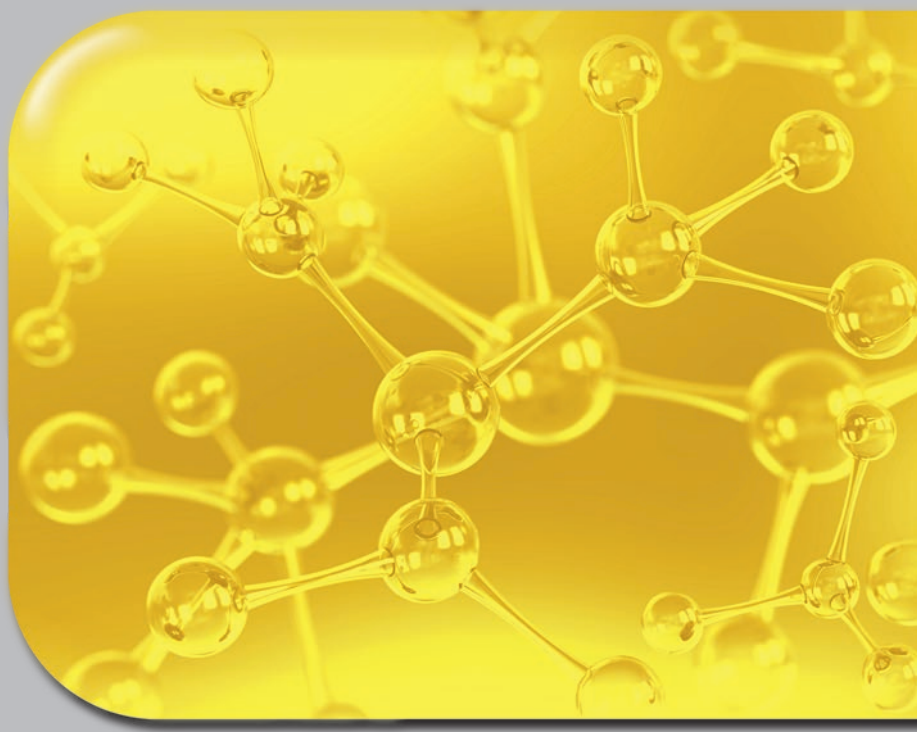
Science of Synthesis

Knowledge Updates 2026/1

Volume Editors
J.-M. Campagne
J. J. Li
M. Oestreich
S. Z. Zard



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Science of Synthesis

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Science of Synthesis presents the important synthetic methods for all classes of compounds and includes:

- Methods critically evaluated by leading scientists
- Background information and detailed experimental procedures
- Schemes and tables which illustrate the reaction scope

Science of Synthesis

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Volume Editors

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J. J. Li (Vols. 16 and 17)
M. Oestreich (Vol. 4)
S. Z. Zard (Vol. 41)

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2026
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Preface

As the pace and breadth of research intensifies, organic synthesis is playing an increasingly central role in the discovery process within all imaginable areas of science: from pharmaceuticals, agrochemicals, and materials science to areas of biology and physics, the most impactful investigations are becoming more and more molecular. As an enabling science, synthetic organic chemistry is uniquely poised to provide access to compounds with exciting and valuable new properties. Organic molecules of extreme complexity can, given expert knowledge, be prepared with exquisite efficiency and selectivity, allowing virtually any phenomenon to be probed at levels never before imagined. With ready access to materials of remarkable structural diversity, critical studies can be conducted that reveal the intimate workings of chemical, biological, or physical processes with stunning detail.

The sheer variety of chemical structural space required for these investigations and the design elements necessary to assemble molecular targets of increasing intricacy place extraordinary demands on the individual synthetic methods used. They must be robust and provide reliably high yields on both small and large scales, have broad applicability, and exhibit high selectivity. Increasingly, synthetic approaches to organic molecules must take into account environmental sustainability. Thus, atom economy and the overall environmental impact of the transformations are taking on increased importance.

