



Science of Synthesis

Dearomatizations

Volume Editor
D. Sarlah



Science of Synthesis

Science of Synthesis is the authoritative and comprehensive reference work for the entire field of organic and organometallic synthesis.

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

Editorial Board

E. M. Carreira (Executive Editor)
M. Faul
S. Kobayashi
G. Koch
C. Nevado
D. Sarlah
T. P. Yoon
S.-L. You

Senior Executive Editor

K. M. Muirhead-Hofmann

Product Manager: Chemistry Databases

A. G. Russell

Executive Editor

T. B. Reeve

Associate Editor

V. S. Rawat

Scientific Editors

R. M. Cowie
M. J. White
F. Wuggenig



Georg Thieme Verlag KG
Stuttgart · New York · Delhi ·
Rio de Janeiro · Beijing



Science of Synthesis

Dearomatizations

Reference Library 2025/4

Volume Editor

D. Sarlah 

Authors

B. An
E. Angelini
S. L. Barlock 
B. R. G. Bissinger
C. G. Bochet 
Y. D. Boyko 
S. Canesi 
J. Collins 
H. Cui
K. Devi
H. Ding
M. S. Fogel 

E. Guillet 
Y.-M. Hou
M. Hu
R. K. Karimov 
K. Koide 
W. Li 
C. Malenfant 
K. Muto 
Z. Nairoukh 
N. P. O'Hare
M. Okumura
D. Sarlah 

A. Shehzad
Z. S. Shellnutt 
Z. Siddiqi 
H. Song
H. D. Vu
M.-Y. Wang 
M. P. Wiesenfeldt 
J. Yamaguchi 
S.-L. You 
X. Zhang 



2026
Georg Thieme Verlag KG
Stuttgart · New York · Delhi ·
Rio de Janeiro · Beijing

© 2026 Thieme. All rights reserved.

Georg Thieme Verlag KG

Oswald-Hesse-Straße 50, 70469 Stuttgart, Germany

www.sos.thieme.com

Cover design: © Thieme

Image: Chemical plant © Yellow Boat/stock.adobe.com,

Lab © totojang1977/stock.adobe.com

General Partner: Dr. Albrecht Hauff

VAT ID number: DE 147 638 607

Legal structure: Limited Partnership

Domicile and Commercial Register:

Stuttgart, HRA 3499

Typesetting: Ziegler + Müller, Einhornstraße 21,

72138 Kirchentellinsfurt, Germany

Date of publication: March 18, 2026

Copyright and all related rights reserved, especially the right of copying and distribution, multiplication and reproduction, as well as of translation. No part of this publication may be reproduced by any process, whether by photostat or microfilm or any other procedure, without previous written consent by the publisher. This also includes the use of electronic media of data processing or reproduction of any kind.

This reference work mentions numerous commercial and proprietary trade names, registered trademarks and the like (not necessarily marked as such), patents, production and manufacturing procedures, registered designs, and designations. The editors and publishers wish to point out very clearly that the present legal situation in respect of these names or designations or trademarks must be carefully examined before making any commercial use of the same. Industrially produced apparatus and equipment are included to a necessarily restricted extent only and any exclusion of products not mentioned in this reference work does not imply that any such selection of exclusion has been based on quality criteria or quality considerations.

*Bibliographic Information published by
Die Deutsche Bibliothek*

Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available on the internet at <www.dnb.de>

Library of Congress Card No.: applied for

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISSN (online) 2566-7297

ISBN (PDF) 978-3-13-245831-4

DOI 10.1055/b000000920

Structure searchable version available at:

sos.thieme.com

Warning! Read carefully the following: Although this reference work has been written by experts, the user must be advised that the handling of chemicals, micro-organisms, and chemical apparatus carries potentially life-threatening risks. For example, serious dangers could occur through quantities being incorrectly given. The authors took the utmost care that the quantities and experimental details described herein reflected the current state of the art of science when the work was published. However, the authors, editors, and publishers take no responsibility as to the correctness of the content. Further, scientific knowledge is constantly changing. As new information becomes available, the user must consult it. Although the authors, publishers, and editors took great care in publishing this work, it is possible that typographical errors exist, including errors in the formulas given herein. Therefore, **it is imperative that and the responsibility of every user to carefully check whether quantities, experimental details, or other information given herein are correct based on the user's own understanding as a scientist.** Scale-up of experimental procedures published in **Science of Synthesis** carries additional risks. In cases of doubt, the user is strongly advised to seek the opinion of an expert in the field, the publishers, the editors, or the authors. When using the information described herein, the user is ultimately responsible for his or her own actions, as well as the actions of subordinates and assistants, and the consequences arising therefrom.

