOM(626)199, 2001JOM(629)114> can be prepared through this methodology.

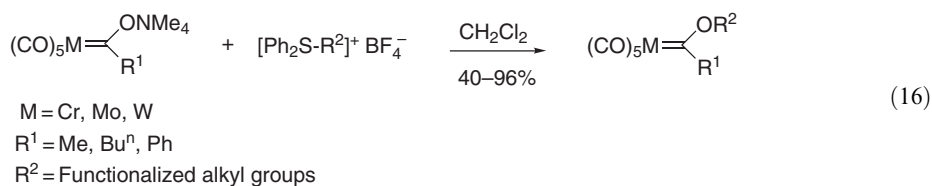


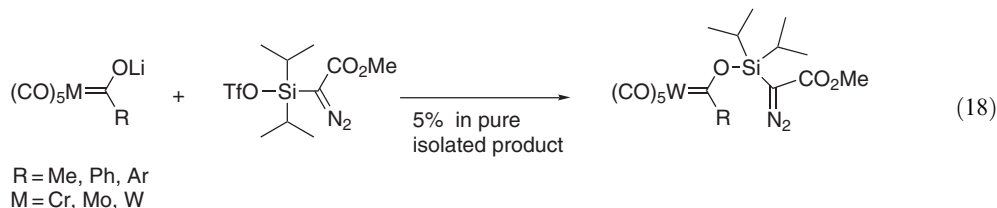
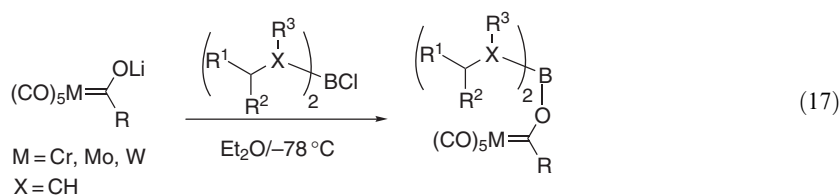
If the Fischer procedure is carried out with a dilithium derivative, then a biscarbene can be formed (Equations (13)–(15)) <1997CB1605, 2001EJ1233, 2001JOM(617–618)280, 2001OM4304>. In certain cases as in Scheme 2 mixed biscarbenes can be obtained by sequential reaction of the chromium acylate intermediate with the alkyllithium and W(CO)₆ <1995G377>.



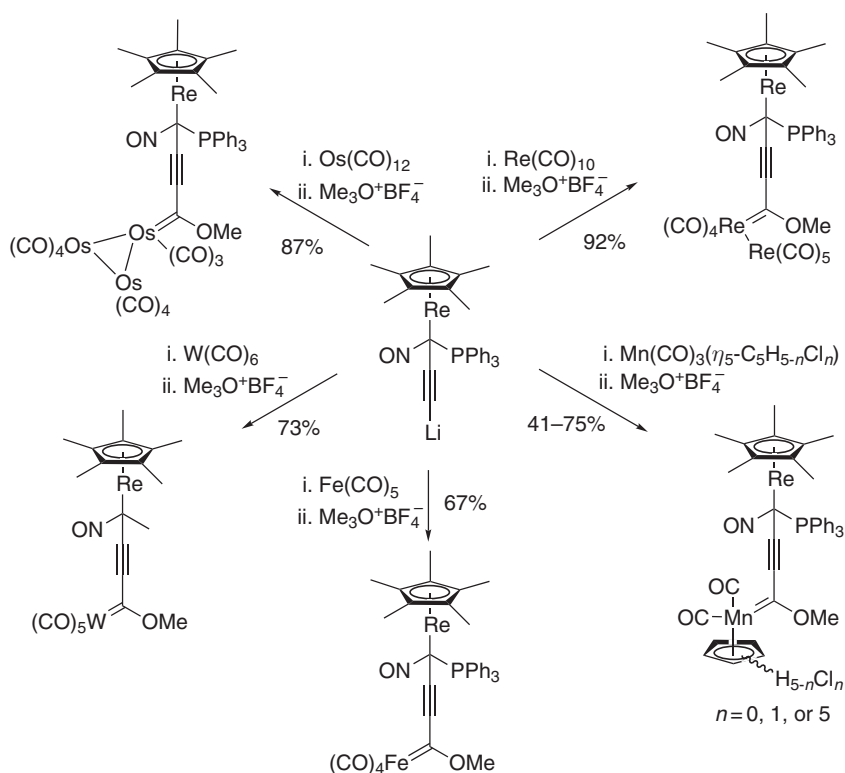
Scheme 2

Although trialkyloxonium salts and alkyl triflates are the most commonly employed alkylating agents in the Fischer reaction, some other reagents have been used to obtain alkoxy carbene complexes. Alkyldiphenylsulfonium salts are known to be a useful alternative to oxonium salts and have been employed in the synthesis of a series of functionalized chromium and tungsten Fischer-type alkoxy carbene complexes starting from the corresponding ammonium salts (Equation (16)) <2000JOC4796>. The treatment of the metal acylate intermediate with dialkylchloroboranes at -78°C leads to unstable dialkylboroxycarbene complexes ($\text{M} = \text{Cr, Mo, W}$) that on warming to room temperature underwent loss of the metal fragment affording oxaborolane derivatives in moderate yields (Equation (17)) <1996JA6090>. Additionally, silyloxycarbene complexes of chromium, molybdenum, and tungsten can be prepared by using (diazomethyl)silyl triflate as alkylating reagent. These compounds are thermolabile but they could be isolated and characterized (Equation (18)). Their manganese counterparts proved more stable <2001JOM(617–618)339>.

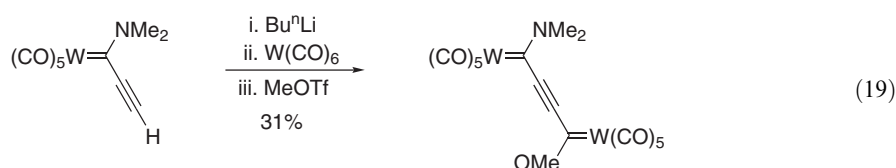


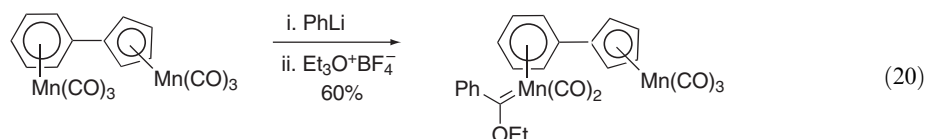


The Fischer method has also been employed to obtain polymetallic carbene complexes starting from metal alkynyllithium derivatives (Scheme 3) <1997OM2008, 1998JA11071, 1998CEJ1033>. Binuclear carbene complexes have been generated from the anions derived from alkynylaminocarbene complexes (Equation (19)) <1999OM2619, 2002OM4425>. Bimetallic carbene complexes have been obtained starting from metal carbonyls (Equation (20)) <1997JCS(D)205, 1997JCS(D)2177, 1997OM2808, 1997OM4056, 2001JOM(617–618)709>.

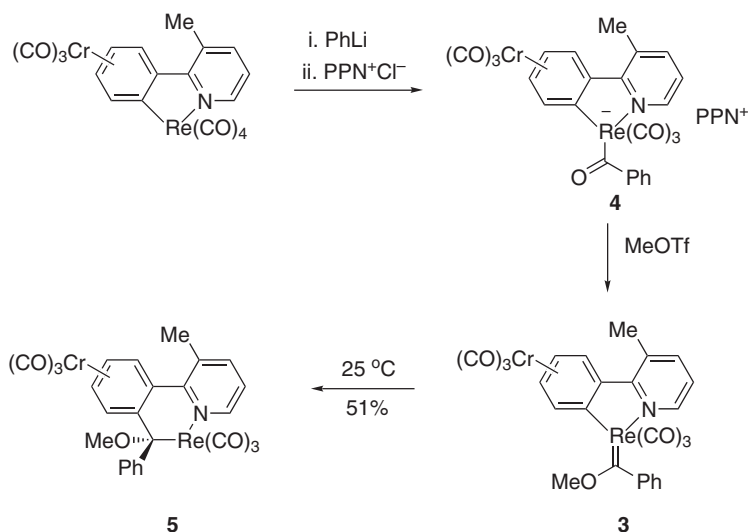


Scheme 3



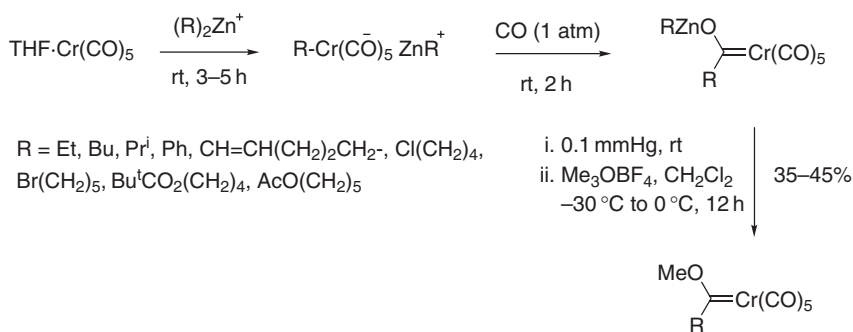


Alkoxyrhenium–carbene complexes **3** could be generated *in situ* from rhenium acylate species **4**. Upon warming to room temperature, migration of the carbene ligand occurs to provide bimetallic compounds **5** (Scheme 4). Alkylation of the manganese analog of **4** led directly to the manganese analog of complex **5** <2000OM5484>.



Scheme 4

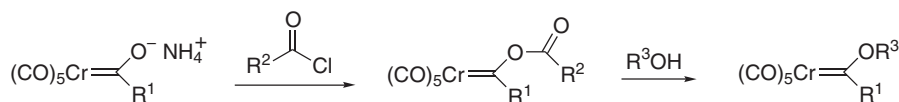
Related to the Fischer procedure is the reaction of functionalized dialkylzincs with photochemically generated $\text{Cr}(\text{CO})_5 \cdot \text{THF}$, to afford, after carbonylation and methylation with Meerwein's reagent, polyfunctional chromium carbene complexes in 35–45% yield (Scheme 5) <1995OM3163>.



Scheme 5

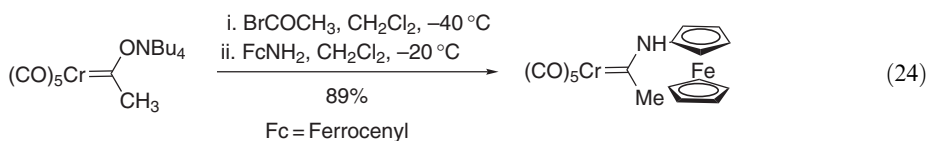
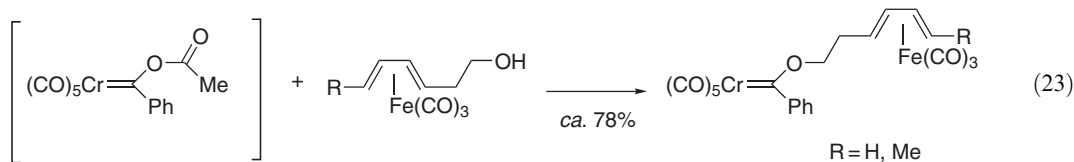
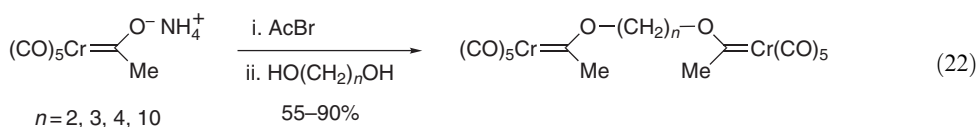
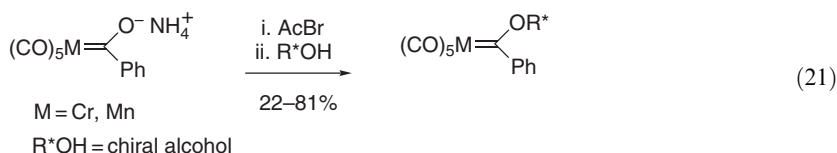
5.25.3.1.2 From “ate” complexes

Carbene complexes with structurally complex alkoxy groups are not directly available by the standard Fischer synthesis, because the corresponding alkyl triflates or oxonium salts are difficult to synthesize. However, acyloxycarbene complexes generated *in situ* by reaction of acid halides with ammonium acylate complexes react cleanly even with structurally complex alcohols, to produce alkoxy carbene complexes in excellent yield (Scheme 6).



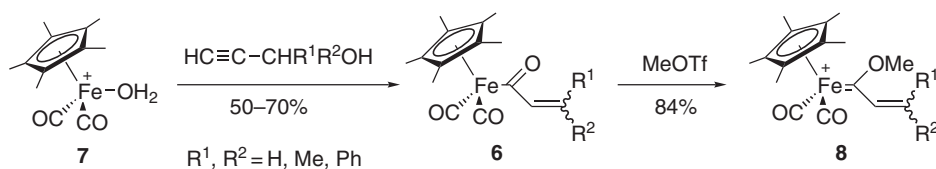
Scheme 6

This method has been used to introduce chiral alcohols in chromium and manganese carbene complexes (Equation (21)) <1997TA1751, 1998EJI339, 2001JOM(621)344, 2001S200>, in the synthesis of biscarbenes (Equation (22)) <1995JA3368, 1996JA2166, 2000OM2179>, or to obtain (η^4 -diene)Fe(CO)₃ complexes bearing a chromium carbene moiety (Equation (23)) <1997OM4435>. If an amine is employed instead of an alcohol, then aminocarbenes are obtained (Equation (24)) <1996CB623, 1997BSF503, 2001JOC8920>.

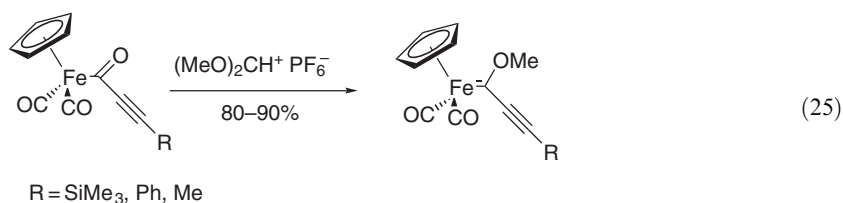


5.25.3.1.3 From acyl complexes

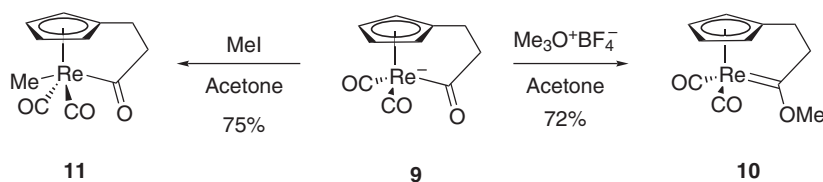
Alkoxy carbene complexes can also be prepared from metal acyl complexes. Acyliron carbene complexes **6** can be obtained in good yield by treatment of complex **7** with 2-alkyn-1-ols. These complexes can be converted into the cationic α,β -unsaturated alkoxy carbenes **8** via *O*-methylation with MeOTf (Scheme 7) <1997SL913>. Other examples using (MeO)₂CH⁺PF₆⁻ as methylating agent have been reported (Equation (25)) <1995SL1194, 1996CB937>.



Scheme 7



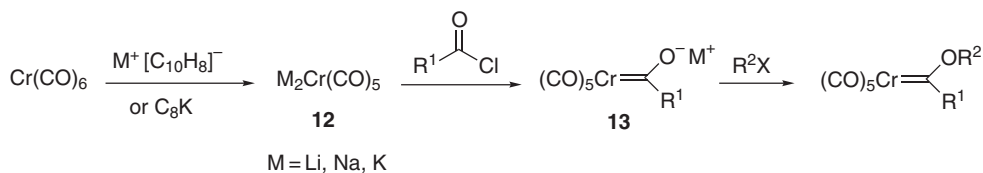
Several alkoxy cobalt and iron Fischer carbene complexes have been prepared by reaction of the corresponding metal acyl complex with triflates or oxonium salts <1995JOM(493)113, 1997CB863, 1997OM124, 1998OM1333>. Regioselective methylation of cyclic rhenium acyl anions **9** can be accomplished by using the adequate correct combination of solvent and alkylating agent (Scheme 8). Reaction of **9** with Me₃O·BF₄ in acetone exclusively gives the *O*-methylated product **10** whereas reaction with MeI in acetone or THF yields the methylacyl complex **11** <1997JA3971>.



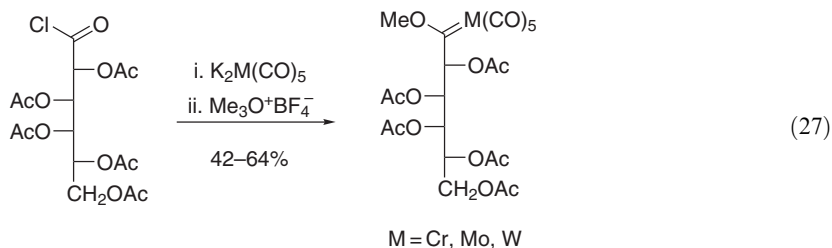
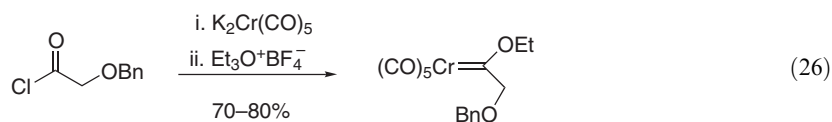
Scheme 8

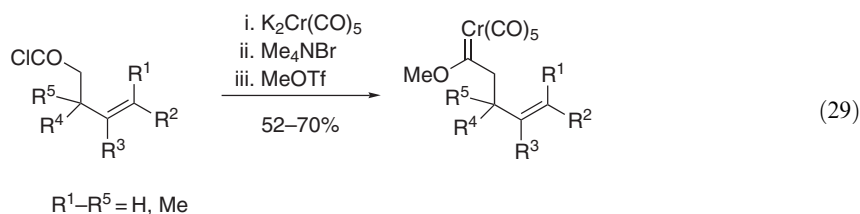
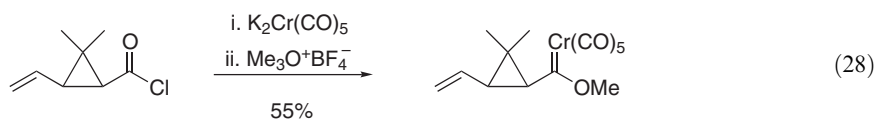
5.25.3.2 Formation of the M=C Double Bond from Acid Derivatives

Chromium hexacarbonyl is easily reduced to the dianion salt **12** by sodium (or lithium) naphthalenide or potassium/graphite intercalate (Scheme 9). Treatment with acid chlorides generates the anionic acyl complex **13** that undergoes *O*-alkylation with an oxonium salt to produce carbene complexes. This procedure has been used in the synthesis of benzyloxymethyl carbene complexes <1997OM2313>, carbene complex functionalized acyclic carbohydrates (and their molybdenum and tungsten analogs) <1997JOM(548)91>, vinylcyclopropyl carbenes <1996JA7873>, and γ,δ -unsaturated carbene complexes <2002OL2121> (Equations (26)–(29)).

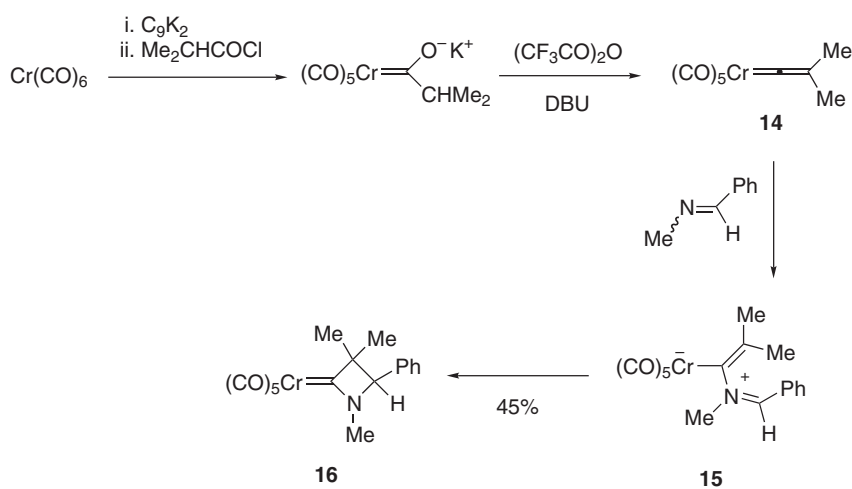


Scheme 9



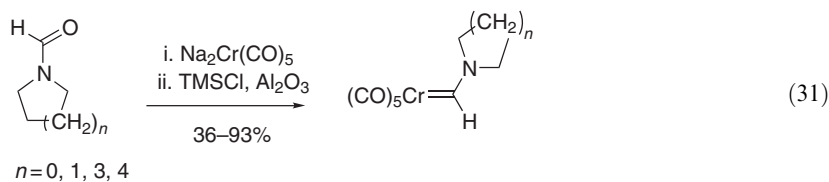
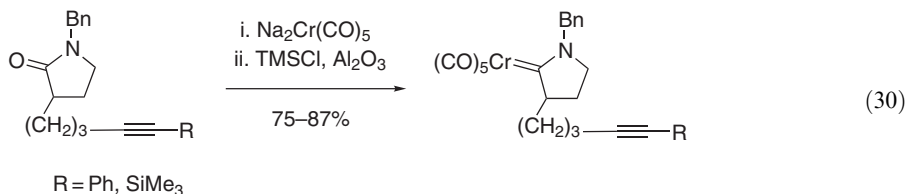


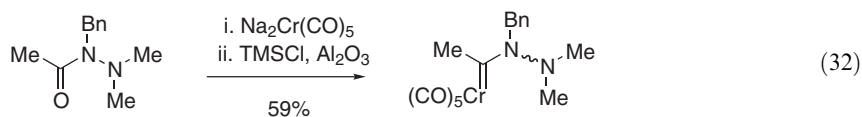
The reduction of Cr(CO)_6 with potassium-graphite (C_9K_2) and subsequent reaction with isobutyryl chloride and trifluoroacetic acid anhydride affords unstable vinylidene complex **14**. The reaction of **14** with *N*-methyl benzylideneamine leads to 2-azetidin-1-ylidene complex **16** through the unstable zwitterionic intermediate complex **15** (Scheme 10) <2001JOM(620)165>.



Scheme 10

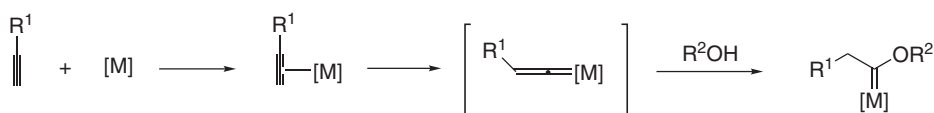
If amides are used instead of acid chlorides, aminocarbene complexes are obtained, this time utilizing trimethylsilyl chloride (TMSCl) to assist the final elimination step (Equations (30) and (31)) <1995OM2760, 1997JOC7247, 1998OM3627>. The use of hydrazides produces hydrazine alkyl Fischer carbene complexes (Equation (32)) <1998CC383>.





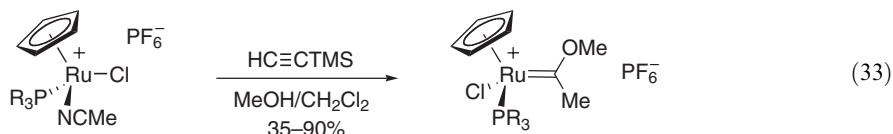
5.25.3.3 Alkyne–Vinylidene and Related Rearrangements

The reaction of terminal alkynes with active $\text{M}(\text{CO})_5$ species (the so-called alkyne–vinylidene rearrangement) constitutes a useful route to obtain alkoxy Fischer carbene complexes. After the initial coordination of the metal with the alkyne triple bond, an intramolecular hydride transfer forms a metal–vinylidene intermediate that in the presence of a nucleophilic reagent (e.g., an alcohol) leads finally to the carbene complex (Scheme 11).

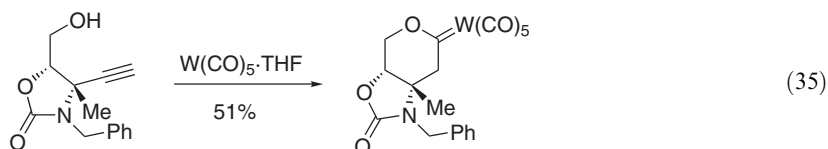
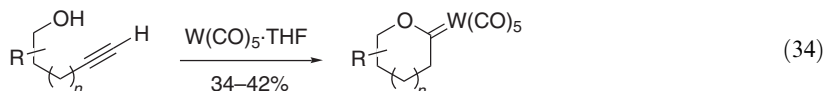


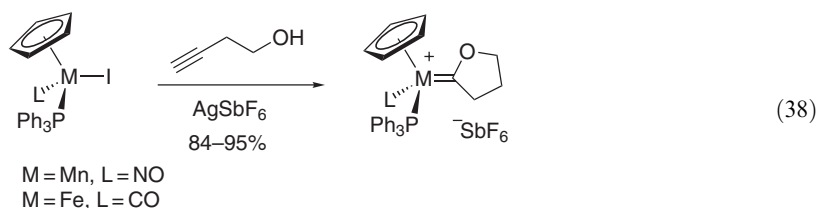
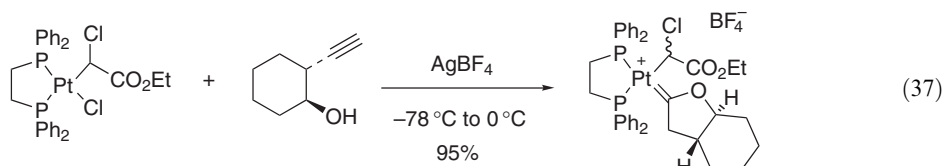
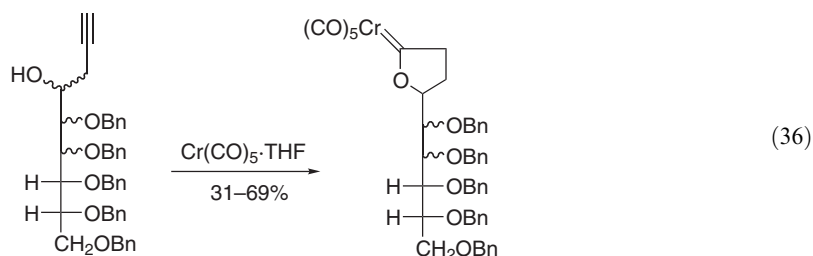
Scheme 11

This sequence has been employed for the synthesis of different cationic ruthenium (Equation (33)) <1997OM5089, 1997OM5528, 1999OM2275, 2000EJ133, 2000OM4740> and platinum complexes <2000JOM(608)34>. When amines or imines are used as nucleophiles, aminocarbenes are formed <1999OM2376, 2000JOM(599)288>.

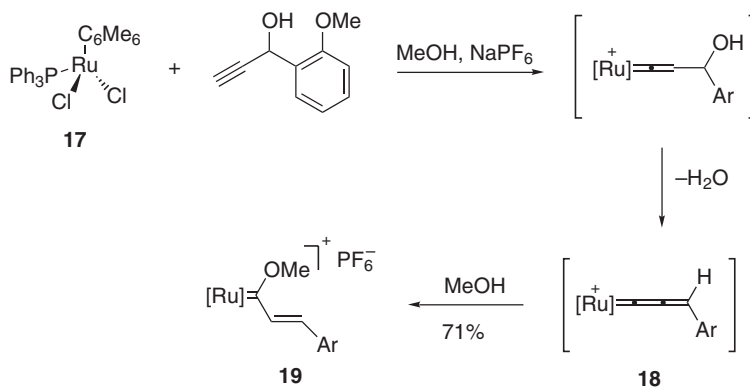


The alkyne–vinylidene rearrangement can be employed in the synthesis of cyclic alkoxy carbene complexes starting from alkynols. In such cases, by intramolecular nucleophilic attack of the OH group onto the metal–vinylidene intermediate, mono- and bicyclic 2-oxacylocarbenes <1996TL4675, 1997T11061, 1997TL7687, 1997TL7691, 1997JOM(539)201, 1997JOM(541)321, 1998EJ1211, 1998OM1602>, carbohydrate-functionalized carbene complexes <1997T5143, 2000JOM(602)37>, platinum carbene complexes <1997OM3083>, and cationic chiral-at-the-metal carbene complexes of manganese and iron, starting from coordinatively unsaturated chiral $[\text{Cp}(\text{NO})(\text{Ph}_3\text{P})]\text{Mn}^+$ and $[\text{Cp}(\text{CO})(\text{Ph}_3\text{P})]\text{Fe}^+$ complexes have been obtained (Equations (34)–(38)) <2001OM4114>.





Propargylic alcohols react slightly different, as shown in [Scheme 12](#) for the permethylbenzene–ruthenium complex [17](#) [<1997JOM\(533\)213>](#). The unstable metal–vinylidene complex formed in the first instance readily dehydrates under the reaction conditions to form allenylidene complex [18](#), which undergoes *in situ* capture with methanol to yield alkenyl ruthenium carbene complex [19](#). This methodology allows for the preparation of α,β -unsaturated Fischer carbene complexes of Cr, W, Ru, and Os ([Figure 4](#)) [<1995OM1938, 1997OM2483, 1999JOM\(589\)11, 2000JOM\(601\)78, 2000OM4, 2002JCS\(D\)1479>](#) and also for the formation of enynylcarbene complexes starting from diyn-3-ols ([Equation \(39\)](#)) [<1996SL435>](#).



Scheme 12

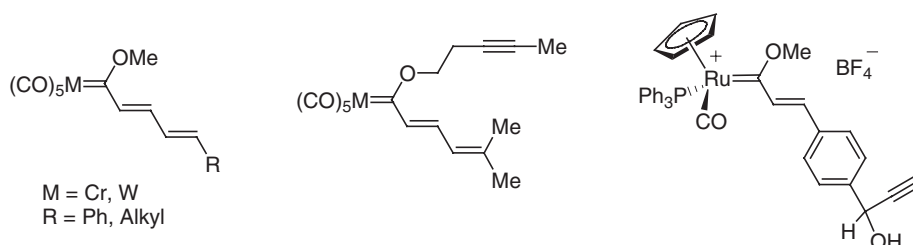
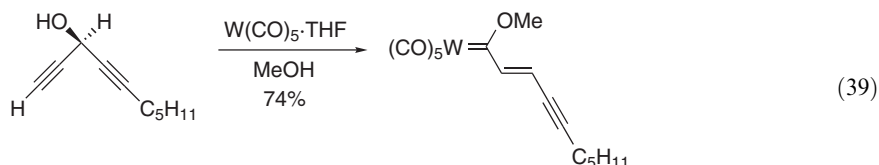
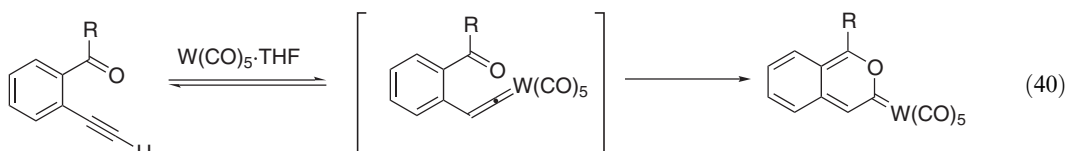


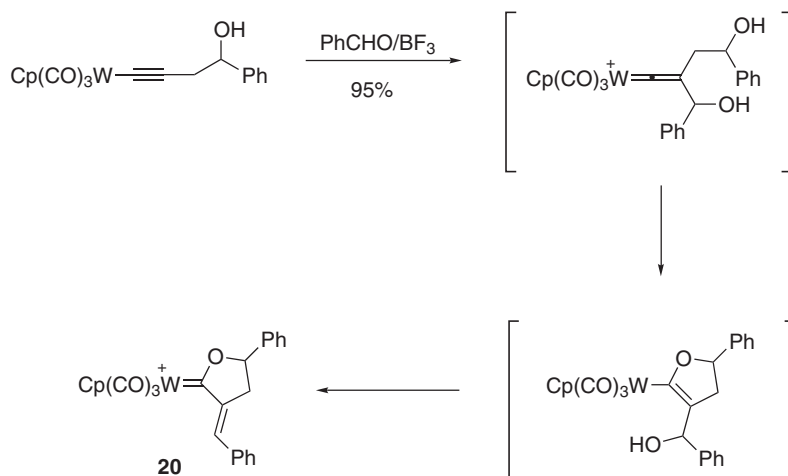
Figure 4



The alkyne-vinylidene rearrangement has also been proposed in the reaction of *o*-ethynylphenyl ketones with $\text{W(CO)}_5\cdot\text{THF}$. Now the vinylidene intermediates are transformed into pyranilidene complexes by electrocyclization (Equation (40)) <2000JA10226, 2001JA5814>. A similar process has been described for alkynyl esters and amides <2000OM5525, 2002JOM(645)228>.



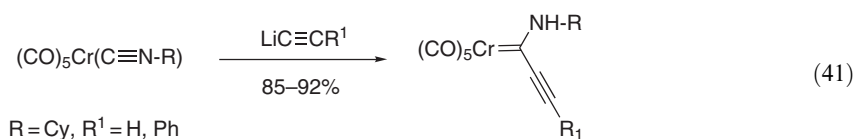
Group 6 metal-vinylidene complexes can be generated by other procedures. The reaction of aldehydes and alkynyltungsten complexes featuring a homopropargyl alcohol group in the presence of Lewis acids, affords α -alkylidene cyclic carbene complexes **20** (Scheme 13) <1997JA4404, 1998JA4520, 1998JOC7289>. The major drawback of this cycloalkenation is that tungsten alkynols are air-sensitive, but the yields are good and carbene complexes **20** undergo a variety of useful transformations.

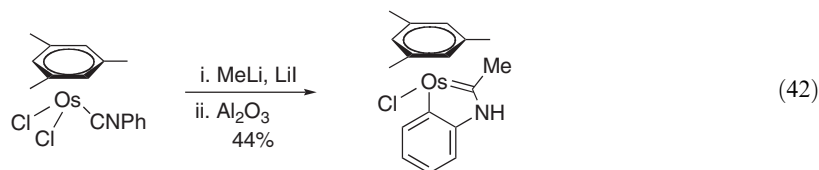


Scheme 13

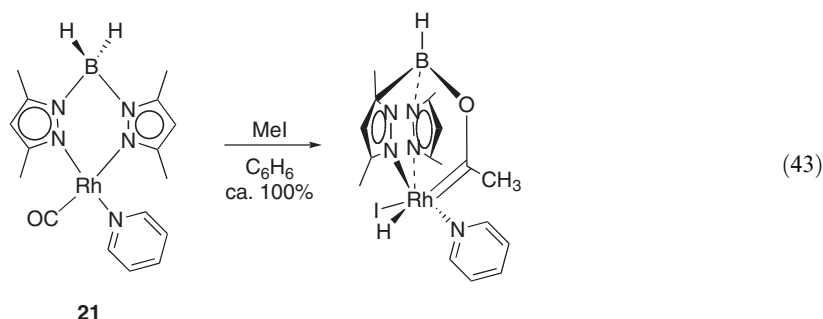
5.25.3.4 Miscellaneous Methods

Aminoalkynylcarbene complexes can be obtained via addition of lithioalkynes to $(\text{CO})_5\text{Cr}$ (isocyanide) complexes (Equation (41)) <1996OM1942>. The addition of methyl lithium to a phenyl isocyanide-osmium complex followed by intramolecular C–H activation generates a metallacyclic aminocarbene-osmium complex (Equation (42)) <2000JOM(593–594)192>.

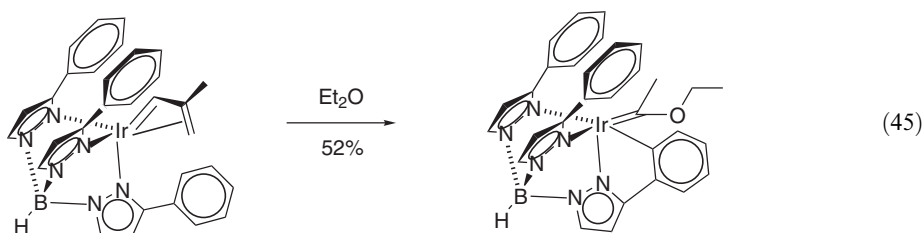
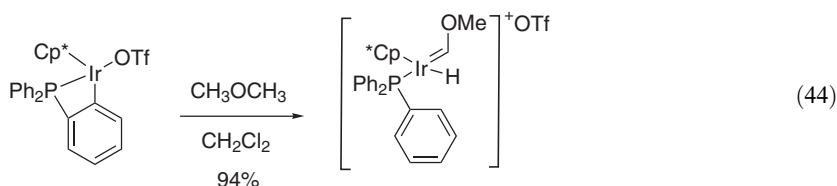




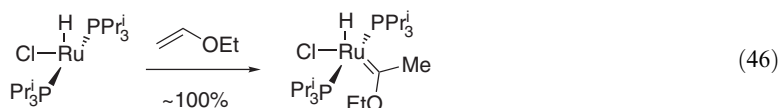
Boryloxycarbene–rhodium complexes can be obtained by coupling complex **21** with MeI in a process involving the transfer to Rh of the boron-bound hydrogen in the bidentate ligand (hydridobis(3,5-dimethylpyrazolyl)borate) (Equation (43)) <2000OM2947>.

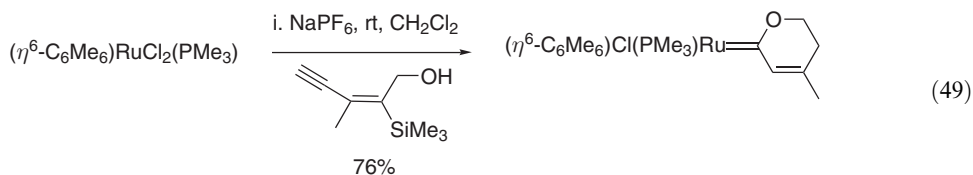
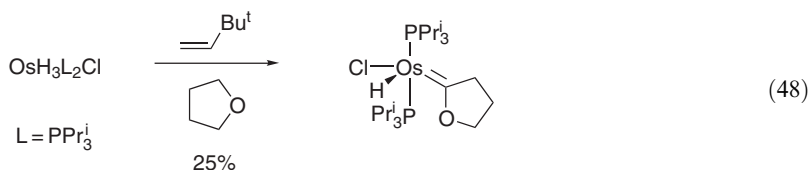
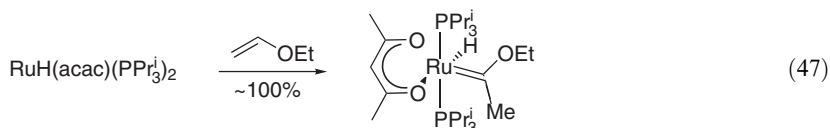


Cationic iridium Fischer carbene complexes have been prepared by intermolecular C–H activation processes in excellent yields (Equation (44)) <1997JA11538>. Analogously, the regioselective activation of two CH bonds of an ether or an amine, RCH_2X ($X = OR', NR'_2$), constitutes an unused synthetic route to Fischer-type carbenes $M = C(R)X$ of iridium (Equation (45)) <1996JA2517, 1998CEJ2225, 2000AG(E)2158> and platinum <1997JA848>.

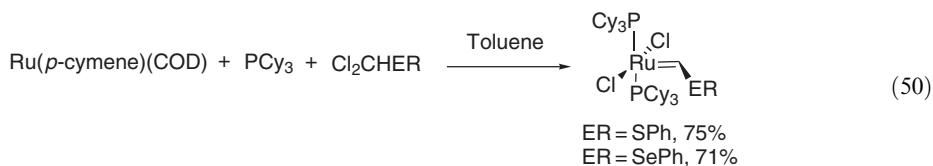


Coupling of ruthenium hydride complexes with vinyl ethers or *N*-vinylamides leads to the corresponding alkoxy- or aminocarbene complexes (Equation (46)) <1998JA9388, 2000OM2281, 2000OM2291, 2000MI9>. Other fluoro, triflate, and acac ruthenium complexes have been used for this kind of transformation (Equation (47)) <2000IC3757>. Cyclic carbene complexes may also be generated from THF and osmium–hydride or ruthenium–hydride complexes. The reaction with the osmium complexes requires *t*-butylethylene as a co-reactant to quench the hydrogen formed (Equation (48)) <2000MI835>. Reaction of ruthenium alkylidene complexes with vinyl ethers also affords ruthenium Fischer-type complexes with good yields <2002OM2153>. Unsaturated cyclic ruthenium carbenes have been prepared via direct activation of enynols by ruthenium(II) complexes (Equation (49)) <1995OM1095>.

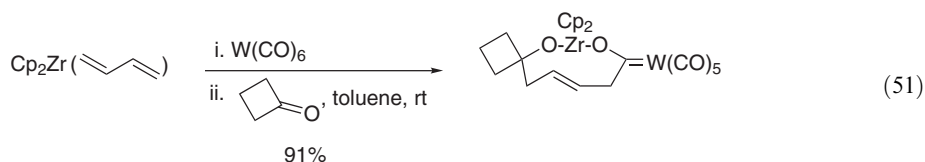




Another convenient route to prepare Fischer carbene ruthenium complexes bearing thio- and selenocarbene ligands is the reaction of $\text{Ru}(p\text{-cymene})(\text{cod})$ with PCy_3 and the corresponding dichloromethylchalcogenide (Equation (50)) <2003OM586>. A methoxyruthenium carbene with an oxygen tripod ligand has also been prepared by this method <1998OM1245>. By reaction of pentacarbonyl($\eta^2\text{-cis-cyclooctene}$)chromium(0) and diaryldiazo compounds, several chromium carbene complexes have been prepared. The homo-heteroatom-stabilized carbene complexes prepared through this route undergo insertion of nucleophilic alkynes such as ynamines or alkoxyacetylenes to give α,β -unsaturated carbene complexes <1998OM4353>.



Metallacyclic zirconoxycarbene–tungsten complexes can be prepared by coupling between (butadiene)zirconocene, tungsten hexacarbonyl and cyclic ketones such as cyclobutanone, cyclo-decanone, and cyclododecanone (Equation (51)) <2000EJO187>.



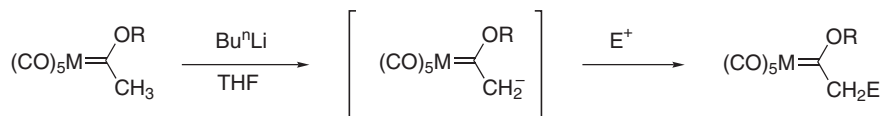
5.25.4 FUNCTIONALIZATION OF PREFORMED CARBENE COMPLEXES WITH RETENTION OF THE CARBENE MOIETY

This section has been structured according to the most important types of reactions in which metal carbenes can be involved with retention of the carbene moiety.

5.25.4.1 α -Carbanion Reactions

Protons α - to the carbene carbon of Fischer carbene complexes are quite acidic ($\text{p}K_a \approx 12$) <1997JA5169, 1997JA5583, 1997OM1926> and can be removed by a variety of bases to give

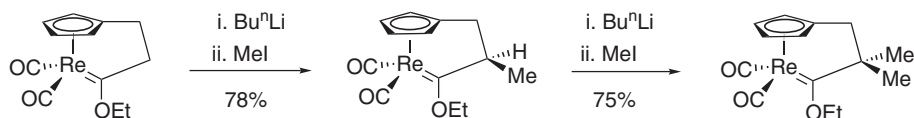
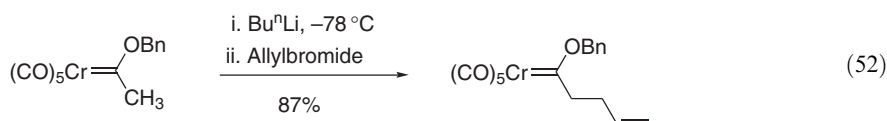
an enolate-type anion stabilized by delocalization into the metal carbonyl fragment, which undergoes alkylation with electrophilic reagents (Scheme 14).



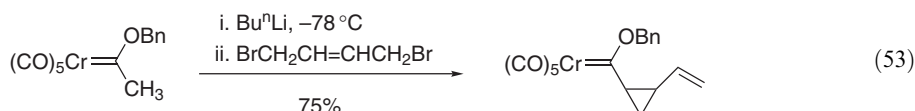
Scheme 14

5.25.4.1.1 Alkylation and acylation

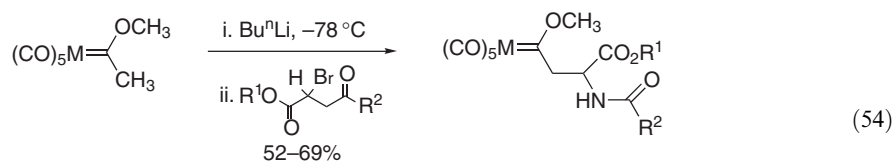
The most general procedure for the α -alkylation of Fischer carbene complexes consists of treatment of the carbene with Bu^nLi in THF followed by reaction of the anion thus formed with an alkyl halide (Equation (52)) <1996JA7873, 1996JA12045, 1997JOC7704>. This method has been employed to obtain mono- and dialkylated products (Scheme 15) <1995OM547, 1997JA5750>. The reaction with *cis*-1,4-dibromo-2-butene as electrophile produces vinylcyclopropane derivatives in high yields (Equation (53)) <1995OM547>.



Scheme 15

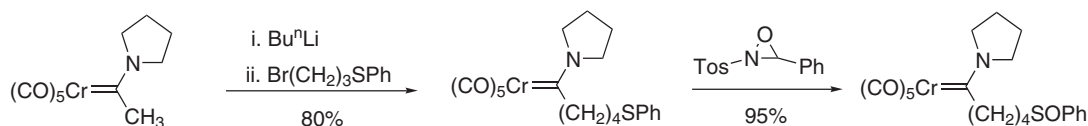


The use of protected α -bromoglycine esters as electrophiles leads to metal-carbene amino acid derivatives (Equation (54)) <1997CB171>, while thioalkyl halides form thioalkyl-substituted amino carbene complexes (Scheme 16) <1995SL666>. In these cases, using *N*-sulfonyloxaziridine or dimethyldioxirane as oxidizing agents, the sulfur atom can be subsequently oxidized to sulfinyl or sulfonyl functions in good yields, while preserving the $\text{M}=\text{C}$ bond.



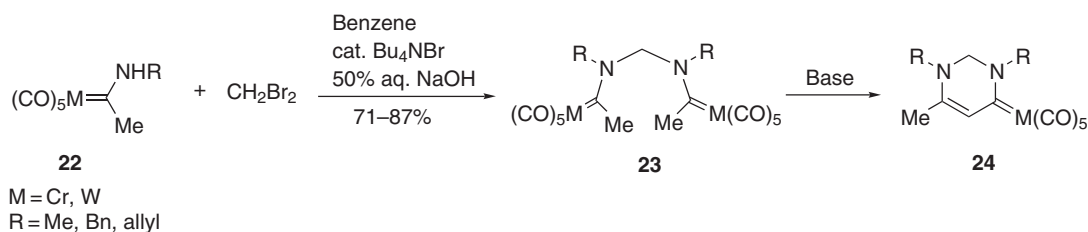
$\text{M} = \text{Cr, W}$

$\text{R}^1 = \text{Me, Bu}^t$; $\text{R}^2 = \text{Ph, OBu}^t$



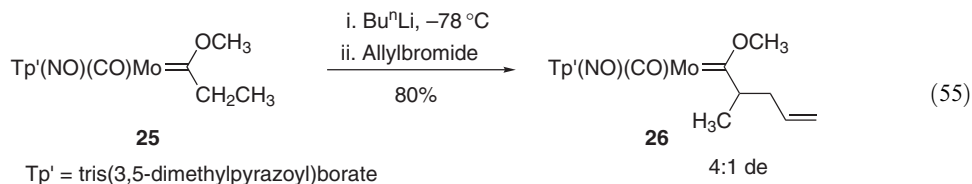
Scheme 16

N-Alkylation competes with *C*-alkylation when alkylaminocarbene complexes **22** are treated with base (Scheme 17) <1995OM3617>. In these cases, biscarbene complexes **23** are formed in the reaction medium by deprotonation of the nitrogen atom and reaction with dibromomethane. These species undergo an intramolecular aldol-type reaction to form cyclic carbene complexes **24** in high yields.

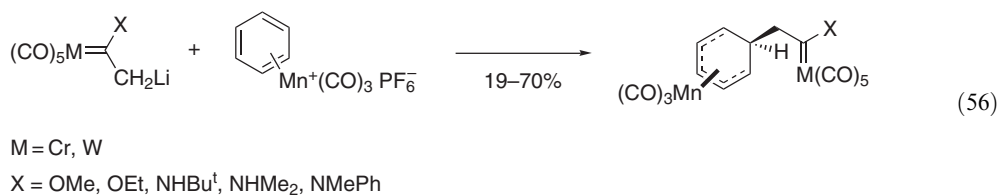


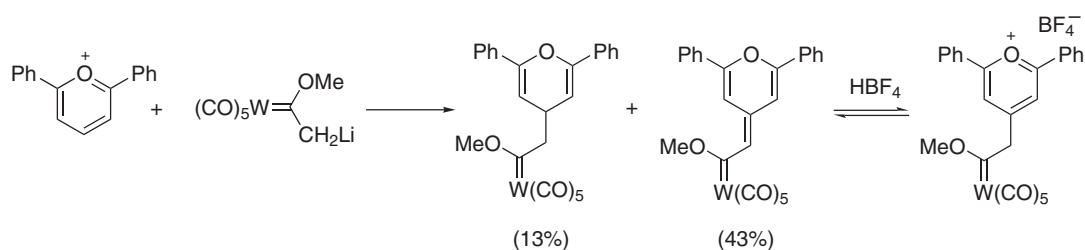
Scheme 17

The diastereoselectivity of the reaction of carbanions derived from chiral-at-the-metal Fischer carbene complexes and alkyl halides was examined. Deprotonation of ethylcarbene complex **25** followed by reaction with allyl bromide afforded the anticipated allylated carbene complex **26** as a 4:1 mixture of diastereoisomers (Equation (55)). The opposite diastereomeric ratio was obtained through deprotonation of the 3-butenylcarbene analog of **25** followed by methylation <1997OM370>.



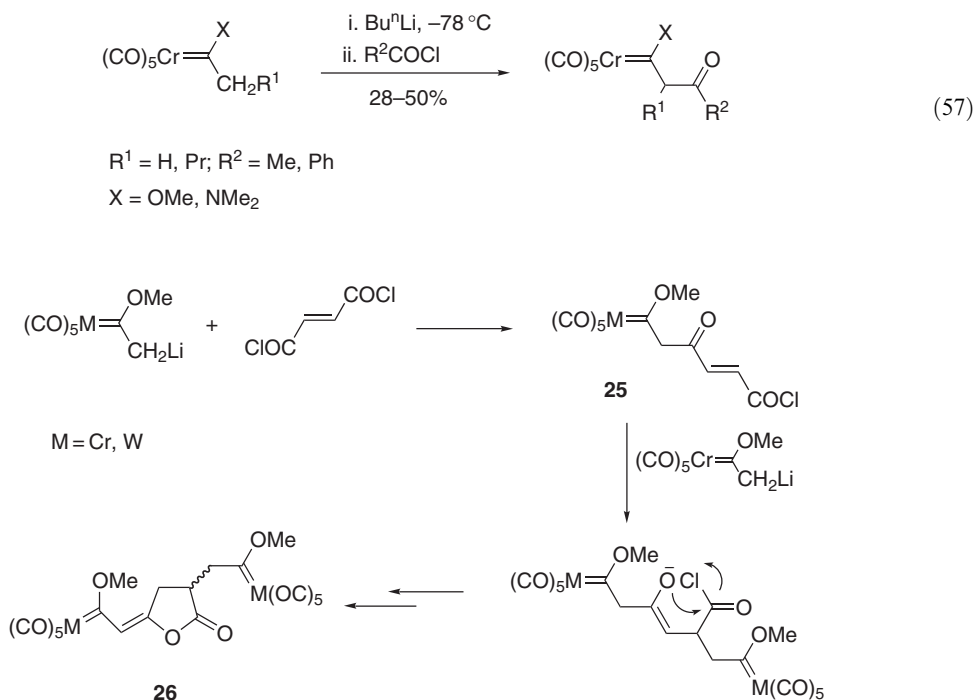
Heterobimetallic compounds were prepared from the reaction of carbene complex anions with cationic polyene-metal complexes (Equation (56)) <1997JOM(545-546)9>. The coupling of carbene complex-derived carbanions with pyrylium salts afforded pyrone derivatives featuring a carbene complex-containing substituent in the 4-position. The oxidation of the 4-alkylpyrone to 4-alkylidenepyrone was induced by the pyrylium salt, that can be regenerated by protonation (Scheme 18) <1997JOM(545-546)447, 1998TL557, 2002T7519>.





Scheme 18

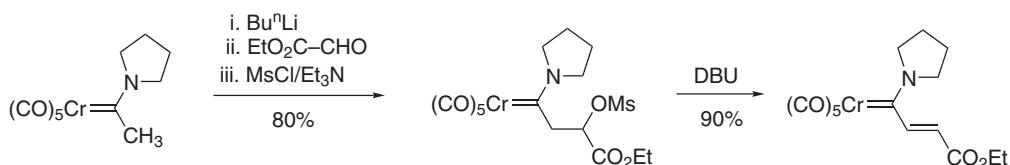
The α -anions of alkylcarbene complexes also react with acid chlorides to form β -keto carbene complexes in moderate yields (Equation (57)) <1998JOM(553)183>. The reaction with fumaroyl chloride as acylating agent leads to monoacylated complexes **25** that add a second molecule of the metal enolate in a conjugate addition, and cyclize to produce biscarbene complexes **26** in moderate yields (Scheme 19) <1997JOM(542)205>.



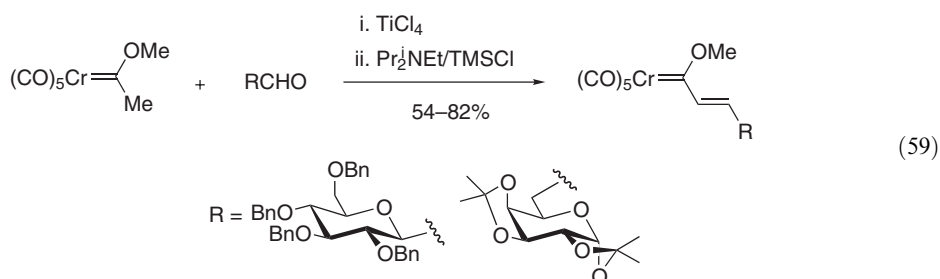
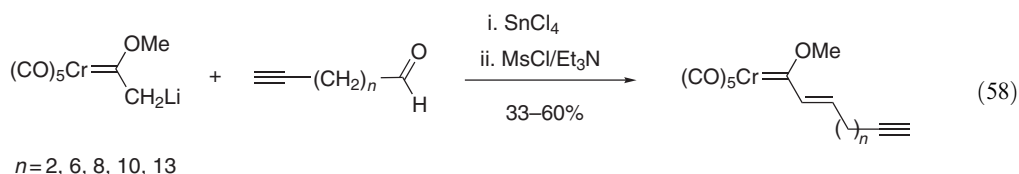
Scheme 19

5.25.4.1.2 Aldol condensations and related processes

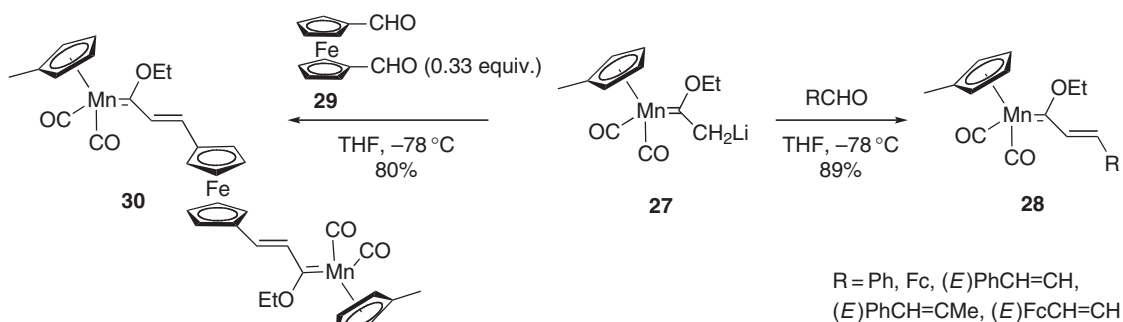
The enolates derived from alkyl Fischer carbene complexes are weak nucleophiles that can take part in aldol condensations with aldehydes. The β -hydroxycarbenes formed during the course of these reactions may undergo dehydration to form α,β -unsaturated complexes and hence, this method is a general and convenient route to alkenyl carbene complexes (Scheme 20) <1998JOC7588, 1999OM3851>. The low nucleophilicity of the enolates makes the addition of a Lewis acid (e.g., SnCl_4 , TiCl_4 , $\text{BF}_3\cdot\text{Et}_2\text{O}$) necessary in many cases (Equation (58)) <1998JA10573, 1998JOC5275, 1998TL1849>. The choice of a Lewis acid compatible with the protective groups of pyranose-derived aldehydes was the major problem in the synthesis of chromium vinylcarbene C-glycosides (Equation (59)) <2001JOM(622)251, 2003JOM(669)1>. TiCl_4 along with a combination of Hünig's base and TMSCl turned out to be the reagents of choice in these cases.



Scheme 20

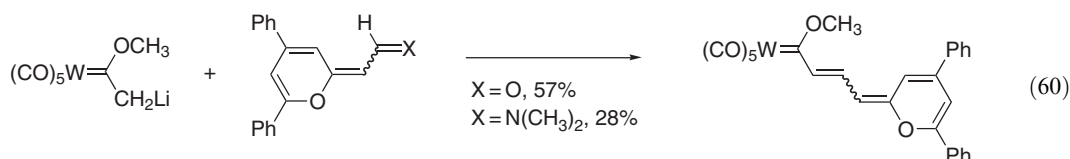


A variety of alkenylcarbene complexes were obtained in a straightforward manner upon aldol condensation of the carbene manganese anion (**27**) with various aromatic and α,β -unsaturated aldehydes (Scheme 21) <1999EJI739>. The reaction was totally stereoselective giving (*E*)- or (all (*E*))-alkenylcarbenes **28** in variable yields. When a dialdehyde like 2,2'-bisformylferrocene **29** was used, the reaction could be directed toward the monocarbene or the biscarbene complex **30** depending on the stoichiometry of the reagents. Other aldehydes like 9-ferrocenyl-2,7-dimethylnonatetra and carotenoid polyene dialdehydes have been condensed with the enolates derived from alkyl, alkoxy, and amino Fischer carbene complexes to obtain long-chain polyene chromium and tungsten mono and biscarbenes in moderate yields <1999JOM(578)247>.

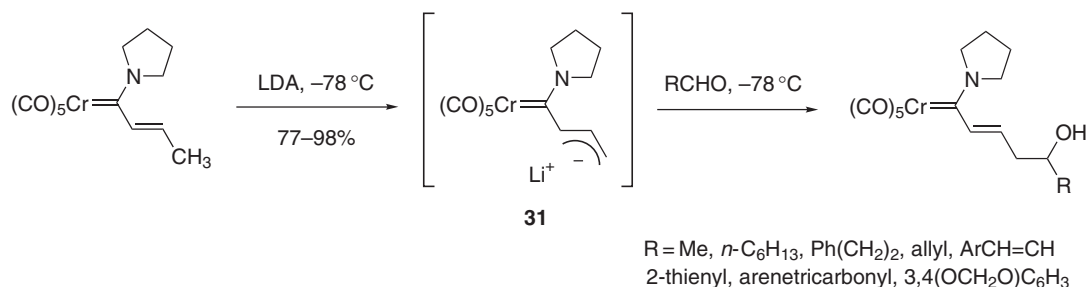


Scheme 21

Condensation of a tungsten carbene enolate with the iminium salt derived from 2-methylenepyran has been reported to give the expected α,β -unsaturated complex, but in low yield. Better results were observed when 2- and 4-methylenepyranaldehydes were employed (Equation (60)) <2001JOM(626)37>.

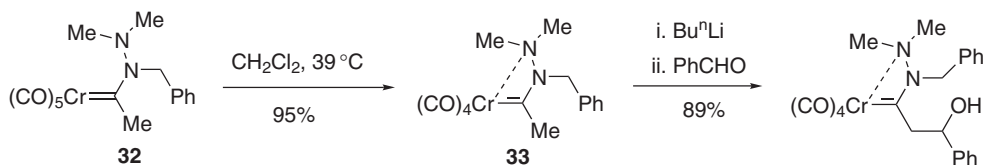


Allyl anions **31**, obtained by γ -deprotonation of α,β -unsaturated carbene complexes react with aliphatic and aromatic aldehydes in the absence of Lewis acids to produce the corresponding aldol products in high yields and complete γ -regioselectivity (Scheme 22) <1997TL3769, 1999JOM(583)111, 2001EJO1149>.



Scheme 22

Due to the presence of a β -nitrogen atom, alkyl(hydrazine)carbene **32**, can be easily transformed into the more stable chelate complex **33**, which after deprotonation with Bu^nLi reacts as nucleophile with aldehydes (Scheme 23), epoxides in the presence of a Lewis acid or alkylhalides <2001JOM(617–618)399>. Analogous behavior has been described for structurally related alkyl(aminophosphino)carbene complexes <1999ICA236>.

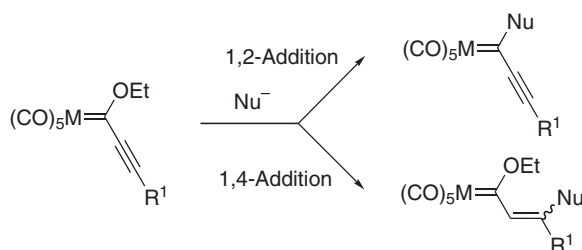


Scheme 23

5.25.4.2 Conjugate Additions Involving Carbene Complexes

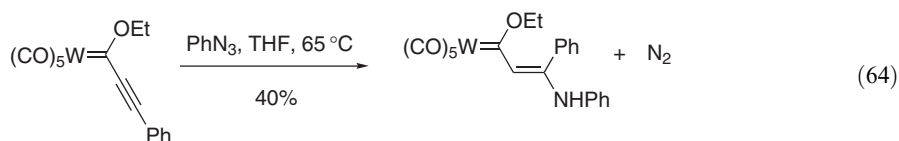
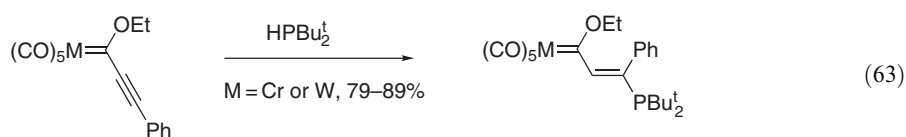
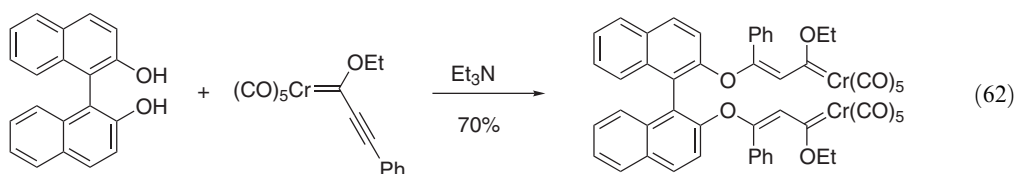
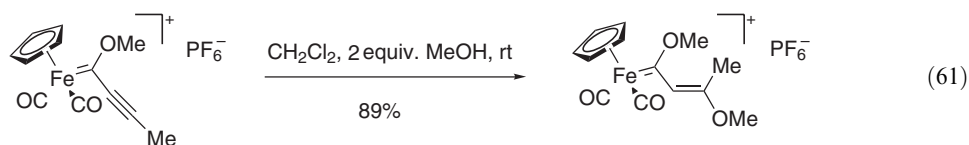
5.25.4.2.1 Carbene as a Michael acceptor

α,β -Unsaturated Fischer carbene complexes behave like the analogous organic counterparts, the α,β -unsaturated esters and amides, in reactions in which the metal center is not involved <1981SCI995, 1982AG(E)711>. Thus they can undergo 1,2- or 1,4-addition processes in the presence of different nucleophiles (Scheme 24) <1995OM2447, 1997AOC163, 1997OM2571, 2000AG(E)3964, 2001JOM(624)5>.

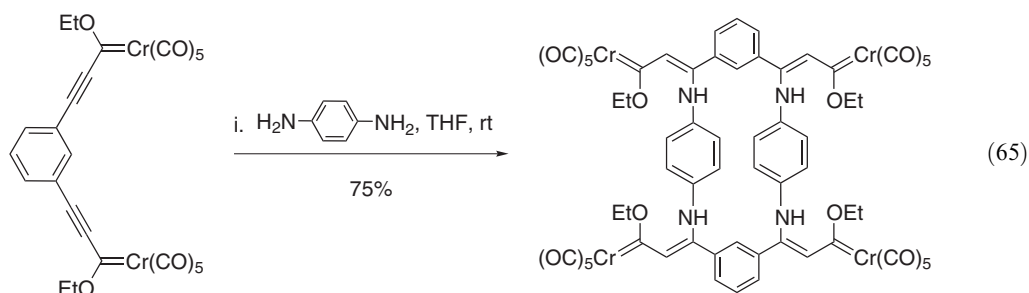


Scheme 24

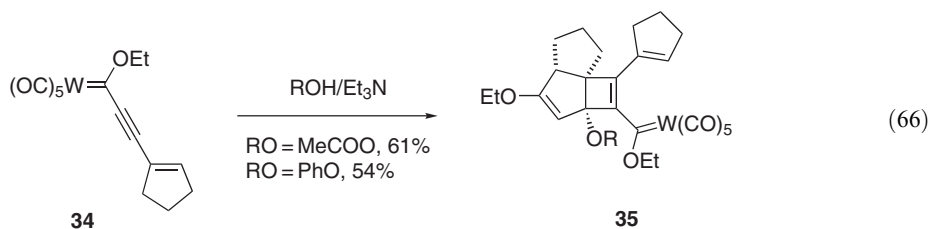
In this way amines <1997CB1647, 1998JOM(556)119, 1999OM1369, 2001OM2183, 2002CC1842, 2003OM384>, alcohols <1997CB1647, 2001CEJ700>, phenols <1996OM4842, 2000EJO1183, 2002CC1842>, thiols <2000EJO3463>, carboxylic acids <2000EJO1183>, phosphanes <1995OM231, 1999OM1369>, and azides <1995SC3329> may be added to this kind of complex to form the 1,4-adducts (Equations (61)–(64)).



Through this methodology sugar moieties have been incorporated into the carbene ligands <1996SL995> and polymetallic cyclophanic structures have been prepared (Equation (65)) <2001OM4304, 2003OL1237>.

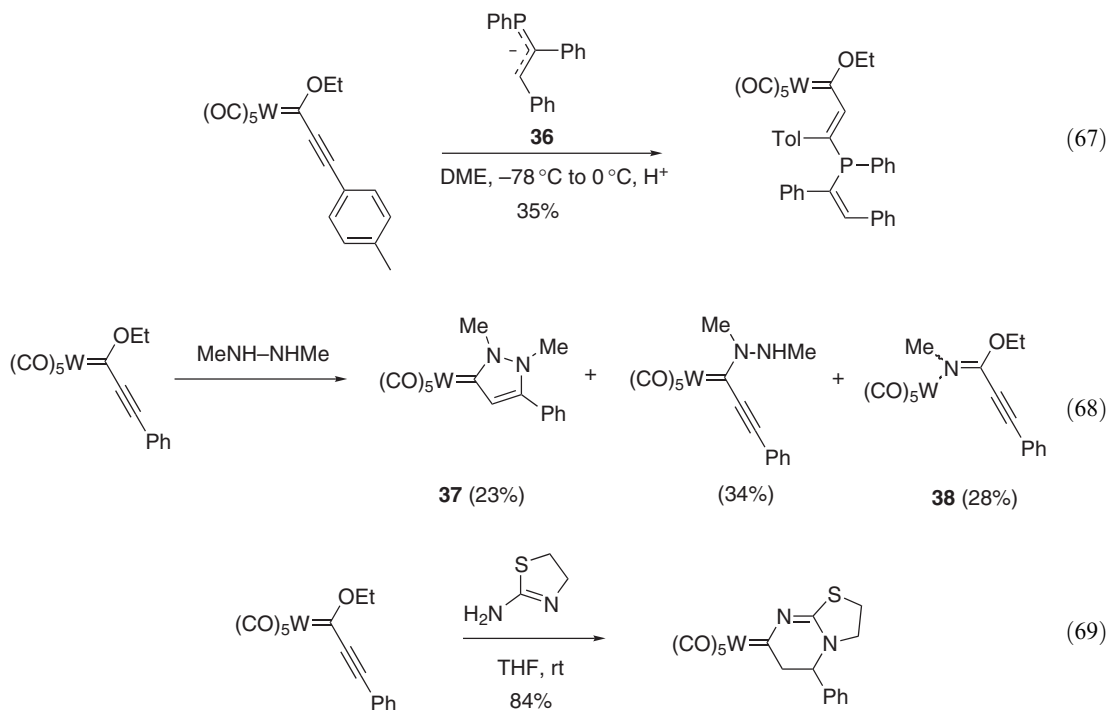


1,4-Addition of carboxylic acids or phenols to [2-(1-cyclopentenyl)ethenyl]carbene complex **34** triggers multistep reactions, which ultimately furnishes (cyclobutenyl)carbene complexes **35** as readily isolable products (Equation (66)) <2000EJO1183>.

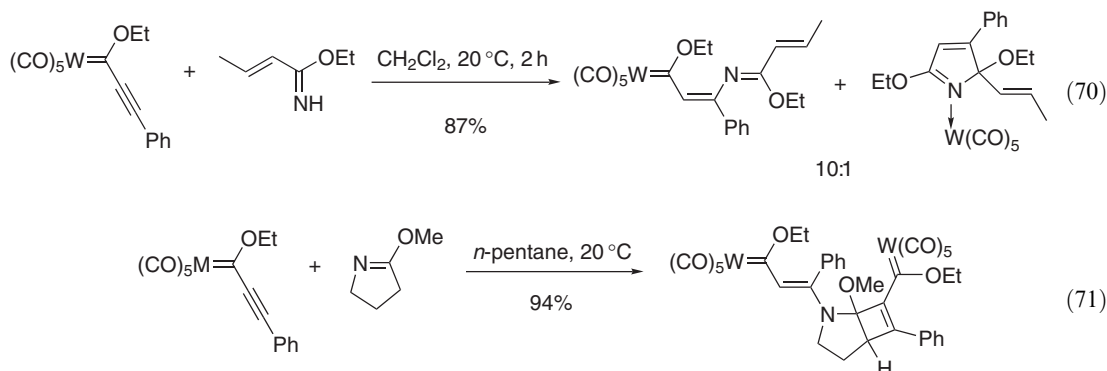


The reactivity of alkynylsubstituted amino- and alkoxytungsten carbene complexes toward 1-phosphallyl anion **36** also leads to new carbene complexes through Michael addition processes (Equation (67)) <1997OM2370>. 1,2-Dimethylhydrazine gave 1,4- and 1,2-addition to yield

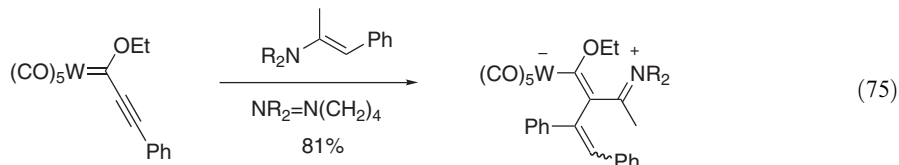
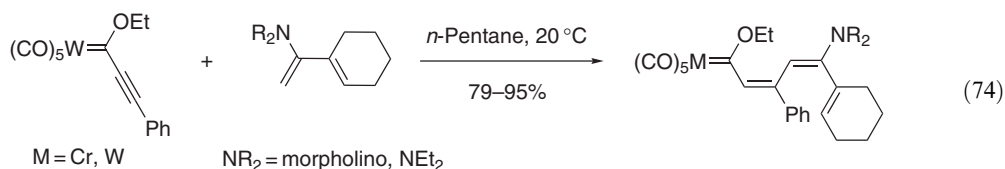
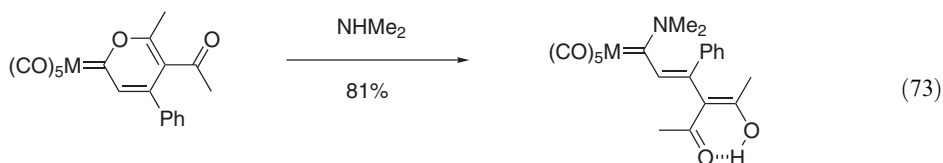
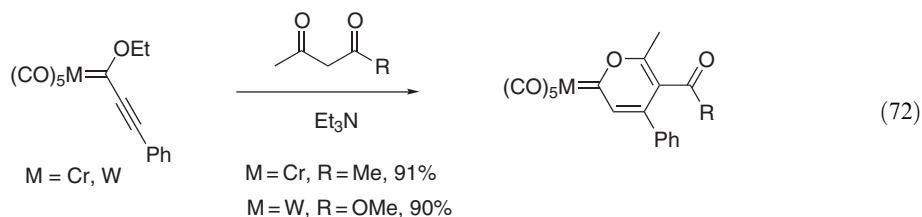
dihydropyrazolylidene metal complex **37**, together with the 1,2-addition product and imidate complex **38** (Equation (68)) <1995OM2447>. 1,3-Dinitrogen systems such as amidines, guanidines, or ureas likewise lead to pyrimidine derivatives (Equation (69)) <1998OM2135>.



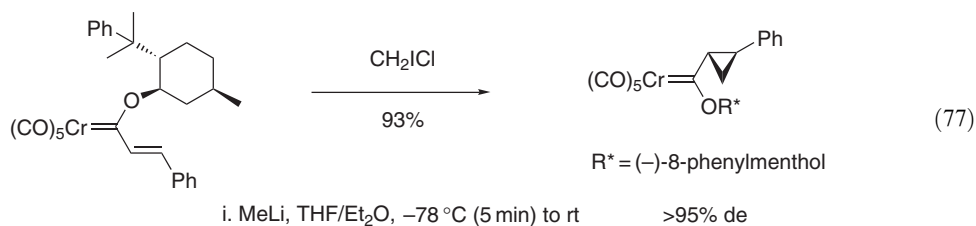
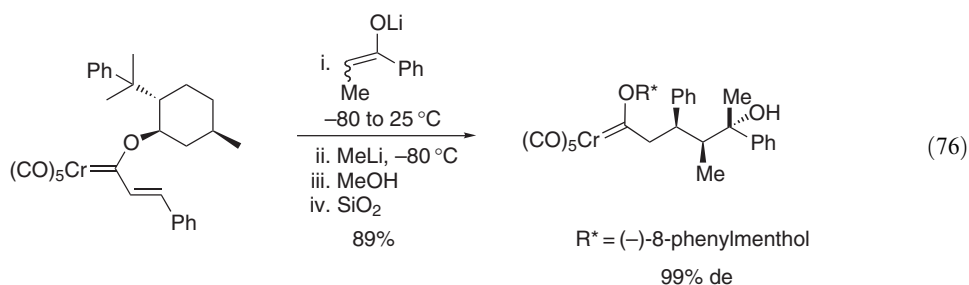
Addition of alkenyl NH imidates to (1-alkynyl)carbene complexes affords 1-metalla-1,3,5,7-octatetraene complexes by Michael addition together with cycloaddition products derived from 1,2-addition processes. However, 1,4-addition is the favored process for tungsten alkynyl complexes (Equation (70)) <1997OM2571>. Otherwise, *O*-alkyllactims add to (1-alkynyl)carbene complexes to form binuclear complexes in a stepwise process consisting of a conjugate addition of the lactim to the triple bond, followed by 1,5-hydrogen shift and [2+2]-cycloaddition (Equation (71)) <1998OM2897>.

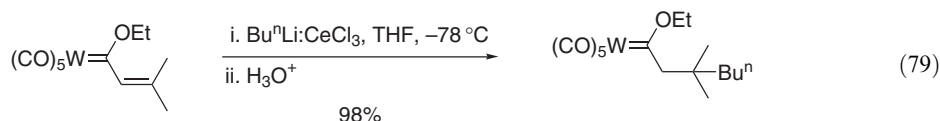
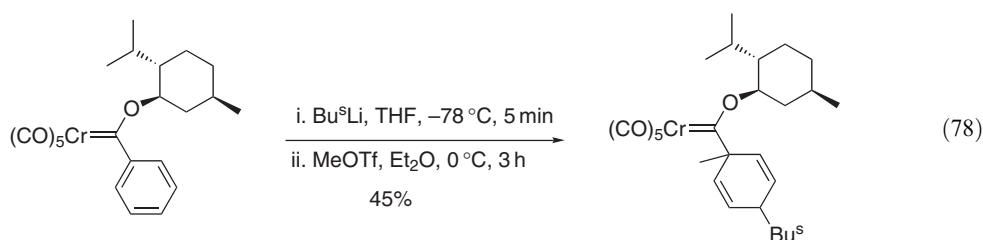


C-Addition of enolizable organic compounds to (1-alkynyl)carbene complexes also occurs <2000EJO17>. Base-catalyzed condensation of enolizable carbonyl compounds with (1-alkynyl)carbene complexes leads to the formation of pyran-2-ylidene complexes (Equation (72)) <1996OM10853, 1997JOM(541)187, 1998TL795>. Ring opening of the pyranylidene complexes by aminolysis affords metallatriene systems (Equation (73)) <1996OM1257, 1997SL621>. Michael addition of enamines to alkynyl complexes has also been reported (Equations (74) and (75)) <1997OM5893, 1998SL1120, 1998TL795, 1999EJO2545, 2001OM3574>. Thus, 6-pyranylidene complexes can also be generated from the Michael addition of cyclic enamines and further hydrolysis of this functionality in the metallaheptatriene primary formed <1996OM5018>.



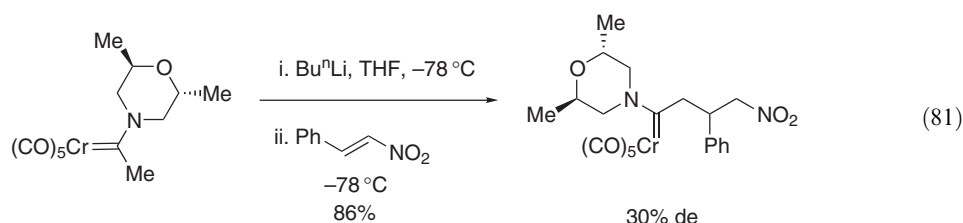
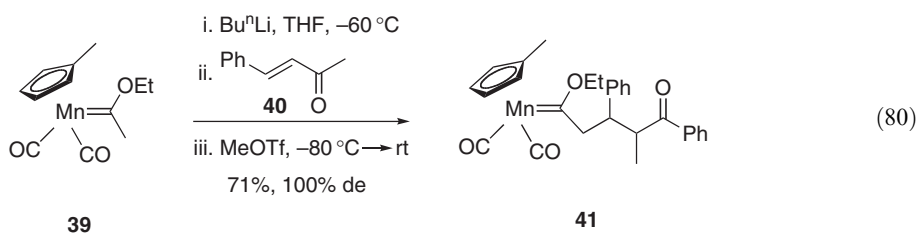
Lithium enolates, including glycine-derived carbanions, have also been incorporated into optically active Fischer vinylcarbene complexes by 1,4-addition with high *syn*-selectivity and high levels of asymmetric induction (Equation (76)) <1995CEJ236, 1999JOC6554, 2002JA9056>. Lithium derivatives such as monohalo- or dibromomethyl lithium have been used for the diastereoselective and enantiomerically pure synthesis of *trans*-substituted cyclopropylmethoxycarbene complexes (Equation (77)) <1995TL3937, 1997JOC6870>. Organolithium reagents give regio- and stereoselective nucleophilic addition to the aromatic ring of (menthyloxy)arylcarbene complexes of chromium. The intermediate anions can be further trapped by MeOTf (Equation (78)) <1996JA13099>. The addition of organozinc compounds to alkynyl complexes has also been reported to form exclusively 1,2-addition adducts <1995JOM(489)C84>. Alkylcerium reagents such as butylcerium undergo quantitative 1,4-addition to α,β -unsaturated Fischer carbene complexes (Equation (79)) <2000T4907>.



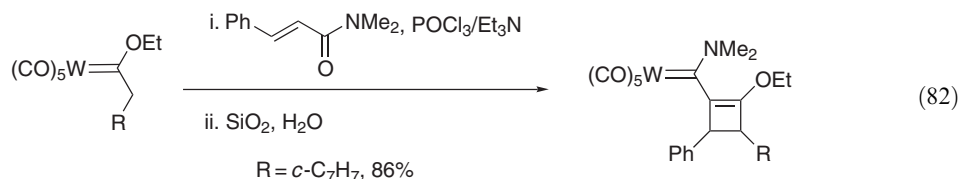


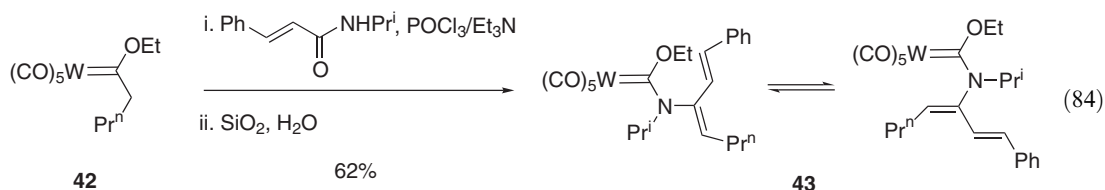
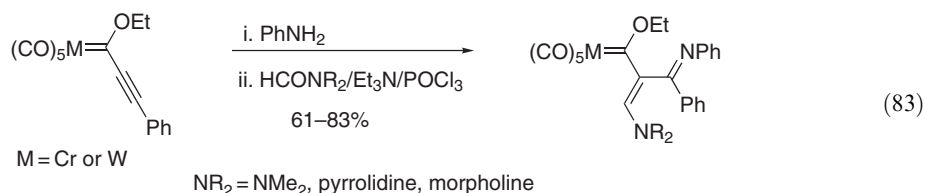
5.25.4.2.2 Carbene as a Michael donor

Carbene anions generated upon deprotonation of the α -carbon atom of alkylalkoxy- or alkylaminocarbene complexes react with a variety of Michael acceptors. Exclusive 1,4-addition is observed with a high degree of stereocontrol in the reaction with enones [\[1995JOM\(486\)279, 1995TL3699, 1996CC2601, 1997OM3873\]](#). Deprotonation of Fischer manganese complex **39** followed by reaction with enone **40** yielded carbene complex **41** after quenching with MeOTf (Equation (80)) [\[2000TL7341\]](#). Similarly, diastereoselective Michael addition processes have also been described using nitroalkenes as electrophiles (Equation (81)) [\[1998EJO2127, 2000TA975, 2001OM485\]](#).



Condensation of (alkyl, ethoxy)carbene complexes with α,β -unsaturated tertiary amides leads to (cyclobutenyl)carbene complexes by 1,4-addition (Equation (82)) [\[2002OM1637\]](#). Bayliss–Hillman-type additions to tertiary α,β -unsaturated acid amides under Vilsmeier conditions can also be done (Equation (83)) [\[2002OM4356\]](#). α -Substituted carbene complexes undergo, under similar conditions, a retro-Fischer reaction. Thus (*n*-butyl, ethoxy)carbene complex **42** yields *N*-enamino complexes **43** (Equation (84)) [\[2002OM2736\]](#).

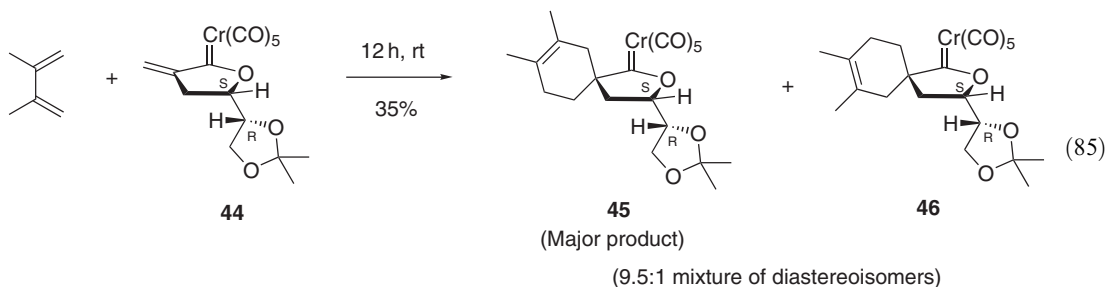




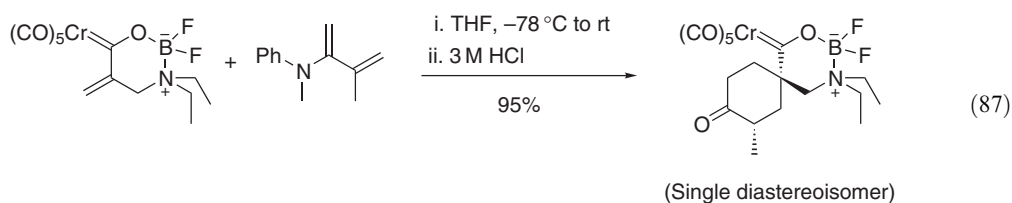
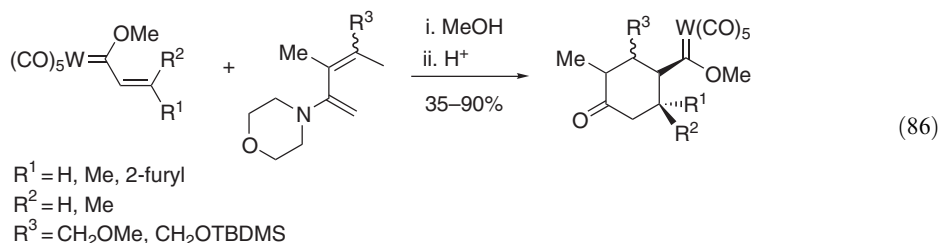
5.25.4.3 Cycloaddition Reactions

α,β -Unsaturated carbene complexes behave as good dienophiles and dipolarophiles in cycloaddition reactions. Due to the presence of the metal fragment, the reaction rates and product selectivities have been observed to be much higher for the reaction of carbene complexes than for the corresponding esters [<1999JCS\(P1\)197>](#).

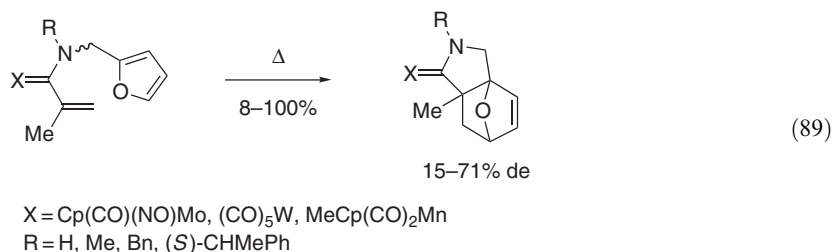
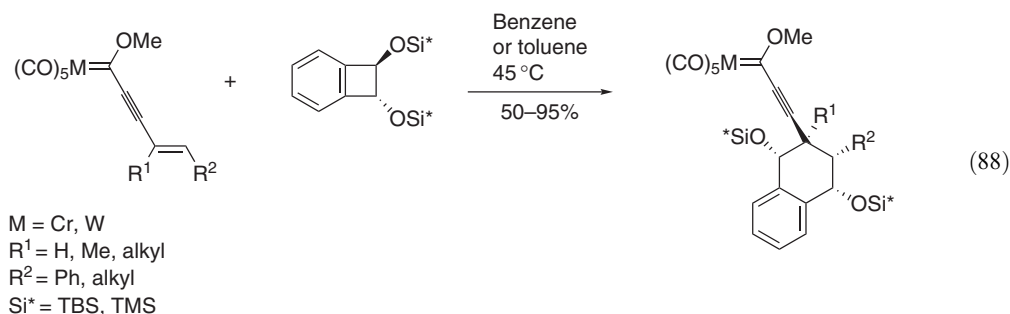
Carbohydrate-derived complexes **44** react with 2,3-dimethylbutadiene to yield a mixture of diastereomeric spirocyclic complexes **45** and **46** (Equation (85)). The addition of the diene takes place preferentially from the sterically less hindered side of the 2-oxacyclopentylidene ring and proceeds via unusual *exo*-addition to the dienophile [<1998OM1602, 1999JOC4206>](#).



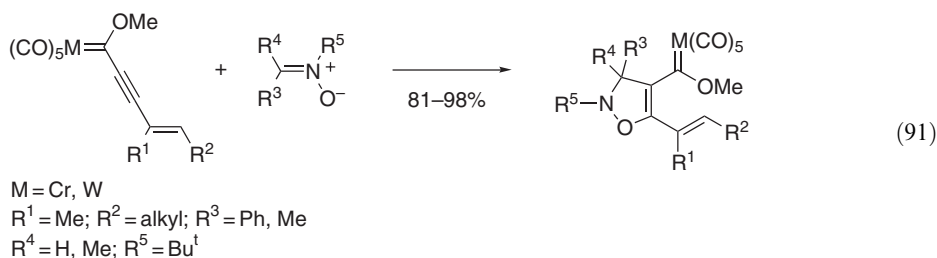
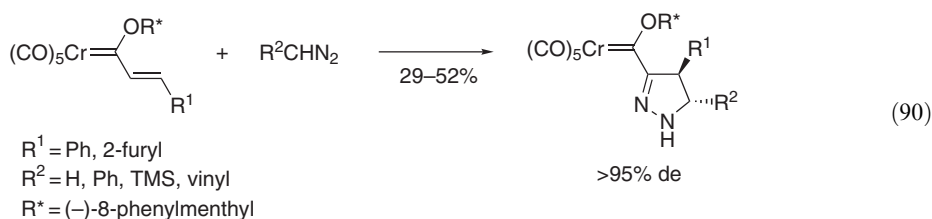
The reaction of alkenyl Fischer carbene complexes and 2-aminobutadienes yields the corresponding Diels–Alder cycloadducts that, after hydrolysis of the enamine function, are turned into ketones in moderate-to-good yields (Equation (86)) [<1997T9323>](#). This procedure has been applied to cyclic alkoxy and boroxycarbenes to obtain spirocarbene complexes in high yields [<1997SL1040, 1998JA2514>](#) (Equation (87)). Other [4+2]-reactions of alkenyl and alkynyl Fischer carbene complexes with substituted dienes and heterodienes have been reported [<1997CEJ1629, 1997JOC9229, 1997JOM\(549\)311, 1997TL1181, 1998CEJ2280, 2000T4951>](#).



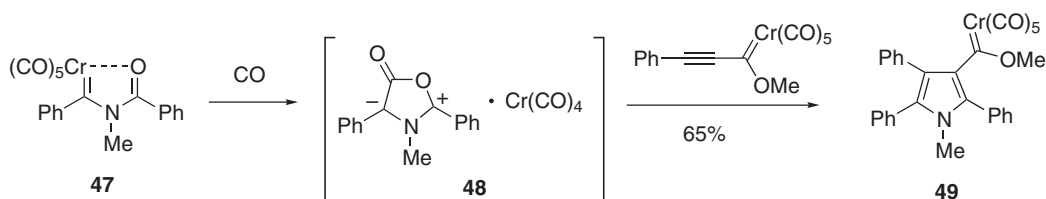
o-Quinodimethanes react with alkynylcarbene complexes producing new tetrahydronaphthyl-alkynyl carbene complexes in good yields (Equation (88)) <2002OL3659>. Intramolecular [4 + 2]-reactions were tested in chiral-*at*-molybdenum α,β -unsaturated carbene complexes, with appended furan rings (Equation (89)) providing the Diels–Alder adducts with moderate diastereoselectivity <1999JOM(583)34>.



The reactivity of α,β -unsaturated Fischer carbene complexes toward diazomethane derivatives (Equation (90)) <1997JCS(P1)2267, 1999CEJ883>, nitrones (Equation (91)) <1995JOC1741, 2001CEJ5318>, *in situ* generated nitrilimines <1998TL4887, 2000EJO1773>, and azomethine ylides <1995SC2043, 2001CEJ3533> have been reported. The mechanistic aspects of this type of [3 + 2]-cycloaddition have been studied <1998JOC7670>. Acylamino chromium carbene complexes **47** are known to be precursors of münchnones **48** formed by insertion of carbon monoxide at room temperature and can be trapped by alkynylchromium carbene complexes to form pyrrole carbene **49** in 65% yield (Scheme 25) <2000JA7398>.