The need to provide a dependable source of information on evaluated synthetic methods in organic chemistry embracing these characteristics was first acknowledged over 100 years ago, when the highly regarded reference source **Houben–Weyl Methoden der Organischen Chemie** was first introduced. Recognizing the necessity to provide a modernized, comprehensive, and critical assessment of synthetic organic chemistry, in 2000 Thieme launched **Science of Synthesis, Houben–Weyl Methods of Molecular Transformations**. This effort, assembled by almost 1000 leading experts from both industry and academia, provides a balanced and critical analysis of the entire literature from the early 1800s until the year of publication. The accompanying online version of **Science of Synthesis** provides text, structure, substructure, and reaction searching capabilities by a powerful, yet easy-to-use, intuitive interface.

From 2010 onward, **Science of Synthesis** is being updated quarterly with high-quality content via **Science of Synthesis Knowledge Updates**. The goal of the **Science of Synthesis Knowledge Updates** is to provide a continuous review of the field of synthetic organic chemistry, with an eye toward evaluating and analyzing significant new developments in synthetic methods. A list of stringent criteria for inclusion of each synthetic transformation ensures that only the best and most reliable synthetic methods are incorporated. These efforts guarantee that **Science of Synthesis** will continue to be the most up-to-date electronic database available for the documentation of validated synthetic methods.

Also from 2010, **Science of Synthesis** includes the **Science of Synthesis Reference Library**, comprising volumes covering special topics of organic chemistry in a modular fashion, with six main classifications: (1) Classical, (2) Advances, (3) Transformations, (4) Applications, (5) Structures, and (6) Techniques. Titles will include *Stereoselective Synthesis*, *Water in Organic Synthesis*, and *Asymmetric Organocatalysis*, among others. With expert-evaluated content focusing on subjects of particular current interest, the **Science of Synthesis Reference Library** complements the **Science of Synthesis Knowledge Updates**, to make **Science of Synthesis** the complete information source for the modern synthetic chemist.

The overarching goal of the **Science of Synthesis** Editorial Board is to make the suite of **Science of Synthesis** resources the first and foremost focal point for critically evaluated information on chemical transformations for those individuals involved in the design and construction of organic molecules.

Throughout the years, the chemical community has benefited tremendously from the outstanding contribution of hundreds of highly dedicated expert authors who have devoted their energies and intellectual capital to these projects. We thank all of these individuals for the heroic efforts they have made throughout the entire publication process to make **Science of Synthesis** a reference work of the highest integrity and quality.

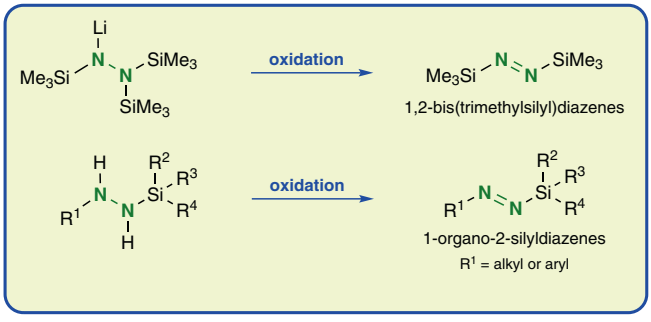
The Editorial Board March 2026

Abstracts

This is an update to the 2022 *Science of Synthesis* review on silyl ethers (Section 4.4.17). Unlike the original review, this update focuses primarily on catalytic methods for the synthesis of silyl ethers via the silylation of alcohols.

Keywords: silyl ethers · catalysis · hydrosilanes · alcohols · dehydrogenative coupling · silylation

This review describes the synthesis of silyldiazenes, a class of azo compounds derived from diazene (diimide, H—N=N—H), wherein at least one of the two hydrogen atoms is substituted by a silyl group. The discussion covers the two primary subclasses of isolable silyldiazenes, 1,2-bis(silyl)diazenes and 1-organo-2-silyldiazenes, which are both invariably prepared by oxidation of silylated hydrazine or hydrazide precursors. The discussion also details the main synthetic applications of 1-organyl-2-silyldiazenes in organic synthesis. These include their use as precursors for the generation of carbanions in nucleophilic arylation and deprotonative silylation reactions, as well as their application in palladium-catalyzed C(sp^2)—N(sp^2) cross-couplings for the synthesis of azobenzenes.