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

E. M. Carreira (Executive Editor, Zurich, Switzerland)

M. Faul (Thousand Oaks, USA)

S. Kobayashi (Tokyo, Japan)

G. Koch (Schlieren, Switzerland)

C. Nevado (Zurich, Switzerland)

D. Sarlah (Houston, USA)

T. P. Yoon (Madison, USA)

S.-L. You (Shanghai, China)

Science of Synthesis Reference Library

Dearomatizations

Hypervalent Halogens in Organic Synthesis

Abiotic Reactions in Live Environments

Modern Strategies in Organofluorine Chemistry (2 Vols.)

DNA-Encoded Libraries

Cross-Dehydrogenative Coupling

Base-Metal Catalysis (2 Vols.)

Dynamic Kinetic Resolution (DKR) and Dynamic Kinetic Asymmetric Transformations (DYKAT)

Electrochemistry in Organic Synthesis

Click Chemistry

Free Radicals: Fundamentals and Applications in Organic Synthesis (2 Vols.)

Dual Catalysis in Organic Synthesis (2 Vols.)

Advances in Organoboron Chemistry towards Organic Synthesis

Photocatalysis in Organic Synthesis

Flow Chemistry in Organic Synthesis

Catalytic Reduction in Organic Synthesis (2 Vols.)

Catalytic Oxidation in Organic Synthesis

N-Heterocyclic Carbenes in Catalytic Organic Synthesis (2 Vols.)

Metal-Catalyzed Cyclization Reactions (2 Vols.)

Applications of Domino Transformations in Organic Synthesis (2 Vols.)

Catalytic Transformations via C–H Activation (2 Vols.)

Biocatalysis in Organic Synthesis (3 Vols.)

C-1 Building Blocks in Organic Synthesis (2 Vols.)

Multicomponent Reactions (2 Vols.)

Cross Coupling and Heck-Type Reactions (3 Vols.)

Water in Organic Synthesis

Asymmetric Organocatalysis (2 Vols.)

Stereoselective Synthesis (3 Vols.)

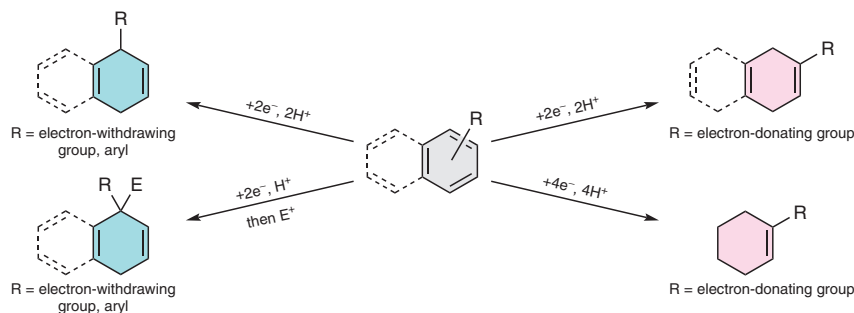
Abstracts

p 3

2.1 Birch and Benkeser Reduction of Aromatic Hydrocarbons

M. S. Fogel^{ID}, Z. S. Shellnutt^{ID}, and K. Koide^{ID}

The Birch reduction, a transformative method for escaping the flatland of aromaticity, has long been a cornerstone of organic synthesis, enabling the conversion of planar aromatic hydrocarbons into more three-dimensional structures. This review provides a comprehensive exploration of the Birch reduction and its modern adaptations, focusing on the selective dearomatization of monoaromatic and polyaromatic systems, including benzene, biphenyl, naphthalene, and anthracene derivatives. Traditional protocols employing alkali metals in liquid ammonia are examined alongside innovative strategies that eliminate hazardous reagents and cryogenic conditions. Key advancements, such as electride salts, mechanochemical techniques, and alternative solvents, have significantly expanded the scope and practicality of Birch-type reductions. The review also delves into the Benkeser reduction, a related process that often leads to deeper hydrogenation, and highlights the strategic use of reductive alkylation for increasing molecular complexity. Through a critical evaluation of each method's advantages and limitations, this review serves as a practical guide for synthetic chemists seeking optimal conditions for their transformations. Additionally, safety considerations and emerging trends in the field are discussed, underscoring the continued evolution and relevance of Birch reductions in modern organic synthesis.