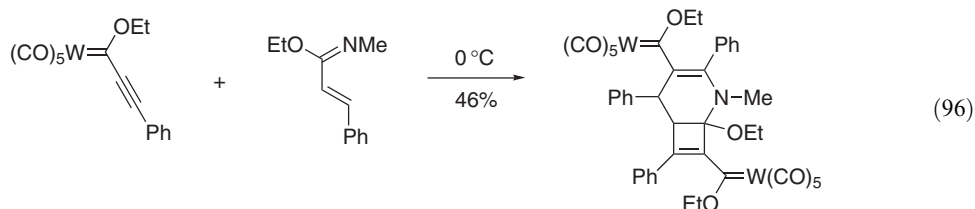
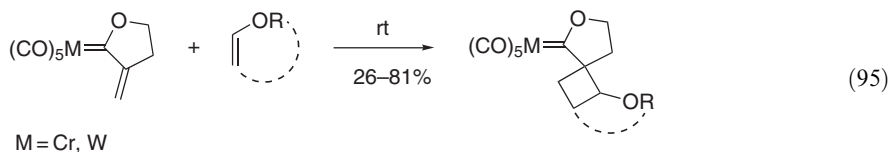
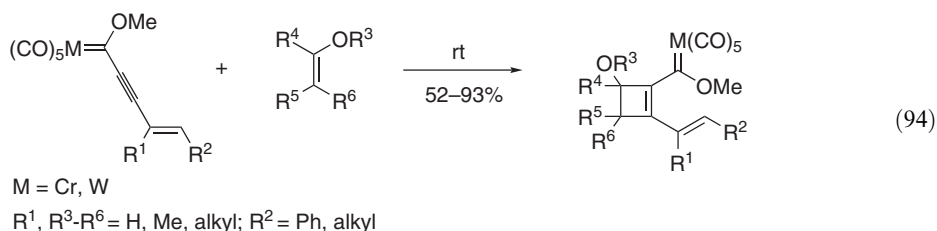
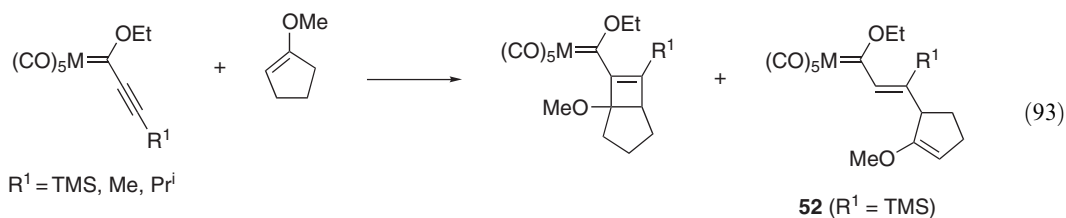
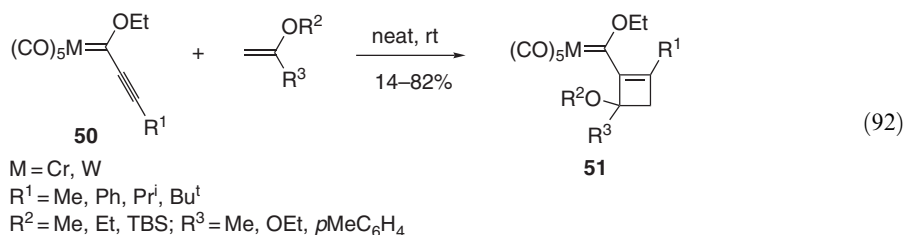


The [2 + 2]-cycloadditions of alkenyl and alkynylcarbene complexes are known. Acetylenic carbene complexes **50** react with enol ethers to yield cyclobutenyl carbene complexes **51**, sometimes accompanied by the corresponding ring-opening products of the cyclobutane (Equation (92))

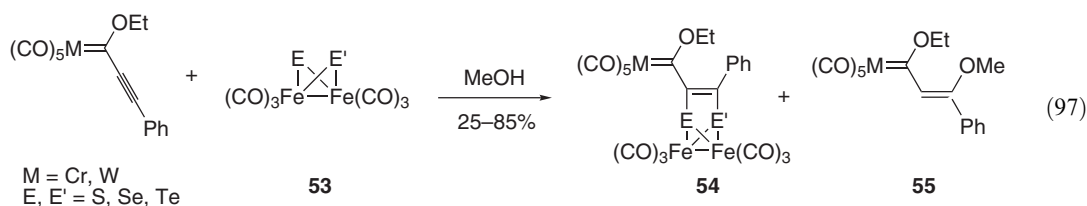


Scheme 25

<1999JCS(P1)197>. Only ring-opening products have been obtained in the reaction of alkynyl-carbene complexes with enamines <2001OM2889> and better yields and more stable products are obtained when cyclic enol ethers are employed. The [2+2]-cycloaddition can compete with the ene reaction and mixtures of cyclobutenes and ene products **52** are obtained (Equation (93)). Alkenylethynylcarbene complexes react with enol ethers regioselectively, only at the alkyne moiety, yielding [2+2]-cycloaddition products (Equation (94)) <2003JOC537>. Exocyclic α,β -unsaturated alkoxy-carbenes react with cyclic and acyclic enol ethers under mild conditions to give four-membered spirobicyclic metal carbenes as single diastereoisomers in moderate-to-good yields (Equation (95)) <2000T4925>. Domino [4+2]/[2+2]-reactions have been described from alkynyl-carbenes and 1-azadienes to form binuclear carbene complexes (Equation (96)) <1998OM1197>.

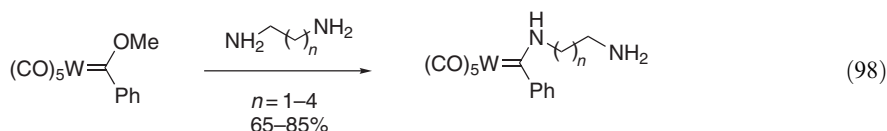


An unusual cycloaddition reaction between iron-bridging chalcogenide complexes **53** ($E, E' = S, Se, \text{ or } Te$) and alkynylcarbene–chromium and tungsten complexes was reported. Fischer carbene bridging diiron complexes **54** were obtained from this reaction, accompanied by the β -methoxycarbene complex **55** formed from Michael addition of the methanol solvent (Equation (97)) <1997OM4392, 1997OM3536>.

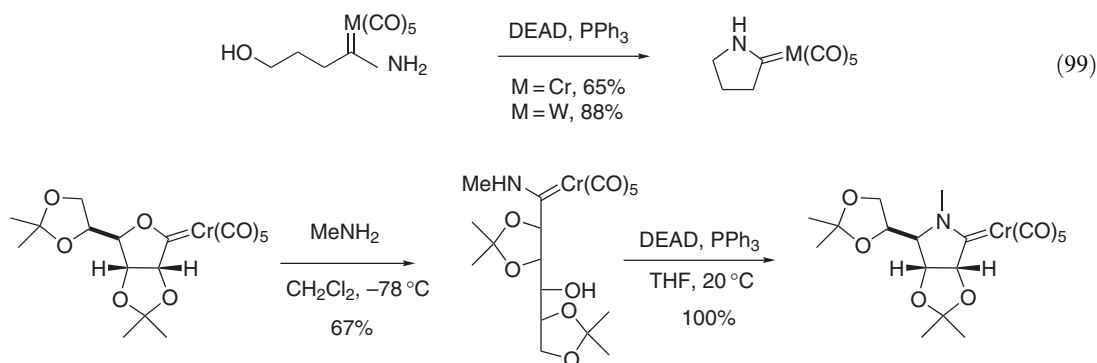


5.25.4.4 Miscellaneous Reactions

Aminocarbene complexes have been prepared by aminolysis of alkoxy-carbene complexes with a variety of amines or amino derivatives (Equation (98)) <1995JA5604, 1995JOM(486)279, 1995OM2447, 1995TL8753, 1996JA1807, 1996TL9385, 1997JOM(548)91, 1999CC925, 1999TL3635, 2001SL757, 2003JA9572>.

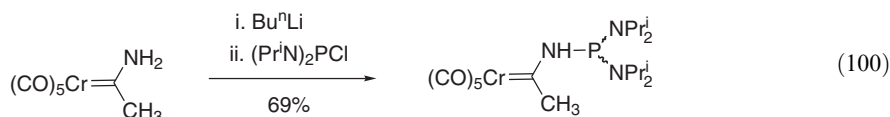


N-Unprotected azacyclopentylidene complexes of chromium or tungsten have been prepared by Mitsunobu cyclization (Equation (99)) <1999TL2919>. Carbohydrate-derived aminocarbenes have been synthesized by aminolysis ring opening followed by Mitsunobu-type ring closure (Scheme 26) <1997CC1217, 1997T5143>.

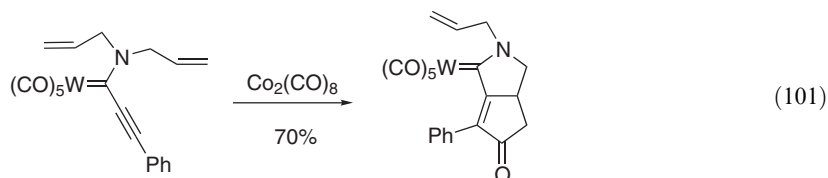


Scheme 26

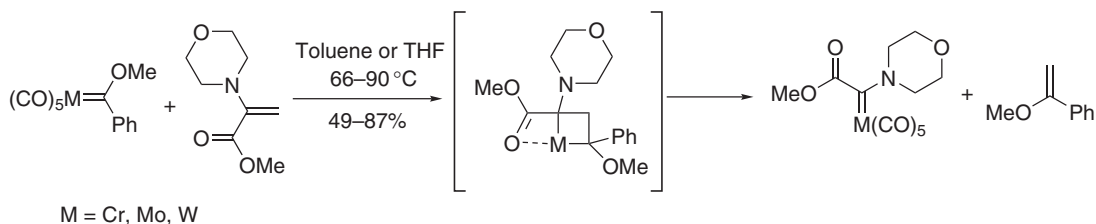
N-Phosphanyl-substituted metal–carbene complexes have been obtained from anions of aminocarbene complexes, generated *in situ* by reaction of their conjugate acids with Bu^iLi or $MeLi$, and bis(diisopropylamino)chlorophospane (Equation (100)) <1997JOM(529)351>.



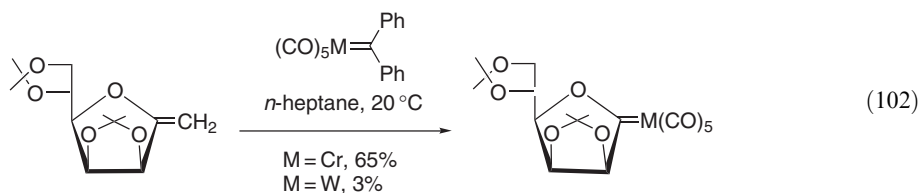
Cobalt aminocarbene complexes have been used to perform inter- and intramolecular Pauson–Khand reactions as an efficient method to access different kinds of aminocarbene complexes (Equation (101)) <1997CB507, 1997OM2808, 1998JA2283, 1999JOM(586)247>.



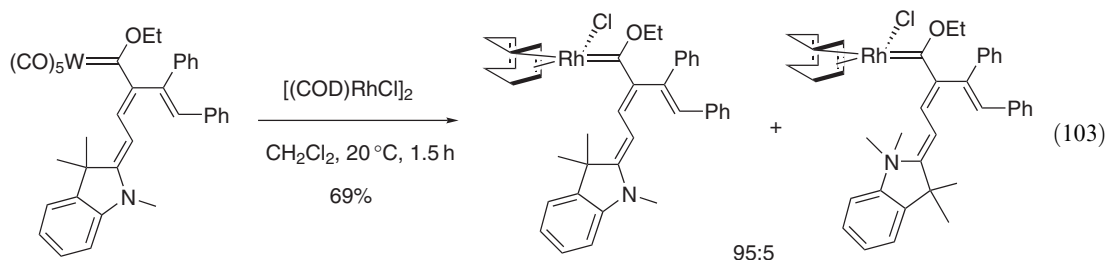
Metathesis of Fischer carbene complexes and enamines forms α -amino acid metal carbenes in yields strongly dependent on the metal used (Scheme 27) <1999JOM(589)11>. Metathesis reactions have also been employed to synthesize biscarbene complexes <2000JOM(606)26> or sugar derivatives (Equation (102)) <1997CC1217, 2001SL757>.



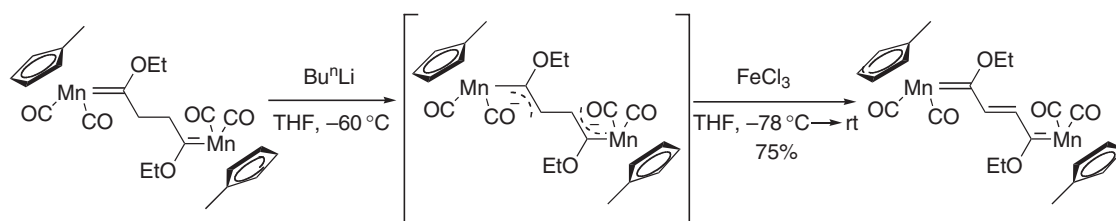
Scheme 27



Rhodium carbene complexes have been prepared by transmetalation reaction of analogous tungsten Fischer carbene complexes with [(COD)RhCl]₂ (Equation (103)) <2001OM3574>.

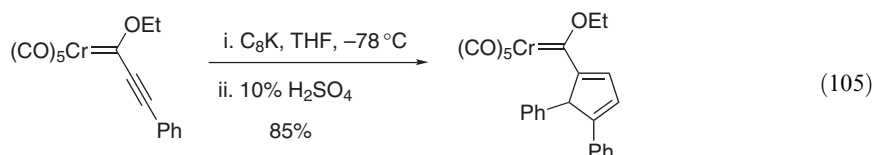
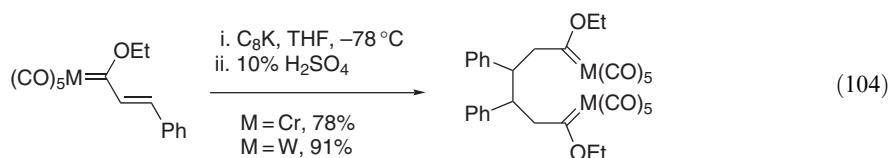


Intramolecular oxidative coupling in the presence of Cu(I), Cu(II), or Fe(III) salts of carbene anions, resulting from *in situ* deprotonation of Fischer-type manganese carbene complexes, produces the corresponding μ -bis(carbene)dimanganese complexes (Scheme 28) <2001JOM(617–618)681>. A biscarbene iron complex has also been prepared by double deprotonation and *in situ* oxidation of the saturated analog with Bu^tOK <2000OM1422>.

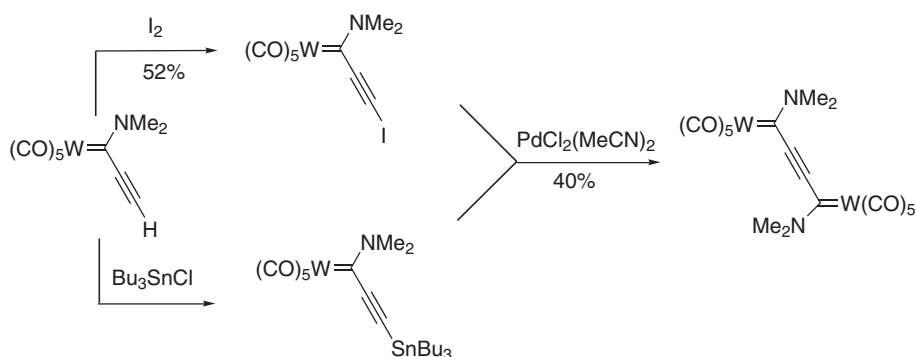


Scheme 28

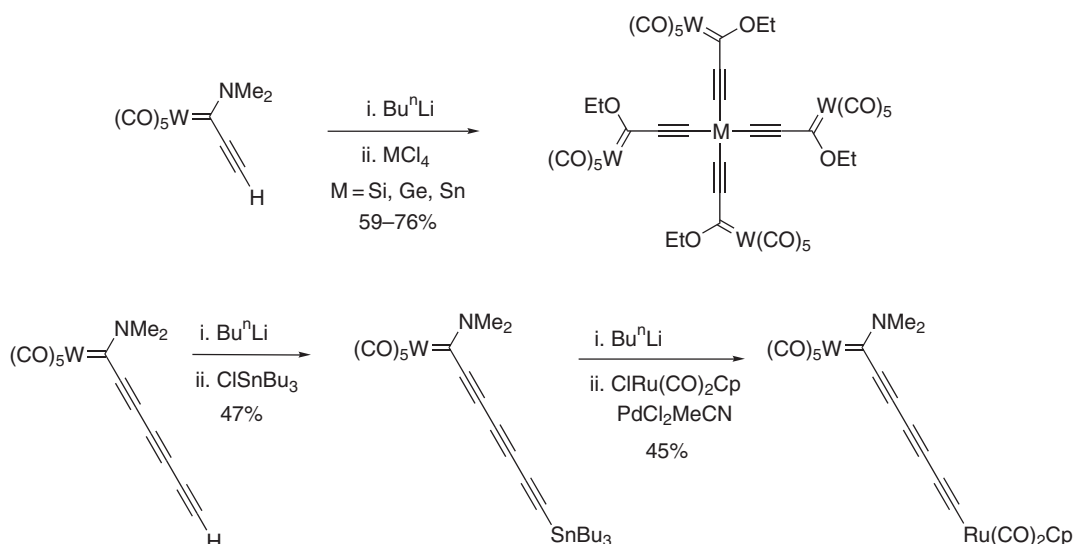
Biscarbene complexes can also be prepared by one-electron reduction of α,β -unsaturated carbene complexes and dimerization of the corresponding anion radical species generated. C_8K or SmI_2 can be the choice to perform these reactions (Equation (104)) <2002AG(E)3442, 2003CEJ905>. The use of C_8K also allows the synthesis of cyclopentadienyl carbene complexes using alkoxyalkynylcarbene complexes as starting materials (Equation (105)) <2002AG(E)3442>.



Palladium or copper coupling reactions produce alkyne-bridged carbene complexes (Scheme 29) <1999OM2619>. Heterobimetallic polynuclear complexes can also be obtained by substitution of alkynyl carbene anions with metal halides or by direct palladium-catalyzed reactions of stannylalkynylcarbene complexes (Scheme 30) <1997CB479, 1997CB1063, 1998EJI191, 1999JOM(578)186>.

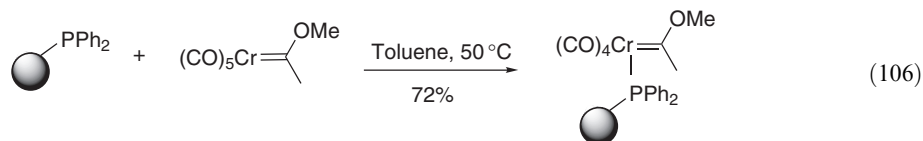


Scheme 29

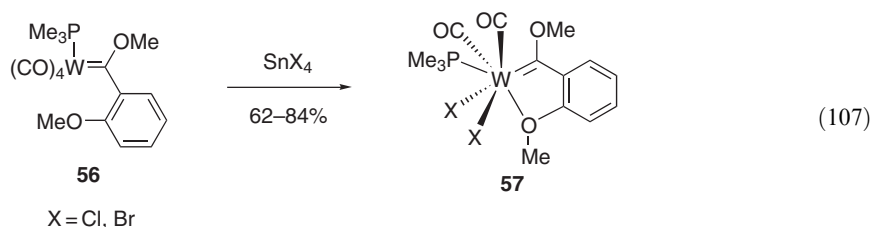


Scheme 30

Polymer-bound Fischer carbene complexes were synthesized by thermal exchange of a CO ligand of pentacarbonyl chromium carbenes with a triphenylphosphine resin (Equation (106)) <1999TL3635>. Similarly, Fischer carbenes have been obtained by exchange reactions with different phosphines <2000JA11509, 2002OM2153, 2003OM1756>.



Finally, phosphino carbene complexes **56** quickly react with SnX_4 ($\text{X} = \text{Cl}, \text{Br}$) affording, by oxidative decarbonylation, heptacoordinated tungsten(II) complexes **57** in good yields as either one or two isomers that do not interconvert (Equation (107)) <2001OM4040>.



REFERENCES

- 1964AG(E)580 E. O. Fischer, A. Maasböl, *Angew. Chem., Int. Ed. Engl.* **1964**, 2, 580–581.
 1981SCI995 R. Hoffmann, *Science* **1981**, 211, 995–1002.
 1982AG(E)711 R. Hoffmann, *Angew. Chem., Int. Ed. Engl.* **1982**, 21, 711–724.
 1994JP11406 H. Jacobsen, G. Schreckenbach, T. Ziegler, *J. Phys. Chem.* **1994**, 98, 11406–11410.
 1995CB157 J. Christoffers, K. H. Dötz, *Chem. Ber.* **1995**, 128, 157–161.
 1995CEJ236 J. Barluenga, J. M. Montserrat, J. Flórez, S. García-Granda, E. Martín, *Chem. Eur. J.* **1995**, 1, 236–242.
 1995COFGT(5)931 P. Quale, Functions doubly bonded to a metal, in *Comprehensive Organic Functional Group Transformations*, Elsevier, Oxford, Vol. 5, pp. 931–960.
 1995COMC-II(12)469 W. D. Wulff, Transition metal carbene complexes: Alkyne and Vinyl ketene chemistry in *Comprehensive Organometallic Chemistry II*, E. W. Abel, F. G. A. Stone, G. Wilkinson, Eds., Pergamon, Oxford, pp. 469–547.
 1995COMC-II(12)549 L. S. Hegedus, Transition metal carbene complexes: Photochemical reactions of carbene complexes in *Comprehensive Organometallic Chemistry II*, E. W. Abel, F. G. A. Stone, G. Wilkinson, Eds., Pergamon, Oxford, pp. 549–576.
 1995G377 S. Maiorana, A. Papagny, E. Licandro, A. Persoons, K. Clay, S. Houbrechts, W. Porzio, *Gazz. Chim. Ital.* **1995**, 125, 377–379.
 1995JA3368 S. Dumas, E. Lastra, L. S. Hegedus, *J. Am. Chem. Soc.* **1995**, 117, 3368–3379.
 1995JA5604 B. Alcaide, L. Casarrubios, G. Domínguez, M. A. Sierra, A. Monge, *J. Am. Chem. Soc.* **1995**, 117, 5604–5605.
 1995JOC1741 K. S. Chan, M. L. Yeung, W. Chan, R. Wang, T. C. W. Mak, *J. Org. Chem.* **1995**, 60, 1741–1747.
 1995JOM(486)279 C. Baldoli, P. Del Buttero, E. Lisandro, S. Maiorana, A. Papagni, A. Zanotti-Gerosa, *J. Organomet. Chem.* **1995**, 486, 279–282.
 1995JOM(489)C84 K. H. Dötz, C. Christoffers, P. Knochel, *J. Organomet. Chem.* **1995**, 489, C84–C86.
 1995JOM(493)113 R. Schobert, F. Hampel, K.-D. Roth, M. Stöss, *J. Organomet. Chem.* **1995**, 493, 113–118.
 1995OM224 H. Jacobsen, T. Ziegler, *Organometallics* **1995**, 14, 224–230.
 1995OM231 R. Aumann, B. Jasper, R. Frölich, *Organometallics* **1995**, 14, 231–237.
 1995OM547 Sk. R. Amin, A. Sarkar, *Organometallics* **1995**, 14, 547–550.
 1995OM1095 N. Ruiz, D. Péron, P. H. Dixneuf, *Organometallics* **1995**, 1995–1097.
 1995OM1938 C. Cosset, I. Del Rio, H. Le Bozec, *Organometallics* **1995**, 14, 1938–1944.
 1995OM2447 R. Aumann, B. Jasper, R. Frölich, *Organometallics* **1995**, 14, 2447–2455.
 1995OM2760 A. Parlier, M. Rudler, H. Rudler, R. Goumont, J.-C. Daran, J. Vaissermann, *Organometallics* **1995**, 14, 2760–2774.
 1995OM3163 H. Stadtmüller, P. Knochel, *Organometallics* **1995**, 14, 3163–3166.
 1995OM3617 Sk. R. Amin, S. S. Sawant, V. G. Puranik, A. Sarkar, *Organometallics* **1995**, 14, 3617–3619.
 1995SC2043 Y. H. Choi, B. S. Kang, Y. Yoon, J. Kim, S. C. Shin, *Synth. Commun.* **1995**, 25, 2043–2050.
 1995SC3329 H. Zhang, K. S. Chan, *Synth. Commun.* **1995**, 25, 3329–3337.
 1995SL666 C. Baldoli, P. Del Buttero, E. Licandro, S. Maiorana, A. Papagni, *Synlett* **1995**, 666–668.
 1995SL1194 K. Rück-Braun, J. Kühn, *Synlett* **1995**, 1194–1196.
 1995TL3699 M. Iyoda, L. Zhao, H. Matsuyama, *Tetrahedron Lett.* **1995**, 36, 3699–3702.
 1995TL3937 J. Barluenga, P. L. Bernard Jr., J. M. Concellón, *Tetrahedron Lett.* **1995**, 36, 3937–3940.

- 1995TL8753 A. Rahm, W. D. Wulff, *Tetrahedron Lett.* **1995**, 36, 8753–8756.
 1996CB623 T. Leese, K. H. Dötz, *Chem. Ber.* **1996**, 129, 623–631.
 1996CB937 K. Rück-Braun, J. Kühn, D. Schollmeyer, *Chem. Ber.* **1996**, 129, 937–944.
 1996CC2601 Y. Shi, W. D. Wulff, G. P. A. Yap, A. L. Rheingold, *J. Chem. Soc., Chem. Commun.* **1996**, 2601–2602.
 1996CRV271 D. F. Harvey, D. M. Sigano, *Chem. Rev.* **1996**, 96, 271–288.
 1996IC775 H. Jacobsen, T. Ziegler, *Inorg. Chem.* **1996**, 35, 775–783.
 1996JA1807 A. Rahm, W. D. Wulff, *J. Am. Chem. Soc.* **1996**, 118, 1807–1808.
 1996JA2166 J. Bao, W. D. Wulff, M. J. Fumo, E. B. Grant, D. P. Heller, M. C. Whitcomb, S.-M. Yeung, *J. Am. Chem. Soc.* **1996**, 118, 2166–2181.
 1996JA2517 H. F. Luecke, B. A. Arndtsen, P. Burger, R. G. Bergman, *J. Am. Chem. Soc.* **1996**, 118, 2517–2518.
 1996JA6090 J. Barluenga, F. Rodríguez, J. Vadeкарd, M. Bendix, F. J. Fañanás, F. López-Ortiz, *J. Am. Chem. Soc.* **1996**, 118, 6090–6091.
 1996JA7873 W. H. Moser, L. S. Hegedus, *J. Am. Chem. Soc.* **1996**, 118, 7873–7880.
 1996JA12045 H. Rudler, M. Audouin, A. Parlier, B. Martin-Vaca, R. Goumont, T. Durand-Réville, J. Vaissermann, *J. Am. Chem. Soc.* **1996**, 118, 12045–12058.
 1996JA13099 J. Barluenga, A. A. Trabanco, J. Flórez, S. García-Granda, E. Martín, *J. Am. Chem. Soc.* **1996**, 118, 13099–13100.
 1996JOC6121 T. E. Kedar, M. W. Miller, L. S. Hegedus, *J. Org. Chem.* **1996**, 61, 6121–6126.
 1996OM105 A. W. Ehlers, S. Dapprich, S. F. Vyboishchikov, G. Frenking, *Organometallics* **1996**, 15, 105–117.
 1996OM1257 R. Aumann, K. Roths, B. Jasper, R. Frölich, *Organometallics* **1996**, 15, 1257–1264.
 1996OM1942 R. Aumann, B. Japer, R. Fröhlich, *Organometallics* **1996**, 15, 1942–1950.
 1996OM4842 R. Aumann, R. Frölich, S. Kotila, *Organometallics* **1996**, 15, 4842–4851.
 1996OM5018 R. Aumann, A. G. Meyer, R. Frölich, *Organometallics* **1996**, 15, 5018–5027.
 1996OM10853 R. Aumann, A. G. Meyer, R. Frölich, *Organometallics* **1996**, 118, 10853–10861.
 1996SL435 C. Cosset, I. Del Río, V. Péron, B. Windmüller, H. Le Bozec, *Synlett* **1996**, 435–436.
 1996SL995 K. H. Dötz, O. Neuß, M. Nieger, *Synlett* **1996**, 995–996.
 1996TL1359 D. K. Hill, J. W. Herdorn, *Tetrahedron Lett.* **1996**, 37, 1359–1362.
 1996TL4675 F. E. McDonald, J. L. Bowman, *Tetrahedron Lett.* **1996**, 37, 4675–4678.
 1996TL9385 R. L. Beddoes, J. E. Painter, P. Quayle, P. Patel, *Tetrahedron Lett.* **1996**, 37, 9385–9386.
 1997AG(E)2376 K. H. Dötz, R. Ehlenz, D. Paetsch, *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 2376–2378.
 1997AOC163 R. Aumann, H. Nienaber, *Adv. Organomet. Chem.* **1997**, 41, 163–242.
 1997BSF503 K. H. Dötz, T. Leese, *Bull. Soc. Chim. Fr.* **1997**, 134, 503–515.
 1997CB171 B. Kayser, K. Polborn, W. Steglich, W. Beck, *Chem. Ber.* **1997**, 130, 171–177.
 1997CB479 C. Hartbaum, G. Roth, H. Fischer, *Chem. Ber.* **1997**, 130, 479–488.
 1997CB507 Kretschik, O.; Nieger, M.; Dötz, K. H. **1997**, 130, 507–513.
 1997CB863 W. Förtsch, F. Hampel, R. Schobert, *Chem. Ber.* **1997**, 130, 863–869.
 1997CB1063 C. Hartbaum, H. Fischer, *Chem. Ber.* **1997**, 130, 1063–1068.
 1997CB1105 A. Longen, M. Nieger, F. Vögtle, K. H. Dötz, *Chem. Ber.* **1997**, 130, 1105–1111.
 1997CB1605 K. H. Dötz, P. Tomuschat, M. Nieger, *Chem. Ber.* **1997**, 130, 1605–1609.
 1997CB1647 J. Kühn, D. Schollmeyer, K. Rück-Braun, *Chem. Ber.* **1997**, 130, 1647–1654.
 1997CC1217 K. H. Dötz, W. Haase, M. Klumpe, M. Nieger, *J. Chem. Soc., Chem. Commun.* **1997**, 1217–1218.
 1997CEJ1629 J. Barluenga, F. Aznar, M. Fernández, *Chem. Eur. J.* **1997**, 3, 1629–1637.
 1997JA848 M. W. Holtcamp, J. A. Labinger, J. E. Bercaw, *J. Am. Chem. Soc.* **1999**, 119, 848–849.
 1997JA3971 C. P. Casey, C. J. Czerwinski, K. A. Fusie, R. K. Hayashi, *J. Am. Chem. Soc.* **1997**, 119, 3971–3978.
 1997JA4404 K.-W. Liang, W.-T. Li, S.-M. Peng, S.-L. Wang, R.-S. Liu, *J. Am. Chem. Soc.* **1997**, 119, 4404–4412.
 1997JA5169 C. F. Bernasconi, A. E. Leyes, *J. Am. Chem. Soc.* **1997**, 119, 5169–5175.
 1997JA5583 C. F. Bernasconi, W. Sun, L. García-Río, K. Yan, K. Kittredge, *J. Am. Chem. Soc.* **1997**, 119, 5583–5590.
 1997JA5750 C. P. Casey, C. J. Czerwinski, D. R. Powell, R. K. Hayashi, *J. Am. Chem. Soc.* **1997**, 119, 5750–5751.
 1997JA11538 F. Luecke, R. G. Begamn, *J. Am. Chem. Soc.* **1997**, 119, 11538–11539.
 1997JCS(D)205 R. Li, J. Chen, Y. You, J. Sie, *J. Chem. Soc., Dalton Trans.* **1997**, 205–211.
 1997JCS(D)1653 Frenking, G.; Pidun, U. **1997**, 1653–1662.
 1997JCS(D)2177 Y. M. Terblans, S. Lotz, *J. Chem. Soc., Dalton Trans.* **1997**, 2177–2182.
 1997JCS(P1)2267 J. Barluenga, F. Fernández-Marí, A. L. Viado, E. Aguilar, B. Olano, *J. Chem. Soc., Perkin Trans. 1* **1997**, 2267–2268.
 1997JOC6870 J. Barluenga, P. L. Bernard Jr., M. Concellón, A. Piñera-Nicolás, S. García-Granda, *J. Org. Chem.* **1997**, 62, 6870–6875.
 1997JOC7247 C. Bouaudeau, A. Parlier, H. Rudler, *J. Org. Chem.* **1997**, 62, 7247–7259.
 1997JOC7704 J. Zhu, C. Deur, L. S. Hegedus, *J. Org. Chem.* **1997**, 62, 7704–7710.
 1997JOC9229 J. Barluenga, M. Tomás, A. Ballesteros, J. Santamaría, A. Suárez-Sobrinio, *J. Org. Chem.* **1997**, 62, 9229–9235.
 1997JOM(529)351 R. Steubel, M. Hobbold, J. Jeske, F. Ruthe, P. G. Jones, *J. Organomet. Chem.* **1997**, 529, 351–356.
 1997JOM(533)213 N. Ruiz, D. Péron, S. Sinbandith, P. H. Dixneuf, C. Baldoli, S. Maiorana, *J. Organomet. Chem.* **1997**, 533, 213–218.
 1997JOM(539)201 V. Péron, E. Porhiel, V. Ferrand, H. Le Bozec, *J. Organomet. Chem.* **1997**, 539, 201–203.
 1997JOM(541)187 Y. Zhengkun, R. Aumann, R. Frölich, K. Roths, J. Hecht, *J. Organomet. Chem.* **1997**, 541, 187–198.

- 1997JOM(541)321 H. Fisher, O. Podschadly, G. Roth, S. Herminhaus, S. Klewitz, J. Heck, S. Houbrechts, T. Meyer, *J. Organomet. Chem.* **1997**, 541, 321–332.
- 1997JOM(542)205 A. Geisbauer, K. Polborn, W. Beck, *J. Organomet. Chem.* **1997**, 542, 205–208.
- 1997JOM(545–546)9 F. Rose-Munch, C. Le Corre-Susanne, F. Balssa, E. Rose, J. Vaisserman, E. Licandro, A. Papagni, S. Maiorana, W. Meng, G. R. Stephenson, *J. Organomet. Chem.* **1997**, 545–546, 9–16.
- 1997JOM(545–546)447 P. Le Poul, F. Robin-Le Guen, M.-C. Sénéchal-Tocquer, B. Caro, *J. Organomet. Chem.* **1997**, 545–546, 447–450.
- 1997JOM(548)91 K. H. Dötz, R. Ehlenz, W. Straub, J. C. Weber, K. Airola, M. Nieger, *J. Organomet. Chem.* **1997**, 548, 91–98.
- 1997JOM(549)311 R. Aumann, Y. Zhengkun, R. Fröhlich, *J. Organomet. Chem.* **1997**, 549, 311–318.
- 1997JPC8887 C. Wang, Y. Wang, H. Liu, K. Lin, L. Chou, K. Chan, *J. Phys. Chem.* **1997**, 101, 8887–8901.
- 1997MI1061 Y. Park, S. Kim, J. Ko, S. O. Kang, *Bull. Korean Chem. Soc.* **1997**, 18, 1061–1066.
- 1997OM124 G. Poignant, S. Nlate, V. Guerschais, A. J. Edwards, P. R. Raithby, *Organometallics* **1997**, 16, 124–132.
- 1997OM370 T. B. Gunnoe, P. S. White, J. L. Templeton, *Organometallics* **1997**, 16, 370–377.
- 1997OM442 N. Fröhlich, U. Pidun, M. Stahl, G. Frenking, *Organometallics* **1997**, 16, 442–448.
- 1997OM1926 C. F. Bernasconi, W. Sun, *Organometallics* **1997**, 16, 1926–1932.
- 1997OM2008 S. B. Falloon, W. Weng, A. M. Arif, J. A. Gladysz, *Organometallics* **1997**, 16, 2008–2015.
- 1997OM2313 A. D. Reed, L. S. Hegedus, *Organometallics* **1997**, 16, 2313–2317.
- 1997OM2370 K. Issberner, E. Niecke, E. Wittchow, K. H. Dötz, M. Nieger, *Organometallics* **1997**, 16, 2370–2376.
- 1997OM2483 M. P. Gamasa, J. Gimeno, C. González-Bernardo, J. Borge, S. García-Granda, *Organometallics* **1997**, 16, 2483–2485.
- 1997OM2571 R. Aumann, R. Fröhlich, F. Zippel, *Organometallics* **1996**, 16, 2571–2580.
- 1997OM2808 L. Jordi, S. Ricart, Viñas, J. M. Moretó, *Organometallics* **1997**, 16, 2808–2818.
- 1997OM3083 G. L. Casty, J. M. Stryker, *Organometallics* **1997**, 16, 3083–3085.
- 1997OM3536 P. Mathur, S. Ghosh, A. Sarkar, C. V. V. Satyanarayana, A. L. Rheingold, L. M. Liable-Sands, *Organometallics* **1997**, 16, 3536–3540.
- 1997OM3873 C. Mongin, N. Lugan, R. Mathieu, *Organometallics* **1997**, 16, 3873–3875.
- 1997OM4056 T. A. Waldbach, R. van Eldik, P. H. van Rooyen, S. Lotz, *Organometallics* **1997**, 16, 4056–4070.
- 1997OM4392 Mathur, S. Ghosh, A. Sarkar, C. V. V. Satyanarayana, V. G. Puranik, *Organometallics* **1997**, 16, 4392–4398.
- 1997OM4435 M.-C. P. Yeh, L.-W. Chuang, S.-C. Chang, M.-L. Lai, C.-C. Chou, *Organometallics* **1997**, 16, 4435–4444.
- 1997OM5089 P. Stepnicka, R. Gyepes, O. Lavastre, P. H. Dixneuf, *Organometallics* **1997**, 16, 5089–5095.
- 1997OM5528 M. A. Jiménez Tenorio, M. Jiménez Tenorio, M. C. Puerta, P. Valerga, *Organometallics* **1997**, 16, 5528–5535.
- 1997OM5893 R. Aumann, K. Roths, R. Fröhlich, *Organometallics* **1997**, 16, 5893–5899.
- 1997SL621 R. Aumann, M. Kößmeier, F. Zippel, *Synlett* **1997**, 621–623.
- 1997SL913 G. Poignant, F. Martin, V. Guerschais, *Synlett* **1997**, 913–914.
- 1997SL1040 J. Barluenga, F. Aznar, S. Barluenga, S. García-Granda, C. Alvarez-Rúa, *Synlett* **1997**, 1040–1042.
- 1997T4105 L. S. Hegedus, *Tetrahedron* **1997**, 53, 4105–4128.
- 1997T5143 R. Ehlenz, O. Neuss, M. Teckenbrock, K. H. Dötz, *Tetrahedron* **1997**, 53, 5143–5158.
- 1997T9323 J. Barluenga, F. Aznar, A. Martín, S. Barluenga, *Tetrahedron* **1997**, 53, 9323–9340.
- 1997T11061 F. E. MacDonald, H. Y. H. Zhu, *Tetrahedron* **1997**, 53, 11061–11068.
- 1997TA1751 K. H. Dötz, C. Stinner, *Tetrahedron Asymmetry* **1997**, 8, 1751–1765.
- 1997TL1181 K. Takeda, Y. Okamoto, A. Nakajima, E. Yoshii, T. Koizumi, *Tetrahedron Lett.* **1997**, 38, 1181–1182.
- 1997TL3769 C. Baldoli, P. Hellier, E. Licandro, S. Maiorana, R. Manzotti, A. Papagni, *Tetrahedron Lett.* **1997**, 38, 3769–3772.
- 1997TL5587 G. A. Peterson, W. D. Wulff, *Tetrahedron Lett.* **1997**, 38, 5587–5990.
- 1997TL6787 C. A. Merlic, D. M. McInnes, Y. You, *Tetrahedron Lett.* **1997**, 38, 6787–6790.
- 1997TL7687 F. E. MacDonald, A. K. Chatterjee, *Tetrahedron Lett.* **1997**, 38, 7687–7690.
- 1997TL7691 F. E. MacDonald, T. C. Olson, *Tetrahedron Lett.* **1997**, 38, 7691–7692.
- 1998CC383 E. Licandro, S. Maiorana, R. Manzotti, A. Papagni, D. Perdicchia, M. Pryce, A. Tripicchio, M. Lanfranchi, *J. Chem. Soc., Chem. Commun.* **1998**, 383–384.
- 1998CEJ1033 S. B. Falloon, S. Szafert, A. M. Arif, J. A. Gladysz, *Chem. Eur. J.* **1998**, 4, 1033–1042.
- 1998CEJ1428 S. F. Vyboishchikov, G. Frenking, *Chem. Eur. J.* **1998**, 4, 1428–1436.
- 1998CEJ2225 E. Gutierrez-Puebla, A. Monge, M. C. Nicasio, E. Carmona, *Chem. Eur. J.* **1998**, 4, 2225–2236.
- 1998CEJ2280 J. Barluenga, F. Aznar, S. Barluenga, M. Fernández, A. Martín, S. García-Granda, A. Piñera-Nicolás, *Chem. Eur. J.* **1998**, 4, 2280–2289.
- 1998EJI191 C. Hartbaum, G. Roth, H. Fischer, *Eur. J. Inorg. Chem.* **1998**, 191–202.
- 1998EJI211 C. Bianchini, A. Marchi, N. Mantovani, L. Marvelli, D. Masi, M. Peruzzini, R. Rossi, *Eur. J. Inorg. Chem.* **1998**, 211–219.
- 1998EJI339 H. Fischer, K. Weissenbach, C. Karl, A. Geyer, *Eur. J. Inorg. Chem.* **1998**, 339–347.
- 1998EJO2127 E. Licandro, S. Maiorana, L. Capella, R. Manzotti, A. Papagni, M. Pryce, C. Graiff, A. Tripicchio, *Eur. J. Org. Chem.* **1998**, 2127–2133.
- 1998JA2283 U. Schick, L. Jordi, S. Ricart, J. Veciana, K. H. Dötz, J. M. Moretó, *J. Am. Chem. Soc.* **1998**, 120, 2283–2289.
- 1998JA2514 J. Barluenga, R. M. Canteli, J. Flórez, S. García-Granda, A. Gutiérrez-Rodríguez, E. Martín, *J. Am. Chem. Soc.* **1998**, 120, 2514–2522.

- 1998JA4520
1998JA9388
- 1998JA10573
1998JA11071
- 1998JOC5275
1998JOC7289
1998JOC7588
1998JOC7670
1998JOM(553)183
1998JOM(556)119
1998MI551
- 1998OM1109
1998OM1197
1998OM1245
1998OM1333
1998OM1492
1998OM1602
1998OM2135
1998OM2897
1998OM3627
1998OM4353
1998SL1120
1998TL557
- 1998TL795
- 1998TL1849
1998TL4887
- 1999CC925
- 1999CC2385
1999CEJ883
- 1999EJI739
1999EJI2037
1999EJO2545
1999ICA236
- 1999JCS(P1)197
- 1999JOC4206
1999JOC6554
- 1999JOM(578)186
1999JOM(578)247
1999JOM(583)34
1999JOM(583)111
- 1999JOM(586)247
- 1999JOM(589)11
1999JOM(590)158
- 1999OM1369
1999OM2275
- 1999OM2376
- 1999OM2619
- 1999OM3851
- 1999TL2919
1999TL3635
- 2000AG(E)2158
2000AG(E)3964
- W.-T. Li, F.-C. Lai, G.-H. Lee, S.-M. Peng, R.-S. Liu, *J. Am. Chem. Soc.* **1998**, *120*, 4520–4521.
J. N. Calter III, G. J. Spivak, H. Gérard, E. Clot, E. R. Davidson, O. Eisenstein, K. G. Caulton, *J. Am. Chem. Soc.* **1998**, *120*, 9388–9389.
H. Wang, W. D. Wulff, *J. Am. Chem. Soc.* **1998**, *120*, 10573–10574.
T. Barkik, W. Weng, J. A. Ramsdem, S. Szafert, S. B. Falloon, A. M. Arif, J. A. Gladysz, *J. Am. Chem. Soc.* **1998**, *120*, 11071–11081.
S. R. Pulley, J. P. Carey, *J. Org. Chem.* **1998**, *63*, 5275–5279.
K.-W. Liang, M. Chandrasekharan, C.-L. Li, R.-S. Liu, *J. Org. Chem.* **1998**, *63*, 7289–7293.
J. Barluenga, L. A. López, S. Martínez, M. Tomás, *J. Org. Chem.* **1998**, *63*, 7588–7589.
M. L. Yeung, W.-K. Li, H.-J. Liu, Y. Wang, K. S. Chan, *J. Org. Chem.* **1998**, *63*, 7670–7673.
C. A. Merlic, F. Wu, *J. Organomet. Chem.* **1998**, *553*, 183–191.
R. Aumann, K. B. Roths, M. Kößmeier, R. Fröhlich, *J. Organomet. Chem.* **1998**, *556*, 119–127.
B. Alcaide, L. Casarrubios, G. Domínguez, M. A. Sierra, *Current Organic Chemistry* **1998**, *2*, 551–574.
Y. Lee, S. Kim, C. Kang, J. Ko, S. O. Kang, P. J. Carrol, *Organometallics* **1998**, *17*, 1109–1115.
R. Aumann, B. Hildmann, R. Fröhlich, *Organometallics* **1998**, *17*, 1197–1201.
W. Leung, E. Y. Y. Chan, W. Wong, *Organometallics* **1998**, *17*, 1245–1247.
R. D. Theys, R. M. Vargas, Q. Wang, M. M. Hossain, *Organometallics* **1998**, *17*, 1333–1339.
M. Torrent, M. Durán, M. Solá, *Organometallics* **1998**, *17*, 1492–1501.
B. Weyerhausen, M. Nieger, K. H. Dötz, *Organometallics* **1998**, *17*, 1602–1607.
R. Polo, J. M. Moretó, S. Ricart, *Organometallics* **1998**, *17*, 2135–2137.
R. Aumann, Y. Zhengkun, R. Fröhlich, *Organometallics* **1998**, *17*, 2897–2905.
D. Dvorák, M. Ludwig, *Organometallics* **1998**, *17*, 3627–3629.
J. Pfeiffer, K. H. Dötz, *Organometallics* **1998**, *17*, 4353–4361.
R. Aumann, M. Kössmeier, A. Jäntti, *Synlett* **1998**, 1120–1122.
B. Caro, P. Le Poul, F. Robin-Le Guen, M.-C. Sénéchal-Tocquer, *Tetrahedron Lett.* **1998**, *39*, 557–560.
R. Aumann, I. J. Göttker-Schnetmann, B. Wibbeling, R. Fröhlich, *Tetrahedron Lett.* **1998**, *39*, 795–798.
H. Wang, R. P. Hsung, W. D. Wulff, *Tetrahedron Lett.* **1998**, *39*, 1849–1852.
J. Barluenga, F. Fernández-Mari, E. Aguilar, A. L. Viado, B. Olano, *Tetrahedron Lett.* **1998**, *39*, 4887–4890.
E. Licandro, S. Maiorana, A. Papagni, D. Perdicchia, R. Manzotti, *J. Chem. Soc., Chem. Commun.* **1999**, 925–926.
D. D. Ellis, P. A. Jelliss, F. Gordon, A. Stone, *J. Chem. Soc., Chem. Commun.* **1999**, 2385–2386.
J. Barluenga, F. Fernández-Mari, A. L. Viado, E. Aguilar, B. Olano, S. García-Granda, C. Moya-Rubiera, *Chem. Eur. J.* **1999**, *5*, 883–896.
C. Mongin, Y. Ortin, N. Lugan, R. Mathieu, *Eur. J. Inorg. Chem.* **1999**, 739–742.
A. Beste, O. Krämer, A. Gerhard, G. Frenking, *Eur. J. Inorg. Chem.* **1999**, 2037–2045.
R. Aumann, I. Göttker-Schnetmann, R. Fröhlich, O. Meyer, *Eur. J. Org. Chem.* **1999**, 2545–2561.
S. Maiorana, A. Papagni, E. Licandro, D. Perdicchia, C. Baldoli, C. Graiff, A. Tiripicchio, *Inorg. Chim. Acta* **1999**, *296*, 236–245.
W. D. Wulff, K. L. Faron, J. Su, J. P. Springer, A. L. Rheingold, *J. Chem. Soc., Perkin Trans. 1* **1999**, 197–219.
B. Weyershausen, M. Nieger, K. H. Dötz, *J. Org. Chem.* **1999**, *64*, 4206–4210.
J. Ezquerro, C. Pedregal, I. Merino, J. Flórez, J. Barluenga, S. García-Granda, M. A. Llorca, *J. Org. Chem.* **1999**, *64*, 6554–6565.
C. Hartbaum, H. Fischer, *J. Organomet. Chem.* **1999**, *578*, 186–192.
O. Brel, A. Fehn, W. Beck, *J. Organomet. Chem.* **1999**, *578*, 247–251.
K. H. Dötz, D. Böttcher, M. Jendro, *J. Organomet. Chem.* **1999**, *583*, 34–41.
E. Licandro, S. Maiorana, A. Papagni, P. Hellier, L. Capella, A. Persoons, S. Houbrechts, *J. Organomet. Chem.* **1999**, *583*, 111–119.
J. Pares, J. M. Moretó, S. Ricart, J. Barluenga, F. J. Fañanás, *J. Organomet. Chem.* **1999**, *586*, 247–253.
K. H. Dötz, D. Paetsch, H. Le Bozec, *J. Organomet. Chem.* **1999**, *589*, 11–20.
H. G. Raubenheimer, Y. Stander, E. K. Marais, C. Thompson, G. J. Kruger, S. Cronje, M. Deetlefs, *J. Organomet. Chem.* **1999**, *590*, 158–168.
R. Aumann, R. Fröhlich, J. Prigge, O. Meyer, *Organometallics* **1999**, *18*, 1369–1380.
E. Rüba, C. Gemel, C. Slugovc, K. Mereiter, R. Schmid, K. Kirchner, *Organometallics* **1999**, *18*, 2275–2280.
C. Bianchini, D. Masi, A. Romero, F. Zanobini, M. Peruzzini, *Organometallics* **1999**, *18*, 2376–2386.
C. Hartbaum, E. Mauz, G. Roth, K. Weissenbach, H. Fischer, *Organometallics* **1999**, *18*, 2619–2627.
K. N. Jayaprakash, P. C. Ray, I. Matsuoka, M. M. Bhadbhade, V. G. Puranik, P. K. Das, H. Nishihara, A. Sarkar, *Organometallics* **1999**, *18*, 3851–3858.
W. Haase, K. H. Dötz, *Tetrahedron Lett.* **1999**, 2919–2920.
S. Maiorana, P. Seneci, T. Rossi, C. Baldoli, M. Ciraco, E. de Magistris, E. Licandro, A. Papagni, S. Provera, *Tetrahedron Lett.* **1999**, 3635–3638.
C. Slugovc, K. Mereiter, S. Trofimenko, E. Carmona, *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2158–2160.
A. de Meijere, H. Schirmer, M. Duetsch, *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3964–4002.

- 2000CR3591 M. A. Sierra, *Chem. Rev.* **2000**, *100*, 3591–3637.
 2000EJ133 K. Urtel, A. Frick, G. Huttner, L. Zsolnai, P. Kircher, P. Rutsch, E. Kaifer, A. Jacobi, *Eur. J. Inorg. Chem.* **2000**, 33–50.
 2000EJO17 R. Aumann, *Eur. J. Org. Chem.* **2000**, 17–31.
 2000EJO187 H. C. Strauch, T. Rinderknecht, G. Erker, R. Frölich, E. Wegelius, F. Zippel, S. Höppener, H. Fuchs, L. Chi, *Eur. J. Org. Chem.* **2000**, 187–192.
 2000EJO1183 H.-P. Wu, R. Aumann, B. Wibbeling, *Eur. J. Org. Chem.* **2000**, 1183–1192.
 2000EJO1773 J. Barluenga, F. Fernández-Marí, R. González, E. Aguilar, G. A. Revelli, A. L. Viado, F. J. Fañanas, B. Olano, *Eur. J. Org. Chem.* **2000**, 1773–1783.
 2000EJO3463 H.-P. Wu, R. Aumann, S. Venne-Dunker, P. Saarenketo, *Eur. J. Org. Chem.* **2000**, 3463–3473.
 2000IC3757 J. N. Coalter III, J. C. Huffman, W. E. Steib, K. G. Caulton, *Inorg. Chem.* **2000**, *39*, 3757–3764.
 2000JA7398 C. A. Merlic, A. Baur, C. C. Aldrich, *J. Am. Chem. Soc.* **2000**, *122*, 7398–7399.
 2000JA10226 N. Iwasawa, M. Shido, K. Maeyama, H. Kusama, *J. Am. Chem. Soc.* **2000**, *122*, 10226–10227.
 2000JA11509 A. Arrieta, F. P. Cossio, I. Fernández, M. Gómez-Gallego, B. Lecea, M. J. Mancheño, M. A. Sierra, *J. Am. Chem. Soc.* **2000**, *122*, 11509–11510.
 2000JOC4796 H. Matsuyama, T. Nakamura, M. Iyoda, *J. Org. Chem.* **2000**, *65*, 4796–4803.
 2000JOM(593–594)192 H. Werner, U. Wecker, *J. Organomet. Chem.* **2000**, *593–594*, 192–201.
 2000JOM(599)288 M. M. Abd-Elzaher, T. Froneck, G. Roth, V. Gvoddev, H. Fisher, *J. Organomet. Chem.* **2000**, *599*, 288–297.
 2000JOM(601)78 K. Ulrich, E. Porhiel, V. Péron, V. Ferrand, H. Le Bozec, *J. Organomet. Chem.* **2000**, *601*, 78–86.
 2000JOM(602)37 B. Weyerhausen, M. Nieger, K. H. Dötz, *J. Organomet. Chem.* **2000**, *602*, 37–44.
 2000JOM(606)26 J. Sueltemeyer, H. Hupfer, K. H. Dötz, M. Nieger, *J. Organomet. Chem.* **2000**, *606*, 26–36.
 2000JOM(608)34 S. Tollari, S. Cenini, A. Peroni, G. Granata, G. Palmisano, F. Demartin, *J. Organomet. Chem.* **2000**, *608*, 34–41.
 2000MI9 J. N. Coalter III, J. C. Bollinger, J. C. Huffman, U. Werner-Zwanzinger, K. G. Caulton, E. R. Davidson, H. Gérard, E. Clot, O. Eisenstein, *New. J. Chem.* **2000**, *24*, 9–26.
 2000MI835 J. N. Coalter III, F. Ferrando, K. G. Caulton, *New. J. Chem.* **2000**, *24*, 835–836. (*as above?*).
 2000OM4 M. A. Esteruelas, A. V. Gómez, A. M. López, M. Oliván, E. Oñate, N. Ruiz, *Organometallics* **2000**, *19*, 4–14.
 2000OM1422 V. Guilleme, V. Mahias, A. Mari, C. Lapinte, *Organometallics* **2000**, *19*, 1422–1426.
 2000OM2179 L. Quast, M. Nieger, K. H. Dötz, *Organometallics* **2000**, *19*, 2179–2183.
 2000OM2281 D. Huang, J. C. Bollinger, W. E. Streib, K. Folting, V. Young Jr., O. Eisenstein, K. G. Caulton, *Organometallics* **2000**, *19*, 2281–2290.
 2000OM2291 H. Gérard, E. Clot, C. Giessner-Prettre, K. G. Caulton, E. R. Davidson, O. Eisenstein, *Organometallics* **2000**, *19*, 2291–2298.
 2000OM2947 J. S. Yeston, R. G. Bergman, *Organometallics* **2000**, *19*, 2947–2949.
 2000OM4740 H. D. Hansen, J. H. Nelson, *Organometallics* **2000**, *19*, 4740–4755.
 2000OM5484 J. Djukic, A. Maise-François, M. Pfeffer, K. H. Dötz, A. De Cian, J. Fischer, *Organometallics* **2000**, *19*, 5484–5499.
 2000OM5525 K. Ohe, K. Miki, T. Yokoi, F. Nishino, S. Uemura, *Organometallics* **2000**, *19*, 5525–5528.
 2000T4597 J. Barluenga, F. J. Fañanas, *Tetrahedron* **2000**, *56*, 4597–4628.
 2000T4907 K. Fuchibe, N. Iwasawa, *Tetrahedron* **2000**, *56*, 4907–4915.
 2000T4925 K. H. Dötz, A. W. Koch, B. Weyershausen, H. Hupfer, M. Nieger, *Tetrahedron* **2000**, *56*, 4925–4934.
 2000T4951 A. Rahm, A. L. Rheingold, W. D. Wulff, *Tetrahedron* **2000**, *56*, 4951–4965.
 2000TA975 E. Licandro, S. Maiorana, C. Baldoli, L. Capella, D. Perdicchia, *Tetrahedron Asymmetry* **2000**, *11*, 975–980.
 2000TL7341 C. Mongin, K. Gruet, N. Lugan, R. Mathieu, *Tetrahedron Lett.* **2000**, *41*, 7341–7345.
 2001CEJ700 H.-P. Wu, R. Aumann, R. Frölich, P. Saarenketo, *Chem. Eur. J.* **2001**, *7*, 700–710.
 2001CEJ3533 J. Barluenga, M. A. Fernández-Rodríguez, E. Aguilar, F. Fernández-Marí, A. Salinas, B. Olano, *Chem. Eur. J.* **2001**, *7*, 3533–3544.
 2001CEJ5318 J. Barluenga, F. Aznar, M. A. Palomero, *Chem. Eur. J.* **2001**, *7*, 5318–5324.
 2001EJ1233 M. Landman, H. Görls, S. Lotz, *Eur. J. Inorg. Chem.* **2001**, 233–238.
 2001EJO1149 A. Papagni, S. Maiorana, E. Licandro, R. Manzotti, C. Baldoli, *Eur. J. Org. Chem.* **2001**, 1149–1155.
 2001EJO2501 Y. Wu, H. Schirmer, M. Noltemeyer, A. de Meijere, *Eur. J. Org. Chem.* **2001**, 2501–2506.
 2001JA5814 N. Iwasawa, M. Shido, K. Maeyama, H. Kusama, *J. Am. Chem. Soc.* **2001**, *123*, 5814–5815.
 2001JOC1297 C. A. Merlic, C. C. Aldrich, J. Albaneze-Walker, A. Saghatelian, J. Mammen, *J. Org. Chem.* **2001**, *66*, 1297–1309.
 2001JOC8920 M. A. Sierra, M. J. Mancheño, R. Vicente, M. Gómez-Gallego, *J. Org. Chem.* **2001**, *66*, 8920–8925.
 2001JOM(617–618)280 M. Landman, H. Görls, S. Lotz, *J. Organomet. Chem.* **2001**, *617–618*, 280–287.
 2001JOM(617–618)339 G. Maas, D. Mayer, *J. Organomet. Chem.* **2001**, *617–618*, 339–345.
 2001JOM(617–618)399 E. Licandro, S. Maiorana, D. Perdicchia, C. Baldoli, C. Graiff, A. Tiripicchio, *J. Organomet. Chem.* **2001**, *617–618*, 399–411.
 2001JOM(617–618)681 A. Rabier, N. Lugan, R. Mathieu, *J. Organomet. Chem.* **2001**, *617–618*, 681–695.
 2001JOM(617–618)709 K. N. Jayaprakash, D. Hazra, K. S. Hagen, U. Samanta, M. M. Bhadhade, V. G. Puramik, A. Sarkar, *J. Organomet. Chem.* **2001**, *617–618*, 709–722.
 2001JOM(620)165 H. Fisher, F. Kirchbauer, A. Früh, M. M. Abd-Elzaher, G. Roth, C. C. Karl, M. Dede, *J. Organomet. Chem.* **2001**, *620*, 165–173.
 2001JOM(621)344 K. Weissenbach, H. Fischer, *J. Organomet. Chem.* **2001**, *621*, 344–351.
 2001JOM(622)251 E. Janes, K. H. Dötz, *J. Organomet. Chem.* **2001**, *622*, 251–258.

- 2001JOM(624)5
2001JOM(626)37
2001JOM(626)199
2001JOM(629)114
2001JOM(635)9
2001OM485
2001OM2183
2001OM2889
2001OM3574
2001OM4040
2001OM4114
2001OM4304
2001S200
2001SL757
2001T5199
2002AG(E)3442
2002CC1842
2002EJO39
2002JA6512
2002JA9056
2002JCS(D)1479
2002JOM(645)228
2002OL2121
2002OL3659
2002OM1637
2002OM2153
2002OM2736
2002OM4182
2002OM4356
2002OM4425
2002T7519
2003CEJ905
2003JA9572
2003JOC537
2003JOM(669)1
2003OL1237
2003OM384
2003OM586
2003OM1756
J. Barluenga, J. Flórez, F. J. Fañanás, *J. Organomet. Chem.* **2001**, 624, 5–17.
F. Robin-le Guen, P. Le Poul, B. Caro, R. Pichon, N. Kervarec, *J. Organomet. Chem.* **2001**, 626, 37–42.
P. D. Woodgate, H. S. Sutherland, C. E. F. Rickard, *J. Organomet. Chem.* **2001**, 626, 199–220.
P. D. Woodgate, H. S. Sutherland, C. E. F. Rickard, *J. Organomet. Chem.* **2001**, 629, 114–130.
G. Frenking, *J. Organomet. Chem.* **2001**, 635, 9–23.
E. Licandro, S. Maiorana, L. Capella, R. Manzotti, A. Papagni, B. Vandoni, A. Albinati, S. H. Chuang, J. Hwu, *Organometallics* **2001**, 20, 485–496.
H.-P. Wu, R. Aumann, R. Frölich, E. Wegelius, *Organometallics* **2001**, 20, 2183–2190.
I. Göttker-Schnetmann, R. Aumann, O. Kataeva, C. Holst, R. Fröhlich, *Organometallics* **2001**, 20, 2889–2904.
I. Göttker-Schnetmann, R. Aumann, K. Bergander, *Organometallics* **2001**, 20, 3574–3581.
R. Stumpf, M. Jaeger, H. Fischer, *Organometallics* **2001**, 20, 4040–4048.
M. F. Semmelhack, A. Lindenschmidt, D. Ho, *Organometallics* **2001**, 20, 4114–4117.
I. Fernández, M. A. Sierra, M. J. Mancheño, M. Gómez-Gallego, S. Ricart, *Organometallics* **2001**, 20, 4304–4306.
R. P. Hsung, W. D. Wulff, S. Chamberlin, Y. Liu, R.-Y. Liu, H. Wang, J. F. Quinn, S. L. B. Wang, A. L. Rheingold, *Synthesis* **2001**, 200–220.
E. Licandro, S. Maiorana, B. Vandoni, D. Perdicchia, P. Paravidino, C. Baldoli, *Synlett* **2001**, 757–760.
C. A. Merlic, Y. You, D. M. McInnes, A. L. Zechman, M. M. Miller, Q. Deng, *Tetrahedron* **2001**, 57, 5199–5212.
M. A. Sierra, P. Ramírez-López, M. Gómez-Gallego, T. Lejon, M. J. Mancheño, *Angew. Chem., Int. Ed. Engl.* **2002**, 41, 3442–3445.
M. A. Sierra, J. C. del Amo, M. J. Mancheño, M. Gómez-Gallego, M. R. Torres, *J. Chem. Soc., Chem. Commun.* **2002**, 1842–1843.
K. H. Dötz, S. Mittenzwey, *Eur. J. Org. Chem.* **2002**, 39–47.
V. Vorogushin, W. D. Wulff, H. Hansen, *J. Am. Chem. Soc.* **2002**, 124, 6512–6513.
J. Barluenga, *J. Am. Chem. Soc.* **2002**, 124, 9056–9057.
B. Weberndörfer, H. Werner, *J. Chem. Soc., Dalton Trans.* **2002**, 1479–1486.
K. Miki, T. Yokoi, F. Nishino, K. Ohe, S. Uemura, *J. Organomet. Chem.* **2002**, 645, 228–234.
B. K. Ghorai, S. Menon, D. L. Johnson, J. W. Herndon, *Org. Lett.* **2002**, 4, 2121–2124.
J. Barluenga, M. A. Fernández-Rodríguez, E. Aguilar, *Org. Lett.* **2002**, 4, 3659–3662.
R. Aumann, D. Vogt, X. Fu, R. Frölich, P. Schwab, *Organometallics* **2002**, 21, 1637–1645.
J. Louie, R. H. Grubbs, *Organometallics* **2002**, 21, 2153–2164.
R. Aumann, X. Fu, D. Vogt, R. Frölich, O. Kataeva, *Organometallics* **2002**, 21, 2736–2742.
M. Cases, G. Frenking, M. Durán, M. Solá, *Organometallics* **2002**, 21, 4182–4191.
R. Aumann, X. Fu, C. Holst, R. Frölich, *Organometallics* **2002**, 21, 4356–4368.
B. Fuss, M. Dede, B. Weiber, H. Fischer, *Organometallics* **2002**, 21, 4425–4431.
B. Caro, P. Le Poul, F. Robin-Le Guen, J.-Y. Saillard, S. Kahlal, C. Moinet, N. Le Poul, J. Vaissermann, *Tetrahedron* **2002**, 58, 7519–7530.
K. Fuchibe, N. Iwasawa, *Chem. Eur. J.* **2003**, 9, 905–914.
M. A. Sierra, I. Fernández, M. J. Mancheño, M. Gómez-Gallego, M. Rosario Torres, F. P. Cossio, A. Arrieta, B. Lecea, A. Poveda, J. Jiménez-Barbero, *J. Am. Chem. Soc.* **2003**, 125, 9572–9573.
J. Barluenga, F. Aznar, M. A. Palomero, *J. Org. Chem.* **2003**, 68, 537–544.
E. Janes, K. H. Dötz, *J. Organomet. Chem.* **2003**, 669, 1–5.
I. Fernández, M. J. Mancheño, M. Gómez-Gallego, M. A. Sierra, *Org. Lett.* **2003**, 5, 1237–1240.
M. A. Sierra, M. J. Mancheño, J. C. del Amo, I. Fernández, M. Gómez-Gallego, M. R. Torres, *Organometallics* **2003**, 22, 384–386.
H. Katayama, M. Nagao, F. Ozawa, *Organometallics* **2003**, 22, 586–593.
J. Barluenga, K. Muniz, M. Tomás, A. Ballesteros, S. García-Granda, *Organometallics* **2003**, 22, 1756–1760.

Biographical sketch



Maria José Mancheño studied chemistry at the Universidad Complutense de Madrid (UCM) where she graduated in 1988 and obtained her Ph.D. in 1993. Then, she did a postdoctoral stay at the University of Maryland (USA) with Professor P. Mariano. In 1992 she was appointed Professor Ayudante at UCM and Professor Asociado in 1997 at the same university. Since 2003 she is Professor Contratado Doctor at UCM. Her current research interests are organic synthesis, organometallic chemistry, photochemistry, as well as environmental chemistry.

Miguel A. Sierra studied chemistry at the Universidad Complutense de Madrid (UCM) and received his doctorate (honors) in 1987. He was appointed Professor Ayudante at UCM in 1987, and after a postdoctoral stay (1988–1989) at the Colorado State University with Prof. Louis S. Hegehus, he returned to Madrid where he was promoted to Professor Titular in 1990. His research encompasses the development of new synthetic processes based on catalytic and stoichiometric reactions of transition metal complexes, the study of their reaction mechanisms, as well as the design, synthesis, and the study of the environmental behavior of new bio-organometallic compounds.

Mar Gómez-Gallego studied chemistry at the Universidad Complutense de Madrid (UCM) where she obtained her Ph.D. in 1987. She continued her scientific education with a Fleming Postdoctoral Fellowship with Professor W. M. Horspool and she returned to Madrid where she was appointed Professor Ayudante in 1990 and then Professor Titular in 1992. Her current research interests are focused on organometallic chemistry as well as the development of new iron-chelating agents and the study of their environmental impact.

5.26

Functions with at Least One Oxygen, $Y=C=O$

P. MOLINA, A. TÁRRAGA, and A. ARQUES
University of Murcia, Murcia, Spain

5.26.1	INTRODUCTION	949
5.26.2	NITROGEN FUNCTIONS: ISOCYANATES, $RN=C=O$	950
5.26.2.1	From Alkyl Halides	950
5.26.2.2	From Amines	950
5.26.2.2.1	Reaction with phosgene, diphosgene, and triphosgene	950
5.26.2.2.2	Reaction with oxalyl chloride	953
5.26.2.2.3	Reaction with carbon monoxide	953
5.26.2.2.4	Reaction with activated carbonates	955
5.26.2.2.5	Reaction with carbon dioxide	957
5.26.2.2.6	Reaction of iminophosphoranes with carbon dioxide	958
5.26.2.2.7	Via β -elimination of haloform	959
5.26.2.3	From Carbamic Acid Derivatives	959
5.26.2.3.1	From carbamates and boron halides	959
5.26.2.4	From Ureas	960
5.26.2.5	From Azides	961
5.26.2.5.1	From arylpalladium(II) azido complexes	961
5.26.2.6	From Nitro and Nitroso Compounds	962
5.26.2.7	From Carboxylic Acid Derivatives	962
5.26.2.7.1	From acyl azides (Curtius rearrangement)	962
5.26.2.7.2	From hydroxamic acid derivatives (Lossen rearrangement)	965
5.26.2.7.3	From rhenium hydrazide complexes	965
5.26.2.7.4	From amides	966
5.26.2.8	From Other Isocyanates	966
5.26.2.9	By Ring Opening of Nitrogen Heterocycles	967
5.26.2.9.1	From four-membered nitrogen heterocycles	967
5.26.2.9.2	From five-membered nitrogen heterocycles	968
5.26.2.10	Blocked Isocyanates	968

5.26.1 INTRODUCTION

Although the formation and spectroscopic behavior of $RP=C=O$, $R_2Si=C=O$, and $RB=C=O$ have been reported to some extent [<1999OM2155, 2001JPC1897, 2002JOM\(641\)156, 1997OM4768, 2000CRV3639>](#), out of all the functions in this chapter, the most relevant one is isocyanate, $RN=C=O$, which, in contrast to the previous ones, has been widely studied and reviewed [<1995COFGT\(5\)961, B-1996MI002, B-1998MI001>](#). This review will survey developments in this area since 1995. No examples of compounds such as $R_2S=C=O$, $R_2Se=C=O$, and related sulfur and selenium derivatives have been reported since 1995 [<1995COFGT\(5\)961>](#).

Isocyanates are esters of isocyanic acid and the first member of this class of compound was prepared by Wurtz in 1848. Organic isocyanates are a fascinating class of compounds, which have found wide-ranging applications in organic synthesis. In this context, stable isocyanates, having the isocyanate group attached to elements other than carbon, have become available in recent years, and silicon, phosphorus, and sulfur isocyanates are important chemical intermediates. In addition, complexes with coordinated isocyanate ligands are thought to be intermediates in some interesting transition metal-catalyzed reactions.

Organic isocyanates are used industrially, in particular in polymer chemistry, where they have found their widest application in the manufacture of polyurethanes by addition of dihydroxy compounds. They are also employed as useful reagents or sometimes used as intermediates in the synthesis of urea and carbamate derivatives, which are used in the production of herbicides and crop protection agents, as well as in the manufacture of antidiabetic drugs.

5.26.2 NITROGEN FUNCTIONS: ISOCYANATES, $RN=C=O$

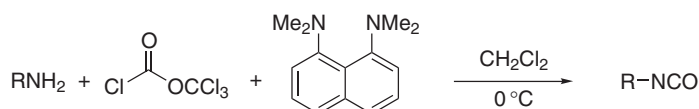
5.26.2.1 From Alkyl Halides

A non-toxic route for the preparation of polymeric isocyanates is based on the nucleophilic displacement of polymer-bound alkyl halides by cyanate ion as a novel route to polymeric isocyanate cross-linkers with no intermediacy of either phosgene or low-molecular-weight isocyanates <1992JPS(A)1911>.

5.26.2.2 From Amines

5.26.2.2.1 Reaction with phosgene, diphosgene, and triphosgene

Trichloromethyl chloroformate (diphosgene) has been used for the preparation of aromatic isocyanates from the corresponding amine hydrochlorides <1976JOC2070>. However, this method could not be extended to aliphatic amines, as illustrated by the lack of success in converting 1,2-diaminohexane hydrochloride into its corresponding diisocyanate. However, it is now established <1996JOC3883> that the reaction of aliphatic amines with diphosgene at 0 °C, in the presence of the non-nucleophilic base 1,8-bis(dimethylamino)naphthalene, affords isocyanates in good to excellent yields (Equation (1)).



<i>R-NCO</i>	Yield (%)
1,6-Diisocyanatohexane	73
Benzyl isocyanate	78
(<i>R</i>)-(+)-Methylbenzyl isocyanate	81
2-Isocyanatoethyl-2-pyridyl disulfide	39

(1)

Furthermore, the products can be obtained in greater than 95% purity by mere extractive work-up of the reaction mixtures, making further purification unnecessary. This is in contrast to most other reported procedures for the preparation of isocyanates, which rely on distillation for the purification of products. Thus, this procedure enables the preparation of heat-sensitive and/or non-volatile isocyanates. Additionally, this technique is useful in the synthesis of isocyanates in small quantities and for generating combinatorial isocyanate libraries. By using this method, 1,2-diisocyanatohexane, benzyl isocyanate, (*R*)-(+)-methylbenzyl isocyanate, and 2-isocyanatoethyl-2-pyridyl disulfide were prepared from their corresponding amines (Equation (1)).

Trichloromethyl chloroformate has also been used for the preparation of new polyisocyanates with chiral centers in the α - and β -positions to the main chain. <1998MI1675, 2002MM185>. The monomers and the structure of the resulting polymer are shown in Figure 1.

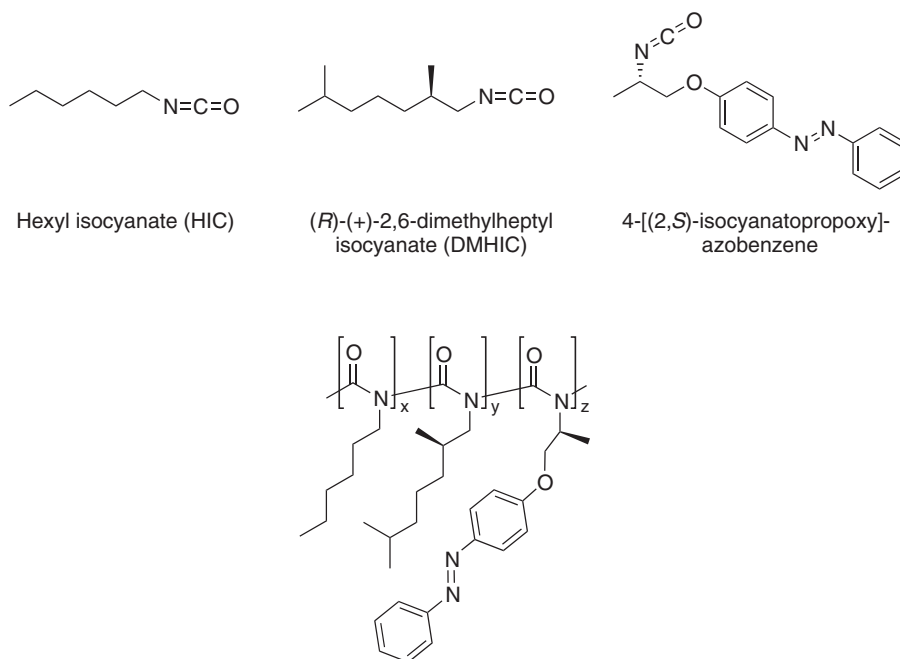


Figure 1 Polyisocyanates prepared by using trichloromethyl chloroformate.

Bis(trichloromethyl) carbonate (BTC, triphosgene) has been employed extensively as a phosgene equivalent and its use was reviewed by Cotarca [<1996S553>](#). It offers an alternative to gaseous and highly toxic phosgene. BTC has been used to synthesize isocyanates and is quickly becoming one of the most utilized carbonates in organic synthesis.

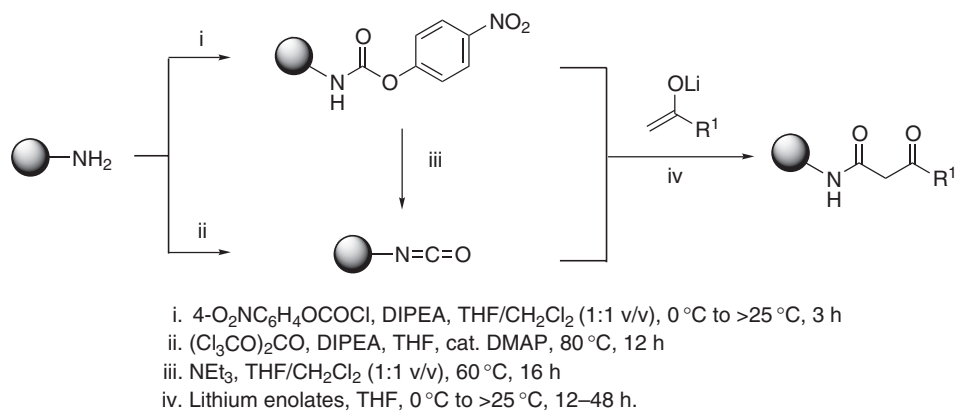
Thus, it has been used as a convenient one-carbon electrophile reagent in the preparation of amino acid ester isocyanates and peptide isocyanates using pyridine or aqueous sodium bicarbonate as a base [<1992JOC7364, 1998JOC9144>](#). By using triphosgene and sodium bicarbonate [<2002OS220>](#) it is possible to minimize the hazard and toxicity of the reagents and waste products. In addition, the mild reaction conditions used are superior to alternative methods for the preparation of amino acid ester isocyanates, which include refluxing amino acid ester hydrochlorides in toluene for several hours while purging with gaseous phosgene [<1952LA217>](#), or treating the amino acid ester hydrochloride with di-*t*-butyl dicarbonate (*t*-BOC)₂O and 4-dimethylaminopyridine (DMAP) [<1997SL925>](#).

A synthetic procedure to enable a straightforward and efficient solid-phase synthesis of immobilized isocyanates and their use for the synthesis of β -ketoamides is outlined in [Scheme 1 <2003TL3939>](#). This reaction was accomplished by treating Rink-amide resin [<1987TL3787>](#) with triphosgene under previously reported conditions [<1997JACS4882>](#). The resulting immobilized isocyanate was treated with cooled lithium enolate solution to give the expected β -ketoamides in high yields and purity.

A practical method for the preparation of peptide isocyanates is based on the addition of a solution of phosgene in toluene to a solution of a peptide (as the hydrochloride salt **1**) in an ice-cooled mixture of dichloromethane and saturated aqueous sodium bicarbonate solution to afford the peptide isocyanate **2** (Equation (2)) [<1996JOC3929>](#).

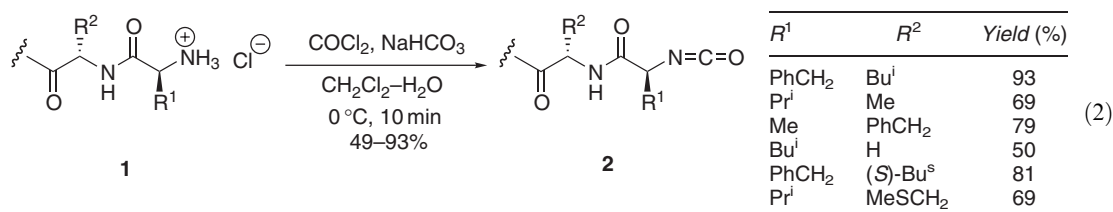
Use of excess triphosgene instead of phosgene gave isocyanates in yields similar to those obtained using phosgene. As the isocyanates produced using triphosgene were contaminated with ~10% of unreacted triphosgene, the use of phosgene was preferred because excess phosgene is removed upon evaporation of the solvent, while unreacted triphosgene is not volatile and is reactive toward nucleophiles.

The peptide isocyanates that are produced by this procedure are generally formed in near quantitative mass recovery and in ~60–100% purity. Because the isocyanates cannot easily be purified, it is desirable to improve this method to allow the generation of isocyanates without side-products (e.g., hydantoins).

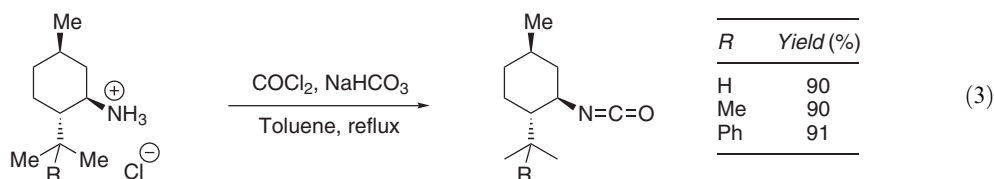


R^1	Yield (%)		R^1	Yield (%)	
	Steps i, iv	Steps ii, iv		Steps i, iv	Steps ii, iv
C ₆ H ₅	>95	>95	3,4-Cl ₂ C ₆ H ₃	>95	>95
4-BrC ₆ H ₄	>95	>95	2-Naphthyl	92	>95
4-MeOC ₆ H ₄	>95	>95	3-Pyridyl	>95	70
4-C ₆ H ₅ C ₆ H ₄	93	76	4-Pyridyl	0	0
3-CF ₃ C ₆ H ₄	91	80	2-Thienyl	>95	>95
3-NCC ₆ H ₄	>95	72	4-O ₂ NC ₆ H ₄	0	0
3-O ₂ NC ₆ H ₄	>95	82			

Scheme 1



The synthesis of enantiopure menthyl, 8-methylmenthyl, and 8-phenylmenthyl isocyanate have been achieved by using the above-mentioned procedure (Equation (3)) <2003S2689>.



Functionalized isocyanates have been prepared using the triphosgene route. Thus, the 2-isocyanato-2'-nitrostilbene **3**, a common intermediate in the synthesis of the alkaloids, cryptotackieine and cryptosanguinolentine, has been prepared in almost quantitative yields from the corresponding amine and triphosgene <1999TL7275, 2001T6197>. Likewise, the 2-azido-2'-isocyanatobiphenyl **4** has been prepared in 57% yield using the same procedure (Figure 2) <1999JOC1121>.

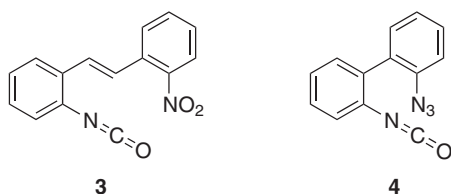
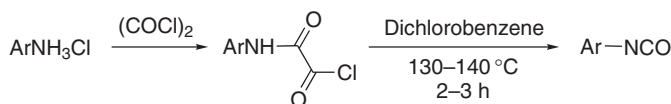


Figure 2 Functionalized isocyanates prepared by using triphosgene.

5.26.2.2.2 Reaction with oxalyl chloride

Acylation of substituted aniline hydrochlorides with oxalyl chloride affords the intermediate oxamic chlorides, which smoothly undergo thermal decomposition to the corresponding isocyanates (Equation (4)). A variety of functional groups are tolerated under the reaction conditions, such as methyl thioethers, esters, and ketones as well as sterically hindered anilines <2004TL4769>.

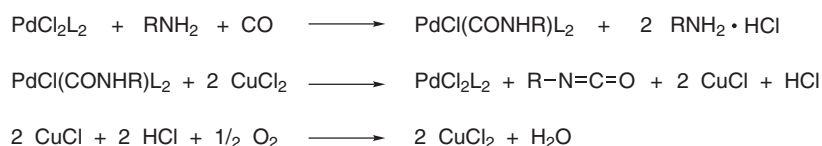


Amine	Methyl carbamate yield (%)
C ₆ H ₅ NH ₂	85
2-MeOC ₆ H ₄ NH ₂	81
2,6-Pr ⁱ ₂ C ₆ H ₃ NH ₂	72
4-MeSC ₆ H ₄ NH ₂	98
3-FC ₆ H ₄ NH ₂	79
2,6-Cl ₂ C ₆ H ₃ NH ₂	74
4-MeCOC ₆ H ₄ NH ₂	71
4-EtO ₂ CC ₆ H ₄ NH ₂	91

(4)

5.26.2.2.3 Reaction with carbon monoxide

Palladium complexes have been used in catalytic conversion of primary and secondary amines into isocyanates or carbamoyl chlorides, respectively. The palladium-based catalytic system is very active and operates in two steps, avoiding the synthesis of phosgene but making use of carbon monoxide and Cl₂ as in phosgene chemistry. In the first step the palladium(II) complex PdCl₂L₂ (L₂ = 2,2' dipyridine (dipy) or 1,10-phenanthroline (phen); L = triphenylphosphine) reacts with the primary amine (RNH₂) and CO to produce the carbamoyl complexes PdCl(CONHR)L₂, which are subsequently reacted with halogen donors (CuCl₂, *N*-chlorosuccinimide, Cl₂, I₂) with elimination of the carbamoyl ligand as isocyanate and quantitative regeneration of the starting Pd(II) complex (Scheme 2). Cl₂ and I₂ are the most effective and selective <2000OM3879>.



Scheme 2

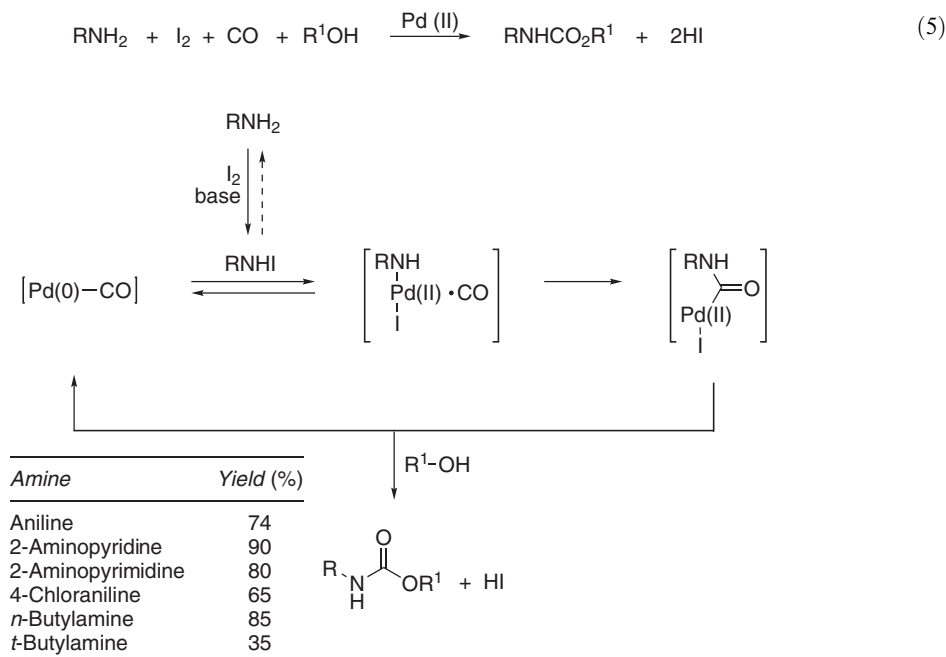
It is worth emphasizing that Pd and Cu complexes can be quantitatively recovered and recycled, making the reaction of potential utility. In fact, the solid mixture (PdCl₂L₂ + CuCl) (Scheme 2) can be treated with an ethanol solution of dipy (stoichiometric amount with respect to Cu), which allows CuCl to be extracted in solution as CuCl(dipy) while PdCl₂L₂ is left as a solid residue.

Alternatively, the recycling of the Pd-catalyst can be more conveniently carried out by reacting the solid mixture of Pd/Cu with an aqueous alcoholic HCl solution under O₂, which converts the insoluble CuCl into soluble CuCl₂, which can be reused.

It is worth noting that the overall process of the amine conversion is catalytic in both palladium and CuCl₂ <2000OM3879>.

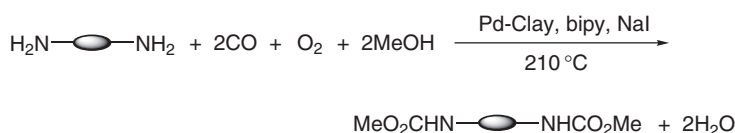
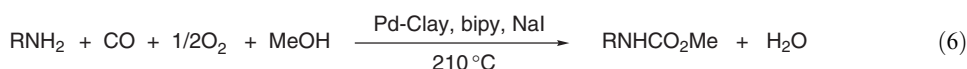
Palladium-catalyzed carbonylation of amines in the presence of iodide is also a very well-known procedure for the preparation of isocyanate precursors. This process is of practical significance because it also avoids phosgenation, but it proceeds only under high pressure (>75 atm CO; 5–10 atm O₂) and at elevated temperatures (150–180 °C) <1984CC399, 1984JOC1458, 1984MI670, 1988MI246>. However, more recently it has been reported that fast amine carbonylation takes place, either when a stoichiometric amount of I₂ was added to a mixture of aniline and a catalytic amount of palladium acetate under CO or when a catalytic amount of I₂ was used instead under a

mixture of CO and O₂ (Equation (5)), but surprisingly no carbonylation occurs when aniline was treated similarly with palladium acetate under CO/O₂, but using an initial charge of iodide salts instead of I₂. The mechanism proposed involves the formation of a carbamate by oxidative addition of an *N*-iodoamine intermediate to a low-valent Pd species prepared *in situ* to give an amido complex, which undergoes β -elimination to give an isocyanate which is then isolated, when an inert solvent is used, or trapped by alcoholic solvents to give the corresponding urethane (Scheme 3) <1995JOC8124>.



Scheme 3

A simple, efficient, and highly selective route has been developed for the preparation of aliphatic, alicyclic, and/or aromatic mono-, di-, and triurethanes from the corresponding amines using montmorillonite-bipyridinypalladium(II) acetate (Pd-Clay), in the presence of NaI as a promoter (Equations (6) and (7)) <1995OM80>.



Amine	Urethane yield (%)
<i>n</i> -C ₆ H ₁₃ NH ₂	83
<i>n</i> -C ₁₂ H ₂₅ NH ₂	81
<i>i</i> -C ₃ H ₇ NH ₂	62
<i>o</i> -C ₆ H ₁₁ NH ₂	91
H ₂ N(CH ₂) ₈ NH ₂	72
H ₂ NCH ₂ (CH ₃)CH(CH ₂) ₃ NH ₂	94
1-NH ₂ -3-CH ₂ NH ₂ -3,5,5'-(CH ₃) ₃ - <i>C</i> -C ₆ H ₇	96
1,3-(NH ₂) ₂ -4-CH ₃ -C ₆ H ₃	69

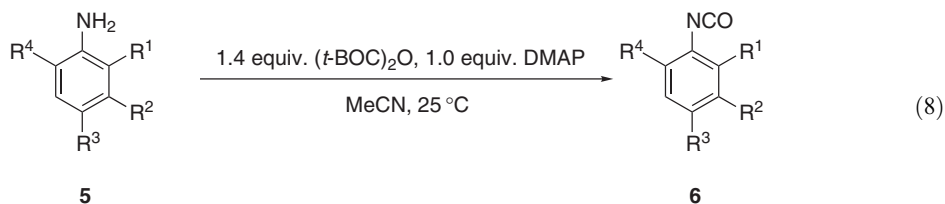
Pd-Clay is prepared by anchoring 2,2'-bipyridine in the interlayers of montmorillonite and subsequent complexation with Pd(OAc)₂ <1987CC1505>. This methodology, coupled with the processes for the conversion of urethanes to isocyanates, constitutes an attractive route for the preparation of commercially important isocyanates from amines by carbonylation.

5.26.2.2.4 Reaction with activated carbonates

Alkyl- and arylamines are converted into isocyanates in high yields by reaction with activated carbonates, such as $(t\text{-BOC})_2\text{O}$, in the presence of a catalytic amount of a nucleophilic nitrogen base, at room temperature <1995AG(E)2497>. Thus, it is reported that the reaction of substituted anilines **5** with $(t\text{-BOC})_2\text{O}$, in the presence of stoichiometric amount of 4-dimethylaminopyridine (DMAP) in an inert solvent (acetonitrile, dichloromethane, ethyl acetate, tetrahydrofuran, and toluene), at room temperature leads to aryl isocyanates **6** within 10 min in almost quantitative yields (Table 1) (Equation (8)) <1995AG(E)2497>.

Table 1 Synthesis of aryl isocyanates **6** from arylamines with $(t\text{-BOC})_2\text{O}$ and a stoichiometric amount of DMAP

6	R^1	R^2	R^3	R^4	Yield (%)
a	Me	H	Me	Me	96
b	Me	H	H	Me	94
c	Pr ⁱ	H	H	Pr ⁱ	99
d	OMe	H	OMe	OMe	97
e	Me	H	H	H	44
f		H	H	H	86
g		H	OMe	H	88
h	Me	H	OMe	H	58
i		H	OMe	H	76
j	Me	Me	OMe	H	89
k	$-(\text{CH}=\text{CH})_2-$		OMe	H	42
l	H	H	OMe	H	41



Similarly, the reaction of sterically hindered alkylamines, such as *t*-butylamine and 1,1,3,3-tetramethylbutylamine, performed in dichloromethane under the same reaction conditions, afforded the corresponding alkyl isocyanates in 49% and 97% yield, respectively. 2-Aminopropane can also be converted into the isocyanate by this method.

Using the same methodology, a broad range of α -amino acid esters were converted into the α -isocyanatocarboxylic acid esters in high yield without racemization <1997SL925>. The isolation of this kind of isocyanate was achieved by low-temperature chromatography and it was observed that sterically hindered amino groups gave rise to better yields of the corresponding isocyanates.