Keywords: silyldiazenes · azo compounds · hydrazines · silylhydrazines · oxidation · nucleophilic arylation · C—H silylation · carbanions · cross coupling · palladium catalysis · azobenzenes

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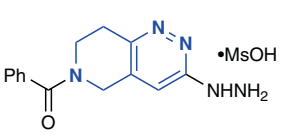
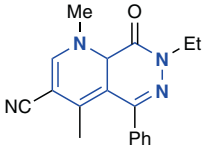
16.18.8 Pyridopyridazines

Manjeet Kumar and Narendra B. Ambhaikar

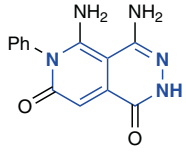
Pyridopyridazines are bicyclic heterocycles composed of a pyridine ring fused to a pyridazine core and exist as six distinct regioisomeric frameworks with multiple functionalization sites. Despite this structural diversity, pyridopyridazine scaffolds remain underexplored, with limited synthetic methodologies often derived from phthalazine chemistry. Most approaches rely on preassembled heteroaromatic units followed by construction of the second ring. Notably, recent years have introduced milder and more efficient strategies, including photocatalytic and metal-catalyzed C—N bond-forming reactions. These advances have improved access to diverse pyridopyridazine frameworks. Recent biological studies are also summarized in this review, highlighting their emerging potential in drug discovery.



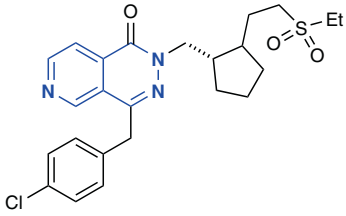
antihypertensive



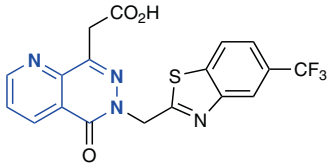
antiasthmatic



antimicrobial



antihistaminic



antidiabetic

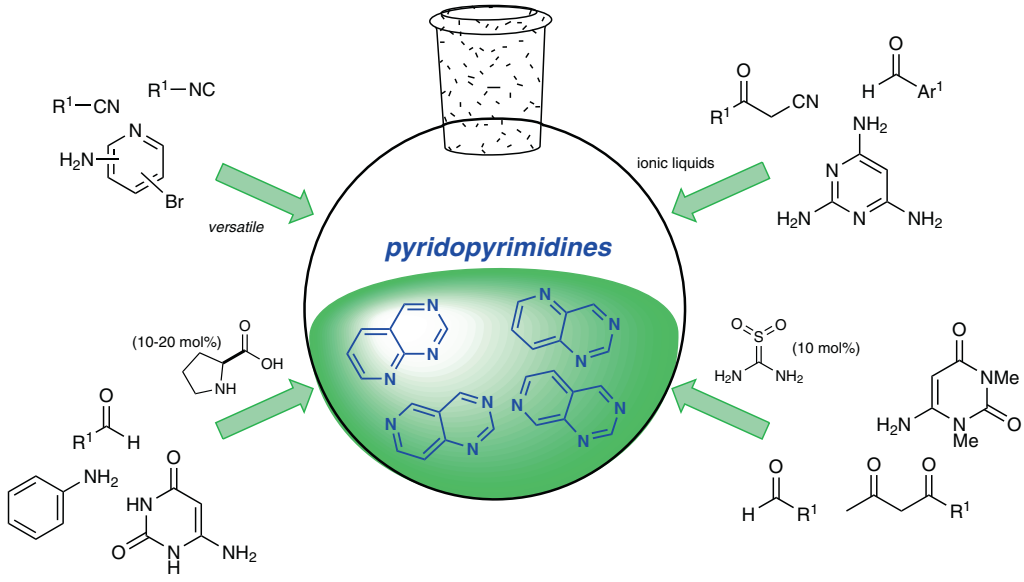
Keywords: pyridopyridazines · fused heterocycles · N-heterocycle synthesis · C—N bond formation · bicyclic compounds · medicinal chemistry

2026 p 95

16.19.6 Pyridopyrimidines

Charles L. Lail, III and Timothy J. Hagen

Pyridopyrimidines are a class of fused biaryl heterocycles where one ring is a pyridine ring, and the other is a pyrimidine ring. Pyridopyrimidines have found use extensively in medicinal chemistry, specifically in the antibacterial and anticancer spaces. The synthesis of pyridopyrimidines has greatly advanced in the last few years. Multicomponent reactions have allowed for increased control over substitution patterns. New catalysts have been developed. The use of ionic liquids and microwave reactors has faciltiated sub-one-hour reaction times. This review covers the key advances in methods for the synthesis of pyridopyrimidines reported between 2012 and 2024.