Keywords: Birch reduction · Benkeser reduction · dearomatization · solvated electrons · alkali metals · liquid ammonia · electride salts · mechanochemistry · reductive alkylation · cyclohexa-1,4-dienes · polyaromatic hydrocarbons · biphenyls · naphthalenes · anthracenes

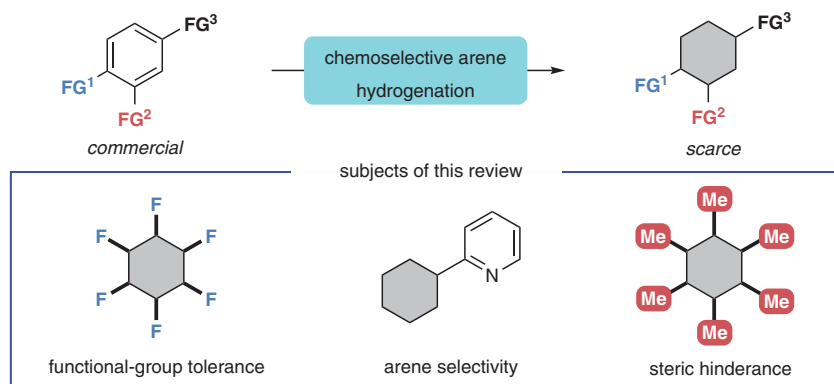
p 55

2.2 Chemoselective Hydrogenation of Arenes

A. Shehzad, H. D. Vu, K. Devi, B. R. G. Bissinger, and M. P. Wiesenfeldt^{ID}

Arene hydrogenation converts widely available arenes into scarce cycloalkanes, making it valuable for the production of bulk chemicals such as cyclohexane and cyclohexene, as well as simple pharmaceuticals such as tranexamic acid. Moreover, the recognition that increasing the proportion of C(sp³)-hybridized carbon atoms in drug candidates improves their clinical success rate has highlighted the enormous potential of arene hydrogenation for lead optimization in drug discovery. However, the development of chemoselective transformations that tolerate the diverse functional groups of complex drug candidates is challenging, as the aromatic stabilization energy increases the kinetic barrier of the reaction and limits the number of applicable catalyst systems. This review presents broadly applicable catalysts and chemoselective transformations with a focus on those that provide access to medicinally relevant cycloalkane motifs. This review also discusses remain-

ing challenges, including the tolerance of strongly coordinating, reducible, or labile functional groups, and identifies promising developments.



Keywords: dearomatization · chemoselective reactions · hydrogenation · arenes · heterogeneous catalysts · homogeneous catalysts · frustrated Lewis pairs · alkaline earth metals

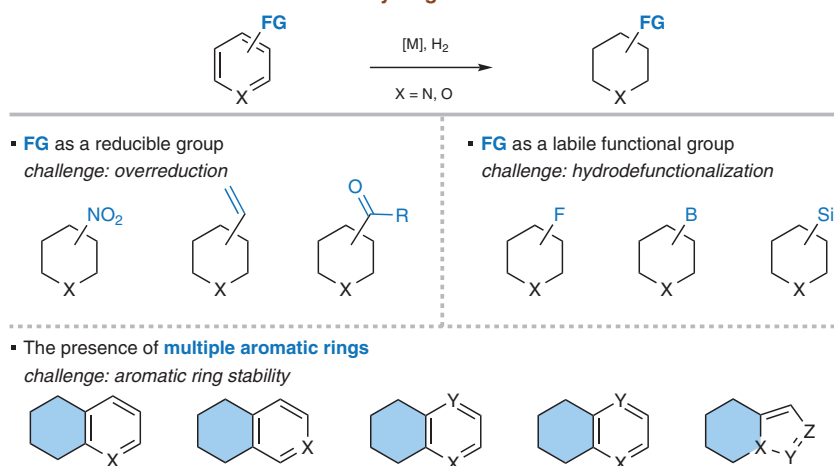
p 89

2.3 Chemoselective Hydrogenation of Heteroarenes

Z. Nairoukh , H. Ding, and M. Hu

The hydrogenation of heteroarenes is considered one of the most valuable synthetic tools, converting unsaturated, flat heteroarenes into their corresponding aliphatic analogues. However, when reactive functional groups are present, achieving chemoselectivity becomes a major challenge. This review highlights the importance of overcoming this challenge by demonstrating the value of the obtained products, which can be incorporated into the synthesis of complex aliphatic architectures.