For ecological reasons it is particularly important to achieve the isocyanation of amines with C1 building blocks that, unlike $(t\text{-BOC})_2\text{O}$, can be synthesized without the use of phosgene. In this context, other activated carbonates, **7**, can be used for the isocyanation of amines in the presence of DMAP (Equation (9)) (Table 2) <1995AG(E)2497>. However, due to its extreme reactivity, $(t\text{-BOC})_2\text{O}$ provides the highest yields in a very rapid reaction.

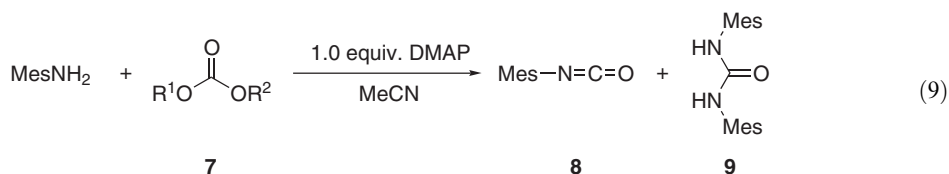
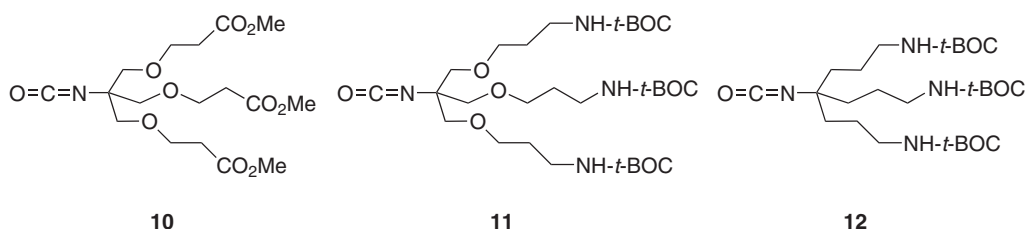
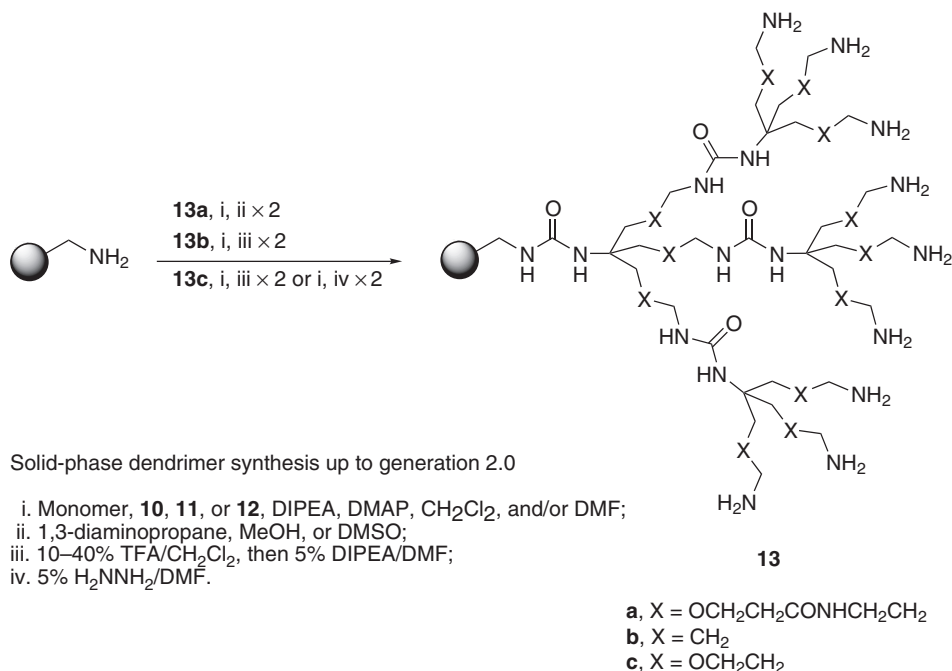


Table 2 DMAP-mediated synthesis of mesityl isocyanate from mesitylamine with the activated carbonates **7** as the C1 building blocks

7	R^1	R^2	T (°C)	t	8 Yield (%)	9 Yield (%)
a	Bu ^t OCO	Bu ^t	25	10 min	96	0
b	Bu ^t CO	Bu ^t	25	4 h	17	64
c	C ₆ H ₅	C ₆ H ₅	82	15 d	0	29
d	4-O ₂ NC ₆ H ₄	4-O ₂ NC ₆ H ₄	25	18 h	19	64
d	4-O ₂ NC ₆ H ₄	4-O ₂ NC ₆ H ₄	82	18 h	9	86

By using this methodology a series of symmetrical AB₃ isocyanate-type monomers (**10**, **11**, and **12**) have been reported (Figure 3) and used for the preparation of tri-branched dendrimers **13** on the solid phase (Scheme 4) <2002TL2475, 2002TL2479, 2003T3945>.

**Figure 3** Symmetrical AB₃ isocyanates prepared by isocyanation of amines.**Scheme 4**

A mild and convenient method for the synthesis and isolation of multi-isocyanates, obtained from the reaction of the corresponding primary amines with di-*t*-butyl tricarbonate has been described <1999TL1021>. This reagent converts almost any primary amine quantitatively into its corresponding isocyanate in less than 5 min at room temperature. For the synthesis of multi-isocyanates such as **14–16**, it is the reagent of choice, since the formation of cyclic ureas is suppressed (Figure 4).

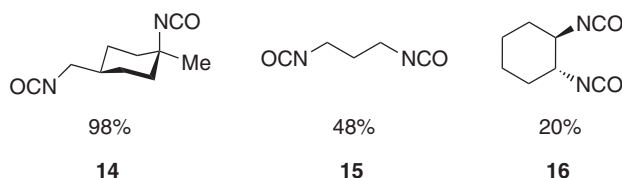
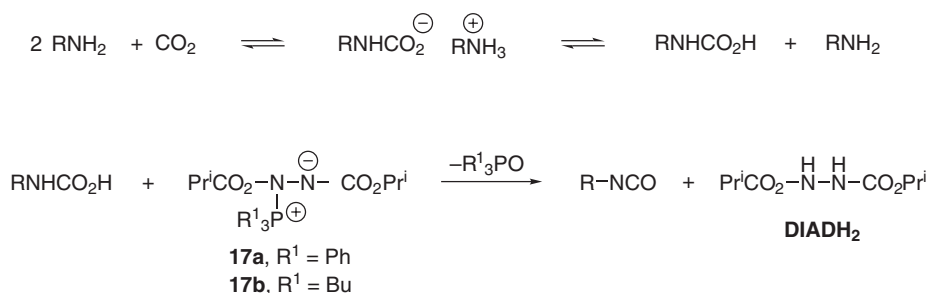


Figure 4 Bis-isocyanates prepared by using di-*t*-butyl tricarboxylate.

In order to test the selectivity of this conversion, poly(propyleneimine) dendrimers of all generations up to the fifth generation with 64 primary amine end groups were treated with this reagent. All dendrimers were converted quantitatively into the multi-functional isocyanates, however, isolation proved to be difficult. Later, compound **14** was used as a building block for a fast and convenient construction of carbonate/urea-based dendrimers <2001JPS(A)3112>.

5.26.2.2.5 Reaction with carbon dioxide

A direct preparation of alkyl and hindered aryl isocyanates has been carried out from primary amines and carbon dioxide using a Mitsunobu zwitterion generated from either diisopropyl azodicarboxylate (DIAD) or di-*t*-butyl azodicarboxylate and triphenylphosphine or tri-*n*-butylphosphine (Scheme 5) <1999JOC3940, 1999TL363>.



Scheme 5

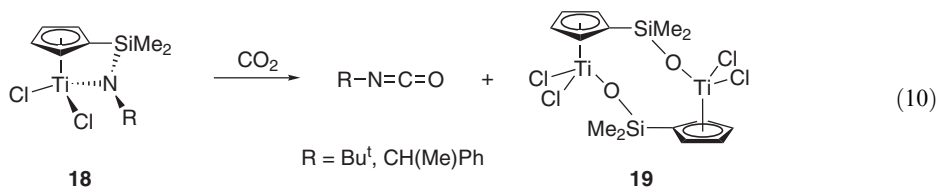
The isocyanates are isolated either by fractional distillation or flash chromatography. Isolated and *in situ* yields are given in Table 3, which also compare the results obtained by using a Ph_3P -derived or a Bu_3P -derived zwitterion, respectively.

Table 3 Yields of isocyanates from reactions of primary amines RNH_2 with the Mitsunobu zwitterion **17a** or **17b** and CO_2

Amine R	17a Yield (%)	17b Yield (%)	Amine R	17a Yield (%)	17b Yield (%)
Pr^i	86	84	$\text{C}_6\text{H}_5\text{CH}_2$	0	
Bu^n	63		2,6-di- $\text{Pr}^i\text{C}_6\text{H}_3$	11	89
Bu^t	84		2,3,6-tri-Me C_6H_2		92
Cyclohexyl	80		2,6-di-Et C_6H_3		75
<i>n</i> -Octyl	65		2,6-di-Me C_6H_3		89
<i>t</i> -Octyl	87		2-Me-6-Et C_6H_3		72
3 α -Cholestanyl	86	90	2- $\text{Pr}^i\text{C}_6\text{H}_4$		0
C_6H_5	0				

Reactions in dichloromethane from -78°C to ambient temperature.

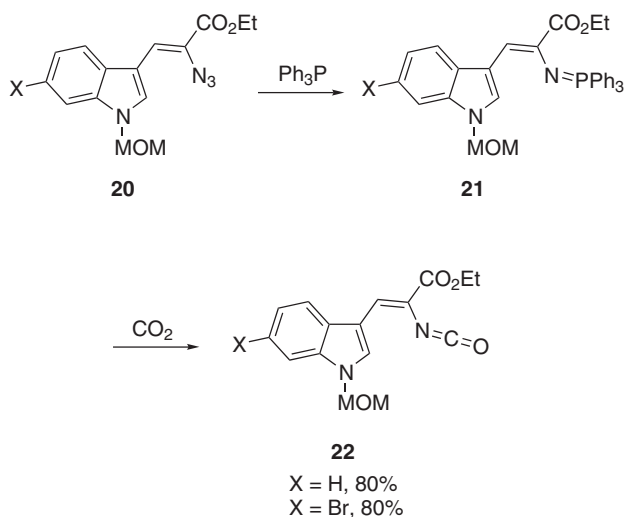
The reaction of the complexes $[\text{Ti}(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_2\text{NRCl}_2)]$ **18** with carbon dioxide leads to the conversion into the oxo-derivative **19** with formation of the alkyl isocyanate (Equation (10)). This is believed to be due to a metathesis process between carbon dioxide and the M—N bond, which is of partial double-bond character <1996OM5577>. Other examples of the metathesis between carbon dioxide and the M—N bond are the reactions of $[\text{M}\{\text{N}(\text{SiMe}_3)_2\}_2]$ (M = Ge and Sn) with carbon dioxide to give $[\text{M}(\text{OSiMe}_3)_2]$, $\text{Me}_3\text{Si}-\text{N}=\text{C}=\text{O}$ and $\text{Me}_3\text{Si}-\text{N}=\text{C}=\text{N}-\text{SiMe}_3$ <1996JACS10912>.



5.26.2.2.6 Reaction of iminophosphoranes with carbon dioxide

Iminophosphoranes are extremely interesting intermediates for the synthesis of a wide variety of unsaturated nitrogen compounds. Reaction of iminophosphoranes is often similar to the isoelectronic phosphoranes. The reactivity of these compounds is a consequence of the polarity of the phosphorus—nitrogen bond as well as the high basicity of these systems, which is influenced by the substituents on the phosphorus atom and, in particular, by those on the nitrogen atom. Iminophosphoranes undergo reactions with a number of carbonyl-containing compounds in a similar way to phosphonium ylides, leading to an excellent method for the preparation of unsaturated nitrogen compounds. The use of iminophosphoranes has become a powerful tool in organic synthetic strategies directed toward the construction of nitrogen-containing heterocycles <1994S1197>.

Ethyl β -indolyl- α -isocyanatoacrylate, **22**, intermediate in the synthesis of the oxoaplysinopsin alkaloids, has been prepared by treatment of the corresponding iminophosphorane **21** with carbon dioxide in a sealed tube <1992TL4491, 1991T2241>. The iminophosphorane was in turn prepared from the corresponding azide **20** and triphenylphosphine (Scheme 6).

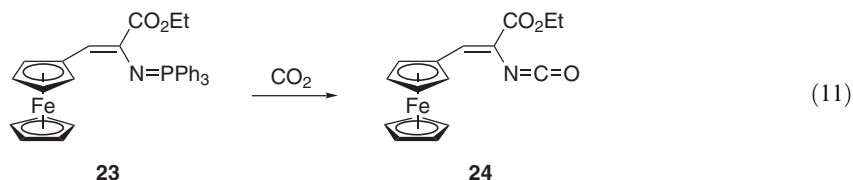


Scheme 6

Likewise, the iminophosphorane derived from polymeric triphenylphosphine and ethyl β -(2-pyridyl)- α -azidoacrylate reacts with carbon dioxide at room temperature to give the corresponding isocyanate, which is cyclized by thermal treatment to give 1-oxo-1*H*-pyrido[1,2-*c*]pyrimidine, which displays inhibitory effects on leukocyte functions and experimental inflammation <2001JMC1011>.

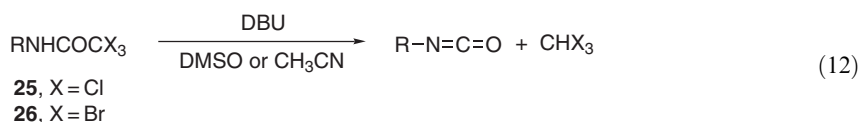
The aforementioned procedure has been applied for the preparation of organometallic-functionalized isocyanates. The (vinylimino)phosphorane **23** available from the corresponding azide and triphenylphosphine, reacts with solid carbon dioxide at 110 °C in a sealed tube to afford

the β -ferrocenylvinyl isocyanate **24** as crystalline solid in 86% yield (Equation (11)); however, when the reaction is carried out at 160 °C a mixture of isocyanate (70%) and bis(β -ferrocenylvinyl)carbodiimide (20%) is obtained <1996TL7829, 1997OM5836>.



5.26.2.2.7 Via β -elimination of haloform

Treatment of *N*-monosubstituted trihaloacetamides **25** and **26** with DBU in dichloromethane at room temperature results in a practically spontaneous elimination of chloroform and formation of the corresponding isocyanate (Equation (12)) <1999TL3235>.



The required trichloro- and tribromoacetamides (**25a–25l**, and **26a–26e**) (Figure 5) were easily prepared by reaction of the appropriate amines with commercial trichloro- and tribromoacetyl chloride, respectively. Similarly, trifluoroacetamides (**27a–27d**) were prepared by reaction of the appropriate aniline with trifluoroacetic anhydride.

RNHCOCX ₃		RNHCOCBr ₃	RNHCOCF ₃
25		26	27
a, R = Ph	g, R = 2-ClC ₆ H ₄	a, R = <i>p</i> -Tol	a, R = <i>p</i> -Tol
b, R = <i>p</i> -Tol	h, R = 3,4-Cl ₂ C ₆ H ₃	b, R = 2,6-Me ₂ C ₆ H ₃	b, R = 4-ClC ₆ H ₄
c, R = 2,6-Me ₂ C ₆ H ₃	i, R = C ₆ H ₅ CH ₂	c, R = 2,4,6-Me ₃ C ₆ H ₂	c, R = 4-MeOC ₆ H ₄
d, R = 2,4,6-Me ₃ C ₆ H ₂	j, R = C ₆ H ₅ CHMe	d, R = 4-ClC ₆ H ₄	d, R = 2,6-Me ₂ C ₆ H ₃
e, R = 4-MeOC ₆ H ₄	k, R = C ₆ H ₅ CH ₂ CH ₂	e, R = C ₆ H ₅ CH ₂	
f, R = 4-ClC ₆ H ₄	l, R = Me ₃ C		

Figure 5 Useful *N*-monosubstituted trihaloacetamides for the preparation of isocyanates using DBU.

As expected from the reaction mechanism, it was found that the rates of reaction of these compounds with base exhibit a strong dependence on the nature of the trihalomethyl group. Thus, while tribromoacetanilides (**26a–26e**) undergo β -elimination of bromoform in DMSO in the presence of DBU at room temperature, and elimination of chloroform from trichloroacetamides (**25a–25j**) requires heating at 80 °C in a polar solvent for several hours, and no reaction is observed for any of the trifluoroacetanilides (**27a–27d**) even on heating at 120 °C for 2 days.

It should be emphasized that due to the excessive sensitivity of isocyanates to moisture and their base-catalyzed hydrolysis, as well as their facile di- and trimerization <B-1967MI004>, isolation was rather difficult. However, by working with sterically hindered trihaloacetanilides (**25c** and **25d** and **26b** and **26c**), possessing the 2,6-dimethyl- and 2,4,6-trimethylphenyl substituents, this problem was solved.

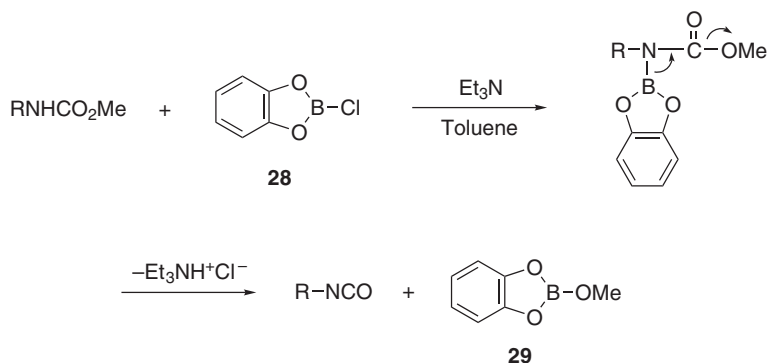
5.26.2.3 From Carbamic Acid Derivatives

5.26.2.3.1 From carbamates and boron halides

The elimination of alcohol from a carbamate constitutes a simple approach to isocyanates, the most widely used methods including thermal decomposition reaction with excess powdered boron or bismuth <1983JP57158746> and germanium oxide <1983JP57158747>, effected at high

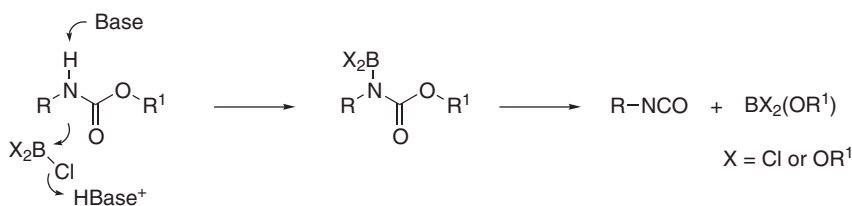
temperature (greater than 300 °C), or using the more-recently developed manganese, molybdenum, tungsten, zinc, or zirconium catalysts.

However, the isolation of an isocyanate from carbamate is complicated by the tendency of the formed isocyanate and alcohol to recombine easily. To avoid this reverse addition, Alper and co-workers [<1995JOC257>](#) reported the use of chlorocatecholborane **28** as a reagent for the interception of the components of the alcohol from the carbamate in the presence of triethylamine, because under these conditions the alcohol is irreversibly removed from the reaction solution, in the form of an alkyl catecholborate **29**. The entire sequence shown in [Scheme 7](#) occurs rapidly in a one-pot reaction giving rise to a simple and highly selective transformation.



Scheme 7

More recently, simple boron halides such as BCl_3 and BBr_3 have also been used as reagents to facilitate the conversion of carbamates into isocyanates ([Scheme 8](#)) [<1998CC2575>](#).



Scheme 8

In most cases, quantitative or near-quantitative conversion to the isocyanates was obtained under relatively mild reaction conditions for a series of aryl, alkyl, alicyclic, and tosyl carbamates. These reactions were found to be highly selective and the isocyanates formed can usually be easily isolated by evaporation of the solvent and trialkyl borate under reduced pressure followed by vacuum distillation. It is worth noting that although BBr_3 , a stronger Lewis acid than BCl_3 , was also effective in this reaction, with isocyanate yields being similar to those obtained by using BCl_3 , appreciable amounts of amine were also produced in some cases, bringing the selectivity of this reagent into question.

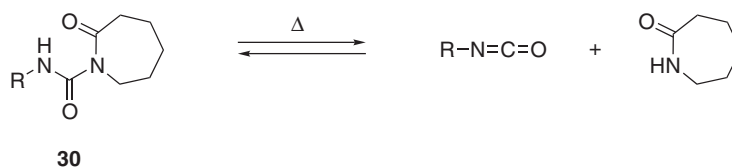
In this context, montmorillonite K-10 has proved to be an efficient catalyst for synthesizing mono- and diisocyanates by de-alcoholysis of a wide range of mono-acid dicarbamates, removing the alcohol efficiently since this is the driving force behind the reaction ([Table 4](#)) [<2002TL1673>](#).

5.26.2.4 From Ureas

The caprolactam-blocked isocyanates **30** are of interest as nontoxic and low volatile organic compound (VOC) curing agents in coating and adhesives industry because the presence of free toxic isocyanates is not desirable in industry [<1999MI148, 2001MI1>](#). In this context, the *N*-carbamoyl derivatives **30** by thermal treatment at temperatures between 160 °C and 180 °C undergo cleavage to give free isocyanates and caprolactam ([Scheme 9](#)) [<2003AG\(E\)5094>](#).

Table 4 Synthesis of isocyanates from carbamates using montmorillonite K-10 as catalyst

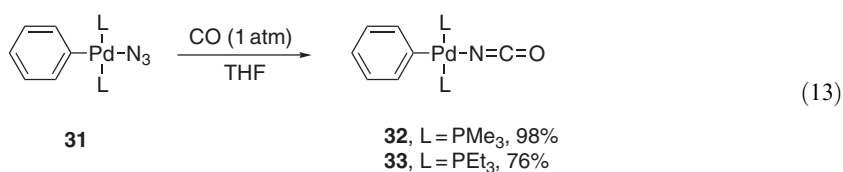
Substrate	Product	Conv. (%)
		96
		99
		86
		93
		67
		12
		73
		25

**Scheme 9**

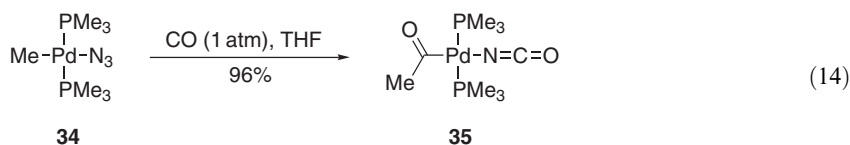
5.26.2.5 From Azides

5.26.2.5.1 From arylpalladium(II) azido complexes

A synthetic route to palladium isocyanato complexes such as *trans*-PdPh(NCO)L₂ (L = PMe₃, **32** or PEt₃, **33**) which uses arylpalladium(II) azido complexes **31** and CO (1 atm) has been described [\[2000JOM\(603\)152\]](#). The reaction smoothly proceeds in THF at room temperature to give the isocyanates **32** and **33** (Equation (13)). It is worth underlining that this reaction occurred cleanly and gave no other by-products such as benzoylisocyanato, PhC(=O)Pd(NCO)L₂, or benzoyl-azido complexes PhC(=O)Pd(N₃)L₂.



However, the reaction of *trans*-PdMe(N₃)(PMe₃)₂ **34** with CO under the same reaction conditions gave the acetylpalladium isocyanato complex *trans*-Pd(COMe)(NCO)(PMe₃)₂ **35** in 96% yield as shown in Equation (14). This reaction results in both CO insertions into the Pd—methyl bond to give an acyl group and conversion of the azido ligand to an isocyanato group coordinated to Pd center.



The different products observed in the preceding two reactions (Equations (13) and (14)) show that CO is inserted into the Pd—methyl bond more easily than the Pd—phenyl bond under mild conditions and vice versa, indicating that the M—C(*sp*²) bond is more kinetically stable than the M—C(*sp*³) bond toward CO.

5.26.2.6 From Nitro and Nitroso Compounds

A very important, appealing synthetic alternative for an industry to produce aromatic isocyanates implies the use of a reductive carbonylation process of the nitroaromatic precursors, giving isocyanates or carbamates, the latter being subsequently cracked into isocyanate.

The first conversion of aromatic nitro compounds to isocyanates by reductive carbonylation was described by Hardy and Bennett <1967TL961> and since then, this reaction has attracted considerable attention for the isocyanate producers. This apparently simple reaction (Equation (15)) is in fact a multistep transformation, and although thermodynamically favorable, it requires the presence of a catalyst to proceed. The most active and selective systems known use group VIII–X transition metals such as ruthenium, rhodium, and palladium complexes <1995OM3751, 1996CRV2035, 1997JACS11049, 1998JOM(551)171, 1998OM1052, 1998OM2199, 2000CCR269>.



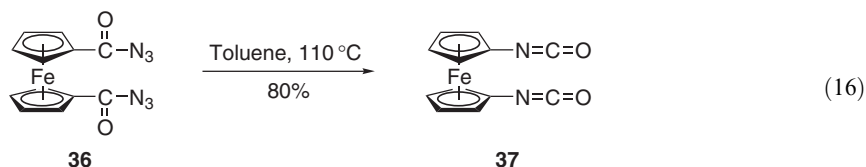
With functionalized nitroaromatics, the nature and position of the substituents on the same aromatic ring will sometimes strongly influence the selectivity and yield of the transformation. This is especially true for other nitro groups and, in general, given a catalytic system, much harsher conditions are needed for total conversion of polynitro aryls relative to the corresponding mononitro substrates. In fact, it is described that the Pd(1,10-phenanthroline)₂(triflate)₂ catalyst system, in combination with an aromatic carboxylic acid, constitutes a powerful catalyst for the reductive carbonylation of aromatic dinitro substrates <1996CC217>.

Mechanistically speaking, however, any carbonylation reaction of polynitro aryls is believed to proceed similarly to the mononitro substrates, but in a stepwise fashion, nitro-isocyanato aryls being formed as intermediates.

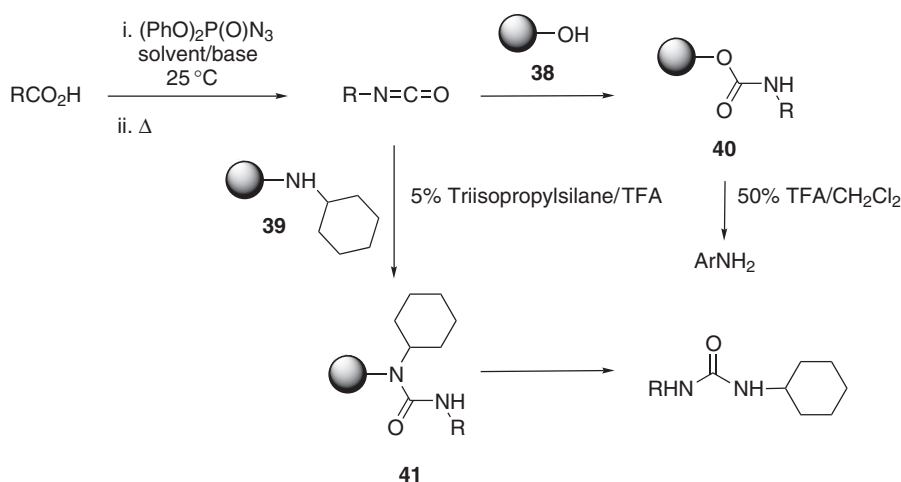
5.26.2.7 From Carboxylic Acid Derivatives

5.26.2.7.1 From acyl azides (Curtius rearrangement)

The Curtius rearrangement has proven itself to be a versatile and important chemical transformation. An important utilitarian feature of this reaction is that a diverse assortment of carboxylic acids can be converted into their corresponding acyl azides, which undergo facile thermal rearrangement to isocyanates in a one-pot reaction. Useful carboxylic acids include aliphatic <2000JOC1280>, aromatic <1999TL9107>, heterocyclic <1999BMC2811>, unsaturated <1999JOC4551>, and chiral acids <1999JOC7763>. Since the number of commercially available carboxylic acids greatly exceeds the corresponding pool of isocyanates, the Curtius rearrangement has been used with great success to access noncommercially available isocyanates as they are required for a particular synthesis. In this context, the 1,1'-ferrocenediacyl azide **36**, prepared from 1,1'-ferrocenedicarboxylic acid by sequential treatment with oxalyl chloride and sodium azide, affords the 1,1'-diisocyanato ferrocene **37** on heating in toluene at reflux (Equation (16)) <2001OM224>.



The acyl azides required for the Curtius rearrangement are usually prepared from acid derivatives such as acid halides and acyl hydrazides <1984TL3701>. Even though several methods are available to accomplish this transformation, the majority involve the conversion of carboxylic acid into acid chlorides or anhydrides, which are then reacted with azide reagents. There are a few reports on the direct conversion of carboxylic acids into acyl azides by using acid activators such as triphosgene [bis(trichloromethyl) carbonate] <2002TL1345>, ethyl chloroformate <1984TL2557>, $\text{NCS-Ph}_3\text{P}$ <1994PS57>, cyanuric acid <2002TL3413>, and diphenylphosphoryl azide <1998TL7235, 1993SC335>. It is worth noting that the last reagent has recently been used to prepare isocyanates, which have been trapped with resin-bound alcohols **38** or amines **39** giving rise to a novel solid-phase synthesis of carbamates **40** <1999TL1721> or N,N' -disubstituted ureas **41** (Scheme 10) <2000OL3309>.



RCO_2H	Amine Yield (%)	RCO_2H	Urea Yield (%)
	>95		81
	>95		
	>95		50
	>95		52
	>95		70
	>95		61
	>95		66
	>95		
	>95		

Scheme 10

A number of alkynyl-substituted phenyl isocyanates **42–44** have been prepared from the corresponding carboxylic acids via a modified Curtius rearrangement using diphenylphosphoryl azide (Figure 6) <2000JOC7977>.

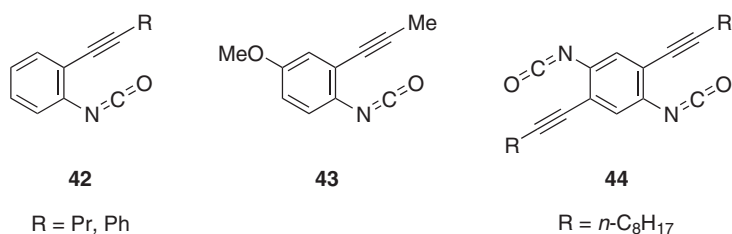


Figure 6 Alkynyl-substituted phenyl isocyanates prepared by a modified Curtius rearrangement.

Alternatively, oxidation of carbonyl compounds to the corresponding acyl azides is also an important synthetic procedure. In this context, preparation of acyl azides directly from aldehydes by using combinations of chromic anhydride—trimethylsilyl azide <1992TL4165> and triazido-chlorosilane-activated MnO_2 <1995TL1341> have also been investigated. More recently, a new, efficient, and practical route for the one-step conversion of aldehydes into the corresponding acyl azides by using Dess–Martin periodinane and sodium azide in CH_2Cl_2 at $0^\circ C$ in high yields has been reported <2003TL3543>.

The Curtius rearrangement from an acyl azide to an isocyanate has been used to achieve the one-pot synthesis of particularly interesting isocyanates such as the first perfluoroaryl isocyanate **45** <2000JOC4949>, hydroxy isocyanates <1992SC411>, poly(phenyl isocyanates) bearing an optically active alkoxyl <2000JPO361> or ester group **46** <1999MM974>, isocyanates **47** used for the one-pot synthesis of dendritic aromatic poly(urea-amides) <2002MM6224>, or isocyanates used as intermediates in peptide and depsipeptide synthesis, e.g., **48** <2003TL1059>, as reagents for photo-affinity labeling experiments <1995JOC7641, 1996SI277, 2000TL4555, 2001TL9297>, or as useful building blocks **49** for alkaloid synthesis (Figure 7) <2000SL1>.

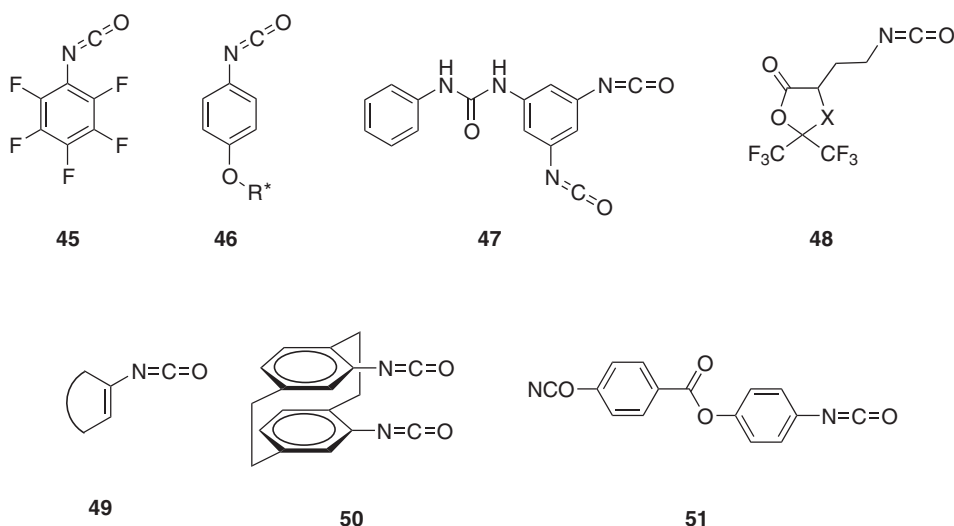
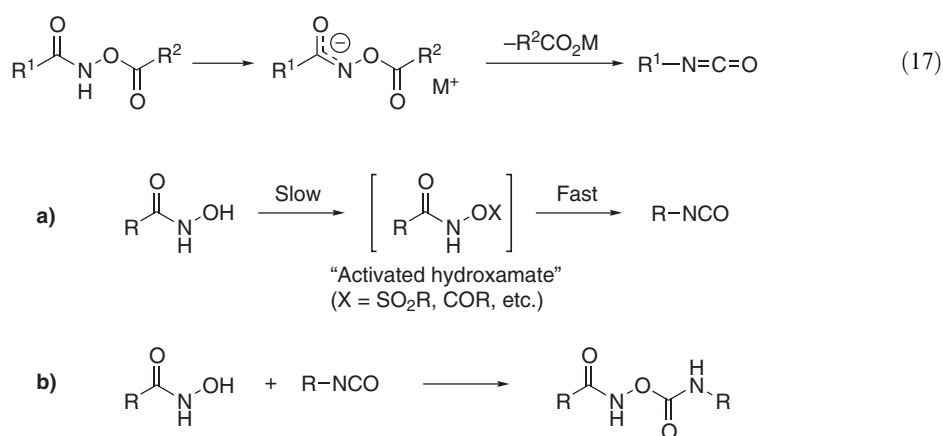


Figure 7 Isocyanates obtained by a Curtius rearrangement.

The bis(isocyanate) **50** has been used as a starting material for the preparation of reusable templates for topochemical reaction control in solution <2002EJOC2298>, whereas the isocyanatocyanate **51** undergoes $Cu(II)$ -acetylacetonate cyclotrimerization to form a network containing alternating cyanurate and isocyanurate cross-links with isotropic organization <2002MI113>.

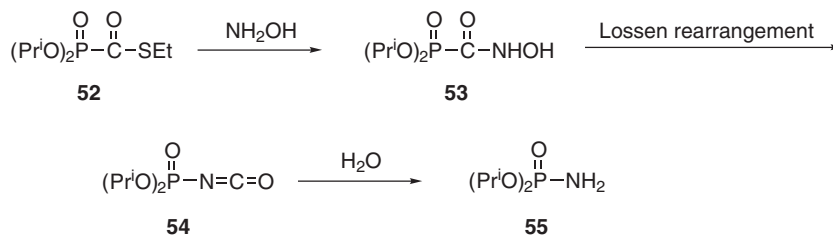
5.26.2.7.2 From hydroxamic acid derivatives (Lossen rearrangement)

The Lossen rearrangement (Equation (17)) in which hydroxamic acids are *O*-activated to create a suitable leaving group for subsequent rearrangement belongs to the category of named classical carboxyl degradation reactions that provide useful isocyanate intermediates from carboxylic acid derivatives. However, a survey of the chemical literature reveals that the Lossen rearrangement receives little attention as a general and practical synthetic method. The reasons for its limited use appear to be twofold: the relative unavailability of hydroxamic acids and the competing formation of self-condensation by-products as a result of unfavorable reaction kinetics <1968JACS1638, 1974AG(E)376>. Specifically, the rate-limiting step is the activation of the hydroxamic acid (Scheme 11a); the consequence of these kinetics is accumulation of isocyanate before complete consumption of the hydroxamic acid. Trapping of the isocyanate by the hydroxamic acid results in dimerization (Scheme 11b) <1989S61>. To overcome the dimerization associated with the classical Lossen rearrangement, it is desirable to initiate the rearrangement on the activated hydroxamate only after the hydroxamic acid is completely consumed. With this aim, some protected forms of the activated hydroxamate have been used <1998JOC10040>.



Scheme 11

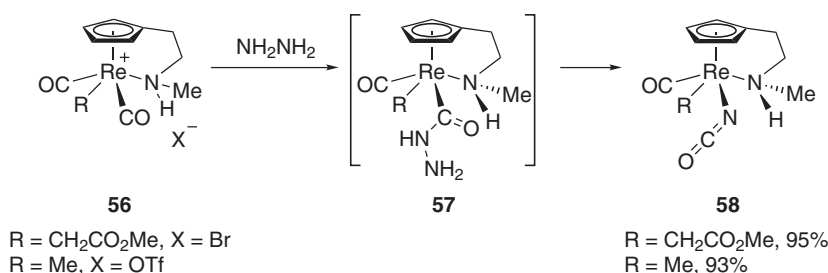
A variation of this reaction implies the spontaneous rearrangement of (phosphonoformyl)-hydroxamate **53**, prepared by reaction of (diisopropylphosphono)thiolformate **52** with hydroxylamine in the presence of pyridine or triethylamine, to diisopropylphosphoramidate **55** in which the phosphonyl group migrates via an unusually easy Lossen rearrangement with formation of the corresponding isocyanate intermediate **54** (Scheme 12) <1997JOC3858>.



Scheme 12

5.26.2.7.3 From rhenium hydrazide complexes

It has been demonstrated that cationic aminorhenium complexes **56** react instantly with hydrazine to give the corresponding hydrazides **57**, which undergo rearrangement and a net loss of one molecule of ammonia to give isocyanate complexes **58**, although the mechanism for this unique transformation is not clear yet (Scheme 13) <1999OM1553>.

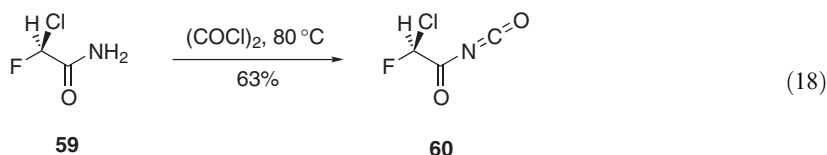


Scheme 13

5.26.2.7.4 From amides

The (*S*)-2-chloro-2-fluoroethanoyl isocyanate **60** may be considered, to some extent, an alternative for trichloroacetyl isocyanate as a possible derivatizing agent for secondary alcohols.

Isocyanate **60** has been prepared from the corresponding (*S*)-amide **59** by reaction with oxalyl chloride in 1,2-dichloroethane (Equation (18)). During this conversion, no racemization is observed, thus confirming the excellent optical stability of the chlorofluoroacetyl moiety <2003CHIR472>.

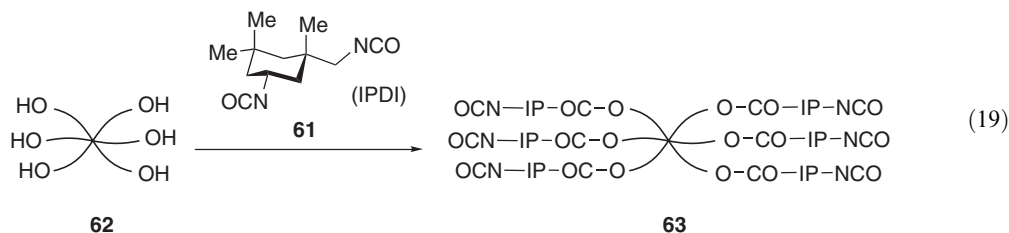


5.26.2.8 From Other Isocyanates

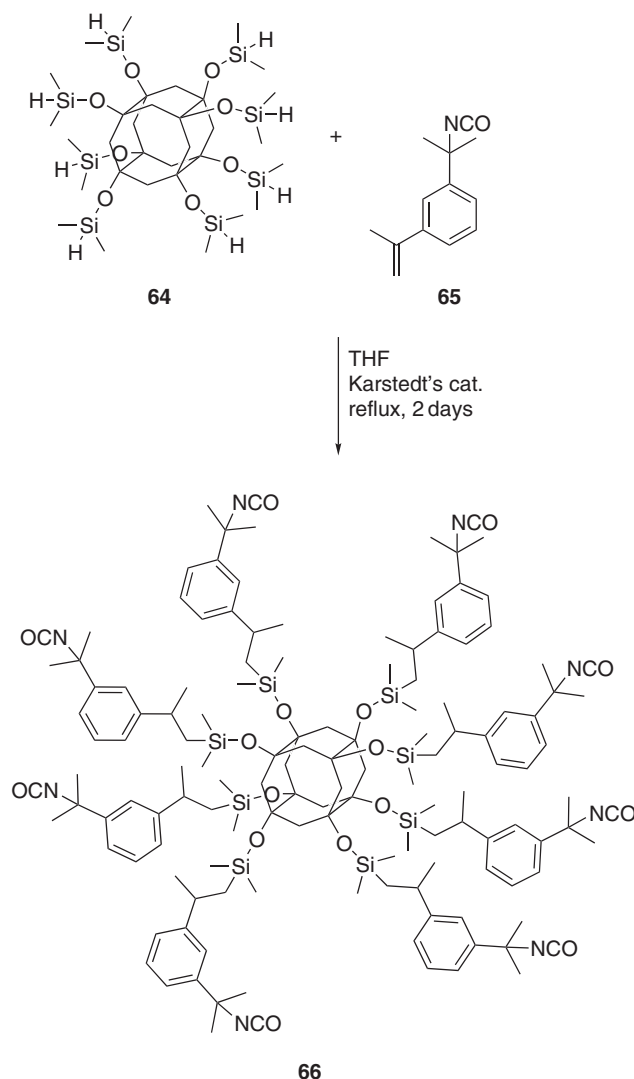
Isophorone diisocyanate (5-isocyanatomethyl-3,3,5-trimethyl-1-cyclohexyl isocyanate, IPDI) **61** contains two isocyanate groups exhibiting different reactivities, i.e., a secondary and a primary isocyanate group.

Relative reactivities of the primary and secondary isocyanate groups in urethane formation depend on the catalyst, the reaction temperature, and the reactivity of the alcohol <1997MI51>. Without added catalyst, IPDI reacts mainly at the alicyclic isocyanate group yielding secondary urethane units. At higher temperatures, the difference in reactivity between alicyclic and primary isocyanate group is reduced. With increasing steric hindrance of the alcohol, the urethane reaction proceeds more selectively toward the formation of primary urethanes. Lewis acids such as dibutyltin dilaurate (DBTDL) preferentially catalyze the reaction of the alicyclic (secondary) isocyanate group. Upon catalysis by a Lewis base, however, the primary isocyanate is more reactive.

In this context, star-shaped hydroxy-terminated poly(alkylene oxide) polymers **62** have been reacted with IPDI to yield NCO-terminated reactive stars **63** (Equation (19)) <2002MI223>.



Alternatively, it has also been described that the synthesis of a new type of polyhedral oligosil-sesquioxane (POSS) macromer **66** with eight active isocyanate groups is suitable for the synthesis of hybrid organic-inorganic urethane nanomaterials, as well as other organic-inorganic dendritic materials or star polymers <2002JACS13998>. The reaction is based on a hydroxylation reaction of 3-(2-propenyl- α,α' -dimethylbenzyl isocyanate (*m*-TMI) **65** with octakis(dimethylsiloxy)-octasilsesquioxane **64** in the presence of the Karstedt's catalyst $[Pt_x(M^{vi}M^{vi})_y]$; $M^{vi}M^{vi}$ = divinyltetramethyldisiloxane)] (Scheme 14).



Scheme 14

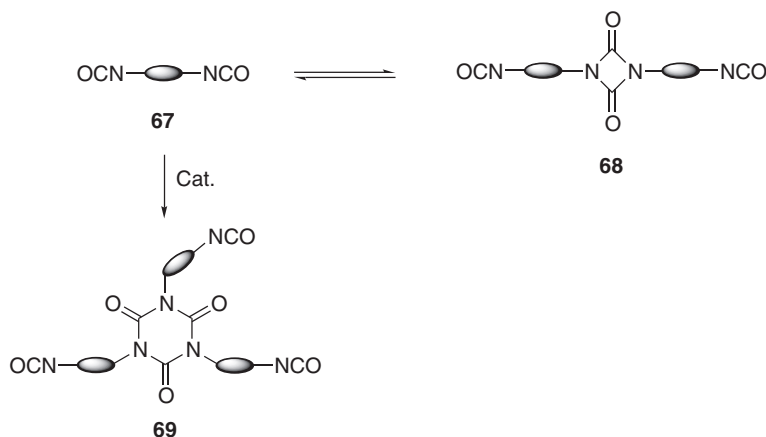
The reaction of *m*-TMI **65** with cyclic and acyclic hydrogenmenthylsiloxane provides well-characterized aliphatic isocyanate siloxanes, which can be used as precursors for star and network polymers [<1991JPS\(A\)1097>](#).

It is worth noting that since Shashoua and co-workers first reported the polymerization of isocyanates with sodium cyanide in dimethylformamide in 1959 [<1959JACS3156>](#), many researchers have studied the synthesis of polyisocyanates [<1995MM4719, 1996CL909>](#). Novak and co-workers synthesized poly(*n*-hexyl isocyanate) (PHIC) using organotitanium initiators without trimer formation through a coordination polymerization [<1991JACS5065>](#) and more recently Lee and co-workers succeeded in the synthesis of well-defined poly[3-(triethoxysilyl)propyl isocyanate] using sodium naphthalene (Na-Naph) and 15-crown-5 in THF at -98°C under high vacuum [<1999MM2085>](#), and in the synthesis of PHIC via anionic polymerization, preventing the formation of trimers by using sodium tetraphenylborate as a common ion salt, which stabilizes the active anion by excess sodium counteranions [<2001MM2408>](#).

5.26.2.9 By Ring Opening of Nitrogen Heterocycles

5.26.2.9.1 From four-membered nitrogen heterocycles

It is known that some monomeric diisocyanates **67** can dimerize or trimerize to give [1,3]diazetidinedi-2,4-diones (uretdiones) **68** or isocyanurates **69** in the presence of special catalysts (Scheme 15).



Scheme 15

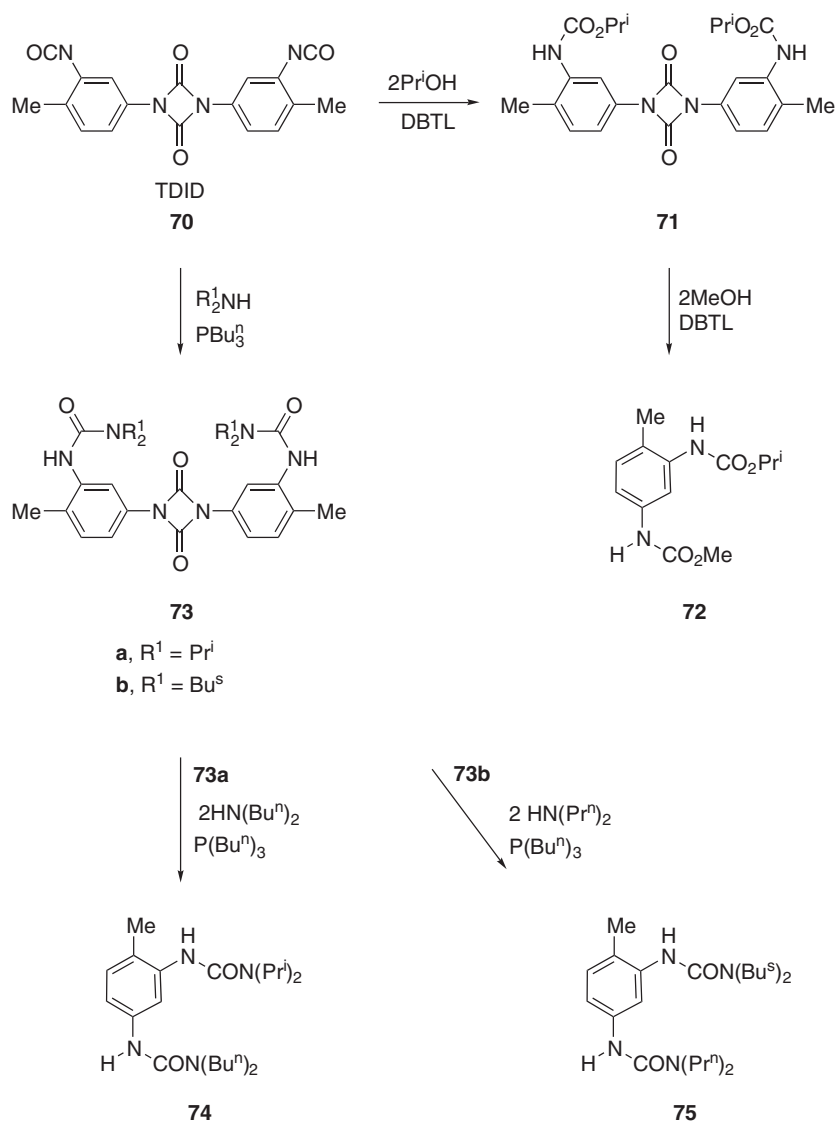
However, the production of uretdiones, unlike the trimerization, is a reversible reaction and then at higher temperatures or in the presence of catalyst they are cleaved to reform the monomers. In this sense, the [1,3]diazetidione-2,4-diones are very useful in the synthesis and technical application of organic polymers, since no toxic by-products are released from the polymer when these cycloaddition products are used as cross-linking agents. Thus, the selective cyclodimerization of monomeric diisocyanates, which contain two $-\text{NCO}$ groups of different reactivity, such as isophorone diisocyanate (IPDI) and 2,4-tolylene diisocyanate (TDI), yields [1,3]diazetidione-2,4-diones bearing free isocyanate groups, which react selectively with nucleophiles. On this basis, a new method for the selective transformation of the NCO groups of asymmetric substituted diisocyanates has been described (Scheme 16) <1999JPR616>. Thus, cyclodimerization of TDI in the presence of a catalytic amount of tri-*n*-butylphosphine gave rise to TDI-dimer **70** (TDID) in moderate yields. As shown in Scheme 16, the advantage of this methodology is the blocking of the isocyanate group at C-4 by the catalytic cyclodimerization. This selective protection is the basis for nucleophilic reactions (i.e., alcohols, amines) at the C-2 isocyanate group, which lead to the formation of the products **71**, **73a**, and **73b**. In one pot, the selective cleavage of the uretdione functionality of **71**, **73a**, and **73b** is followed by reaction with different nucleophiles to produce selectively derivatives such as carbamates and ureas, i.e., **72**, **74**, and **75**.

5.26.2.9.2 From five-membered nitrogen heterocycles

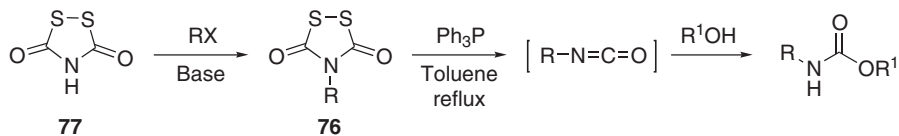
A number of methods have been reported for the cleavage of *N*-alkyl-1,2,4-dithiazolidine-3,5-dione **76** to primary amines by using triaryl- or trialkylphosphines under partly aqueous conditions <1979MI160>. However, more recently, a method for the *in situ* alkylation of 1,2,4-dithiazolidine-3,5-dione **77** with alkyl halides, under mild basic conditions, and subsequent cleavage with triphenylphosphine under anhydrous conditions to give isocyanates, has demonstrated the potential synthetic utility of this heterocyclic system as a protected isocyanate “building block,” which is stable under acidic, weakly basic, and photolytic conditions (Scheme 17) <2000SL1622>.

5.26.2.10 Blocked Isocyanates

Polyurethanes have one of the widest ranges of polymer applications throughout the world: fibers, elastomers, foams, skins, adhesives, coatings, etc. Polyurethane coatings can be produced based on internally (uretdione) or externally masked isocyanate prepolymers as cross-linkers for hydroxy-functional polymer binders. A rapid reaction between a polyfunctional isocyanate and a hydroxy-terminated oligomer leads to urethane linkage. The high reactivity and high toxicity of isocyanates do not allow their storage or their use in one-component systems. A solution particularly used in the coating and paint industries to overcome these drawbacks consists of blocking isocyanates with compounds, which can release the isocyanates on heating. Then the free isocyanate groups are able to react with the hydroxyl component during curing.



Scheme 16



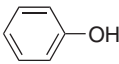
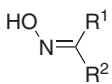


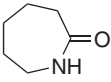
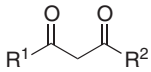

<i>R</i>	<i>X</i>	Base	76 Yield (%)
Bn	Br	NaHCO ₃	96
4-BnOC ₆ H ₄ CH ₂	Br	NaHCO ₃	80
Me	I	NaHCO ₃	78
Allyl	Br	NaHCO ₃	90
EtO ₂ CCH ₂	Br	NaHCO ₃	87
Bn	Br	Cs ₂ CO ₃	60
Bn	Cl	Cs ₂ CO ₃	42
Propargyl	Br	Cs ₂ CO ₃	47
Bu ⁱ O ₂ CCH ₂	Br	Cs ₂ CO ₃	77

<i>R</i>	<i>R</i> ¹	Urethane Yield (%)
Bn	Et	75
Bn	Bn	65
Bn	4-BrBn	60
Bn	4-MeOBn	55
EtO ₂ CCH ₂	4-O ₂ NBn	52
Me	4-O ₂ NBn	90

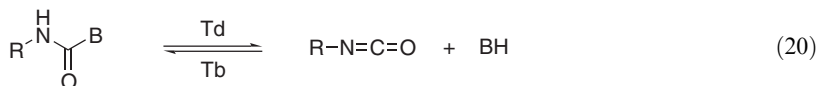
Scheme 17

Both aliphatic and aromatic isocyanates can be blocked by a variety of agents. The most widely and commercially used agents are phenols, alcohols, oximes, and azaheterocycles <1999MI148, 2001MI1, 2000MI1745>. These blocking agents are characterized by the temperature range where the unblocking reaction is expected (Table 5).

Table 5 Some blocking agents for isocyanates

Blocking agent	T_d (°C)	Blocking agent	T_d (°C)
	>180		130
Phenol		Oxime	
	180		110
Triazole		Formate	
	150		130
Caprolactame		Diketone	
	160		
Imidazoline			

The blocking and deblocking reactions are in equilibrium according to Equation (20), where BH, Tb, and Td represent blocking reagent, blocking and deblocking temperatures, respectively.



Catalysts play an important role in the deblocking or thermal dissociation of the blocked isocyanates. Notably, organometallic compounds (e.g., dibutyltin dilaurate) and tertiary amines are capable of lowering both the deblocking temperature and the time of the deblocking reaction as compared to uncatalyzed systems. The deblocking temperature is investigated by means of simultaneous thermal analysis and quadrupole mass spectrometry system (STA/QMS) <2000MI95>.

REFERENCES

- 1952LA217
 1959JACS3156
 1967TL961
 B-1967MI004
 1968JACS1638
 1974AG(E)376
 1976JOC2070
 1979MI160
 1983JP57158746
 1983JP57158747
 1984CC399
 1984JOC1458
 1984MI670
 1984TL2557
- S. Goldschmidt, M. Wick, *Justus Liebigs Ann. Chem.* **1952**, 575, 217–231.
 V. E. Shashoua, *J. Am. Chem. Soc.* **1959**, 81, 3156–3156.
 W. B. Hardy, R. P. Bennett, *Tetrahedron Lett.* **1967**, 8, 961–962.
 H. Ulrich, *Cycloaddition Reactions of Heterocumulenes*, Academic Press, New York, USA, **1967**.
 D. G. Hoare, A. Olson, D. E. Koshland Jr., *J. Am. Chem. Soc.* **1968**, 90, 1638–1643.
 L. Bauer, O. Exner, *Angew. Chem., Int. Ed. Engl.* **1974**, 13, 376–384.
 K. Kurita, T. Matsumura, Y. Iwakura, *J. Org. Chem.* **1976**, 41, 2070–2071.
 G. Barany, R. B. Merrifield, *Anal. Biochem.* **1979**, 95, 160–170.
 Okuda, S. Japanese Patent JP, 57 158 746 (1982) (Chem. Abstr. 1983, **98**, 144386b).
 Okuda, S. Japanese Patent J P 57 158 747 (1982) (Chem. Abstr. 1983, **99**, 105872h).
 S. Fukuoka, M. Chono, M. Kohno, *J. Chem. Soc., Chem. Commun.* **1984**, 399–400.
 S. Fukuoka, M. Chono, M. Kohno, *J. Org. Chem.* **1984**, 49, 1458–1460.
 S. Fukuoka, M. Chono, M. Kohno, *Chemtech* **1984**, 670–676.
 S. Kobayashi, K. Kamiyama, T. Iimori, M. Ohno, *Tetrahedron Lett.* **1984**, 25, 2557–2560.

- 1984TL3701 P. Laszlo, E. Polla, *Tetrahedron Lett.* **1984**, 25, 3701–3704.
- 1987CC1505 B. M. Choudary, P. Bharathi, *J. Chem. Soc., Chem. Commun.* **1987**, 1505–1506.
- 1987TL3787 H. Rink, *Tetrahedron Lett.* **1987**, 28, 3787–3790.
- 1988MI246 S. P. Gupte, R. V. Chaudhari, *J. Catal.* **1988**, 114, 246–258.
- 1989S61 J. Pihuleac, L. Bauer, *Synthesis* **1989**, 61–64.
- 1991JACS5065 E. P. Timothy, M. N. Bruce, *J. Am. Chem. Soc.* **1991**, 113, 5065–5066.
- 1991JPS(A)1097 G. Zhou, J. Smid, *J. Polym. Sci., Polym. Chem., Part A* **1991**, 29, 1097–1105.
- 1991T2241 P. Molina, P. Almendros, P. M. Fresneda, *Tetrahedron* **1991**, 50, 2241–2254.
- 1992JOC7364 J. S. Nowick, N. A. Powell, T. M. Nguyen, G. Noronha, *J. Org. Chem.* **1992**, 57, 7364–7366.
- 1992JPS(A)1911 S. R. Gaonkar, K. Srinivasan, G. Sudesh Kumar, *J. Polym. Sci., Polym. Chem., Part A* **1992**, 30, 1911–1916.
- 1992SC411 G. A. Roth, E. L. McClymont, *Synth. Commun.* **1992**, 22, 411–420.
- 1992TL4165 J. G. Lee, K. H. Kwak, *Tetrahedron Lett.* **1992**, 33, 3165–3166.
- 1992TL4491 P. Molina, P. M. Fresneda, P. Almendros, *Tetrahedron Lett.* **1992**, 33, 4491–4494.
- 1993SC335 J. W. Gilman, Y. A. Otonari, *Synth. Commun.* **1993**, 23, 335–341.
- 1994PS57 P. Froeyen, *Phosphorus Sulfur Silicon* **1994**, 89, 57–61.
- 1994S1197 P. Molina, M. J. Vilaplana, *Synthesis* **1994**, 1197–1218.
- 1995AG(E)2497 H.-J. Knoelker, T. Braxmeier, G. Schlechtingen, *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 2497–2500.
- 1995COFGT(5)961 P. Molina, A. Tarraga, Functions with at least one oxygen, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 961–1020.
- 1995JOC257 V. L. K. Valli, H. Alper, *J. Org. Chem.* **1995**, 60, 257–258.
- 1995JOC7641 K. Burger, E. Windeisen, R. Pires, *J. Org. Chem.* **1995**, 60, 7641–7645.
- 1995JOC8124 I. Pri-Bar, J. Schwartz, *J. Org. Chem.* **1995**, 60, 8124–8125.
- 1995MM4719 C. A. Khatri, M. M. Vaidya, K. Levon, S. K. Jha, M. M. Green, *Macromolecules* **1995**, 28, 4719–4728.
- 1995OM80 V. L. K. Valli, H. Alper, *Organometallics* **1996**, 14, 80–82.
- 1995OM3751 P. Wehman, V. E. Kaasjager, W. G. J. de Lange, F. Hartl, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. Fraanje, K. Goubitz, *Organometallics* **1995**, 14, 3751–3761.
- 1995TL1341 S. S. Elmorsy, *Tetrahedron Lett.* **1995**, 36, 1341–1342.
- 1996CC217 P. Wehman, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Chem. Soc., Chem. Commun.* **1996**, 217–218.
- 1996CL909 J. Wang, R. Nomura, T. Endo, *Chem. Lett.* **1996**, 909–910.
- 1996CRV2035 A. M. Tafesh, J. Weiguny, *Chem. Rev.* **1996**, 96, 2035–2052.
- 1996JACS10912 L. R. Sita, J. R. Babcock, R. Xi, *J. Am. Chem. Soc.* **1996**, 118, 10912–10913.
- 1996JOC3883 S. Th. Sigurdsson, B. Seeger, U. Kutzke, F. Eckstein, *J. Org. Chem.* **1996**, 61, 3883–3884.
- 1996JOC3929 J. S. Nowick, D. L. Holmes, G. Noronha, E. M. Smith, T. M. Nguyen, S.-L. Huang, *J. Org. Chem.* **1996**, 61, 3929–3934.
- 1996OM5577 S. Ciruelos, T. Cuenca, R. Gómez, P. Gómez-Sal, A. Manzanero, P. Royo, *Organometallics* **1996**, 15, 5577–5585.
- 1996S553 L. Cotarca, P. Delogu, A. Nardelli, V. Sunjic, *Synthesis* **1996**, 553–576.
- 1996S1277 R. Pires, K. Burger, *Synthesis* **1996**, 1277–1279.
- 1996TL7829 P. Molina, A. Pastor, M. J. Vilaplana, M. C. Ramirez de Arellano, *Tetrahedron Lett.* **1996**, 37, 7829–7832.
- B-1996MI002 H. Ulrich, *Chemistry and Technology of Isocyanates*, John Wiley & Sons, Chichester, Sussex England, **1996**.
- 1997JACS4882 R. J. Booth, J. C. Hodges, *J. Am. Chem. Soc.* **1997**, 119, 4882–4886.
- 1997JACS11049 S. J. Skoog, W. L. Gladfelter, *J. Am. Chem. Soc.* **1997**, 119, 11049–11060.
- 1997JOC3858 C. J. Salomon, E. Breuer, *J. Org. Chem.* **1997**, 62, 3858–3861.
- 1997MI51 R. Lomölder, F. Plogmann, P. Speier, *J. Coat. Technol.* **1997**, 69, 51–57.
- 1997OM4768 M.-A. David, D. K. Wicht, D. S. Glueck, G. P. A. Yap, L. M. Liable-Sands, R. Rheingold, *Organometallics* **1997**, 16, 4768–4770.
- 1997OM5836 P. Molina, A. Pastor, M. J. Vilaplana, M. D. Velasco, *Organometallics* **1997**, 16, 5836–5843.
- 1997SL925 H.-J. Knölker, T. Braxmeier, *Synlett* **1997**, 925–928.
- 1998CC2575 D. C. D. Butler, H. Alper, *J. Chem. Soc., Chem. Commun.* **1998**, 23, 2575–2576.
- 1998JOC9144 J. S. Nowick, D. L. Holmes, G. Noronha, E. M. Smith, T. M. Nguyen, S.-L. Huang, E. H. Wang, *J. Org. Chem.* **1998**, 63, 9144–9144.
- 1998JOC10040 J. A. Stafford, S. S. Gonzales, D. G. Barrett, E. M. Suh, P. L. Feldman, *J. Org. Chem.* **1998**, 63, 10040–10044.
- 1998JOM(551)171 I. L. Eremenko, S. E. Nefedov, A. A. Sidorov, M. O. Ponina, P. V. Danilov, T. A. Stromnova, I. P. Stolarov, S. B. Katser, S. T. Orlova, M. N. Vargaftik, I. I. Moiseev, Yu. A. Ustynyuk, *J. Organomet. Chem.* **1998**, 551, 171–194.
- 1998MI1675 S. Mayer, R. Zentel, *Macromol. Chem. Phys.* **1998**, 199, 1675–1682.
- 1998OM1052 N. Masciocchi, F. Ragaini, S. Cenini, A. Sironi, *Organometallics* **1998**, 17, 1052–1057.
- 1998OM2199 F. Paul, J. Fischer, P. Ochsenbein, J. A. Osborn, *Organometallics* **1998**, 17, 2199–2206.
- 1998TL7235 H. Shao, M. Colucci, S. Tong, H. Zhang, A. L. Castelano, *Tetrahedron Lett.* **1998**, 39, 7235–7238.
- B-1998MI001 H. A. Staab, H. Bauer, K. M. Schneider, *Azolidines in Organic Synthesis and Biochemistry*, Wiley-VCH Verlag, Weinheim, Germany, **1998**.
- 1999BMC2811 M. E. Arranz, J. A. Diaz, S. T. Ingate, M. Witvrouw, C. Pannecouque, J. Balzarini, E. De Clercq, S. Vega, *Bioorg. Med. Chem.* **1999**, 7, 2811–2822.
- 1999JOC1121 M. Alajarin, P. Molina, P. Sánchez-Andrada, M. C. Foces-Foces, *J. Org. Chem.* **1999**, 64, 1121–1130.

- 1999JOC3940 D. Saylik, M. J. Horvath, P. S. Elmes, W. R. Jackson, C. G. Lovel, K. Moody, *J. Org. Chem.* **1999**, *64*, 3940–3946.
- 1999JOC4551 G. C. G. Pais, M. E. Maier, *J. Org. Chem.* **1999**, *64*, 4551–4554.
- 1999JOC7763 K. B. Wiberg, C. Oesterle, *J. Org. Chem.* **1999**, *64*, 7763–7767.
- 1999JPR616 N. Risch, U. Westerwelle, J. Kiene, R. Keuper, *J. Prakt. Chem.* **1999**, *341*, 616–619.
- 1999MI148 D. A. Wicks, Z. W. Wicks Jr., *Progress in Organic Coatings* **1999**, *36*, 148–172.
- 1999MM974 K. Maeda, Y. Okamoto, *Macromolecules* **1999**, *32*, 974–980.
- 1999MM2085 J.-S. Lee, S.-W. Ryu, *Macromolecules* **1999**, *32*, 2085–2087.
- 1999OM1553 T.-F. Wang, C.-C. Hwu, C.-W. Tsai, Y.-S. Wen, *Organometallics* **1999**, *18*, 1553–1558.
- 1999OM2155 G. Maier, H. P. Reisenauer, H. Egenolf, *Organometallics* **1999**, *18*, 2155–2161.
- 1999TL1021 H. W. I. Peerling, E. W. Meijer, *Tetrahedron Lett.* **1999**, *40*, 1021–1024.
- 1999TL1721 S. Sunami, T. Sagara, M. Ohkubo, H. Morishima, *Tetrahedron Lett.* **1999**, *40*, 1721–1724.
- 1999TL3235 S. Braverman, M. Cherkinsky, L. Kedrova, A. Reisman, *Tetrahedron Lett.* **1999**, *40*, 3235–3238.
- 1999TL363 M. J. Horvath, D. Saylik, P. S. Elmes, W. R. Jackson, C. G. Lovel, K. Moody, *Tetrahedron Lett.* **1999**, *40*, 363–366.
- 1999TL7275 P. M. Fresneda, P. Molina, S. Delgado, *Tetrahedron Lett.* **1999**, *40*, 7275–7278.
- 1999TL9107 Y. Hitotsuyanagi, M. Kobayashi, H. Morita, H. Itokawa, K. Takeya, *Tetrahedron Lett.* **1999**, *40*, 9107–9110.
- 2000CCR269 P. Frederic, *Coord. Chem. Rev.* **2000**, *203*, 269–323.
- 2000CRV3639 J. Escudie, H. Ranaivonjatovo, L. Rigon, *Chem. Rev.* **2000**, *100*, 3639–3696.
- 2000JOC1280 H.-P. Guan, M. B. Ksehati, Y.-C. Cheng, J. C. Drach, E. R. Kern, J. Zemlicka, *J. Org. Chem.* **2000**, *65*, 1280–1290.
- 2000JOC4949 K. A. H. Chehade, H. P. Spielmann, *J. Org. Chem.* **2000**, *65*, 4949–4953.
- 2000JOC7977 Q. Zhang, C. Shi, H.-R. Zhang, K. K. Wang, *J. Org. Chem.* **2000**, *65*, 7977–7983.
- 2000JOM(603)152 Y.-J. Kim, Y.-S. Kwak, S.-W. Lee, *J. Organomet. Chem.* **2000**, *603*, 152–160.
- 2000JPO361 K. Hino, K. Maeda, Y. Okamoto, *J. Phys. Org. Chem.* **2000**, *13*, 361–367.
- 2000MI95 M. Gedan-Smolka, L. Haeussler, D. Fischer, *Thermochim. Acta* **2000**, *351*, 95–105.
- 2000MI1745 X. Tassel, D. Barbry, L. Tighzert, *Eur. Polym. J.* **2000**, *36*, 1745–1751.
- 2000OL3309 M. T. Migawa, E. E. Swayze, *Org. Lett.* **2000**, *2*, 3309–3311.
- 2000OM3879 M. Aresta, P. Giannoccaro, I. Tommasi, A. Dibenedetto, A. M. Manotti Lanfredi, F. Ugozzoli, *Organometallics* **2000**, *19*, 3879–3889.
- 2000SL1 J. H. Rigby, *Synlett* **2000**, 1–12.
- 2000SL1622 D. J. Cane-Honeysett, M. D. Dowle, M. E. Wood, *Synlett* **2000**, 1622–1624.
- 2000TL4555 T. Rühl, L. Hennig, Y. Hatanaka, K. Burger, P. Welzel, *Tetrahedron Lett.* **2000**, *41*, 4555–4558.
- 2001JMC1011 P. Molina, E. Aller, A. Lorenzo, P. López-Cremades, I. Rioja, A. Ubeda, M. Terencio, M. J. Alcaraz, *J. Med. Chem.* **2001**, *44*, 1011–1014.
- 2001JPC1897 R. Becerra, J. P. Cannady, R. Walsh, *J. Phys. Chem. (A)* **2001**, *105*, 1897–1903.
- 2001JPS(A)3112 H. W. I. Peerlings, R. A. T. M. Van Benthem, E. W. Meijer, *J. Polym. Sci., Polym. Chem., Part A* **2001**, *39*, 3112–3120.
- 2001MI1 D. A. Wicks, Z. W. Wicks Jr., *Progress in Organic Coatings* **2001**, *41*, 1–83.
- 2001MM2408 Y.-D. Shin, S.-Y. Kim, J.-H. Ahn, J.-S. Lee, *Macromolecules* **2001**, *34*, 2408–2410.
- 2001OM224 D. van Leusen, B. Hessen, *Organometallics* **2001**, *20*, 224–226.
- 2001T6197 P. M. Fresneda, P. Molina, S. Delgado, *Tetrahedron* **2001**, *57*, 6197–6202.
- 2001TL9297 T. Rühl, L. Hennig, Y. Hatanaka, K. Burger, P. Welzel, *Tetrahedron Lett.* **2001**, *42*, 9297–9297.
- 2002EJOC2298 H. Zitt, I. Dix, H. Hopf, P. G. Jones, *Eur. J. Org. Chem.* **2002**, 2298–2307.
- 2002JACS13998 D. Neumann, M. Fisher, L. Tran, J. G. Matison, *J. Am. Chem. Soc.* **2002**, *124*, 13998–13999.
- 2002JOM(641)156 H. Bornemann, W. Sander, *J. Organomet. Chem.* **2002**, *641*, 156–164.
- 2002MI113 W. Mormann, C. Kuckertz, *Macromolecular Symposia* **2002**, *181*, 113–122.
- 2002MI223 H. Götz, U. Beginn, C. F. Bartelink, H. J. M. Grünbauer, M. Möller, *Macromol. Mater. Eng.* **2002**, *287*, 223–230.
- 2002MM185 R. Mruk, R. Zentel, *Macromolecules* **2002**, *35*, 185–192.
- 2002MM6224 M. Okaniwa, K. Takeuchi, M. Asai, M. Ueda, *Macromolecules* **2002**, *35*, 6224–6231.
- 2002OS220 J. H. Tsai, L. R. Takaoka, N. A. Powell, J. S. Nowick, *Org. Synth.* **2002**, *78*, 220–224.
- 2002TL1345 V. K. Gumaste, B. M. Bhawal, A. R. A. S. Deshmukh, *Tetrahedron Lett.* **2002**, *43*, 1345–1346.
- 2002TL1673 P. Uriz, M. Serra, P. Salagre, S. Castillon, C. Claver, E. Fernandez, *Tetrahedron Lett.* **2002**, *43*, 1673–1676.
- 2002TL2475 S. Lebreton, N. Newcombe, M. Bradley, *Tetrahedron Lett.* **2002**, *43*, 2475–2479.
- 2002TL2479 S. Lebreton, N. Newcombe, M. Bradley, *Tetrahedron Lett.* **2002**, *43*, 2479–2482.
- 2002TL3413 B. P. Bandgar, S. S. Pandit, *Tetrahedron Lett.* **2002**, *43*, 3413–3414.
- 2003AG(E)5094 S. Maier, T. Loontjens, B. Scholtens, R. Mülhaupt, *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 5094–5097.
- 2003CHIR472 P. Vodicka, L. Streinz, B. Koutek, M. Budesinsky, J. Ondracek, I. Cisarova, *Chirality* **2003**, *15*, 472–478.
- 2003S2689 M. C. Schopohl, K. Bergander, O. Kataeva, R. Fröhlich, S. R. Waldvogel, *Synthesis* **2003**, 2689–2694.
- 2003T3945 S. Lebreton, S.-E. How, M. Buchholz, B.-E. Yingyongnarongkul, M. Bradley, *Tetrahedron* **2003**, *59*, 3945–3953.
- 2003TL1059 G. Radics, R. Pires, B. Koks, S. M. El-Kousy, K. Burger, *Tetrahedron Lett.* **2003**, *44*, 1059–1062.
- 2003TL3543 D. S. Bose, A. V. N. Reddy, *Tetrahedron Lett.* **2003**, *44*, 3543–3545.
- 2003TL3939 A. G. Groß, H. Deppe, A. Schober, *Tetrahedron Lett.* **2003**, *44*, 3939–3942.
- 2004TL4769 L. M. Oh, P. G. Spoor, R. M. Goodman, *Tetrahedron Lett.* **2004**, *45*, 4769–4771.

Biographical sketch

Pedro Molina was born in Totana (Murcia), Spain, in 1945. He received his Ph.D. in organic chemistry at the University of Murcia in 1973. After a postdoctoral stay at University of East Anglia (UK) with Professor A. R. Katritzky (1975–1977), he joined the University of Murcia where he became Full Professor in 1982. His interests focus on the development of iminophosphorane-based synthetic methods and their applications to the synthesis of marine alkaloids, nitrogen-substituted metallocenes and chemosensors.

Alberto Tárraga Tomás was born in Almansa (Albacete) in 1953. He studied chemistry at the University of Murcia (Spain) where he also obtained his Ph.D. in 1979. After postdoctoral studies in the group of Professor Katritzky at the University of East Anglia, Norwich (UK), in 1980, and at the University of Florida (EEUU), in 1981, he joined the group of Professor P. Molina at the University of Murcia. From 1984 he held a position as an assistant professor at the University of Murcia and since March 2004 he is Full Professor at the same University. The major focus of his research interest relates to organic heterocyclic chemistry, to natural product synthesis, and to the development of general synthetic methodologies for the preparation of redox-active derivatives, bearing donor–acceptor diads linked by a π -spacer to study the intramolecular electron-transfer phenomenon and, consequently, to evaluate the molecular-wire character of the used spacers as well as their capability of both selective ion or molecule binding and reporting on the recognition event through an appropriate physical response (electrochemical or fluorescent) in order to study the behavior of such derivatives as electrochemical or fluorescent sensors.

Antonio Arques Adame was born in Badajoz in 1952. He studied chemistry at the University of Murcia (Spain) where he also obtained his Ph.D. in 1980. He joined the group of Prof. P. Molina at the University of Murcia and from 1984 he held a position as an assistant professor at the University of Murcia. The major focus of his research interest relates to heterocyclic chemistry using iminophosphorane methodology. His current research interest is focused on the development of heterodifunctional ferrocene-coordination ligands and their application to organic synthesis.

5.27

Functions with at Least One Chalcogen Other Than Oxygen

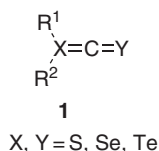
R. A. AITKEN

University of St. Andrews, St. Andrews, UK

5.27.1	CHALCOGEN FUNCTIONS	975
5.27.2	NITROGEN FUNCTIONS	976
5.27.2.1	Functions Based on Nitrogen and Sulfur	976
5.27.2.1.1	<i>Isothiocyanates from amines and their derivatives</i>	976
5.27.2.1.2	<i>Isothiocyanates from thioureas</i>	979
5.27.2.1.3	<i>Isothiocyanates from halides</i>	979
5.27.2.1.4	<i>Isothiocyanates from thiocyanates</i>	980
5.27.2.1.5	<i>Isothiocyanates from alcohols or derivatives</i>	982
5.27.2.1.6	<i>Isothiocyanates from aldehydes or ketones</i>	982
5.27.2.1.7	<i>Isothiocyanates from alkenes</i>	982
5.27.2.1.8	<i>Isothiocyanates by cleavage of nitrogen–sulfur-containing heterocycles</i>	983
5.27.2.1.9	<i>Isothiocyanates from thionoesters</i>	985
5.27.2.1.10	<i>Isothiocyanates from allylsilanes and allylstannanes</i>	985
5.27.2.1.11	<i>Acyl isothiocyanates</i>	986
5.27.2.2	Functions Based on Nitrogen and Selenium or Tellurium	986
5.27.2.2.1	<i>Isoselenocyanates from selenocyanates</i>	986
5.27.2.2.2	<i>Isoselenocyanates from amines and their derivatives</i>	986
5.27.2.2.3	<i>Isoselenocyanates by cleavage of nitrogen–selenium heterocycles</i>	987
5.27.2.2.4	<i>Acyl and imidoyl isoselenocyanates</i>	987
5.27.2.2.5	<i>Isotellurocyanates</i>	988
5.27.3	PHOSPHORUS, ARSENIC, ANTIMONY, OR BISMUTH FUNCTIONS	988
5.27.4	METALLOID FUNCTIONS	988
5.27.5	METAL FUNCTIONS	988

5.27.1 CHALCOGEN FUNCTIONS

Compounds in this section would have the structure **1**. In chapter 5.27.1 in COFGT (1995), it was reported that these were unknown and it appears that this is still the case.



5.27.2 NITROGEN FUNCTIONS

5.27.2.1 Functions Based on Nitrogen and Sulfur

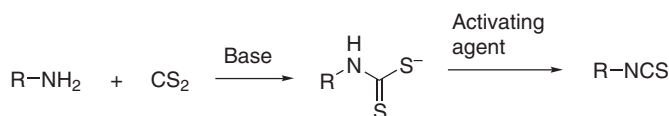
This section describes syntheses of organic isothiocyanates containing the C—N=C=S functional group. Since the publication of chapter 5.27.2.1 in <1995COFGT(5)1021>, there have been a large number of advances and these are categorized according to the function undergoing transformation to the isothiocyanate, with routes to acyl isothiocyanates considered in a separate section at the end.

5.27.2.1.1 Isothiocyanates from amines and their derivatives

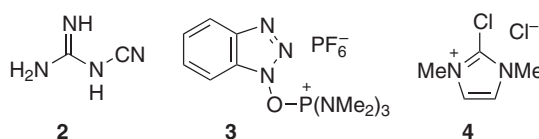
This remains one of the most common approaches to isothiocyanates and, as in COFGT (1995) <1995COFGT(5)1021>, the methods are subdivided according to whether the amine is reacted with (i) carbon disulfide, (ii) thiophosgene, or (iii) another thiocarbonyl reagent, with methods starting from simple amine derivatives rather than free amines considered separately in Section 5.27.2.1(iv).

(i) Carbon disulfide

Amines react with carbon disulfide in the presence of a base to give dithiocarbamates and subsequent treatment with an “activating agent” is generally required to convert these into isothiocyanates (Scheme 1). New improved agents introduced for this purpose include cyanoguanidine **2** (“dicyandiamide”) which gives yields of 70–90% for a range of alkyl isothiocyanates <1994OPP555>, the BOP peptide coupling reagent **3** which gives yields of 63–97% for five examples <1995CC1995>, and the chloroimidazolium salt **4** which gives yields of over 90% for a range of alkyl, aryl, and benzyl isothiocyanates <1999JOC6984, 2000JOC7774>. Clay-supported copper(II) nitrate (“claycop”) is also effective, giving yields of 45–85% for a range of alkyl, aryl, and benzyl isothiocyanates, and this reagent also converts dithiocarbamates derived from α -aminoesters into the corresponding isothiocyanates, a transformation said to be problematic using thiophosgene <1997TL8743>. The previously reported method involving reaction of an amine with carbon disulfide, ethyl chloroformate, and a base required subsequent base-induced decomposition to produce the isothiocyanate. This has now been improved in a convenient one-pot procedure which makes the base-induced decomposition unnecessary and gives yields of 54–86% directly for a range of 12 aryl and haloaryl isothiocyanates <2000OPP571>. Access to a range of acetoxyalkyl and acetoxyaryl isothiocyanates is provided by a one-pot method involving treatment of the corresponding amino alcohols with carbon disulfide and triethylamine followed by acetic anhydride and either DABCO or triethylamine. Examples prepared by this method include AcO(CH₂)₄NCS, AcO(CH₂)₅NCS, AcO(CH₂)₆NCS, AcO(CH₂)₂O(CH₂)₂NCS, and the *ortho*-, *meta*-, and *para*-isomers of AcOC₆H₄NCS <2000SC141>. The method for oxidative decomposition of dithiocarbamates using hydrogen peroxide to afford isothiocyanates has been greatly improved by using a water-miscible solvent such as THF <1997JOC4539, 2000JOC275>. This method is effective for alkyl, aryl, and benzyl isothiocyanates with yields generally over 90% and is also applicable to bis(isothiocyanates) such as SCN(CH₂)₆NCS (92%).

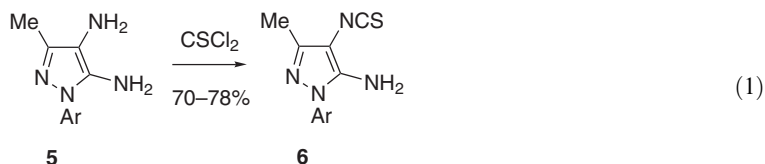


Scheme 1



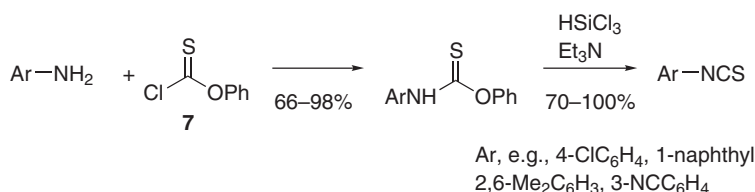
(ii) Thiophosgene

This well-established method has continued to be commonly used, but there have been few significant new developments. One result of interest is the complete regioselectivity observed in the reaction of a series of pyrazole-4,5-diamines **5** which gave exclusively the 4-isothiocyanates **6** (Equation (1)) <1999AP337>.

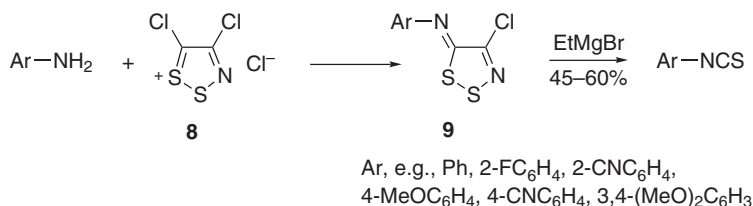


(iii) Other thiocarbonyl derivatives

Reaction of aromatic amines with phenyl chlorothionoformate **7** followed by treatment with trichlorosilane and triethylamine affords good yields of the corresponding isothiocyanates (Scheme 2) <2000JOC6237>. The dithiazolium salt **8**, readily prepared from chloroacetonitrile and disulfur dichloride, forms the basis of a convenient new two-step method for conversion of aromatic amines into the corresponding isothiocyanates <1997CC881, 1998JCS(P1)889>. The initially formed adducts **9** are decomposed by treatment with ethylmagnesium bromide to give the products in moderate overall yield (Scheme 3), and the method has also been applied to 4,4'-diaminodiphenyl sulfone (38%) and 4,4'-diaminodiphenyl sulfide (11%) <2000JCS(P1)563>. While oxidative cleavage of compounds **9** with MCPBA generally gives ArNH—C(=S)—CN, the 4-nitrophenyl compound behaves differently and gives the isothiocyanate, ArNCS, in 90% yield <1995JCS(P1)1659>.



Scheme 2

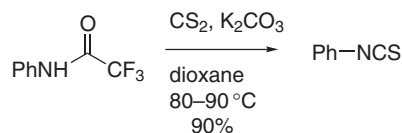


Scheme 3

(iv) From amine derivatives

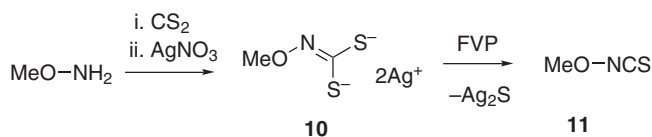
New processes in which a simple amine derivative is directly transformed into an isothiocyanate include reactions starting from amides, disilver salts of dithiocarbamates, iminophosphoranes, a 1,2-azaphosphete, carbonimidoyl dichlorides, a carbodiimide, and an azomethine imine.

The previously described reaction of trifluoroacetanilide with base and CS₂ to give phenyl isothiocyanate has been improved by working in boiling dioxane rather than acetonitrile at rt <2000JOU1173>. Under these conditions addition of sodium hydroxide is unnecessary (Scheme 4).



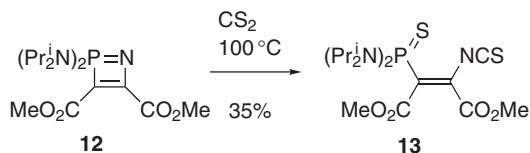
Scheme 4

Although they are not isolable at rt, the first simple alkoxy isothiocyanates have been isolated in an inert gas matrix at 10 K and observed by IR spectroscopy <1999JCS(P2)1869>. Treatment of methoxyamine with carbon disulfide followed by silver nitrate gives the salt **10** and when this is subjected to FVP, silver sulfide is eliminated and the product **11** is collected in the cold-trap (Scheme 5). The same method has also been used to generate $\text{Pr}^{\text{I}}\text{O}-\text{NCS}$.



Scheme 5

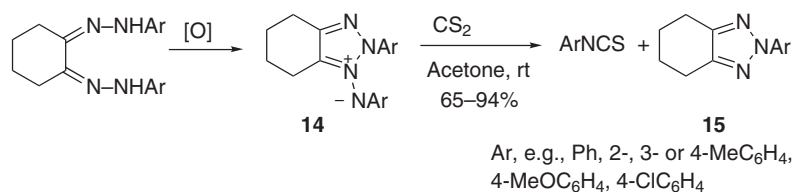
Iminophosphoranes are known to react readily with carbon disulfide to give isothiocyanates in a Wittig-like process. Since iminophosphoranes are readily formed by reaction of an azide with a P(III) reagent, direct one-pot conversion of an azide to the isothiocyanate becomes possible. Several examples of this procedure have been reported including formation of propargyl isothiocyanates using Ph_3P followed by CS_2 <2001EJO1089> and sugar isothiocyanates using $(\text{EtO})_3\text{P}/\text{CS}_2$ <1998JCS(P1)2193>. A special example of this process occurs when the 1,2-azaphosphete **12**, effectively a cyclic iminophosphorane, reacts with carbon disulfide at 100°C to give the product **13** (Scheme 6) <1994JA8087>.



Scheme 6

Reaction of carbonimidoyl dichlorides $\text{RN}=\text{CCl}_2$ with a variety of sulfur-containing reagents to give isothiocyanates has been known for sometime. New developments in this area include formation of $\text{Cl}_3\text{C}-\text{CH}(\text{Cl})-\text{NCS}$ in 65% yield using P_2S_5 in toluene at 80°C <1994JGU788>, formation of 2-cyanophenyl isothiocyanate in 80% yield using sodium sulfide and sodium carbonate <1995PHA21>, and conversion of $\text{C}_6\text{F}_5\text{N}=\text{Cl}_2$ into $\text{C}_6\text{F}_5\text{NCS}$ using either thiourea or sodium diethyl dithiocarbamate <1996JFC(79)13>.

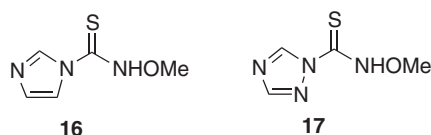
In what appears to be a new functional group interconversion of carbodiimides, treatment of DCC with Lawesson's reagent gives cyclohexyl isothiocyanate in 80% yield <1999JCS(D)3419>. The cyclic azomethine imines **14**, readily formed by the oxidation of arylhydrazones of cyclohexane-1,2-dione, react with carbon disulfide in acetone at rt to give aryl isothiocyanates together with the by-product **15** (Scheme 7) <2000JCS(P1)4335>.



Scheme 7

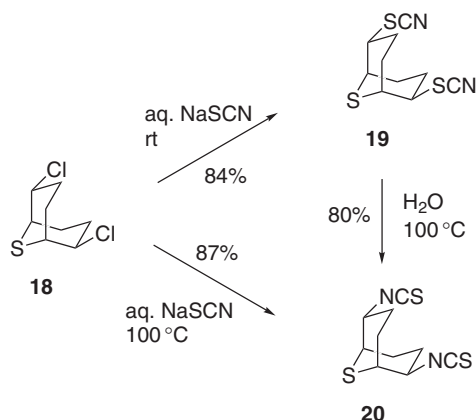
5.27.2.1.2 Isothiocyanates from thioureas

Since the publication of chapter 5.27.2.1.3 in <1995COFGT(5)1021>, a new general route to aryl isothiocyanates has been described. This depends on the fact that arylamines, ArNH_2 , react readily with tetramethylthiuram disulfide, $\text{Me}_2\text{N}-\text{C}(=\text{S})\text{S}-\text{SC}(=\text{S})\text{NMe}_2$, to give the unsymmetrical thioureas $\text{ArNHC}(=\text{S})\text{NMe}_2$. These are then decomposed using acetic anhydride or, preferably, hydrochloric or sulfuric acid in dioxane to give the isothiocyanates, ArNCS . This method is tolerant of the presence of OH or SH groups and has been used to obtain 3-isothiocyanato-4-methylbenzoic acid in 93% yield <1999BAU739>, 2-hydroxy-5-isothiocyanatobenzoic acid in 85% yield <1999BAU2290>, and 5-isothiocyanato-2-mercaptobenzoxazole in 67% yield <1999BAU767>. Methoxy isothiocyanate **11** has also been generated for matrix isolation by FVP of the heterocyclic *N*-methoxythioureas **16** and **17** <1999JCS(P2)1869>.

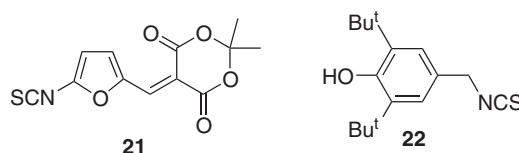


5.27.2.1.3 Isothiocyanates from halides

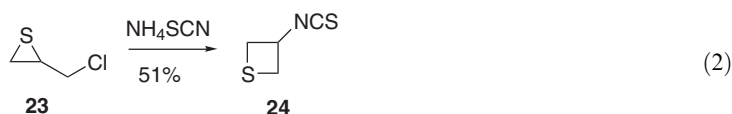
As described in chapter 5.27.2.1.8 of COFGT (1995), reaction of alkyl halides with the ambidentate thiocyanate anion may give either the thiocyanate or the isothiocyanate. The former is often the kinetic product but may be transformed into the thermodynamically more favorable isothiocyanate upon heating or by Lewis acid catalysis. A number of studies have now served to clarify this picture. Reaction of benzyl chloride with KSCN under conditions of phase-transfer catalysis initially gives PhCH_2SCN and this is the product isolated at temperatures below 100°C . Under more forcing conditions this is isomerized by the phase-transfer catalyst, most efficiently by Ph_4AsCl or $\text{Ph}_3\text{P}=\text{N}=\text{PPh}_3\text{Cl}$, to afford PhCH_2NCS <1990ZN(B)1091>. Inclusion of zinc chloride in the reaction ensures that the isothiocyanate is produced, as, for example, in the case of $\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2\text{SCH}_2\text{Br}$ and $\text{C}_8\text{F}_{17}\text{CH}_2\text{CH}_2\text{SCH}_2\text{Br}$, which react with KSCN and ZnCl_2 at 60°C to give $\text{R}_\text{F}\text{CH}_2\text{CH}_2\text{SCH}_2\text{NCS}$ in yields of 84% and 65%, respectively <1996JFC(79)27>. The dichloride **18** reacts with aqueous NaSCN at rt to give the dithiocyanate **19**, but in boiling water the product is the diisothiocyanate **20** and boiling **19** in water transforms it into **20** (Scheme 8) <2001JOC4386>. Other isothiocyanates which have been formed from their thiocyanate isomers include pent-4-enyl isothiocyanate, formed by treatment with potassium iodide and calcium carbonate <1996MI293>, compound **21** formed in 75% yield by heating in boiling acetone for 1.5 h <1994CHE289>, and compound **22** formed in 75% yield by heating neat under argon at 150°C <1994BAU93>.