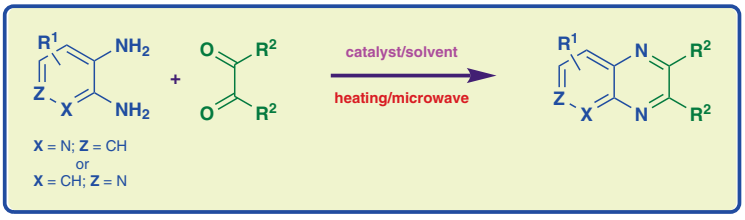
Keywords: pyridopyrimidines · pyrido[2,3-*d*]pyrimidines · pyrido[3,2-*d*]pyrimidines · pyrido[3,4-*d*]pyrimidines · pyrido[4,3-*d*]pyrimidines · heterocycles · heterocyclic chemistry · multicomponent reactions · organic synthesis · pyridines · pyrimidines · ionic liquids

2026 p 135

16.20.4 **Pyridopyrazines**

Faridoon and Guiping Zhang

This review reports synthetic methods for the preparation of pyridopyrazines published between 2010 and 2024, providing an updated account of the earlier *Science of Synthesis* contributions on this ring system (Sections 16.20 and 16.20.3). Pyridopyrazines are an important class of heterocyclic compounds with diverse applications in medicinal chemistry, including as antidiabetic, anticancer, antifungal, and anti-inflammatory agents. The most common approach to synthesizing pyrido[2,3-*b*]pyrazines and pyrido[3,4-*b*]pyrazines remains the reactions of pyridinediamines with carbonyl compounds. Herein, we describe recent advancements in reported reaction conditions, with a focus on greener catalysts and solvent systems.



Keywords: pyridopyrazines · pyridinediamines · 1,2-diketones · condensations · metal catalysts · boron compounds · cyclizations · heterocycles

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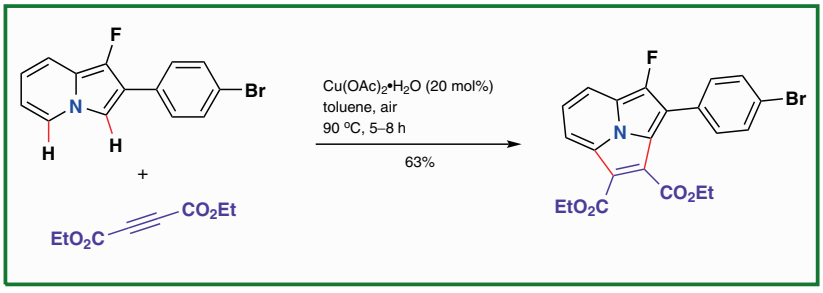
17.7.8 **Cyclazines**

Jie Jack Li

This review is an update to Section 17.7 and covers synthetic methods for the preparation of cyclazines published since 2004. Cyclazines are frequently prepared by cycloadditions. For instance, [2.2.3]cyclazines can be assembled via the [8 + 2]-cycloaddition reaction of indolizines with alkyne derivatives. In the same vein, cyclazines can be also prepared by cycloaddition of indolizines with alkene derivatives followed by aromatization via oxidation. Similarly, azacyclazines have been produced by the cycloaddition of imidazo[1,2-*a*]-pyridines with alkyne derivatives. Ullazines are often synthesized by annulation of *N*-arylpyrroles with alkynes. Finally, azaullazines may be assembled by annulation of *N*-arylimidazoles with alkynes.



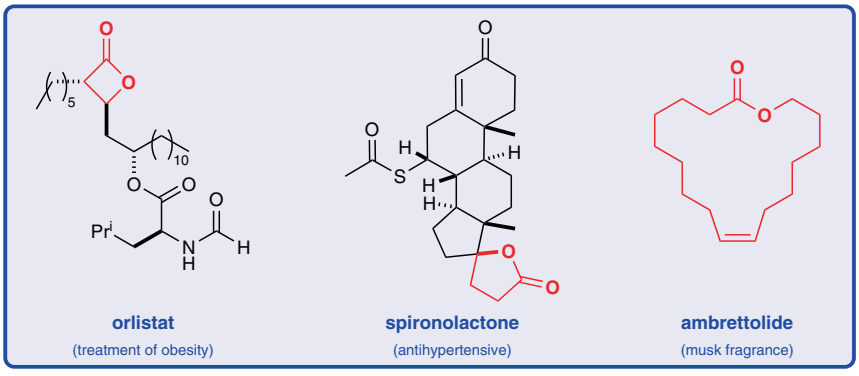
Keywords: annulenes · acetylenedicarboxylate · azacyclazines · azatriquinacenes · azaullazines · cyclazines · cyclazinones · cycloaddition · diazacyclazines · diazaullazines · Groebke–Blackburn–Bienaymé (GBB) reaction · indolizines · triazaullazines · ullazines