chemoselective hydrogenation of heteroarenes

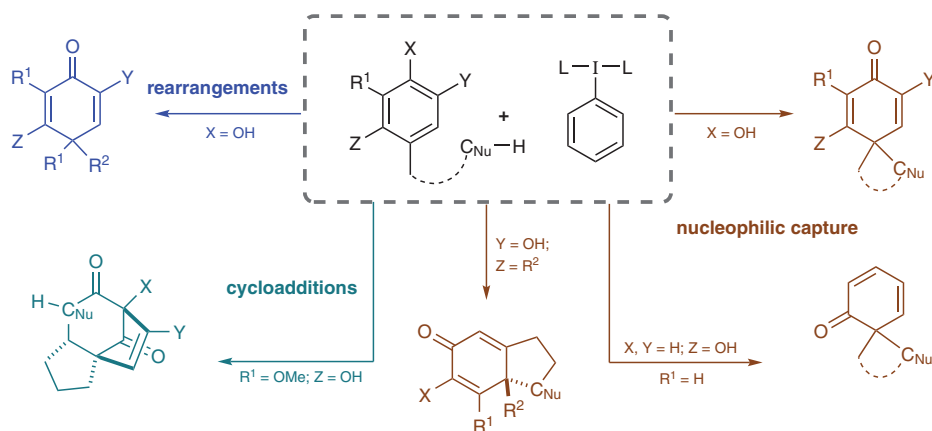


Keywords: dearomatization · hydrogenation · reduction · chemoselectivity · heteroarenes · N-heterocycles · aliphatic heterocycles · functional groups

3.1 Dearomatizations of Phenols Involving C–C Bond Formation

E. Guillet^{id}, C. Malenfant^{id}, and S. Canesi^{id}

Hypervalent iodine compounds are environmentally benign reagents that effectively activate phenols to generate reactive species, which can then be trapped by a variety of nucleophiles. Among these, carbon-based nucleophiles have garnered significant interest because they enable the rapid formation of a quaternary carbon center as well as a polyfunctionalized dienone subunit. Therefore, the efficient transformation of inert aromatics into key intermediates for the synthesis of complex structures has become a widely used strategy. This review summarizes the various methods reported in the literature for the formation of C–C bonds via phenol dearomatization mediated by iodanes. The transformations discussed include nucleophilic capture, rearrangements, and cycloadditions, with stereoselective approaches also considered.

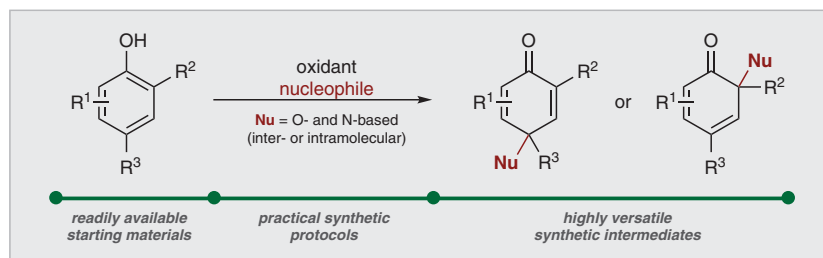


Keywords: dearomatization · aromatics · C–C bond formation · cyclization · cycloaddition · iodanes · perfluorinated alcohols · phenols · rearrangements · umpolung reactivity

3.2 Oxidative Dearomatizations of Phenols Involving Heteronucleophiles

E. Angelini and D. Sarlah 

Oxidation of phenols is a fundamental dearomatization transformation that introduces nucleophiles to substituted phenols with concurrent loss of aromaticity. The resulting unsaturated cyclohexadienone products serve as valuable synthetic intermediates, enabling numerous applications in natural products and medicinal chemistry. This review provides a survey of oxidative dearomatizations of phenols that introduce heteronucleophiles. Using a range of nitrogen- and oxygen-based nucleophiles in an inter- or intramolecular setting, as well as the introduction of fluoride, these simple protocols provide rapid and controlled access to products that are ideally functionalized for the construction of many complex molecules.