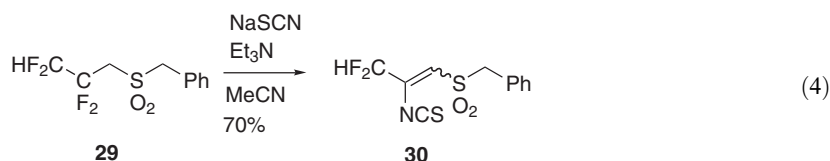
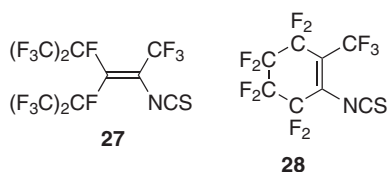
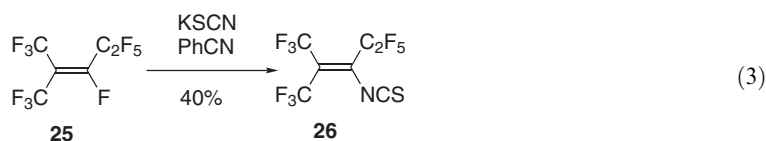
Scheme 8



New variations in the formation of glycosyl isothiocyanates include the use of solvent-free conditions which involve heating a melt of a glycosyl bromide and KSCN at 190 °C for 10 min to give the product in 41–74% yield [<1995SI228>](#). Treatment of penta-*O*-acetyl D-glucopyranose with trimethylsilyl isothiocyanate and catalytic tin(IV) chloride gives the product with the glycosidic acetoxy group replaced by NCS in 75–85% yield [<1998JCS\(P1\)947>](#). Reaction of the chloromethylthiirane **23** with ammonium thiocyanate in benzene/water at 50 °C gives the isothiocyanatothietane **24** (Equation (2)) [<2000JOU565>](#).

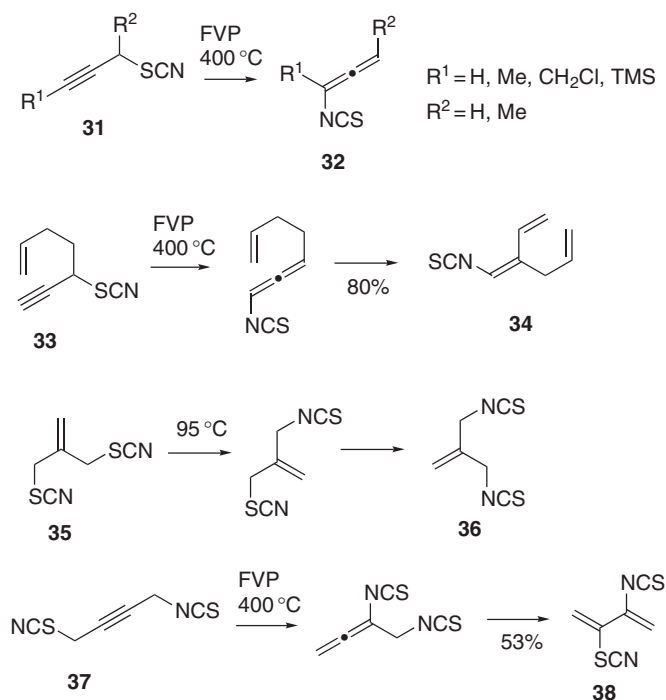


A separate class of reactions involves treatment of branched perfluoroalkenes with metal thiocyanates resulting in replacement of a vinylic fluorine atom by NCS. The first example described was reaction of perfluoro-2-methylpent-2-ene **25** with KSCN in benzonitrile at rt to give **26** (Equation (3)) [<1990BAU2599>](#). An improved yield of 93% was later reported for the same reaction [<1995H\(40\)1015>](#), and other isothiocyanates such as **27** (64%) and **28** (53%) were obtained by reaction with NaSCN in acetonitrile [<1995JOU465>](#). A somewhat similar process is involved in the reaction of the benzyl tetrafluoropropyl sulfone **29** with NaSCN and triethylamine to give the vinylic isothiocyanate **30** (Equation (4)) [<2002EJO1619>](#).



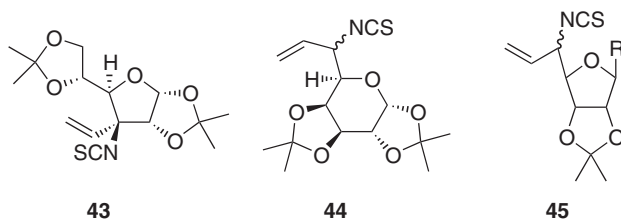
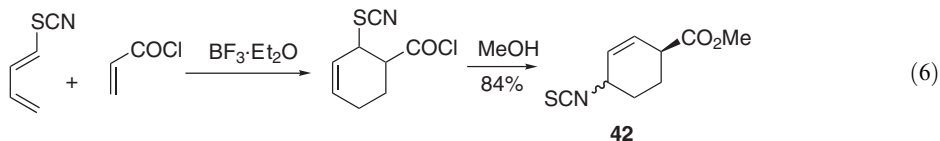
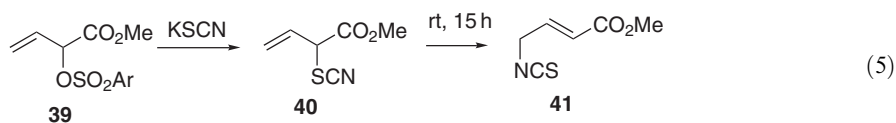
5.27.2.1.4 Isothiocyanates from thiocyanates

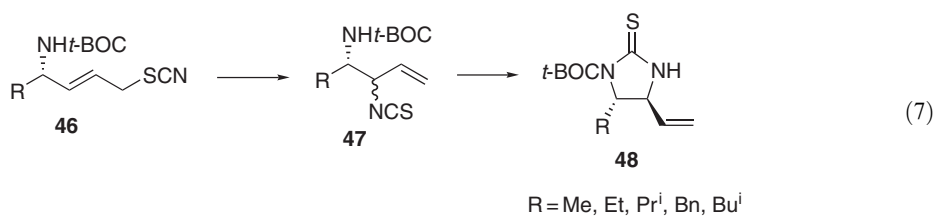
Although the isomerization of thiocyanates to isothiocyanates was considered in the previous section, the [3,3]-sigmatropic rearrangement of allyl thiocyanates is considered here which is a quite different process. The range of examples described in chapter 5.27.2.1.8 in COFGT (1995) has been expanded considerably (Scheme 9). Full details of the conversion of propargyl thiocyanates **31** into allenyl isothiocyanates **32** upon FVP at 400 °C have appeared [<2002SI423>](#). The process may be combined with a Cope rearrangement as in the conversion of **33** into **34** by FVP at 400 °C [<1998AG\(E\)3289>](#), and both the bis(thiocyanate) **35** [<1994JOC5109>](#) and the thiocyanate/isothiocyanate **37** [<2001EJO1089>](#) undergo double rearrangement under similar conditions to give products **36** and **38**, respectively.



Scheme 9

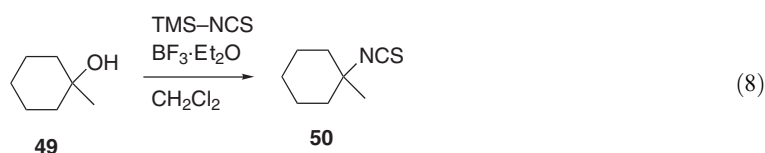
Reaction of the α -*p*-nitrobenzenesulfonyl ester **39** with KSCN initially gives a mixture of products **40** and **41** (Equation (5)) but this is converted entirely into **41** after 15 h at rt <1996JOC5567>. Lewis-acid-catalyzed cycloaddition of 1-thiocyanatobutadiene with acryloyl chloride followed by methanolysis gives the rearranged product **42** (Equation (6)) <1994CC1001>. Rearrangement of allyl thiocyanates to allyl isothiocyanates has also been applied in carbohydrate chemistry to obtain products such as **43** <1997TL5569>, **44** <2000TL525>, and **45** <2001TL4401>. Rearrangement of the chiral thiocyanates **46** occurs upon heating at 80 °C in xylene to give a mixture of diastereomers **47** (Equation (7)), but only one of these undergoes cyclization to give **48** as the final product <1997TL875>.





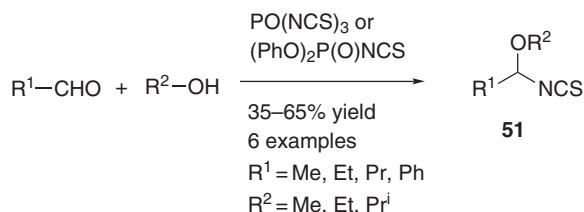
5.27.2.1.5 Isothiocyanates from alcohols or derivatives

There have been few new developments since the publication of chapter 5.27.2.1.9 in <1995COFGT(5)1021>, but treatment with trimethylsilyl isothiocyanate in the presence of BF₃·Et₂O does provide a new method for direct conversion of alcohols such as **49** into the isothiocyanate **50** (Equation (8)) <1999BCJ85>. The method is limited in scope since several closely related alcohols instead undergo dehydration to give alkenes. Depending on the conditions, treatment of alcohols, ROH, and also thiols, RSH, and trimethylsilyl ethers, ROTMS, with NH₄SCN under Mitsunobu conditions (Ph₃P/DEAD) gives either the corresponding isothiocyanates, RNCS, or the thiocyanates, RSCN <2004S92>.



5.27.2.1.6 Isothiocyanates from aldehydes or ketones

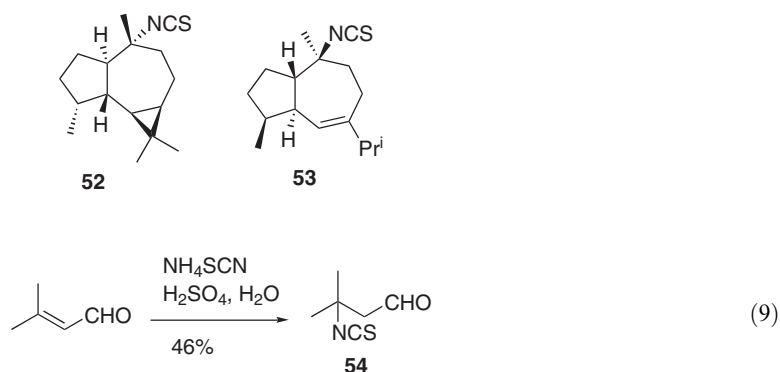
The only significant new development since the publication of chapter 5.27.2.1.10 in <1995COFGT(5)1021> is the formation of α-alkoxyalkyl isothiocyanates **51** by treatment of a mixture of aldehyde and alcohol with either PO(NCS)₃ or (PhO)₂P(O)NCS (Scheme 10) <1997CCC1491>.



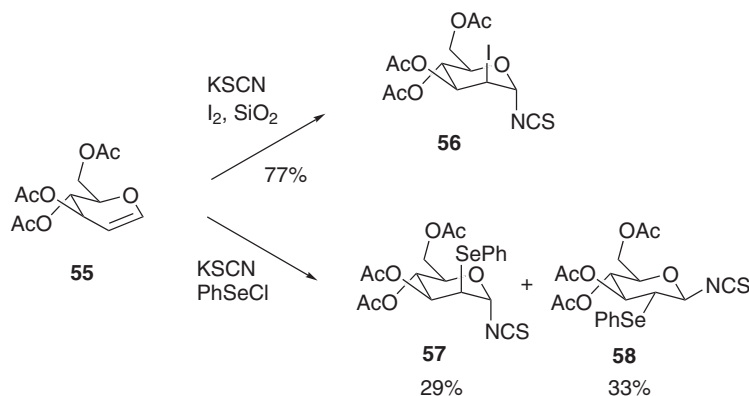
Scheme 10

5.27.2.1.7 Isothiocyanates from alkenes

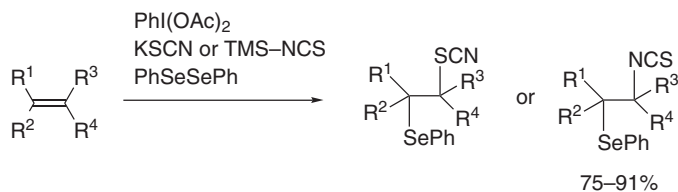
Several new methods starting from alkenes have been reported since the publication of chapter 5.27.2.1.11 in <1995COFGT(5)1021>. Addition of HSCN to the exocyclic methylene group of terpenoid derivatives has been used to obtain products such as **52**, formed in 97% yield <1994JOC2880>, and **53**, formed in 40% yield and accompanied by 42% of the thiocyanate isomer <1999BCJ85>. This method has also been extended to α,β-unsaturated carbonyl compounds as exemplified by the formation of compound **54** (Equation (9)) <1994CHE943>.



A number of methods for 1,2-functionalization of alkenes have also been introduced. Treatment of glycols such as **55** with silica-supported KSCN and iodine gives mainly the product **56** [<1994T2877>](#), while reaction of the same starting material with PhSeCl followed by KSCN gives a mixture of **57** and **58** (Scheme 11) [<1999S2049>](#). Interaction of $\text{PhI}(\text{OAc})_2$ with diphenyl diselenide and either KSCN or trimethylsilyl isothiocyanate at rt leads to *in situ* formation of PhSeSCN which adds to alkene double bonds giving either 2-selenoalkyl thiocyanates or 2-selenoalkyl isothiocyanates (Scheme 12) [<2000EJO1865>](#). While less substituted alkenes such as oct-1-ene, vinylcyclohexane, and cyclohexene give the thiocyanates, more highly substituted compounds such as α -methylstyrene, 1-methylcyclohexene, geranial, and geranyl acetate all give the isothiocyanates.



Scheme 11

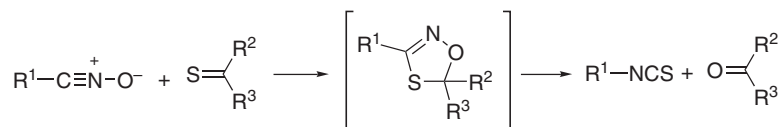


Scheme 12

5.27.2.1.8 Isothiocyanates by cleavage of nitrogen–sulfur-containing heterocycles

There has been considerable progress in this area since the publication of chapter 5.27.2.1.13 in [<1995COFGT\(5\)1021>](#), mostly involving 1,3-dipolar cycloaddition of nitrile oxides with thiocarbonyl compounds. The resulting 1,4,2-oxathiazoles are unstable under the reaction conditions and fragment with migration to give a carbonyl compound and an isothiocyanate (Scheme 13). (Note: A brief discussion of this method appeared erroneously in chapter 5.27.2.1.6 of [<1995COFGT\(5\)1021>](#) where the nitrile oxides were confused with cyanates.) Representative

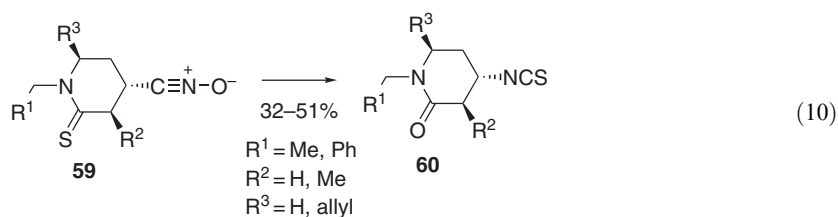
examples of this method are shown in Table 1. For the last example mentioned, using thiourea, the nitrile oxides may be generated either by the usual base treatment of preformed hydroximoyl chlorides or, in a one-pot procedure, from oximes $\text{RCH}=\text{NHOH}$ by treatment with NCS or $\text{HCl/Oxone}^{\text{®}}$ in DMF followed by addition of thiourea and triethylamine <1997TL1597>, or by treatment of aliphatic nitro compounds RCH_2NO_2 with 4-chlorophenyl isocyanate, thiourea, and triethylamine <1994SC1101>. A recent example of this reaction which appears to occur intramolecularly involves conversion of the nitrile oxides **59**, generated from the corresponding nitro compounds with phenyl isocyanate and Et_3N , into the isothiocyanates **60** in 32–51% yield (Equation (10)) <2002TL1325>.



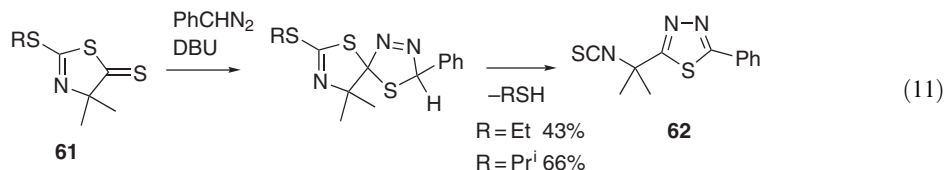
Scheme 13

Table 1 Isothiocyanates from nitrile oxides and thiocarbonyl compounds

Nitrile oxide	Thiocarbonyl compound	Product	Yield (%)	References
$\text{Ph}-\text{C}\equiv\text{N}-\text{O}^-$		$\text{Ph}-\text{NCS}$	—	<1994BSF313>
			—	<1994CL1691>
			76	<1996BCJ719>
			65	<2000H(53)571>
	KSCN		80	<2002CCC665>
			97	<2000AJC137>
$\text{R}-\text{C}\equiv\text{N}-\text{O}^-$ wide variety of alkyl, aryl, and benzyl groups (30 examples)		$\text{R}-\text{NCS}$	70–99	<1993TL8283, 1994SC1101, 1997TL1597, 1998SC1879>

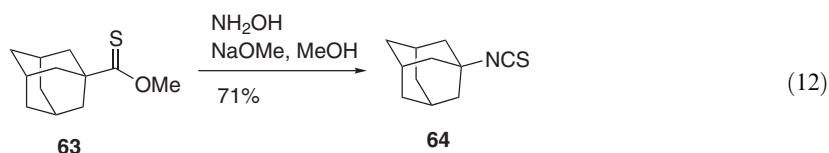


Finally in this section, reaction of thiazoline-5-thiones **61** with phenyldiazomethane and DBU leads to base-induced decomposition of the initially formed adducts (Equation (11)) to give the isothiocyanate-containing thiadiazole **62** <1994HCA1076>.



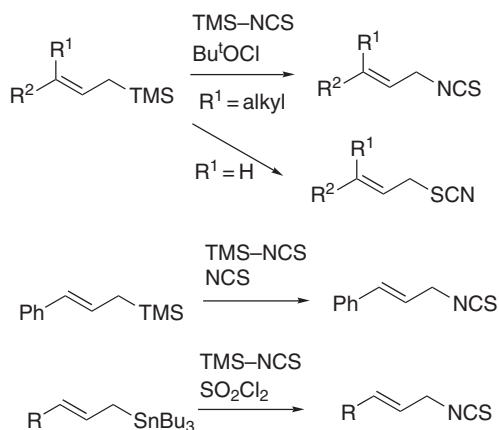
5.27.2.1.9 Isothiocyanates from thionoesters

In an apparently unprecedented functional group transformation, treatment of the adamantyl thionoester **63** with hydroxylamine and sodium methoxide in methanol gives the isothiocyanate **64** directly (Equation (12)) <1994JOU1776>.



5.27.2.1.10 Isothiocyanates from allylsilanes and allylstannanes

In the presence of a halogen oxidizing agent, trimethylsilyl isothiocyanate may act as a source of SCN^+ and thus allow conversion of allylic silanes and stannanes into either the corresponding thiocyanates or isothiocyanates according to the groups present and conditions used [<1997PS\(120/121\)385>](#). Some typical examples which give the isothiocyanates are shown in [Scheme 14](#).



Scheme 14

5.27.2.1.11 Acyl isothiocyanates

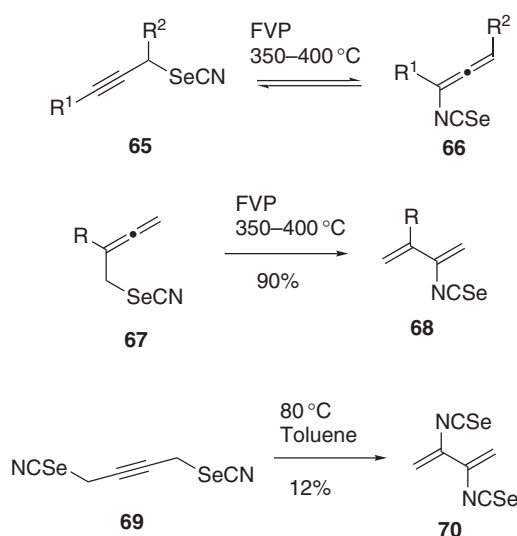
There have only been three significant developments in this area since the publication of chapter 5.27.2.1.14 in <1995COFGT(5)1021>. Reaction of silyl esters RC(O)OSiPr^i_3 and $\text{RC(O)OSiMe}_2\text{Bu}^t$ with $\text{Ph}_3\text{P(SCN)}_2$ affords the corresponding acyl isothiocyanates, RC(O)NCS , in over 90% yield for a range of aryl, benzyl and alkyl groups R <2002SC3653>. Similarly, either carboxylic acids or their trimethylsilyl esters, RC(O)OTMS , may be converted into the corresponding acyl isothiocyanates by treatment with NH_4SCN under Mitsunobu conditions ($\text{Ph}_3\text{P/DEAD}$) <2004S92>. A variety of substituted benzoyl chlorides have been directly converted into the corresponding benzoyl isothiocyanates for use *in situ* under conditions of solid-liquid phase-transfer catalysis, typically using solid KSCN or NH_4SCN in CH_2Cl_2 with 3 mol.% of PEG-400 or PEG-600 as catalyst <1995JCR(S)138, 1998SC2851, 1998SC3243, 2000SC493>.

5.27.2.2 Functions Based on Nitrogen and Selenium or Tellurium

Since the publication of chapter 5.27.2.2 in <1995COFGT(5)1021>, there have been relatively few significant developments. These are described here according to the functional group undergoing transformation into the isoselenocyanate with acyl and imido-yl isoselenocyanates described separately at the end.

5.27.2.2.1 Isoselenocyanates from selenocyanates

This new method, involving [3,3]-sigmatropic rearrangement of allyl and propargyl selenocyanates, is analogous to that described earlier in this chapter for thiocyanates (Section 5.27.2.1.4) and has afforded access to the first vinyl isoselenocyanates <1995AG(E)1627>. Representative examples are shown in Scheme 15. For simple propargyl selenocyanates **65**, FVP leads to establishment of an equilibrium which lies mainly in favor of the allenyl isoselenocyanate **66** for $\text{R}^1 = \text{H}$ and $\text{R}^2 = \text{H}$ or Me, but leads to only 20% of this form for $\text{R}^1 = \text{Me}$ and $\text{R}^2 = \text{H}$. In contrast, FVP of selenocyanatomethylallenes **67** leads to complete conversion into the isoselenocyanatodienes **68** for R = H and Me. In the case of **69**, FVP is unsuccessful but heating in toluene for 24 h leads to conversion into the bis(isoselenocyanate) **70**.

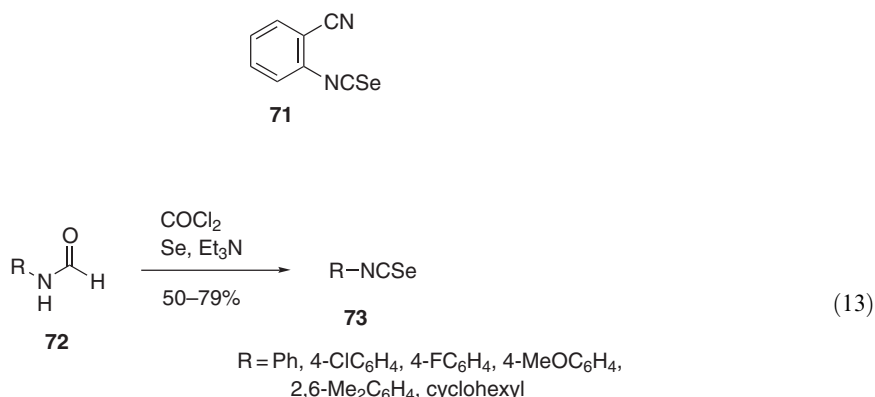


Scheme 15

5.27.2.2.2 Isoselenocyanates from amines and their derivatives

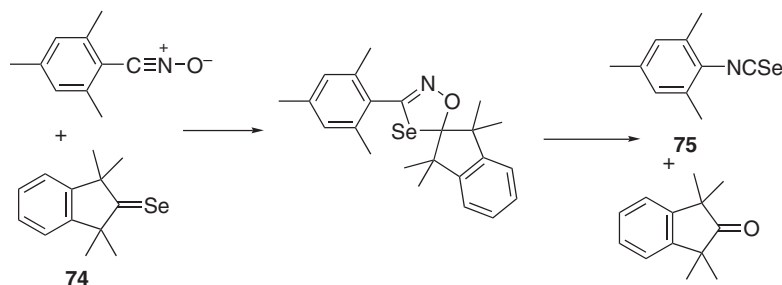
There have only been two significant developments since the publication of chapter 5.27.2.2.3 in <1995COFGT(5)1021>. The conversion of carbonimidoyl dichlorides, ArN=CCl_2 , into

isosenocyanates which previously required treatment with 2 equiv. of KSeCN has now been achieved using NaSeH/Na₂CO₃ as exemplified by the formation of compound **71** in 81% yield <1995PHA21>. Conversion of *N*-formylamines **72** into isosenocyanates **73** was previously possible in two steps by dehydration to isocyanides using Ph₃P/CCl₄/Et₃N and then treatment with selenium. This has now been achieved in a convenient one-pot procedure by treatment with phosgene, selenium, and triethylamine for a range of alkyl and aryl groups (Equation (13)) <1994T639>.



5.27.2.2.3 Isosenocyanates by cleavage of nitrogen–selenium heterocycles

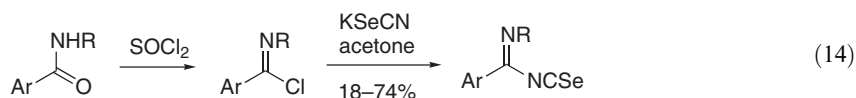
A single example of this new approach, analogous to the method of Scheme 13 for isothiocyanates, is provided by cycloaddition of a nitrile oxide to the selenone **74** to give an intermediate 1,4,2-oxaselenazole which fragments to give isosenocyanate **75** (Scheme 16) <1994CL1691>.



Scheme 16

5.27.2.2.4 Acyl and imido isosenocyanates

Since the publication of chapter 5.27.2.2.5 in <1995COFGT(5)1021>, there have been few new developments in this area. Reaction of RCOCl (R = Ph and Bu^t) with KSeCN in acetone has been used to obtain RCONCSe for use *in situ* <1999CCC1673>. The range of known imido isosenocyanates has been expanded by formation of 14 further examples using reaction of the imido chloride with KSeCN in acetone (Equation (14), R = Ph, benzyl, and *p*-substituted benzyl) <2000HCA1576, 2002HCA1102>.



5.27.2.2.5 Isotellurocyanates

In chapter 5.27.2.2.6 of <1995COFGT(5)1021> it was stated that isotellurocyanates were unknown and this is still the case. The approach outlined in Scheme 16 using the tellurone corresponding to 74 gave only mesityl isocyanide and elemental tellurium, suggesting that R–NCTe may be inherently unstable with respect to decomposition to R–NC and Te <1994CL1691>.

5.27.3 PHOSPHORUS, ARSENIC, ANTIMONY, OR BISMUTH FUNCTIONS

There have been no significant developments in the chemistry of compounds containing the $P=C=S$ function since the publication of chapter 5.27.3 in <1995COFGT(5)1021> and the heavier atom analogs containing As, Sb, or Bi in place of P and/or Se or Te in place of S all remain unknown.

5.27.4 METALLOID FUNCTIONS

As noted in chapter 5.27.4 of <1995COFGT(5)1021>, compounds with the functions $B=C=S$, $Si=C=S$, and $Ge=C=S$ as well as their selenium and tellurium analogs are unknown.

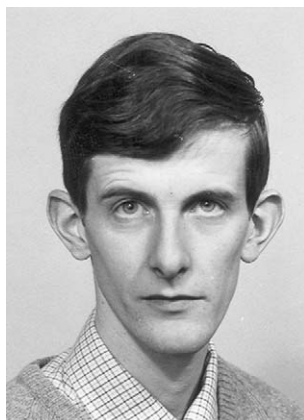
5.27.5 METAL FUNCTIONS

Compounds containing the functions $M=C=S$, $M=C=Se$, or $M=C=Te$, where M is a metal further bonded to organic groups remain unknown.

REFERENCES

- 1990BAU2599 V. Ya. Popkova, E. I. Mysov, M. V. Galakhov, V. K. Osmanov, L. S. German, *Bull. Acad. Sci. USSR (Engl. Transl.)* **1990**, 39, 2599–2602.
- 1990ZN(B)1091 E. V. Dehmlow, G. O. Torossian, *Z. Naturforsch., Teil B* **1990**, 45, 1091–1092.
- 1993TL8283 J. N. Kim, E. K. Ryu, *Tetrahedron Lett.* **1993**, 34, 8283–8284.
- 1994BAU93 D. B. Gorbunov, V. N. Voznesenskii, V. V. Ershov, G. A. Nikiforov, *Russ. Chem. Bull.* **1994**, 43, 93–97.
- 1994BSF313 B. Sain, D. Prajapati, A. R. Mahajan, J. S. Sandhu, *Bull. Soc. Chim. Fr.* **1994**, 131, 313–316.
- 1994CC1001 J. Schoepfer, C. Marquis, C. Pasquier, R. Neier, *J. Chem. Soc., Chem. Commun.* **1994**, 1001–1002.
- 1994CHE289 G. D. Krapivan, N. I. Val'ter, T. Ya. Kaklyugina, V. G. Kul'nevich, *Chem. Heterocycl. Compd. (Engl. Transl.)* **1994**, 30, 289–295.
- 1994CHE943 A. D. Shutalev, M. T. Pagaev, L. A. Ignatova, *Chem. Heterocycl. Compd. (Engl. Transl.)* **1994**, 30, 943–952.
- 1994CL1691 M. Minoura, T. Kawashima, R. Okazaki, *Chem. Lett.* **1994**, 1691–1692.
- 1994HCA1076 M. Petit, A. Linden, G. Mloston, H. Heimgartner, *Helv. Chim. Acta* **1994**, 77, 1076–1086.
- 1994JA8087 K. Bieger, J. Tejeda, R. Réau, F. Dahan, G. Bertrand, *J. Am. Chem. Soc.* **1994**, 116, 8087–8094.
- 1994JGU788 R. N. Vydzhak, V. S. Brovarets, B. S. Drach, *Russ. J. Gen. Chem. (Engl. Transl.)* **1994**, 64, 788–789.
- 1994JOC2880 C. C. da Silva, V. Almagro, J. Zukerman-Schpector, E. E. Castellano, A. J. Marsaioli, *J. Org. Chem.* **1994**, 59, 2880–2881.
- 1994JOC5109 D. W. Emerson, R. L. Titus, S. M. Steinberg, M. D. Jones, *J. Org. Chem.* **1994**, 59, 5109–5110.
- 1994JOU1776 Yu. E. Klimko, S. D. Isaev, A. G. Yurchenko, *Russ. J. Org. Chem. (Engl. Transl.)* **1994**, 30, 1776–1783.
- 1994OPP555 T. Yamamoto, A. Terada, T. Muramatsu, K. Ikeda, *Org. Prep. Proced. Int.* **1994**, 26, 555–557.
- 1994SC1101 J. N. Kim, J. H. Song, E. K. Ryu, *Synth. Commun.* **1994**, 24, 1101–1105.
- 1994T639 D. H. R. Barton, S. I. Parekh, M. Tajbakhsh, E. A. Theodorakis, C.-L. Tse, *Tetrahedron* **1994**, 50, 639–654.
- 1994T2877 F. Santoyo-González, F. García-Calvo-Flores, J. Isac-García, F. Hernández-Mateo, P. García-Mendoza, R. Robles-Díaz, *Tetrahedron* **1994**, 50, 2877–2894.
- 1995AG(E)1627 K. Banert, C. Toth, *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 1627–1629.
- 1995CC1995 U. Boas, M. H. Jakobsen, *J. Chem. Soc., Chem. Commun.* **1995**, 1995–1996.
- 1995COFGT(5)1021 J. Gilmore, P. T. Gallagher, Functions with at least one chalcogen other than oxygen, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 1021–1060.
- 1995H(40)1015 V. Ya. Popkova, F. M. Dolgushin, M. Yu. Antipin, A. I. Yanovsky, Yu. T. Struchkov, *Heterocycles* **1995**, 40, 1015–1026.
- 1995JCR(S)138 T.-B. Wei, J.-C. Chen, X.-C. Wang, Y.-M. Zhang, *J. Chem. Res. (S)* **1995**, 138–139.
- 1995JCS(P1)1659 T. Besson, C. W. Rees, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1659–1662.
- 1995JOU465 G. G. Furin, *Russ. J. Org. Chem. (Engl. Transl.)* **1995**, 31, 465–468.
- 1995PHA21 W. D. Pfeiffer, P. Pazdera, A. Hertzheim, J. Mücke, *Pharmazie* **1995**, 50, 21–25.
- 1995S1228 T. K. Lindhorst, C. Kieburg, *Synthesis* **1995**, 1228–1230.
- 1996BCJ719 S. Watanabe, T. Yamamoto, T. Kawashima, N. Inamoto, R. Okazaki, *Bull. Chem. Soc. Jpn.* **1996**, 69, 719–724.

- 1996JFC(79)13 T. D. Petrova, V. E. Platonov, L. N. Shchegoleva, A. M. Maksimov, A. Haas, M. Schelvis, M. Lieb, *J. Fluorine Chem.* **1996**, 79, 13–25.
- 1996JFC(79)27 H. Trabelsi, M. A. Jouani, A. Cambon, *J. Fluorine Chem.* **1996**, 79, 27–31.
- 1996JOC5567 R. V. Hoffman, B. S. Severns, *J. Org. Chem.* **1996**, 61, 5567–5573.
- 1996MI293 P. M. Lösel, M. Lindemann, J. Scherkenbeck, J. Maier, B. Engelhard, C. A. M. Campbell, J. Hardie, J. A. Pickett, L. J. Wadhams, A. Elbert, G. Thielking, *Pesticide Sci.* **1996**, 48, 293–303.
- 1997CC881 T. Besson, J. Guillard, C. W. Rees, M. Thérissod, *Chem. Commun.* **1997**, 881–882.
- 1997CCC1491 J. Bernát, P. Kristian, J. Guspanová, J. Imrich, T. Busová, *Collect. Czech. Chem. Commun.* **1997**, 62, 1491–1496.
- 1997JOC4539 G. Li, H. Tajima, T. Ohtani, *J. Org. Chem.* **1997**, 62, 4539–4540.
- 1997PS(120/121)385 Y. Tanabe, K. Mori, N. Kawabata, *Phosphorus, Sulfur, and Silicon* **1997**, 120–121, 385–386.
- 1997TL875 M. Martinková, J. Gonda, *Tetrahedron Lett.* **1997**, 38, 875–878.
- 1997TL1597 J. N. Kim, K. S. Jung, H. J. Lee, J. S. Son, *Tetrahedron Lett.* **1997**, 38, 1597–1598.
- 1997TL5569 J. Gonda, M. Bednáriková, *Tetrahedron Lett.* **1997**, 38, 5569–5572.
- 1997TL8743 H. M. Mesharam, S. Dale, J. S. Yadav, *Tetrahedron Lett.* **1997**, 38, 8743–8744.
- 1998AG(E)3289 K. Banert, W. Fendel, J. Schlott, *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 3289–3292.
- 1998JCS(P1)889 T. Besson, J. Guillard, C. W. Rees, V. Thiéry, *J. Chem. Soc., Perkin Trans. 1* **1998**, 889–892.
- 1998JCS(P1)947 N. Al-Masoudi, N. A. Hassan, Y. A. Al-Soud, P. Schmidt, A. E.-D. M. Gaafar, M. Weng, S. Marino, A. Schoch, A. Amer, J. C. Jochims, *J. Chem. Soc., Perkin Trans. 1* **1997**, 947–953.
- 1998JCS(P1)2193 S. Kötter, U. Krallmann-Wenzel, S. Ehlers, T. K. Lindhorst, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2193–2200.
- 1998SC1879 K. S. Jung, H. J. Lee, H. N. Song, J. N. Kim, *Synth. Commun.* **1998**, 28, 1879–1884.
- 1998SC2851 T. Wei, Y. Zhang, *Synth. Commun.* **1998**, 28, 2851–2859.
- 1998SC3243 Y. Zhang, T. Wei, J. Lus, *Synth. Commun.* **1998**, 28, 3243–3248.
- 1999AP337 C. B. Vicentini, M. Manfrini, M. Mazzanti, A. Scatturin, C. Romagnoli, D. Mares, *Arch. Pharm. (Weinheim, Ger.)* **1999**, 332, 337–342.
- 1999BAU739 L. V. Boi, I. Korzha, N. Barba, *Russ. Chem. Bull.* **1999**, 48, 739–742.
- 1999BAU767 L. V. Boi, A. Zadorozhnyi, N. Barba, *Russ. Chem. Bull.* **1999**, 48, 767–770.
- 1999BAU2290 L. V. Boi, H. Al-Ebaisat, *Russ. Chem. Bull.* **1999**, 48, 2290–2293.
- 1999BCJ85 N. Iwasawa, M. Funahashi, S. Hayakawa, T. Ikeno, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1999**, 72, 85–98.
- 1999CCC1673 J. Sibor, D. Zurek, R. Marek, M. Kutý, O. Humpa, J. Marek, P. Pazdera, *Collect. Czech. Chem. Commun.* **1999**, 64, 1673–1695.
- 1999JCS(D)3419 M. StJ. Foreman, R. J. Mortimer, A. M. Z. Slawin, J. D. Woollins, *J. Chem. Soc., Dalton Trans.* **1999**, 3419–3430.
- 1999JCS(P2)1869 A. T. Bech, R. Flammang, C. T. Pedersen, M. W. Wong, C. Wentrup, *J. Chem. Soc., Perkin Trans. 2* **1999**, 1869–1874.
- 1999JOC6984 T. Isobe, T. Ishikawa, *J. Org. Chem.* **1999**, 64, 6984–6988.
- 1999S2049 C. Uriel, F. Santoyo-González, *Synthesis* **1999**, 2049–2052.
- 2000AJC137 D. J. Collins, T. C. Hughes, W. M. Johnson, *Aust. J. Chem.* **2000**, 53, 137–141.
- 2000EJO1865 R. Margarita, C. Mercanti, L. Parlanti, G. Piancatelli, *Eur. J. Org. Chem.* **2000**, 1865–1870.
- 2000H(53)571 E. M. Rakib, M. Benchidmi, E. M. Essassi, A. E. Bouadili, M. Khouili, J. M. Barbe, M. D. Pujol, *Heterocycles* **2000**, 53, 571–577.
- 2000HCA1576 Y. Zhou, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2000**, 83, 1576–1598.
- 2000JCS(P1)563 T. Besson, J. Guillard, C. W. Rees, *J. Chem. Soc., Perkin Trans. 1* **2000**, 563–566.
- 2000JCS(P1)4335 R. N. Butler, L. M. Wallace, *J. Chem. Soc., Perkin Trans. 1* **2000**, 4335–4338.
- 2000JOC275 S. Sasaki, M. Mizuno, K. Naemura, Y. Tobe, *J. Org. Chem.* **2000**, 65, 275–283.
- 2000JOC6237 X. Zhang, Y. K. Lee, J. A. Kelley, T. R. Burke, Jr., *J. Org. Chem.* **2000**, 65, 6237–6240.
- 2000JOC7774 T. Isobe, K. Fukuda, T. Tokunaga, H. Seki, K. Yamaguchi, T. Ishikawa, *J. Org. Chem.* **2000**, 65, 7774–7778.
- 2000JOU565 M. A. Allakhverdiev, R. K. Alekperov, N. A. Shirinova, N. A. Akperov, *Russ. J. Org. Chem. (Engl. Transl.)* **2000**, 36, 565–567.
- 2000JOU1173 K. T. Petko, L. M. Yagupol'skii, *Russ. J. Org. Chem. (Engl. Transl.)* **2000**, 36, 1173–1177.
- 2000OPP571 Z. Lin, X. Qian, Z. Liu, Z. Li, G. Song, *Org. Prep. Proced. Int.* **2000**, 32, 571–573.
- 2000SC141 K. Hara, H. Tajima, *Synth. Commun.* **2000**, 30, 141–146.
- 2000SC493 T.-B. Wei, Y.-M. Zhang, L.-M. Gao, *Synth. Commun.* **2000**, 30, 493–500.
- 2000TL525 J. Gonda, E. Zavacká, M. Budesínský, I. Cisarová, J. Podlaha, *Tetrahedron Lett.* **2000**, 41, 525–530.
- 2001EJO1089 K. Banert, M. Hagedorn, A. Müller, *Eur. J. Org. Chem.* **2001**, 1089–1103.
- 2001JOC4386 A. Converso, K. Burov, A. Marzinzik, K. B. Sharpless, M. G. Finn, *J. Org. Chem.* **2001**, 66, 4386–4392.
- 2001TL4401 J. Gonda, M. Martinková, M. Walko, E. Zavacká, M. Budesínský, I. Cisarová, *Tetrahedron Lett.* **2001**, 42, 4401–4404.
- 2002CCC665 L. Janovec, G. Suchár, J. Imrich, P. Kristian, V. Sasinková, J. Alföldi, E. Sedlák, *Collect. Czech. Chem. Commun.* **2002**, 67, 665–678.
- 2002EJO1619 V. M. Timoshenko, Ya. V. Nikolin, A. N. Chernergera, Yu. G. Shermolovich, *Eur. J. Org. Chem.* **2002**, 1619–1627.
- 2002HCA1102 P. K. Atanassov, Y. Zhou, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2002**, 85, 1102–1117.
- 2002S1423 K. Banert, S. Groth, H. Hückstädt, J. Lehmann, J. Schlott, K. Vrobel, *Synthesis* **2002**, 1423–1433.
- 2002SC3653 N. Iranpoor, H. Firouzabadi, H. R. Shaterian, *Synth. Commun.* **2002**, 32, 3653–3657.
- 2002TL1325 J. G. Sosnicki, S. Westerlich, *Tetrahedron Lett.* **2002**, 43, 1325–1328.
- 2004S92 N. Iranpoor, H. Firouzabadi, B. Akhlaginia, R. Azadi, *Synthesis* **2004**, 92–97.

Biographical sketch

Alan Aitken was born in the Dumfries and Galloway area of SW Scotland. He studied at the University of Edinburgh, where he obtained a B.Sc. in 1979 and his Ph.D. in 1982 under the direction of Dr. I. Gosney and Professor J. I. G. Cadogan. After spending two years as a Fulbright Scholar in the laboratories of Professor A. I. Meyers at Colorado State University, he was awarded a Royal Society Warren Research Fellowship and moved to the University of St. Andrews in 1984 where he has been a Senior Lecturer since 1997. His research interests are in the area of synthetic and mechanistic organic chemistry including asymmetric synthesis, synthetic use of flash vacuum pyrolysis, heterocyclic chemistry, organophosphorus, and organosulfur chemistry.

5.28

Functions with at Least One Nitrogen and No Chalcogens

A. E. GRAHAM

University of Wales Swansea, Swansea, UK

5.28.1	FUNCTIONS BASED ON NITROGEN: CARBODIIMIDES ($RN=C=NR$)	991
5.28.1.1	Introduction	991
5.28.1.2	Unsymmetrical Carbodiimides ($R^1N=C=NR^2$)	992
5.28.1.2.1	<i>Via metal salts</i>	992
5.28.1.2.2	<i>Via phosphorus reagents</i>	993
5.28.1.2.3	<i>Via acid chlorides and related reagents</i>	993
5.28.1.2.4	<i>Via isocyanates and isothiocyanates</i>	995
5.28.1.2.5	<i>Via imidoyl dichlorides</i>	1000
5.28.1.2.6	<i>Via isonitrile reagents</i>	1000
5.28.1.2.7	<i>Via oxidation of selenoureas</i>	1000
5.28.1.2.8	<i>Via metathesis</i>	1001
5.28.1.2.9	<i>Via rearrangement</i>	1003
5.28.1.2.10	<i>Miscellaneous</i>	1004
5.28.1.3	Symmetrical Carbodiimides ($RN=C=NR$)	1004
5.28.1.3.1	<i>Carbodiimides of the type $RN=C=NR$, where $R = SiR_3^1$</i>	1004
5.28.1.3.2	<i>Carbodiimides of the type $RN=C=NR$, where $R = \text{alkyl or aryl}$</i>	1005
5.28.1.4	Other Related Derivatives	1005
5.28.1.4.1	<i>Carbodiimides of the type $MN=C=NM$, where $M = \text{metal}$</i>	1005
5.28.1.4.2	<i>Carbodiimides of the type $MN=C=NR$, where $M = \text{metal}$; $R = \text{alkyl or aryl}$</i>	1006
5.28.2	METALLOID DERIVATIVES, $R^1-M=C=N-R^2$ ($M = \text{Si, Sn}$)	1006
5.28.3	PHOSPHORUS, ARSENIC, ANTIMONY, AND BISMUTH FUNCTIONS ($RN=C=PR_3$)	1007
5.28.4	METAL DERIVATIVES ($R^1-M=C=N-R^2$)	1007

5.28.1 FUNCTIONS BASED ON NITROGEN: CARBODIIMIDES ($RN=C=NR$)

5.28.1.1 Introduction

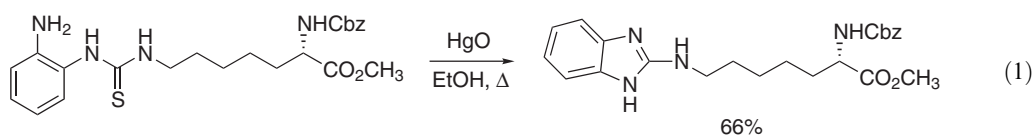
The synthesis of both symmetrical and unsymmetrical carbodiimides has continued to attract significant synthetic interest given the importance of these compounds as precursors for the synthesis of heterocyclic ring systems. This chapter reviews developments in the area since [<1995COFGT\(5\)1061>](#) paying particular attention to new applications of well-established methodology. Recent work in this area has centered on the development of methodology for the transformation of polymer-supported materials for use in combinatorial and high-throughput synthesis. New synthetic methods have also been developed, in particular, the metal-mediated heterocumulene metathesis processes are particularly noteworthy, as are approaches which avoid the use of the environmentally damaging and highly toxic reagents that have traditionally been used. Finally, the use of silylcarbodiimides as precursors for the synthesis of ceramic materials is an increasingly popular approach.

5.28.1.2 Unsymmetrical Carbodiimides ($R^1N=C=NR^2$)

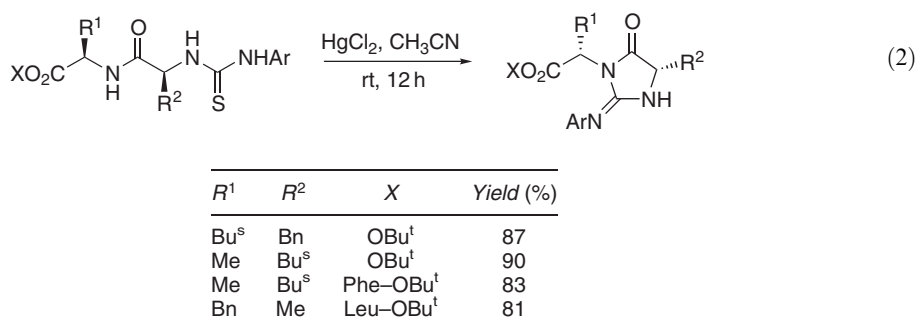
In recent years the synthesis of unsymmetrical carbodiimides has most commonly been achieved starting from ureas or thioureas [<1995COFGT\(5\)1061>](#). In particular, there has been considerable interest in the development of reagents to replace the toxic phosgene and mercury(II) oxide commonly used with ureas and thioureas, respectively. In addition, there have been significant developments in the use of polymer-supported ureas that have required a reinvestigation of this important transformation.

5.28.1.2.1 Via metal salts

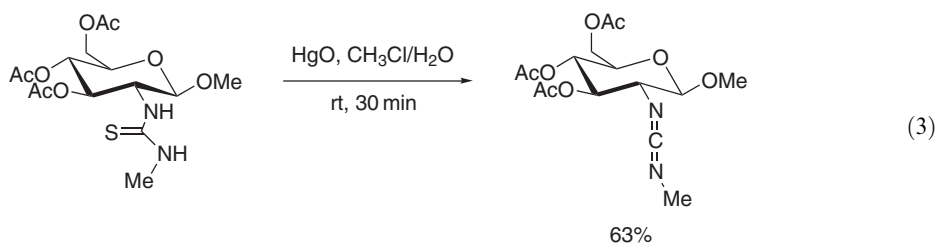
The generation of carbodiimides from thioureas using metal salts continues to be used despite the toxicity and environmental impact of these materials. Their use in solid-phase synthesis, however, is not applicable due to the formation of the insoluble mercury(II) sulfide by-product. When used in solution-phase synthesis, particularly for the synthesis of the guanidine functional group, the intermediate carbodiimide is not isolated but simply reacted in the presence of an amine. The use of mercury(II) chloride in this reaction sequence has been reviewed [<1997T5291>](#). Recent studies have extended the use of mercury salts to consider the cyclodesulfurization of thioureas derived from amino acids without epimerization of the chiral center ([Equation \(1\)](#)) [<1999TL1103>](#).



A limited study showed that the treatment of thioureas derived from di- and tripeptides with mercury(II) chloride is an effective method for the generation of the corresponding carbodiimides. The carbodiimides were not isolated but instead underwent cyclization to generate iminohydantoins in good-to-excellent yields ([Equation \(2\)](#)) [<2003OL1201>](#).

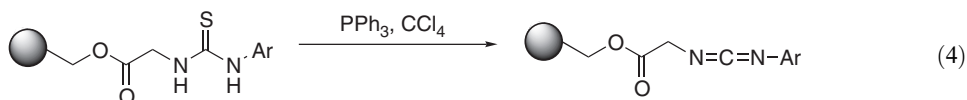


Mercury(II) oxide has been used to desulfurize the readily accessible *N*-methyl-*N'*-glycosylthiourea and *N,N'*-bis(glycosyl)thiourea derivatives into the corresponding carbodiimides in chloroform/water at room temperature in good yields ([Equation \(3\)](#)) [<2002CAR1171>](#).



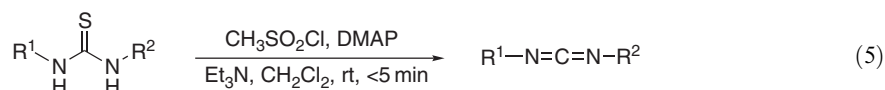
5.28.1.2.2 Via phosphorus reagents

The use of phosphorus reagents such as triphenylphosphine–carbon tetrachloride–triethylamine, bromotriphenylphosphonium bromide (PPh_3Br_2)–triethylamine and phosphorus pentachloride for the dehydration of ureas or the desulfurization of thioureas has been long established. Recently the application of these reagents to the synthesis of polymer-supported carbodiimides has revealed some interesting anomalies. In particular, it was reported that while the triphenylphosphine–carbon tetrachloride–triethylamine reagent combination does not produce the carbodiimide product on reaction with thioureas supported on the Wang resin <2000TL6989>, the carbodiimide is produced when triethylamine is excluded (Equation (4)) <2002T1739>.



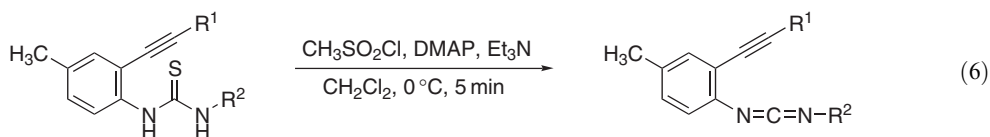
5.28.1.2.3 Via acid chlorides and related reagents

Thioureas are rapidly and efficiently desulfurized by a combination of methanesulfonyl chloride and triethylamine in the presence of a catalytic quantity of 4-dimethylaminopyridine at room temperature (Equation (5)) <1995SC43>. Using this approach, it was possible to isolate phenylmethylcarbodiimide in good yield, a compound that has been reported to be prone to polymerization <1981S373>.



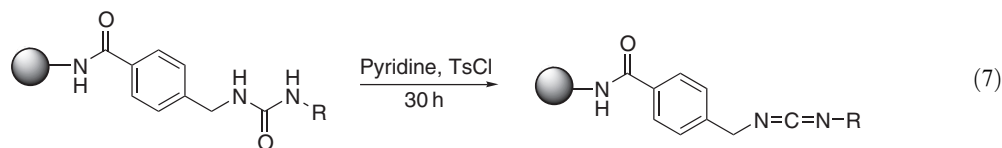
Ar	R ¹	Yield (%)
Ph	Me	91
Ph	Pr ⁱ	97
Ph	PhCH ₂ CH ₂	95
Ph	Ph	95
Ph	2-furyl	85
	Pr ⁱ	100
	Bu ⁱ	100

This approach has also been used for the first synthesis of a unique series of enyne-carbodiimides, which are isolated in good overall yields (Equation (6)) <1998AG(E)2371>. Additional examples of this class of compounds have been generated using an aza-Wittig approach (see Section 5.28.1.2.4).

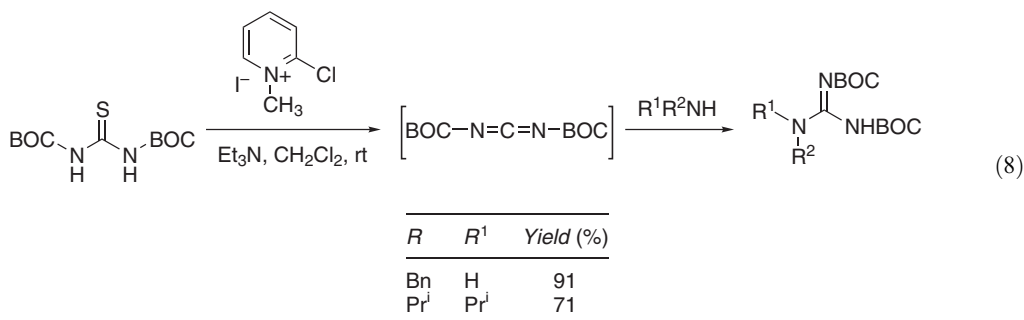


R ¹	R ²	Yield (%)
Ph	Ph	71
TMS	Ph	91
Ph	2,6-Me ₂ C ₆ H ₃	86

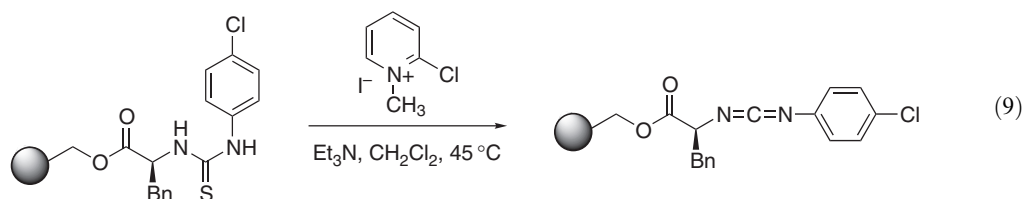
Treatment of ureas supported on the Rink amide resin with sulfonyl chlorides has been studied as an effective approach to the generation of polymer-supported carbodiimides [<2002JCC167>](#). Optimum conditions involved using a large excess of toluenesulfonyl chloride (9 equiv.) in pyridine over extended reaction times (Equation (7)).



The continuing efforts to replace the mercury(II) salts commonly used in thiourea desulfurizations have led to the introduction of 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) as a useful alternative. The range of this reagent has been extended to include the *in situ* formation of *N,N*-bis(*t*-butoxycarbonyl)carbodiimide from *N,N*-bis(*t*-butoxycarbonyl)thiourea. The carbodiimide was not isolated, but instead reacted to generate the corresponding guanidine derivative (Equation (8)) [<1997JOC1540>](#).

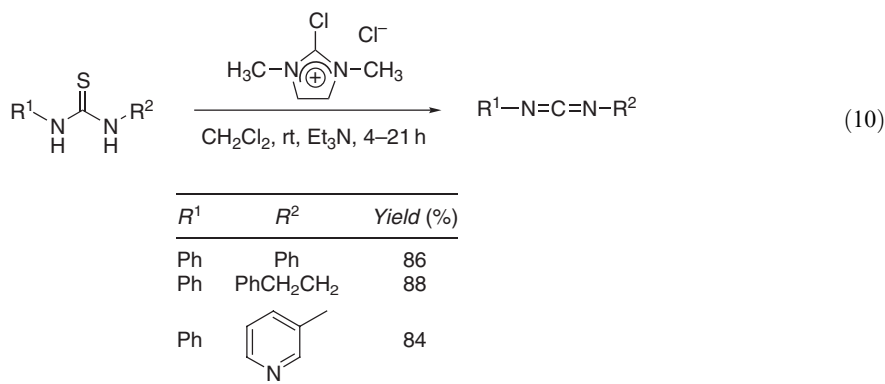


The Mukaiyama reagent has also found use in the synthesis of polymer-supported carbodiimides [<2000TL6989, 2003JOC1611>](#), again used directly in the synthesis of substituted guanidines and 2-aminoimidazolinones (Equation (9)).

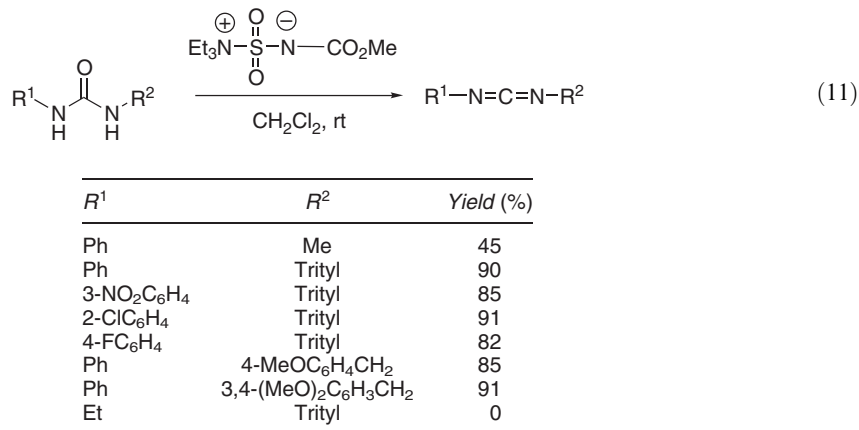


An extensive study of the use of the Mukaiyama reagent for the synthesis of a library of guanidine-based compounds has displayed the generality of this reagent in both solid-phase and conventional solution-phase synthesis of carbodiimides [<2000JCC276>](#).

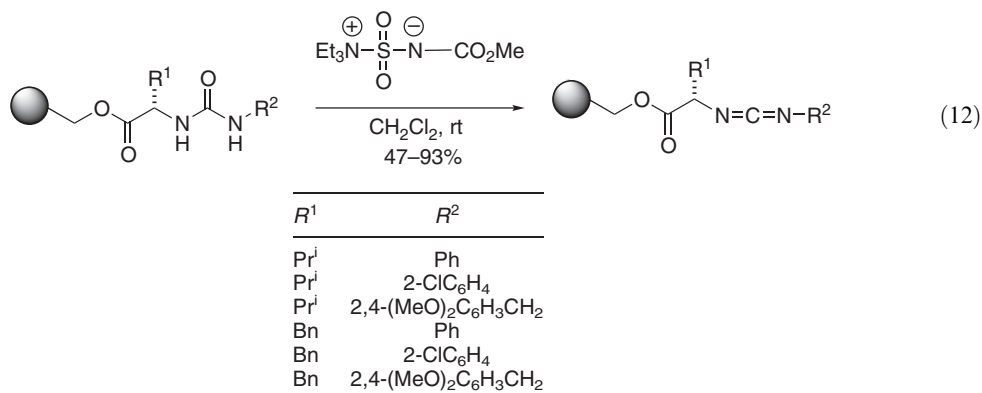
The chloroamidinium reagent 2-chloro-1,3-dimethylimidazolinium chloride has recently been described as an efficient reagent for the desulfurization of thioureas containing aromatic substituents to give carbodiimides. The use of an aliphatic thiourea gave poor conversions to the carbodiimide product (Equation (10)) [<1999JOC6984>](#).



The commercially available (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt (Burgess reagent), has been applied as a dehydrating reagent for the synthesis of *N*-protected carbodiimides from ureas <1997TL6799>. This reagent is better known for the related conversion of primary amides into nitriles under mild conditions <1988TL2155> and is a mild, nonbasic reagent compatible with various functional groups. The procedure is extremely simple utilizing an excess of the dehydrating reagent in dichloromethane (Equation (11)). Minimal purification of the product is required since the by-products of the reaction are either water soluble or volatile.



Recently, the scope of this reaction was further extended to include the reactions of a wide range of ureas derived from optically pure amino acids supported on the Merrifield resin <2002TL6857>. More established procedures using either *p*-toluenesulfonyl chloride–ethyldiisopropylamine, or trifluoroacetic acid–triethylamine gave incomplete conversions of the ureas into carbodiimides. It was finally established that the conversion could be effectively achieved using either carbon tetrabromide–triphenylphosphine or the Burgess reagent. The procedure using the Burgess reagent is the preferred route as it avoids the formation of the triphenylphosphine oxide by-product and gives the product in high purity. The carbodiimide product was not isolated, but underwent reaction with a range of secondary amines to produce 4*H*-imidazolones in moderate-to-excellent yields (47–93%) (Equation (12)).

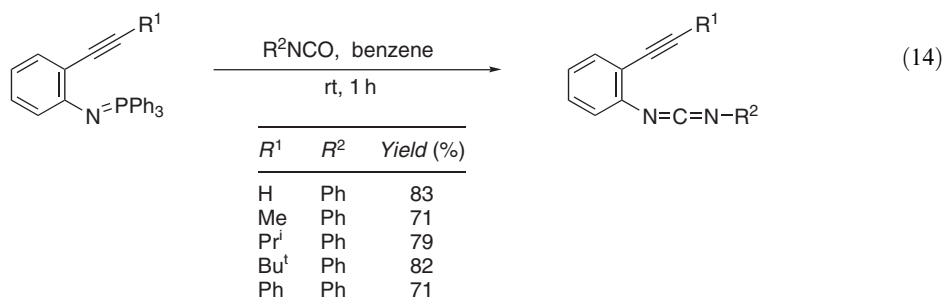


5.28.1.2.4 Via isocyanates and isothiocyanates

The application of aza-Wittig chemistry to isothiocyanates is becoming an increasingly popular route for the synthesis of unsymmetrical carbodiimides used in the construction of heterocyclic compounds <2003SL714, 1997JOC4085, 2001JOC6576, 1997T4521>. The iminophosphorane intermediate is easily prepared either from the amine using dibromotriphenylphosphorane, or through a Staudinger reaction between an azide and a trivalent phosphorus reagent (Equation (13)).

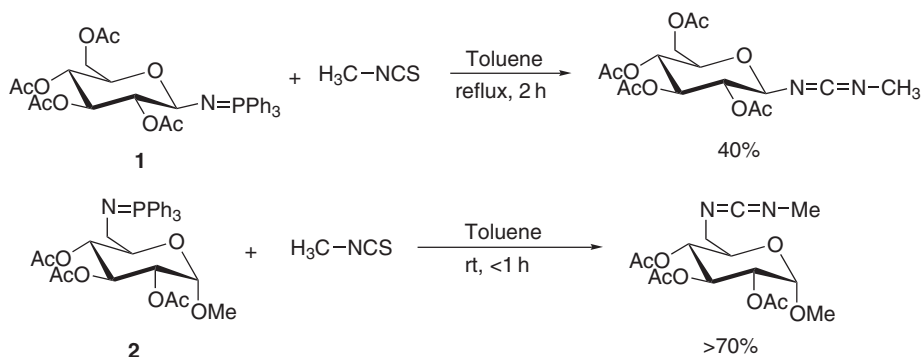


This approach has been used extensively for the synthesis of a number of examples of the enyne-carbodiimides (Equation (14)) <1999JOC925, 2000JOC7977, 2002JMC3497, 2002JOC5412>.



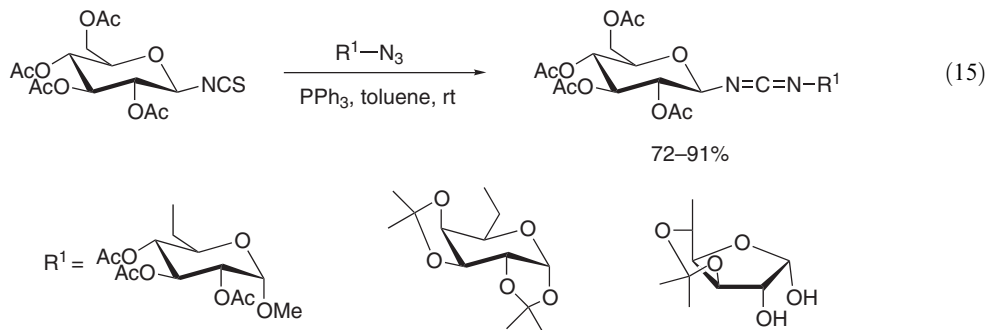
The application of this protocol for the synthesis of carbodiimide-linked pseudooligosaccharides has also attracted much attention, since they are useful synthetic intermediates for the generation of glycomimetics containing phosphodiester surrogates. This pathway is highly attractive as the reaction takes place under essentially neutral conditions and so is compatible with all the commonly used hydroxyl-protecting group strategies used in carbohydrate chemistry.

It is important to note that for the synthesis of unsymmetrical sugar carbodiimides, two regioisomeric synthetic pathways exist and the reactivity of the coupling components can be significantly different. The reaction of glycosyl phosphinimine **1** with methyl isothiocyanate proceeds only slowly at room temperature, and appreciable yields are only obtained in refluxing toluene over extended periods of time. In contrast the analogous route, in which the phosphinimine function resides away from the anomeric position **2**, proceeds efficiently at room temperature and is complete within 1 h (Scheme 1) <1997TL4161>.

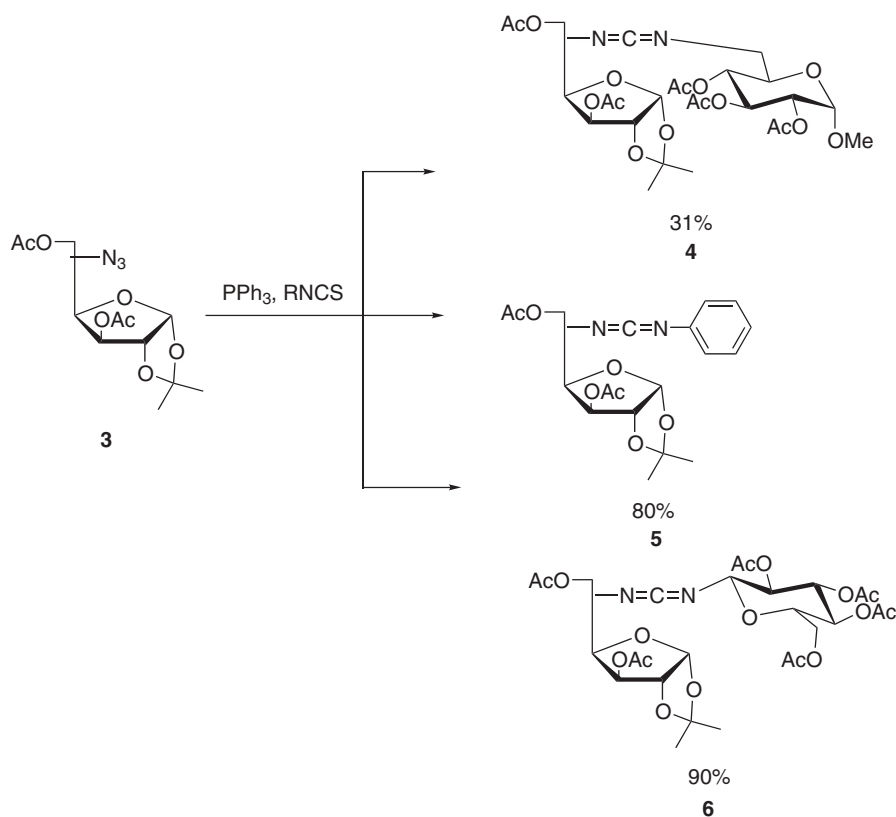


Scheme 1

It is thought that this difference in reactivity can be ascribed to the particular electronic properties of the anomeric position of carbohydrates resulting in the stabilization of the phosphoimine and a subsequent reduction in nucleophilicity. A similar reactivity trend is observed for the reaction of glycosyl isothiocyanates with sugar azides, which proceeds rapidly to give the carbodiimide products in high yield (Equation (15)) <1997CAR261>.

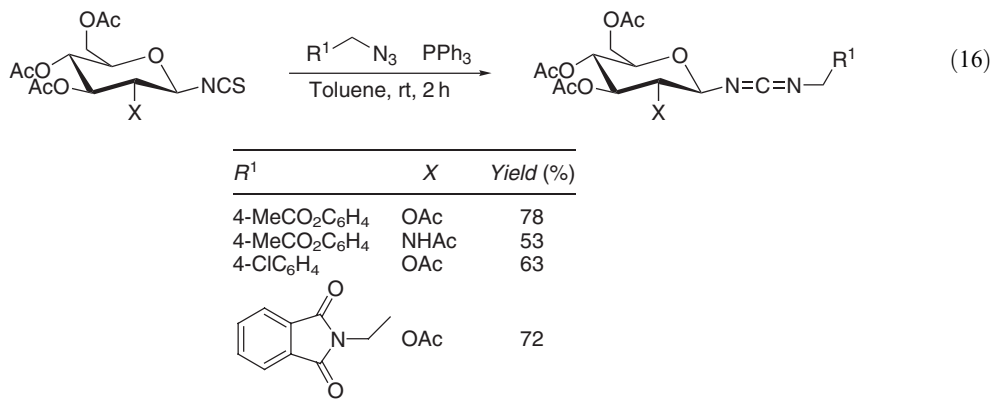


A similar approach using the per-*O*-protected azide **3** furnished the sugar carbodiimide adducts **4–6** (Scheme 2). The yield of these reactions was found to vary depending on whether the isothiocyanate bore an electron-withdrawing or electron-donating substituent <2001JOC7604, 2002CC848>.

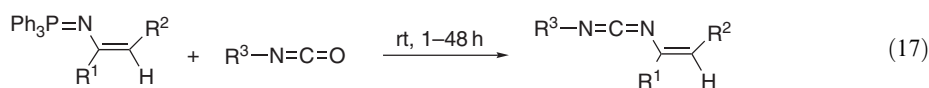


Scheme 2

The versatility of this approach has been further demonstrated by the synthesis of a series of glycosyl carbodiimides, which are useful precursors for the synthesis of guanidinyloglycoside natural products (Equation (16)) <2001JOC8243>.

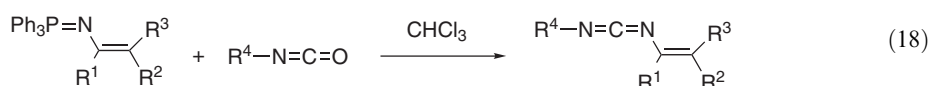


Aza-Wittig chemistry has also found application in the synthesis of a series of stable unsymmetrical conjugated carbodiimides (Equation (17)) <1998JCS(P1)3065>.



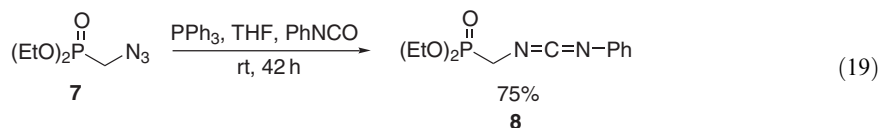
R^1	R^2	R^3	Yield (%)
Ph	Ph	Ph	80
Ph	4-MeC ₆ H ₄	Ph	97
Ph	4-MeOC ₆ H ₄	Ph	70
Ph	4-ClC ₆ H ₄	Ph	75
<i>o</i> -C ₆ H ₁₁	Ph	Ph	86
Me	Ph	Ph	51
Ph	Ph	4-MeC ₆ H ₄	90

A similar approach has been applied for the synthesis in high yields of a series of related unsymmetrical carbodiimides derived from β -amino esters (Equation (18)) <2001H1641>. Reaction of unsubstituted phosphazenes ($R^1 = \text{H}$) with phenyl isocyanate produced no carbodiimide product. However, reaction with ethyl isocyanate produced a diazetidine species produced by *in situ* dimerization of the initially produced carbodiimide.

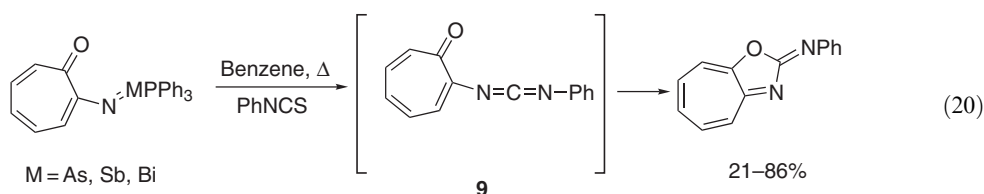


R^1	R^2	R^3	R^4	Yield (%)
Me	CO ₂ Me	H	Et	78
Me	CO ₂ Me	H	Pr ⁿ	67
Me	CO ₂ Me	H	Ph	80

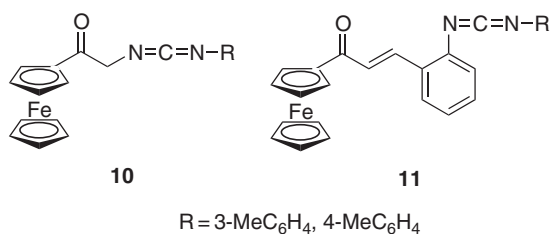
Reaction of the unstable phosphazene, generated *in situ* by the Staudinger reaction of diethyl azidomethylphosphonate **7** and triphenylphosphine, with phenyl isocyanate at room temperature leads to the production of *N*-phosphorylmethylcarbodiimide **8** in good yield (Equation (19)) <2003T2617>.



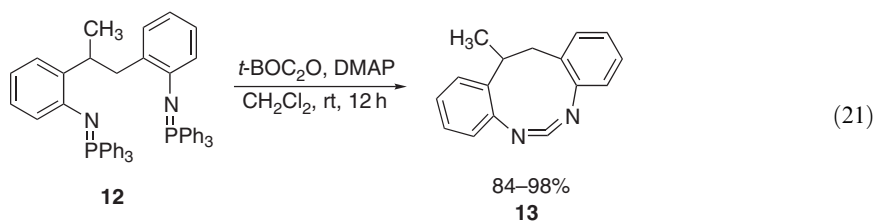
Iminopnictoranes of the general structure $\text{RN}=\text{MPh}_3$ (where R = tropon-2-yl; M = As, Sb, and Bi) have been shown to undergo efficient aza-Wittig reaction with phenyl isothiocyanate to generate the carbodiimide **9**, which was not isolated but cyclized under the reaction conditions (Equation (20)) <2001JCS(P1)1901>.



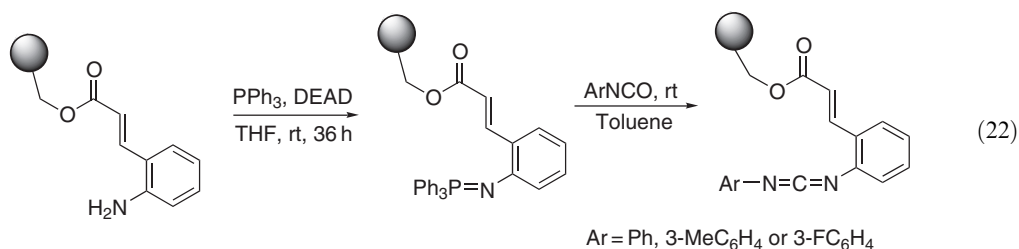
The novel ferrocene-containing carbodiimides **10** and **11**, generated from the corresponding azides, have been reported as intermediates in the synthesis of ferrocenyl oxazoles <1999T14701>.



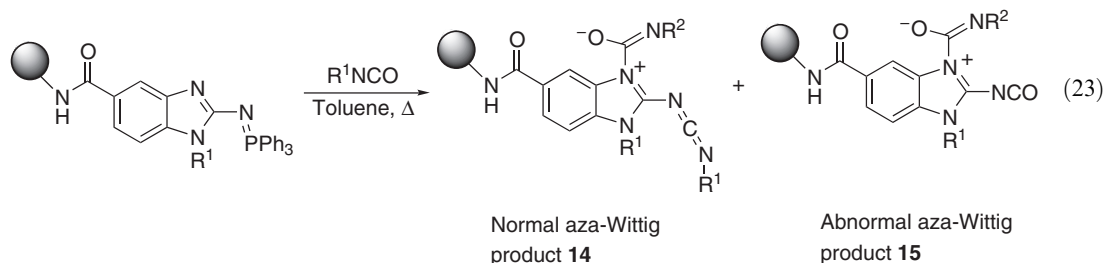
The bis(iminophosphorane) **12** undergoes conversion into the macrocyclic carbodiimide **13** using either a combination of 2 equiv. of *t*-BOC anhydride with an equivalent of 4-dimethylaminopyridine in dichloromethane at room temperature, or by reaction with carbon dioxide in a sealed tube in excellent yields (Equation (21)) <1996JOC4289>.



The synthesis of polymer-supported carbodiimides as intermediates in the synthesis of guanidines and nitrogen-containing heterocycles has been described using aza-Wittig chemistry <1997TL3377>. In particular, a combination of DEAD and triphenylphosphine is reported to give a facile and efficient conversion under mild, neutral conditions of aryl amines into aryl iminophosphoranes, which undergo reaction with aryl isocyanates under standard conditions (Equation (22)) <1997TL8651>.



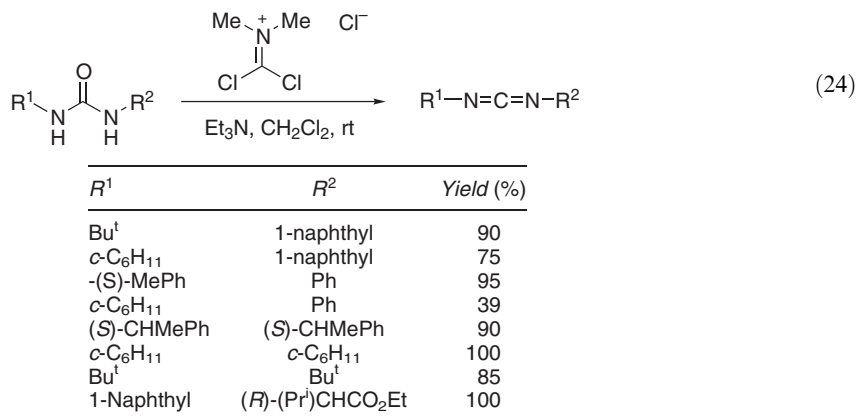
Interestingly, it has been shown that in some cases the product of reaction of polymer-supported iminophosphoranes with isocyanates is dependent on the nature of the isocyanate and the reaction temperature (Equation (23)) <2003TL3705>. Alkyl isocyanates reacted to give the expected carbodiimide products such as **14**; however, reaction with aryl isocyanates gave mixtures of carbodiimides **14** and the isocyanate **15**. These products resulted from the expected aza-Wittig reaction, in addition to products derived from an abnormal aza-Wittig reaction that does not proceed through the expected carbodiimide. Instead, the initially formed betaine intermediate decomposes by loss of triphenylphosphinimide to generate the isocyanate. The product distribution of the reaction could be shifted in favor of the carbodiimide by reducing the reaction temperature. Neither the isocyanate nor the carbodiimide were isolated and underwent intramolecular heterocyclization under the reaction conditions.



<i>R</i> ¹	<i>R</i> ²	Selectivity (%)	
		14	15
3-Methoxypropyl	Et	100	0
3-Methoxypropyl	Ph	52	48
Pr ⁱ	Ph	55	45
Pr ⁱ	4-NO ₂ C ₆ H ₄	5	95

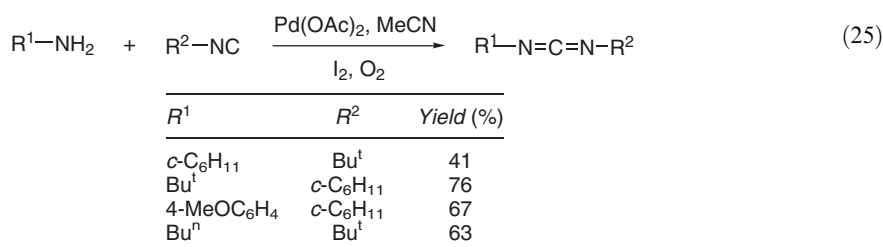
5.28.1.2.5 Via imidoyl dichlorides

Commercially available dimethylphosgeniminium chloride has been introduced as a dehydrating agent to effect the dehydration of ureas to carbodiimides in the presence of triethylamine [<1996TL7047>](#). The development of conditions that utilize more benign reagents is highly desirable and avoids the use of toxic reagents such as phosgene. The reaction produces the corresponding carbodiimides in excellent yields under mild reaction conditions with minimal purification of the product required ([Equation \(24\)](#)).

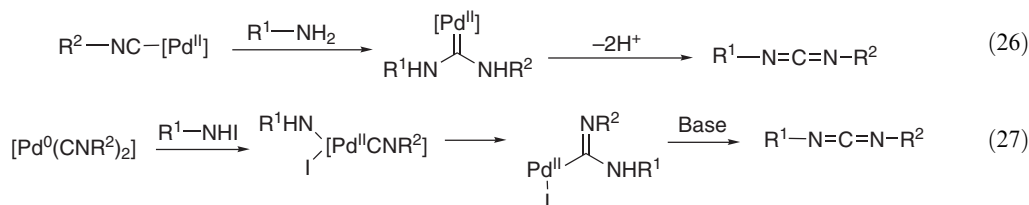


5.28.1.2.6 Via isonitrile reagents

The reaction of isonitriles with an excess of an amine in the presence of catalytic quantities of iodine and palladium acetate in an oxygen atmosphere provides carbodiimides in good yields ([Equation \(25\)](#)) [<1997CC347>](#).

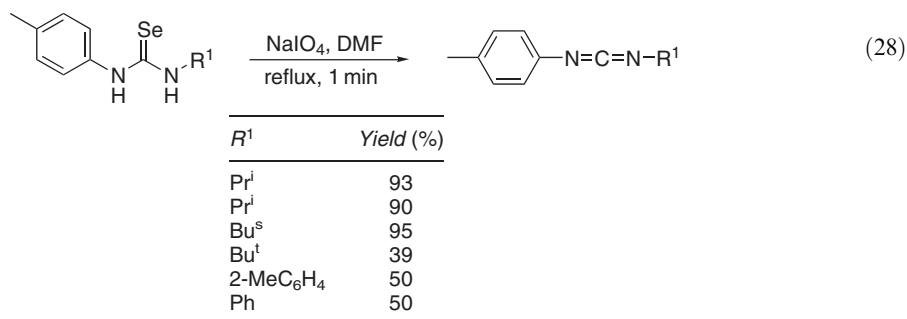


It is proposed that this reaction proceeds either by oxidation of a palladium-carbene complex ([Equation \(26\)](#)) or alternatively by oxidative addition of the iodamine to a palladium(0) isonitrile complex ([Equation \(27\)](#)).

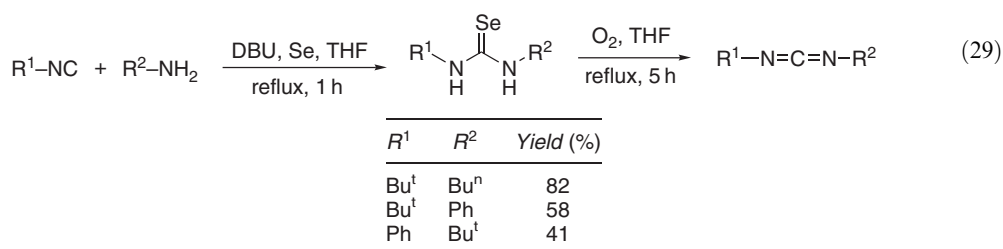


5.28.1.2.7 Via oxidation of selenoureas

Recently, the synthesis of unsymmetrical carbodiimides has been achieved by oxidation of the corresponding selenoureas [<1999JOC6473>](#). The use of selenoureas in place of thioureas is attractive given their increased reactivity that allows somewhat milder reaction conditions to be employed. The selenoureas are themselves generated in a one-pot procedure via the selenocyanates. The choice of oxidant is critical in determining the products of the reaction, with sodium periodate in dimethyl formamide giving the highest yield of the desired carbodiimide ([Equation \(28\)](#)). Other common oxidizing agents such as potassium permanganate, sodium perchlorate, hydrogen peroxide, and sodium chromate gave none of the carbodiimide product.



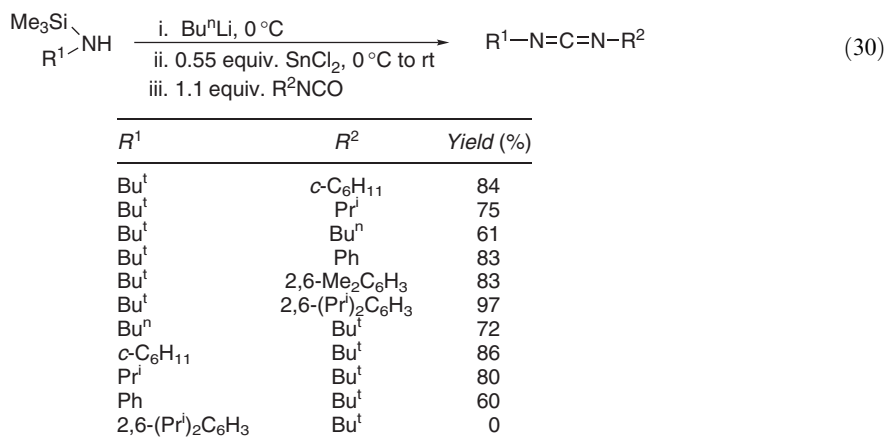
Subsequent studies have shown that molecular oxygen in the presence of an excess of DBU is a sufficiently strong oxidant to achieve the desired transformation to the carbodiimide. The choice of base is crucial, with no formation of the carbodiimide observed when triethylamine or *N*-methylpyrrolidine were employed as the basic component. The reaction sequence was extended to provide a one-pot process starting from the isocyanide (Equation (29)) <1999SL75>.



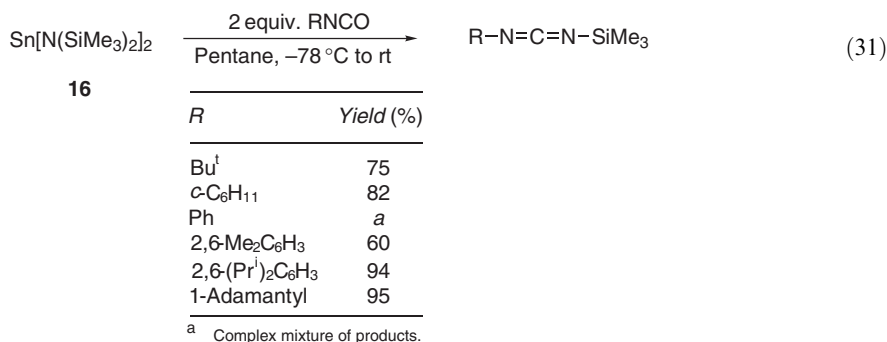
The reaction is envisaged to proceed by deprotonation and dimerization of the selenourea to generate a diselenide that is deprotonated to generate the carbodiimide product.

5.28.1.2.8 Via metathesis

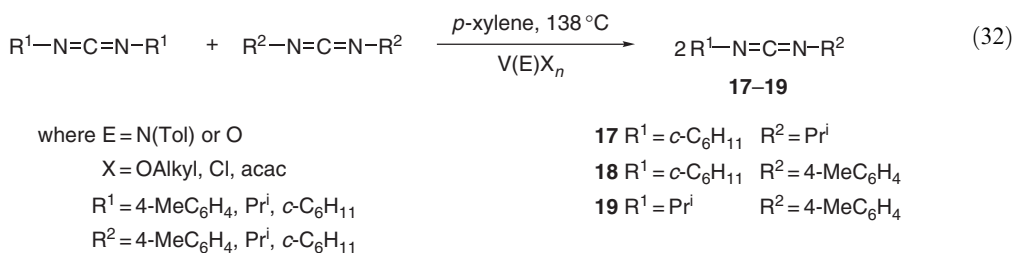
A new development in the synthesis of carbodiimides has been the introduction of metal-mediated heterocumulene metathesis processes. Although it has been known that group 5 and 6 imido complexes can catalyze the cross-metathesis of carbodiimides, it is only recently that useful synthetic protocols have been developed. The reaction of isocyanates with divalent tin(II) bisamides has been shown to proceed efficiently to give carbodiimide products in good yield provided that the bisamide does not complex strongly to metal salts (Equation (30)) <1998JACS5585>. The synthetic utility and scope of this procedure is greatly aided by the *in situ* generation of the tin(II) bisamides, so enabling the transformation to be carried out in a one-pot procedure and allowing a wide range of bisamides to be synthesized and used.



Additionally, a series of unsymmetrical silylated carbodiimides was synthesized by the reaction of commercially available bis[bis(trimethylsilyl)amino]tin(II) **16** with isocyanates at low temperatures (Equation (31)) <1998JACS5585>.

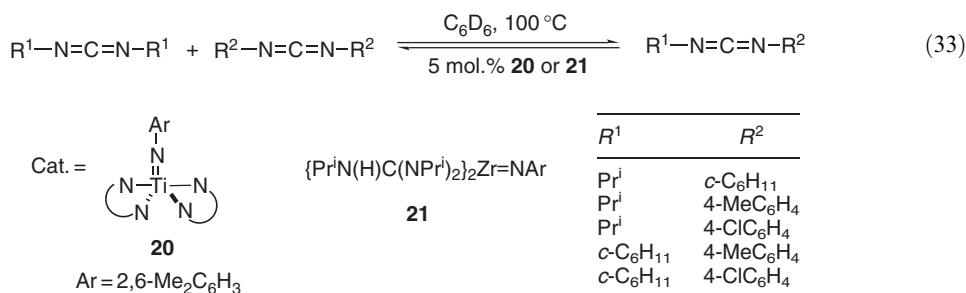


Catalytic quantities of vanadium oxo and imido complexes have been used as catalysts for the metathesis of *N,N'*-dialkylcarbodiimides and *N,N'*-diarylcarbodiimides in *p*-xylene (Equation (32)) <1999JOM200>.

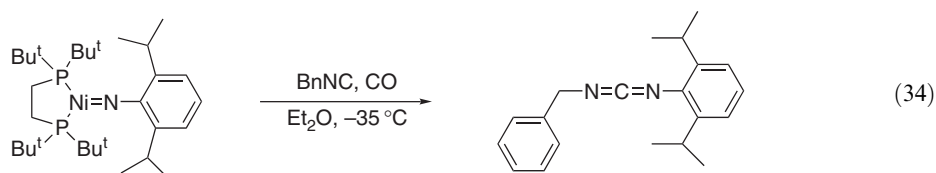


Catalyst	Catalyst Mol.%	Carbodiimide	Yield (%)
V(NTol)(OBu ^t) ₃	5	17	32
V(NTol)Cl ₃	4	17	63
V(O)(OBu ^t) ₃	5	17	44
V(O)(OPr ⁱ) ₃	7	17	61
V(O)(acac) ₂	5	17	69
V(NTol)(OBu ^t) ₃	4	18	70
V(NTol)Cl ₃	5	18	65
V(O)(OBu ^t) ₃	4	18	60
V(O)(OPr ⁱ) ₃	5	18	60
V(O)(acac) ₂	6	18	50
V(NTol)(OBu ^t) ₃	3	19	61
V(NTol)Cl ₃	5	19	50
V(O)(OBu ^t) ₃	6	19	41
V(O)(OPr ⁱ) ₃	5	19	41
V(O)(acac) ₂	4	19	49

Subsequent studies have reported the successful metathesis reaction of alkylcarbodiimides catalyzed by group 4 and 5 imido complexes such as **20** and **21** (Equation (33)) <2003CC2612>. It was noted that, in addition to the expected unsymmetrical carbodiimides, products derived from the exchange of carbodiimides with the amido ligand of the catalyst are also observed. No cross-metathesis was observed in the reaction of an alkyl- and arylcarbodiimide under identical conditions with **20**; however, catalyst **21** is competent for metathesis of all combinations of aryl- and alkylcarbodiimides.