2026 p 233

20.6.2 **Lactones**

Vincent Coeffard and Xavier Moreau

Lactones are an important class of oxygen-containing heterocycles found in a myriad of natural products and synthetic compounds with diverse biological activities. Owing to their great structural diversity and complexity, the development of selective strategies for the preparation of lactones of all ring sizes, from small ring lactones to macrolactones, has become a popular topic in organic chemistry. This update to the original 2007 *Science of Synthesis* contribution highlights major developments in lactone synthesis that have emerged in recent years.



Keywords: lactones · lactonization · macrolactones · esters · carboxylic acids · spirolactones · transition-metal catalysis · C—H functionalization · asymmetric synthesis ·

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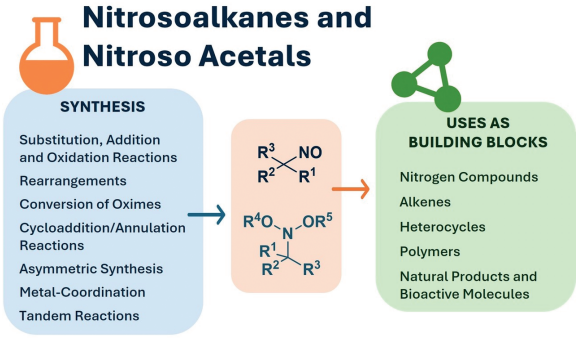
41.2.3 **Nitrosoalkanes and Nitroso Acetals (*N*,*N*-Dialkoxyamines)**

Maria I. L. Soares, Susana M. M. Lopes, Ana Lúcia Cardoso, Marta Pineiro, and Teresa M. V. D. Pinho e Melo

Nitrosoalkanes and nitroso acetals (*N*,*N*-dialkoxyamines) have emerged as highly versatile intermediates in modern organic synthesis, despite their intrinsic instability and tendency toward tautomerization and dimerization. This review provides an updated and comprehensive overview of their synthesis, reactivity, and applications. Recent advances include continuous-flow methodologies that enhance safety and efficiency, as well as innovative strategies for in situ generation to overcome instability issues. Synthetic approaches encompass substitution, addition, oxidation, and rearrangement reactions, enabling access to geminal chloronitroso compounds, metal-coordinated nitrosoalkanes, and structurally diverse nitroso acetals. Tandem and cascade processes have gained prominence for rapidly increasing molecular complexity with excellent regio- and stereocontrol, including catalytic asymmetric variants. Applications extend beyond classical transformations, such as oxidation to nitroalkanes, reduction to amines, and heterocycle formation via cycloaddition reactions, to cutting-edge uses in polymer synthesis, radical-mediated processes, and the functionalization of nitrosoalkane-metal complexes for C—H activation and alkene exchange. These developments underscore the growing role of nitroso compounds as strategic building blocks for complex architectures, biologically active molecules, and advanced materials, reinforcing their importance in contemporary synthetic chemistry.



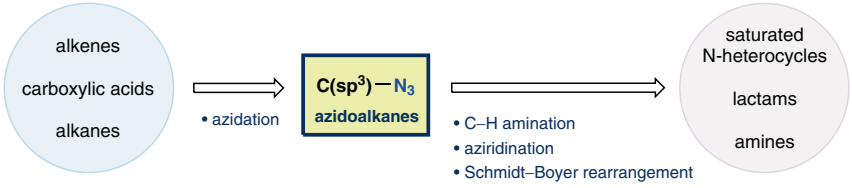
Keywords: nitrosoalkanes · nitroso acetals · cycloaddition reactions · annulation reactions · tandem reactions · rearrangements · C–H activation · radical processes · continuous-flow synthesis · geminal chloronitroso compounds · alkenes · nitrogen compounds · heterocycles · polymer synthesis · metal complexes