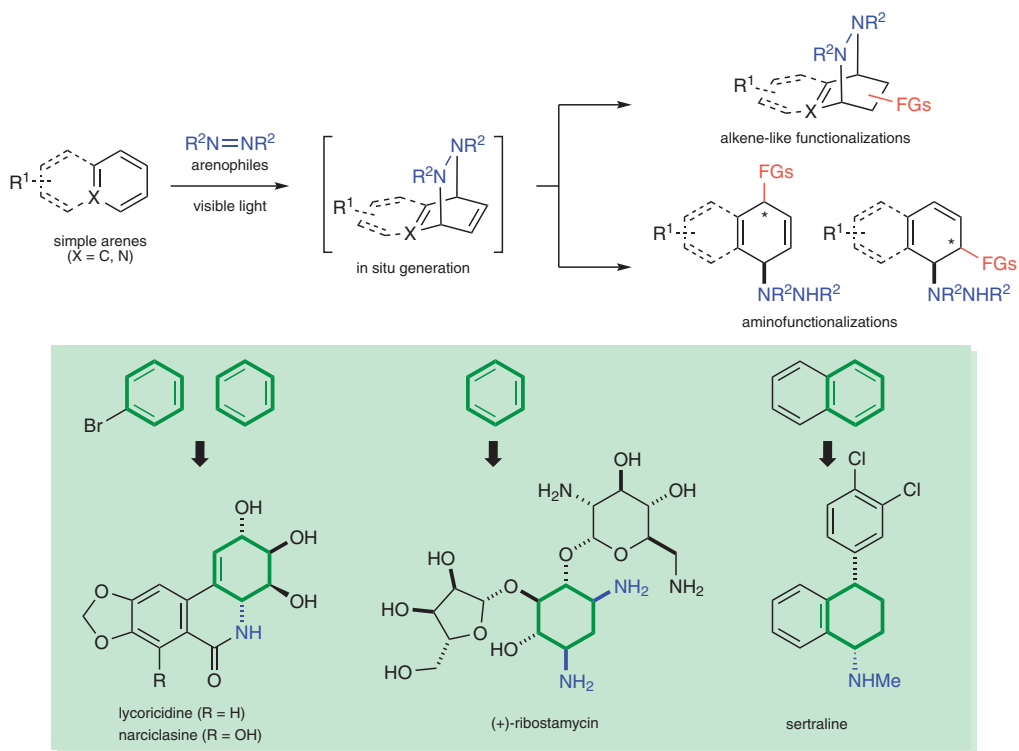


Keywords: dearomatization · phenols · aromatic compounds · hypervalent iodine reagents · cyclohexadienones

4.1 Arenophile-Mediated Photochemical Dearomative Functionalization

M. Okumura

Dearomatizations have long been recognized as an important class of reactions, with significant progress achieved; however, the utilization of simple and nonactivated arenes remains a challenging endeavor due to their inherent inertness and the difficulty of achieving selective transformations. This review highlights an emerging dearomatization approach that enables selective conversion of such arenes under mild conditions: arenophile-mediated photochemical dearomative functionalization. This methodology provides efficient access to alicyclic structures, offering both functional and stereochemical complexity, including C–C, C–B, C–N, C–O and C–H bond formations. Applications in the synthesis of complex bioactive compounds are also presented to demonstrate the unique versatility of this strategy.

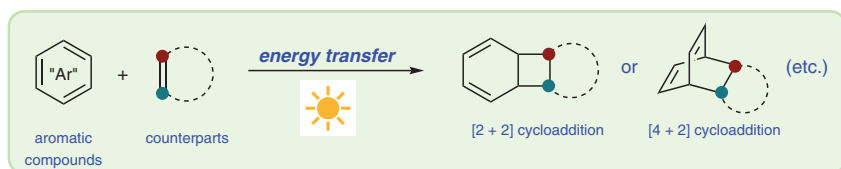


Keywords: dearomatization · arenophiles · MTAD · TETRADs · alkene functionalization · transition-metal catalysis · asymmetric catalysis · aromatic compounds

4.2 Photosensitized Dearomatization of (Hetero)Arenes

H. Cui, B. An, and X. Zhang 

Dearomatization reactions constitute a powerful strategy to convert aromatic compounds into three-dimensional scaffolds, which have found wide applications in organic synthesis, medicinal chemistry, and materials science. Distinct from ground-state dearomatization, the photosensitized dearomatization of (hetero)arenes capitalizes on excited-state reactivities, enabling the achievement of thermodynamically disfavoured transformations along with the generation of intriguing scaffolds. This review summarizes recent advances in the photosensitized dearomatization of (hetero)arenes according to the type of (hetero)arene. Mediated by appropriate photosensitizers, a series of (hetero)arenes are engaged in photocycloaddition, difunctionalization, or sensitized reduction.