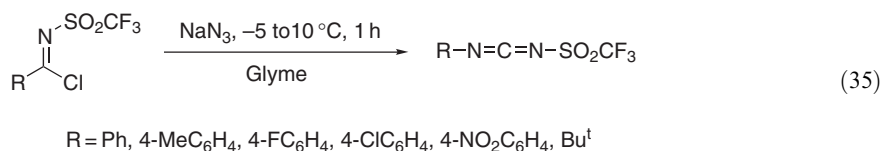


Carbodiimides have also been reported as products in the metathesis reactions of imidozirconocene catalysts with heterocumulenes <2000OM4795, 2001OM1792>, in the reaction of iridium guanidinate and ureylene complexes with heterocumulenes <2002JACS9010>, and in carbodiimide cross-metathesis reactions catalyzed by iminophosphoranes of the type $\text{Cl}_3\text{P}=\text{NR}$ in a process related to the Wittig reaction <2000CC1375, 2002JACS10698, 2003IC3438>. Carbodiimides are also formed by insertion of carbon monoxide into complexes formed between nickel(II) imido catalysts and isocyanides (Equation (34)) <2002CC1840>.

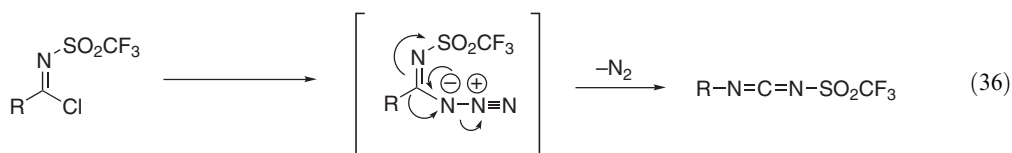


5.28.1.2.9 Via rearrangement

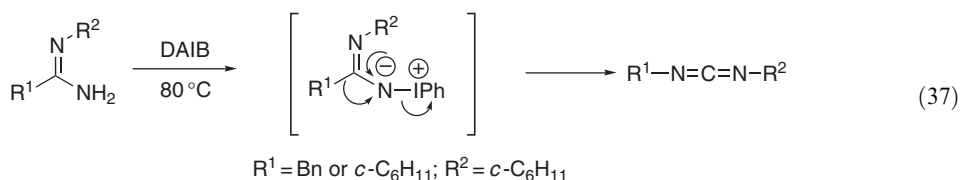
The Curtius rearrangement of tetrazoles and related heterocyclic ring systems has long been recognized as a potential route to carbodiimides, and a number of highly reactive and unstable carbodiimides have been identified as intermediates in these pathways <2001EJOC2209, 2002JOC8538>. However, these approaches are seldom useful for preparative routes given the harsh reaction conditions frequently employed. Recently, however, it has been demonstrated that imidoyl chlorides bearing an *N*-trifluoromethanesulfonyl substituent undergo reaction with sodium azide to produce carbodiimides instead of the expected tetrazole products (Equation (35)) <2001EJOC1225>.



It is proposed that the carbodiimides are produced by a Curtius rearrangement, with tetrazole ring closure being disfavored due to a reduction in nucleophilicity of the imine nitrogen by the triflate substituent (Equation (36)). The carbodiimides produced, however, are extremely unstable and undergo polymerization on storage or at elevated temperatures.

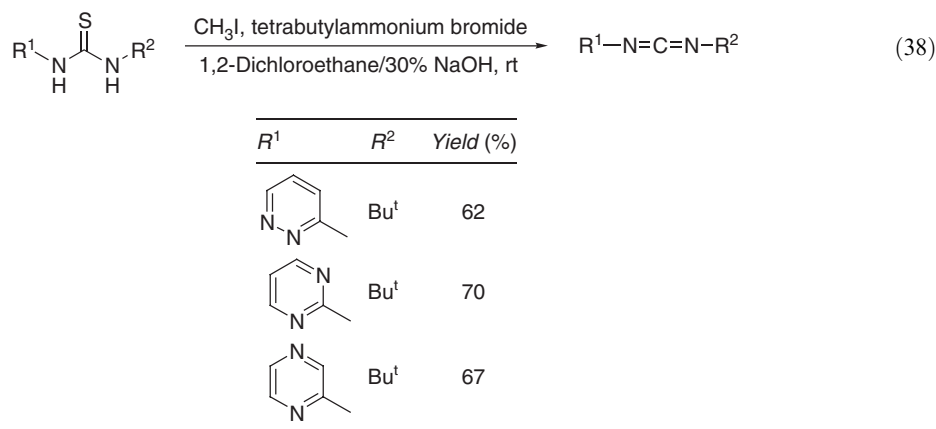


The reaction of amidines with the hypervalent iodine reagent (diacetoxyiodo)benzene (DAIB) has been found to give urea products derived from carbodiimide intermediates <1997JCS(P1)2319>. The reaction is highly dependent on the oxidant used, the reaction temperature, and the structure of the amidine. It is thought that the carbodiimide intermediates are produced by a process related to the Hoffmann rearrangement (Equation (37)).

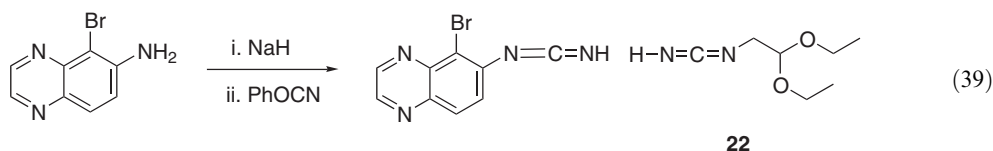


5.28.1.2.10 Miscellaneous

The reaction of thioureas with alkylating agents, such as iodomethane, under phase-transfer conditions in 1,2-dichloroethane:30% aqueous NaOH has been shown to produce carbodiimides in good yields (Equation (38)) <1995JHC13>. Interestingly, carrying out the reaction in a homogeneous solution (aqueous potassium hydroxide:2-propanol:THF) results not in the formation of the carbodiimide but in isolation of the *S*-methyl isothiurea product. Additionally, it was shown that carbodiimide products could also be obtained in the absence of iodomethane, albeit in lower yield owing to the formation of significant amounts of the by-product. The conversion of the thiourea in the absence of iodomethane requires that a solvent exhibiting alkylating properties (dichloromethane or 1,2-dichloroethane) be used, suggesting that an *S*-alkyl isothiurea intermediate is involved.



The reaction of 6-amino-5-bromoquinoxaline with phenyl cyanate under deprotonating conditions has been shown to produce the carbodiimide product (Equation (39)) <1997JMC18>. In a related approach, reaction of aminoacetaldehyde diethyl acetal with cyanogen bromide produced the novel carbodiimide **22** in good yield.

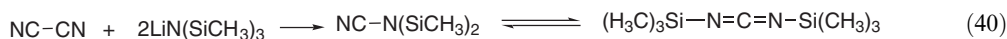


5.28.1.3 Symmetrical Carbodiimides (RN=C=NR)

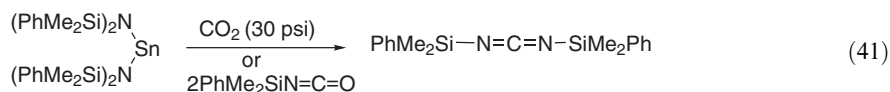
5.28.1.3.1 Carbodiimides of the type $\text{RN}=\text{C}=\text{NR}$, where $\text{R} = \text{SiR}_3^1$

In recent years, there has been increasing interest in the synthesis of main group element carbodiimides as these materials have potential applications as polymerization catalysts as well as for the synthesis of new materials for structural and electronic applications <B-1997MI001>. The methods outlined in the previous Section (5.28.1.2) are applicable for the synthesis of symmetrical carbodiimides by choice of suitable starting materials; however, a limited number of procedures generate symmetrical carbodiimides and are unsuitable for the synthesis of unsymmetrical materials.

N,N'-Bis(trimethylsilyl)carbodiimide is produced in excellent yield by the addition of lithium bis(trimethylsilyl)amide to cyanogen. It is proposed that the lithium amide reacts to produce initially lithium cyanide and cyanobis(trimethylsilyl)amine, which then tautomerizes to the more stable carbodiimide (Equation (40)) <1996JACS330>.



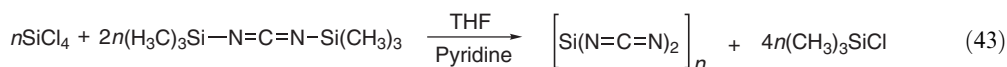
N,N'-Bis(triorganosilyl)carbodiimides are also produced in the reaction of group 14 bisamides of the type $M[N(SiR_3)_2]_2$ (where $M = Ge$ or Sn) with carbon dioxide [<1996JACS10912>](#) or dimethylphenylsilyl isocyanate (Equation (41)) [<1999OM4437>](#).



Organosilicon carbodiimides have attracted considerable attention as precursor compounds for the synthesis of carbide/nitride ceramics [<1997AG\(E\)603>](#). This has led to the synthesis and characterization of a number of polymeric silylcarbodiimides and polymeric dialkylsilylcarbodiimides from dichlorosilanes and cyanamide (Equation (42)) [<B-1996MI725>](#).

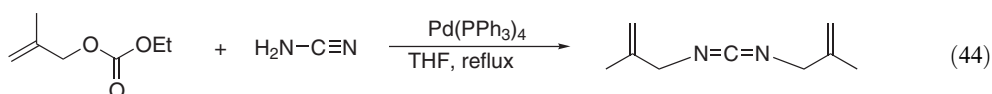


The related silicon carbodiimides have also been synthesized starting from bis(trimethylsilyl)-carbodiimide and tetrachlorosilane (Equation (43)) [<1998CM2964>](#).



5.28.1.3.2 Carbodiimides of the type $RN=C=NR$, where $R = \text{alkyl or aryl}$

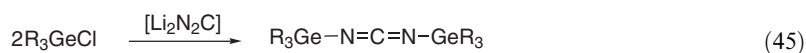
Ethyl 2-methylallyl carbonate undergoes a palladium(0)-catalyzed addition reaction with cyanamide in refluxing THF to produce the symmetrical carbodiimide *N,N'*-bis(2-methylallyl)carbodiimide as a minor product [<1998T14869>](#) (Equation (44)).



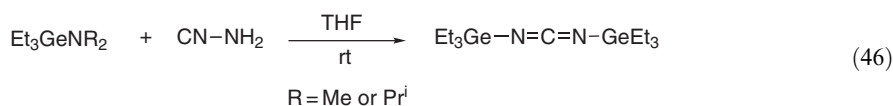
5.28.1.4 Other Related Derivatives

5.28.1.4.1 Carbodiimides of the type $MN=C=NM$, where $M = \text{metal}$

Bis(triethylgermyl)- and bis(trimesitylgermyl)carbodiimides are produced by addition of triethylchlorogermane or trimesitylchlorogermane to the bis(lithium) salt of cyanamide (Equation (45)). Alternatively, the bis(triethylgermyl)carbodiimides are also produced from the reaction of *N*-(triethylgermyl)- or *N*-(triisopropylgermyl)dialkylamines with cyanamide in quantitative yields (Equation (46)) [<1998JOM191>](#). The related bis(dimesitylchlorogermyl)carbodiimide was prepared using similar methodology [<1998OM623>](#).

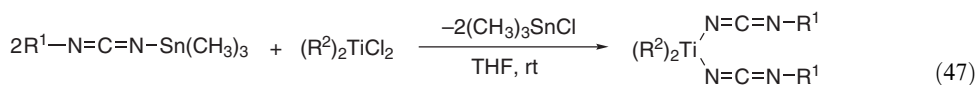


<i>R</i>	Yield (%)
Et	63
2,4,6-Me ₃ C ₆ H ₂	75



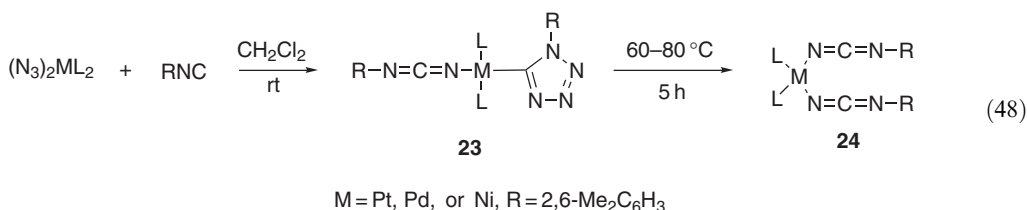
5.28.1.4.2 Carbodiimides of the type $\text{MN}=\text{C}=\text{NR}$, where $\text{M} = \text{metal}$; $\text{R} = \text{alkyl or aryl}$

The generation of metal complexes containing the carbodiimide moiety has attracted interest since they are sterically undemanding and can undergo subsequent functionalization at the terminal nitrogen. A number of carbodiimidotitanium complexes have been synthesized by the selective transmetallation reactions of (silyl)(stannyl)carbodiimides with bis(cyclopentadienyl)titanium dichloride to produce stable complexes in good yields (Equation (47)) <1998OM2926>.



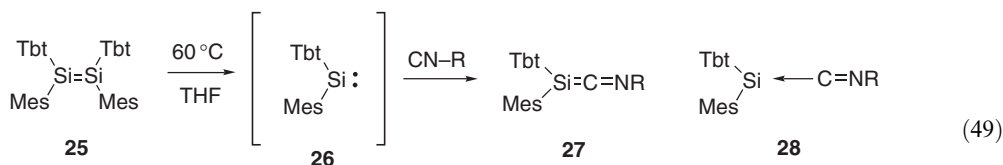
R^1	R^2	Yield (%)
SiPr_3^j	Cp	85
SiBu^jPh_2	Cp	94
SiPr_3^j	Cp^*	45
Ph	Cp	95

A series of carbodiimido metal complexes of the type **23** have been synthesized by the reaction of bis(azido)-group 10 complexes with 2 equiv. of 2,6-dimethylphenyl isocyanide. These materials undergo thermally induced rearrangement to produce the corresponding bis(carbodiimido) complexes **24** at moderate temperatures (Equation (48)) <2000JOM152, 2002JCS(D)144, 2002JCS(D)3611>.



5.28.2 METALLOID DERIVATIVES, $\text{R}^1\text{-M}=\text{C}=\text{N-R}^2$ ($\text{M} = \text{Si, Sn}$)

The sterically hindered disilene **25** undergoes thermal decomposition to produce the corresponding silylene **26**, which reacts with bulky isocyanides to generate unstable silylketenimines **27**. Spectroscopic studies of these compounds have suggested that the product is best described as a Lewis acid-base complex of the type **28** (Equation (49)) <1997JACS1456, 2003CEJ3530>.

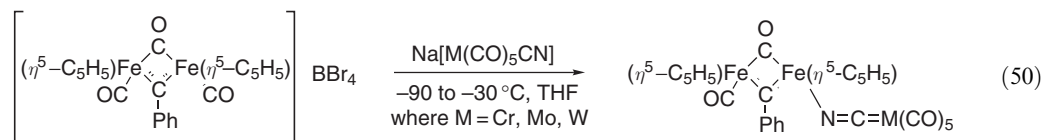


5.28.3 PHOSPHORUS, ARSENIC, ANTIMONY, AND BISMUTH FUNCTIONS ($\text{RN}=\text{C}=\text{PR}_3$)

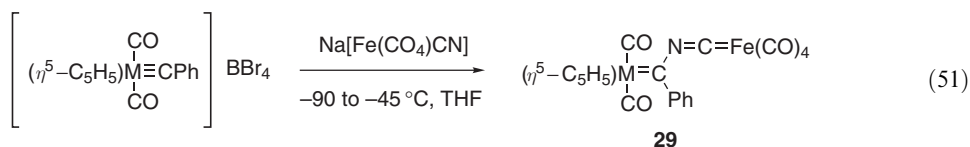
Recent progress in the chemistry of 1,3-phosphazaallenes has been reviewed recently <2000CRV3639>.

5.28.4 METAL DERIVATIVES ($\text{R}^1-\text{M}=\text{C}=\text{N}-\text{R}^2$)

The highly electrophilic cationic carbyne diiron complex, $[\text{Fe}_2(\mu\text{-CO})(\mu\text{-CPh})(\text{CO})_2(\eta\text{-C}_5\text{H}_5)_2]^+$, reacts with anionic carbonyl metal compounds such as $\text{Na}[\text{MCO}_5\text{CN}]$ to produce novel bridged carbyne complexes (Equation (50)) <2003OM1816, 2000OM3784>.



The related carbyne complexes $[\eta^5\text{-C}_5\text{H}_5(\text{CO})_2\text{M}\equiv\text{CC}_6\text{H}_5][\text{BBr}_4]$ ($\text{M} = \text{Mn}$ or Re) react in a similar manner to produce complexes of the type **29** (Equation (51)) <2002CCR109>.



REFERENCES

- 1981S373 C. Palomo, R. Mestres, *Synthesis* **1981**, 373–374.
 1988TL2155 D. A. Claremont, B. T. Phillips, *Tetrahedron Lett.* **1988**, 29, 2155–2158.
 1995COFGT(5)1061 R. Muthyala, Functions with at least one nitrogen and no chalcogens, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 1061–1089.
 1995JHC13 G. Heinisch, B. Matuszczak, G. Purstinger, D. Rakowitz, *J. Hetrocyc. Chem.* **1995**, 32, 13–16.
 1995SC43 J. B. Fell, G. M. Coppola, *Synth Commun.* **1995**, 25, 43–47.
 B-1996MI725 A. Kienzle, K. Wurm, J. Bill, F. Aldinger, R. Riedel, in *Organosilicon Chemistry II—From Molecules to Materials*, N. Auner, J. Weis, Eds., Weinheim, Germany, **1996**, pp. 725–731.
 1996JACS330 C. D. Bryan, A. W. Cordes, J. D. Goddard, R. C. Haddon, R. G. Hicks, C. D. MacKinnon, R. C. Mawhinney, R. T. Oakley, T. T. M. Palstra, A. S. Perel, *J. Am. Chem. Soc.* **1996**, 118, 330–338.
 1996JACS10912 L. R. Sita, J. R. Babcock, R. Xi, *J. Am. Chem. Soc.* **1996**, 118, 10912–10913.
 1996JOC4289 P. Molena, M. Alajarín, P. Sánchez-Andrada, J. S. Carrió, M. Martínez-Ripoll, J. E. Anderson, M. L. Jimeno, J. Elguero, *J. Org. Chem.* **1996**, 61, 4289–4299.
 1996TL7047 T. Schlama, V. Gouverneur, C. Mioskowski, *Tetrahedron Lett.* **1996**, 37, 7047–7048.
 1997AG(E)603 R. Riedel, A. Greiner, G. Miehe, W. Dressler, H. Fues, J. Bill, F. Aldinger, *Angew. Chem., Int. Ed. Eng.* **1997**, 36, 603–606.
 1997CC347 I. Pri-Bar, J. Schwartz, *J. Chem. Soc., Chem. Commun.* **1997**, 347–348.
 1997CAR261 J. M. G. Fernández, C. O. Mellet, V. M. D. Pérez, J. Fuentes, J. Kovács, I. Pintér, *Carbohydr. Res.* **1997**, 304, 261–270.
 1997JACS1456 N. Takeda, H. Suzuki, N. Tokitoh, R. Okazaki, *J. Am. Chem. Soc.* **1997**, 119, 1456–1457.
 1997JCS(P1)2319 C. A. Ramsden, H. L. Rose, *J. Chem. Soc., Perkin. Trans. 1* **1997**, 2319–2327.
 1997JMC18 S. A. Munk, D. A. Harcourt, P. N. Arasasingham, J. A. Burke, A. B. Kharlamb, C. A. Manlapaz, E. U. Padillo, D. Roberts, E. Runde, L. Williams, L. A. Wheeler, M. E. Garst, *J. Med. Chem.* **1997**, 40, 18–23.
 1997JOC1540 Y. F. Yong, J. A. Kowalski, M. A. Lipton, *J. Org. Chem.* **1997**, 62, 1540–1542.
 1997JOC4085 J. M. Chezal, G. Delmas, S. Mavel, H. Elakmaoui, J. Métin, A. Diez, Y. Blache, A. Gueiffier, M. Rubiralta, J. C. Teulade, O. Chavignon, *J. Org. Chem.* **1997**, 62, 4085–4087.
 B-1997MI001 A. W. Weimar, in *Carbide, Nitride and Boride Materials Synthesis and Processing*, Chapman and Hall, **1997**, 735.
 1997T4521 J. Barluenga, M. Ferro, F. Palacios, *Tetrahedron* **1997**, 53, 4521–4530.
 1997T5291 C. Levallet, J. Lerpiniere, S. Y. Ko, *Tetrahedron* **1997**, 53, 5291–5304.
 1997TL3377 D. H. Drewry, S. W. Gerritz, J. A. Linn, *Tetrahedron Lett.* **1997**, 38, 3377–3380.
 1997TL4161 J. M. G. Fernández, C. O. Mellet, V. M. D. Pérez, J. Fuentes, J. Kovács, I. Pintér, *Tetrahedron Lett.* **1997**, 38, 4161–4164.
 1997TL6799 M. R. Barvian, H. D. Hollis Showalter, A. M. Doherty, *Tetrahedron Lett.* **1997**, 38, 6799–6802.

- 1997TL8651 F. Wang, J. R. Hauske, *Tetrahedron Lett.* **1997**, 38, 8651–8654.
- 1998AG(E)2371 M. Schmittl, J. Stefen, B. Engels, C. Lennartz, M. Hanrath, *Angew. Chem., Int. Ed. Eng.* **1998**, 37, 2371–2373.
- 1998CM2964 R. Riedel, E. Kroke, A. Greiner, A. O. Gabriel, L. Ruwisch, J. Nicolich, *Chem. Mater.* **1998**, 10, 2964–2979.
- 1998JACS5585 J. R. Babcock, L. R. Sita, *J. Am. Chem. Soc.* **1998**, 120, 5585–5586.
- 1998JCS(P1)3065 T. Saito, T. Ohkubo, H. Kuboki, M. Maeda, K. Tsuda, T. Karakasa, S. Satsumabayashi, *J. Chem. Soc., Perkin. Trans. 1* **1998**, 3065–3080.
- 1998JOM191 M. Dahrouch, M. Rivière-Baudet, H. Gornitzka, G. Bertrand, *J. Organomet. Chem.* **1998**, 562, 191–195.
- 1998OM623 M. Dahrouch, M. Rivière-Baudet, J. Satgé, M. Mauzac, C. J. Cardin, J. H. Thorpe, *Organometallics* **1998**, 17, 623–629.
- 1998OM2926 G. Veneziani, S. Shimada, M. Tanaka, *Organometallics* **1998**, 17, 2926–2929.
- 1998T14869 S. Cerezo, J. Cortés, M. Moreno-Mañas, R. Plexats, A. Roglans, *Tetrahedron* **1998**, 54, 14869–14884.
- 1999JOC925 C. Shi, Q. Zhang, K. K. Wang, *J. Org. Chem.* **1999**, 64, 925–932.
- 1999JOC6473 M. Koketsu, N. Suzuki, H. Ishihara, *J. Org. Chem.* **1999**, 64, 6473–6475.
- 1999JOC6984 T. Isobe, T. Ishikawa, *J. Org. Chem.* **1999**, 64, 6984–6988.
- 1999JOM200 K. R. Birdwhistell, J. Lanza, J. Pasos, *J. Organomet. Chem.* **1999**, 584, 200–205.
- 1999JOM4437 J. R. Babcock, L. Liable-Sands, A. L. Rheingold, L. R. Sita, *Organometallics* **1999**, 18, 4437–4441.
- 1999SL75 S. Fujiwara, T. Matsuya, H. Maeda, T. Shin-ike, N. Kambe, N. Sonoda, *Synlett* **1999**, 75–76.
- 1999T14701 A. Tarraga, P. Molina, D. Curiel, J. L. López, M. Desamparados Velasco, *Tetrahedron* **1999**, 55, 14701–14718.
- 1999TL1103 J. J. Perkins, A. E. Zartman, R. S. Meissner, *Tetrahedron Lett.* **1999**, 40, 1103–1106.
- 2000CC1375 S. A. Bell, S. J. Geib, T. Y. Meyer, *J. Chem. Soc., Chem. Commun.* **2000**, 1375–1376.
- 2000CRV3639 J. Escudié, H. Ranaivonjatovo, L. Rignon, *Chem. Rev.* **2000**, 100, 3639–3696.
- 2000JCC276 J. Chen, M. Pattarawarapan, A. J. Zhang, K. Burgess, *J. Comb. Chem.* **2000**, 2, 276–281.
- 2000JOC7977 Q. Zhang, C. Shi, H. Zang, K. K. Wang, *J. Org. Chem.* **2000**, 65, 7977–7983.
- 2000JOM152 Y.-J. Kim, Y.-S. Kwak, S.-W. Lee, *J. Organomet. Chem.* **2000**, 603, 152–160.
- 2000OM3784 Y. Liu, R. Wang, J. Sun, J. B. Chen, *Organometallics* **2000**, 19, 3784–3790.
- 2000OM4795 R. L. Zuckermann, R. G. Bergman, *Organometallics* **2000**, 19, 4795–4809.
- 2000TL6989 D. H. Drewry, C. Ghiron, *Tetrahedron Lett.* **2000**, 41, 6989–6992.
- 2001EJOC1225 L. V. Yagupolskii, S. V. Shelyazhenko, I. I. Maletina, V. N. Petrik, E. B. Rusanov, A. N. Chernega, *Eur. J. Org. Chem.* **2001**, 1225–1233.
- 2001EJOC2209 G. I. Yranzo, J. Elguero, R. Flammang, C. Wentrup, *Eur. J. Org. Chem.* **2001**, 2209–2220.
- 2001H1641 F. Palacois, M. Legido, I. Pérez de Heredia, J. M. Ezpeleta, G. Rubiales, *Heterocycles* **2001**, 55, 1641–1651.
- 2001JOC6576 J. M. Chezal, E. Moreau, G. Delmas, A. Gueffier, Y. Blache, G. Grassy, C. Lartigue, O. Chavignon, J. C. Teulade, *J. Org. Chem.* **2001**, 66, 6576–6584.
- 2001JOC7604 M. I. García-Moreno, J. M. Benito, C. O. Mellet, J. M. G. Fernández, *J. Org. Chem.* **2001**, 66, 7604–7614.
- 2001JOC8243 P. Lin, C. L. Lee, M. M. Sim, *J. Org. Chem.* **2001**, 66, 8243–8247.
- 2001JCS(P1)1901 M. Nitta, Y. Mitsumoto, H. Yamamoto, *J. Chem. Soc., Perkin. Trans. 1* **2001**, 1901–1907.
- 2001OM1792 R. L. Zuckerman, R. G. Bergman, *Organometallics* **2001**, 20, 1792–1807.
- 2002CC848 M. I. García-Moreno, P. Díaz-Pérez, C. O. Mellet, J. M. G. Fernández, *J. Chem. Soc., Chem. Commun.* **2002**, 848–849.
- 2002CC1840 D. J. Mindiola, G. L. Hillhouse, *J. Chem. Soc., Chem. Commun.* **2002**, 1840–1841.
- 2002CAR1171 L. Kovács, E. Ösz, Z. Györgydeák, *Carbohydr. Res.* **2002**, 337, 1171–1178.
- 2002CCR109 J. B. Chen, R. Wang, *Coord. Chem. Rev.* **2002**, 231, 109–149.
- 2002JACS9010 A. W. Holland, R. G. Berman, *J. Am. Chem. Soc.* **2002**, 124, 9010–9011.
- 2002JACS10698 S. A. Bell, T. Y. Meyer, S. J. Geib, *J. Am. Chem. Soc.* **2002**, 124, 10698–10705.
- 2002JCC167 T. P. Hopkins, J. M. Dener, A. M. Boldi, *J. Comb. Chem.* **2002**, 4, 167–174.
- 2002JCS(D)144 Y.-J. Kim, Y.-S. Kwak, Y.-S. Joo, S.-W. Lee, *J. Chem. Soc., Dalton Trans.* **2002**, 144–151.
- 2002JCS(D)3611 Y.-J. Kim, Y.-S. Joo, J.-T. Han, W.-S. Han, S.-W. Lee, *J. Chem. Soc., Dalton Trans.* **2002**, 3611–3618.
- 2002JMC3497 T. H. M. Jonkers, S. van Miert, K. Cimanga, C. Bailly, P. Colson, M. De Pauw-Gillet, H. van den Heuvel, M. Claeys, F. Lemièr, E. L. Esmans, J. Rozenski, L. Quirjnen, L. Maes, R. Dommissie, G. L. F. Lemièr, A. Vlietinck, L. Pieters, *J. Med. Chem.* **2002**, 45, 3497–3508.
- 2002JOC5412 X. Lu, J. L. Petersen, K. K. Wang, *J. Org. Chem.* **2002**, 67, 5412–5415.
- 2002JOC8538 C. Addicot, M. W. Wong, C. Wentrup, *J. Org. Chem.* **2000**, 67, 8538–8546.
- 2002T1739 J. P. Kilburn, J. Lau, R. C. F. Jones, *Tetrahedron* **2002**, 58, 1739–1743.
- 2002TL6857 U. E. W. Lange, *Tetrahedron Lett.* **2002**, 43, 6857–6860.
- 2003CC2612 T.-G. Ong, G. P. A. Yap, D. S. Richeson, *J. Chem. Soc., Chem. Commun.* **2003**, 2612–2613.
- 2003IC3438 M. C. Burland, T. Y. Meyer, *Inorg. Chem.* **2003**, 42, 3438–3444.
- 2003JOC1611 J. Li, G. Zhang, Z. Zhang, E. Fan, *J. Org. Chem.* **2003**, 68, 1611–1614.
- 2003CEJ3530 N. Takeda, T. Kajiwar, H. Suzuki, R. Okazaki, N. Tokitoh, *Chem. Eur. J.* **2003**, 9, 3530–3543.
- 2003OL1201 G. Evindar, R. A. Batey, *Org. Lett.* **2003**, 5, 1201–1204.
- 2003OM1816 S. Zhang, Q. Xu, J. B. Chen, *Organometallics* **2003**, 22, 1816–1826.
- 2003SL714 P. Molina, E. Aller, A. Lorenzo, *Synlett* **2003**, 714–716.
- 2003T2617 F. Palacois, A. M. Ochoa de Retana, E. Martínez de Marigorta, M. Rodríguez, J. Pagalday, *Tetrahedron* **2003**, 59, 2617–2623.
- 2003TL3705 C. E. Hoesl, A. Nefzi, R. A. Houghten, *Tetrahedron Lett.* **2003**, 44, 3705–3708.

Biographical sketch

Andy Graham was born in Liverpool. He graduated from the University of Liverpool in 1989, where he also obtained his Ph.D. in 1993 under the direction of Professor Phillip Page and Professor Kevin Park. Following a Royal Society Fellowship at the EHICS Strasbourg, with Professor Guy Solladié, he returned to the UK to complete postdoctoral positions at the University of York with Professor Richard Taylor and at the University of Liverpool with Professor Stan Roberts, before moving to Ireland to take up a lectureship at University College Cork. He moved to the University of Wales Swansea in 2001. His research interests include supercritical fluids as a medium for organic synthesis, the development of novel supported catalysts, cycloaddition and rearrangement reactions in natural product synthesis, and the synthesis of novel biologically active peptidomimetics.

5.29

Functions with Heteroatoms Other Than Chalcogen or Nitrogen ($Y^1=C=Y^2$)

K. AFARINKIA

King's College London, London, UK

5.29.1	FUNCTIONS WITH AT LEAST ONE PHOSPHORUS, ARSENIC, ANTIMONY, OR BISMUTH (AND NO CHALCOGEN OR NITROGEN)	1011
5.29.1.1	Group 15 Functions	1011
5.29.1.1.1	<i>Dicoordinated phosphorus and arsenic functions</i>	1011
5.29.1.1.2	<i>Higher-coordinated phosphorus functions</i>	1012
5.29.1.2	Metalloid Functions	1016
5.29.1.3	Metal Functions	1017
5.29.2	FUNCTIONS WITH AT LEAST ONE METALLOID (AND NO CHALCOGEN OR GROUP 15 ELEMENT FUNCTION)	1018
5.29.2.1	Derivatives with One Metalloid Function	1018
5.29.2.2	Derivatives with Two Metalloid Functions	1018
5.29.3	COMPOUNDS BEARING TWO METAL FUNCTIONS	1019

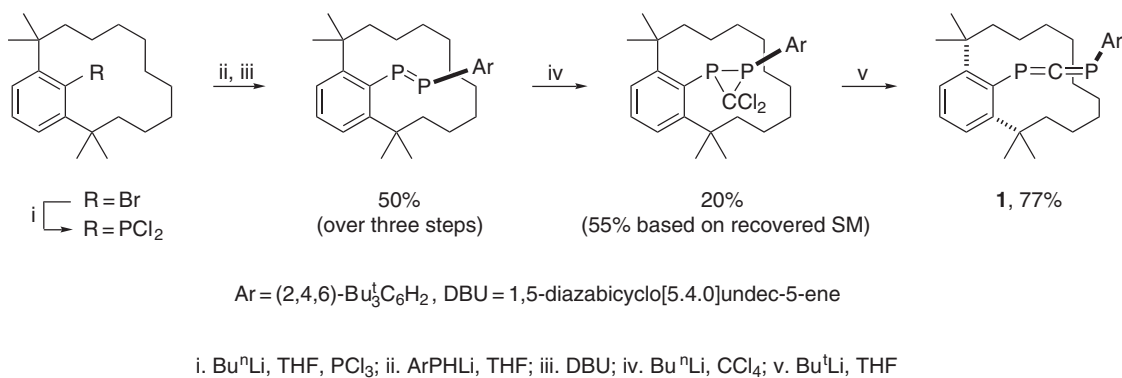
5.29.1 FUNCTIONS WITH AT LEAST ONE PHOSPHORUS, ARSENIC, ANTIMONY, OR BISMUTH (AND NO CHALCOGEN OR NITROGEN)

There has been a small, but significant increase in our knowledge of preparative routes to these functions since COFGT (1995) <[1995COFGT\(5\)1091](#)>. Although few new preparative methods are introduced, a wider range of these functions, with various Y and Y' atoms, has appeared. Elimination remains the most popular route for their synthesis. However, there are now more examples of these functions prepared by alternative routes.

5.29.1.1 Group 15 Functions

5.29.1.1.1 *Dicoordinated phosphorus and arsenic functions*

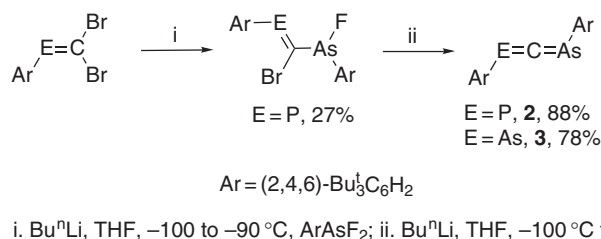
The $P=C=P$ functions, generally referred to as “carbodiphosphoranes” or “phosphaallenes,” are the most common examples in this functional group series. Introduction of bulky substituent groups remains the best means of bestowing kinetic stability to “phosphaallenes” so that they can be isolated and studied. The use of carbene insertion into a $P=P$ bond for the synthesis of these functions has continued to grow <[1993JOM\(453\)77](#), [1992JOM\(436\)169](#), [1993PS\(76\)41](#)>. For



Scheme 1

instance, the metacyclophane-type substituted phosphallaene **1** has been reported (Scheme 1) <2002CC3012>.

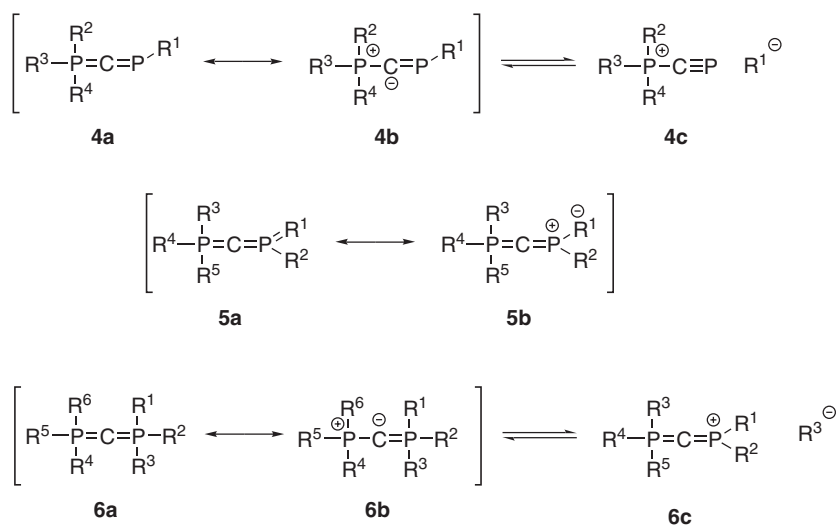
Both arsaphosphaallene **2** <1998OM1631> and diarsaallene **3** <2000JA12880> have been prepared (Scheme 2) and their structures confirmed by X-ray crystallography.



Scheme 2

5.29.1.1.2 Higher-coordinated phosphorus functions

One of the key features of $Y^1=C=Y^2$ functions, when Y^1 or Y^2 can have multiple valency and coordination numbers, is that the molecules can be represented in different resonance forms. This gives rise to much structural diversity in higher-coordinated phosphorus functions. Indeed, phosphallaenes with higher-coordinated phosphorus atoms can be represented by a number of different resonance forms such as **4a** and **4b**, **5a** and **5b**, and **6a** and **6b** (Scheme 3), depending



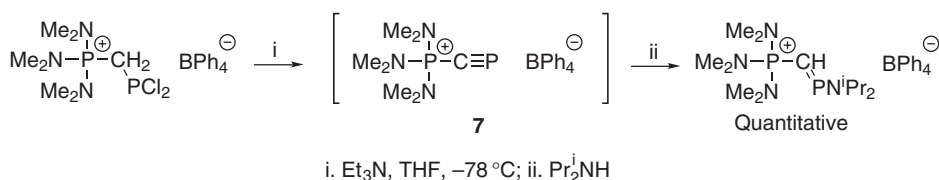
Scheme 3

on the nature and number of substituents. Dissociation to form ionic species from covalent counterparts, for instance **4c** from **4ab** and **6c** from **6ab**, can further diversify the structures of member of this functional group family.

The major advance since <1995COFGT(5)1091> is that mixed valency phosphaaallenes have been prepared and studied. However, there has not been any further example of functions with only carbon attached to phosphorus.

(i) Functions with one tetracoordinated and one monocoordinated phosphorus atom

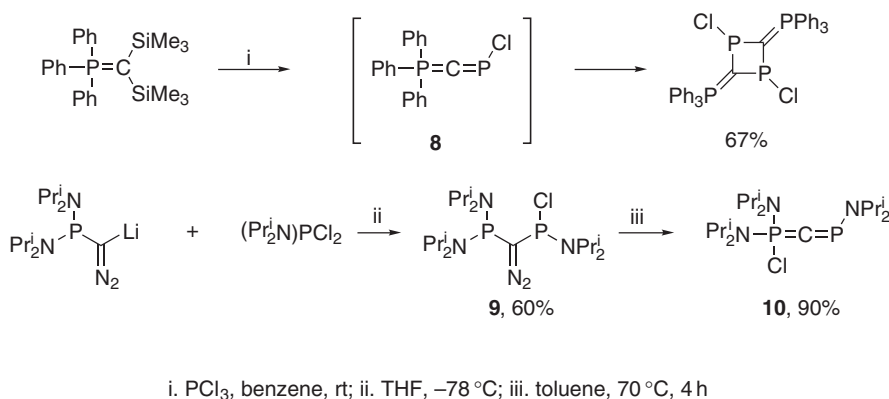
Only a single example is known in the literature. Compound **7** could not be isolated but was characterized spectroscopically in solution at room temperature. Addition of nucleophiles is reported to occur at a phosphorus atom (Scheme 4) <1991CC302>.



Scheme 4

(ii) Functions with one tetracoordinated and one dicoordinated phosphorus atom

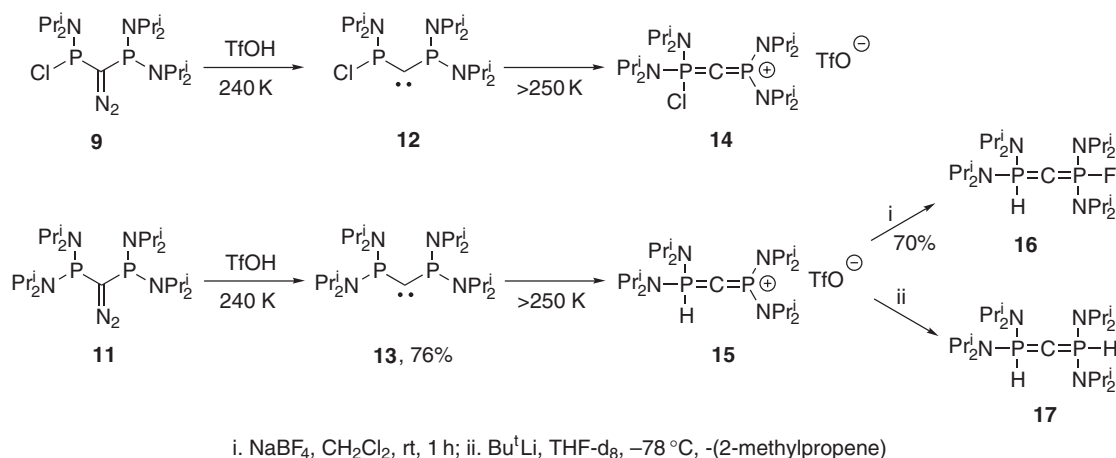
Some reported examples of this function, e.g., **8**, rapidly dimerize to a 1,3-diphosphetane and are not isolable as phosphaaallenes (Scheme 5) <1997CB1519, 1993PS(76)13, 1995AG(E)1853, 1994PS(93/94)321>. However, Bertrand and co-workers <2000AG(E)3319> have reported the preparation of **10** (Scheme 5).



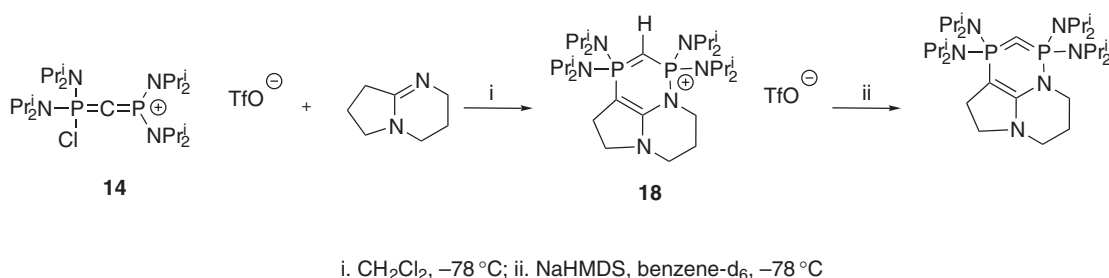
Scheme 5

(iii) Functions with one tetracoordinated and one tricoordinated phosphorus atom

Diazo compounds **9** and **11** lose nitrogen at around -25 °C to afford the corresponding carbene species **12** and **13** which are stable at room temperature. Compound **13** is a stable, moisture-sensitive, yellow solid and has been characterized by crystallography, but compound **12** can only be characterized spectroscopically (Scheme 6) <1992JA10959, 1996IC46, 1993AG(E)1167>. Both compounds have carbodiphosphorane resonance forms, although their character is best described as carbene-like. Compound **15** can be transformed to phosphaaallenes **16** and **17** with the latter being only characterized spectroscopically (Scheme 6) <1993AG(E)1167>. Most interestingly, **14** reacts with DBN to afford **18** which loses a proton after treatment with an organometallic base, to afford only the second-ever known cyclic phosphaaallene (Scheme 7) <1995CC2339>.

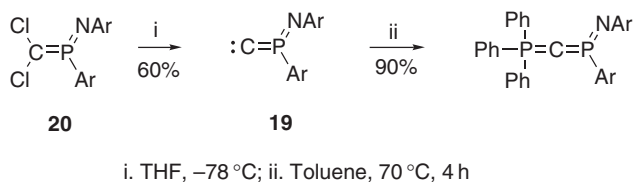


Scheme 6



Scheme 7

Iminophosphoranylidene carbene **19** generated by α -elimination from **20** undergoes a reaction with phosphines to afford a phosphallene (Scheme 8) <1996PS(110)613, 1994AG(E)982>.



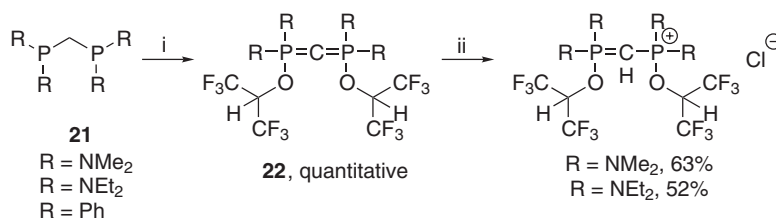
Scheme 8

(iv) Functions with two tetracoordinated phosphorus atoms

Treatment of methylene diphosphane **21** with hexafluoroacetone affords carbodiphosphorane **22**. The central carbon atom in **22** is nucleophilic and reacts with a range of electrophiles, whereas nucleophiles add to the terminal phosphorus atoms (Scheme 9) <2001EJI2377, 1999EJI1665, 1996PS(110)493, 1998CC1203>.

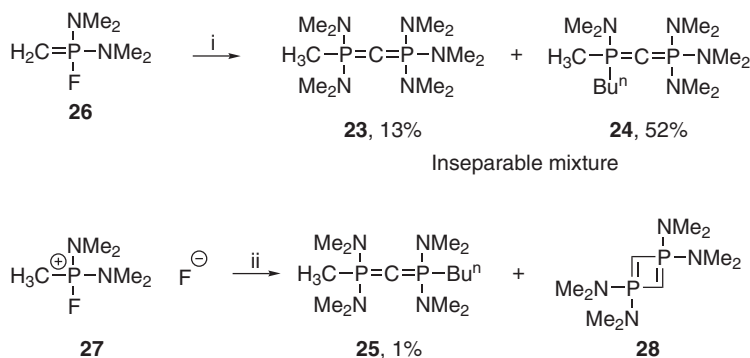
Carbodiphosphoranes **23–25** have been isolated as minor products in an unprecedented reaction by treatment of ylide **26** and difluorophosphorane **27** with butyllithium (Scheme 10) <1992ZN(B)947>.

Treatment of 1,4-diphosphetene **28** with alcohols is also reported to afford carbodiphosphoranes such as **29** (Scheme 11) <1992PS(72)49>. Interestingly, active methylene compound **30** afforded a bisylide compound **31** (the structure of which has been confirmed by X-ray crystallography) and not the carbodiphosphorane (Scheme 11) <2000ZAAC(626)1739>.



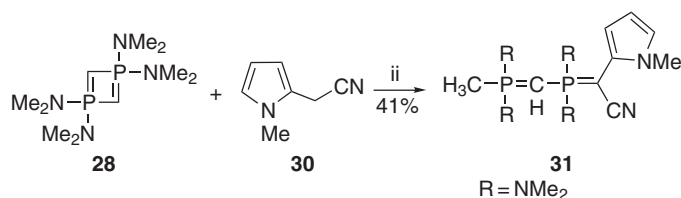
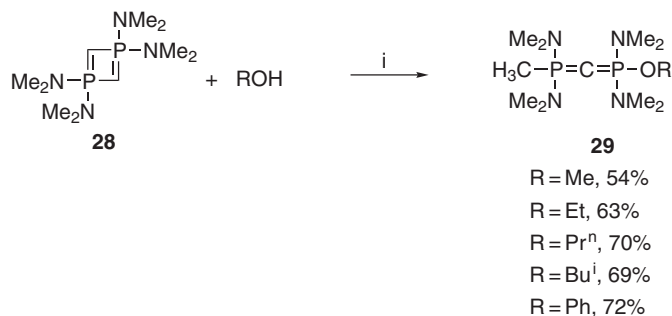
i. (CF₃)₂CO, hexane, 20 °C; ii. HCl(ether), hexane, 20 °C

Scheme 9



i. BuⁿLi, TMEDA, hexane, 50 °C; ii. BuⁿLi (2 equiv.), pentane, -70 °C

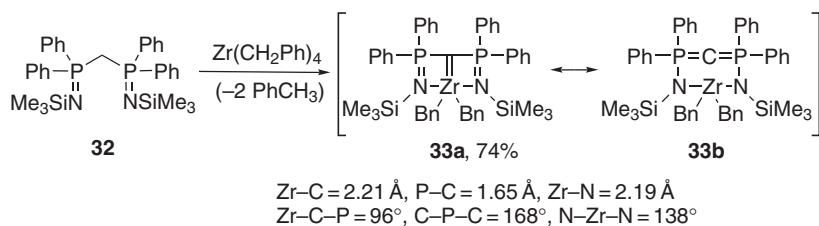
Scheme 10



i. Ether, -10 °C; ii. THF, 0 °C

Scheme 11

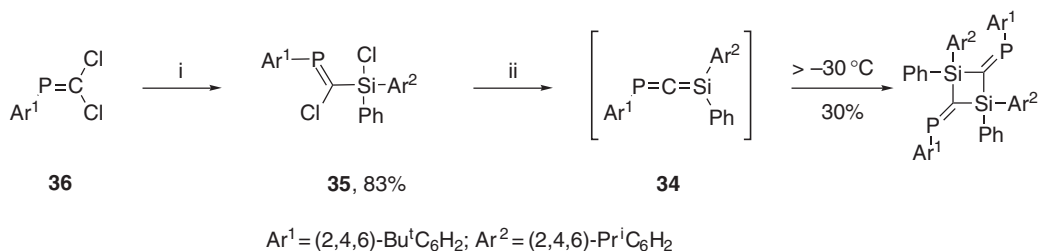
Finally, it should be noted that in the recent literature a large number of reports have appeared on the chelation of bisimines such as **32** to metals [<1999OM4226>](#). The products of these reactions are generally referred to as having structure **33a**. This is a resonance form of **33b** (Scheme 12). However, all known X-ray crystallographic data on these compounds indicate a bent P=C=P bond and a carbon-metal bond. Therefore, these species are not covered further in this review.



Scheme 12

5.29.1.2 Metalloid Functions

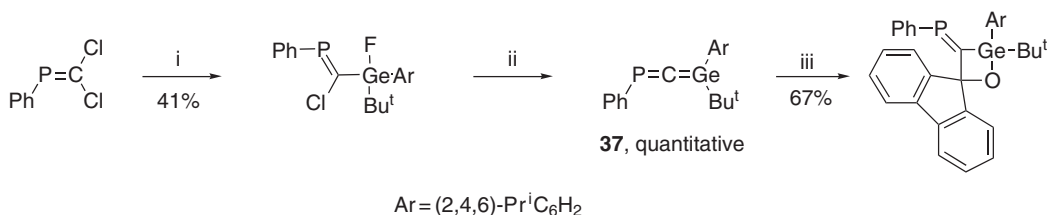
As was discussed in <1995COFGT(5)1091>, the only previously known example of the $\text{P}=\text{C}=\text{Si}$ function was reported to dimerize to afford a disilatane. A further example, compound **34**, has now been reported <1994CEJ774> that can be characterized spectroscopically at -30°C . However, this compound also dimerizes to a disilatane. Compound **34** was prepared by elimination of HCl from **35**, itself prepared by treatment of dichlorophosphaalkene **36** with an organolithium base and trapping of the resulting anion with a bis(aryl)dichlorosilane (Scheme 13) <1999CEJ774>.



i. Bu^iLi , THF, -78°C , $\text{Ar}^2(\text{Ph})\text{SiCl}_2$; ii. Bu^tLi , toluene- d_8 , -80°C

Scheme 13

Two examples of the $\text{P}=\text{C}=\text{Ge}$ function, compound **37** (Scheme 14) <2002JOM(643)202> and compound **38** (Scheme 15) <1996OM3070>, have also been reported. Compound **37**, unlike its silicon analog **34** and the other known germaphosphaallene **38**, is stable at room temperature and therefore its structure could be confirmed by X-ray crystallography. It was made by a similar method to that used for the synthesis of silicon analog **34** starting from dichlorophosphaalkene by treatment with organolithium base and trapping of the resulting anion with a difluorogermane (Scheme 14).

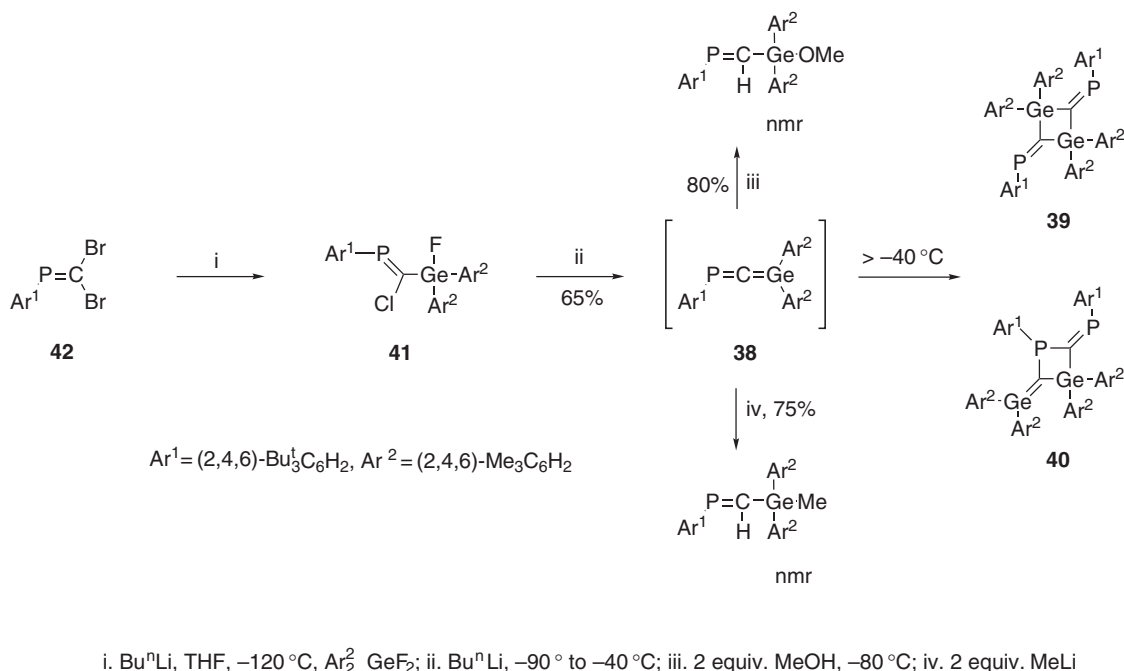


i. Bu^iLi , ether, -90°C , $\text{Ar}(\text{Bu}^t)\text{GeF}_2$ then warm to rt; ii. Bu^tLi , ether, -80°C to rt; iii. 9-fluorenone, ether, rt, 1 h

Scheme 14

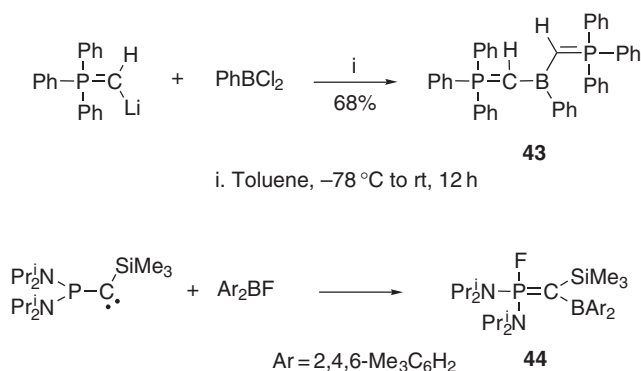
However, compound **38** can only be characterized spectroscopically at -60°C . This compound, like the silicon analog **34**, dimerizes to a digermatane **39** and germaphosphetane **40** when warmed (Scheme 15). Germaphosphaallene **38** was prepared by elimination of LiF from **41**, itself

prepared by treatment of dibromophosphaalkene **42** with organolithium base and trapping of the resulting anion with dimesityldifluorogermane (Scheme 15) <1996OM3070>. Nucleophilic attack on germaphosphaallene **38** is reported to occur at germanium (Scheme 15) <1996OM3070>. Furthermore, compound **37** undergoes formal [2+2]-cycloadditions with ketones such as 9-fluorenone (Scheme 14) <2002JOM(643)202>.



Scheme 15

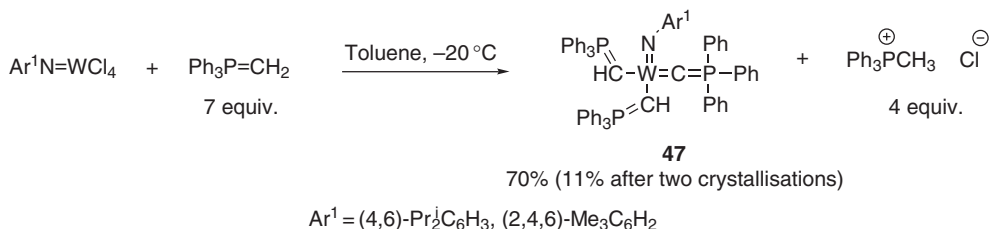
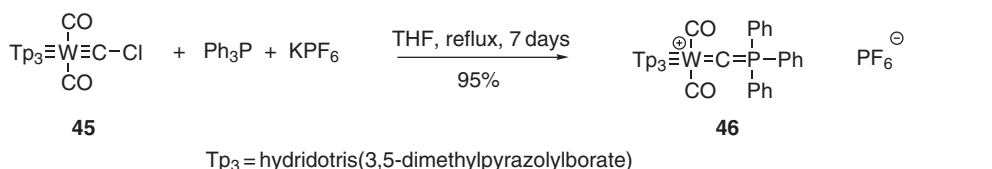
Two attempted syntheses of boron analogs failed to give boraphosphaallene, affording instead analogs **43** and **44** with no further elimination (Scheme 16) <2001AG(E)2662, 2003AG(E)2651> even though the diboryl analog is known (see Section 5.29.2.2).



Scheme 16

5.29.1.3 Metal Functions

Tungsten continues to be the only metal that can form a monomeric $\text{M}=\text{C}=\text{P}$ function. Nucleophilic displacement of chloride ion in **45** affords compound **46** (Scheme 17) <1991OM1954, 2001JA4992> and compound **47** has been prepared by a novel route (Scheme 17) <2002OM2356>.

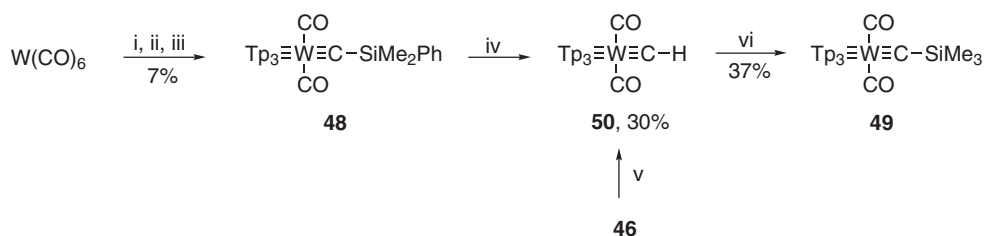


Scheme 17

5.29.2 FUNCTIONS WITH AT LEAST ONE METALLOID (AND NO CHALCOGEN OR GROUP 15 ELEMENT FUNCTION)

5.29.2.1 Derivatives with One Metalloid Function

The only known examples with this function appear to be compounds **48** and **49**. Deprotonation of terminal carbide **50** (prepared from desilylation of **48** or by reduction of compound **46**) and trapping of the carbanion with silylating agent affords **49** (Scheme 18) <2001JA4992>. Although other terminal carbides and their deprotonation are known (see Section 5.29.3) <1997CC1995> and a theoretical study on them has been carried out <2000OM2698>, no other example of this function has been reported to date.



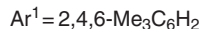
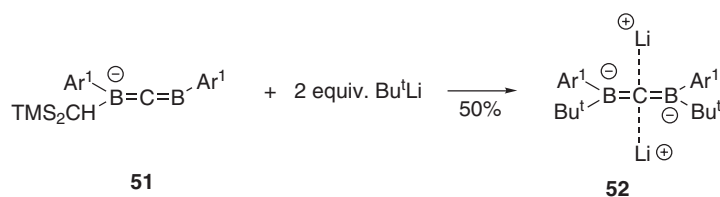
i. Me₂PhSiLi, ether/THF (10:1), 0 °C; ii. Tf₂O, -78 °C; iii. KTp, MeOH, -78 °C to rt; iv. TBAF, THF, 0 °C; v. 1.2 equiv. NaHBEt₃, THF, -78 °C to rt; vi. Bu^tLi, THF, -78 °C, TMSOTf

Tp₃ = hydridotris(3,5-dimethylpyrazolyl)borate)

Scheme 18

5.29.2.2 Derivatives with Two Metalloid Functions

Diboraallenes **51** and **52** are the only examples of this functional group in the recent literature (Scheme 19) <2001AG(E)2662>. In the solid state, compound **52** contains two lithium cations girding the central carbon atom. This feature is also seen in functions with two metals (see Section 5.29.3).

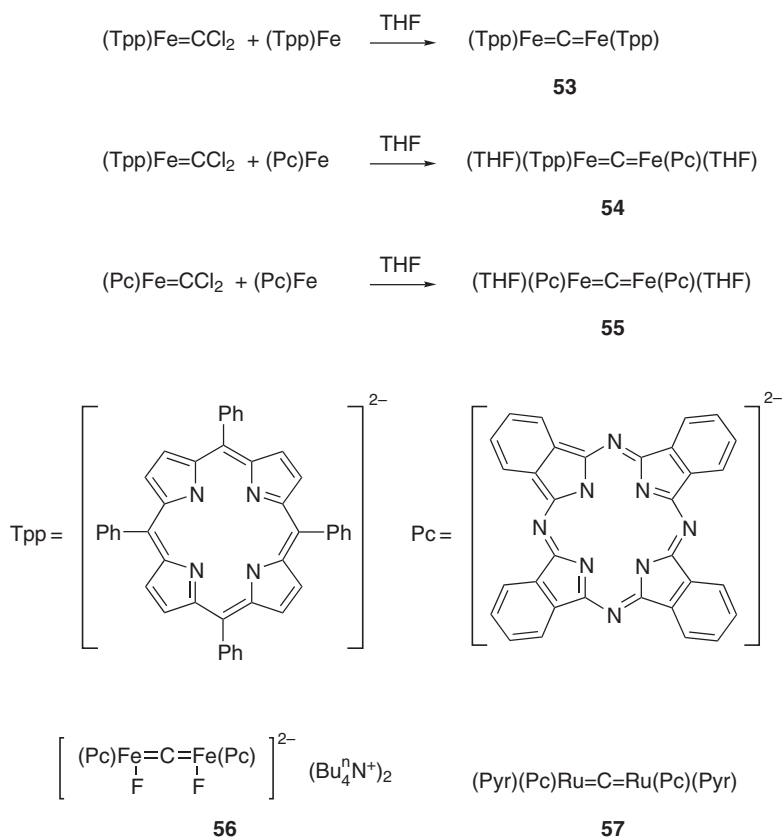


Scheme 19

5.29.3 COMPOUNDS BEARING TWO METAL FUNCTIONS

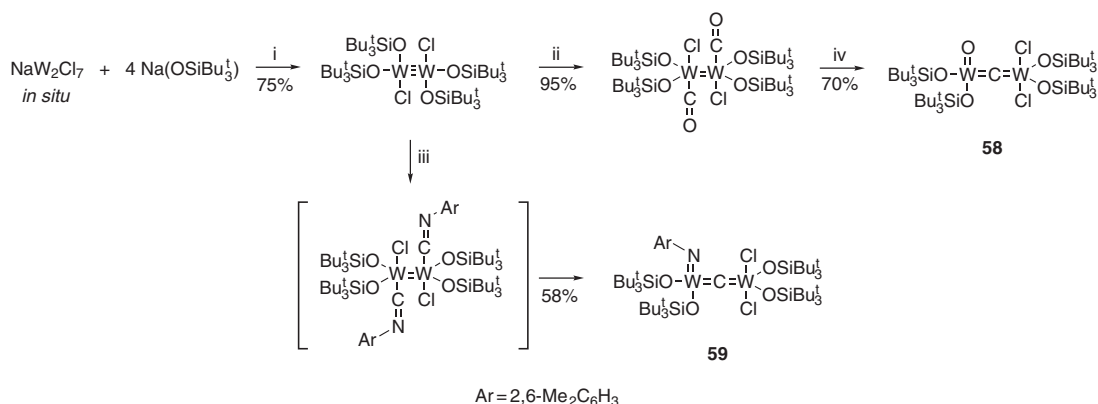
Organometallic compounds with $\text{M}^1=\text{C}=\text{M}^2$, also known as μ -carbides, have continue to grow in numbers and diversity. The subject of μ -carbides along with other μ -hydrocarbons has been reviewed [<1993AG\(E\)923>](#). Examples of wirelike cumulenic analogs with three ($\text{M}^1=\text{C}=\text{C}=\text{C}=\text{M}^2$) and five ($\text{M}^1=\text{C}=\text{C}=\text{C}=\text{C}=\text{C}=\text{M}^2$) carbon atoms are reported [<1994OM4179, 1998JA11071>](#).

Further examples of $\text{Fe}=\text{C}=\text{Fe}$ functions, compounds **53–55** [<1998ZAAC\(624\)1235>](#), and **56** [<1998ZAAC\(624\)107>](#), and the $\text{Ru}=\text{C}=\text{Ru}$ function, compound **57** [<1997ZAAC\(623\)967>](#), where metal is coordinated by a phthalocyanine (Pc) or tetraphenylporphyrin (tpp) ligand, have been reported (Scheme 20).



Scheme 20

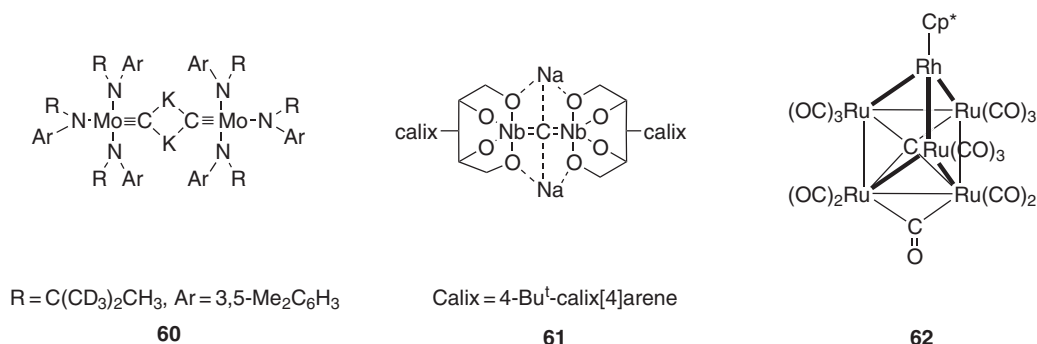
Compounds **58** and **59** have been prepared by dissociation of carbon monoxide across a $\text{W}\equiv\text{W}$ bond (Scheme 21) [<1993JA10422>](#).



i. THF, reflux, 12 h; ii. CO, hexane; iii. ArN=C:, toluene, 5 min; iv. Toluene, 20 °C, 4 h

Scheme 21

Compounds **60** <1997CC1995>, **61** <2000JA538>, and **62** <1994AX(C)1233> are the only other fully characterized compounds of this type in the literature (Scheme 22). In all three compounds, the carbon atom is encapsulated inside a metal cage. Interestingly, compounds **60** and **61** are stabilized by girding alkali metals in a manner similar to that reported for diboraallene compound **52**.



Scheme 22

REFERENCES

- 1991CC302 U. Fleischer, H. Grützmacher, U. Krüger, *J. Chem. Soc., Chem. Commun.* **1991**, 302–303.
 1991OM1954 G. M. Jamison, P. S. White, J. L. Templeton, *Organometallics* **1991**, 10, 1954–1959.
 1992JA10959 M. Soleilhavoup, A. Bacierdo, O. Treutler, R. Ahlrich, M. Nieger, G. Bertrand, *J. Am. Chem. Soc.* **1992**, 114, 10959–10961.
 1992ZN(B)947 W. Plass, M. Spahn, G. Heckmann, *Z. Naturforsch B* **1992**, 47, 947–951.
 1992PS(72)49 E. Fluck, K. Lange, G. Heckmann, *Phosphorus Sulfur Silicon* **1992**, 72, 49–54.
 1992JOM(436)169 R. El-Ouatib, C. Garot, G. Etemad-Moghadam, M. Koenig, *J. Organomet. Chem.* **1992**, 436, 169–177.
 1993PS(76)41 G. Etemad-Moghadam, R. El-Ouatib, D. Ballivet-Tkatchenko, M. Koenig, *Phosphorus Sulfur Silicon* **1993**, 76, 41–43.
 1993JOM(453)77 R. El-Ouatib, D. Ballivet-Tkatchenko, G. Etemad-Moghadam, M. Koenig, *J. Organomet. Chem.* **1993**, 453, 77–84.
 1993AG(E)923 W. Beck, B. Neimer, M. Wieser, *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 923–949.
 1993AG(E)1167 M. Soleilhavoup, A. Baceiredo, G. Bertrand, *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 1167–1169.
 1993PS(76)13 A. Schmidpeter, G. Jochem, M. Thiele, *Phosphorus Sulfur Silicon* **1993**, 76, 13–16.
 1993JA10422 R. L. Miller, P. T. Wolczanski, A. L. Rheingold, *J. Am. Chem. Soc.* **1993**, 115, 10422–10423.
 1994AX(C)1233 T. Adatia, M. McPartlin, J. Morris, H. Curtis, J. Lewis, *Acta Cryst. (C)* **1994**, C50, 1233–1235.

- 1994CEJ774 L. Rigon, H. Ranaivonjatovo, J. Escudié, A. Dubourg, J.-P. Declercq, *Chem. -Eur. J.* **1999**, *5*, 774–781.
- 1994OM4179 N. Carleton, J. F. Corrigan, S. Doherty, R. Pixner, Y. Sun, N. J. Taylor, A. J. Carty, *Organometallics* **1994**, *13*, 4179–4182.
- 1994AG(E)982 W. Schilbach, V. von der Gönna, D. Gudat, M. Nieger, E. Niecke, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 982–983.
- 1994PS(93/94)321 A. Schmidpeter, H.-P. Schrödel, G. Jochem, *Phosphorus Sulfur Silicon* **1994**, *93/94*, 321–324.
- 1995AG(E)1853 H.-P. Schrödel, G. Jochem, A. Schmidpeter, H. Nöth, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1853.
- 1995CC2339 P. Dyer, O. Guerret, F. Dahan, A. Baceiredo, G. Bertrand, *J. Chem. Soc., Chem. Commun.* **1995**, 2339–2340.
- 1995COFGT(5)1091 K. Afarinkia, M. V. Vinader, Functions with heteroatoms other than chalcogen or nitrogen ($Y=C=Y'$), in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 1091–1098.
- 1996OM3070 H. Ramdane, H. Ranaivonjatovo, J. Escudié, S. Mathieu, N. Knouzi, *Organometallics* **1996**, *15*, 3070–3075.
- 1996PS(110)493 I. Shevchenko, *Phosphorus Sulfur Silicon* **1996**, *110*, 493–496.
- 1996PS(110)613 E. Niecke, P. Becker, A. Fuchs, M. Nieger, T. Schiffer, W. W. Schoeller, *Phosphorus Sulfur Silicon* **1996**, *110*, 613–616.
- 1996IC46 P. Dyer, A. Baceiredo, G. Bertrand, *Inorg. Chem.* **1996**, *35*, 46–50.
- 1997CB1519 H.-P. Schrödel, A. Schmidpeter, *Chem. Ber./Recueil* **1997**, *130*, 1519–1527.
- 1997CC1995 J. C. Peters, A. L. Odom, C. C. Commins, *J. Chem. Soc., Chem. Commun.* **1997**, 1995–1996.
- 1997ZAAC(623)967 A. Kienast, C. Bruhn, H. Homborg, *Z. Anorg. Allg. Chemie* **1997**, *623*, 967–972.
- 1998JA11071 T. Bartik, W. Q. Weng, J. A. Ramsden, S. Szafert, S. B. Falloon, A. M. Arif, J. A. Gladysz, *J. Am. Chem. Soc.* **1998**, *120*, 11071–11081.
- 1998ZAAC(624)1235 L. Galich, A. Kienast, H. Huckstadt, H. Homborg, *Z. Anorg. Allg. Chemie* **1998**, *624*, 1235–1242.
- 1998ZAAC(624)107 A. Kienast, H. Homborg, *Z. Anorg. Allg. Chemie* **1998**, *624*, 107–112.
- 1998CC1203 I. Shevchenko, *J. Chem. Soc., Chem. Commun.* **1998**, 1203–1204.
- 1998OM1631 H. Ranaivonjatovo, H. Ramdane, H. Gornitzka, J. Escudié, J. Stagé, *Organometallics* **1998**, *17*, 1631–1633.
- 1999CEJ774 L. Rigon, H. Ranaivonjatovo, J. Escudié, A. Dubourg, J.-P. Declercq, *Chem. Eur. J.* **1999**, *5*, 774–781.
- 1999OM4226 R. P. K. Babu, R. McDonald, S. A. Decker, M. Klobuskowski, R. G. Cavell, *Organometallics* **1999**, *18*, 4226–4229.
- 1999EJI1665 I. Shevchenko, R. Mikolenko, S. Loss, H. Grützmacher, *Eur. J. Inorg. Chem.* **1999**, 1665–1671.
- 2000OM2698 Y. Chen, W. Petz, G. Frenking, *Organometallics* **2000**, *19*, 2698–2706.
- 2000JA538 A. Caselli, E. Solari, R. Scopelliti, C. Floriani, *J. Am. Chem. Soc.* **2000**, *122*, 538–539.
- 2000AG(E)3319 T. Kato, H. Gornitzka, A. Baceiredo, G. Bertrand, *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3319–3321.
- 2000JA12880 M. Bouslikhane, H. Gornitzka, J. Escudié, H. Ranaivonjatovo, H. Ramdane, *J. Am. Chem. Soc.* **2000**, *122*, 12880–12881.
- 2000ZAAC(626)1739 W. Plass, M. Spahn, E. Fluck, *Z. Anorg. Allg. Chemie* **2000**, *626*, 1739–1746.
- 2001AG(E)2662 Y. Sahin, M. Hartmann, G. Geiseler, D. Schweikart, C. Balzereit, G. Frenking, W. Massa, A. Brendth, *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2662–2665.
- 2001JA4992 A. E. Enriquez, P. S. White, J. L. Templeton, *J. Am. Chem. Soc.* **2001**, *123*, 4992–5002.
- 2001EJI2377 I. V. Shevchenko, R. N. Mikolenko, E. Lork, G.-V. Röschenthaler, *Eur. J. Inorg. Chem.* **2001**, 2377–2383.
- 2002CC3012 K. Toyota, A. Nakamura, M. Yoshifuji, *J. Chem. Soc., Chem. Commun.* **2002**, 3012–3013.
- 2002JOM(643)202 Y. El Harouch, H. Gornitzka, H. Ranaivonjatovo, J. Escudié, *J. Organomet. Chem.* **2002**, *643*, 202–208.
- 2002OM2356 X. Li, M. Schopf, J. Stephan, K. Harms, J. Sundermeyer, *Organometallics* **2002**, *21*, 2356–2358.
- 2003AG(E)2651 F. Jiang, P. J. Shapiro, F. Fahs, B. Twamley, *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 2651–2653.

Biographical sketch

Dr. Kamyar Afarinkia was born in Tehran, Iran in 1963. After graduating from Imperial College, University of London, UK in 1987, he studied for a Ph.D. under the supervision of Professor Charles Rees, CBE FRS and Professor Sir John Cadogan CBE FRS at the same institution. In 1990, he took up a postdoctoral position at Johns Hopkins University, Baltimore, USA, under the supervision of Professor Gary H. Posner, working on the synthesis of vitamin D₃ analogs. In 1992, he returned to UK and was appointed as a Senior Scientist at Glaxo R&D in Ware, Hertfordshire where he worked as a medicinal chemist in projects on hypertension and diabetes. In 1995, he was appointed to his current position at King's College, University of London. His area of research includes application of asymmetric organophosphorus reagent in synthesis, chemistry of α -amino and α -hydroxy phosphonic acids, total synthesis of natural products, and the Diels–Alder cycloaddition of 2(H)-pyran-2-ones, 2(H)-pyridin-2-ones, and 2(H)-1,4-oxazin-2-ones.

5.30

Nitriles with a Heteroatom Attached to the Cyanocarbon

P. J. RUTLEDGE

University College Dublin, Dublin, Republic of Ireland

5.30.1	SINGLY BONDED OXYGEN DERIVATIVES— $\text{ROC}\equiv\text{N}$ (CYANATES)	1024
5.30.1.1	Cyanate Formation via Thermolysis of Thiatriazoles	1024
5.30.1.2	Cyanate Formation via the Reaction of Alcohols or Phenols with Cyanogen Halides	1025
5.30.1.3	Cyanate Formation from <i>O</i> -Alkyl Thiocarbamates and Thiocyanates	1026
5.30.1.4	Cyanate Formation from <i>O</i> -Alkyl <i>N</i> -Hydroxythiocarbamates	1027
5.30.1.5	Cyanate Formation from Cyanic Acid or Metal Cyanates	1027
5.30.1.6	New Approaches to Organic Cyanates	1027
5.30.2	THIOCYANATES— $\text{RSC}\equiv\text{N}$	1027
5.30.2.1	Formation of the R—SCN Bond	1028
5.30.2.1.1	Formation of the R—SCN bond by reaction with nucleophilic sulfur	1028
5.30.2.1.2	Formation of the R—SCN bond by reactions with electrophilic sulfur	1032
5.30.2.1.3	Formation of the R—SCN bond by homolytic reactions	1033
5.30.2.2	Formation of the RS—CN Bond	1034
5.30.2.2.1	Nucleophilic cyanation of sulfur	1034
5.30.2.2.2	Electrophilic cyanation of sulfur	1035
5.30.2.2.3	Reductive cyanation of sulfur	1036
5.30.2.3	Formation of Acyl Thiocyanates	1036
5.30.2.4	Formation of Sulfonyl Cyanides	1036
5.30.2.5	Formation of RSCN by Fragmentation/Rearrangement Reactions	1036
5.30.3	SELENO- AND TELLUROCYANATES— $\text{RSeC}\equiv\text{N}$ and $\text{RTeC}\equiv\text{N}$	1037
5.30.3.1	Selenocyanates— $\text{RSeC}\equiv\text{N}$	1037
5.30.3.1.1	Formation of the R—SeCN bond	1037
5.30.3.1.2	Formation of the RSe—CN bond	1041
5.30.3.2	Tellurocyanates— $\text{RTeC}\equiv\text{N}$	1042
5.30.3.2.1	Formation of the R—TeCN bond	1042
5.30.3.2.2	Formation of the RTe—CN bond	1042
5.30.4	SINGLY BONDED NITROGEN DERIVATIVES— $\text{R}_2\text{NC}\equiv\text{N}$ (CYANAMIDES)	1043
5.30.4.1	Formation of an R—NCN Bond	1043
5.30.4.1.1	Formation of an R—NCN bond leading to alkylcyanamides	1043
5.30.4.1.2	Formation of an R—NCN bond leading to arylcyanamides	1044
5.30.4.1.3	Formation of an R—NCN bond leading to acyl- or iminocyanamides	1045
5.30.4.2	Formation of the RN—CN Bond	1047
5.30.4.2.1	Formation of the RN—CN bond by reaction with nucleophilic cyanide	1047
5.30.4.2.2	Formation of the RN—CN bond by reaction with electrophilic cyanide	1048
5.30.4.3	Dehydration, Rearrangement, and Fragmentation Reactions to Give Cyanamides	1050
5.30.4.3.1	Dehydration and equivalent reactions leading to cyanamides	1050
5.30.4.3.2	Rearrangement and fragmentation reactions leading to cyanamides	1051
5.30.4.4	Reactions on the Carbon α to NCN Leading to Cyanamides	1053
5.30.5	SINGLY BONDED PHOSPHORUS, ANTIMONY, ARSENIC, AND BISMUTH DERIVATIVES— $\text{R}_2\text{P—C}\equiv\text{N}$, $\text{R}_2\text{Sb—C}\equiv\text{N}$, $\text{R}_2\text{As—C}\equiv\text{N}$, $\text{R}_2\text{Bi—C}\equiv\text{N}$	1053
5.30.5.1	Phosphorus(III) Derivatives	1054
5.30.5.1.1	Formation of an R—PCN bond	1054
5.30.5.1.2	Formation of the P—CN bond	1054
5.30.5.1.3	Modification of the substitution pattern at phosphorus(III)	1054

5.30.5.2	Phosphorus(V) Derivatives	1055
5.30.5.2.1	Formation of an R—PCN bond	1055
5.30.5.2.2	Formation of the P—CN bond	1055
5.30.5.2.3	Modification of the substitution pattern at phosphorus(V)	1056
5.30.5.3	Antimony Derivatives	1057
5.30.5.4	Arsenic Derivatives	1057
5.30.5.5	Bismuth Derivatives	1057
5.30.6	SINGLY BONDED METALLOID DERIVATIVES— $R_3SiC\equiv N$, $R_2BC\equiv N$, AND $R_3GeC\equiv N$	1058
5.30.6.1	R_3SiCN Compounds	1058
5.30.6.2	R_2BCN Compounds	1059
5.30.6.3	R_3GeCN Compounds	1061
5.30.7	SINGLY BONDED METAL DERIVATIVES	1061
5.30.7.1	Group 1 and 2 Derivatives	1062
5.30.7.2	Transition Metal Derivatives	1062
5.30.7.2.1	Nickel derivatives	1062
5.30.7.2.2	Palladium derivatives	1062
5.30.7.2.3	Platinum derivatives	1063
5.30.7.2.4	Copper derivatives	1064
5.30.7.2.5	Gold derivatives	1064
5.30.7.2.6	Mercury derivatives	1065
5.30.7.2.7	Derivatives of other transition metals	1065
5.30.7.3	Group 13 Derivatives	1066
5.30.7.3.1	Aluminum derivatives	1066
5.30.7.3.2	Gallium derivatives	1066
5.30.7.3.3	Indium derivatives	1067
5.30.7.3.4	Thallium derivatives	1067
5.30.7.4	Group 14 Derivatives	1067
5.30.7.4.1	Tin derivatives	1067
5.30.7.4.2	Lead derivatives	1068
5.30.8	HETERONITRILIUM COMPOUNDS WITH THE GENERAL FORMULA $RXC\equiv N^+—Y$	1068
5.30.8.1	N-Protonated Heteronitrilium Salts— $RX—CN^+—H$	1069
5.30.8.2	N-Carbon-linked Heteronitrilium Salts— $RX—CN^+—CR_3$	1069
5.30.8.2.1	Alkylthionitrilium salts— $RS—CN^+—CR_3$ X^-	1069
5.30.8.2.2	Cyanamidium salts— $R_2N—CN^+—CR_3$ X^-	1069
5.30.8.2.3	Nitriliumborates— $R_3B^-—CN^+—CR_3$	1069
5.30.8.2.4	Nitrilium organometallates— $R_nM^-—CN^+—CR_3$	1070
5.30.8.3	Heteronitrile Oxides— $RX—CN^+—O^-$	1070
5.30.8.4	Other Derivatives— $RX—CN^+—Y$	1070
5.30.8.4.1	Silylnitrilimines— $R_3Si—CN^+—N^-—R$ and phosphoranylnitrilimines— $R_2P(X)—CN^+—N^-—R$	1070
5.30.8.4.2	Diazonitriliumborates— $R_3B^-—CN^+—N_2R$	1071
5.30.8.4.3	Cyanamidiummetallates— $R_2N—CN^+—MX_n^-$	1071
5.30.8.4.4	Boro-nitrilium borates— $R_3B^-—CN^+—BR_3^-$ X^+	1072

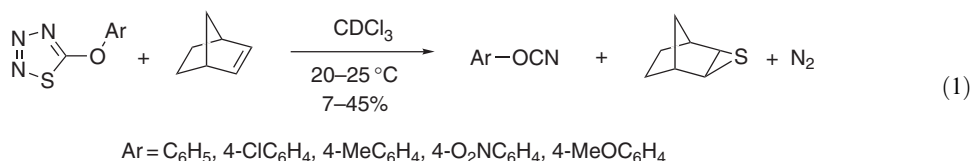
5.30.1 SINGLY BONDED OXYGEN DERIVATIVES— $ROC\equiv N$ (CYANATES)

Chapter 5.30.1 in COFGT (1995) <1995COFGT(5)1099> detailed five general approaches to the formation of organic cyanates: via thermolysis of thiatriazoles, via reaction of phenols or alcohols with cyanogen halides, from *O*-alkyl thiocarbamates and thiocyanates, from *O*-alkyl hydroxythiocarbamates, and from cyanic acid or metal cyanates. Since then new syntheses have been developed directly in or closely related to four of these five areas; several new approaches to organic cyanates have also been reported, and these will be discussed in a separate section at the end.

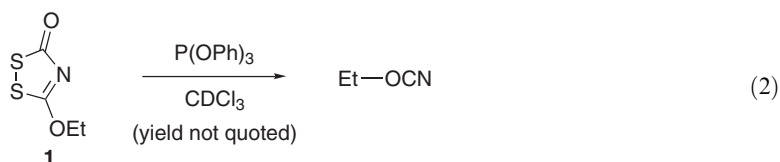
5.30.1.1 Cyanate Formation via Thermolysis of Thiatriazoles

Chapter 5.30.1.1 of COFGT (1995) <1995COFGT(5)1099> discussed the thermal decomposition of various 5-alkoxy- and 5-aryloxy-1,2,3,4-thiatriazoles at relatively low temperatures (20–45 °C), giving rise to the corresponding alkyl or aryl cyanates, along with nitrogen gas and elemental sulfur.

An alternative means of promoting thiatriazole decomposition has been developed in a more recent approach, in which a strained olefin (*trans*-cyclooctene or norbornene) brings about rearrangement of 5-(4-chlorophenoxy)-1,2,3,4-thiatriazole to *p*-chlorophenyl cyanate (Equation (1)) <2001EJO1959>. The reaction proceeds at 20–25 °C, and the alkene is itself converted into the episulfide (the synthetic motivation behind this research).



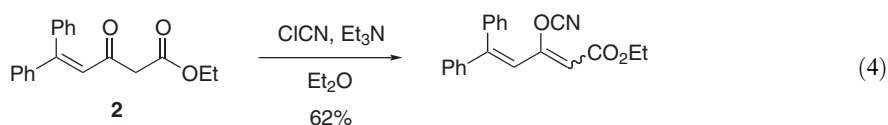
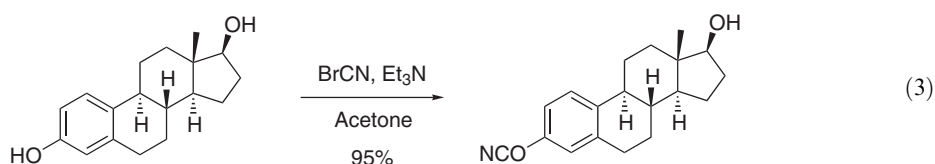
In related chemistry, the dithiazolinone **1** has been desulfurized by treatment with triphenyl phosphite in chloroform, which prompts rearrangement to yield *O*-ethyl cyanate (Equation (2)) <1996JOC6639>.



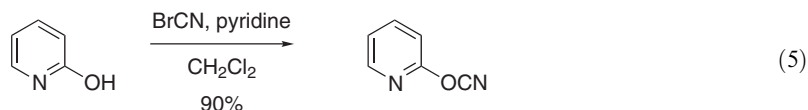
5.30.1.2 Cyanate Formation via the Reaction of Alcohols or Phenols with Cyanogen Halides

The reaction of alcohols and phenols with cyanogen halides was discussed in detail in chapter 5.30.1.2 of COFGT (1995) <1995COFGT(5)1099>. Phenols with bulky substituents in both *ortho*-positions and alcohols ROH bearing bulky R groups can be converted into the corresponding cyanates, via reaction of their potassium or sodium salts with cyanogen bromide or chloride at low temperatures. Alternatively, the alcohol may be reacted with a solution of cyanogen chloride and triethylamine in acetone or dichloromethane. The earlier edition also discussed the use of sodium hydride or thallium alkoxides as the base in this reaction.

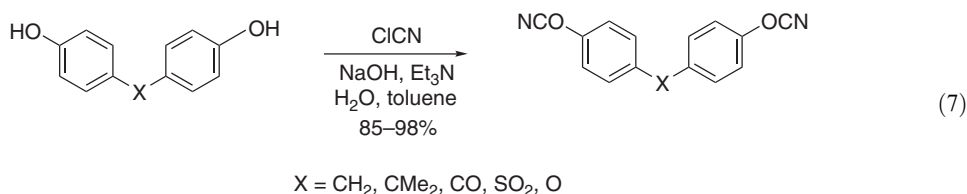
There have been several further applications of this approach to both alkyl and aryl cyanates in COFGT (1995). [1-H₂]-Pentadecafluorooctan-1-ol <1995JFC101>, 2,6-dihydroxyanthraquinone <1996JPR681>, and *estra*-1,3,5(10)-triene-3,17 β -diol <1998MI228> have all been converted into the corresponding cyanates using the combination of cyanogen bromide and triethylamine. In the latter example, reaction occurs exclusively at the more acidic phenolic OH group, leaving the D ring alcohol unmodified (Equation (3)). The combination of cyanogen chloride and triethylamine has been used to derivatize the β -keto ester **2** (Equation (4)), such that the product formed is an enol cyanate <2001TL6133>.



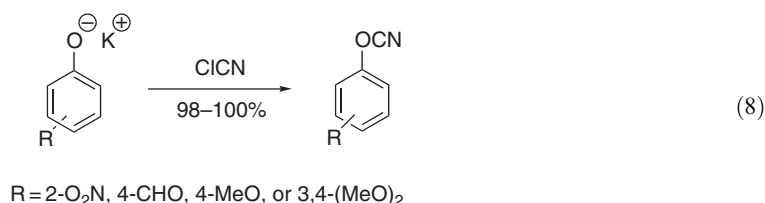
2-Pyridyl cyanate has been prepared from the alcohol by reaction with cyanogen bromide and pyridine <1996SC3709> or with sodium ethoxide as the base <1995ZOR934> (Equation (5)), and adamantan-1-ol has been converted into its cyanate using potassium hydride and cyanogen bromide (Equation (6)) <2002JA5258>.



An efficient biphasic system has been developed, which uses a toluene/water mixture in conjunction with cyanogen chloride, sodium hydroxide, and triethylamine at lowered temperature ($<10^{\circ}\text{C}$) [<2000JAP2000159741>](#). In this way, various phenyl bis(cyanates) have been prepared on a 100 g scale in extremely high yields and excellent purity for use in polymer chemistry (Equation (7)). This approach is built on earlier work on a smaller scale [<1999JAP11255735, 1999JAP11228522>](#).



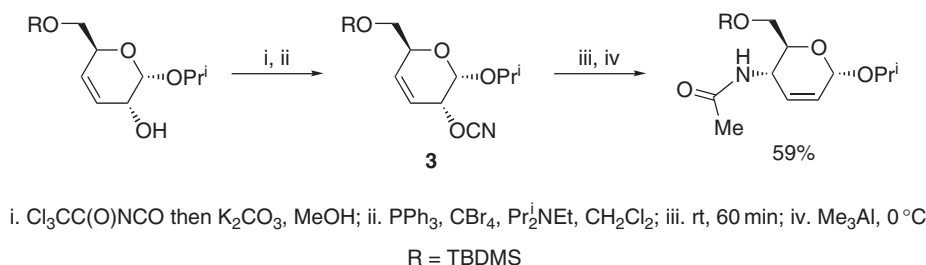
Finally, there have been some interesting studies aimed at the development of “gas–solid” reaction techniques for the conversion of phenols into their cyanates [<1998CEJ2467>](#). Thus, the solid potassium phenolate is treated with gaseous cyanogen halide (bromide or chloride), generating cyanates in quantitative yields (Equation (8)). This reaction boasts improved yields over alternative procedures, and simplicity in the work-up.



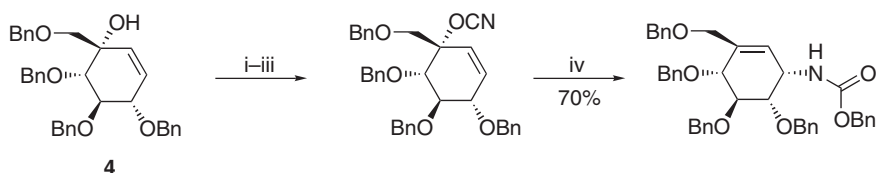
5.30.1.3 Cyanate Formation from *O*-Alkyl Thiocarbamates and Thiocyanates

O-Alkyl thiocarbamates and thiocyanates have been used as precursors to organic cyanates, as reviewed in chapter 5.30.1.3 of COFGT (1995) [<1995COFGT\(5\)1099>](#). Various metal oxides—including mercury(II), silver(I), lead(II), and copper(II) oxides—have been shown to promote the decomposition of *O*-alkyl thiocarbamates to cyanates. In a closely related transformation, thiocyanates can be converted into imidothiocarbamates, which break down to organic cyanates on treatment with mercury(II) oxide.