2026 p 413

41.8.3 Azidoalkanes

Minh Hai Hoang, Bendik Grømer, and Shunsuke Chiba

This review highlights the recent developments in the synthesis of azidoalkanes and their synthetic applications. The new synthetic methodologies through azidation of readily available feedstocks such as alkenes, carboxylic acids, and alkanes have led to significant diversification in the accessibility and structural complexity of azidoalkanes. Various approaches for the efficient conversion of azidoalkanes into diverse nitrogen-containing compounds, such as saturated N-heterocycles, lactams, and amines, have also been developed, enabling the expansion of chemical spaces, especially valuable in drug discovery programs.



Keywords: azides · azidation · alkenes · alkanes · carboxylic acids · amination · saturated N-heterocycles · lactams · amines

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Volume 17: Six-Membered Hetarenes with Two Unlike or More Than Two Heteroatoms and Larger Hetero-Rings

Chemical (cont.)

Name Used in Text	Abbreviation Used in Tables and on Arrow in Schemes	Abbreviation Used in Experimental Procedures
1,2-dimethoxyethane	DME	DME
dimethylacetamide	DMA	DMA
dimethyl acetylenedicarboxylate	DMAD	DMAD
2-(dimethylamino)ethanol	$Me_2N(CH_2)_2OH$	2-(dimethylamino)ethanol
4-(dimethylamino)pyridine	DMAP	DMAP
dimethylformamide	DMF	DMF
dimethyl sulfide	DMS	DMS
dimethyl sulfoxide	DMSO	DMSO
1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2-(1*H*)-one	DMPU	DMPU
ethyl diazoacetate	EDA	EDA
ethylenediaminetetraacetic acid	edta	edta
hexamethylphosphoric triamide	HMPA	HMPA
hexamethylphosphorous triamide	HMPT	HMPT
iodomethane	MeI	MeI
N-iodosuccinimide	NIS	NIS
lithium diisopropylamide	LDA	LDA
lithium hexamethyldisilazanide	LiHMDS	LiHMDS
lithium isopropylcyclohexylamide	LICA	LICA
lithium 2,2,6,6-tetramethylpiperidide	LTMP	LTMP
lutidine	lut	lut
methylaluminum bis(2,6-di-*tert*-butyl-4-methyl-phenoxide)	MAD	MAD
methyl ethyl ketone	MEK	methyl ethyl ketone
methylmaleimide	NMM	NMM
4-methylmorpholine *N*-oxide	NMO	NMO
1-methylpyrrolidin-2-one	NMP	NMP
methyl vinyl ketone	MVK	methyl vinyl ketone
petroleum ether	PE[a]	petroleum ether
N-phenylmaleimide	NPM	NPM
polyphosphoric acid	PPA	PPA
polyphosphate ester	PPE	polyphosphate ester
potassium hexamethyldisilazanide	KHMDS	KHMDS
pyridine	pyridine[b]	pyridine
pyridinium chlorochromate	PCC	PCC
pyridinium dichromate	PDC	PDC
pyridinium 4-toluenesulfonate	PPTS	PPTS
sodium bis(2-methoxyethoxy)aluminum hydride	Red-Al	Red-Al

[a] Used to save space; abbreviation must be defined in a footnote.
[b] py used on arrow in schemes.

Chemical (cont.)

Name Used in Text	Abbreviation Used in Tables and on Arrow in Schemes	Abbreviation Used in Experimental Procedures
tetrabutylammonium bromide	TBAB	TBAB
tetrabutylammonium chloride	TBACl	TBACl
tetrabutylammonium fluoride	TBAF	TBAF
tetrabutylammonium iodide	TBAI	TBAI
tetracyanoethene	TCNE	tetracyanoethene
tetrahydrofuran	THF	THF
tetrahydropyran	THP	THP
2,2,6,6-tetramethylpiperidine	TMP	TMP
trimethylamine *N*-oxide	TMANO	trimethylamine *N*-oxide
N,*N*,*N*′,*N*′-tetramethylethylenediamine	TMEDA	TMEDA
tosylmethyl isocyanide	TosMIC	TosMIC
trifluoroacetic acid	TFA	TFA
trifluoroacetic anhydride	TFAA	TFAA
trimethylsilyl cyanide	TMSCN	TMSCN