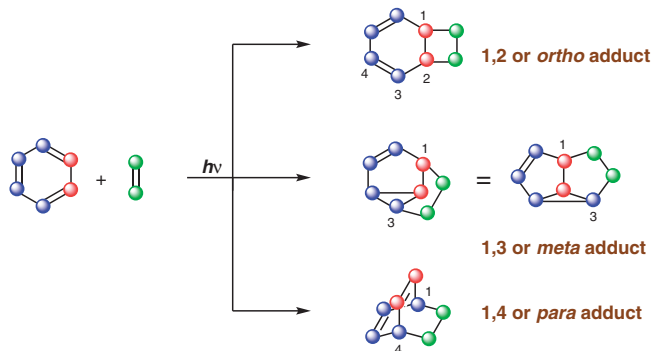


Keywords: dearomatization · arenes · heteroarenes · energy transfer · photocycloaddition · photosensitizers · visible light

4.3 Nonsensitized Arene–Alkene Cycloadditions

C. G. Bochet 

Benzene-like arenes are notoriously stable toward cycloadditions, because their double bonds are part of a delocalized system of molecular orbitals. Upon photochemical excitation with ultraviolet light, their electronic configuration is altered, leading to unusual or enhanced reactivity. In particular, cycloadditions with alkenes become possible, in [2 + 2] (also known as *ortho*-cycloaddition), [3 + 2] (*meta*-), and [4 + 2] (*para*-) modes. These reactions provide a rapid rise in molecular complexity, combining relatively simple units in an intricate way. With appropriate functional groups placed at suitable positions, the photoproduct can be converted into a high-added-value chemical or intermediate in one or very few additional steps.

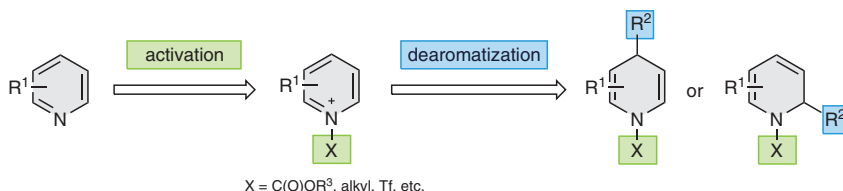


Keywords: dearomatization · aromaticity · bicyclic compounds · organic photochemistry · [2 + 2] cycloadditions · [3 + 2] cycloadditions · [4 + 2] cycloadditions

5.1 Dearomatization of Activated Pyridines

Y. D. Boyko^{id} and S. L. Barlock^{id}

Dearomatization of pyridines constitutes a powerful technique to rapidly introduce complexity to commodity chemicals. This strategy affords products containing reactive functional handles uniquely suited for further chemical elaboration into densely substituted and stereochemically defined sp^3 -rich compounds. Reviewed herein are pyridine activation modes and methods for the concomitant regioselective formation of new C–H and C–C bonds.

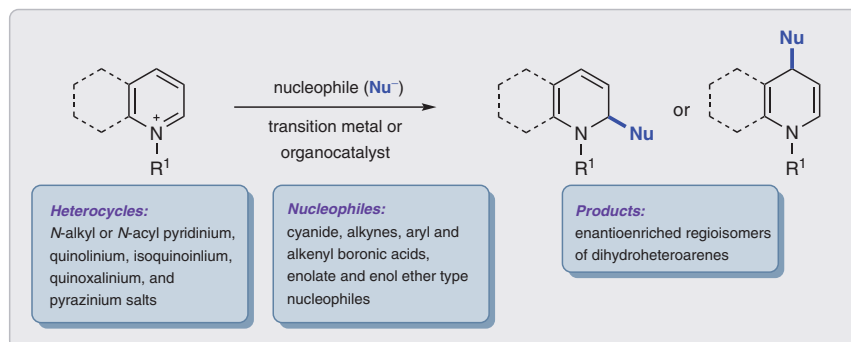


Keywords: dearomatization · electrophilic activation · dihydropyridines · pyridines · piperidines · hydride addition · C–C bond formation

5.2 Asymmetric Dearomatization of Pyridinium Salts and Other N-Heteroarenes

R. K. Karimov^{id} and N. P. O'Hare

Nonaromatic nitrogen heterocycles bearing stereogenic centers are essential scaffolds in medicinal chemistry, agrochemicals, and pharmaceuticals. Among the strategies to access these structures, nucleophilic dearomatization has emerged as a powerful approach for converting planar aromatic systems into three-dimensional saturated or partially saturated frameworks, enabling further functionalization and enhancing molecular complexity. In recent years, asymmetric variants of these transformations have gained prominence for their ability to generate enantioenriched heterocycles while forming new C–C bonds in a single step. This review highlights advances in catalytic asymmetric nucleophilic dearomatization (AND) methods, typically mediated by chiral transition-metal complexes or organocatalysts, which enable diverse $C(sp)-C(sp^3)$, $C(sp^2)-C(sp^3)$, and $C(sp^3)-C(sp^3)$ bond formations. These developments provide efficient routes to piperidines and related saturated and partially saturated six-membered nitrogen heterocycles, expanding synthetic capabilities and offering new opportunities for drug discovery and chemical biology.