Although there have been no recent reports on the formation of cyanates from *O*-alkyl thiocarbamates or *O*-alkyl thiocyanates, there has been some interesting chemistry developed to dehydrate carbamic acids, giving rise to cyanate products. (The resulting allylic cyanates have then been prompted to undergo sigmatropic rearrangement, affording the corresponding isocyanates, which can then be trapped with a suitable nucleophile.) In one recent report, the cyanate **3** was prepared from the corresponding alcohol: initial reaction with trichloroacetyl isocyanate (Cl₃CC(O)NCO) at 0°C followed by treatment with methanolic potassium carbonate gave the carbamate, then triphenylphosphine, carbon tetrabromide, and diisopropylethylamine were used to effect dehydration. The cyanate **3** was not isolated, but rearranged to the isocyanate, which could then be trapped with trimethylaluminum (Scheme 1) [<1996JCS\(P1\)377, 1997JCS\(P1\)1449>](#). A similar approach has been used with the carbocyclic substrate **4** (Scheme 2) [<1999HCA645>](#). Alternatively, the combination of triflic anhydride and diisopropylethylamine has also been employed to effect this type of dehydration [<1997CEJ453>](#).



Scheme 1



i. $\text{Cl}_3\text{CC}(\text{O})\text{NCO}$; ii. K_2CO_3 , MeOH; iii. PPh_3 , CBr_4 , Et_3N ; iv. rt then BnOH

Scheme 2

5.30.1.4 Cyanate Formation from *O*-Alkyl *N*-Hydroxythiocarbamates

The rearrangement of *O*-alkyl *N*-hydroxythiocarbamates to organic cyanates, carbon dioxide, ethanol, and sulfur was reviewed in chapter 5.30.1.4 of COFGT (1995) <1995COFGT(5)1099>. However, there have been no further developments in this area.

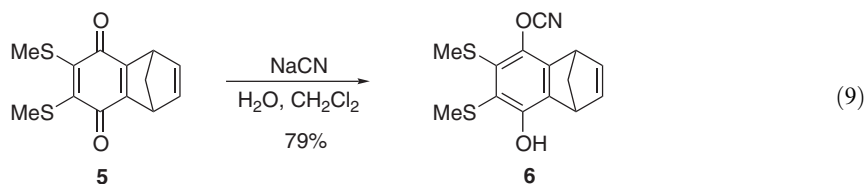
5.30.1.5 Cyanate Formation from Cyanic Acid or Metal Cyanates

The final route to organic cyanates discussed in chapter 5.30.1.5 of COFGT (1995) <1995COFGT(5)1099> sees the use of cyanic acid or its metal salts to convert organic halides or diazoalkanes into the cyanate functionality. Thus, HO-CN , NaOCN , and AgOCN have all been applied in reactions with iodopropanes, -butanes, and 1-chloropentane.

Since the publication of COFGT (1995), there have been few developments in the use of cyanic acid salts to prepare organic cyanates. However, there have been two reports of *O*-heteroatom-linked “cyanates”: a cyclic boron derivative, a cyanatotriazaborole, formed from the chlorotriazaborole and silver cyanate <1999EJI1193>, and the interesting compound trimethyltelluronium cyanate generated in excellent yield from the reaction of trimethyltelluronium iodide and silver cyanate <2002EJI2701>.

5.30.1.6 New Approaches to Organic Cyanates

Finally, there is one newly developed route to an organic cyanate that does not easily fit into any of the subdivisions discussed above. In what is overall the reductive addition of cyanide to the naphthalene-5,6-dione derivative **5**, sodium cyanide reacts with this electrophile in an unexpected fashion, giving rise to the hydroquinoid product **6** in good yield (Equation (9)) <2000JCS(P1)3692>. This transformation is proposed to involve initial attack of the hard nucleophile directly at the carbonyl carbon, followed by “symbiotic reattack of oxygen onto the incoming group” <2000JCS(P1)3692>.



5.30.2 THIOCYANATES— $\text{RSC}\equiv\text{N}$

As was observed in chapter 5.30.2 of COFGT (1995) <1995COFGT(5)1099>, most routes to organic thiocyanates ($\text{RSC}\equiv\text{N}$, R = carbon) involve formation of the R—S bond, although construction of the S—CN linkage is also utilized in a small but important group of syntheses.

5.30.2.1 Formation of the R—SCN Bond

Chapter 5.30.2.1 of COFGT (1995) <1995COFGT(5)1099> detailed a range of routes to organic thiocyanates using reagents in which the SCN moiety is already extant, reactions leading to formation of the R—S bond. A significant majority of these approaches used a nucleophilic source of sulfur (the thiocyanate anion ^-SCN or equivalent) although several routes using electrophilic sulfur (thiocyanogen $(\text{SCN})_2$ or a cyanogen halide) and also homolytic reactivity were also described. This section is subdivided according to the nature of the SCN source.

5.30.2.1.1 Formation of the R—SCN bond by reaction with nucleophilic sulfur

Simple displacement of a leaving group by the thiocyanate anion appears to be a straightforward route to the R—SCN functionality, and chapter 5.30.2.2.1 of COFGT (1995) details many approaches of this type. However, this apparent simplicity is complicated by the ambident nature of the thiocyanate nucleophile, which means that significant quantities of the alternative isothiocyanate product are formed along with the thiocyanate in many reactions. Furthermore, many thiocyanates undergo equilibration to the more stable isothiocyanate once formed. Nonetheless, employing nucleophilic thiocyanate represents a very useful and widely used route to organic thiocyanates, and a great number of different reactions of this type were discussed in the earlier edition. It is perhaps helpful to consider them in four broad categories: displacement of a leaving group X from an alkyl halide, sulfonate, or equivalent starting material R—X; attack of thiocyanate on an alternative carbon electrophile—an activated alcohol or amine, a small ring such as an epoxide, aziridine or oxaziridine, or a Michael acceptor; addition to a carbon–carbon multiple bond via prior reaction with an electrophile; and nucleophilic attack on an aromatic system, usually a diazotized arylamine.

(i) Formation of the R—SCN bond via displacement of X from R—X

The simplest and most common synthesis of organic thiocyanates is by reaction of a thiocyanate salt (sodium, potassium, or ammonium) with an alkyl halide, a reaction discussed in some detail in chapter 5.30.2.2.1 of COFGT (1995) <1995COFGT(5)1099>. The transformation has been effected with a wide range of alkyl halides, often utilizing phase-transfer catalysis, and occasionally a solid-supported thiocyanate source. It was noted that formation of the isothiocyanate increases with temperature and with increased substitution of the alkyl halide. The use of trimethylsilyl isothiocyanate (TMSNCS) was also discussed, and so too the use of alternative leaving groups such as sulfonates and cyclic sulfates.

This remains an efficient and popular route to organic thiocyanates, and since the 1990s a wide variety of alkyl halides have been converted into the corresponding thiocyanates by reaction with the thiocyanate anion or equivalent. Potassium thiocyanate is the most commonly used source of ^-SCN , though the sodium and silver salts are also used, and TMSNCS finds increasing utility as an alternative <2001TL8479>. The standard solvents of nucleophilic substitution are most commonly used (DMF, DMSO, acetone, and acetonitrile), although alcohols (ethanol and methanol) and occasionally aqueous systems have also been exploited. A range of representative examples is summarized in Table 1.

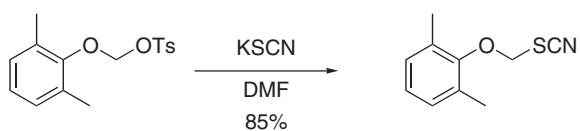
Several reports have emerged recently on the use of alternative phase-transfer catalysts in the conversion of alkyl halides into thiocyanates, including trialkylphosphonium bromides <1998SC583, 2000JCS(P2)1851> and aza-crowns <1999ZOR1110>. There have also been reports on the inclusion of other additives, among them are zinc(II) chloride <1996JFC27> and zirconium (benzyl-diethylammonium-methylphosphonate chloride)phosphate <1995SC2435>.

A sulfonate leaving group represents a useful alternative for displacement by ^-SCN , and this approach has also been widely used. Representative examples are shown (Equations (10) and (11)) <2002JMC3984, 1997CAR271, 2002T1611>. The substitution of sulfonates by thiocyanate generally requires elevated temperatures, longer reaction times, or both. Cyclic sulfates represent a variation of the sulfonate theme, and various furanoses of general structure **7** have been opened using potassium thiocyanate (Equation (12)) <1997JOC3944>. A series of related pyranose derivatives has also been converted into thiocyanates in this fashion <1999CEJ1512>, and a similar approach has been used to ring-open a cyclic thiophosphonate derivative of glycerol <1996ZOR1100>.

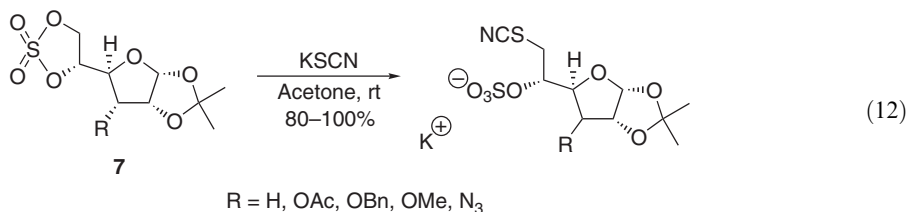
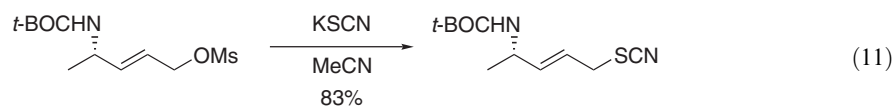
Table 1 Thiocyanates RSCN prepared from alkyl halides and potassium thiocyanate (KSCN)

<i>RX</i>	<i>Solvent/Temperature</i>	<i>Yield (%)</i>	<i>References</i>
	DMF, 100 °C	78	<1997CPB1447>
	DMSO, rt	75	<1995JOC813>
	DMF, 130 °C	89	<1995CPB1516>
	MeOH, Δ	95	<1996CPB122>
	Acetone, rt	95 ^a	<1997JPR473>
	MeCN, rt	76 ^b	<1998TL8353>
	DMF, rt	95 ^c	<1995T4763>
	Acetone, Δ	85	<2000SL1004>
	DMF, 90 °C	81	<1995JOC813>

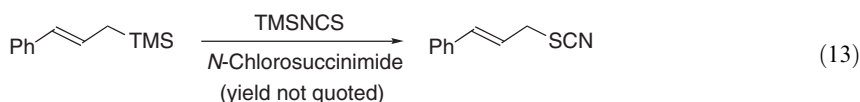
^a Yield for conversion to the dithiocyanate. ^b R = tetra-*O*-acetyl-β-*D*-glucopyranose. ^c Ar = *p*-MeO-C₆H₄.



(10)



Several other less common leaving groups have been used in substitution reactions with nucleophilic thiocyanate. These include dimethyl sulfide from a sulfonium cation [<2001T2871>](#), the trimethylsilyl moiety from a range of allyl silanes (Equation (13)) [<1997PS385>](#), and the 1H-tetra-*sol*-5-ylsulfanyl group [<1997BSF653>](#).

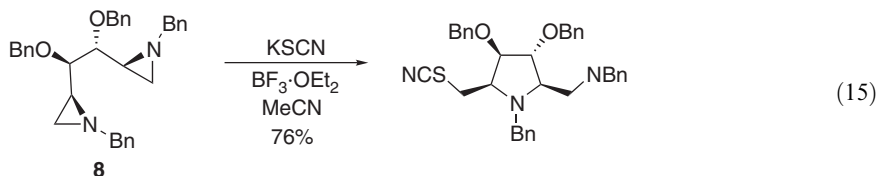
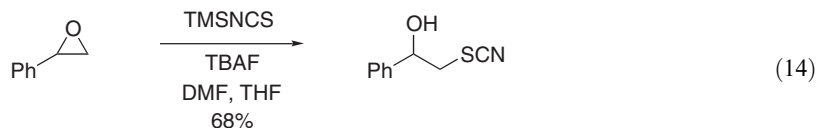


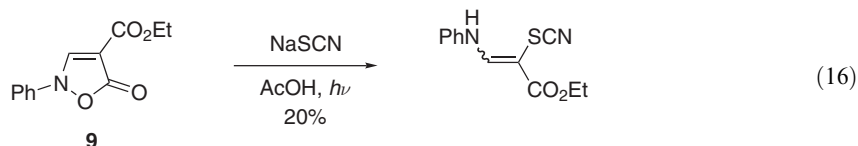
Finally, the reagent Ph₃P(SCN)₂ (generated *in situ* from ammonium thiocyanate, triphenylphosphine, and bromine) has been used to convert a range of thiols into their thiocyanates in excellent yields [<2002TL3439>](#). Ph₃P(SCN)₂ exists in equilibrium with Ph₃P⁺(SCN) and ⁻SCN, so the reaction proceeds via a desulfuration/thiocyanation mechanism, and thus formation of the R—SCN bond.

(ii) *Formation of the R—SCN bond by attack of nucleophilic thiocyanate on other carbon electrophiles*

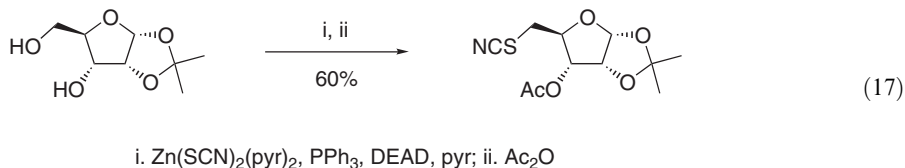
Chapter 5.30.2.1.1 of COFGT (1995) [<1995COFGT\(5\)1099>](#) also considered the reaction of a thiocyanate nucleophile with epoxides, aziridines, and oxaziridines, noting that this reaction is catalyzed by Lewis acids such as titanium(IV) isopropoxide or by palladium(0). COFGT (1995) also discussed the reaction of potassium thiocyanate with alcohols and amines that had undergone prior or *in situ* activation (under Mitsunobu conditions for example, or with the combination of triphenylphosphine and thiocyanogen).

Several new methods have been exploited for the opening of epoxides and aziridines with thiocyanate since the 1990s. The combination of sodium thiocyanate and titanium trichloride has been used to open a range of simple epoxides, though products were often obtained as mixtures of regioisomers [<1997TL8699>](#). Styrene oxide and related epoxides have been converted into the corresponding α -hydroxy thiocyanates in good yields using TMSNCS and a source of fluoride ions (Equation (14)) [<1997JCS\(P1\)671>](#). Furthermore, the bisaziridine **8** has been opened using potassium thiocyanate and boron trifluoride etherate to initiate a cascade ring closure (Equation (15)) [<1995TL8015>](#). In another interesting ring-opening/decarboxylation reaction, the isoxazolone **9** has been converted into an α,β -unsaturated ester by treating sodium thiocyanate and acetic acid with irradiation (Equation (16)) [<1995AJC567>](#).





In the same time period, surprisingly few new reports on the conversion of alcohols or amines into thiocyanates have emerged. In one study, Mitsunobu conditions were used to convert a tricyclic alcohol into the thiocyanate in low yield (20%) [<2000JA4583>](#). Another approach proved more fruitful, using triphenylphosphine, DEAD, and the bis(pyridine) complex of zinc thiocyanate to convert several protected furanoses into the corresponding primary thiocyanates (Equation (17)) [<2000CCC1745>](#).

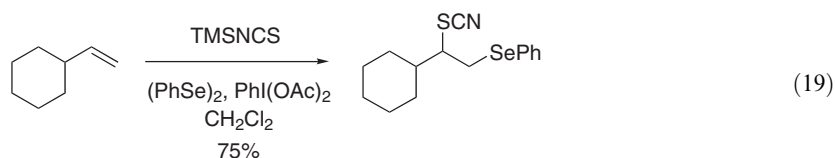
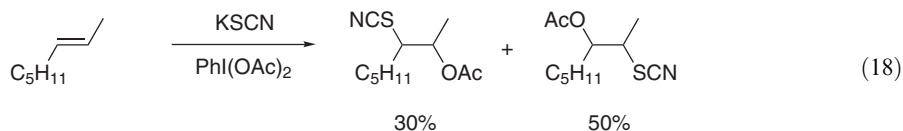


Finally, there has been one recent report on the reaction of potassium thiocyanate with an α,β -unsaturated ketone in a Michael reaction [<2001JA8089>](#).

(iii) *Formation of the R—SCN bond by reaction of an alkene with an electrophile and ^-SCN*

The third general method for forming the R—SCN bond using nucleophilic sulfur reviewed in COFGT (1995) involves addition of thiocyanate and an electrophilic co-reactant across a carbon–carbon multiple bond. Isothiocyanic acid (HNCS) itself generally gives mixtures of thiocyanate and isothiocyanate, but halogen-promoted thiocyanation using a range of halogens or PhSe—SCN was discussed as a more selective alternative. The reaction of terminal alkynes in a similar fashion, using isothiocyanic acid and mercury(II) thiocyanate, was also considered.

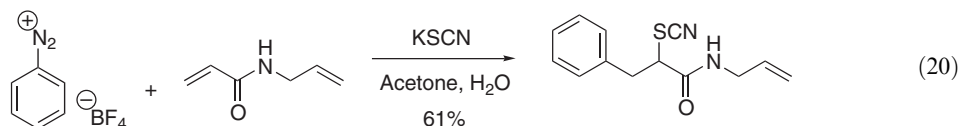
A considerable amount of new chemistry has emerged in this area since the publication of COFGT (1995). The hypervalent iodine reagent bis(acetoxy)iodobenzene (BAIB) has been applied in a number of reactions in which thiocyanate and acetate are added across a carbon–carbon double bond [<1996TL1889, 1997CC1237, 1998TL3847>](#). For example, reaction of 2-octene with BAIB and potassium thiocyanate gives two regioisomeric products (Equation (18)) [<1997CC1237>](#). While this reaction is believed to involve electrophilic addition to the alkene, the inclusion of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) or magnesium perchlorate in the reaction mixture is expected to promote a radical pathway [<1996TL1889>](#). The combination of BAIB and TMS—NCS has also been used to effect this transformation [<1998TL3847>](#), though product mixtures are again obtained. Better yields and regioselectivity have been achieved using the hypervalent iodine reagent, potassium thiocyanate, and diphenyl selenide in the thiocyanation/ phenylselenation of assorted alkenes (Equation (19)) [<2000EJO1865>](#).



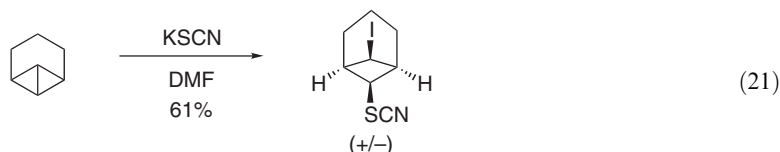
The addition of thiocyanate and an alkoxy group across a terminal alkene has been achieved using potassium thiocyanate in conjunction with *N*-bromosuccinimide and methanol, although the α -thiocyanato ether products are generally formed alongside α -bromo ether side-products

<1997JCR(M)1901, 1998SC583>. A related approach has also been used to add H—SCN across the carbon–carbon triple bond of several terminal alkynes <1998JCS(P1)1013>.

In another recent advance, a great deal of work has been done to develop a system for the combined arylation/thiocyanation of an alkene, using potassium thiocyanate and an aryl diazonium tetrafluoroborate (Equation (20)) <1996ZOB639, 1997ZOR1068, 1999ZOB995, 1999KFZ16, 2000PJC1567>.



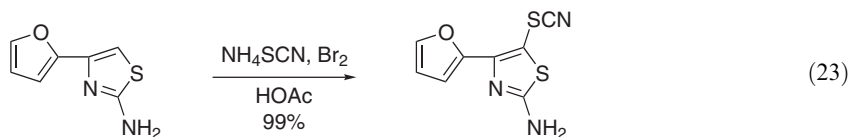
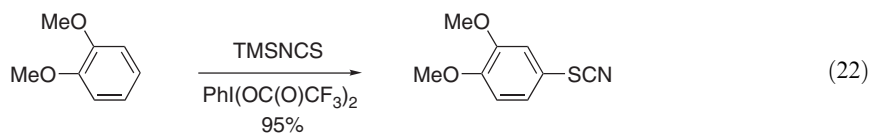
Finally, in some related chemistry, the combination of potassium thiocyanate and iodine in DMF has been applied to ring-open a highly strained cyclopropane (Equation (21)) <2002ZOR845>.



(iv) *Formation of the R—SCN bond in aryl thiocyanates*

Chapter 5.30.2.1.1 of COFGT (1995) <1995COFGT(5)1099> reviewed nucleophilic displacement of N₂ from aromatic diazonium salts as the principal route to aromatic thiocyanates, although substantially less work had been done in this area. The use of copper(I) thiocyanate under Sandmeyer conditions represented the optimal conditions, and other transition metal catalysts have also been used.

There have only been a small number of advances in this area since the publication of COFGT (1995). Hypervalent iodine, in the form of bis(trifluoroacetoxy)iodobenzene, has been used with TMSNCS to thiocyanate a wide range of electron-rich aromatic systems (Equation (22)) <1995JOC7144>. Selectfluor has been used in a similar capacity to facilitate reaction between potassium thiocyanate and an aromatic ring <2002JOC4487>, and so too bromine in combination with sodium bromide <1997JMC3707, 2000JMC843> or acetic acid <2000EJM853>. Finally, ammonium thiocyanate has been used as an alternative source of thiocyanate, with bromine in acetic acid to add thiocyanate to a range of heterocyclic systems (Equation (23)) <2002KFZ983>.



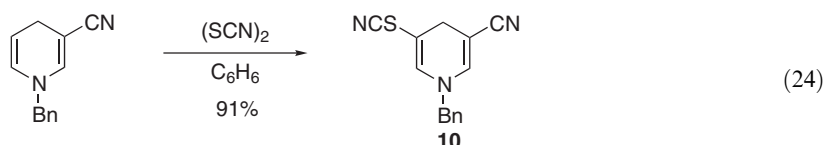
It is perhaps worth noting that thiocyanated aromatic compounds are often formed as side products in the alkene arylation/thiocyanation reaction discussed in (iii) above, but only in low yield (below 20%) and often alongside the isothiocyanate isomer.

5.30.2.1.2 Formation of the R—SCN bond by reactions with electrophilic sulfur

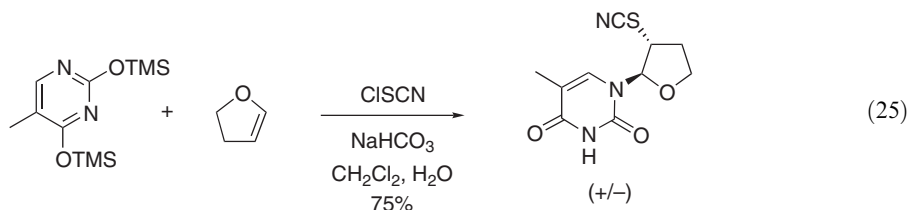
The main sources of electrophilic SCN covered in chapter 5.30.2.1.2 of COFGT (1995) <1995COFGT(5)1099> are thiocyanogen ((SCN)₂) and thiocyanogen halides (XSCN), which behave in a similar fashion to the halogens (X₂) in adding to activated alkenes and electron-rich aromatic

systems. It was noted that a Friedel–Crafts-type catalyst significantly enhances the reactivity of thiocyanogen with alkenes and aromatic rings. Reactions of enols, and other carbon nucleophiles—including aryl- and alkylolithiums, and acetylide anions—with thiocyanogen were also discussed.

Thiocyanogen, bromocyanogen, and chlorocyanogen remain the reagents of choice for this type of chemistry. However, there have not been many new reactions reported in this area. The attack of thiocyanogen on 3-cyano-*N*-benzyl-1,4-dihydropyridine has been exploited to directly afford the vinylic thiocyanate **10** (Equation (24)) <2000CEJ1763>. This is an oxidative transformation in which the natural tendency of the 1,4-dihydropyridine to undergo “biomimetic” oxidation to the pyridinium salt is effectively switched off. A cobalt(III)-mediated reaction between thiocyanogen and various alkenes has also been reported recently <2002IJC(A)970>, although regioisomeric mixtures result.



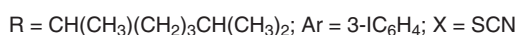
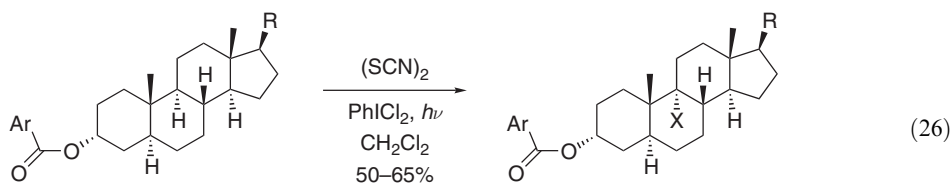
In an important new application of chlorothiocyanogen, the thiocyanating reagent and a range of *O*- and *N*-nucleophiles derived from purine and pyrimidine bases have been added across the carbon–carbon double bonds of assorted alkenes <2002SC343>. The alkenes used in this chemistry are generally electron-rich, and include dihydrofuran (Equation (25)), dihydropyran, *N*-vinyl-2-pyrrolidinone, 9-vinylcarbazole, and isobutyl vinyl ether.

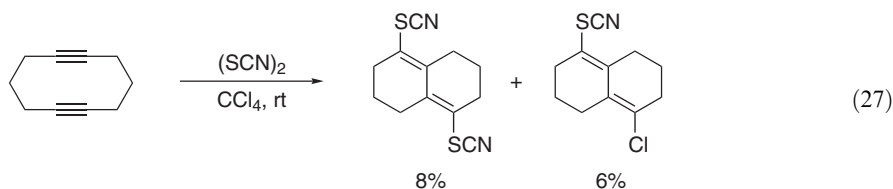


5.30.2.1.3 Formation of the R–SCN bond by homolytic reactions

Chapter 5.30.2.1.3 of COFGT (1995) <1995COFGT(5)1099> noted that the radical addition of thiocyanogen to alkenes or alkynes can be achieved using a peroxide initiator or UV light, but that product mixtures are likely, with the ratios achieved quite dependent on the precise conditions used. Benzylic and allylic thiocyanations under radical conditions were also discussed, and so too the use of Barton esters and methanesulfonyl isothiocyanate (MsNCS) as a route to thiocyanates.

There have been two further developments in this area since then. Several steroidal derivatives have been treated with thiocyanogen and bis(chloro)iodobenzene with irradiation (Equation (26)) <1997JCS(P1)339>, to effect radical thiocyanation at tertiary centers (although this combination of reagents does give rise to a mixture of products in low-to-moderate yields overall). In other experiments, the addition of thiocyanogen to 1,6-cyclodecadiyne has been shown to prompt cyclization to the bicyclo[4.4.0]deca-1,6-diene ring system (Equation (27)), albeit in extremely low yield. A radical mechanism has been proposed to rationalize this reaction <1997TL1541>.





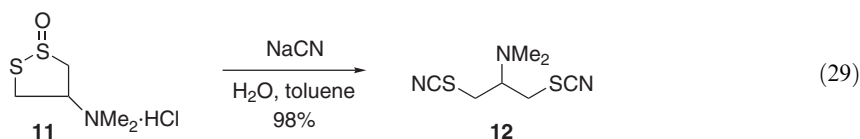
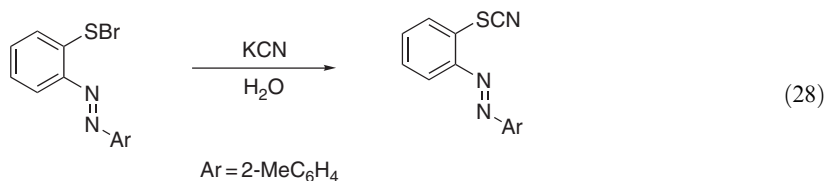
5.30.2.2 Formation of the RS—CN Bond

It was noted in chapter 5.30.2.2 of COFGT (1995) <1995COFGT(5)1099> that the synthesis of an organic thiocyanate by forming the S—CN linkage avoids competing formation of the isothiocyanate, although it does not preclude isomerization of the product once formed. Three general classes of reaction were considered in COFGT (1995): the reaction of nucleophilic cyanide with electrophilic sulfur, combination of a cyanogen halide with a sulfur nucleophile, and a reductive procedure from a sulfinate or sulfonyl chloride.

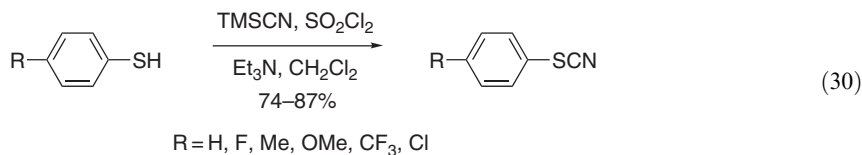
5.30.2.2.1 Nucleophilic cyanation of sulfur

Chapter 5.30.2.2.1 of COFGT (1995) <1995COFGT(5)1099> surveyed the reaction of nucleophilic cyanide (either a metal cyanide (LiCN, NaCN, and KCN) or TMS—CN) to displace leaving groups from a variety of sulfur electrophiles. These included sulfenyl halides, sulfenyl thiocyanates, thiosulfates, disulfides, *N*-arylthiohydantoin, and *N*-arylthioisatins.

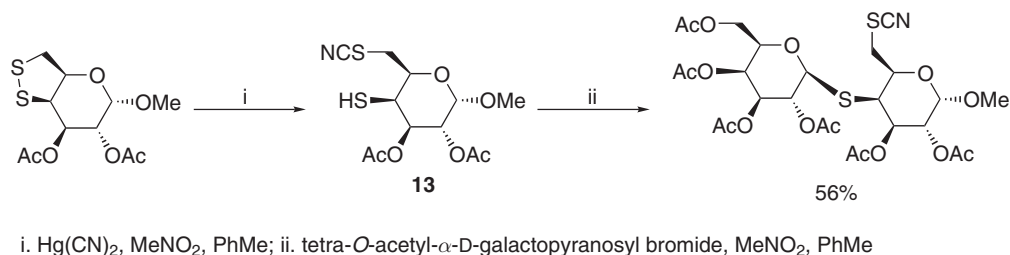
Quite a number of new approaches of this type have been reported since the publication of COFGT (1995). Simple cyanide salts have been reacted with sulfenyl chlorides <1998SUL19>, sulfenyl bromides (Equation (28)) <1997DOK777>, and thiosulfonates <1996BSF515, 1999SC3289>, the last of these a solid-state reaction performed in the absence of solvent. Additionally, tetra-*n*-butylammonium cyanide has been used to displace the leaving group from a range of thiotriflates <2002TA2635>, and in one synthesis of ¹⁴C-labeled methyl thiocyanate, potassium cyanide was reacted directly with elemental sulfur, the resulting intermediate then being trapped with dimethyl sulfate <2002MI510>. In a final application of simple cyanide salts, the dithiolane-1-oxide **11** was ring-opened with sodium cyanide to give the bis(thiocyanate) **12** (Equation (29)) <2000JAP2000086619>.



TMSCN has also found further application in this area of heteronitrile chemistry. This cyanating agent has been used to convert sulfenyl chlorides into the corresponding thiocyanates, by reaction in acetonitrile at room temperature for 1 h <2001TL699>. Various substituted benzene thiols have been converted into their thiocyanates by reaction with sulfonyl chloride (SO₂Cl₂) and TMSCN in dichloromethane (Equation (30)) <2001SC1355>.



In a last new approach to the nucleophilic cyanation of sulfur, mercury(II) cyanide has been used to reductively open a cyclic disulfide <1999M1137>. The free thiol **13** was not isolated but trapped directly by reaction with a galactopyranosyl bromide to furnish a sulfide-linked disaccharide product (Scheme 3).

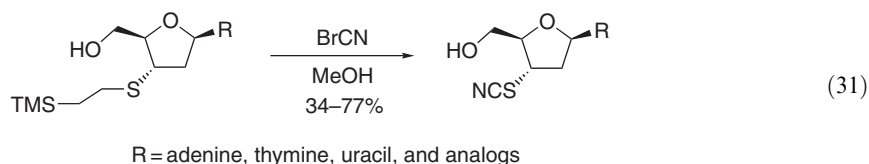


Scheme 3

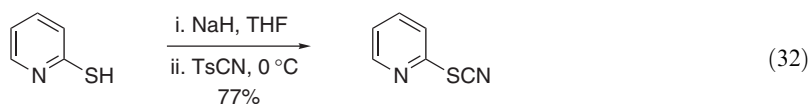
5.30.2.2.2 Electrophilic cyanation of sulfur

Only a handful of reactions of this type were discussed in chapter 5.30.2.2.2 of COFGT (1995) <1995COFGT(5)1099>. Cyanogen halides have been used to cleave thioethers, 2-nitro-5-thiocyanatobenzoic acid exploited as an alternative cyanating agent for thiols, and a two-step process developed in which bromocyanogen is used to alkylate the resulting thiolates.

There have been several new developments in this area since the 1990s, including the application of new reagents for the cyanation of thiols. The cyanogen halides have found particular application in this area. In an extension of the gas–solid route to organic cyanates discussed above, the sodium thiolate of 3-*H*-benzothiazole-2-thione has been treated with cyanogen bromide or cyanogen chloride to afford its thiocyanate in quantitative yield <1998CEJ2467>. In addition, the thiocyanates of pyridine-2-thione and quinoline-2-thione have been prepared in good yield by reaction of the thiones with base (sodium hydroxide <2000MI135> or sodium hydride <1997H745>) followed by cyanogen bromide. Finally, cyanogen bromide has been applied in the von Braun reaction of several 2-(trimethylsilyl)ethyl sulfides, resulting in selective cleavage of the silylated side chain (Equation (31)) <2002JOC1898>. This approach has been used to prepare thiocyanate derivatives of adenosine, thymidine, uridine, and various model systems in moderate-to-excellent yields.



The first of the new reagents to be used in this area is toluene-4-sulfonyl cyanide (TsCN), which has been applied to cyanate pyridine thione and the analogous derivatives of various quinoline, pyrimidine, and purine heterocycles (Equation (32)) <1997H745>. Formation of the disulfide competes, although this side reaction is minimized by performing the reaction at 0 °C. Imidazole-1-carbonitrile is a second source of electrophilic cyanide that has recently been applied to the cyanation of thiols <2000OL795>. Benzene thiol and 2,3-dimethoxythiophenol have both been converted into their thiocyanates by reaction with butyllithium to generate the thiolate and then the imidazole reagent (Equation (33)).





5.30.2.2.3 Reductive cyanation of sulfur

Chapter 5.30.2.2.3 of COFGT (1995) <1995COFGT(5)1099> briefly discussed several reactions of this type, in which TMSCN or diethylphosphoryl cyanide are used to convert arylsulfinate salts or arylsulfinic acids directly into aryl thiocyanates.

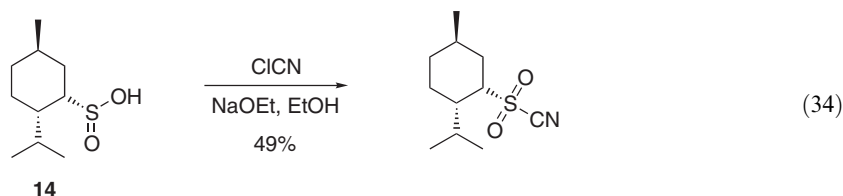
5.30.2.3 Formation of Acyl Thiocyanates

Just three reactions of this type were reviewed in chapter 5.30.2.3 of COFGT (1995) <1995COFGT(5)1099>: thiocarboxylate salts with chlorocyanogen; carboxylic acids with pyro-catechyl phosphoryl chloride and thiocyanogen; and thiourea, butyllithium, and methyl iodide. There have been no further developments in this area.

5.30.2.4 Formation of Sulfonyl Cyanides

The combination of sulfinic acids with cyanogen chloride in water represents the sole access to compounds of this type as reviewed in chapter 5.30.2.4 of COFGT (1995) <1995COFGT(5)1099>, although it was noted that the conversion of sulfonyl chlorides into sulfonates by reaction with sulfite and bicarbonate offers an alternative starting material for this reaction.

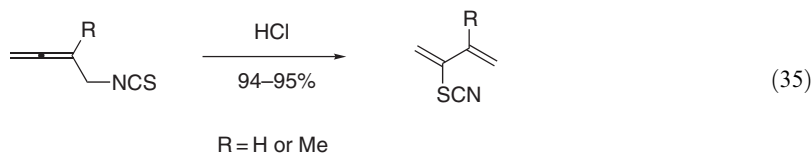
There has been one new reaction of this type reported in recent years, involving reaction of the sulfinic acid **14** with sodium ethoxide and then cyanogen chloride (Equation (34)) <1997H1745>.

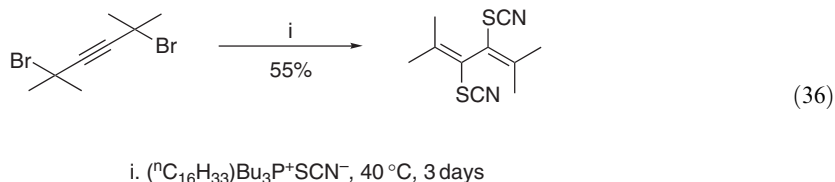


5.30.2.5 Formation of RSCN by Fragmentation/Rearrangement Reactions

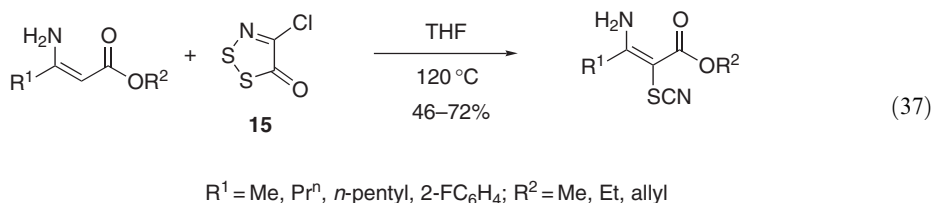
Chapter 5.30.2.5 of COFGT (1995) <1995COFGT(5)1099> discussed three routes to organic thiocyanates via fragmentation and rearrangement reactions: the rearrangement of *N*-arylthioformamides when treated with phosgene and triethylamine; the reaction of 2-imino-5,6-dihydro-4*H*-1,3-thiazines with diethyl phosphoryl chloride or sulfonyl chlorides; and ring cleavage of a suitably substituted thiazole.

An interesting new rearrangement has come to light in recent years, whereby allenyl and propargyl isothiocyanates have been shown to rearrange via a [3,3]-sigmatropic mechanism, to thiocyanates (Equations (35) and (36)) <1999PS325, 2001EJO1089>. This work has shown that it is possible to convert an isothiocyanate into the thermodynamically less favored thiocyanate, providing that a more stable carbon skeleton is created in the process, and the rearrangement has been successfully exploited in the efficient synthesis of various vinylic thiocyanates.





Finally, 4-chloro-5*H*-1,2,3-dithiazol-5-one **15** has been successfully exploited in preparing thiocyanates from a variety of α,β -unsaturated β -amino esters, in a reaction that is part fragmentation, part rearrangement (Equation (37)) <1999TL6439>.



5.30.3 SELENO- AND TELLUROCYANATES— $\text{RSeC}\equiv\text{N}$ AND $\text{RTeC}\equiv\text{N}$

Since the publication of chapter 5.30.3 in COFGT (1995) <1995COFGT(5)1099>, several new routes to seleno- and tellurocyanates have emerged, and many of the synthetic pathways described therein have found further application in a range of new contexts. These new approaches and applications are discussed below, along with brief consideration of the principal syntheses reviewed in the earlier volume.

5.30.3.1 Selenocyanates— $\text{RSeC}\equiv\text{N}$

The principal routes to selenocyanates (RSeCN) described in chapter 5.30.3.1 of COFGT (1995) <1995COFGT(5)1099> involve reaction of the selenocyanato functionality (in either nucleophilic or electrophilic guise) to form the R—SeCN bond, or construction of the RSe—CN linkage via combination of an alkali metal cyanide with an appropriate source of electrophilic selenium.

5.30.3.1.1 Formation of the R—SeCN bond

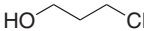
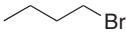
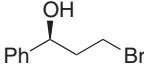
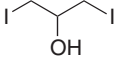
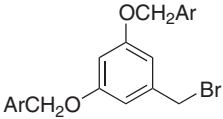

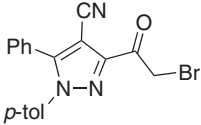
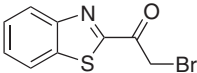
Four general methods for forming the R—SeCN bond were described in chapter 5.30.3.1.1 of COFGT (1995): formation by nucleophilic substitution reactions, reaction with electrophilic selenium, additions to double bonds, and homolytic reactions. There have been further advances in the first three of these areas since 1995.

(i) Formation of the R—SeCN bond by nucleophilic substitution reactions

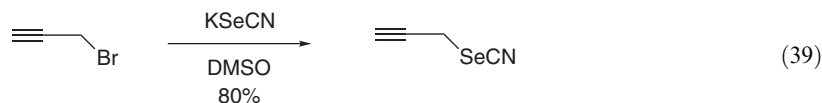
Nucleophilic substitution by potassium selenocyanate (KSeCN) remains the most common route into this class of compound. A wide range of alkyl halides, tosylates, diazotized arylamines, and epoxides have all been exploited as electrophiles in reactions with potassium selenocyanate.

Since 1995, a wide range of organic selenocyanates have been prepared from the reaction of potassium selenocyanate with various alkyl and benzyl halides, including alkyl chlorides, bromides, and iodides, benzylic bromides and chlorides, and α -bromocarbonyl compounds. A selection of representative examples is summarized in Table 2. There has also been one interesting report describing the preparation of allenyl and propargylic selenocyanates from the corresponding bromides and chlorides (Equations (38) and (39)) <1995AG(E)1627>.

Table 2 Selenocyanates RSeCN prepared from alkyl halides and potassium selenocyanate (KSeCN)

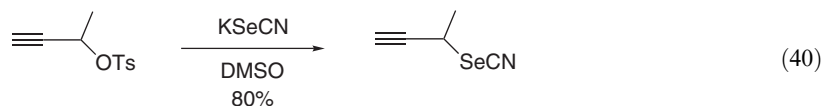
<i>RX</i>	<i>Solvent/temperature</i>	<i>Yield (%)</i>	<i>References</i>
	Acetone, Δ	72	<1995CJC113>
	DMF, 60 °C	97	<1997T12147>
	DMF, 60 °C	73	<1997CEJ1894>
	Acetone, Δ	75 ^a	<1996CJC533>
	CH ₃ CN, 20 °C	100 ^b	<2000BCJ1857>
	EtOH, Δ	71	<1995MI211, 1997CC1021>
	EtOH, rt	85	<1996MI493>
	EtOH, Δ	90	<1997PS43>

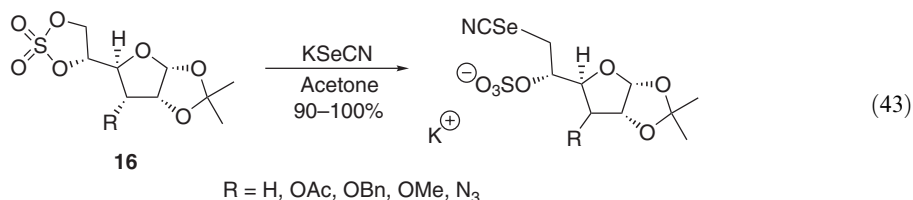
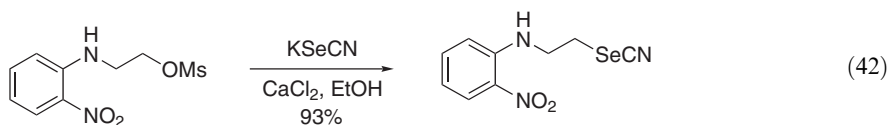
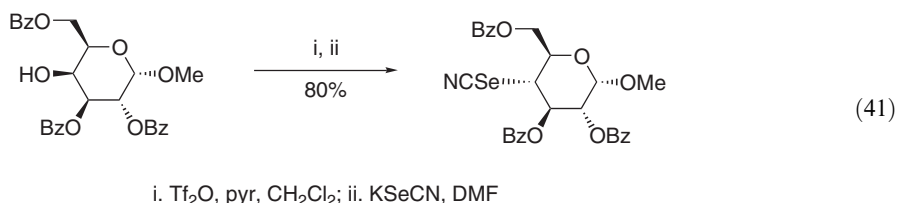
^a Yield for conversion into the diselenocyanate. ^b Ar = 3,5-di(3,5-dimethoxybenzyloxy)phenyl.



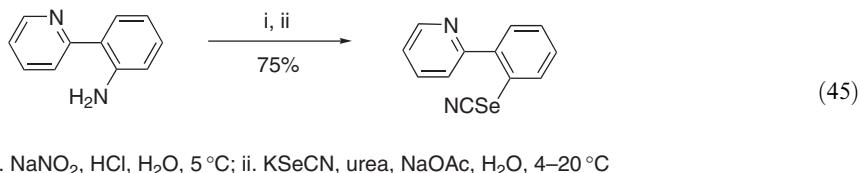
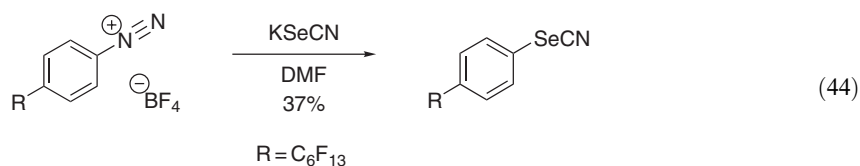
In an extension of this approach, a telluriated selenium cyanate has been prepared by reaction of the tellurium halide with potassium selenocyanate <2002EJI2701>. This Te—SeCN compound has also been generated using silver(I) selenocyanate as the selenium source.

Sulfonates offer another class of reaction partner of KSeCN, and a variety of *p*-toluenesulfonates, methanesulfonates, and trifluoromethanesulfonates have been used as substrates for this reaction <1999TL1181, 2001MI93>; representative examples are shown (Equations (40)–(42)) <1995AG(E)1627, 1995JA9783, 1995MI871>. In an interesting variation on this theme, a range of cyclic sulfates of general structure **16** have been opened using the selenocyanate nucleophile, affording 6-selenocyanato-5-*O*-sulfo furanose derivatives (Equation (43)) <1995CC461, 1997JOC3944>.

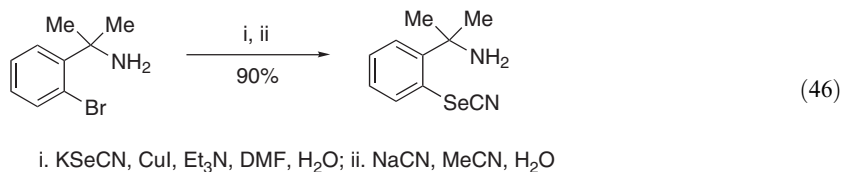




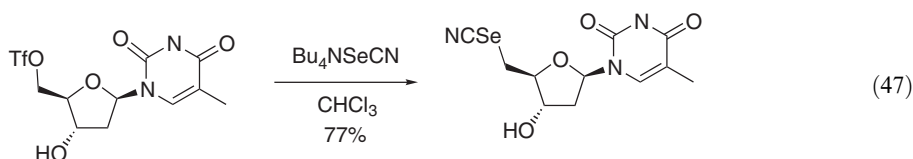
The main route to aryl selenocyanates remains reaction of KSeCN with a diazotized aromatic compound and this approach has been utilized to access a number of compounds in this class [\(<1996JHC1275, 2001BMC1459, 2002JA1902, 2002JCS\(P1\)1568>\);](#) two representative examples are shown ([Equations \(44\) and \(45\)](#)) [\(<1999OL269, 1999T14261, 2000JCS\(P1\)1429>\).](#)



An alternative approach to the selenocyanation of aromatic rings has also emerged recently, by which nonactivated aryl bromides can be converted into the corresponding aryl selenocyanates in excellent yields ([Equation \(46\)](#)) [\(<2000JOC8152>\).](#) This transformation involves direct reaction of the aromatic compound with potassium selenocyanate and an equimolar amount of copper(I) iodide, in the presence of amine base, then subsequent treatment with sodium cyanide. The selenation reaction appears feasible in a range of solvents, including DMF, acetonitrile, and THF.



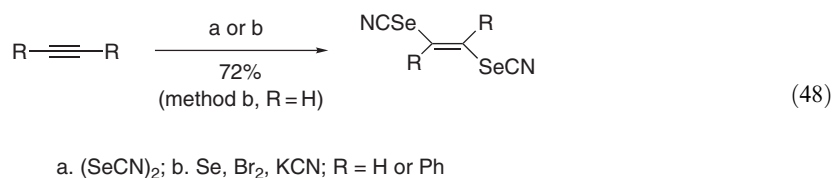
Finally, in a slight variation on the use of potassium selenocyanate as the source of SeCN , tetra-*n*-butylammonium selenocyanate has been exploited in a range of similar reactions, and used to displace the triflate leaving group in several carbohydrate derivatives ([Equation \(47\)](#)) [\(<1999TL1181, 2001MI93>\).](#)



(ii) *Reaction with electrophilic selenium*

An alternative approach to R—SeCN bond formation reported in COFGT (1995) <1995COFGT(5)1099> exploited selenocyanogen (SeCN)₂ as an electrophilic source of selenium, in reactions with several organocuprates (though organolithium compounds and Grignard reagents fail to react with (SeCN)₂ in a similar way).

One interesting new application of selenocyanogen to the synthesis of organic selenocyanates has been recently reported, in which the triple bond of an alkyne acts as the reaction partner for electrophilic selenium <1998PS587>. This methodology results in the addition of (SeCN)₂ across the triple bond to give a doubly vinylic 1,2-diselenocyanate as the (*E*)-stereoisomer (Equation (48), path (a)), and so this transformation might equally be considered in the following section.

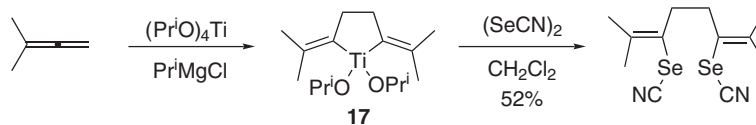


(iii) *Additions to double bonds*

The third method for forming the R—SeCN bond discussed in COFGT (1995) involves addition to carbon–carbon double bonds. Iodine, thallium(III) acetate in alcohol, and copper(II) halides in alcohol or acetonitrile have all been used with KSeCN to add the selenocyanate group and an iodide or alkoxide moiety across the alkene. Several new reactions of this type have been reported recently (further to the reaction of alkynes discussed in Section 5.30.3.1.1.(ii) above).

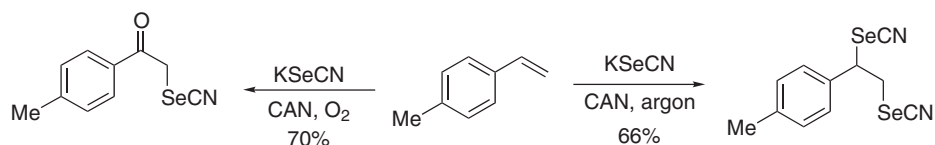
In the first of these, the combination of elemental selenium, bromine, and potassium cyanide has been used to add the selenocyanate group to both ends of several alkynes (Equation (48), path b) <1996RTC443>, a transformation similar to that achieved with selenocyanogen and discussed in Section 5.30.3.1.1.(ii) above.

Second, a new route has been developed which exploits the intermediacy of titanacyclopentadienes such as **17** in the conversion of alkynes and allenes into vinylic selenocyanates (and thence onward to 1,2-diselenins) (Scheme 4) <1999AG(E)1604>.

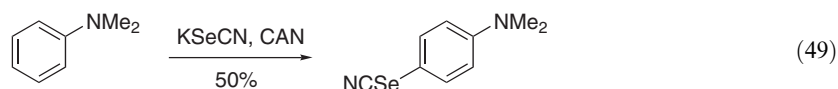


Scheme 4

In the third, new application that broadly fits into this class, a transformation has recently been developed whereby the addition of KSeCN to alkenes is mediated by cerium(IV) ammonium nitrate (CAN) <2002EJO2363>. In the presence of oxygen, α-selenocyanato ketones are generated from styrene and related alkenes, while under an atmosphere of argon, the corresponding bis(selenocyanate) derivatives are formed (Scheme 5). This transformation has also been applied to some electron-rich aromatic systems, including indole, *N*-methylpyrrole, and *N,N*-dimethylaniline (Equation (49)).



Scheme 5

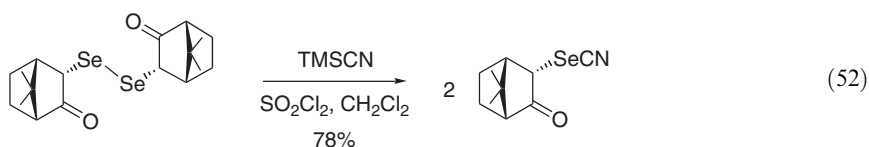
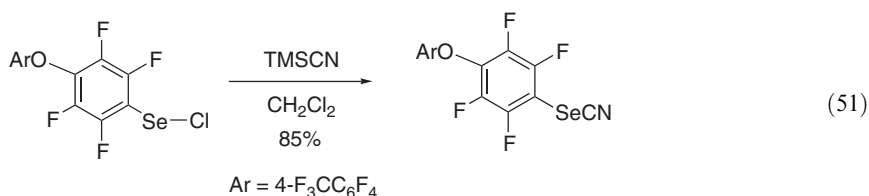
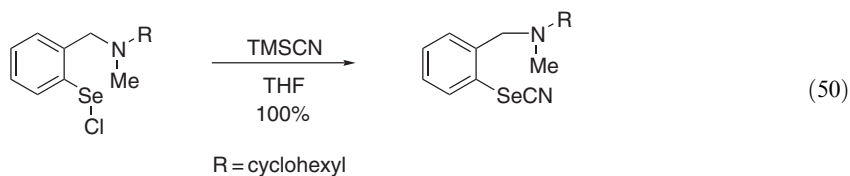
*(iv) Homolytic reactions*

The final method of R—SeCN bond formation reviewed in COFGT (1995) [<1995COFGT\(5\)1099>](#) was a radical approach, exploiting a decarboxylative selenocyanation reaction en route to L-selenomethionine and L-selenocysteine. There have been no further developments in this area.

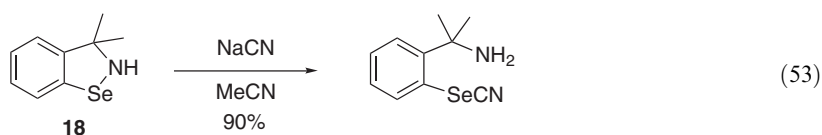
5.30.3.1.2 Formation of the RSe—CN bond

A small number of reactions of this type were discussed in chapter 5.30.3.1.2 of COFGT (1995) [<1995COFGT\(5\)1099>](#), the most common being the combination of a selenyl halide with a metal cyanide, or with trimethylsilyl cyanide (TMSCN).

The commercial availability of TMSCN has opened up this second route as a more attractive option. Various selenocyanates have been prepared from the corresponding selenyl chlorides using this reagent (Equations (50) and (51)) [<1996JA8077, 1999EJI1359, 2000JA1343, 2002JA1902>](#), and also one alkyl selenocyanate, via a reaction which first cleaves the diselenide (Equation (52)) [<1995JOC703>](#).



Several new reports have also appeared detailing work in which sodium cyanide is used as the source of the cyano group, in reactions with aryldiselenides [<2000BCJ1857>](#) and also to open the intriguing azaselenocycle **18** (Equation (53)) [<2000JOC8152>](#).



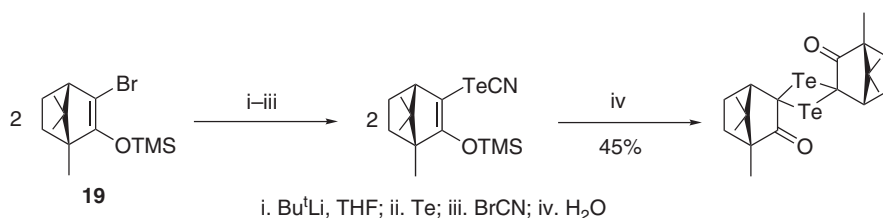
5.30.3.2 Tellurocyanates— $\text{RTeC}\equiv\text{N}$

It was noted in chapter 5.30.3.2 of COFGT (1995) <1995COFGT(5)1099> that tellurocyanates are notoriously unstable, and as a result only a few stable compounds of this type had ever been made. This remains the case, and only a scattering of new approaches have been reported since 1995.

5.30.3.2.1 Formation of the R—TeCN bond

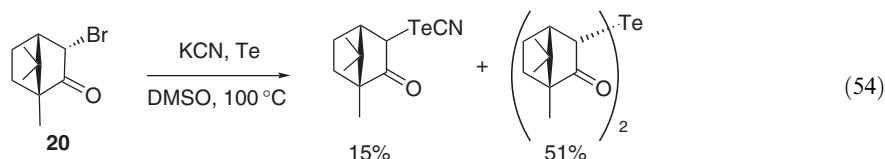
The one method of this type discussed in the earlier volume used potassium tellurocyanate (which was generated *in situ*) in reaction with benzyl halides. The methodology was, however, limited to benzylic systems.

Two new approaches to R—TeCN bond formation have emerged since 1995. In the first, Back and co-workers <1995JOC4657> have prepared the vinyl tellurocyanate derivative of camphor from 3-bromocamphor trimethylsilyl enol ether **19** by reaction with *t*-butyllithium, followed by elemental tellurium, and finally cyanogen bromide (Scheme 6). (The vinyl tellurocyanate was subsequently hydrolyzed to afford several ditelluretanes via dimerization of the telluroketone intermediate.)



Scheme 6

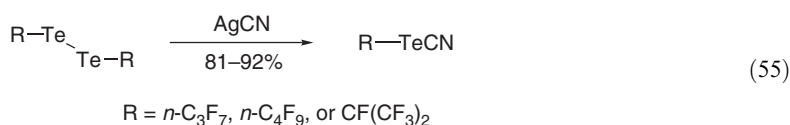
In a related approach, reported in the same paper <1995JOC4657>, potassium cyanide and elemental tellurium were applied to convert the α -bromo ketone **20** into the corresponding tellurocyanate and the ditelluride derivative (Equation (54)). Both of the above transformations achieve formation of both the R—Te and Te—CN bonds in the one step.

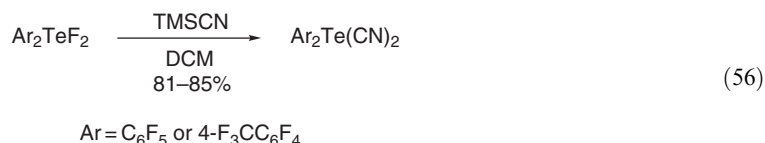


5.30.3.2.2 Formation of the RTe—CN bond

Chapter 5.30.3.2.2 of COFGT (1995) <1995COFGT(5)1099> discussed routes to several tellurocyanates via reaction of alkyl- and aryltellurium halides and diphenyl ditelluride with potassium or silver(I) cyanide. A second approach used borohydride to reduce a ditelluride, and then cyanogen bromide to trap the intermediate.

Two new approaches of this type have surfaced in recent years. In the first, silver cyanide has been used to cleave a range of perfluoroalkyl ditellurides <2000JCS(D)11>, giving rise to several different fluorinated alkyl tellurocyanates (Equation (55)). The second recently reported method applies TMSCN to displace both fluoride ligands from bis(pentafluorophenyl)tellurium difluoride and also the *p*-trifluoromethyl analog (Equation (56)) <2001JFC207>.





5.30.4 SINGLY BONDED NITROGEN DERIVATIVES— $\text{R}_2\text{NC}\equiv\text{N}$ (CYANAMIDES)

Chapter 5.30.4 of COFGT (1995) reviewed a wide array of routes to organic cyanamides <1995COFGT(5)1099>, with the majority of these approaches proceeding via formation of either the $\text{R}-\text{NCN}$ bond or the $\text{RN}-\text{CN}$ linkage. Several syntheses exploiting rearrangement or other modification of an intact $\text{R}-\text{N}-\text{C}-\text{N}$ unit were also discussed. A similar distribution is apparent in approaches to cyanamides that have appeared since the publication of COFGT (1995), although this chapter is organized slightly differently to its predecessor: reactions forming an $\text{R}-\text{NCN}$ link are considered together in the first section as previously; however, a combined section detailing approaches to formation of the $\text{RN}-\text{CN}$ bond (considering both nucleophilic and electrophilic cyanide sources) is second, and then a combined consideration of dehydration, rearrangement, and fragmentation approaches to cyanamides. Finally, reactions on the carbon α to NCN that lead to cyanamides are discussed.

Preparations of dicyanamides were considered throughout chapter 5.30.4 of COFGT (1995), alongside the corresponding syntheses of the cyanamides themselves, a pattern that will be followed in this chapter also. It was noted in COFGT (1995) that dicyanamide itself ($\text{HN}(\text{CN})_2$) can be prepared from calcium cyanamide and cyanogen bromide, while sodium dicyanamide ($\text{NaN}(\text{CN})_2$) is conveniently made from the reaction of *N*-cyano-*S*-methylisothiurea with sodium hydroxide.

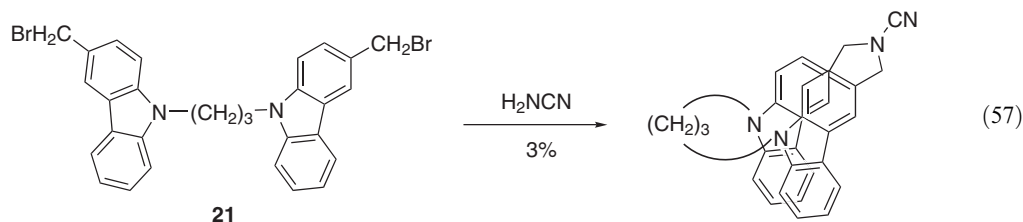
5.30.4.1 Formation of an $\text{R}-\text{NCN}$ Bond

5.30.4.1.1 Formation of an $\text{R}-\text{NCN}$ bond leading to alkylcyanamides

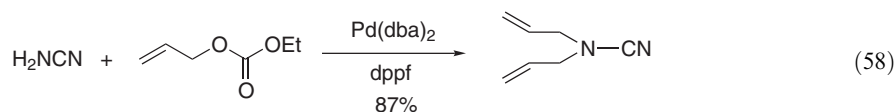
The principal method of this type discussed in chapter 5.30.4.1.1 of COFGT (1995) <1995COFGT(5)1099> was the direct reaction of cyanamide, dicyanamide, or a cyanamide salt with a carbon electrophile. It was noted that direct alkylation can give a mixture of mono- and disubstituted products, and that the singly alkylated compounds tend to be unstable, combining to form di- and trimers. Reactions of cyanamide with alkyl halides, dimethyl sulfate, or an aziridinone were discussed. The combination of cyanamide with an alkene, in the presence of electrophilic bromine or selenium, was also surveyed. The use of cyanogen azide (N_3CN , caution!) as a highly reactive source of the NCN unit in reactions with 1,2-dihydropyridines, simple alkanes and alkynes was also covered. Finally in this section of COFGT (1995), a range of less common reaction systems was considered, including: *N*-cyanocarbamates with alkylating agents; sodium nitrocyanoamide with an alkyl iodide and *m*CPBA; azonitriles with dienes in Diels–Alder chemistry; calcium cyanamide with a vinylsulfonic acid; radical cyclization of mono-substituted alkylcyanamides; the combination of *N*-substituted-*N*-chlorocyanamides with alkenes; and the reaction of a dialkylcyanamide with a powerful alkylating agent such as trimethyloxonium tetrafluoroborate, giving rise to *N*-cyano-*N,N,N*-trialkylammonium salts.

The combination of cyanamide with an organic halide has been used in a variety of contexts since 1995. Most preparations of this type to be published in that time involve the second alkylation of a mono-substituted alkyl- or arylcyanamide, using an alkyl halide and base. For example, isopropylcyanamide, phenylcyanamide, and a range of cyclopropyl- and cyclobutylcyanamides have been methylated using the combination of sodium hydroxide and methyl iodide with benzyltriethylammonium chloride as a phase-transfer catalyst <2000S1148>. Alternatively, a wide array of phenylcyanamide derivatives have been deprotonated with sodium hydride, then treated with methyl iodide in THF or DMF <1997JMC4281, 1998JMC3048, 1998JA6433, 2002BMCL1583>. In one preparation involving dialkylation of cyanamide itself, the phase-transfer catalyst Aliquat[®] 336 (tricaprylmethylammonium chloride) has been utilized with sodium hydroxide and the appropriate organic chloride in syntheses of dimethyl-, diethyl-, and

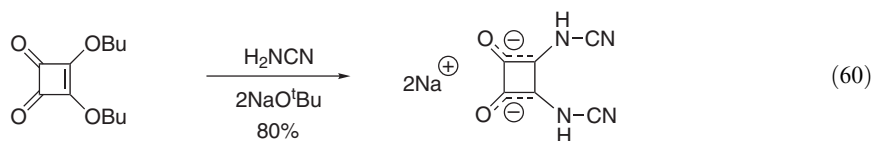
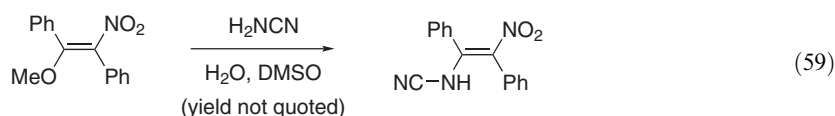
dibenzylcyanamide <1999PS169>. The same combination of base and catalyst has also been used to dialkylate cyanamide with much longer hydrocarbon chains (C₁₆ or C₁₈) <2002OPP643>. Tani and co-workers <2001CC1914> have reported an elegant cyclization reaction whereby cyanamide is reacted with the dibromide **21** to form a carbazophane (Equation (57)) <2001CC1914>.



Various alkenes (principally vinylbenzene derivatives) have been reacted with cyanamide and an electrophilic halide source (*N*-chloro-, *N*-bromo-, or *N*-iodosuccinimide) to furnish the corresponding α -halocyanamides in low-to-moderate yields <1996BMCL2553, 2001JMC3531>. Moreover, methodology has been recently developed whereby palladium(0) is used to transfer an allyl group from allyl ethyl carbonate to cyanamide (Equation (58)) <1998T14869>. This approach has also been extended to several cyclization reactions affording medium and large heterocycles, although yields are considerably lower <1998T14885>.



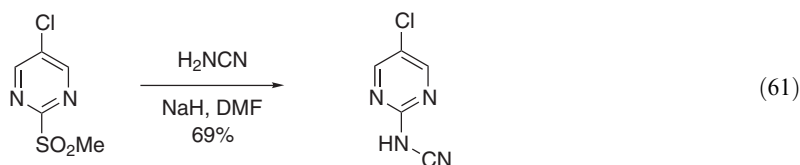
Finally, two approaches have been recently explored in which cyanamide formally combines with an enol ether to displace an alkoxide (Equations (59) and (60)) <1999JOC2897, 2001JCS(D)1529>.

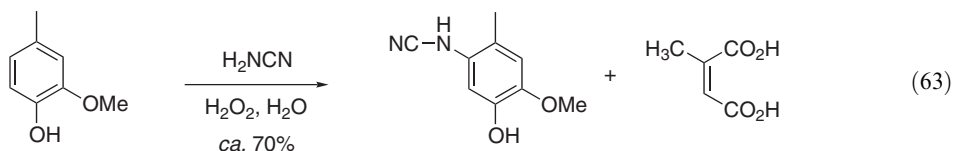
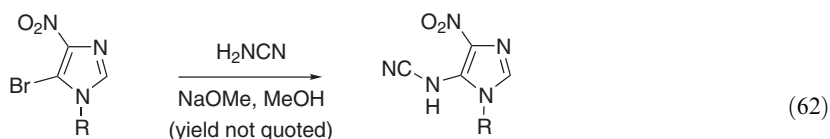


5.30.4.1.2 Formation of an R–NCN bond leading to arylocyanamides

Nucleophilic attack by cyanamide on an appropriately substituted aromatic system represents the primary route to organic cyanamides of this type, as discussed in chapter 5.30.4.1.2 of COFGT (1995) <1995COFGT(5)1099>. Thus, reactions of cyanamide or cyanamide salts with aromatic diazonium species or alternative aromatic electrophiles such as trialkylammonium triazines and 2-methanesulfonylpyrimidine were considered in COFGT (1995).

There have been few reactions of this type reported recently. The nucleophilic attack of cyanamide on two heterocyclic systems has been reported: a chloropyrimidine (Equation (61)) <1996AJC573> and a nitroimidazole (Equation (62)) <2001JA12147>. Also, the combination of cyanamide and hydrogen peroxide has been used to introduce a cyanamide unit to cresol via a radical mechanism (Equation (63)), although this study was more mechanistic than synthetic in nature <1998JCS(P2)2309>.



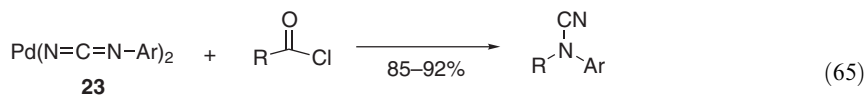
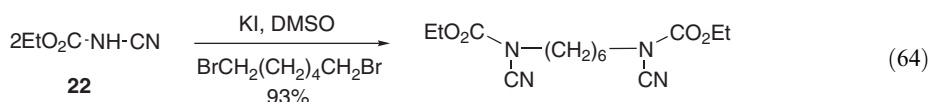


5.30.4.1.3 Formation of an R–NCN bond leading to acyl- or iminocyanamides

(i) Preparations of acylcyanamides

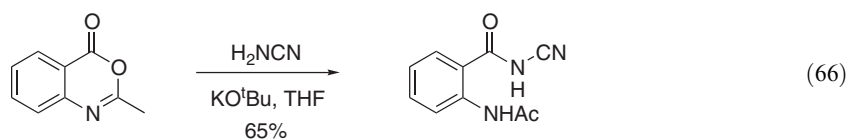
Chapter 5.30.4.1.3 of COFGT (1995) <1995COFGT(5)1099> noted that simple acylcyanamides are unstable, often decomposing to *N*-acyl-*N*-cyanoguanidines. Nonetheless, several fruitful synthetic approaches were discussed, including the reaction of cyanamide with acylating agents such as *N*-hydroxysuccinimide esters, the alkylation of unsubstituted acylcyanamides, and the reaction of bis(trimethylstannyl)carbodiimide with an acid chloride or chloroformate. Three approaches to the preparation of *N*-cyanoureas were also considered, the reactions of cyanamide with an isocyanate, cyanamide with an amide and sodium hypochlorite, and 3-alkyl-2-(*N*-cyanoamino)thiazolidines with an alkoxide.

Several new approaches to compounds of this type have been made over recent years. In the first of these, the combination of potassium iodide and an alkyl halide in DMSO has been applied to alkylate an existing acylcyanamide <1996AP535>. Thus, cyanocarbamic acid ethyl ester **22** has been alkylated with *n*-butyl, *n*-pentyl, *n*-hexyl, and benzyl halides, and also 1,6-dibromohexane (Equation (64)). In a complementary approach, a palladium(0)-mediated method has been developed for acylating a metal-bound diimide, providing a route to several acylcyanamides <2002JCS(D)3611>. In this approach, the bis(carbodiimide)palladium(0) complex **23** is treated with an acid chloride, and the acylating agent reacts with the distal nitrogen of the metal-bound diimide (Equation (65)). An alternative procedure using methyl chloroformate in the direct acylation of *N*-cyanoaniline has also been reported <2002SC803>.



Ar = 2,6-Me₂C₆H₃; R = Ph, PhO, 2-thiophenyl

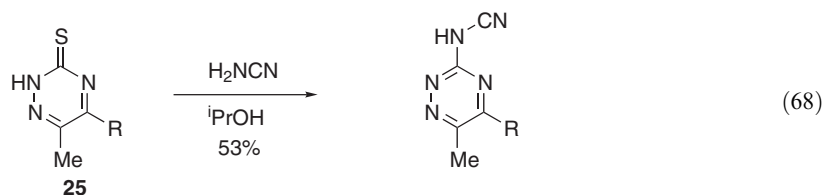
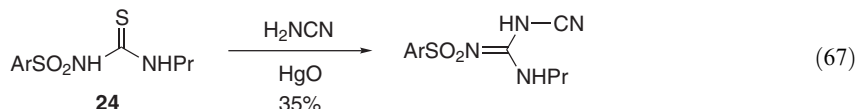
Finally, ring opening of an oxazinone with nucleophilic cyanamide has been employed to furnish a cyanamide product, formally a derivative of *o*-aminobenzoic acid (Equation (66)) <2001EJM597>.



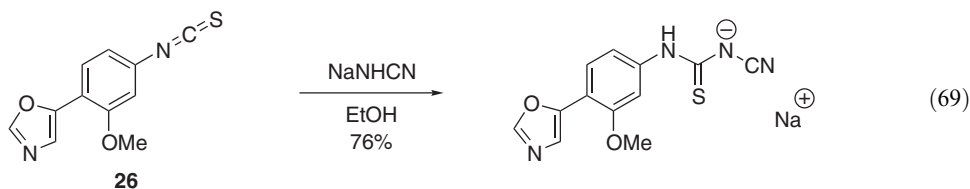
(ii) Preparations of iminocyanamides

The principal methods for synthesizing iminocyanamides covered in COFGT (1995) <1995COFGT(5)1099> were from the reaction of ureas with triphenylphosphine and carbon tetrachloride, followed by cyanamide and an amine base, or the displacement of ammonia from an amidine by nucleophilic cyanamide. Several approaches to the synthesis of cyanoguanidines from thioureas, *N*-aryl thiocarbamates, or the combination of cyanamide with trichloromethyl carbinols were also discussed briefly.

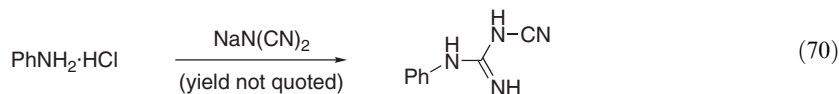
A large number of new routes to iminocyanamide and cyanoguanidine derivatives have been developed recently, harnessing a number of different precursors. The thiourea **24** has been converted into an iminocyanamide using cyanamide and mercury(II) oxide (Equation (67)) <1996SC4299>, and the pyridazine thione **25**, which could be considered a cyclic “thiourea equivalent,” by reaction with cyanamide in isopropanol (Equation (68)) <2003PS279>.



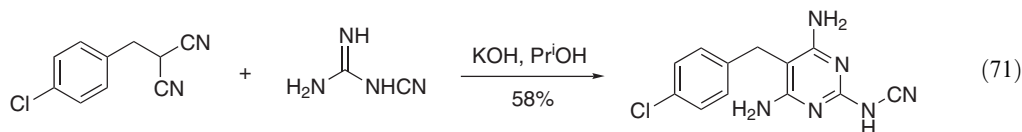
1-Isothiocyanato-3-methoxy-4-(oxazol-5-yl)benzene **26** (Equation (69)) <2002BMCL2931>, 1-isothiocyanato-2-nitrobenzene <1998JMC3159>, benzimidic acid methyl ester <2003BMCL297>, and a 2-methylsulfanylthiazol-4-one <2001BMCL981, 2002H857> have all been converted into cyanamide derivatives by reaction with nucleophilic cyanamide.

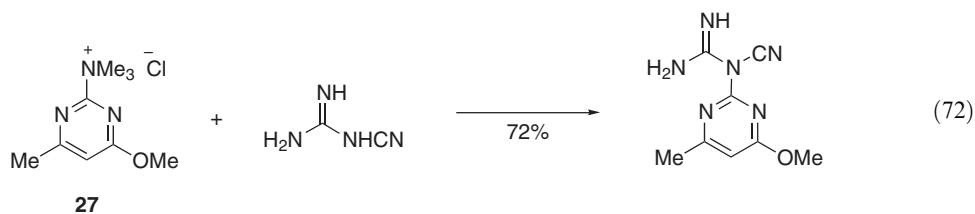


The direct conversion of amines into cyanoguanidines by reaction with sodium dicyanamide ($\text{NaN}(\text{CN})_2$) has been reported recently <1995MI1299, 1997BMCL1721, 1999BMC509>. For example, anilinium hydrochloride can be converted directly into the corresponding cyanoguanidine (Equation (70)) <1997BMCL1721>, and likewise a range of aliphatic and aromatic primary amines. *N*-Cyanocarbodithioimide $((\text{MeS})_2\text{C}=\text{N}-\text{CN})$ has also been used in place of cyanamide in this transformation—this reagent is treated first with aqueous ammonia prior to reaction with the corresponding primary amine <1997BMCL1721>.

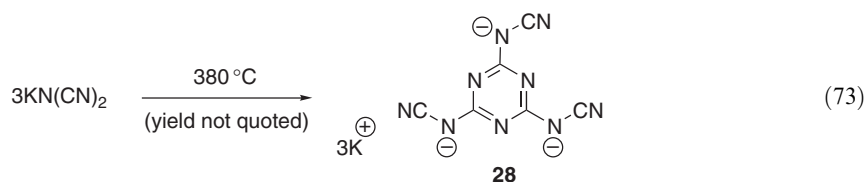


A range of cyclic cyanoguanidines has been prepared using an interesting new cyclization <1995PS11, 1997IJC(B)394, 1999IJC(B)445, 1999MI107, 2001S1509>. This reaction combines a geminal dinitrile with cyanoguanidine under basic conditions to generate a cyanamido-substituted pyrimidine (Equation (71)) <1995PS11>. In another approach to cyanamido-substituted nitrogen heterocycles, cyanoguanidine has been used to displace trimethylamine from the pyrimidine **27** (Equation (72)) <2001KGS349>.





There has also been one reported synthesis in which nucleophilic attack by cyanamide on an α,β -unsaturated ester triggered cyclization and dimerization to generate several polycyclic cyano-guanidine derivatives [<1999JHC209>](#). Finally, thermolysis of the potassium or rubidium salts of dicyanamide at 380 °C has been shown to effect trimerization, leading to the tricyanamido triazine **28** (Equation (73)) [<2001CEJ5372>](#).

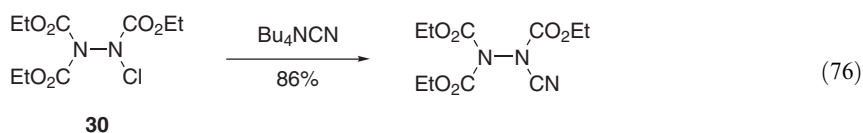
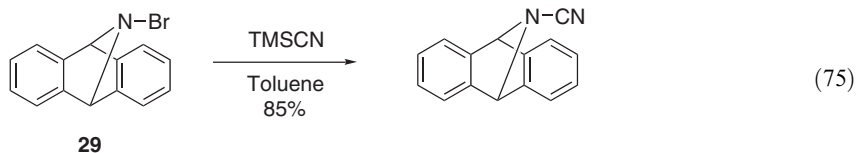
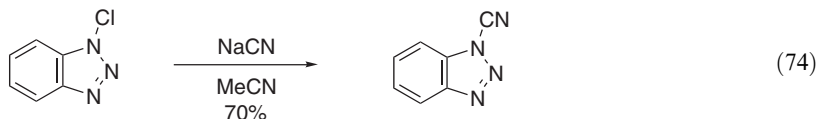


5.30.4.2 Formation of the RN—CN Bond

5.30.4.2.1 Formation of the RN—CN bond by reaction with nucleophilic cyanide

Chapter 5.30.4.4 of COFGT (1995) [<1995COFGT\(5\)1099>](#) noted that very few preparations of this type were available for consideration. However, two approaches were known at that time: the reaction of aromatic nitroso compounds with sodium cyanide in DMSO and the reaction of aryl azides with potassium cyanide followed by dimethyl sulfate to afford arylcyanotriazenes (albeit in low yield).

Three new reactions involving nucleophilic cyanide in formation of the RN—CN bond have been described since the publication of COFGT (1995), and each sees displacement of a halide leaving group from nitrogen. In the first, 1-chloro-1*H*-benzotriazole was treated with sodium cyanide in acetonitrile to furnish the corresponding cyano derivative in good-to-moderate yield (Equation (74)) [<1998JOC401>](#). The second approach exploits TMSCN as source of the cyano group, in reaction with the anthracene derivative **29** (Equation (75)) [<2001CC125>](#). Finally, tetra-*n*-butylammonium cyanide has been used to displace chloride from the *N*-chlorohydrazine **30** (Equation (76)) [<2002T2085>](#).



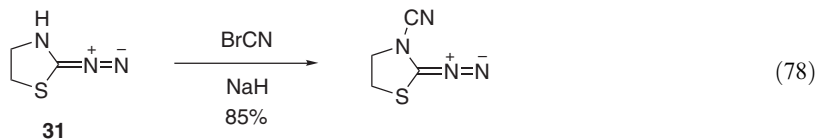
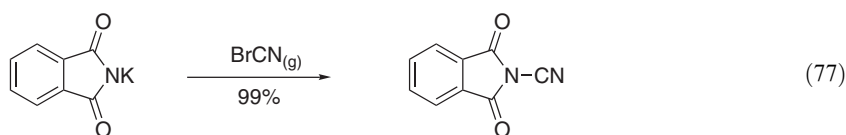
5.30.4.2.2 Formation of the RN—CN bond by reaction with electrophilic cyanide

The reaction of a nitrogen nucleophile with electrophilic cyanide (a cyanogen halide or equivalent), covered in chapter 5.30.4.6 of COFGT (1995) <1995COFGT(5)1099>, constitutes one of the most generally applicable and widely used routes to organic cyanamides. This section is further subdivided according to the nature of the nitrogen nucleophile.

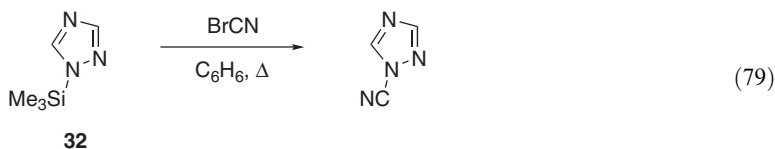
(i) Reaction of primary and secondary nitrogen with electrophilic cyanide

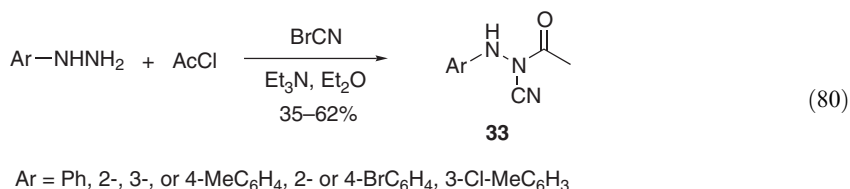
Chapter 5.30.4.6.1 of COFGT (1995) discussed, in detail, the reactions of nucleophilic primary and secondary amines to displace X (most commonly Cl or Br) from XCN. It was noted that while primary amines may give rise to both mono- and dicyanamide products, careful choice of conditions can afford considerable selectivity. Numerous reagent combinations have been used for the cyanation of primary and secondary amines—both aliphatic and aryl—and a variety of these were reviewed COFGT (1995). These included cyanogen bromide with sodium hydroxide, sodium bicarbonate, calcium carbonate or magnesium carbonate under aqueous conditions, cyanogen chloride with triethylamine in ether or THF, sodium cyanide with methanesulfonyl chloride or chlorine, ethyl thiocyanate with cadmium(II) oxide in chloroform, and phenyl isocyanate with sodium hydride. The cyanation of amidines and guanidines with a cyanogen halide and potassium hydroxide was also discussed, and so too methods for cyanating amides, sulfonamides, phthalimides, succinimides, hydrazides, and hydantoins.

The reaction of a primary or secondary amine with a cyanogen halide and base remains a very widely used route to organic cyanamides. Numerous solvent and base combinations have been utilized over recent years, including: sodium bicarbonate in ethanol <2001TL2455> or methanol <2003BMCL107>, sodium acetate <2001JMC3199> or ammonium acetate <1996MI377> in methanol, potassium hydroxide and ether under phase-transfer conditions <1999PS169>, triethylamine in dichloromethane <2001JMC94, 2002BMC3049>, and triethylamine plus DMAP in DMSO <1997T16835>. In an extension of the “gas–solid” approaches to cyanates (Section 5.30.1.2) and thiocyanates (Section 5.30.2.2.2) discussed above, the same workers have used gaseous cyanogen halide with trimethylamine gas to convert amines into cyanamides <1998CEJ2467>. Thus, assorted primary and secondary amines (principally aniline derivatives) have been transformed into the corresponding cyanamides in quantitative yields. This approach has also been extended to the cyanation of benzimidazole and of the potassium salt of phthalimide (Equation (77)). *N*-Cyanomaleimide has been prepared from maleimide by reaction with electrophilic cyanide <1998ACS608>, and the diazo-substituted heterocycle **31** has also been cyanated by reaction with cyanogen bromide (Equation (78)) <2003H161>.

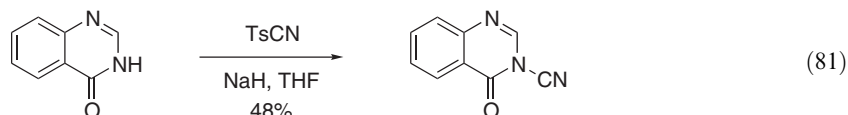


It is also interesting to note the use of an alternative nitrogen reaction partner for cyanogen bromide, the *N*-silylamine **32** which has been converted into 1,2,4-triazole-1-carbonitrile upon reaction with the electrophilic cyanide source (Equation (79)) <1995ZOR934>. Attempts to cyanate 4-methylimidazole with cyanogen bromide have been hampered by problems with regioselectivity <1999AJC159>. Finally, cyanogen bromide has been used to cyanate various *N*-acylated phenylhydrazine derivatives, affording cyanamides of general structure **33** (Equation (80)) <1997TL3115>.





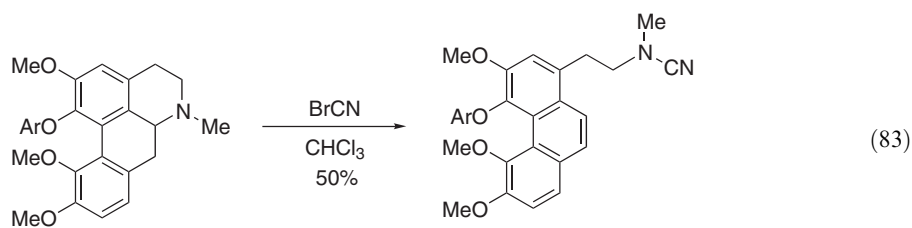
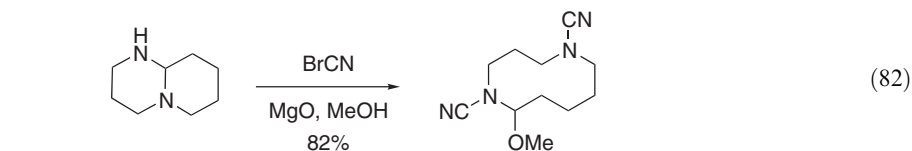
Several alternative sources of electrophilic cyanide have also been used in the preparation of organic cyanamides. 1-Cyanoimidazole has been applied to cyanate aniline in good yields [<2000OL795>](#) and 4-toluenesulfonyl cyanide (TsCN) used in combination with sodium hydride to cyanate several amines, including indole and 3*H*-quinazolin-4-one ([Equation \(81\)](#)) [<1997H443, 1997H745>](#).



(ii) *Reaction of tertiary nitrogen with electrophilic cyanide*

The reaction of tertiary nitrogen nucleophiles with cyanogen halides was considered in chapter 5.30.4.6.2 of COFGT (1995) [<1995COFGT\(5\)1099>](#). In the first instance, this interaction affords a cyanoammonium salt. However, the equivalent of X[−] released from the cyanogen halide generally returns to dealkylate the quaternary nitrogen in a selective transformation known as the von Braun reaction. The application of this chemistry to demethylate tertiary amines of general formula R₂NCH₃ was discussed in COFGT (1995), and so too the use of the von Braun reaction to cleave cyclic amines. It was also noted that the cyanoammonium intermediate may instead be trapped by other nucleophiles, such as methanol or water (affording a methyl ether or an alcohol), or in an intramolecular fashion to generate small or medium ring ethers (with inversion of configuration). Elimination was noted as another alternative reaction pathway for the cyanoammonium species to follow. Finally, the use of the von Braun reaction in syntheses of methyl(trimethylsilyl)cyanamide and bromoacetonitrile was considered briefly.

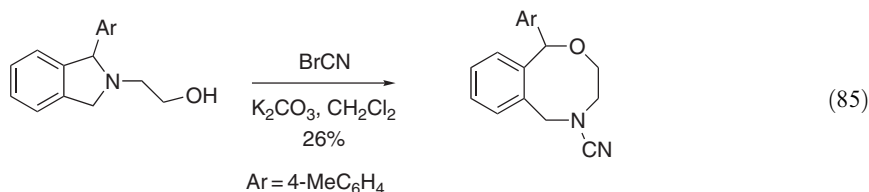
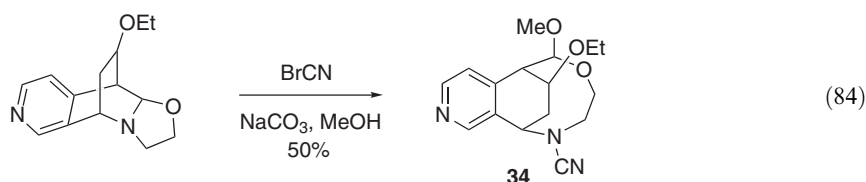
The principal uses of the von Braun reaction detailed above have all found further application since the publication of COFGT (1995). An assortment of tertiary methylamines R₂NCH₃ has been demethylated by treatment with cyanogen bromide in chloroform or dichloromethane [<1995SC829, 1996H1497, 1997BMC369, 1998T9143, 1998JOC4392>](#). Furthermore, cyanogen bromide has been used to ring-open two cyclic tertiary amines in related applications of von Braun chemistry, relieving the strain of a bridgehead nitrogen ([Equation \(82\)](#)) [<1999AJC1131>](#) and bringing aromaticity to the central ring of a phenanthrene system ([Equation \(83\)](#)) [<1996JNP738>](#).



Ar = 1-hydroxymethyl-3,4-dimethoxyphenyl

A similar approach has also been used in a ring-expansion route to the nine-membered ring of **34** ([Equation \(84\)](#)) [<1995TL9475>](#). Intramolecular attack by an alcohol nucleophile has been used in what amounts to another ring expansion transformation overall ([Equation \(85\)](#))

<2002AJC577>. Finally, attempts have been made to use cyanogen bromide for the debenzyla-
tion of an *N*-benzylpyrrolidine in a deprotection event with moderate success <2002BMC3277>.



(iii) *Reaction of a tertiary aromatic nitrogen with electrophilic cyanide*

Chapter 5.30.4.6.3 of COFGT (1995) <1995COFGT(5)1099> covered the few reported examples of electrophilic cyanation of tertiary aromatic nitrogen centers, a reaction which initially gives rise to a quaternary ammonium ion. This species then usually undergoes further reaction, either attack of a nucleophile at a ring carbon adjacent to the nitrogen (in the case of quinoline) or deprotonation of the salt to form an anion.

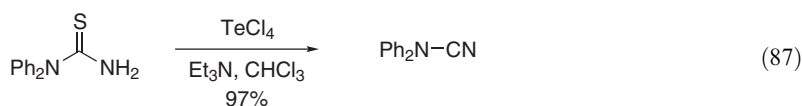
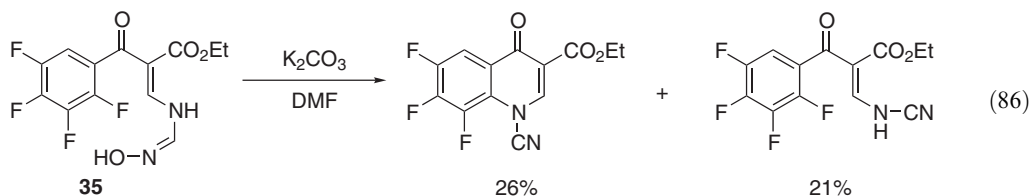
There have been no further developments in this area since the publication of COFGT (1995).

5.30.4.3 Dehydration, Rearrangement, and Fragmentation Reactions to Give Cyanamides

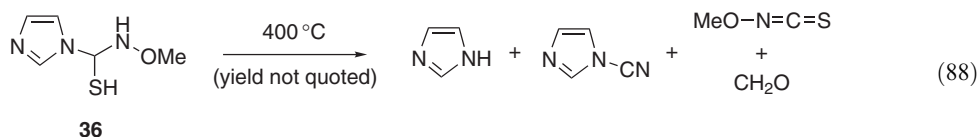
5.30.4.3.1 Dehydration and equivalent reactions leading to cyanamides

Various different dehydration-like reactions were considered in chapter 5.30.4.2 of COFGT (1995) <1995COFGT(5)1099>, most commonly starting from a urea or hydroxyformamidine (Ar—NH—C=N—OH) functionality. The reactions of ureas with potassium superoxide in aprotic media, or with trichloromethyl chloroformate were discussed, and so too was the dehydration of a hydroxyformamidine with phosphorus oxychloride or ethanolic potassium hydroxide, or with phosgene and triethylamine. Also considered were the combination of *N*-(chlorosulfonyl)imino-carbonyl chloride (Cl₂C=N—SOCl) with a diarylamine, bromodenitrogenation of a guanidine with NBS, and the reaction of an isothiocyanate with 4-aminotriazolium iodide.

Several new dehydration-type pathways to cyanamides have emerged in recent years. The hydroxyformamidine **35** gives two cyanamide products on treatment with base (Equation (86)), one of which is formed via an intramolecular nucleophilic aromatic substitution of fluoride <2000JHC297>. Furthermore, a variety of conditions have been exploited for the elimination of hydrogen sulfide from thioureas, including tellurium tetrachloride (Equation (87)) <1995JCR(S)152>, lead triacetate <2002EJM23>, and silver fluoride <2002HAC561>.