Ligands

acetylacetonato	acac
2,2′-bipyridyl	bipy
1,2-bis(dimethylphosphino)ethane	DMPE
2,3-bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene	NORPHOS
2,2′-bis(diphenylphosphino)-1,1′-binaphthyl	BINAP
1,2-bis(diphenylphosphino)ethane	dppe (not diphos)
1,1′-bis(diphenylphosphino)ferrocene	dppf
bis(diphenylphosphino)methane	dppm
1,3-bis(diphenylphosphino)propane	dppp
1,4-bis(diphenylphosphino)butane	dppb
2,3-bis(diphenylphosphino)butane	Chiraphos
bis(salicylidene)ethylenediamine	salen
cyclooctadiene	cod
cyclooctatetraene	cot
cyclooctatriene	cte
η^5-cyclopentadienyl	Cp
dibenzylideneacetone	dba
6,6-dimethylcyclohexadienyl	dmch
2,4-dimethylpentadienyl	dmpd
ethylenediaminetetraacetic acid	edta
isopinocampheyl	Ipc
2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane	Diop
norbornadiene (bicyclo[2.2.1]hepta-2,5-diene)	nbd
η^5-pentamethylcyclopentadienyl	Cp^*

Radicals

acetyl	Ac
aryl	Ar
benzotriazol-1-yl	Bt
benzoyl	Bz
benzyl	Bn
benzyloxycarbonyl	Cbz
benzyloxymethyl	BOM
9-borabicyclo[3.3.1]nonyl	9-BBN
tert-butoxycarbonyl	Boc
butyl	Bu
sec-butyl	*s*-Bu
tert-butyl	*t*-Bu
tert-butyldimethylsilyl	TBDMS
tert-butyldiphenylsilyl	TBDPS
cyclohexyl	Cy
3,4-dimethoxybenzyl	DMB
ethyl	Et
ferrocenyl	Fc
9-fluorenylmethoxycarbonyl	Fmoc
isobutyl	iBu
mesityl	Mes
mesyl	Ms
4-methoxybenzyl	PMB
(2-methoxyethoxy)methyl	MEM
methoxymethyl	MOM
methyl	Me
4-nitrobenzyl	PNB
phenyl	Ph
phthaloyl	Phth
phthalimido	NPhth
propyl	Pr
isopropyl	iPr
tetrahydropyranyl	THP
tolyl	Tol
tosyl	Ts
triethylsilyl	TES
triflyl, trifluoromethanesulfonyl	Tf
triisopropylsilyl	TIPS
trimethylsilyl	TMS
2-(trimethylsilyl)ethoxymethyl	SEM
trityl [triphenylmethyl]	Tr

General

absolute	abs
anhydrous	anhyd
aqueous	aq
boiling point	bp
catalyst	no abbreviation
catalytic	cat.
chemical shift	δ
circular dichroism	CD
column chromatography	no abbreviation
concentrated	concd
configuration (in tables)	Config
coupling constant	*J*
day	d
density	*d*
decomposed	dec
degrees Celsius	°C
diastereomeric ratio	dr
dilute	dil
electron-donating group	EDG
electron-withdrawing group	EWG
electrophile	E^+
enantiomeric excess	ee
enantiomeric ratio	er
equation	eq
equivalent(s)	equiv
flash-vacuum pyrolysis	FVP
gas chromatography	GC
gas chromatography-mass spectrometry	GC/MS
gas–liquid chromatography	GLC
gram	g
highest occupied molecular orbital	HOMO
high-performance liquid chromatography	HPLC
hour(s)	h
infrared	IR
in situ	in situ
in vacuo	in vacuo
lethal dosage, e. g. to 50 % of animals tested	LD_{50}
liquid	liq
liter	L
lowest unoccupied molecular orbital	LUMO
mass spectrometry	MS
medium-pressure liquid chromatography	MPLC
melting point	mp
milliliter	mL
millimole(s)	mmol
millimoles per liter	mM
minute(s)	min
mole(s)	mol
nuclear magnetic resonance	NMR
nucleophile	Nu^-
optical purity	op
phase-transfer catalysis	PTC
proton NMR	^{1}H NMR