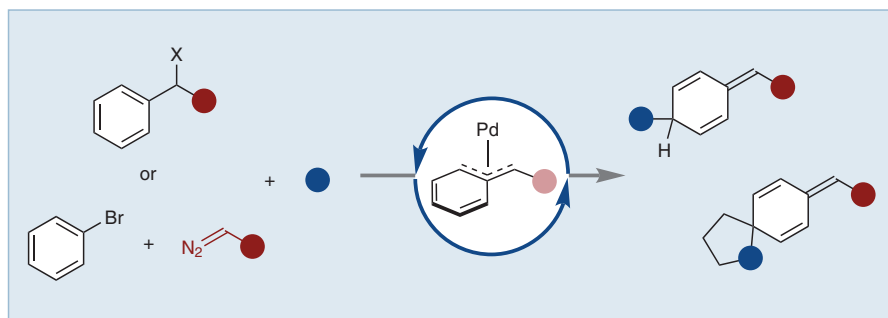


Keywords: asymmetric dearomatizations · pyridinium salts · quinolinium salts · isoquinolinium salts · piperidines · chiral thiourea catalysis · chiral phosphoric acid catalysis · hydrogen-bond-donor catalysis · arylations · alkynylations · hydrazones · enantioselectivity · nucleophilic additions · dihydropyridines · organocatalysis · transition-metal catalysis · stereoselective transformations · heterocycle functionalization

6.1 Palladium-Catalyzed Dearomative Functionalization of Arenes

K. Muto^{1b} and J. Yamaguchi^{1b}

Palladium catalysis plays a pivotal role in organic synthesis, encompassing applications in cross-couplings and hydrogenations, among other transformations. Recent progress in palladium chemistry has helped enable catalytic dearomative functionalizations. In particular, catalysis involving benzyl-palladium species has been applied to achieve dearomative functionalization of a wide range of aromatic systems, including challenging substrates such as electronically unbiased benzenes, without the need to use an excess amount of the arene starting materials. This review primarily focuses on dearomative functionalization via benzyl-palladium species, incorporating applications of these methodologies in the synthesis of natural products.

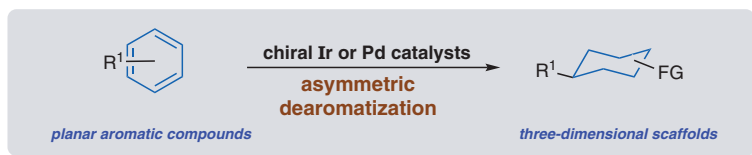


Keywords: dearomatization · arenes · aromatic compounds · alicyclic compounds · palladium catalysis · benzylpalladium species · multicomponent reactions

6.2 CADA Reactions Involving Palladium and Iridium Catalysis

H. Song, Y.-M. Hou, and S.-L. You^{1b}

Catalytic asymmetric dearomatization (CADA) reactions have become a powerful tool for synthesizing enantioenriched spirocyclic and fused polycyclic compounds from simple planar aromatic precursors. These reactions have significantly expanded the synthetic toolbox, enabling the efficient construction of diverse chiral scaffolds and facilitating access to a wide range of biologically active molecules and natural products. This review focuses on two prominent types of CADA reactions: asymmetric allylic dearomatization and asymmetric dearomatization via cross-coupling, catalyzed by palladium or iridium complexes. The discussion is organized based on the type of transition-metal catalyst employed, offering insights into the mechanistic features and synthetic applications of these transformations.