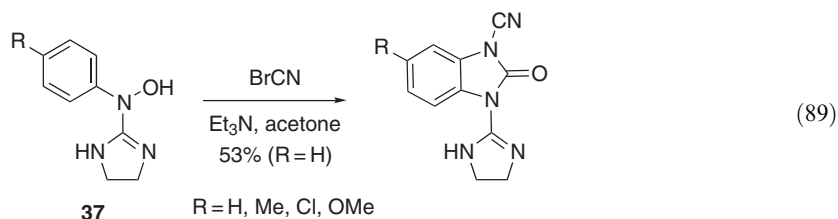
Finally, *N*-cyanoimidazole has been generated as one of several products from the thermal decomposition of *N*-(imidazol-1-ylmercaptomethyl)-*O*-methylhydroxylamine **36** at high temperature (Equation (88)) <1999JCS(P2)1869>.



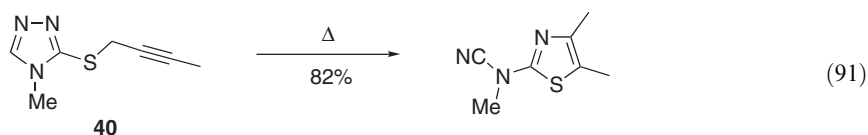
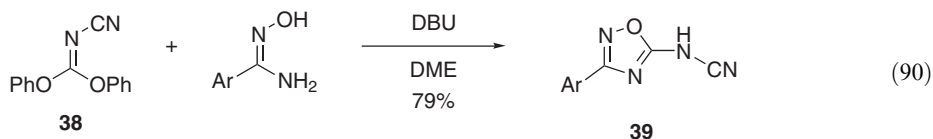
5.30.4.3.2 Rearrangement and fragmentation reactions leading to cyanamides

Chapter 5.30.4.3 of COFGT (1995) considered the thermolysis or flash-vacuum pyrolysis of various nitrogen-rich ring systems to afford substituted cyanamides of varying complexity <1995COFGT(5)1099>. Systems susceptible to this fragmentation include ylides such as triazolopyrimidinium bromide, tetrazolopyrimidines, lithiated tetrazoles, and the addition product of quinoline and *N*-phenylaminochloroimidate (PhNH—N=C(Cl)—CO₂Me). Furthermore, the products of 1,3-dipolar cycloaddition reactions between acyl nitrile oxides and dihydrooxazoles or dihydrothiazoles have been shown to rearrange affording cyanoacetamides. Finally, the rearrangement of functionalized diaziridinimines on heating was also discussed.

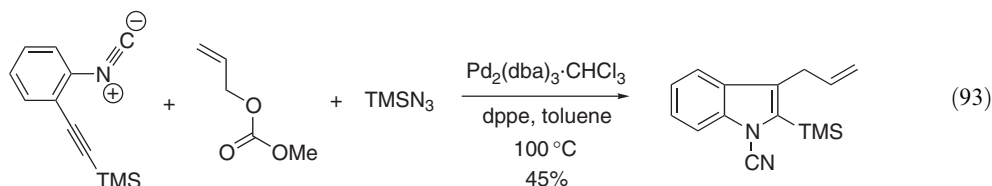
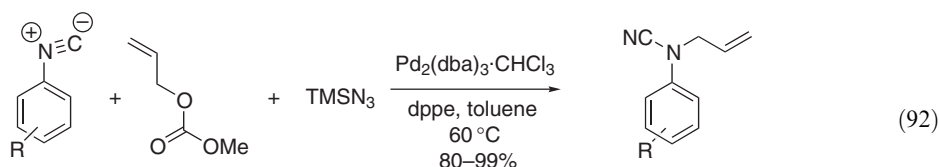
A considerable number of rearrangement and fragmentation reactions have been harnessed to generate cyanamide products since 1995. Substituted hydroxylamines such as **37** have been found to undergo what is believed to be a tandem 1,4-diaza-3-oxy-Cope rearrangement/nucleophilic substitution sequence upon treatment with bromocyanogen and triethylamine, giving rise to cyanamide products (Equation (89)) <1998AP241>.



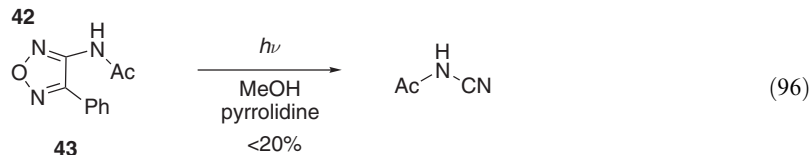
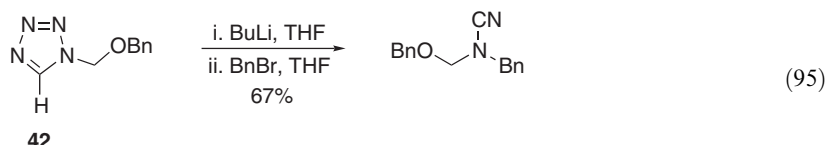
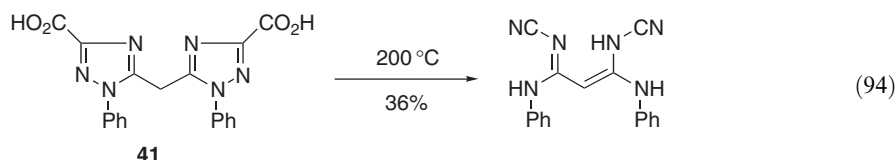
In a second rearrangement route to cyanamidated heterocycles, *N*-hydroxybenzamidines and the diphenyl carbonate derivative **38** combine on treatment with DBU to give oxadiazoles of general structure **39** (Equation (90)) <1999JMC1161>. Furthermore, thermolytic rearrangement of substituted triazoles such as **40** has been used to generate cyanamido thiazoles (Equation (91)) <1999H475>.



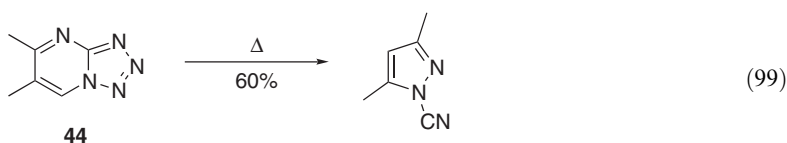
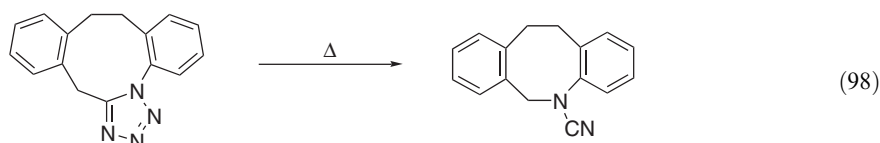
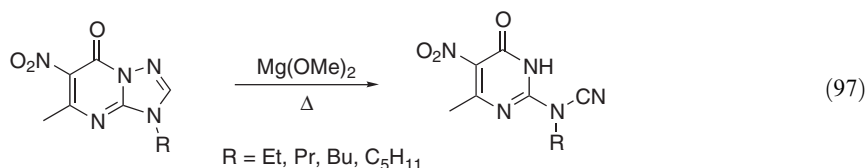
In another new application of palladium(0) catalysis to the synthesis of cyanamides, Yamamoto and co-workers <2001JA9453, 2002JA11940, 2002AG(E)1780> have developed a three-component system for the preparation of *N*-aryl-*N*-allylcyanamides. This reaction combines an aryl isocyanide with allyl carbonate and trimethylsilyl azide, mediated by palladium(0) in toluene or THF (Equation (92)), and has been applied to make a large number of allylcyanamides. Moreover, when a trimethylsilyl ethynyl moiety is present on the aromatic ring *ortho* to the isocyanide group, cyclization to afford *N*-cyanoindoles has been achieved in reasonable yields (considering the complexity of the transformation) (Equation (93)) <2002JA11940>.



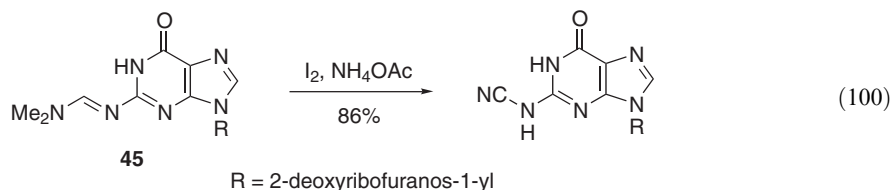
Various nitrogen-rich heterocycles have been converted into cyanamide products by fragmentation under thermolytic or photolytic conditions. The bistriazole **41** collapses at 200 °C to a cyanamide/cyanimino derivative (Equation (94)) <1999JOC6756>. 1-Methyltetrazole has been converted into methylcyanamide <1995TL1759> by lithiation and fragmentation, and 1-benzyl-oxy-methyltetrazole **42** was fragmented in a similar manner, with the resulting intermediate being trapped by benzyl bromide (Equation (95)) <2000TL2805>. The furazan **43** affords *N*-acetylcyanamide as a minor product upon photolysis (Equation (96)) <1995JOC4096>.



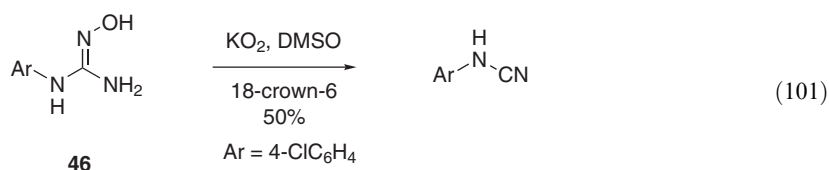
Several nitrogen-rich bi- and tricycles have been thermolyzed to cyanamide products (Equations (97)) and Equation (98)) <2001IZV655, 2001RRC439>, including various tetrazolo-pyrimidines like **44** which afford cyanopyrazoles by a fragmentation/ring-contraction pathway (Equation (99)) <2000TL2699, 2002JOC8538>.



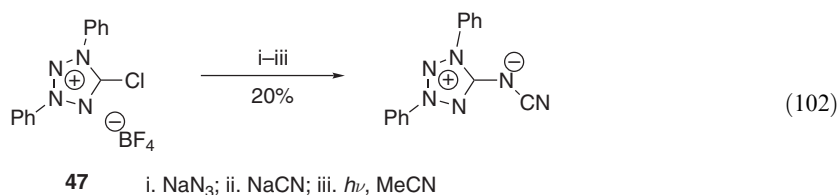
The fragmentation of acyclic and exocyclic systems has also been exploited as a route to cyanamides. Thus treatment of the purine derivative **45** with iodine and ammonium acetate generates an exocyclic cyanamide (Equation (100)) <1995TL4373>.



There has been considerable interest in the breakdown of guanidoxime derivatives with structures similar to *p*-chlorophenylguanidoxime **46**, given the putative role of such a group in the enzymatic biosynthesis of nitric oxide. Thus, the fragmentation of **46** on treatment with potassium superoxide and 18-crown-6 in DMSO has been reported to give primarily the cyanamide product, in moderate yield (Equation (101)) <1995TL6059>. There have been several attempts to promote this reaction in a biomimetic fashion, using enzymes, enzyme mimics, and photochemistry <1996TL4393, 2001MI202, 2000BMCL1775>.



Finally, it is worth considering briefly the mesoionic heterocycle **47**, which has been converted into a cyanated derivative by treatment with sodium azide, followed by sodium cyanide and finally irradiation (Equation (102)) <1998EJO121, 2001JCS(P1)2476>.



5.30.4.4 Reactions on the Carbon α to NCN Leading to Cyanamides

Only a limited number of such reactions were discussed in chapter 5.30.4.5 of COFGT (1995) <1995COFGT(5)1099>. The Michael-retro-Michael reaction of *N*-cyanocarboimide ((MeO)₂C=N—CN) with carbon nucleophiles was considered, and so too the reactions of *N*-cyanocarbodithioimide ((MeS)₂C=N—CN) with diaminobenzenes, or with ammonia and sodium hydroxide followed by arylamines. Finally, the treatment of alkyldicyanamides with aqueous sulfuric acid or hydrogen sulfide was mentioned briefly. No further developments in this area have been reported.

5.30.5 SINGLY BONDED PHOSPHORUS, ANTIMONY, ARSENIC, AND BISMUTH DERIVATIVES—R₂P—C≡N, R₂Sb—C≡N, R₂As—C≡N, R₂Bi—C≡N

Chapter 5.30.5 of COFGT (1995) <1995COFGT(5)1099> considered phosphorus(III) and phosphorus(V) nitrile derivatives in turn, with each subsection further subdivided into discussion of reactions that form an R—PCN bond, and of transformations leading to a new P—CN link. Several recently developed routes to phosphorus nitriles involve the transformation of existing cyanophosphorus compounds in which neither C—PCN nor P—CN bonds are formed. These approaches are discussed in separate subsections after consideration of chemistry leading to formation of C—PCN and P—CN links.

5.30.5.1 Phosphorus(III) Derivatives

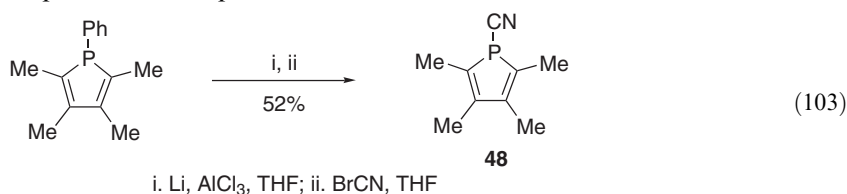
5.30.5.1.1 Formation of an R—PCN bond

The primary methods for the preparation of R_2P-CN compounds by C—PCN bond formation discussed in the earlier work involve combination of phosphorus tricyanide with a trialkyl phosphite, or the reaction of sodium diethyl phosphite with a quaternized heterocycle. There have been no further developments in this area of late.

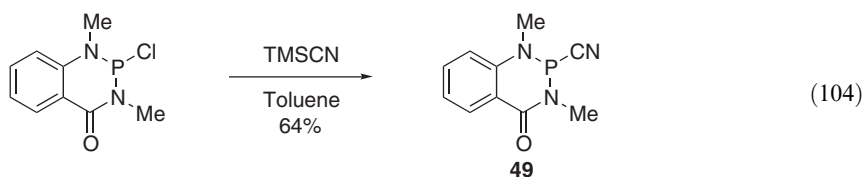
5.30.5.1.2 Formation of the P—CN bond

Chapter 5.30.5.1.2 of COFGT (1995) <1995COFGT(5)1099> noted that formation of the P—CN bond has been achieved through reaction of phosphorus halides with various trialkyl- or alkoxy-dialkylsilyl cyanides. Alternatively, the reaction of alkyl- or aryl-halophosphines with silver cyanide has been widely used to prepare the corresponding nitrile derivatives and a similar reaction of mercury(II) cyanide with iodotrifluoromethylphosphine was also discussed. A range of procedures for making cyanophosphines from halo-, dialkylaminomethyl- or dialkylaminophosphines and hydrogen cyanide or cyanogen halides was also surveyed. Finally, the preparation of cyanophosphines from isocyanides upon treatment with 2,2'-azobisisobutyronitrile (AIBN) at elevated temperatures was briefly discussed.

In a new P—CN bond-forming route to a phosphorus(III) nitrile compound, the heterocycle **48** has been prepared in moderate yield by reaction of the *P*-phenyl precursor with lithium metal and aluminum trichloride followed by cyanogen bromide (Equation (103)) <2002TA1097>, and investigated as a ligand at palladium and platinum.

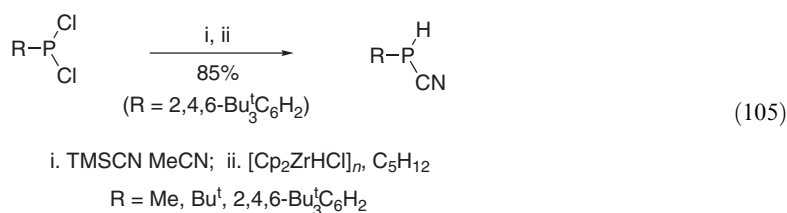


In addition, several cyano-substituted benzodiaza- and benzoxaza-phosphorinanone derivatives such as **49** have been prepared (Equation (104)), and further elaborated in reactions with various quinones <1995PS69>.

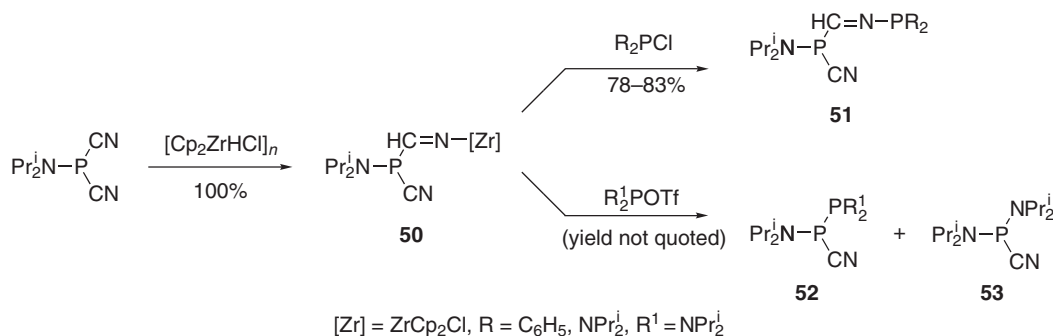


5.30.5.1.3 Modification of the substitution pattern at phosphorus(III)

The most significant route to new phosphorus(III) nitrile derivatives to have emerged in during the 1990s uses Schwartz's reagent ($[Cp_2ZrHCl]_n$) in the hydrozirconation of a dicyanophosphine <2001OM25, 2003EJO385>. A range of dicyanophosphines $RP(CN)_2$ was prepared by reaction of the corresponding dichlorophosphines with TMSCN or silver cyanide and then treated with Schwartz's reagent. With alkyl- and arylphosphines, this affords the corresponding hydrocyanophosphines via a substitution pathway (Equation (105)) <2001OM25>.

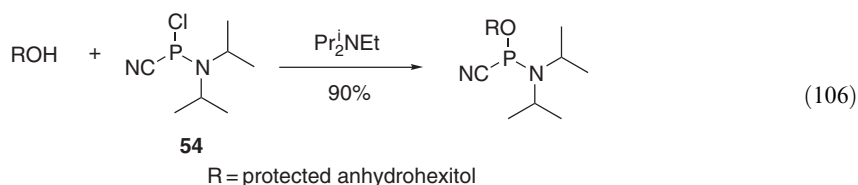


However, with (diisopropylamino)dicyanophosphine, hydrozirconation across one of the cyano groups is observed; monozirconation proceeds in quantitative yield (Scheme 7). The resulting zirconated compound **50** can be elaborated with a range of electrophiles. Reaction with chlorophosphanes ($R_2\text{PCl}$) proceeds smoothly to afford the corresponding *N*-phosphanyl analogs **51**, while a similar reaction with the iminium salt $[\text{CH}_2\text{NMe}_2]\text{Cl}$ gives rise to the *N*-alkylamino aldimido derivative. In contrast, reaction of the monozirconated species **50** with 1 equiv. of $(\text{Pr}_2^i\text{N})_2\text{POTf}$ prompts formation of the diphosphane **52** and a cyanophosphane **53** <2003EJO385>.



Scheme 7

A different series of impressively functionalized cyanophosphines has been prepared by a less elaborate transformation, namely, displacement of chloride from a chlorocyanophosphine (Equation (106)) <2001MI781>. During the synthesis of 1,5-anhydrohexitol nucleoside congeners, the reaction of the halophosphine **54** with several protected sugars afforded the corresponding nucleoside analogs in good-to-excellent yields.



5.30.5.2 Phosphorus(V) Derivatives

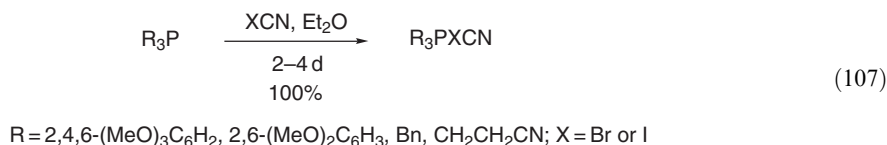
5.30.5.2.1 Formation of an R–PCN bond

Few reactions of this type were known at the time of the publication of COFGT (1995) (chapter 5.30.2.1), although the earlier edition did discuss the combination of cyanoethoxythioacetylphosphine with various aldehydes and α -keto esters to yield phosphorus(V) cyanides, and also reaction of a nitrile oxide with triphenylphosphine. No new reactions of this sort have emerged in recent years.

5.30.5.2.2 Formation of the P–CN bond

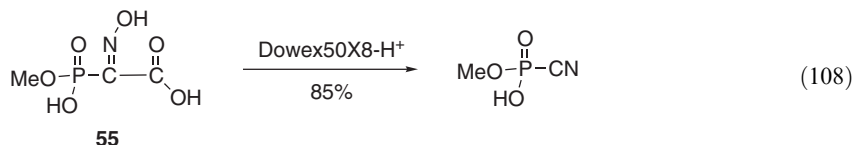
COFGT (1995) (chapter 5.30.5.2.2) discussed a number of reactions similar to those affording phosphorus(III) nitriles from the corresponding halides. Thus, phosphorus(V)-nitrile derivatives can be made through the combination of phosphorus(V) dichlorides with alkoxydimethylsilyl cyanides, silver cyanide, or potassium cyanide. Cyanodimethylphosphine oxide has been prepared by the oxidative addition of cyanide to chlorodimethylphosphine by treatment with cyanogen chloride and then acetic acid. A related transformation was also observed when certain alkoxydialkyl phosphinites and alkythiodialkyl phosphinites were treated with hydrogen cyanide and triethylamine.

In some new chemistry to emerge in the last few years, several cationic phosphorus(V)-nitrile compounds have been prepared by direct reaction of assorted triorganophosphines with cyanogen bromide or cyanogen iodide (Equation (107)) <1998JCS(D)1919>. These moisture-sensitive compounds were prepared primarily due to interest in their solid state structural chemistry, but this study does represent the first synthesis of a new class of phosphorus(V)-nitrile derivatives. The synthetic approach is very similar to the reaction of halo- or alkylaminophosphines with cyanogen halides discussed in detail in chapter 5.30.5.1.2 of COFGT (1995) and covered briefly above.

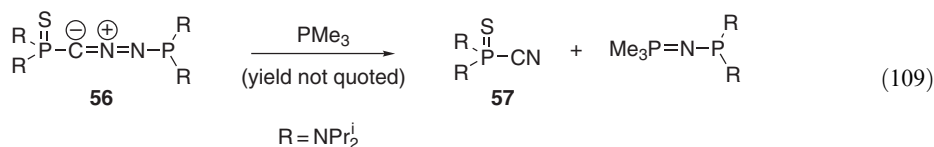


5.30.5.2.3 Modification of the substitution pattern at phosphorus(V)

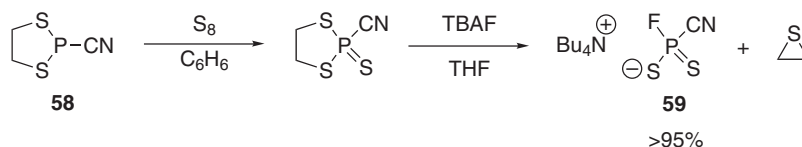
Two rearrangements have been reported in which part of the C≡N bond is formed in the key step. In the first of these, fragmentation of the α-(hydroxyimino)phosphonoacetic acid **55** at pH 1.5 gives rise to methylphosphorocyanidate in high yield, along with a small amount of methyl phosphate (Equation (108)) <1995TL9437>. This reaction is thought to proceed via initial conversion into the (Z)-oxime, which then undergoes fragmentation to the cyano compound, and the same transformation of acid **55** is promoted by heating with cyclohexylamine hydrochloride in ethanol or acetonitrile <1996PS790>.



Reaction of the nitrilimine **56** with trimethylphosphine at −78 °C also in effect brings about C≡N bond formation (Equation (109)), and this reaction represents an interesting route to the thioxyphosphoranylnitrile **57** <1997JOC292>.



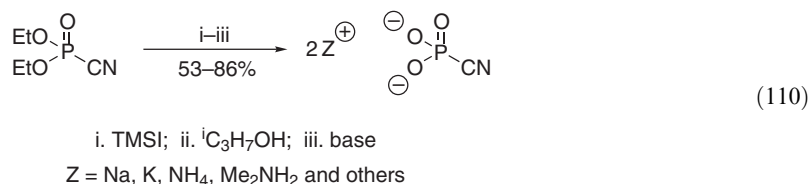
Two routes have recently emerged for the synthesis of charged phosphorus(V) nitrile analogs. Reaction at the phosphorus center is key to a newly-developed rearrangement of the 3-cyano-1,3,2-dithiaphospholane **58** <1998CC2611>. Oxidation of the dithiaphospholane by treatment with elemental sulfur or B₂S₃ is followed by addition of TBAF to drive rearrangement to the charged phosphonofluorodithioate **59** and thiirane (Scheme 8). The ionic product is stable at ambient temperature.



Scheme 8

Finally, studies in a Monsanto group working on the herbicide Round UpTM have led to the development of routes to both organic and inorganic salts of cyanophosphonate dianions <1999JOC2958>. By treating diethyl cyanophosphonate with iodotrimethylsilane, followed by

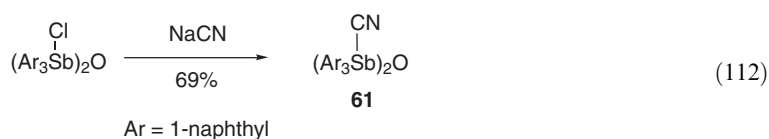
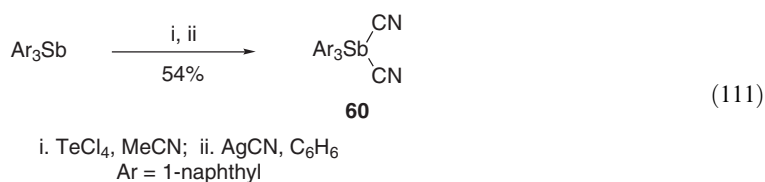
isopropanol and finally base, cleavage of the alkyl groups from the phosphonate ester has been achieved in good yields (Equation (110)). Removing a single alkyl ester group has also been achieved, giving rise to the corresponding monoanions.



5.30.5.3 Antimony Derivatives

At the time of publication of COFGT (1995) (chapter 5.30.5.2), two routes to antimony nitrile derivatives were known. Thus, the reaction of sodium cyclopentadienide with potassium chlorodicyanoantimony(III) or trichlorodicyanoantimonate(III) achieved C—SbCN bond formation, while the oxidative addition of cyanogen halides to triarylstibines had shown to allow access to triorganostibine(V) derivatives.

Two new preparations of antimony(V)-nitrile derivatives have been published in recent years. In the first of these, the reaction of tri- α -naphthylantimony(III) with tetrachlorotelluride in acetonitrile followed by silver cyanide in benzene affords the antimony(V)-bisnitrile derivative **60** (Equation (111)) <2002SRI399>. In related experiments, the μ -oxybis[tri(α -naphthyl)antimony(V)] nitrile **61** has been prepared in fairly good yield by the reaction of sodium cyanide with organoantimony chloride precursor in a mixture of methanol and benzene (Equation (112)) <2002SRI569>.



5.30.5.4 Arsenic Derivatives

There have been no further developments in the corresponding arsenic chemistry since chapter 5.30.5.4 of COFGT (1995) was written. There remain two primary routes to arsenic compounds of this type: the reaction of triarylarisines with cyanogen halides, and cyanide displacement of the halide from chloroarsines.

5.30.5.5 Bismuth Derivatives

As with the arsenic derivatives mentioned above, there has been no progress in this area since the publication of chapter 5.30.5.5 in COFGT (1995). The reaction of triarylbismuth compounds with cyanogen iodide affords diarylbismuth(III) nitriles, while bismuth(V) cyanides can be accessed via reaction of triarylbismuth(V) halides with potassium or sodium cyanide.

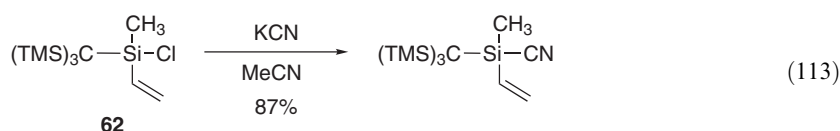
5.30.6 SINGLY BONDED METALLOID DERIVATIVES— $R_3SiC\equiv N$, $R_2BC\equiv N$, AND $R_3GeC\equiv N$

5.30.6.1 R_3SiCN Compounds

Chapter 5.30.6.1 of COFGT (1995) noted the synthetic versatility of compounds in this class, with trimethylsilyl cyanide (TMSCN) foremost in this regard—so much so that it is readily available from commercial sources. Nonetheless, attempts are ongoing to improve synthetic access to the trimethylsilyl derivative, and synthesis is a necessity when more complex analogs are required.

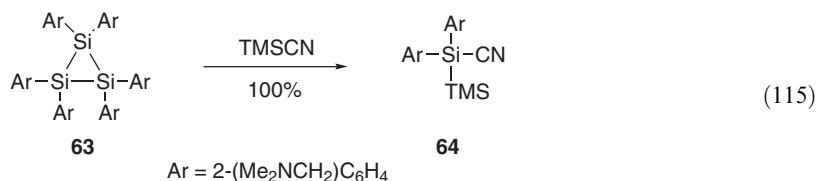
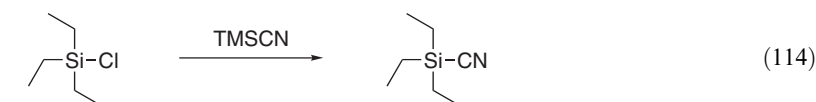
Thus, COFGT (1995) discussed a variety of routes to TMSCN and other trialkylsilyl cyanides. A significant majority of these involved reactions of halotrialkylsilanes (often trimethylsilyl chloride, TMS—Cl) and a source of cyanide. Potential cyanide sources included hydrogen cyanide with either lithium hydride or triethylamine, lithium cyanide (preformed by reaction of butyllithium and TMSCN), sodium or potassium cyanide with a range of phase transfer, and other catalysts, like silver cyanide, potassium mercury(II) cyanide in DMF, mercury(II) cyanide in benzene, thallium(III) cyanide, and even TMSCN itself, in exchange reactions with more complex halotrialkylsilanes (a reaction that is catalyzed by potassium fluoride). Alternatively, the combinations of hexaalkyldisilazanes with hydrogen cyanide, trialkylmethoxysilanes with trimethylacetyl cyanide, bis(trimethylsilyl) sulfate and potassium cyanide, and dialkyltrimethylsilyl phosphites with alkyl thiocyanates at elevated temperatures all afford trialkylsilyl cyanides with varying ease and in varying yields. Finally, the intriguing reaction of several tertiary isocyanides with tris(trimethylsilyl)silane under radical conditions, affording tris(trimethylsilyl)silyl cyanide, was also discussed.

Several approaches to cyanosilane derivatives have been developed over the last eight years, involving a range of different reagents and chemistry. Two of these are reactions that use potassium cyanide and a halotrialkylsilane as reaction partners. The first is a variation on the preparation of TMSCN from TMSCl, a reaction discussed in some detail in COFGT (1995), and the procedure used exploits potassium iodide and *N*-methyl-2-pyrrolidone to achieve a yield ~80% (although the reaction does take 3 days to complete) <1996T12061>. In a related preparation, KCN has been heated with the very bulky vinyl silyl halide **62** in acetonitrile, giving rise to the corresponding vinyl silyl cyanide in high yield (Equation (113)) <2000JOM222>.

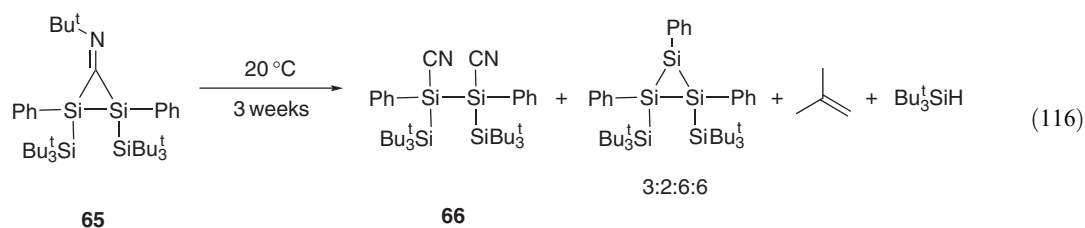


A second improved route to TMSCN has also been published, utilizing the hexamethyldisilazane/hydrogen cyanide combination. In the modified procedure, the HCN is passed slowly into a flask which is fitted with a 0°C cold-finger condenser and holds the disilazane at reflux. TMSCN was isolated in good yield (73%) and high purity after distillation <1996ICA(245)97>.

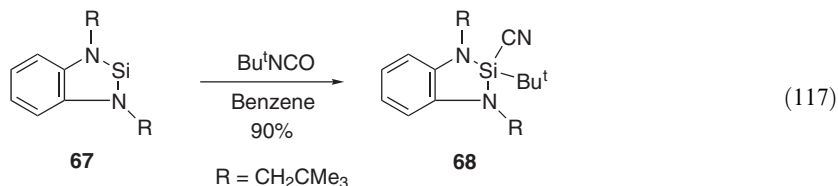
TMSCN has itself been further exploited as the source of cyanide in several exchange reactions with other silyl compounds. Thus, reaction of TMSCN with triethylsilyl chloride (TESCl) proceeds smoothly to give triethylsilyl cyanide (Equation (114)) <2000SC433>. Treatment of the remarkable cyclic trisilane **63** with excess TMSCN at room temperature affords the disilane **64** in quantitative yield (Equation (115)) <1995TL8187>.



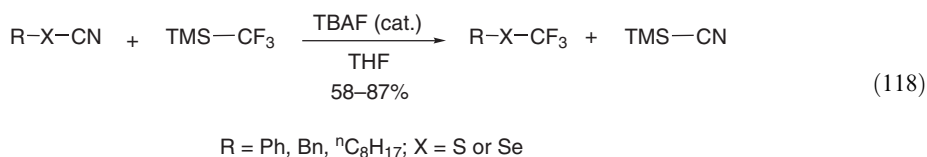
The cyclo-disilane **65** has been shown to rearrange to the silyl cyanide derivative **66** and a cyclic trisilane upon standing for an extended period (Equation (116)) <2002CEJ2730>.



One synthesis of an organosilicon cyanide has emerged recently in which both the Si—CN and the R—SiCN bonds are formed in one step <1998POL999, 2001ZAAC1048>, setting this chemistry apart from the various procedures discussed above. Thus, treatment of the silylene **67** with *t*-butyl isocyanate in benzene gives the silyl cyanide product **68** in high yield (Equation (117)).



Finally, there has been one report in which TMSCN is effectively formed as an unwanted by-product: the reaction of trifluoromethyltrimethylsilane (TMS—CF₃) with a wide range of thio- and selenocyanates has been developed as a route to the corresponding trifluoromethyl thio- and selenoethers, and 1 equiv. of TMSCN is generated in the process (Equation (118)) <1997TL65>.

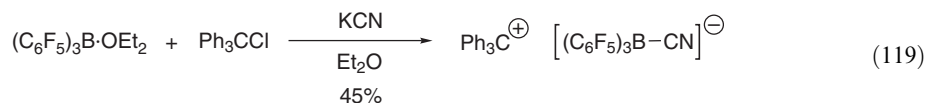


5.30.6.2 R₂BCN Compounds

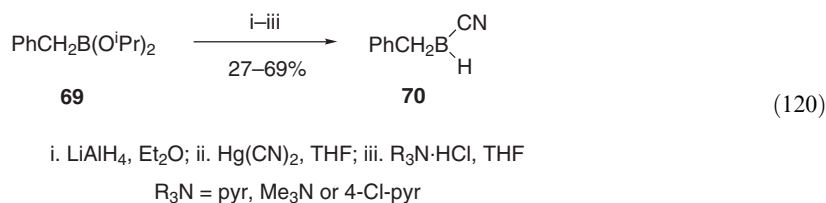
Relatively few compounds of this type were prepared during the 1990s, and chapter 5.30.6.2 of COFGT (1995) made mention of just four routes to them. The most common was reaction of a dialkylboron halide with a source of cyanide, most often TMSCN or silver cyanide. The reaction of a thioborane (R₂BSR¹) and hydrogen cyanide offered an alternative route, although this approach had not been widely applied. Finally, two routes involving cyanogen halides were reviewed: iodocyanogen used in a single case with dimethylboron iodide and carbon disulfide as the solvent, and a vinylboron cyanide identified as a transient intermediate in the reaction of a vinylborane and cyanogen bromide (en route to a *trans*-alkene).

A variety of new chemistry has emerged in this area over recent years. A range of cyanide sources has been used in these new approaches, and it is on this basis that the different routes are further subdivided below.

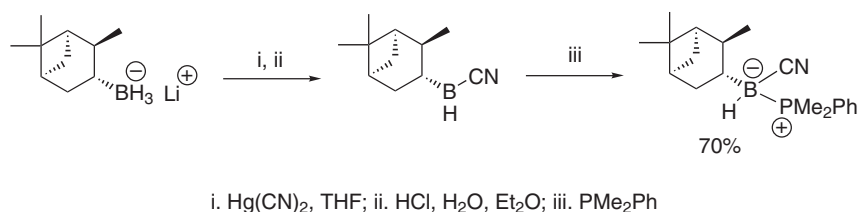
Potassium cyanide has been used to react with a triarylborane diethyl ether complex (Equation (119)) <2001JA223>; triphenylmethyl chloride is included in the reaction mixture to provide an appropriate counterion for the anionic product. This reaction proceeds in low to moderate yield.



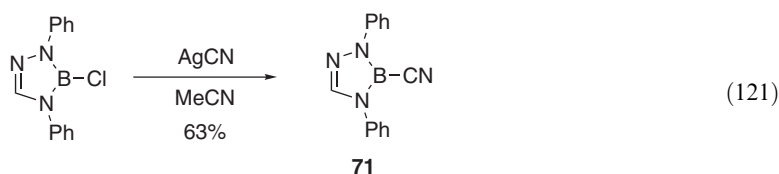
Alternatively, the mercury(II) and silver(I) salts have been employed as the source of cyanide. The boronate starting material **69** was first reduced with lithium aluminum hydride, then treated with mercury(II) cyanide, and finally with an alkylammonium chloride to furnish benzylic cyanoboranes of general structure **70** (Equation (120)) <2000CC2275>. The yields for this conversion vary from poor to quite reasonable, depending on the ammonium chloride used in the final step.



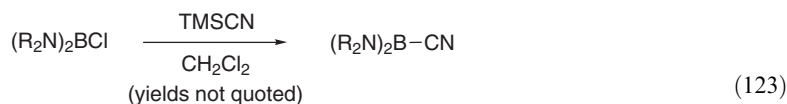
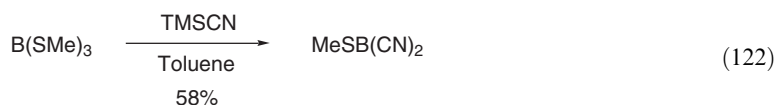
Mercury(II) cyanide has also been used in the synthesis of monoisopinocampheylcyanoborane (Ipc-BHCN), en route to several enantiomerically pure phosphinoborane adducts (Scheme 9) <1999JA1090>. Silver(I) cyanide has been utilized in the preparation of the cyanotriazaborole **71** (Equation (121)) <1999EJ1193>.



Scheme 9

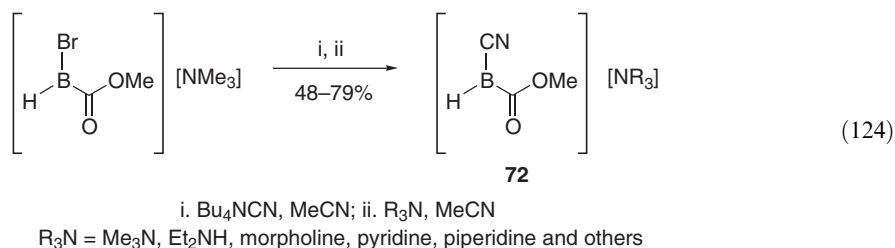


Two approaches employing TMSCN as the cyanide source have been reported during the early 2000s. In the first of these, trithiomethylborane is reacted with TMSCN in toluene at room temperature (Equation (122)) <2000JA7735>. Alternatively, TMSCN has been used to displace a chloride leaving group from a range of bis(dialkylamino)boron halides (Equation (123)) <2002CC1392>. This reaction also proceeds at room temperature, with dichloromethane as the preferred solvent, and can take up to 24 h depending on the nature of the amino group on the boron. The resulting bis(dialkylamino)ciano boranes were then employed as reagents for Strecker-type aminative cyanation of aldehydes and ketones.

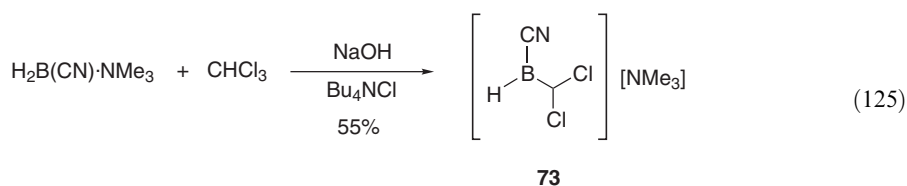


R_2N = Et_2N , $^i\text{Pr}_2\text{N}$, pyrrolidine, morpholine or Bn_2N

Tetra-*n*-butylammonium cyanide has been used in one recent preparation of an acylborane–nitrile derivative, displacing a bromide leaving group from bromo(methoxycarbonylborane) trimethylamine complex over 24 h to give cyano(methoxycarbonylborane) **72** in complexes with a range of amines (Equation (124)) <2002JCS(P1)300>.



Finally, in one very interesting approach, the trimethylamine complex of cyanoborane has been exploited as the source of cyanide, in a reaction that forms the $\text{R}-\text{BCN}$ bond (in marked contrast to other routes discussed previously, all of which build the $\text{B}-\text{CN}$ linkage). In this transformation, cyanoborane is treated with chloroform and sodium hydroxide under phase transfer conditions to afford (dichloromethyl)cyanoborane as its trimethylamine complex **73** (Equation (125)) <2000T6039>. A small amount of the dialkylated product is also isolated, and the triphenylphosphine complex of cyanoborane can be used equally successfully. The (dichloromethyl)cyanoborane product rearranges to chloro(chloromethyl)cyanoborane on standing in solution.



A variety of complexes derived from sodium cyanoborohydride have also been prepared, by reacting the reducing agent with assorted amine <1999MI306, 2000S1229, 2001PHA36, 2001BMCL1245, 2002AAC294>, diol <2001T1581> and phosphine or phosphite <2002MI581> ligands. This chemistry is not considered further here.

5.30.6.3 R_3GeCN Compounds

A limited number of reports on compounds of this type were extant when chapter 5.30.6.3 of COFGT (1995) was published, and many of these date from over half a century ago. Four routes to trialkylgermanium cyanides were reviewed: the combination of trialkylgermanium oxides with hydrogen cyanide, reaction of organogermanium halides with silver(I), mercury(II), or lead(II) cyanides, displacement by potassium cyanide of the sulfonate from triethylgermanium ethylsulfonate, and reaction of (triphenylgermanium)mercury(II) with copper(II) cyanide at room temperature. There have been no further developments in this area since that time.

5.30.7 SINGLY BONDED METAL DERIVATIVES

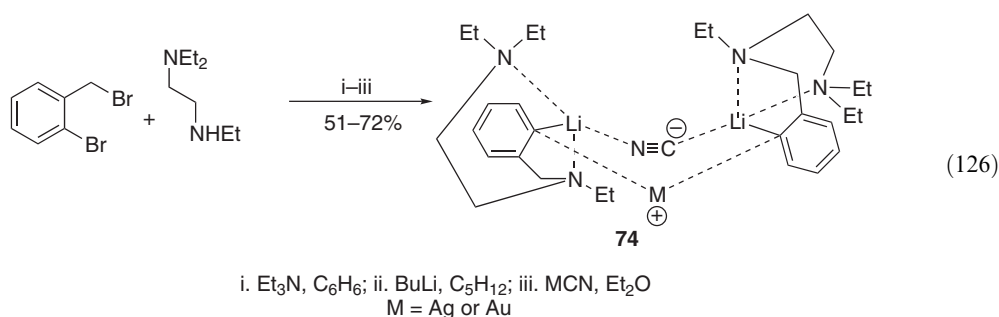
In keeping with the boundaries defined in chapter 5.30.7 of COFGT (1995), this section considers metal derivatives containing the subunit $\text{R}_n-\text{M}-\text{CN}$, where M is a metal atom and R is a carbon atom. Situations in which R is a CO group or an additional cyano ligand have again been omitted, in order to exclude compounds that are simply coordination complexes of the cyano ligand.

Complexes in which R constitutes a η^5 -cyclopentadienyl group or a η^6 -aryl ligand are also not considered in detail for similar reasons. Nonetheless, it is worth noting that several new complexes of this type have been reported in recent years, including derivatives of titanium <1996JOM127, 2002OM1011>, zirconium <1995OM3435>, chromium <2001EJ12783>, molybdenum <1998JOM117, 2001JCS(D)1732>, manganese, <2001EJ12783> and rhenium <1995JA111730>. Furthermore, compounds in which the group R_n is a η^3 -allyl moiety are also considered to be transition metal complexes, and are accordingly not discussed further. Only molybdenum <2003OM1540>, ruthenium, <1995IZV968> and rhodium <1995IZV968> complexes of this type have been prepared in recent years.

5.30.7.1 Group 1 and 2 Derivatives

Very few compounds of this type have ever been reported. Chapter 5.30.7.1 of COFGT (1995) discussed a single report on the synthesis of alkylberyllium cyanides from dimethylberyllium and hydrogen cyanide. There have been no further developments in this area.

There has, however, been one report detailing the preparation of several intriguing cyano-bridged aryllithium compounds, which could be considered to fulfill the qualifying molecular formula " R_n-M-CN " <2002JA11675>. The reaction of diamine-chelated aryllithium dimers with silver(I) or gold(I) cyanide affords structures of the type **74** (Equation (126)), which could be considered as lithium-nitrile derivatives. These argentate and aurate complexes have been characterized by multinuclear NMR studies.



5.30.7.2 Transition Metal Derivatives

Chapter 5.30.7.2 of COFGT (1995) reviewed nitrile derivatives of transition metals from the last three groups of the *d*-block elements—nickel, palladium, and platinum; copper and gold; and mercury. Further appropriate cyano derivatives of all these metals have been reported since that volume was published. However, several qualifying compounds of other transition metals have also been prepared—namely, iron, ruthenium, and cobalt. Derivatives of these “new” metals are considered together at the end of this section, in order to maintain consistency with the section numbering used in the previous volume.

5.30.7.2.1 Nickel derivatives

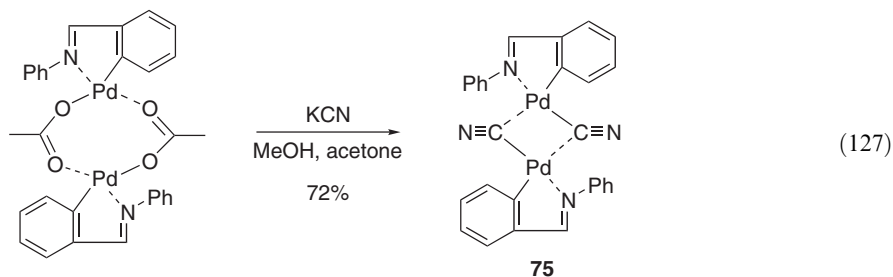
Two general routes to nickel cyanide derivatives were discussed in chapter 5.30.7.2.1 of COFGT (1995): displacement of a leaving group (most commonly a halide) from nickel by the cyanide anion, as its potassium, sodium, or silver salt (one or two phosphine ligands were invariably required to stabilize the product); or oxidative addition of aryl nitriles to tetrakis(trialkylphosphine)nickel, a facile reaction often occurring at room temperature. There have been no further developments in this area.

5.30.7.2.2 Palladium derivatives

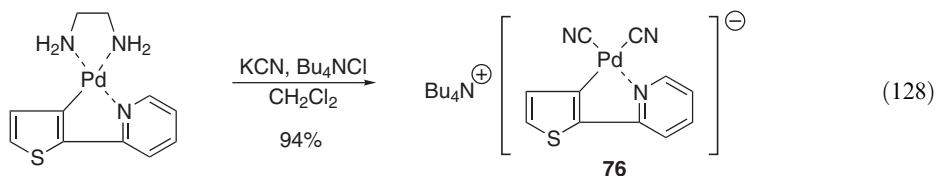
The preparations of palladium cyanide compounds reviewed in chapter 5.30.7.2.2 of COFGT (1995) closely mirror those used to access the corresponding nickel derivatives. Thus, the displacement of a halide leaving group by potassium cyanide provides one main route, with methanol, ethanol, acetone, and benzene all useful solvents; precipitation of the potassium halide is a key driving force for this reaction. Alternatively, palladium-nitrile compounds may be prepared by oxidative addition of aryl nitriles to tris(triphenylphosphine)palladium(II), or alternatively to palladium(II) chloride in the presence of potassium metal and triethylphosphine in DME.

Several new compounds of this type have been prepared over the past eight years, with displacement of a leaving group from an extant palladium(II) complex the most common approach. In most of the derivatives thus formed, the additional carbon–palladium bond in the general formula R_n-M-CN comes from a bidentate species which is also linked to the metal

through a nitrogen atom. For example, the cyano-bridged dipalladium compound **75** has been made in good yield from reaction of dimeric $[\text{Pd}(\text{N-benzylideneaniline})(\mu\text{-OOCCH}_3)]_2$ with potassium cyanide in a mixture of methanol and acetone (Equation (127)) <2002MI425>.



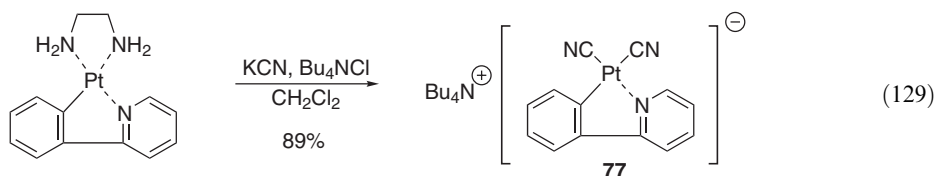
Similarly, the anionic 2-(2-pyridyl)thienyldicyanopalladium complex **76** and a similar 2-(2-pyridyl)phenyl derivative have been made in excellent yield through displacement of *N*-linked diamino ligands by cyanide (Equation (128)) <2002ZOB869>.



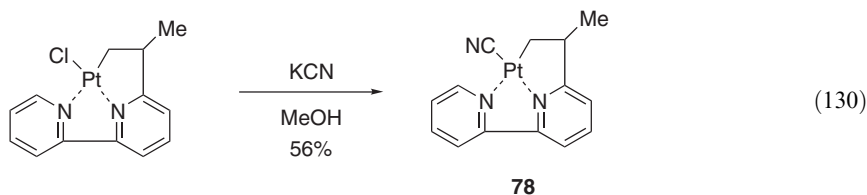
5.30.7.2.3 Platinum derivatives

Like their nickel and palladium counterparts, the principal routes to platinum cyanides discussed in chapter 5.30.7.2.3 of COFGT (1995) utilized displacement of a leaving group from platinum by potassium cyanide, or oxidative addition of an organic nitrile to tetrakis(triphenylphosphine)platinum(0). Both iodide and trifluoroacetate proved suitable leaving groups in the first approach, and neutral moieties such as cyclooctadiene and triethylphosphine can also be substituted by potassium cyanide, when benzene is the solvent and 18-crown-6 is also present. The one reported oxidative addition route to a platinum-nitrile compound varies slightly from that seen with nickel and palladium, in that the aliphatic nitrile 1,1,1-tricyanoethane has been used (rather than the aryl nitriles employed with the other metals).

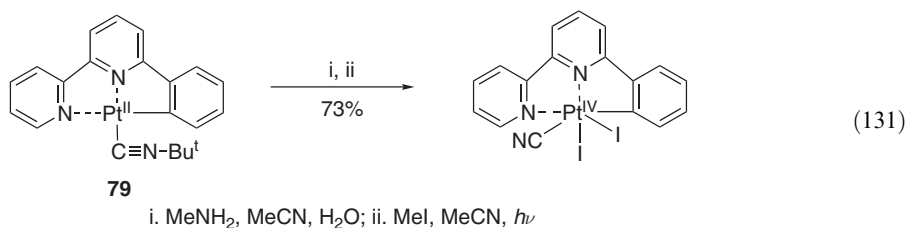
Several new routes to platinum compounds of this type have been harnessed since 1995. In an approach similar to that used with palladium (Section 5.30.7.2.2), the anionic 2-(2-pyridyl)phenyldicyanoplatinum(II) complex **77** and the corresponding 2-(2-pyridyl)thienyl complex have been prepared by cyanide displacement of *N*-linked ligands from the corresponding diamino precursors (Equation (129)) <1995ACS313, 2002ZOB869>. These same platinum-nitrile compounds have also been made from reaction of potassium cyanide and tetra-*n*-butylammonium chloride with the corresponding dichloro platinum(II) complexes, and with chloro-bridged diplatinum precursors <1995ACS313>.



Displacement of a chloro ligand has also been used to prepare the monocyano platinum compound **78** <2002EJ13336>, an alkylplatinum nitrile compound (Equation (130)).



Finally, there has been one report of a platinum(IV)-cyano compound of the type R_n-M-CN <1999OM3327>, formed in an interesting photochemical reaction of the platinum(II)-isonitrile complex **79**, methylamine and methyl iodide (Equation (131)).



5.30.7.2.4 Copper derivatives

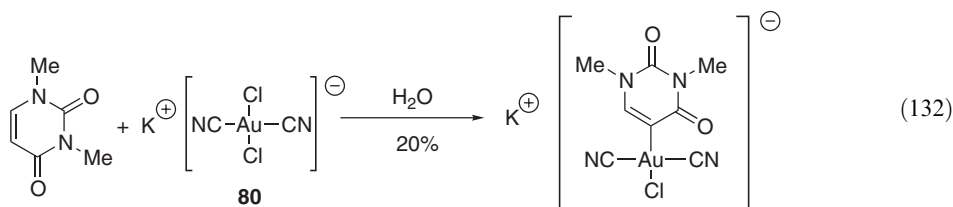
Chapter 5.30.7.2.4 of COFGT (1995) did not review the chemistry of cyanocuprates, on account of uncertainties over their precise structure. A single route to copper nitrile derivatives was reviewed, that being the addition of phenylacetylene to copper(I) cyanide.

In keeping with the precedent established in COFGT (1995), organocuprates are not discussed in any detail here, on account of uncertainties over the precise structure of these compounds. However, there have been several recent reports on the preparation and utilization of these copper-nitrile derivatives in synthesis <1996SL18, 2001JOM47, 2002JMC2877, 2002JOM109>. The preparation of these compounds invariably starts from alkyl chlorides, bromides, or iodides, and proceeds via organolithiums, Grignard reagents, or often organozinc compounds.

5.30.7.2.5 Gold derivatives

Halide displacement by a cyanide nucleophile was the primary route to gold cyanides discussed in chapter 5.30.7.2.5 of COFGT (1995), specifically the reaction of potassium cyanide with R_2AuCl or R_2AuI . Silver nitrate could be added to precipitate the halide side-product, and additional phosphine or amine ligands were generally required to stabilize the organogold cyanide products. The other synthesis of gold nitrile derivatives reviewed in the earlier volume saw addition of the ylide triphenylphosphoniomethanide to gold(I) cyanide, followed by oxidative addition of chlorine, bromine or iodine to give a range of *trans*-cyanodihalogold(III) compounds.

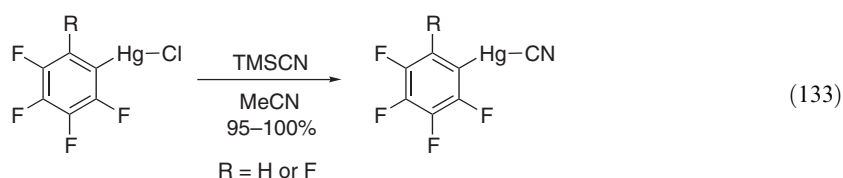
There has been one report of new cyano-gold compounds in recent times, chemistry which sees the synthesis of several interesting gold-pyrimidine conjugates, anionic derivatives of 1,3-dimethyluracil. These compounds are formed by displacement of a chloride leaving group from *trans*- $K[Au(CN)_2Cl]$ **80** on reaction with 1,3-dimethyluracil under aqueous conditions (Equation (132)) <1998JOM127>. This methodology has not been extended beyond the uracil derivatives—similar reactions with other nucleobase analogues led instead to *N*-linked gold complexes, or the protonated nucleobase acting as a counterion to the $[Au(CN)_2Cl(C5\text{-dimethyluracil})]$ anion. In fact, much improved yields of the organic cyano-gold complex (up to 82%) are achieved when a protonated purine base is included in the reaction mixture (and acts as the counterion in the isolated product).



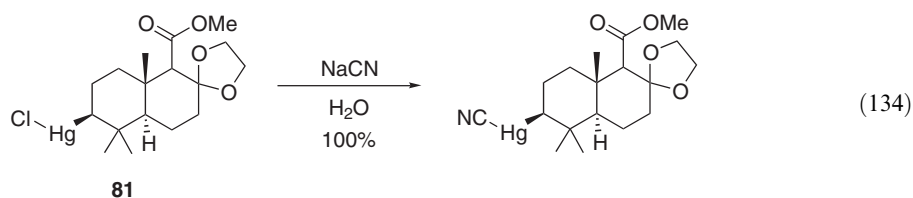
5.30.7.2.6 Mercury derivatives

Chapter 5.30.7.2.6 of COFGT (1995) covered two main routes to organomercury cyanides. The first involves the familiar displacement of a leaving group (usually acetate or iodide) from RHgX , with potassium or silver cyanide providing the nucleophile. In the second, mercury(II) cyanide is reacted with a range of aryltrifluorosilanes, resulting in cleavage of the C—Si bond and transfer of the aryl group to mercury. Bis(phenylacetylene)mercury has also been reacted with mercury(II) cyanide in a similar fashion. The earlier volume also reviewed an isolated report of an interesting route to benzylmercury(II) cyanide from bisbenzylmercury and tetracyanoethylene, via a highly colored charge transfer complex.

Three new studies on the preparation of cyano-mercury derivatives have emerged since publication of the earlier volume. In the first, displacement of a chloride leaving group from several arylmercury halides has been achieved, using TMSCN as the source of cyanide <2003OM1275>. Several polyfluoroaromatic cyanomercury(II) compounds have been formed by this approach (Equation (133)). These include derivatives incorporating two Hg—CN moieties bound to one aromatic ring, which have been prepared and utilized as Lewis acid catalysts in cyanosilylation reactions <2003OM1275>.

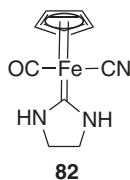


Chloride displacement from an organomercury halide is also central to the second recent report in this area <1995MI2>. Both the substituted decalin system **81** (Equation (134)) and a simpler cyclohexyl derivative have been used in this approach. Subsequent reaction of the R—Hg—CN compound with a peracid afforded the corresponding alcohol.

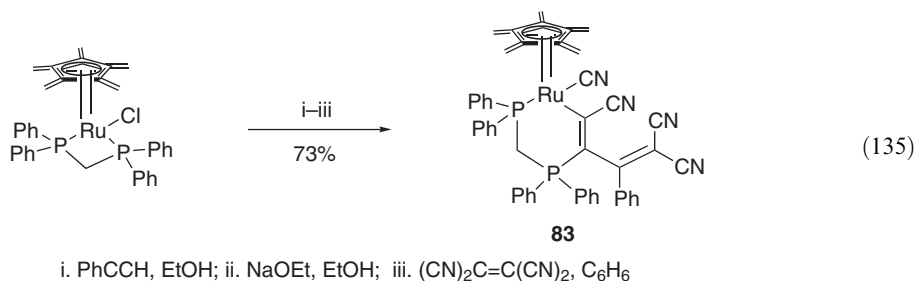


5.30.7.2.7 Derivatives of other transition metals

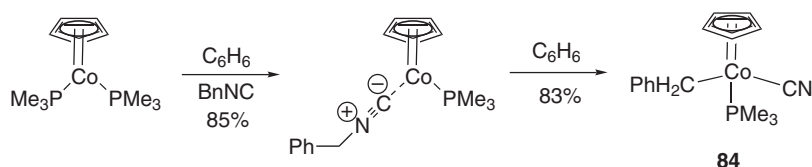
$\text{R}_n\text{—M—CN}$ compounds of iron, ruthenium and cobalt have all been prepared in recent years, though each of them only in one isolated case. The mononuclear iron(II)-cyano complex **82** has been prepared from reaction of the so-called “tetraferrioazaalenium” complex with 1,2-diaminoethane <1999ICA266>. This complex incorporates a η^5 -cyclopentadienyl group at iron, but also a cyclic diaminocarbene, derived from the diamine co-reactant.



Ruthenium compounds such as **83** have been prepared in good yields from the corresponding $\text{Cp}^*\text{—Ru—phosphine}$ complex by reaction with phenylethyne, sodium ethoxide, and then tetracyanoethene (Equation (135)) <2002JOM141>.



Finally, reaction of the cobalt cyclopentadienyl complex CpCo(PMe₃)₂ with 1 equiv. of benzylisonitrile gives rise to the Co-isonitrile complex, which has been found to undergo an intramolecular oxidative addition reaction at room temperature to afford the organo-cobalt-nitrile derivative **84** (Scheme 10) <1998JOM45>. This rearrangement has not been extended to other isonitriles—the intermediate complex formed from the tolylisonitrile analog, for example, is quite stable, and does not undergo an equivalent rearrangement.



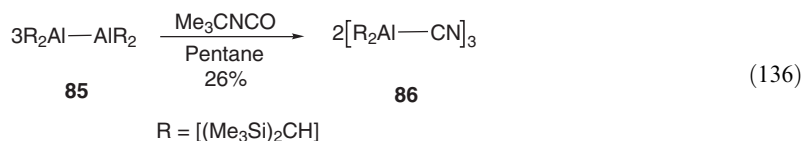
Scheme 10

5.30.7.3 Group 13 Derivatives

5.30.7.3.1 Aluminum derivatives

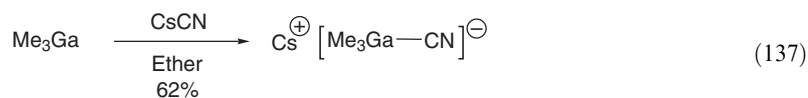
Only a few routes to organoaluminium cyanides were extant at the time that chapter 5.30.7.3.1 of COFGT (1995) was published, and all of these involved reaction of suitable alkylaluminum compounds with hydrogen cyanide or trimethylsilyl cyanide. Dialkylaluminum chlorides have been reacted with TMSCN, and trialkylaluminums and dialkylaluminum hydrides have been treated with hydrogen cyanide, in a range of solvents, giving organoaluminum cyanides.

Two new syntheses of organoaluminum cyanides have emerged since 1995. The first of these uses excess TMSCN with trimethylaluminium, giving the first alkylaluminum dicyanide <1996ICA97>. In the second new approach, *t*-butyl isocyanate was utilized as a source of the cyanide unit in a reaction with the dialane **85** that cleaves the Al—Al bond and furnishes the novel aluminium cyanide **86** (Equation (136)) <1995ZAAC823>. An X-ray crystal structure reveals that the trimer **86** is cyclic.

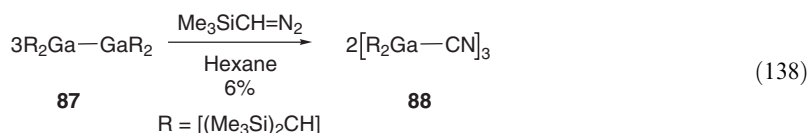


5.30.7.3.2 Gallium derivatives

Chapter 5.30.7.3.2 of COFGT (1995) discussed only one organogallium cyanide, dimethylgallium cyanide, which had been prepared by reaction of trimethylgallium with either hydrogen cyanide or trimethylgermyl cyanide. Since that time two new organogallium cyanides have been prepared, by quite different routes. Treatment of trimethylgallium with 1 equiv. of caesium cyanide at 20 °C affords the metalated compound Cs[Me₃GaCN] (Equation (137)) <1998ZAAC1642>. Furthermore, combining the same reagents in a 2:1 ratio in the absence of solvent gives a different organogallium metallate Cs[CN(GaMe₃)₂], bridged through the shared cyano group.



In a reaction closely related to some of the organoaluminum chemistry discussed above (Section 5.30.7.3.1) but utilizing a different organosilicon reagent in the conversion, the sterically hindered digallane **87** has been found to fragment when treated with trimethylsilyldiazomethane (Equation (138)) <1999EJI201>. This reaction gives rise in low yield to the dialkylgallium(III) cyanide **88**, which, like the corresponding aluminum compound **86**, forms a cyclic trimer in the crystalline state, as shown by X-ray crystallography.



5.30.7.3.3 Indium derivatives

The only compound mentioned in chapter 5.30.7.3.3 of COFGT (1995) is dimethylindium cyanide (Me_2InCN), prepared from the reaction of trimethylindium and hydrogen cyanide. No further derivatives of this type have been prepared.

5.30.7.3.4 Thallium derivatives

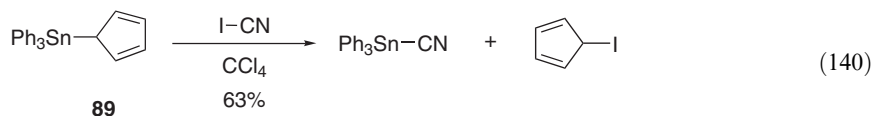
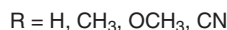
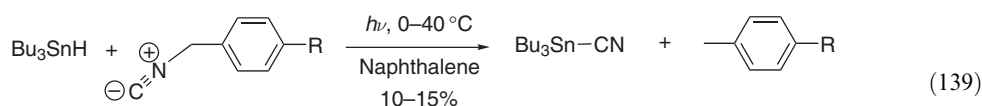
Three general routes to thallium cyanide compounds were reviewed in chapter 5.30.7.3.4 of COFGT (1995): displacement of a leaving group (either perchlorate or iodide) by potassium cyanide from a diarylthallium iodide or perchlorate; reaction of thallium(III) acetate with methyl pentafluorosilicate, ammonium fluoride, and sodium cyanide in water (in which both the cyano group and the methyl group are transferred to thallium); and the transfer of a cyano group to a diarylthallium chloride from other metal cyanide compounds, either mercury(II) cyanide or trialkyltin cyanides. There have been no further developments in this area since 1995.

5.30.7.4 Group 14 Derivatives

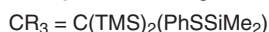
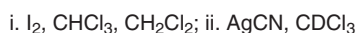
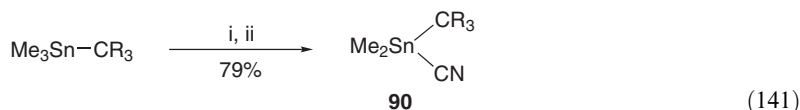
5.30.7.4.1 Tin derivatives

The main route to trialkyl and triaryltin cyanides that had emerged by the time chapter 5.30.7.4.1 of COFGT (1995) was published involved displacement of a leaving group from R_3SnX by cyanide. With X as a chloride or iodide, silver cyanide had been used, while acetyl cyanide had been shown to react well with trialkyltin isopropoxide. Acyloxystannanes were also known to react with trimethylsilyl cyanide, with RCO_2^- effectively the leaving group in that reaction. The earlier volume also made mention of an interesting route to trimethyltin cyanide from benzyl-trimethylstannane and tetracyanoethylene, a reaction which proceeds via a highly coloured charge transfer complex similar to that seen for dibenzylmercury (see Section 5.30.7.2.6).

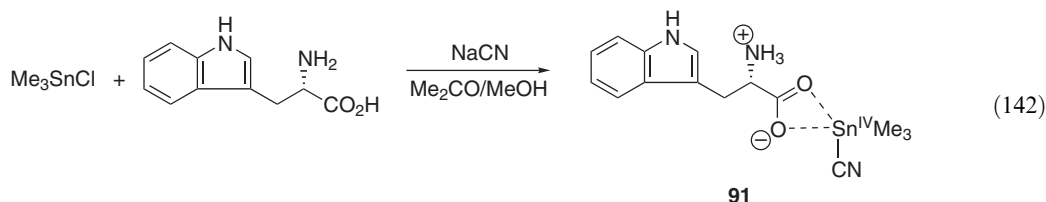
Several routes to tin cyanide derivatives have been studied over recent years. In the first of these, Kim and co-workers have investigated the reaction of tri-*n*-butyltin hydride with various benzylic isonitriles under photolytic conditions, to afford the tri-*n*-butyltin cyanide in moderate yield (Equation (139)) <1997TL5303>. Alternatively, reaction of the η^1 -cyclopentadienylstannane **89** with iodocyanogen in carbon tetrachloride offers a new route to triphenyltin cyanide (Equation (140)), a transformation in which the tin-cyclopentadienyl bond is cleaved preferentially <1997JIC443>.



A multistep sequence has been developed as a route to the sterically encumbered organotin cyanide **90** (Equation (141)) <1996JOM109>. The bulky tetraalkylstannane precursor is formed *in situ* from trimethyltin chloride and the corresponding trisilylated alkyl lithium compound. Treatment with iodine displaces one of the methyl groups from tin to give a monoiodostannane, and then silver cyanide displaces iodide to afford the final trialkyltin cyanide product.



Finally, the tin(IV)-cyanide complex **91** has been prepared via the multicomponent reaction of trimethyltin chloride, sodium cyanide, and the amino acid tryptophan in a mixture of acetone and methanol (Equation (142)) <1995PS243>.



5.30.7.4.2 Lead derivatives

Chapter 5.30.7.4.2 of COFGT (1995) reviewed two routes to organolead cyanides, both originating with hexaphenyldilead. Reaction of the dilead compound either with iodocyanogen in carbon tetrachloride, or with hydrogen cyanide and a peracid, gave rise to two equivalents of triphenyllead cyanide. There have been no further developments in this area since that time.

5.30.8 HETERONITRILIUM COMPOUNDS WITH THE GENERAL FORMULA $\text{RXC}\equiv\text{N}^+-\text{Y}$

Chapter 5.30.8 of COFGT (1995) began with the observation that many species of the general formula $\text{RX}-\text{CN}^+-\text{Y}$ are highly reactive, existing as transient intermediates in various reactions, and only a limited number of these compounds are isolable or even characterizable (other than by deduction based on the structures of their reaction products). If the group Y bears a negative charge, then the species is formally a 1,3-dipole, and thus a likely candidate to participate in 1,3-dipolar cycloaddition reactions with alkenes. The earlier work gave brief consideration to the chemistry of benzenesulfonylcarbonitrile oxide as a representative example, but other species of this type were not discussed further. This precedent is to be followed here also, and species of the type $\text{RX}-\text{CN}^+-\text{Y}$ that exist only as intermediates are not considered.

In keeping with the conventions of the earlier edition, this section is subdivided according to the nature of the group Y in $\text{RX}-\text{CN}^+-\text{Y}$, and then further by the nature of the heteroatom X.

5.30.8.1 *N*-Protonated Heteronitrilium Salts— $\text{RX—CN}^+\text{—H}$

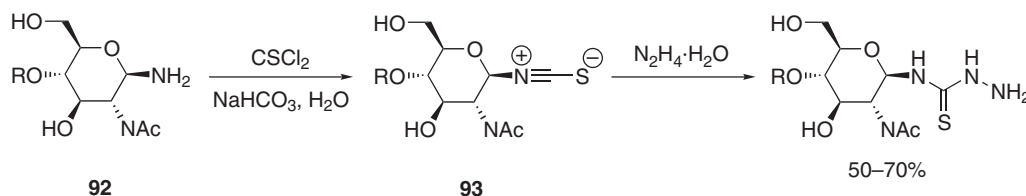
No compounds of this type had been prepared and isolated at the time that chapter 5.30.8.1 of COFGT (1995) was written and no such compounds have been reported since then.

5.30.8.2 *N*-Carbon-linked Heteronitrilium Salts— $\text{RX—CN}^+\text{—CR}_3$

5.30.8.2.1 Alkylthionitrilium salts— $\text{RS—CN}^+\text{—CR}_3 \text{X}^-$

Only one example of this particular functionality was featured in chapter 5.30.8.2.1 of COFGT (1995): the reaction of methyl thiocyanate, benzoyl chloride and antimony pentachloride to give *N*-benzoyl-*C*-(methylthio)nitrilium hexachloroantimonate, and only limited characterization details were available on this compound.

In the intervening period, only one further approach to this type of compound has been reported. The reaction of lactosamines **92** and other amino-sugar derivatives with phosgene has been exploited to prepare 1,3-dipolar nitrilium thiolate derivatives such as **93**, which might be broadly classified in this class (although these compounds were not isolated, and instead converted immediately to the corresponding thiosemicarbazides by treatment with hydrazine) (Scheme 11) <1998JOC7134>.



R = galactose or *N*-acetylgalactosamine

Scheme 11

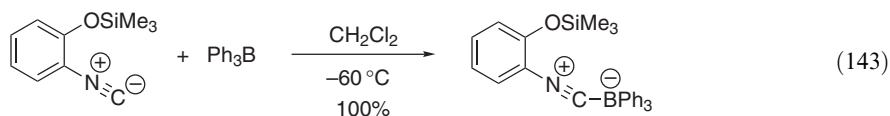
5.30.8.2.2 Cyanamidium salts— $\text{R}_2\text{N—CN}^+\text{—CR}_3 \text{X}^-$

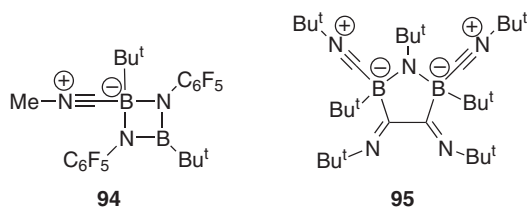
Chapter 5.30.8.2.2 of COFGT (1995) featured a limited though significant number of compounds from this class <1995COFGT(5)1099>, each accessed through a different combination of reaction partners. The reactions of an alkyl halide with a carbodiimide, of an alkyl or aryl isocyanide with an *N*-chlorodialkylamine and SbCl_5 , of a dialkylcyanamide ($\text{R}_2\text{N—C}\equiv\text{N}$) with a tertiary alkyl chloride and SbCl_5 , or of acetyl chloride, diisopropylcarbodiimide and SbCl_5 were all discussed as potential routes to cyanamidium salts. There have been no further reports in this area since that time.

5.30.8.2.3 Nitriliumborates— $\text{R}_3\text{B}^-\text{—CN}^+\text{—CR}_3$

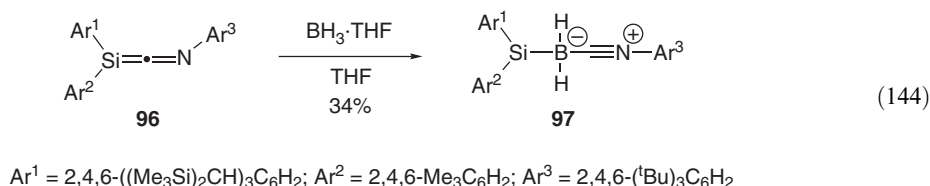
Two synthetic avenues to nitriliumborates were reviewed in chapter 5.30.8.2.3 of COFGT (1995). The first was *N*-alkylation of a cyanoborate and the second involved reaction of a borane with an isonitrile.

The second of these approaches has been applied on several occasions in recent years. In the first of these, 2-(trimethylsilyloxy)phenyl isocyanide was added to triphenylborane at low temperature, affording the corresponding nitrilium borate (Equation (143)) <1996OM1251>. Using a similar approach, the two azaborocycles **94** and **95** have been prepared by the same research team <1995CB1029, 1995CB1037>.





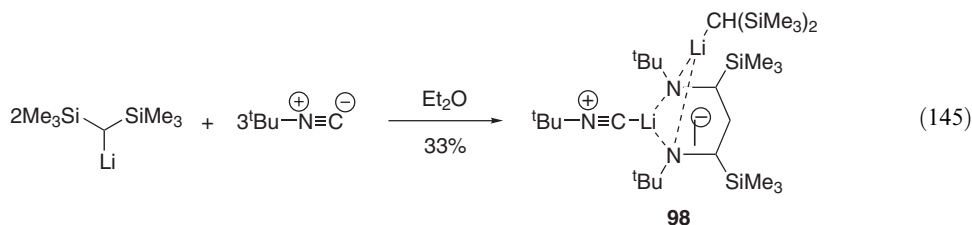
In one new route to compounds of this type, it has been discovered that the addition of borane to the heterocumulene **96** gives rise to the corresponding silylated nitriliumborate **97** (Equation (144)) <2001CL1076>. Furthermore, when the initial product **97** is heated at 120 °C, rearrangement is observed, in which an aryl group migrates from silicon to boron to afford the *B*-aryl nitriliumborate.



5.30.8.2.4 Nitrilium organometallates— $R_nM^+ \text{---} \text{CN}^- \text{---} \text{CR}_3$

The complexes of isonitriles with transition metals may fit the general formula $R_nM^+ \text{---} \text{CN}^- \text{---} \text{CR}_3$, and such complexes are numerous. However, isonitrile complexes were considered beyond the scope of chapter 5.30.8.2.4 in the COFGT (1995).

Myriad examples of transition-metal-complexed isonitriles have been reported, and also several interesting derivatives of assorted actinides, lanthanides, and the group-2 metals. However, these complexes are beyond the scope of the present review. Very few other examples of compounds from this class have been reported. The lithium derivative **98**, which has been prepared from bis(trimethylsilyl)methyl lithium and *t*-butyl isonitrile, could perhaps be considered in this category, although its structure is not straightforward (Equation (145)) <1998CC201>.



5.30.8.3 Heteronitrile Oxides— $\text{RX---CN}^+ \text{---} \text{O}^-$

Heteronitrile oxides are reactive 1,3-dipoles, and accordingly no such compounds have been isolated and characterized.

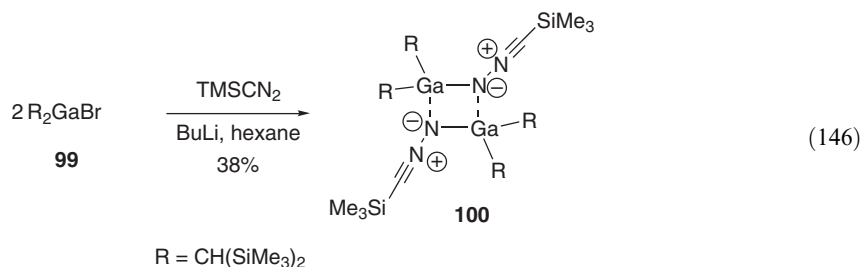
5.30.8.4 Other Derivatives— $\text{RX---CN}^+ \text{---} \text{Y}$

5.30.8.4.1 Silylnitrilimines— $\text{R}_3\text{Si---CN}^+ \text{---} \text{N}^- \text{---} \text{R}$ and phosphoranylnitrilimines— $\text{R}_2\text{P}(\text{X})\text{---CN}^+ \text{---} \text{N}^- \text{---} \text{R}$

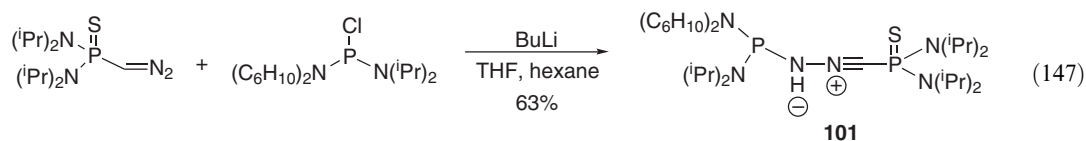
Only a scattering of compounds from these classes were discussed in chapter 5.30.8.4.1 of COFGT (1995). Two routes to the silicon derivative bis(triisopropylsilyl)nitrilimine ($^i\text{Pr}_3\text{Si---C}\equiv\text{N---N}^- \text{---} \text{Si}^i\text{Pr}_3$) were reviewed: the combination of triisopropylsilyl chloride (2 equiv.)

and bis(trimethylstannyl)diazomethane, and the reaction of triisopropylsilyldiazomethane with butyllithium followed by triisopropylsilyl chloride. The reaction of triisopropylsilyldiazomethane with butyllithium followed by chlorobis(diisopropylamino)borane to give the *N*-borylnitrilimine was also mentioned. A similar route to the corresponding phosphorus derivative was discussed, the reaction of di-*t*-butylthioxophosphoranyldiazomethane with butyllithium and then chlorobis(diisopropylamino)-phosphine to give the phosphoranylnitrilimine (although this product is highly unstable, and decomposes within 72 h).

One new approach to silyl derivatives of this type has been reported recently, that being the reaction of trimethylsilyldiazomethane and butyllithium with the organogallium halide **99**, which gives rise to the cyclic azagallium compound **100** (Equation (146)) <1999EJ771>.



Two new syntheses of phosphoranylnitrilimines have emerged in the same time period. The first of these combines a phosphoranyldiazomethane and a chlorophosphine in THF and hexanes to give the phosphoranylnitrilimine **101** (Equation (147)) <1997JA2819>. The second sees reaction of an existing phosphoranylnitrilimine very similar in structure to **101**, which is combined with *o*-chloranil (a quinone) and triisopropylsilyl triflate to form a modified phosphoranylnitrilimine <1996JA5216>.



5.30.8.4.2 Diazonitriliumborates—R₃B[−]—CN⁺—N₂R

Just one preparation of this type was reviewed in chapter 5.30.8.4.2 of COFGT (1995): the reaction of potassium triphenylcyanoborate and benzenediazonium tetrafluoroborate to give the diazonium salt, which rearranges itself to the diazonitrilium borate. No new chemistry has emerged in this area since publication of the earlier edition.

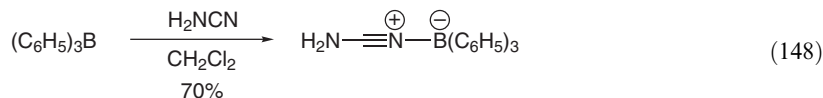
5.30.8.4.3 Cyanamidiummetallates—R₂N—CN⁺—MX_n[−]

Chapter 5.30 of COFGT (1995) touched briefly on the one report to emerge regarding cyanamidiummetallates, the preparation of pentachloroantimonate and trichloroferrate derivatives during preparation of cyanamidium salts <1995COFGT(5)1099>. It was also observed that the corresponding trifluoroborates, trichloroaluminates, tetrachlorotitanates, and dichlorozincates had been prepared as part of the same study.

Several compounds that fit into this class have been prepared since 1995. Thus, several complexes of organic cyanamides with copper <2002IC3313> and platinum <2002ICA395, 1995JOM89> have been made and characterized. Moreover, several *N,N*-dialkylcyanamide complexes of molybdenum have been prepared, and shown to promote reaction of a complexed dinitrogen ligand <2003IC2157>.

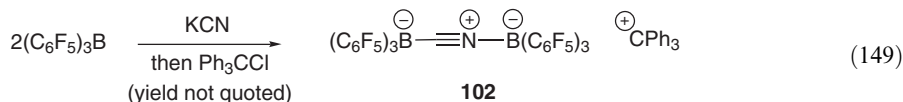
There has also been one report on the preparation of a compound of general formula R₂N—CN⁺—MX_n[−], in which M is boron: the cyanamidium complex of triphenylborane (Equation (148)) <2002ZAAC745>. This report also details preparation of the cyanogen iodide

complex of this same borane, its general formula $\text{I}-\text{CN}^+-\text{BR}_3^-$. The preparation of an iodo-heteronitrilium $\text{I}-\text{CN}^+-\text{I}$ as its hexafluoroarsenate salt has also been recorded <1997JCS(D)553>.



5.30.8.4.4 Boro-nitrilium borates— $\text{R}_3\text{B}^--\text{CN}^+-\text{BR}_3^- \text{X}^+$

While this class of compounds was not considered in the earlier edition, one report of a compound of this type has come to light in the intervening period. This involves reaction of a triarylborane, potassium cyanide, and trityl chloride to prepare the bis-boron compound **102** (Equation (149)) <1999CC1533>.



There has also been one report of an *N*-boronitrilium species reported as a ligand at lowspin iron(II), having been generated *in situ* from tetraphenylborate and sodium cyanide <1996IC4523> (although this product could be considered to be a transition metal complex of the isonitrile $\text{C}\equiv\text{N}^+-\text{BPh}_3^-$).

REFERENCES

- 1995ACS313 P.-I. Kvam, J. Songstad, *Acta Chem. Scand.* **1995**, 49, 313–324.
 1995AG(E)1627 K. Banert, C. Toth, *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 1627–1629.
 1995AJC567 K. H. Ang, R. H. Prager, C. M. Williams, *Aust. J. Chem.* **1995**, 48, 567–575.
 1995CB1029 S. Luckert, E. Eversheim, M. Mueller, B. Redenz-Stormanns, U. Englert, P. Paetzold, *Chem. Ber.* **1995**, 128, 1029–1035.
 1995CB1037 C. Kloefkorn, M. Schmidt, T. Spaniol, T. Wagner, O. Costisor, P. Paetzold, *Chem. Ber.* **1995**, 128, 1037–1043.
 1995CC461 F. Santoyo-Gonzalez, F. Garcia-Calvo-Flores, P. Garcia-Mendoza, F. Hernandez-Mateo, J. Isac-Garcia, M. D. Perez-Alvarez, *J. Chem. Soc., Chem. Commun.* **1995**, 461–462.
 1995CJC113 I. Cordova-Reyes, E. VandenHoven, A. Mohammed, B. M. Pinto, *Can. J. Chem.* **1995**, 73, 113–116.
 1995CPB1516 M. Kuwahara, Y. Kawano, H. Shimazu, H. Yamamoto, Y. Ashida, A. Miyake, *Chem. Pharm. Bull.* **1995**, 43, 1516–1522.
 1995COFGT(5)1099 I. K. Boddy, A. J. Ford, Nitriles with a heteroatom attached to the cyanocarbon, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5, pp. 1099–1149.
 1995IZV968 A. A. Bezrukova, V. S. Khandkarova, P. V. Petrovskii, A. Z. Rubeshov, Y. S. Vygodskii, K. P. Butin, T. V. Magdesieva, G. A. Pirogova, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1995**, 968–973.
 1995JA9783 S. Mehta, J. S. Andrews, B. D. Johnston, B. Svensson, B. M. Pinto, *J. Am. Chem. Soc.* **1995**, 117, 9783–9790.
 1995JA111730 P. C. Cagle, O. Meyer, K. Weickhardt, A. M. Arif, J. A. Gladysz, *J. Am. Chem. Soc.* **1995**, 117, 11730–11744.
 1995JCR(S)152 Y. Aso, K. Omote, S. Takagi, T. Otsubo, F. Ogura, *J. Chem. Res. (S)* **1995**, 152–153.
 1995JFC101 R. A. Moss, C.-S. Ge, *J. Fluorine Chem.* **1995**, 73, 101–105.
 1995JOC703 T. G. Back, B. P. Dyck, M. Parvez, *J. Org. Chem.* **1995**, 60, 703–710.
 1995JOC813 I. Erden, F.-P. Xu, A. Sadoun, W. Smith, G. Sheff, M. Ossun, *J. Org. Chem.* **1995**, 60, 813–820.
 1995JOC4096 S. Buscemi, N. Vivona, T. Caronna, *J. Org. Chem.* **1995**, 60, 4096–4101.
 1995JOC4657 T. G. Back, B. P. Dyck, M. Parvez, *J. Org. Chem.* **1995**, 60, 4657–4659.
 1995JOC7144 Y. Kita, T. Takada, S. Mihara, B. A. Whelan, H. Tohma, *J. Org. Chem.* **1995**, 60, 7144–7148.
 1995JOM89 M. F. C. Guedes da Silva, E. M. P. R. P. Branco, Y. Wang, J. J. R. F. da Silva, A. J. L. Pombeiro, R. Bertani, R. A. Michelin, M. Mozzon, F. Benetollo, *J. Organomet. Chem.* **1995**, 490, 89–99.
 1995MI2 D.-C. Ha, E.-S. Yu, *Bull. Korean Chem. Soc.* **1995**, 16, 2–4.
 1995MI211 H. Ahlbrecht, J. Harbach, R. W. Hoffmann, T. Ruhland, *Liebigs Ann. Org. Bioorg. Chem.* **1995**, 211–216.
 1995MI871 G. Hornyak, A. Feller, K. Lempert, *ACH-Models Chem.* **1995**, 132, 871–885.
 1995MI1299 L. K. Revelle, A. M. Rutter, J. A. Wilson, *J. Agric. Food Chem.* **1995**, 43, 1299–1301.
 1995OM3435 W. W. Lukens Jr., R. A. Andersen, *Organometallics* **1995**, 14, 3435–3439.
 1995PS11 V. J. Ram, M. Nath, *Phosphorus Sulfur* **1995**, 105, 11–15.
 1995PS69 A. Vollbrecht, I. Neda, A. Fischer, P. G. Jones, R. Schmutzler, *Phosphorus Sulfur* **1995**, 107, 69–78.

- 1995PS243 N. S. Jalil Neelam, S. A. Saidu, *Phosphorus Sulfur* **1995**, 106, 243–248.
1995SC829 J. Marton, S. Miklos, S. Hosztafi, S. Makleit, *Synth. Commun.* **1995**, 25, 829–848.
1995SC2435 X.-K. Fu, S.-Y. Wen, *Synth. Commun.* **1995**, 25, 2435–2442.
1995T4763 J. Fetter, H. Vasarhelyi, M. Kajtar-Peredy, K. Lempert, J. Tamas, G. Czira, *Tetrahedron* **1995**, 51, 4763–4778.
1995TL1759 Y. Satoh, N. Marcopulos, *Tetrahedron Lett.* **1995**, 36, 1759–1762.
1995TL4373 B. Mullah, A. Andrus, H. Zhao, R. A. Jones, *Tetrahedron Lett.* **1995**, 36, 4373–4376.
1995TL6059 N. Sennequier, J.-L. Boucher, P. Battioni, D. Mansuy, *Tetrahedron Lett.* **1995**, 36, 6059–6062.
1995TL8015 L. Campanini, A. Dureault, J.-C. Depezay, *Tetrahedron Lett.* **1995**, 36, 8015–8018.
1995TL8187 J. Belzner, H. Ihmels, M. Noltemeyer, *Tetrahedron Lett.* **1995**, 36, 8187–8190.
1995TL9437 B. A. Kashemirov, M. Fujimoto, C. E. McKenna, *Tetrahedron Lett.* **1995**, 36, 9437–9440.
1995TL9475 E. Magnier, Y. Langlois, C. Merienne, *Tetrahedron Lett.* **1995**, 36, 9475–9478.
1995ZAAC823 W. Uhl, U. Schütz, W. Hiller, M. Heckel, *Z. Anorg. Allg. Chem.* **1995**, 621, 823–828.
1995ZOR934 P. P. Purygin, S. V. Pan'kov, *Zh. Org. Khim.* **1995**, 31, 934–936.
1996AJC573 B. C. Elmes, G. Holan, G. T. Wernert, D. A. Winkler, *Aust. J. Chem.* **1996**, 49, 573–579.
1996AP535 K. Rehse, S. Bade, *Arch. Pharm.* **1996**, 329, 535–540.
1996BMCL2553 S.-H. Jung, J.-S. Song, H.-S. Lee, S.-U. Choi, C.-O. Lee, *Bioorg. Med. Chem. Lett.* **1996**, 6, 2553–2558.
1996BSF515 J.-B. Baudin, M.-G. Commenil, S. A. Julia, Y. Wang, *Bull. Soc. Chim. Fr.* **1996**, 133, 515–529.
1996CPB122 M. Kuwahara, Y. Kawano, H. Shimazu, Y. Ashida, A. Miyake, *Chem. Pharm. Bull.* **1996**, 44, 122–131.
1996CJC533 I. Cordova-Reyes, H. Hu, J.-H. Gu, E. VandenHoven, A. Mohammed, *Can. J. Chem.* **1996**, 74, 533–543.
1996H1497 J. L. Ralbovsky, P. M. Scola, E. Sugino, C. Burgos-Garcia, S. M. Weinreb, M. Parvez, *Heterocycles* **1996**, 43, 1497–1512.
1996ICA97 A. Westwood, D. Nicholls, *Inorg. Chim. Acta* **1996**, 245, 97–99.
1996ICA(245)97 A. Westwood, D. Nicholls, *Inorg. Chim. Acta* **1996**, 245, 97–99.
1996IC4523 P. I. Amrhein, A. J. Lough, R. H. Morris, *Inorg. Chem.* **1996**, 35, 4523–4525.
1996JA5216 N. Dubau-Assibat, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* **1996**, 118, 5216–5220.
1996JA8077 M. Iwaoka, S. Tomoda, *J. Am. Chem. Soc.* **1996**, 118, 8077–8084.
1996JCS(P1)377 Y. Ichikawa, C. Kobayashi, M. Isobe, *J. Chem. Soc., Perkin Trans. 1* **1996**, 377–382.
1996JFC27 H. Trabelsi, M. A. Jouani, A. Cambon, *J. Fluorine Chem.* **1996**, 79, 27–31.
1996JHC1275 D.-K. Kim, Y.-W. Kim, J. S. Gam, G. Kim, J. Lim, *J. Heterocycl. Chem.* **1996**, 33, 1275–1283.
1996JNP738 S.-S. Lee, R. W. Doskotch, *J. Nat. Prod.* **1996**, 59, 738–743.
1996JOC6639 L. Chen, T. R. Thompson, R. P. Hammer, G. Barany, *J. Org. Chem.* **1996**, 61, 6639–6645.
1996JOM109 D. A. Antonov, C. Eaborn, D. J. Smith, P. B. Hitchcock, E. Molla, V. I. Rozenberg, W. A. Stancyk, A. Kowaleska, *J. Organomet. Chem.* **1996**, 521, 109–112.
1996MI377 K. S. Kim, R. V. Moquin, L. Qian, R. A. Morrison, S. M. Seiler, *Med. Chem. Res.* **1996**, 6, 377–383.
1996MI493 N. M. Hassan, A. A. Fahmi, F. F. Abd-El-Mageid, A. O. Abdelhamid, *J. Chin. Chem. Soc.* **1996**, 43, 493–496.
1996OM1251 M. Tamm, T. Luegger, F. E. Hahn, *Organometallics* **1996**, 15, 1251–1256.
1996JOM127 U. Thewalt, W. Nuding, *J. Organomet. Chem.* **1996**, 512, 127–130.
1996JPR681 K. Butke, H.-J. Niclas, *J. Prakt. Chem.* **1996**, 338, 681–683.
1996PS790 C. E. McKenna, B. A. Kashemirov, M. Fujimoto, *Phosphorus Sulfur* **1996**, 111, 790–790.
1996RTC443 V. A. Potapov, S. V. Amosova, G. N. Dudareva, V. Y. Shestakova, A. R. Zhinkin, *Recl. Trav. Chim. Pays-Bas* **1996**, 115, 443–443.
1996SC3709 J. S. Koo, J. I. Lee, *Synth. Commun.* **1996**, 26, 3709–3713.
1996SC4299 P. Deprez, J.-P. Vevert, *Synth. Commun.* **1996**, 26, 4299–4310.
1996SL18 D. Enders, S. von Berg, B. Jandeleit, *Synlett.* **1996**, 18–20.
1996T12061 K. Usami, M. Isobe, *Tetrahedron* **1996**, 52, 12061–12090.
1996TL1889 A. De Mico, R. Margarita, A. Mariani, G. Piancatelli, *Tetrahedron Lett.* **1996**, 37, 1889–1892.
1996TL4393 T. Ishikawa, M. Ikeno, T. Sakamaki, K. Sato, K. Higuchi, *Tetrahedron Lett.* **1996**, 37, 4393–4396.
1996ZOB639 B. D. Grishchuk, E. Y. Kudrik, P. M. Gorbovoi, N. I. Ganushchak, G. Y. Zagrichuk, B. I. Kaspruk, *Zh. Obshch. Khim.* **1996**, 66, 639–642.
1996ZOR1100 E. E. Nifant'ev, D. A. Predvoditelev, M. A. Malenkovskaya, *Zh. Org. Khim.* **1996**, 66, 1100–1108.
1997BSF653 T. Patonay, A. Levai, L. Hegedus, E. Patonay-Peli, *Bull. Soc. Chim. Fr.* **1997**, 134, 653–667.
1997BMC369 J. Marton, C. Simon, S. Hosztafi, Z. Szabo, A. Marki, *Bioorg. Med. Chem.* **1997**, 5, 369–382.
1997BMCL1721 H. Tsubouchi, K. Ohguro, K. Yasumura, H. Ishikawa, M. Kikuchi, *Bioorg. Med. Chem. Lett.* **1997**, 7, 1721–1724.
1997CAR271 V. Moreau, J. C. Norrild, H. Driguez, *Carbohydr. Res.* **1997**, 300, 271–277.
1997CC1021 K. R. Prabhu, S. Chandrasekaran, *J. Chem. Soc., Chem. Commun.* **1997**, 1021–1022.
1997CC1237 A. De Mico, R. Margarita, A. Mariani, G. Piancatelli, *J. Chem. Soc., Chem. Commun.* **1997**, 1237–1238.
1997CEJ453 T. M. Tagmose, M. Bols, *Chem. -Eur. J.* **1997**, 3, 453–462.
1997CEJ1894 T. Wirth, G. Fragale, *Chem. -Eur. J.* **1997**, 3, 1894–1902.
1997CPB1447 M. Kuwahara, Y. Kawano, M. Kajino, Y. Ashida, A. Miyake, *Chem. Pharm. Bull.* **1997**, 45, 1447–1457.
1997DOK777 S. G. Kochin, A. S. Antsyshkina, G. G. Sadikov, A. S. Burlov, V. A. Kogan, A. D. Garnovskii, *Dokl. Akad. Nauk SSSR* **1997**, 355, 777–779.
1997H443 I. Nagasaki, Y. Suzuki, K. Iwamoto, T. Higashino, A. Miyashita, *Heterocycles* **1997**, 46, 443–450.
1997H745 A. Mayashita, I. Nagasaki, A. Kawano, Y. Suzuki, K. Iwamoto, T. Higashino, *Heterocycles* **1997**, 45, 745–755.

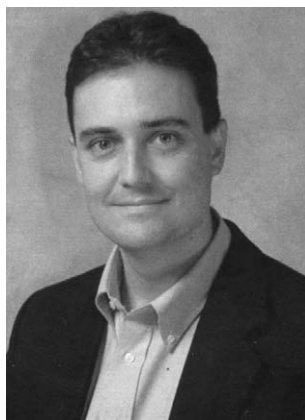
- 1997H1745 J. M. Blanco, O. Caamaño, F. Fernández, X. García-Mera, I. Nieto, J. E. Rodríguez-Borges, *Heterocycles* **1997**, 45, 1745–1750.
- 1997IJC(B)394 V. J. Ram, M. Nath, *Indian J. Chem., Sect. B* **1997**, 36, 394–398.
- 1997JA2819 J.-L. Faure, R. Reau, M. W. Wong, R. Koch, C. Wentrup, G. Bertrand, *J. Am. Chem. Soc.* **1997**, 119, 2819–2824.
- 1997JCR(M)1901 Y. Fort, C. Gottardi-Duboscq, *J. Chem. Res. (M)* **1997**, 1901–1916.
- 1997JCS(D)553 T. M. Klapötke, *J. Chem. Soc., Dalton Trans.* **1997**, 553–557.
- 1997JCS(P1)339 D. Wiedenfeld, *J. Chem. Soc., Perkin Trans. 1* **1997**, 339–347.
- 1997JCS(P1)671 Y. Tanabe, K. Mori, Y. Yoshida, *J. Chem. Soc., Perkin Trans. 1* **1997**, 671–675.
- 1997JCS(P1)1449 Y. Ichikawa, M. Osada, I. I. Ohtani, M. Isobe, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1449–1455.
- 1997JIC443 P. C. Srivastava, P. Singh, M. Tangri, A. Sinha, S. Bajpai, *J. Indian Chem. Soc.* **1997**, 74, 443–445.
- 1997JMC3707 S. E. Hagen, J. V. N. V. Prasad, F. E. Boyer, J. M. Domagala, E. L. Ellsworth, *J. Med. Chem.* **1997**, 40, 3707–3711.
- 1997JMC4281 L.-Y. Hu, J. Guo, S. S. Magar, J. B. Fischer, K. J. Burke-Howie, G. J. Durant, *J. Med. Chem.* **1997**, 40, 4281–4289.
- 1997JOC292 F. Palacios, J. Pagalday, V. Piquet, F. Dahan, A. Baceiredo, G. Bertrand, *J. Org. Chem.* **1997**, 62, 292–296.
- 1997JOC3944 F. G. Calvo-Flores, P. Garcia-Mendoza, F. Hernandez-Mateo, J. Isac-Garcia, F. Santoyo-Gonzalez, *J. Org. Chem.* **1997**, 62, 3944–3961.
- 1997JPR473 E. H. Moerkved, C. Wang, *J. Prakt. Chem.* **1997**, 339, 473–476.
- 1997PS43 A. M. Farag, K. M. Dawood, Z. E. Kandeel, *Phosphorus Sulfur* **1997**, 130, 43–51.
- 1997PS385 Y. Tanabe, K. Mori, N. Kawabata, *Phosphorus Sulfur* **1997**, 120, 385–386.
- 1997T12147 K. Krief, C. Delmotte, W. Dumont, *Tetrahedron* **1997**, 53, 12147–12158.
- 1997T16835 A. M. Echavarren, N. Tamayo, O. de Frutos, A. Garcia, *Tetrahedron* **1997**, 53, 16835–16846.
- 1997TL65 T. Billard, S. Large, B. Langlois, *Tetrahedron Lett.* **1997**, 38, 65–68.
- 1997TL1541 H. Weigl, R. Gleiter, *Tetrahedron Lett.* **1997**, 38, 1541–1542.
- 1997TL3115 M. T. V. L. Carvalho, A. M. Lobo, P. S. Branco, S. Prabhakar, *Tetrahedron Lett.* **1997**, 38, 3115–3118.
- 1997TL5303 S. S. Kim, H. Kim, K. W. Yang, *Tetrahedron Lett.* **1997**, 38, 5303–5306.
- 1997TL8699 A. Olszewski-Ortar, P. Gros, Y. Fort, *Tetrahedron Lett.* **1997**, 38, 8699–8702.
- 1997ZOR1068 E. E. Bilaya, N. D. Obushak, N. I. Ganushchak, *Zh. Org. Khim.* **1997**, 33, 1068–1071.
- 1998ACS608 L. Eberson, O. Persson, *Acta Chem. Scand.* **1998**, 52, 608–621.
- 1998AP241 F. Sączewski, T. Debowski, J. Petrusiewicz, H. Trzeciak, E. Krzysztanek, *Arch. Pharm.* **1998**, 331, 241–248.
- 1998CC201 P. B. Hitchcock, M. F. Lappert, M. Layh, *J. Chem. Soc., Chem. Commun.* **1998**, 201–202.
- 1998CC2611 I. Tworowska, W. Dabkowski, *J. Chem. Soc., Chem. Commun.* **1998**, 2611–2612.
- 1998CEJ2467 G. Kaupp, J. Schmeyer, J. Boy, *Chem. -Eur. J.* **1998**, 4, 2467–2474.
- 1998EJO121 S. Araki, K. Yamamoto, M. Yagi, T. Inoue, H. Fukagawa, *Eur. J. Org. Chem.* **1998**, 121–127.
- 1998JA6433 A. Tanatani, K. Yamaguchi, I. Azumaya, R. Fukutomi, K. Shudo, H. Kagechika, *J. Am. Chem. Soc.* **1998**, 120, 6433–6442.
- 1998JCS(D)1919 S. M. Godfrey, C. A. McAuliffe, R. G. Pritchard, J. M. Sheffield, *J. Chem. Soc., Dalton Trans.* **1998**, 1919–1923.
- 1998JCS(P1)1013 Y. Masuda, M. Murata, M. Ikeda, S. Watanabe, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1013–1014.
- 1998JCS(P2)2309 J. F. Kadla, C. R. Cornman, *J. Chem. Soc., Perkin Trans. 2* **1998**, 2309–2313.
- 1998JMC3048 M. C. Maillard, M. E. Perlman, O. Amitay, D. Baxter, D. Berlove, *J. Med. Chem.* **1998**, 41, 3048–3061.
- 1998JMC3159 C. Walpole, S. Y. Ko, M. Brown, D. Beattie, E. Campbell, *J. Med. Chem.* **1998**, 41, 3159–3173.
- 1998JOC401 T. V. Hughes, S. D. Hammond, M. P. Cava, *J. Org. Chem.* **1998**, 63, 401–402.
- 1998JOC4392 A. Coop, J. W. Janetka, J. W. Lewis, K. C. Rice, *J. Org. Chem.* **1998**, 63, 4392–4396.
- 1998JOC7134 E. C. Rodriguez, L. A. Marcaurelle, C. R. Bertozzi, *J. Org. Chem.* **1998**, 63, 7134–7135.
- 1998JOM45 H. Werner, G. Horlin, W. D. Jones, *J. Organomet. Chem.* **1998**, 562, 45–51.
- 1998JOM117 I. S. Goncalves, F. E. Kuhn, A. D. Lopes, A. J. Parola, F. Pina, J. Sotomayor, C. C. Romao, *J. Organomet. Chem.* **1998**, 560, 117–124.
- 1998JOM127 F. Zamora, E. Zangrando, M. Furlan, L. Randaccio, B. Lippert, *J. Organomet. Chem.* **1998**, 552, 127–134.
- 1998MI228 P. Lidström, T. A. Bonasera, M. Marquez-M, S. Nilsson, M. Bergström, *Steroids* **1998**, 63, 228–234.
- 1998POL999 B. Gehrhuis, M. F. Lappert, *Polyhedron* **1998**, 17, 999–1000.
- 1998PS587 V. A. Potapov, S. V. Amosova, B. V. Petrov, *Phosphorus Sulfur* **1998**, 136, 587–590.
- 1998SC583 A. Mandelair, Y. Fort, *Synth. Commun.* **1998**, 28, 583–592.
- 1998SUL19 F. A. G. El-Essawy, S. M. Yassin, I. A. El-Sakka, A. F. Khatat, I. Sotofte, J. O. Madsen, A. Senning, *Sulfur Lett.* **1998**, 22, 19–32.
- 1998T9143 J. Marton, Z. Szabo, S. Garadnay, S. Miklos, S. Makleit, *Tetrahedron* **1998**, 54, 9143–9152.
- 1998T14869 S. Cerezo, J. Cortes, M. Moreno-Manas, R. Pleixats, A. Roglans, *Tetrahedron* **1998**, 54, 14869–14884.
- 1998T14885 S. Cerezo, J. Cortes, J.-M. Lopez-Romero, M. Moreno-Manas, T. Parella, *Tetrahedron* **1998**, 54, 14885–14904.
- 1998TL3847 M. Bruno, R. Margarita, L. Parlanti, G. Piancatelli, M. Trifoni, *Tetrahedron Lett.* **1998**, 39, 3847–3848.
- 1998TL8353 A. P. Esteves, A. M. Freitas, C. M. Raynor, R. J. Stoodley, *Tetrahedron Lett.* **1998**, 39, 8353–8356.
- 1998ZAAC1642 M. R. Kopp, B. Neumueller, *Z. Anorg. Allg. Chem.* **1998**, 624, 1642–1646.
- 1999AJC159 P. B. W. McCallum, R. T. Weavers, M. R. Grimmett, A. G. Blackman, *Aust. J. Chem.* **1999**, 52, 159–165.

- 1999AJC1131 D. J. Bergmann, E. M. Campi, R. W. Jackson, A. F. Patti, *Aust. J. Chem.* **1999**, 52, 1131–1138.
1999AG(E)1604 E. Block, M. Birringer, C. He, *Angew. Chem., Int. Ed. Engl.* **1999**, 38, 1604–1607.
1999BMC509 F. Leroux, B. J. van Keulen, J. Daliens, N. Pommery, J. P. Henichart, *Bioorg. Med. Chem.* **1999**, 7, 509–516.
1999CC1533 S. J. Lancaster, D. A. Walker, M. Thornton-Pett, M. Bochmann, *J. Chem. Soc., Chem. Commun.* **1999**, 1533–1534.
1999CEJ1512 J. Isac-Garcia, F. G. Calvo-Flores, F. Hernandez-Mateo, F. Santoyo-Gonzalez, *Chem. -Eur. J.* **1999**, 5, 1512–1525.
1999EJ1201 W. Uhl, F. Hannemann, *Eur. J. Inorg. Chem.* **1999**, 201–207.
1999EJ1771 W. Uhl, F. Hannemann, W. Saak, R. Wartchow, *Eur. J. Inorg. Chem.* **1999**, 771–776.
1999EJ1193 L. Weber, M. Schnieder, H.-G. Stammer, B. Neumann, W. Schoeller, *Eur. J. Inorg. Chem.* **1999**, 1193–1198.
1999EJ11359 T. M. Klapötke, B. Krumm, K. Polborn, *Eur. J. Inorg. Chem.* **1999**, 1359–1366.
1999H475 D. K. Bates, M. Xia, M. Aho, H. Mueller, R. R. Raghavan, *Heterocycles* **1999**, 51, 475–479.
1999HCA645 P. Kapferer, F. Sarabia, A. Vasella, *Helv. Chim. Acta* **1999**, 82, 645–656.
1999ICA266 K.-H. Trylus, U. Kernbach, I. Brudgam, W. P. Fehlhammer, *Inorg. Chim. Acta* **1999**, 291, 266–278.
1999JCB445 H. A. Allimony, H. A. Saad, F. A. A. El-Mariah, *Indian J. Chem. Sect. B* **1999**, 38, 445–451.
1999JA1090 P. Vedrenne, V. Le Guen, L. Toupet, T. Le Gall, C. Mioskowski, *J. Am. Chem. Soc.* **1999**, 121, 1090–1091.
1999JAP11255735 Okamoto, S.; Watanabe, H. Jpn. Patent. 11255735 (**1999**) (*Chem. Abs.* 131, 214077).
1999JAP11228522 Okamoto, S.; Watanabe, H. Jpn. Patent. 11228522 (**1999**) (*Chem. Abs.* 131, 157655).
1999JCS(P2)1869 A. T. Bech, R. Flammang, C. T. Pedersen, M. W. Wong, C. Wentrup, *J. Chem. Soc., Perkin Trans. 2* **1999**, 1869–1873.
1999JHC209 J. Svetlik, T. Liptaj, F. Turecek, *J. Heterocycl. Chem.* **1999**, 36, 209–215.
1999JMC1161 Y. Song, D. T. Connor, A. D. Sercel, R. J. Sorenson, R. Doubleday, *J. Med. Chem.* **1999**, 42, 1161–1169.
1999JOC2897 C. F. Bernasconi, A. E. Leyes, Z. Rappoport, *J. Org. Chem.* **1999**, 64, 2897–2902.
1999JOC2958 P. J. Lennon, S. G. Vulfson, E. Civade, *J. Org. Chem.* **1999**, 64, 2958–2961.
1999JOC6756 A. Abboto, S. Bradamante, A. Facchetti, G. A. Pagani, *J. Org. Chem.* **1999**, 64, 6756–6763.
1999KFZ16 B. D. Grishchuk, L. I. Vlasik, A. V. Blinder, P. M. Gorbovoi, G. Y. Zagrichuk, *Khim. Farm. Zh.* **1999**, 33, 16–17.
1999MI107 J. Charris, J. Dominguez, G. Lobo, F. Riggione, *Pharm. Pharmacol. Commun.* **1999**, 5, 107–110.
1999MI306 M. G. Vigorita, R. Maccari, R. Ottana, F. Monforte, *Med. Chem. Res.* **1999**, 9, 306–321.
1999MI1137 I. Wenzl, H. Kaehlig, F. M. Unger, W. Schmid, *Monatsh. Chem.* **1999**, 130, 1137–1145.
1999OL269 D. Crich, X. Hao, M. A. Lucas, *Org. Lett.* **1999**, 1, 269–271.
1999OM3327 S.-W. Lai, M. C.-W. Chan, K.-K. Cheung, C.-M. Che, *Organometallics* **1999**, 18, 3327–3336.
1999PS169 D. Keil, H. Hartmann, *Phosphorus Sulfur* **1999**, 152, 169–184.
1999PS325 K. Banert, W. Fendel, A. Müller, B. Müller, J. Schlott, *Phosphorus Sulfur* **1999**, 153, 325–326.
1999SC3289 K. Fujiki, E. Yoshida, *Synth. Commun.* **1999**, 29, 3289–3294.
1999T14261 D. Crich, X. Hao, M. Lucas, *Tetrahedron* **1999**, 55, 14261–14268.
1999TL1181 A. M. Belostotskii, J. Lexner, A. Hassner, *Tetrahedron Lett.* **1999**, 40, 1181–1184.
1999TL6439 Y. S. Park, K. Kim, *Tetrahedron Lett.* **1999**, 40, 6439–6442.
1999ZOB995 B. D. Grishchuk, G. Y. Zagrichuk, V. S. Baranovskii, P. M. Gorbovoi, *Zh. Obshch. Khim.* **1999**, 69, 995–997.
1999ZOR1110 G. O. Torosyan, D. N. Oganessian, H. R. Carril'o, E. Musluoglu, V. Ahsen, *Zh. Org. Khim.* **1999**, 35, 1110–1115.
2000BCJ1857 Y. Takaguchi, S. Suzuki, T. Mori, J. Motoyoshiya, H. Aoyama, *Bull. Chem. Soc. Jpn.* **2000**, 73, 1857–1860.
2000BMCL1775 G. M. Keseru, G. T. Balogh, T. Karancsi, *Bioorg. Med. Chem. Lett.* **2000**, 10, 1775–1777.
2000CC2275 L. Charoy, A. Valleix, L. Toupet, T. L. Gall, P. P. van Chuong, C. Mioskowski, *J. Chem. Soc., Chem. Commun.* **2000**, 2275–2276.
2000CCC1745 J. Moravcova, L. Spilova, J. Capkova, F. Chery, P. Rollin, *Collect. Czech. Chem. Commun.* **2000**, 65, 1745–1753.
2000CEJ1763 R. Lavilla, R. Kumar, O. Coll, C. Masdeu, A. Spada, J. Bosch, E. Espinosa, E. Molins, *Chem. -Eur. J.* **2000**, 6, 1763–1772.
2000EJM853 A. K. Gadad, C. S. Mahajanshetti, S. Nimbalkar, A. Raichurkar, *Eur. J. Med. Chem.* **2000**, 35, 853–857.
2000EJO1865 R. Margarita, C. Mercanti, L. Parlanti, G. Piancatelli, *Eur. J. Org.* **2000**, 1865–1870.
2000JA4583 H. Abe, S. Aoyagi, C. Kibayashi, *J. Am. Chem. Soc.* **2000**, 122, 4583–4592.
2000JA7735 D. Williams, B. Pleune, J. Kouvetakis, M. D. Williams, R. A. Andersen, *J. Am. Chem. Soc.* **2000**, 122, 7735–7741.
2000JA1343 S. Shuto, I. Sugimoto, H. Abe, A. Matsuda, *J. Am. Chem. Soc.* **2000**, 122, 1343–1351.
2000JAP2000086619 Kihara, K.; Tamura, G. Jpn. Patent 20000086619 (**2000**) (*Chem. Abs.* 132, 236801).
2000JAP2000159741 Okamoto, S.; Watabe, H. Jpn. Patent 2000159741 (**2000**) (*Chem. Abs.* 133, 17279).
2000JCS(D)11 M. Baum, J. Beck, A. Haas, W. Herrendorf, C. Monsé, *J. Chem. Soc., Dalton Trans.* **2000**, 11–15.
2000JCS(P1)1429 H. Ehara, M. Noguchi, S. Sayama, T. Onami, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1429–1431.
2000JCS(P1)3692 C. Di Vitta, I. P. de Arruda Campos, J. P. S. Farah, J. Zukerman-Schpector, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3692–3694.
2000JCS(P2)1851 N. Ohtani, S. Murakawa, K. Watanabe, D. Tsuchimoto, D. Sato, *J. Chem. Soc., Perkin Trans. 2* **2000**, 1851–1856.
2000JHC297 H. Miao, V. Cecchetti, O. Tabarrini, A. Fravolini, *J. Heterocycl. Chem.* **2000**, 37, 297–301.

- 2000JMC843 F. E. Boyer, J. V. N. V. Prasad, J. M. Domagala, E. L. Ellsworth, C. Gajda, S. E. Hagen, L. J. Markosi, B. D. Tait, E. A. Lunney, A. Palovsky, D. Ferguson, N. Graham, T. Holler, D. Hupe, C. Nouhan, P. J. Tummino, A. Urumov, E. Zeikus, G. Zeikus, S. J. Gracheck, J. M. Sanders, S. VanderRoest, J. Brodfuehrer, K. Iyer, M. Sinz, S. V. Gulnik, J. W. Erickson, *J. Med. Chem.* **2000**, *43*, 843–858.
- 2000JOC8152 I. Erdelmeier, C. Taihan-Lomont, J.-C. Yadan, *J. Org. Chem.* **2000**, *65*, 8152–8157.
- 2000JOM222 K. D. Safa, M. G. Asadi, A. Abri, A. Mohammadpour, H. Kiae, *J. Organomet. Chem.* **2000**, *598*, 222–227.
- 2000MI135 A. A. Elbahnsawy, M. K. A. Ibrahim, G. F. Ahmed, A. F. S. Ahmed, *Indian J. Heterocycl. Chem.* **2000**, *10*, 135–140.
- 2000OL795 Y. Wu, D. C. Limburg, D. E. Wilkinson, G. S. Hamilton, *Org. Lett.* **2000**, *2*, 795–797.
- 2000PJC1567 E. E. Bila, M. D. Obushak, M. I. Ganushchak, *Pol. J. Chem.* **2000**, *74*, 1567–1573.
- 2000S1148 S. A. Bakunov, A. V. Rukavishnikov, A. V. Tkachev, *Synthesis* **2000**, 1148–1159.
- 2000S1229 F. Effenberger, J. M. Endtner, B. Miehllich, J. S. R. Muentner, M. S. Vollmer, *Synthesis* **2000**, 1229–1236.
- 2000SC433 R. F. Cunico, *Synth. Commun.* **2000**, *30*, 433–436.
- 2000SL1004 H. Mues, U. Kazmaier, *Synlett* **2000**, 1004–1006.
- 2000T6039 L. Monnier, J.-G. Delcros, B. Carboni, *Tetrahedron* **2000**, *56*, 6039–6046.
- 2000TL2699 D. Simoni, R. Rondanin, G. Furno, E. Aiello, F. P. Invidiata, *Tetrahedron Lett.* **2000**, *41*, 2699–2703.
- 2000TL2805 B. C. Bookser, *Tetrahedron Lett.* **2000**, *41*, 2805–2809.
- 2001BMC1459 H. E. Ganther, *Bioorg. Med. Chem.* **2001**, *9*, 1459–1466.
- 2001BMCL981 B. Hu, M. Malamas, J. Ellingboe, E. Largis, S. Han, R. Mulvey, J. Tillett, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 981–984.
- 2001BMCL1245 R. Xu, L. P. Dwoskin, V. P. Grinevich, G. Deaciuc, P. A. Crooks, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1245–1248.
- 2001CC125 D. J. Mindiola, Y.-C. Tsai, R. Hara, Q. Chen, K. Meyer, C. C. Cummins, *J. Chem. Soc., Chem. Commun.* **2001**, 125–126.
- 2001CC1914 K. Tani, Y. Tohda, H. Takemura, H. Ohkita, S. Ito, M. Yamamoto, *J. Chem. Soc., Chem. Commun.* **2001**, 1914–1915.
- 2001CEJ5372 E. Irran, B. Jürgens, W. Schnick, *Chem. -Eur. J.* **2001**, *7*, 5372–5381.
- 2001CL1076 N. Takeda, T. Kajiwarra, N. Tokitoh, *Chem. Lett.* **2001**, 1076–1077.
- 2001EJI2783 V. Jacob, G. Huttner, E. Kaifer, P. Kircher, P. Rutsch, *Eur. J. Inorg. Chem.* **2001**, 2783–2795.
- 2001EJM597 F. Rogister, D. Laeckmann, P.-O. Plasman, F. V. Eylen, M. Ghyoot, C. Maggetto, J.-F. Liegeois, J. Geczy, A. Herchuelz, J. Delarge, B. Masereel, *Eur. J. Med. Chem.* **2001**, *36*, 597–614.
- 2001EJO1089 K. Banert, M. Hagedorn, A. Mueller, *Eur. J. Org. Chem.* **2001**, 1089–1103.
- 2001EJO1959 W. Adam, R. M. Bargon, *Eur. J. Org. Chem.* **2001**, 1959–1962.
- 2001IZV655 E. N. Ulomsky, V. V. Voronin, V. L. Rusinov, O. N. Chupakhin, *Izv. Akad. Nauk Ser. Khim.* **2001**, *50*, 655–661.
- 2001JA223 J. Zhou, S. J. Lancaster, D. A. Walker, S. Beck, M. Thornton-Pett, M. Bochmann, *J. Am. Chem. Soc.* **2001**, *123*, 223–237.
- 2001JA8089 Y. Chiang, A. J. Kresge, Y. Zhu, *J. Am. Chem. Soc.* **2001**, *123*, 8089–8094.
- 2001JA9453 S. Kamijo, T. Jin, Y. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 9453–9454.
- 2001JA12147 J. C. Niles, J. S. Wishnok, S. R. Tannenbaum, *J. Am. Chem. Soc.* **2001**, *123*, 12147–12154.
- 2001JCS(D)1529 P.-L. Fabre, A. M. Galibert, B. Soula, F. Dahan, P. Castan, *J. Chem. Soc., Dalton Trans.* **2001**, 1529–1536.
- 2001JCS(D)1732 J. H. Shin, W. Savage, V. J. Murphy, J. B. Bonanno, D. G. Churchill, G. Parkin, *J. Chem. Soc., Dalton Trans.* **2001**, 1732–1753.
- 2001JCS(P1)2476 S. Araki, H. Hattori, K. Ogawa, M. Kuzuya, T. Inoue, H. Yamamura, M. Kawai, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2476–2482.
- 2001JFC207 T. M. Klapötke, B. Krumm, P. Mayer, K. Polborn, O. P. Ruscitti, *J. Fluorine Chem.* **2001**, *112*, 207–212.
- 2001JMC94 J.-P. Falgoutret, R. M. Oballa, O. Okamoto, G. Wesolowski, Y. Aubin, R. M. Rydzewski, P. Prasit, D. Riendeau, S. B. Rodan, M. D. Percival, *J. Med. Chem.* **2001**, *44*, 94–104.
- 2001JMC3199 S. Dijols, C. Perollier, D. Lefevre-Groboillot, S. Pethe, R. Attias, J.-L. Boucher, D. J. Stuehr, D. Mansuy, *J. Med. Chem.* **2001**, *44*, 3199–3202.
- 2001JMC3531 R. Kumar, D. Rai, S. K. Sharma, H. A. Saffran, R. Blush, D. L. J. Tyrrell, *J. Med. Chem.* **2001**, *44*, 3531–3538.
- 2001JOM47 M. Moller, M. Husemann, G. Boche, *J. Organomet. Chem.* **2001**, *624*, 47–52.
- 2001KGS349 V. V. Dovlatyan, K. A. Eliazyan, V. A. Pivazyanyan, *Khim. Geterotsikl. Soedin.* **2001**, *37*, 349–351.
- 2001MI93 A. M. Belostotskii, H. Keren-Yeshuah, J. Lexner, A. Hassner, *Nucleos. Nucleot. Nucl.* **2001**, *20*, 93–101.
- 2001MI202 C. Moali, J.-L. Boucher, A. Renodon-Corniere, D. J. Stuehr, D. Mansuy, *Chem. Res. Toxicol.* **2001**, *14*, 202–210.
- 2001MI781 A. Van Aerschot, M. Meldgaard, F. Volders, G. Schepers, J. Rizenski, P. Herdewijn, *Nucleos. Nucleot. Nucl.* **2001**, *20*, 781–784.
- 2001OM25 A. Maraval, A. Igau, C. Lepetit, A. Chrostowska, J.-M. Sotiropoulos, G. Pfister-Guillouzo, B. Donnadiou, J.-P. Majoral, *Organometallics* **2001**, *20*, 25–34.
- 2001PHA36 E. Reimann, W. Erdle, *Pharmazi* **2001**, *56*, 36–40.
- 2001RRC439 A. Popescu, D. Istrati, C. Draghici, A. Banciu, D. Mihaiescu, C. Ciuculescu, A. Britzchi, M. D. Banciu, *Rev. Roum. Chim.* **2001**, *46*, 439–444.
- 2001S1509 M. Kidwai, P. Sapra, K. R. Bhushan, P. Misra, *Synthesis* **2001**, 1509–1512.

- 2001SC1355 I. W. J. Still, I. D. G. Watson, *Synth. Commun.* **2001**, 31, 1355–1359.
2001TL2455 B. B. Snider, S. M. O'Hare, *Tetrahedron Lett.* **2001**, 42, 2455–2458.
2001T2871 J. Forrester, R. V. H. Jones, L. Newton, P. N. Preston, *Tetrahedron* **2001**, 57, 2871–2884.
2001T1581 B. Jiang, Y. Kan, A. Zhang, *Tetrahedron* **2001**, 57, 1581–1584.
2001TL699 T. Uyehara, K. Onda, N. Nozaki, M. Karikomi, M. Ueno, T. Sato, *Tetrahedron Lett.* **2001**, 42, 699–702.
2001TL6133 K. Banert, A. Melzer, *Tetrahedron Lett.* **2001**, 42, 6133–6135.
2001TL8479 P.-Y. Renard, H. Schwebel, P. Vayron, E. Leclerc, S. Dias, C. Mioskowski, *Tetrahedron Lett.* **2001**, 42, 8479–8481.
2001ZAAC1048 B. Gehrhuis, P. B. Hitchcock, M. F. Lappert, *Z. Anorg. Allg. Chem.* **2001**, 627, 1048–1054.
2002AAC294 R. Maccari, R. Ottana, F. Monforte, M. G. Vigorita, *Antimicrob. Agents Chemother.* **2002**, 46, 294–299.
2002AG(E)1780 S. Kamijo, T. Jin, Y. Yamamoto, *Angew. Chem., Int. Ed. Engl.* **2002**, 41, 1780–1782.
2002AJC577 A. E. Rosamilia, P. A. Mayes, R. Papadopoulos, E. M. Campi, W. R. Jackson, L. Rash, B. Jarrott, *Aust. J. Chem.* **2002**, 55, 577–585.
2002BMC3049 M. Xian, N. Fujiwara, Z. Wen, T. Cai, S. Kazuma, A. J. Janczuk, X. Tang, V. V. Telyatnikov, Y. Zhang, X. Chen, Y. Miyamoto, *Bioorg. Med. Chem.* **2002**, 10, 3049–3055.
2002BMC3277 R. M. Rydzewski, C. Bryant, R. Oballa, G. Wesolowski, S. B. Rodan, K. E. Bass, D. H. Wong, *Bioorg. Med. Chem.* **2002**, 10, 3277–3284.
2002BMCL1583 F. Dumont, A. Sultana, R. N. Waterhouse, *Bioorg. Med. Chem. Lett.* **2002**, 12, 1583–1586.
2002BMCL2931 E. J. Iwanowicz, S. H. Watterson, C. Liu, H. H. Gu, T. Mitt, K. Leftheris, J. C. Barrish, C. A. Fleener, K. Rouleau, N. Z. Sherbina, D. L. Hollenbaugh, *Bioorg. Med. Chem. Lett.* **2002**, 12, 2931–2934.
2002CC1392 M. Suginoe, A. Yamamoto, Y. Ito, *J. Chem. Soc., Chem. Commun.* **2002**, 1392–1393.
2002CEJ2730 N. Wiberg, W. Niedermayer, K. Polborn, P. Mayer, *Chem. -Eur. J.* **2002**, 8, 2730–2739.
2002EJI2701 T. M. Klapoetke, B. Krumm, P. Mayer, H. Piotrowski, I. Schwab, M. Vogt, *Eur. J. Inorg. Chem.* **2002**, 2701–2709.
2002EJI3336 A. Zucca, S. Stoccoro, M. A. Cinelli, G. Minghetti, M. Manassero, M. Sansoni, *Eur. J. Inorg. Chem.* **2002**, 3336–3346.
2002EJM23 D. D. Wirth, M. M. He, B. A. Czeskis, K. M. Zimmerman, U. Roettig, W. Stenzel, M. I. Steinberg, *Eur. J. Med. Chem.* **2002**, 37, 23–34.
2002EJO2363 V. Nair, A. Augustine, T. G. George, *Eur. J. Org. Chem.* **2002**, 2363–2366.
2002IC3313 S.-M. Kuang, D. G. Cuttall, D. R. McMillin, P. E. Fanwick, R. A. Walton, *Inorg. Chem.* **2002**, 41, 3313–3322.
2002ICA395 C. M. P. Ferreira, M. F. C. Guedes da Silva, T. Duarte, J. J. R. Frausto da Silva, A. J. L. Pombeiro, R. A. Michelin, V. Y. Kukushkin, *Inorg. Chim. Acta* **2002**, 334, 395–402.
2002IJC(A)970 B. D. Gupta, D. Mandal, V. Dixit, *Indian J. Chem. Sect. A* **2002**, 41, 970–972.
2002H857 B. Hu, M. Malamas, J. Ellingboe, *Heterocycles* **2002**, 57, 857–870.
2002HAC561 W. Tyrre, *Heteroatom Chem.* **2002**, 13, 561–566.
2002JA1902 M. Iwaoka, H. Komatsu, T. Katsuda, S. Tomoda, *J. Am. Chem. Soc.* **2002**, 124, 1902–1909.
2002JA5258 R. A. Moss, F. Zheng, J.-M. Fede, Y. Ma, R. R. Sauers, J. P. Toscano, B. M. Showalter, *J. Am. Chem. Soc.* **2002**, 124, 5258–5259.
2002JA11675 C. M. P. Kronenburg, J. T. B. H. Jastrzebski, J. Boersma, M. Lutz, A. L. Spek, G. van Koten, *J. Am. Chem. Soc.* **2002**, 124, 11675–11683.
2002JA11940 S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, 124, 11940–11945.
2002JCS(D)3611 Y.-J. Kim, Y.-S. Joo, J.-T. Han, W. S. Han, S. W. Lee, *J. Chem. Soc. Dalton Trans.* **2002**, 3611–3618.
2002JCS(P1)300 B. Gyoeri, Z. Berente, R. Kiraly, I. Lazar, *J. Chem. Soc., Perkin Trans. 1* **2002**, 300–301.
2002JCS(P1)1568 Z. Casar, I. Leban, A. Majcen-Le Marechal, D. Lorcy, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1568–1573.
2002JMC2877 S. H. Woo, S. Frechette, E. Abou Khalil, G. Bouchain, A. Vaisburg, N. Bernstein, O. Moradei, S. Leit, M. Allan, M. Fournel, M.-C. Trachy-Bourget, Z. Li, J. M. Besterman, D. Delorme, *J. Med. Chem.* **2002**, 45, 2877–2885.
2002JMC3984 E. Elhalem, B. N. Bailey, R. Docampo, I. Ujvary, S. H. Szajnman, J. B. Rodriguez, *J. Med. Chem.* **2002**, 45, 3984–3999.
2002JOC1898 S. Chambert, F. Thomasson, J.-L. Decout, *J. Org. Chem.* **2002**, 67, 1898–1904.
2002JOC4487 R. G. Syvret, K. M. Butt, T. P. Nguyen, V. L. Bullock, E. D. Rieth, *J. Org. Chem.* **2002**, 67, 4487–4493.
2002JOC8538 C. Addicott, M. W. Wong, C. Wentrup, *J. Org. Chem.* **2002**, 67, 8538–8546.
2002JOM109 A. M. Caporusso, L. A. Aronica, R. Geri, M. Gori, *J. Organomet. Chem.* **2002**, 648, 109–118.
2002JOM141 M. I. Bruce, B. W. Skelton, A. H. White, N. N. Zaitseva, *J. Organomet. Chem.* **2002**, 650, 141–150.
2002KFZ983 N. O. Saldabol, J. Popelis, V. Slavinska, *Khim. Farm. Zh.* **2002**, 38, 983–991.
2002MI425 A. M. Santana, A. E. Mauro, H. E. Zorel Jr., M. P. D. Mattioli, N. V. A. De Lucca, *J. Therm. Anal. Calorim.* **2002**, 67, 425–431.
2002MI510 H. Matloubi, M. Ghandi, N. Saemian, *Appl. Radiat. Isot.* **2002**, 57, 501–504.
2002MI581 K. Vyakaranam, G. Rana, B. F. Spielsvogel, J. A. Maguire, N. S. Hosmane, *Nucleos. Nucleot. Nucl.* **2002**, 21, 581–598.
2002OM1011 G. Greidanus-Strom, C. A. G. Carter, J. M. Stryker, *Organometallics* **2002**, 21, 1011–1013.
2002OPP643 L. Lattuada, F. Uberti, *Org. Prep. Proced. Int.* **2002**, 34, 643–646.
2002SC343 J. Chmiewski, M. Haun, K. Topmiller, J. Ward, K. M. Church, *Synth. Commun.* **2002**, 32, 343–353.
2002SC803 G. H. Lee, H. W. Lee, C. S. Pak, *Synth. Commun.* **2002**, 32, 803–812.
2002SRI569 P. Raj, S. Agnihotri, K. Singhal, *Synth. React. Inorg. Metal-Org. Chem.* **2002**, 32, 569–581.
2002SRI399 S. Agnihotri, P. Raj, K. Singhal, *Synth. React. Inorg. Metal-Org. Chem.* **2002**, 32, 399–417.

- 2002T1611 J. Gonda, M. Martinkova, J. Imrich, *Tetrahedron* **2002**, 58, 1611–1616.
- 2002T2085 V. Benin, P. Kaszynski, J. G. Radziszewski, *Tetrahedron* **2002**, 58, 2085–2090.
- 2002TA1097 J. Hydrio, M. Gouygou, F. Dallemer, J.-C. Daran, G. G. A. Balavoine, *Tetrahedron Asymmetry* **2002**, 13, 1097–1102.
- 2002TA2635 A. Garcia Martinez, E. Teso Vilar, F. Moreno Jimenez, A. M. Alvarez Garcia, P. Pinilla Rodriguez, *Tetrahedron Asymmetry* **2002**, 13, 2635–2639.
- 2002TL3439 N. Iranpoor, H. Firouzabadi, H. R. Shaterian, *Tetrahedron Lett.* **2002**, 43, 3439–3441.
- 2002ZAAC745 W. Fraenk, T. M. Klapötke, B. Krumm, P. Mayer, H. Piotrowski, M. Vogt, *Z. Anorg. Allg. Chem.* **2002**, 628, 745–750.
- 2002ZOB869 K. P. Balashev, Y. A. Ivanov, T. V. Taraskina, E. A. Cherezova, *Zh. Obshch. Khim.* **2002**, 72, 869–870.
- 2002ZOR845 V. A. Vasin, A. V. Semenov, V. V. Razin, *Zh. Org. Khim.* **2002**, 38, 845–851.
- 2003BMCL107 M. L. P. Price, W. C. Guida, T. E. Jackson, J. A. Nydick, P. L. Gladstone, J. C. Juarez, F. Donate, R. J. Ternansky, *Bioorg. Med. Chem. Lett.* **2003**, 13, 107–110.
- 2003BMCL297 Y. Song, L. Clizbe, C. Bhakta, W. Teng, P. Wong, B. Huang, K. Tran, U. Sinha, G. Park, A. Reed, R. M. Scarborough, B. Y. Zou, *Bioorg. Med. Chem. Lett.* **2003**, 13, 297–300.
- 2003EJO385 A. Maraval, A. Igau, B. Donnadieu, J.-P. Majoral, *Eur. J. Org. Chem.* **2003**, 385–394.
- 2003IC2157 S. M. P. R. M. Cunha, M. F. C. Guedes da Silva, A. J. L. Pombeiro, *Inorg. Chem.* **2003**, 42, 2157–2164.
- 2003H161 N. Maezaki, A. Furusawa, S. Uchida, T. Tanaka, *Heterocycles* **2003**, 59, 161–167.
- 2003OM1275 J. B. King, F. P. Gabbai, *Organometallics* **2003**, 22, 1275–1280.
- 2003OM1540 J. Perez, V. Riera, A. Rodriguez, R. Lopez, T. L. Sordo, *Organometallics* **2003**, 22, 1540–1545.
- 2003PS279 T. M. Abdel-Rahman, A. A. Shalaby, I. F. Nassar, *Phosphorus, Sulfur* **2003**, 178, 279–292.

Biographical sketch

Peter Rutledge was born in Auckland, New Zealand in 1973. He completed his schooling in Auckland and his B.Sc. and M.Sc. degrees at the University of Auckland. In 1995 he moved to the Northern Hemisphere to commence his doctoral studies with Professor Sir Jack Baldwin in the Dyson Perrins Laboratory and Magdalen College, Oxford. Upon completing his D.Phil. in 1999, he remained at the Dyson Perrins as a Departmental Research Assistant in the Baldwin Group, continuing research on the application of pseudo-time-resolved protein crystallography to study the mechanisms of penicillin and cephalosporin biosynthesis. While a postdoc in Oxford he also held teaching posts as a College Lecturer at his old college Magdalen (2000–2001) and at Somerville College (2001–2002). In February 2003, Peter moved to his current position as a lecturer in Chemical Biology at University College Dublin, in the newly established Centre for Synthesis and Chemical Biology and the Department of Chemistry. His research centres on the application of proteins to solve chemical and environmental problems, the study of enzyme mechanism—particularly in the crystalline state—and the development of small-molecule enzyme mimics with applications in bioremediation and synthesis.

5.31

Triple-bonded Heteroatom Derivatives Other Than Nitriles with Another Heteroatom Attached to the *sp*-Carbon Atom

U. BERGSTRÄßER

Technical University of Kaiserslautern, Kaiserslautern, Germany

5.31.1	TRIPLY BONDED PHOSPHORUS ATTACHED TO THE <i>sp</i> -CARBON ATOM	1081
5.31.1.1	Elimination Reactions	1083
5.31.1.1.1	Elimination of hydrogen halides	1083
5.31.1.1.2	Elimination of chlorotrimethyl silane	1085
5.31.1.1.3	Elimination of hexamethyldisiloxane	1085
5.31.1.2	Rearrangement Reactions	1086
5.31.1.2.1	Amino-substituted phosphalkynes	1086
5.31.1.2.2	Lewis base-induced rearrangements of 1-alkynylphosphines	1087
5.31.1.2.3	Isomerization under flash vacuum pyrolysis conditions	1087
5.31.1.2.4	Rearrangements of phosphalkenes	1088
5.31.1.3	From Other Phosphalkynes	1089
5.31.1.4	From Phosphinodiazalkanes	1089
5.31.2	TRIPLY BONDED ARSENIC ATTACHED TO THE <i>sp</i> -CARBON ATOM	1089

5.31.1 TRIPLY BONDED PHOSPHORUS ATTACHED TO THE *sp*-CARBON ATOM

A detailed comprehensive review on the synthesis of phosphalkynes can be found in COFGT (1995) and covers the literature up to 1995 <1995COFGT(5)1151>. Since then, no new synthetic methods are described in the literature. The present review will summarize the essential protocols and supplement them with some minor new developments in the synthesis of phosphalkynes.

Phosphalkynes represent an example of low-coordinated phosphorus compounds since they contain a monocoordinated (σ^1), trivalent (λ^3) phosphorus atom. Depending on the substituent R, these compounds can be classified into two groups: nonstabilized, short-lived phosphalkynes (Table 1) with relatively small substituents [R = H, Me, Et, Buⁿ, CH₂=CH—, F, Cl (**1–3**)] and kinetically stabilized phosphalkynes (Table 2) with sterically hindering substituents [R = Bu^t, TMS, 2,4,6-trimethylphenyl, 2,4,6-tri-*t*-butylphenyl (**4a**, **4b** and **5a**, **5b**)].

The parent compound of phosphalkynes (the name methylidynephosphines is also used for these structures) H—C≡P **1** was first proposed by Albers <1950AG451> and first generated by Gier by passing a stream of phosphine gas through a rotating arc struck between graphite electrodes <1961JA1769>. Twenty years later, the first kinetically stabilized phosphalkyne Bu^t—C≡P **4a**

Table 1 Examples of short-lived phosphalkynes, etc.

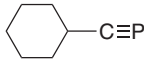
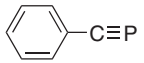
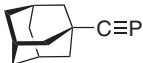
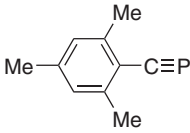
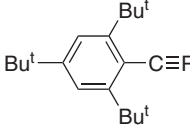
<i>Phosphaalkyne</i>	<i>References</i>
H—C≡P 1	<B-1996MI004, 2001JOC7864, 1995COFGT(5)1151>
Me—C≡P 2a	<2001JOC7864, 1995COFGT(5)1151>
Et—C≡P 2b	<2001JOC7864, 1995COFGT(5)1151>
Bu ⁿ —C≡P 2c	<2001JOC7864, 1995COFGT(5)1151>
Ph—CH ₂ —CH ₂ —C≡P 2d	<2001JOC7864>
H ₂ C=CH—CH ₂ —C≡P 2e	<2001JOC7864>
H ₂ C=CH—(CH ₂) ₂ —C≡P 2f	<2001JOC7864>
H ₂ C=CH—C≡P 2g	<1995COFGT(5)1151>
 —C≡P 2h	<2001JOC7864, 1995COFGT(5)1151>
 —C≡P 2i	<1995COFGT(5)1151>
F—C≡P 3a	<1995COFGT(5)1151>
Cl—C≡P 3b	<2001JOC7864, 1995COFGT(5)1151>

Table 2 Selected examples of kinetically stabilized phosphalkynes^a

<i>Phosphaalkyne</i>	<i>References</i>
Bu ^t —C≡P 4a	<B-1996MI003, B-1995MI002, 1995COFGT(5)1151>
TMS—C≡P 4b	<1996OM4904, 1995COFGT(5)1151>
 —C≡P 4c	<B-1996MI003, 1995COFGT(5)1151>
 —C≡P 5a	<1998S1305, 1995COFGT(5)1151>
 —C≡P 5b	<1995COFGT(5)1151>

^a More derivatives R—C≡P with R = 1-methylcyclohex-1-yl, 1-methylcyclopent-1-yl, 2-methylbut-2-yl, and 2,3,3-trimethylbut-2-yl are described in COFGT (1995).

was prepared by Becker <1981ZN(B)16>. The original protocol was optimized and generalized by Regitz <B-1996MI003, 1987CB1645, 1986JOM(306)39>. Compound **4a**, for example, was formed in yields exceeding 93%, so that is employed most frequently for reactivity studies on this class of compounds. The important role of phosphalkynes as building blocks in heterocyclic chemistry has been amply demonstrated. The exceptional cycloaddition <1988AG(E)1484, 1994JHC663, B-1990MI001, B-1998MI006, 1999PJC135, B-1995MI002, 2002JOM(643-644)409> and cyclooligomerization <B-1999MI007, B-1995MI002, 1997CB823, 1998EJI1597> potential is well documented in the literature. The transition metal-assisted syntheses of rings and cage compounds from phosphalkynes, open a new field in low-coordinated phosphorus chemistry <1997AOC1, 1999AG(E)3183, 2000EJI1869, B-2001MI008, 1998AG(E)1233, 2003TCC215, 2003ZN(B)44>.

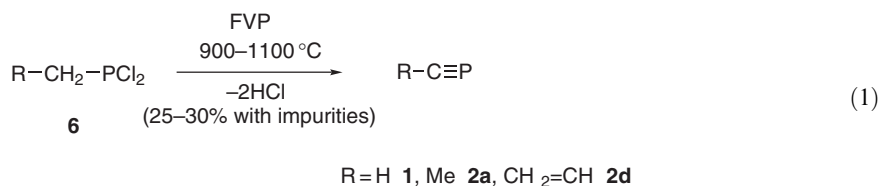
Phosphalkynes are generally characterized by ^{13}C - and ^{31}P -NMR spectroscopy ($\delta_{\text{C}} = 154$ to 201 ppm; $\delta_{\text{P}} = +96$ to -205 ppm) <1990CRV191, 1999IC157>. The P/C bond length was estimated by a high-precision, low-temperature X-ray diffraction study on $\text{Bu}^t\text{-C}\equiv\text{P}$ as $1.548(1)$ Å <1991HAC665, 1995CC505> and on $\text{Ar-C}\equiv\text{P}$ (Ar = 2,4,6-tri-*t*-butylphenyl) as $1.516(13)$ Å <1988CC171>.

5.31.1.1 Elimination Reactions

5.31.1.1.1 Elimination of hydrogen halides

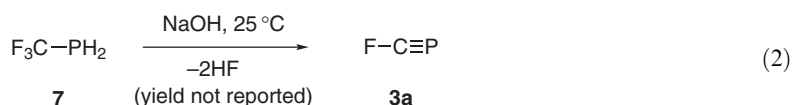
(i) Intramolecular

(a) *Flash vacuum pyrolysis (FVP) conditions.* The FVP method enables the preparation of phosphalkynes (**1**, and **2a** and **2d**) starting from dichlorophosphines **6** (Equation (1) and Table 1).

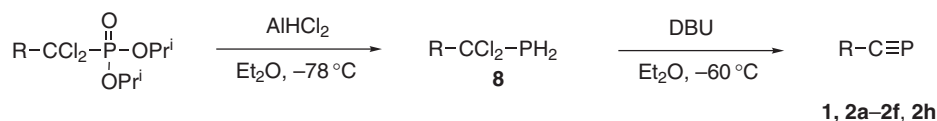


The reaction must be performed in the presence of a basic absorption agent (e.g., potassium hydroxide, 1,3,5-tricyclohexylhexahydro-*s*-triazine, or potassium hydroxide/potassium carbonate) in order to prevent the addition of hydrogen chloride to the phosphalkynes <1995COFGT(5)1151, 1994ZAAC418>.

(b) *At room temperature and low temperatures.* The first example described was the synthesis of fluorophosphaethyne **3a** from trifluoromethylphosphine **7** (Equation (2)) <1978JA446, 1979CC653>.



Denis described the preparation of various phosphalkynes (**1**, and **2a-2f** and **2h**) in ethereal solutions by HCl-elimination from α -dichlorophosphines **8** at low temperature (-60°C) and in the presence of an excess of the strong base diazabicyclo[5.4.0]undec-5-ene (DBU) (Scheme 1) <2001JOC7864>. The phosphalkynes prepared by this method are listed in Table 3.



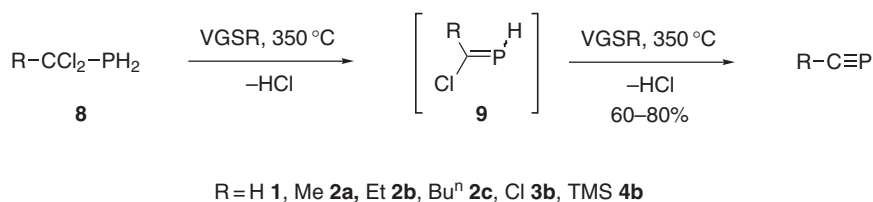
Scheme 1

Table 3 Ethereal solutions of phosphalkynes $R-C\equiv P$ synthesized by low temperature HCl-elimination with DBU

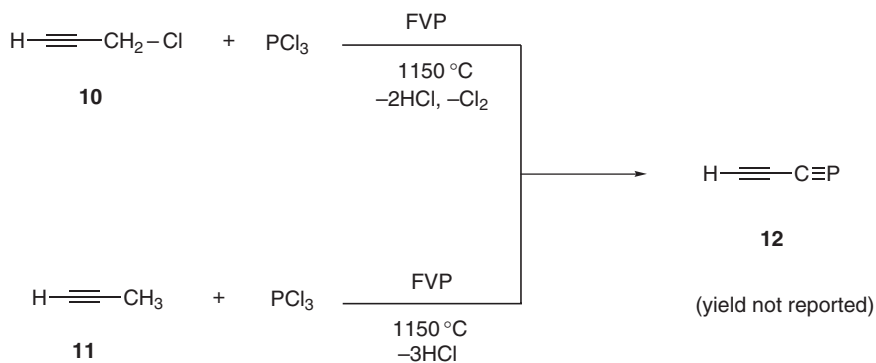
Phosphalkyne	<i>R</i>	δ (^{31}P)	Yield ^a (%)
1	H	−32	20
2a	Me	−61	75
2b	Et	−62	77
2c	Bu ⁿ	−59	81
2d	Ph-CH ₂ -CH ₂	−56.8	60 ^b
2e	H ₂ C=CH-CH ₂	−52	75
2f	H ₂ C=CH-(CH ₂) ₂	−57	72
2h	C ₆ H ₁₁	−62	73 ^b

^a Determined by ^1H or/and ^{31}P -NMR spectroscopy with internal reference.^b Crude product.

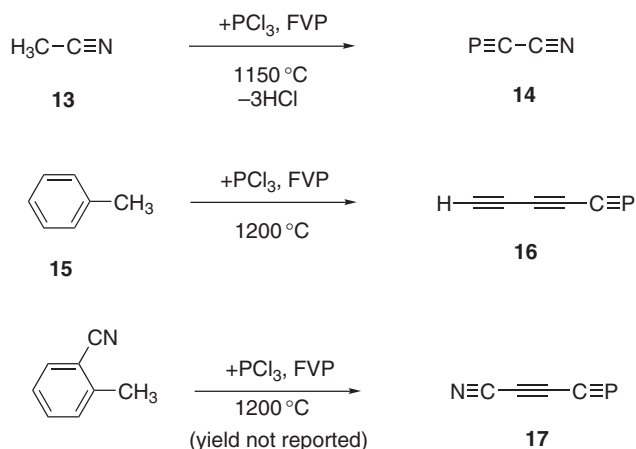
(c) *Vacuum gas–solid reactions (VGSR)*. The preparation of various phosphalkynes by bis-dehydrohalogenation of volatile α -dichlorophosphines **8** on potassium carbonate at 350 °C was first described by Denis in 1991 using the VGSR technique (Scheme 2) <1991AG(E)196, B-1997MI005, 2002CEJ4919>.

**Scheme 2**(ii) *Intermolecular*

The co-pyrolysis of PCl_3 and propargyl chloride **10** or propyne **11** under FVP conditions has been utilized for the synthesis of phosphabutadiyne **12** (Scheme 3) <1981JSP(90)512, 2000CPL(319)411>.

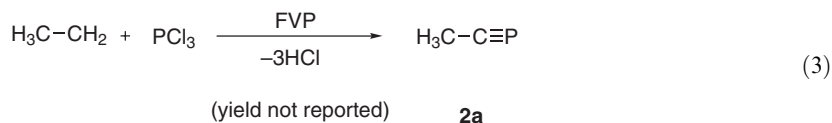
**Scheme 3**

This procedure was also successful for the preparation of NC_2P **14** starting from acetonitrile **13** (Scheme 4) <2000JCP(113)1465>. During pyrolysis experiments with toluene **15** and PCl_3 , Bizzocchi and co-workers observed that together with the expected $\text{Ph}-\text{C}\equiv\text{P}$ <1982JSP(92)158> considerable amounts of HC_3P **12** were also found <2000CPL(319)411>. A detailed study of this reaction allowed the preparation of phosphahexatriyne **16** <2003JCP(119)170>. A more efficient method for the synthesis of **16** was found based on co-pyrolysis of cyclopentene and PCl_3 <2003MI001>. The unstable NC_4P **17** was detected in the pyrolysis products of phosphorus trichloride and 2-cyanotoluene <2003JSP(221)186>.



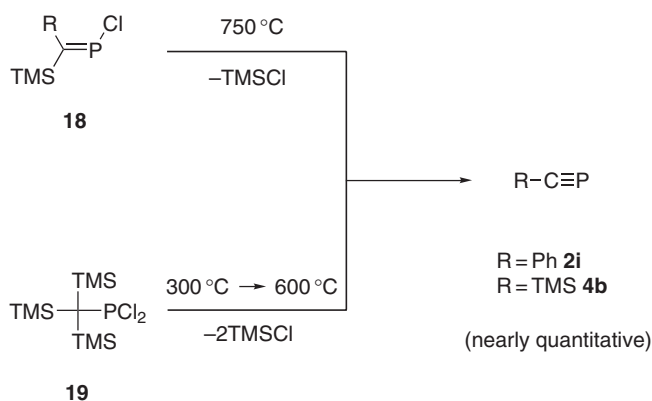
Scheme 4

Under similar conditions starting from ethane, the synthesis of phosphaaalkyne **2a** was possible (Equation (3)) <2003JSP(218)53>.



5.31.1.1.2 Elimination of chlorotrimethyl silane

The preparation of phenylphosphaethyne **2i** and trimethylsilylphosphaethyne **4b** by elimination of chlorotrimethylsilane from *p*-chloro(trimethylsilyl)phosphaethene **18** and tris(trimethylsilyl)methyldichlorophosphine **19** (Scheme 5) was described in <1995COFGT(5)1151> and no further examples have been reported.



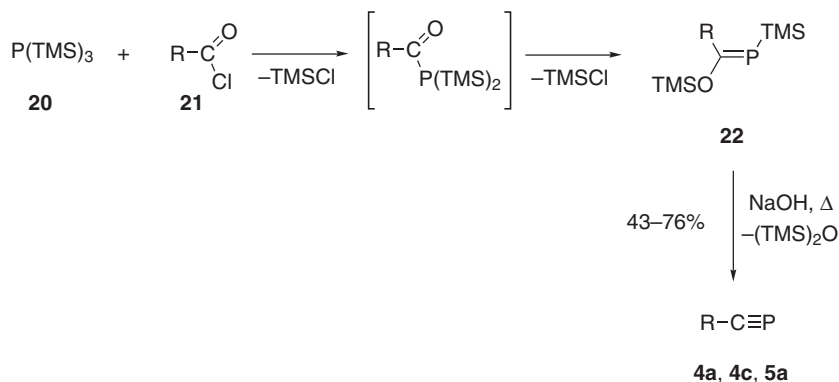
Scheme 5

5.31.1.1.3 Elimination of hexamethyldisiloxane

(i) In the presence of sodium hydroxide

At present, this is the most frequently employed method for the synthesis of kinetically stabilized phosphaaalkynes. A detailed description of this procedure was found in <1995COFGT(5)1151>. Starting from phosphaaalkenes **22**, which are readily accessible from

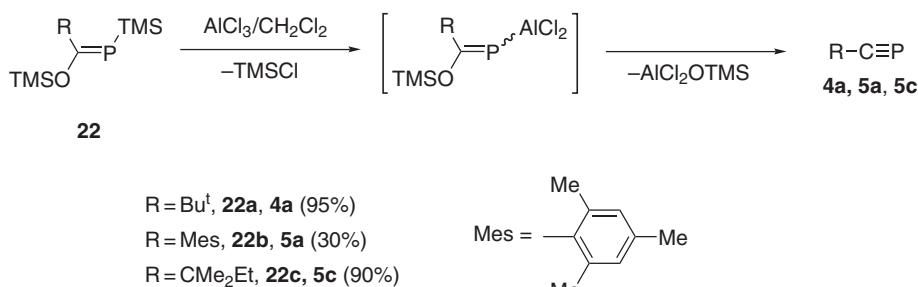
the reaction of tris(trimethylsilyl)phosphine **20** with acyl chlorides **21**, a sodium hydroxide-catalyzed β -elimination of hexamethyldisiloxane at 160–180 °C yields the phosphalkynes (**4a** and **4c**, and **5a**) (Scheme 6) <B-1996MI003>.



Scheme 6

(ii) In the presence of eliminating agents other than sodium hydroxide

The elimination of hexamethyldisiloxane was also realizable by tetra(*n*-butyl)ammonium fluoride on silica gel to prepare 1-adamantylphosphaethyne **4c** <1986S31>, or diiron nonacarbonyl to form *t*-butylphosphaethyne **4a** <1987CC980>. In 1996, Regitz and co-workers described an efficient and quantitative synthesis of *t*-butylphosphaethyne **4a** from **22a** in the presence of stoichiometric amount of aluminum trichloride at low temperatures (–10 °C) <1996CB489>. Under similar conditions 2,4,6-trimethylphenylphosphaethyne **5a** was synthesized by aluminum trichloride-initiated elimination of hexamethyldisiloxane from **22b** in dichloromethane at –60 °C (Scheme 7) <1998S1305>.



Scheme 7

(iii) In the absence of an auxiliary reagent

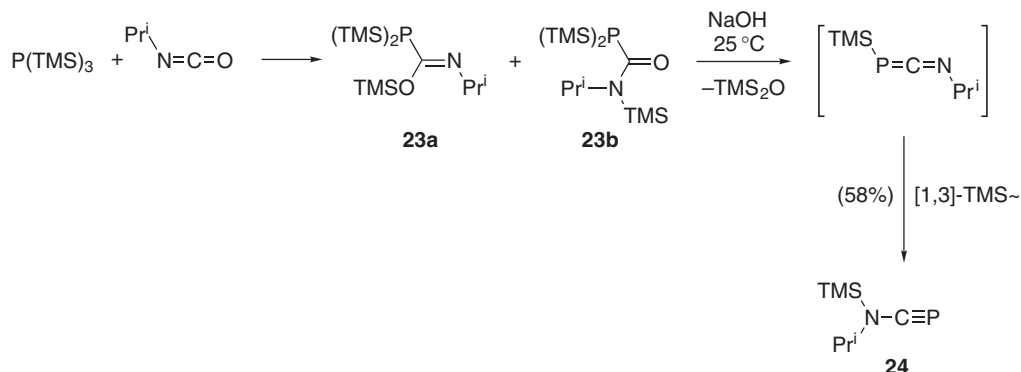
The synthesis of 1-triptycylphosphaethyne and 2,4,6-tris(*t*-butyl)phenylphosphaethyne does not require the presence of an elimination reagent <1985TL5507, 1986TL171>.

5.31.1.2 Rearrangement Reactions

5.31.1.2.1 Amino-substituted phosphalkynes

Only very few examples of isolable amino-substituted phosphalkynes are known, e.g., *N,N*-diisopropylaminophosphaethyne <1990CB2317>, 2,2,6,6-tetramethylpiperidinophosphaethyne <1993HAC365>, and *N*-trimethylsilyl-*N*-isopropylphosphaethyne **24** <1989AG(E)53>. The

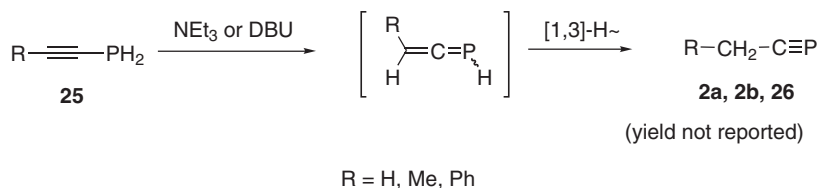
reaction of tris(trimethylsilyl)phosphine with isopropyl isocyanate in Et₂O gave a tautomeric mixture of the phosphines **23a** and **23b**, which when treated with NaOH in tetraglyme gave the target aminophosphaethyne **24** (Scheme 8).



Scheme 8

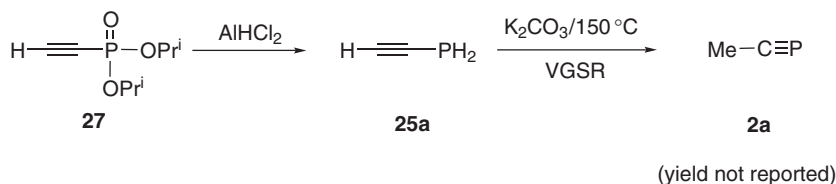
5.31.1.2.2 Lewis base-induced rearrangements of 1-alkynylphosphines

Low-temperature treatment of 1-alkynylphosphines **25** with a catalytic amount of a Lewis base (NEt₃ or DBU) results in the formation of the phosphalkynes (**2a** and **2b**, and **26**) (Scheme 9) <1992CC415>.



Scheme 9

The phosphapropyne **2a** was also prepared by a similar reaction under VGSR conditions. The reduction of ethynylphosphonic acid diisopropylester **27** followed by the base-induced rearrangement of the ethynylphosphine **25a** with potassium carbonate results in generation of **2a** (Scheme 10) <1994NJC629, 2002CEJ4919>.

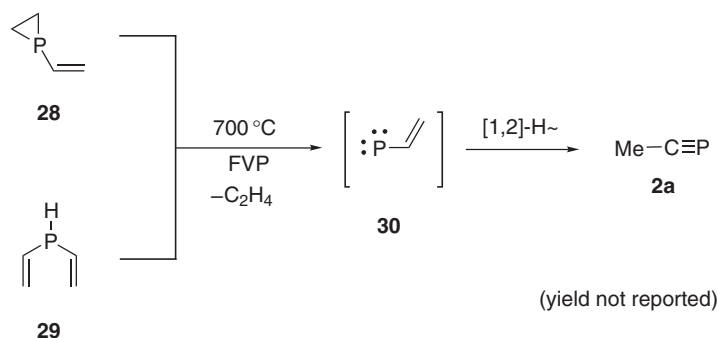


Scheme 10

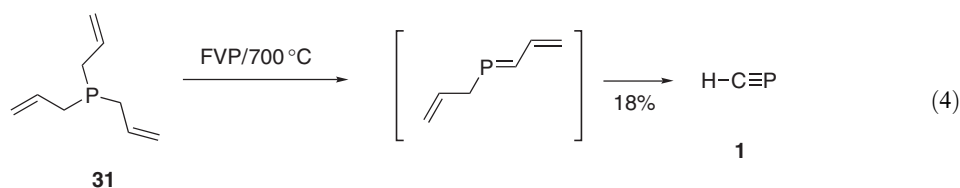
5.31.1.2.3 Isomerization under flash vacuum pyrolysis conditions

Phosphapropyne **2a** can be prepared from 1-vinylphosphirane **28** as well as from divinylphosphine **29** under FVP conditions. Compound **2a** is formed by a rearrangement of a vinylphosphinidene intermediate **30** (Scheme 11) <1992CC1799, 1996OM4904>.

Phosphaethyne **1** can also be synthesized by means of the same methodology starting from triallylphosphine **31** (Equation (4)) <B-1996MI004>.



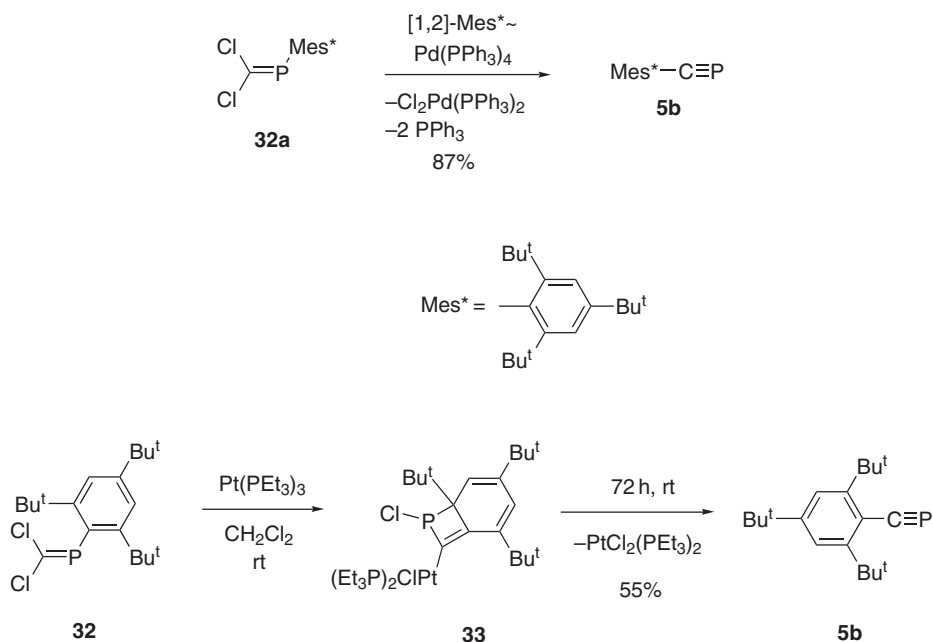
Scheme 11



5.31.1.2.4 Rearrangements of phosphalkenes

(i) Transition metal-catalyzed rearrangements

The reaction of the readily available 2,2-dichloro-1-phosphalkene **32a** with a Pd(0)-complex affords the (2,4,6-tri-*t*-butylphenyl)phosphaethyne **5b** in almost quantitative yield [\[1992TL2981\]](#) and was described in detail in [\[1995COFGT\(5\)1151\]](#). (2,4,6-Tri-*t*-butyl-3,5-dideuterophenyl)phosphaethyne and (2,4,6-tri-*t*-butyl-*d*₉-phenyl)phosphaethyne were prepared according to this procedure (Equation (5)) [\[2003JPC\(A\)9652\]](#). Also Bickelhaupt and co-workers [\[1997JOM\(529\)107\]](#) observed a Pd(0)-induced rearrangement of Br₂C=P—Mes*. Additionally a platinum(0)-promoted conversion of Cl₂C=P—Mes* and Br₂C=P—Mes* was studied by Angelici and co-workers (Scheme 12) [\[1993OM4265, 1994OM2444\]](#). The isolation and X-ray structure of intermediate **33** gave insight into the mechanism of formation of the phosphacetylene **5b**.

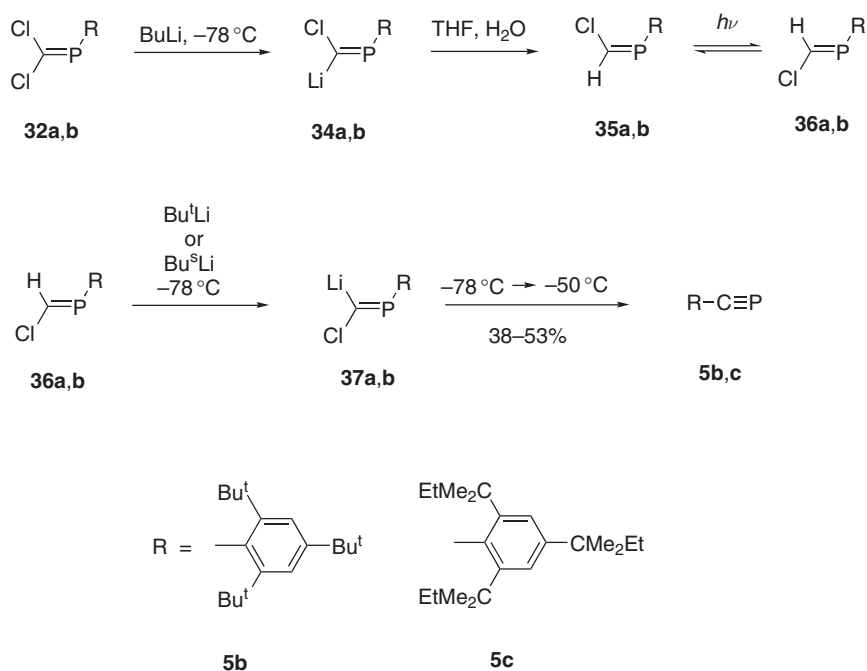


Scheme 12

(ii) *Alkylolithium-initiated rearrangements*

The halogen–metal exchange between *n*-butyllithium and 2,2-dichloro-1-(2,4,6-tri-*t*-butylphenyl)-1-phosphaethene **32a** or 2,2-dichloro-1-(2,4,6-tri-*t*-pentylphenyl)-1-phosphaethene **32b** gives selectively the phosphanylidene carbenoids (*Z*)-**34**. When the irradiation of the lithio-compound was carried out in wet tetrahydrofuran (THF), an equilibrium was established between (**35a** and **35b**) and (**36a** and **36b**). The isolable compounds (**36a** and **36b**) were then allowed to react with *s*- or *t*-butyllithium at -78°C , and on warming the reaction mixture to -48°C the formation of (**5b** and **5c**) via a [1,2]-rearrangement (Fritsch–Buttenberg–Wiechell rearrangement) of (*E*)-(**37a** and **37b**) was completed in 10 min at that temperature (Scheme 13) <1992CL1053, 1988CL1733>.

Bickelhaupt and co-workers described the formation of phosphalkyne **5b** by the reaction of 2,2-iodo-1-(2,4,6-tri-*t*-butylphenyl)-1-phosphaethene **38** with *n*-butyllithium and TMSCl (Equation (6)) <1991CB2677>.



Scheme 13

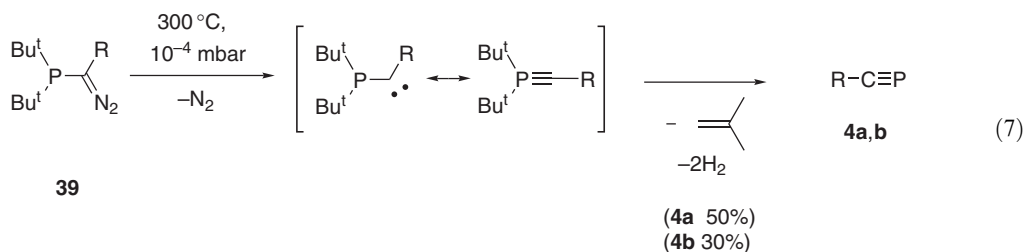


5.31.1.3 From Other Phosphalkynes

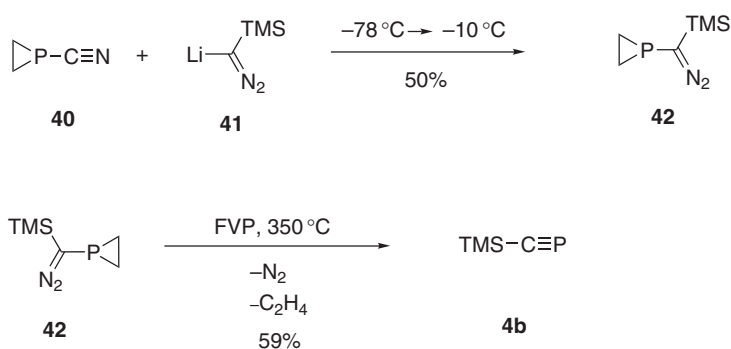
No further advances have occurred in this area since the publication of chapter 5.31.1.3 in <1995COFGT(5)1151>.

5.31.1.4 From Phosphinodiazalkanes

The loss of nitrogen, 2-methylpropene, and hydrogen from the phosphinodiazalkanes **39** under FVP gives rise to phosphalkynes (**4a** and **4b**) (Equation (7)) <1988AG(E)1484, 1990CRV191>.



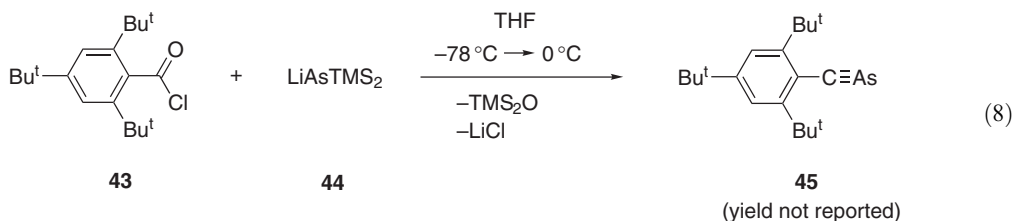
The 1-[diazo(trimethylsilyl)methyl]phosphirane **42** was synthesized by reaction of α -lithiodiazo(trimethylsilyl)methane **41** and 1-cyanophosphirane **40**. FVP at 350°C of **42** led to the formation of (trimethylsilyl)phosphaethyne **4b** with loss of ethylene and nitrogen (Scheme 14) <1996OM4904>.



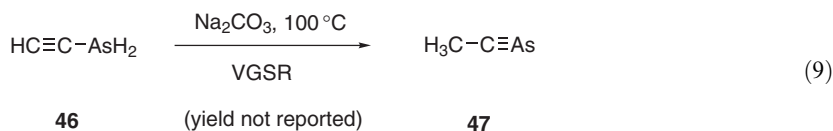
Scheme 14

5.31.2 TRIPLY BONDED ARSENIC ATTACHED TO THE *sp*-CARBON ATOM

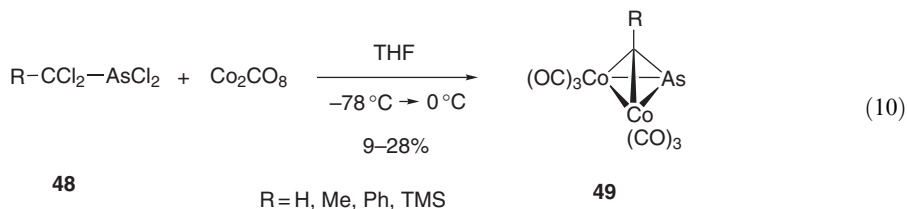
The first kinetically stabilized arsaalkyne, 2,4,6-tris(*t*-butyl)phenylarsaethyne **45**, was prepared by elimination of hexamethyldisiloxane from a mixture of 2,4,5-tris(*t*-butyl)benzoyl chloride **43** and lithium bis(trimethylsilyl)arsine **44** at room temperature (Equation (8)) <1986AG(E)264>. Reactions of **45** with transition metal complexes have been described <1996CC631, 1994CC2061>.



Arsapropyne **47** has been prepared by VGSR reaction by base-induced rearrangement of 1-ethynylarsine **46** with sodium carbonate (Equation (9)) <1994JA8930, 1995JST175, 1995OM4732, 1995IC5694, 2002CEJ4919>.



Arsaalkynedicobalt hexacarbonyls **49** were prepared by the reaction of *in situ* generated (dichloroalkyl)arsenic dichlorides **48** with $\text{Co}_2(\text{CO})_6$ at low temperatures (Equation (10)) <1978JA6783, 1982OM859>.



REFERENCES

- 1950AG451 H. Albers, *Angew. Chem.* **1950**, 61, 451.
 1961JA1769 T. E. Gier, *J. Am. Chem. Soc.* **1961**, 83, 1769–1770.
 1978JA446 H. W. Kroto, J. F. Nixon, N. P. Simmons, N. P. C. Westwood, *J. Am. Chem. Soc.* **1978**, 100, 446–448.
 1978JA6783 D. Seyferth, J. S. Merola, *J. Am. Chem. Soc.* **1978**, 100, 6783–6784.
 1979CC653 H. Eshtiagh-Hosseini, H. W. Kroto, J. F. Nixon, *J. Chem. Soc., Chem. Commun.* **1979**, 653–654.
 1981JSP(90)512 H. W. Kroto, J. F. Nixon, K. Ohno, *J. Mol. Spectrosc.* **1981**, 90, 512–516.
 1981ZN(B)16 G. Becker, G. Gresser, W. Uhl, *Z. Naturforsch., Teil B* **1981**, 36, 16–19.
 1982JSP(92)158 J. C. T. R. Burckett-St. Laurent, H. W. Kroto, J. F. Nixon, K. Ohno, *J. Mol. Spectrosc.* **1982**, 92, 158–161.
 1982OM859 D. Seyferth, J. S. Merola, R. S. Henderson, *Organometallics* **1982**, 1, 859–866.
 1985TL5507 G. Märkl, H. Sejpka, *Tetrahedron Lett.* **1985**, 26, 5507–5510.
 1986AG(E)264 G. Märkl, H. Sejpka, *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 264.
 1986JOM(306)39 W. Rösch, U. Vogelbacher, T. Allspach, M. Regitz, *J. Organomet. Chem.* **1986**, 306, 39–53.
 1986S31 T. Allspach, M. Regitz, G. Becker, W. Becker, *Synthesis* **1986**, 31–36.
 1986TL171 G. Märkl, H. Sejpka, *Tetrahedron Lett.* **1986**, 27, 171–174.
 1987CB1645 W. Rösch, U. Hees, M. Regitz, *Chem. Ber.* **1987**, 120, 1645–1652.
 1987CC980 A. R. Barron, A. H. Cowley, S. W. Hall, *J. Chem. Soc., Chem. Commun.* **1987**, 980–981.
 1988AG(E)1484 M. Regitz, P. Binger, *Angew. Chem., Int. Ed. Engl.* **1988**, 27, 1484–1508.
 1988CC171 A. M. Arif, A. R. Barron, A. H. Cowley, S. W. Hall, *J. Chem. Soc., Chem. Commun.* **1988**, 171–172.
 1988CL1733 M. Yoshifuji, T. Niitsu, N. Inamoto, *Chem. Lett.* **1988**, 1733–1734.
 1989AG(E)53 R. Appel, M. Poppe, *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 53–54.
 1990CRV191 M. Regitz, *Chem. Rev.* **1990**, 90, 191–213.
 B-1990MI001 M. Regitz, *Phosphaalkynes—New building blocks in Heteroatom Chemistry*, E. Block, Ed., Wiley-VCH, New York, **1990**, pp. 225–322.
 1990CB2317 J. Grobe, D. Le Van, B. Lüth, M. Hegemann, *Chem. Ber.* **1990**, 123, 2317–2321.
 1991AG(E)196 J.-C. Guillemin, T. Janati, P. Guenot, P. Savignac, J.-M. Denis, *Angew. Chem., Int. Ed. Engl.* **1991**, 30, 196–198.
 1991HAC665 A. N. Chernega, M. Y. Antipin, Y. T. Struchkov, M. F. Meidine, J. F. Nixon, *Heteroatom Chem.* **1991**, 665–667.
 1991CB2677 S. J. Goede, F. Bickelhaupt, *Chem. Ber.* **1991**, 124, 2677–2684.
 1992CC415 J. C. Guillemin, T. Janati, J. M. Denis, *J. Chem. Soc., Chem. Commun.* **1992**, 415–416.
 1992CC1799 S. Haber, P. LeFloch, F. Mathey, *J. Chem. Soc., Chem. Commun.* **1992**, 1799–1800.
 1992CL1053 M. Yoshifuji, H. Kawanami, Y. Kawai, K. Toyota, M. Yasunami, T. Niitsu, N. Inamoto, *Chem. Lett.* **1992**, 1053–1056.
 1992TL2981 V. D. Romancko, M. Sanchez, T. V. Sarina, M.-R. Mazières, R. Wolf, *Tetrahedron Lett.* **1992**, 33, 2981–2982.
 1993HAC365 A. N. Chernega, G. N. Koidan, A. P. Marchenko, A. A. Korkin, *Heteroatom Chem.* **1993**, 4, 365–368.
 1993OM4265 H. Jun, R. J. Angelici, *Organometallics* **1993**, 12, 4265–4266.
 1994CC2061 P. B. Hitchcock, C. Jones, J. F. Nixon, *J. Chem. Soc., Chem. Commun.* **1994**, 2061–2062.
 1994JA8930 J.-C. Guillemin, L. Lassalle, P. G. Drean, P. Wlodarczak, J. Demaison, *J. Am. Chem. Soc.* **1994**, 116, 8930–8936.
 1994JHC663 M. Regitz, *J. Heterocycl. Chem.* **1994**, 31, 663–677.
 1994NJC629 W. Dong, S. Lacombe, D. Gonbeau, G. Pfister-Guillouzo, *Nouv. J. Chem.* **1994**, 18, 629–641.
 1994OM2444 H. Jun, V. G. Young Jr., R. J. Angelici, *Organometallics* **1994**, 13, 2444–2453.
 1994ZAAC418 H. Bock, M. Bankmann, *Z. Anorg. Allg. Chem.* **1994**, 620, 418–430.
 1995JST175 P. Drean, G. Wlodarczak, J. Demaison, J.-C. Guillemin, L. Lassalle, *J. Mol. Struct.* **1995**, 349, 175–178.
 1995OM4732 V. Metail, A. Senio, L. Lassalle, J.-C. Guillemin, G. Pfister-Guillouzo, *Organometallics* **1995**, 14, 4732–4735.
 1995IC5694 L. Lassalle, S. Legoupy, J.-C. Guillemin, *Inorg. Chem.* **1995**, 34, 5694–5697.
 1995CC505 M. Y. Antipin, A. N. Chernega, K. A. Lysenko, T. Y. Struchkov, J. F. Nixon, *J. Chem. Soc., Chem. Commun.* **1995**, 505–506.
 1995COFGT(5)1151 W.-G. Veeck, M. Regitz, Triple-bonded heteroatom derivatives other than nitriles with another heteroatom attached to the sp-carbon atom, in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Eds., Elsevier, Oxford, **1995**, Vol. 5 pp. 1151–1160.

- B-1995MI002 M. Regitz, A. Hoffmann, U. Bergsträßer, *Phosphaalkynes—starting point for the synthesis of phosphorous-carbon cage compounds*, in *Modern Acetylene Chemistry*, P. J. Stang, F. Diederich, Eds., VCH Weinheim, **1995**, pp. 173–201.
- 1996CB489 B. Breit, M. Regitz, *Chem. Ber.* **1996**, *129*, 489–494.
- 1996OM4909 D. J. Berger, P. P. Gaspar, P. LeFloch, F. Mathey, R. S. Grev, *Organometallics* **1996**, *15*, 4909–4915.
- 1996CC631 M. D. Francis, D. E. Hibbs, M. B. Hursthouse, C. Jones, K. M. Abdul Malik, *J. Chem. Soc., Chem. Commun.* **1996**, 631–632.
- B-1996MI003 W. Rösch, T. Allspach, U. Bergsträßer, M. Regitz, (2,2-Dimethylpropylidyne)phosphane (tert-butylphosphaacetylene), (adamant-1-ylmethylidyne)phosphane (1-adamantylphosphaacetylene) in *Synthetic Methods of Organometallic and Inorganic Chemistry*, W. A. Herrmann, Ed., Thieme, Stuttgart, **1996**, pp. 11–16.
- B-1996MI004 P. LeFloch, F. Mathey, *Methylidynephosphane (phosphaethyne) in synthetic Methods of Organometallic and Inorganic Chemistry*, W. A. Herrmann, Ed., Thieme, Stuttgart, **1996**, pp. 8–10.
- 1997AOC1 L. Weber, *Adv. Organomet. Chem.* **1997**, *41*, 1–67.
- 1997CB823 A. Mack, M. Regitz, *Chem. Ber.* **1997**, *130*, 823–834.
- 1997JOM(529)107 M. van der Sluis, A. Klootwijk, J. B. M. Wit, F. Bickelhaupt, N. Veldman, A. L. Spek, P. W. Jolly, *J. Organomet. Chem.* **1997**, *529*, 107–119.
- B-1997MI005 J.-M. Denis, A.-C. Gaumont, *Gas-Phase Reactions in Organic Synthesis*, Gordon & Breach Science Publishers, UK, **1997**, pp. 195–235.
- 1998AG(E)1233 F. Tabellion, A. Nachbauer, S. Leininger, C. Peters, F. Preuss, M. Regitz, *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1233–1235.
- 1998EJI1597 A. Hoffmann, A. Mack, R. Goddard, P. Binger, M. Regitz, *Eur. J. Inorg. Chem.* **1998**, *11*, 1597–1603.
- B-1998MI006 K. B. Dillon, F. Mathey, J. F. Nixon, in *Phosphorus: The Carbon Copy*, Wiley, New York, **1998**, pp. 40–88.
- 1998S1305 A. Mack, E. Pierron, T. Allspach, U. Bergsträßer, M. Regitz, *Synthesis* **1998**, 1305–1313.
- 1999AG(E)3183 P. Kramkowski, M. Scheer, *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3183–3186.
- 1999IC157 K. Hübner, P. Schwerdtfeger, *Inorg. Chem.* **1999**, *38*, 157–164.
- 1999PJC135 M. Regitz, U. Bergsträßer, *Pol. J. Chem.* **1999**, *73*, 135–150.
- B-1999MI007 A. Mack, M. Regitz, in *Advances in Strained and Interesting Organic Molecules*, JAI Press, Greenwich, **1999**, pp. 199–221.
- 2000CPL(319)411 L. Bizzocchi, C. Degli Esposti, P. Botschwina, *Chem. Phys. Lett.* **2000**, *319*, 411–417.
- 2000EJI1869 P. Kramkowski, M. Scheer, *Eur. J. Inorg. Chem.* **2000**, *8*, 1869–1876.
- 2000JCP(113)1465 L. Bizzocchi, C. Degli Esposti, P. Botschwina, *J. Chem. Phys.* **2000**, *113*, 1465–1472.
- 2001JOC7864 J.-C. Guillemin, T. Janati, J.-M. Denis, *J. Org. Chem.* **2001**, *66*, 7864–7868.
- B-2001MI008 F. Mathey, Ed., *Phosphorus-Carbon Heterocyclic Chemistry*, Pergamon, Oxford, **2001**, chap. 5.3.10.
- 2002CEJ4919 O. Mó, M. Yáñez, J.-C. Guillemin, El H. Riague, J.-F. Gal, P.-C. Maria, C. D. Poliart, *Chem.-Eur. J.* **2002**, *8*, 4919–4929.
- 2002JOM(643-644)409 A. Mack, S. Danner, U. Bergsträßer, H. Heydt, M. Regitz, *J. Organomet. Chem.* **2002**, *643–644*, 409–415.
- 2003JCP(119)170 L. Bizzocchi, C. Degli Esposti, P. Botschwina, *J. Chem. Phys.* **2003**, *119*, 170–175.
- 2003JSP(218)53 L. Bizzocchi, L. Cludi, C. Degli Esposti, *J. Mol. Spectrosc.* **2003**, *218*, 53–57.
- 2003JSP(221)186 L. Bizzocchi, C. Degli Esposti, *J. Mol. Spectrosc.* **2003**, *221*, 186–191.
- 2003MI001 L. Bizzocchi, C. Degli Esposti, P. Botschwina, *Phys. Chem. Chem. Phys.* **2003**, *5*, 4090–4095.
- 2003TCC215 H. Heydt, *Top. Curr. Chem.* **2003**, *223*, 215–249.
- 2003ZN(B)44 C. Peters, U. Fischbeck, F. Tabellion, M. Regitz, F. Preuss, *Z. Naturforsch., Teil B* **2003**, *58*, 44–51.
- 2003JPC(A)9652 D. Gimes, Y. Berchadsky, J.-P. Finet, D. Siri, P. Tordo, *J. Phys. Chem. A* **2003**, *107*, 9652–9657.

Biographical sketch

Uwe Bergsträßer was born in 1965 at St. Ingbert (Germany), studied at the University of Kaiserslautern, where he obtained a Diploma in Chemistry in 1989 and a Dr. Rer. Nat. in 1992 under the direction of Professor M. Regitz. He took his permanent position as scientific co-worker in the Department of Organic Chemistry at the Technical University of Kaiserslautern in March 1993 and his scientific interests include all aspects of phosphorus heterocyclic chemistry. He is responsible for X-ray crystallography and since 2003 he has been working in the group of Professor Jens Hartung on all aspects of oxygen heterocyclic chemistry in particular, oxygen-centered radicals and vanadium-catalyzed oxidation reactions.