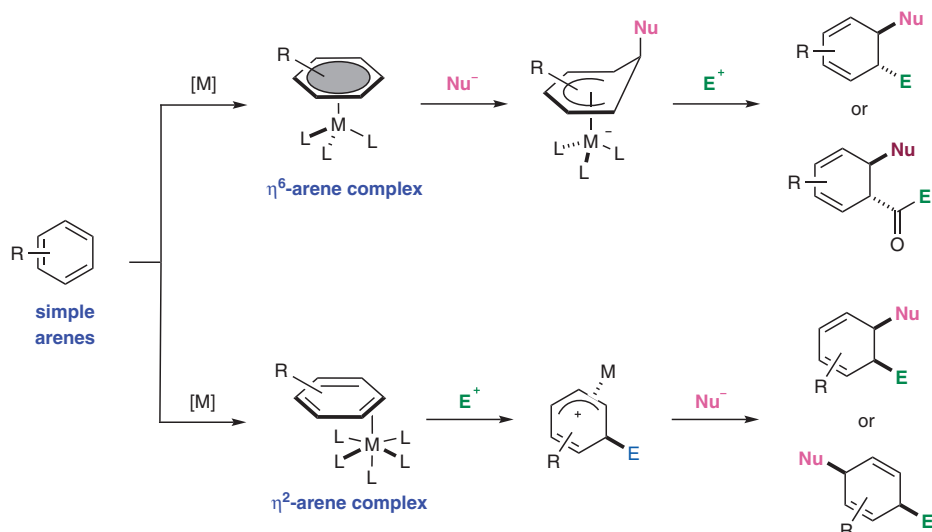


Keywords: dearomatization · allylic substitution · aromatic compounds · asymmetric catalysis · catalytic asymmetric dearomatization (CADA) · cross-coupling reactions · iridium catalysis · palladium catalysis · Heck reaction

6.3 Dearomatizations of Metal-Bound Arenes

M.-Y. Wang^{1b} and W. Li^{1b}

The chemical reactivity of arenes can be dramatically altered by their coordination to a transition metal. η^6 -Coordination with Lewis acids $\text{Cr}(\text{CO})_3$, $\text{Mo}(\text{CO})_3$, $[\text{Mn}(\text{CO})_3]^+$, and $[\text{Ru}(\text{Cp})]^+$ reduces the electron density of arenes, while η^2 -coordination with some metals makes the aromatic system more electron-rich. Based on these two activation strategies, a number of dearomatizations of arenes have been realized. In this review, the development of the dearomatization of metal-bound arenes is summarized, highlighting recent achievements over the last decade.

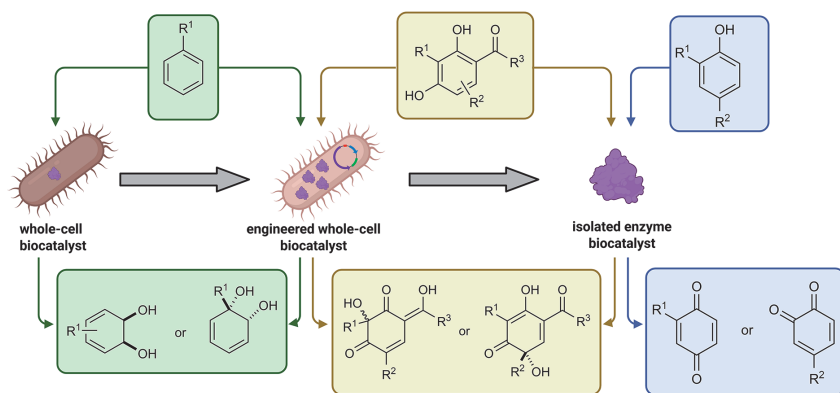


Keywords: dearomatization · arenes · η^6 -coordination · η^2 -coordination · chromium · manganese · molybdenum · ruthenium · osmium · rhenium · tungsten · arene reduction · dearomative hydrofunctionalization · dearomative difunctionalization · dearomative carbonylation · cyclohexadienes · cyclohexenes

7 Enzymatic Oxidative Dearomatization Reactions

J. Collins 

Nature has long possessed the ability to perform oxidative dearomatization reactions. These transformations are found throughout a variety of metabolic and biosynthetic pathways, but they historically remained largely out of reach for most practicing synthetic organic chemists. New advancements have successfully lowered the barrier to entry for these methods and have made the exquisite selectivity offered by these enzymatic systems available to the general practitioner. This review presents Rieske dearomatizing dioxygenases, flavin-dependent monooxygenases, and laccases/tyrosinases as key examples of applied enzymatic dearomatization reactions. In many cases, the presented biocatalytic reactions offer methods for oxidative dearomatization that are complementary to some examples presented in this volume. In others, the selectivity offered by the enzymes provide wholly unique capabilities. Throughout the review an effort has been made to highlight a diversity of biocatalytic reactions and formulations in the hopes of maximizing the accessibility of these enzyme-based methods.

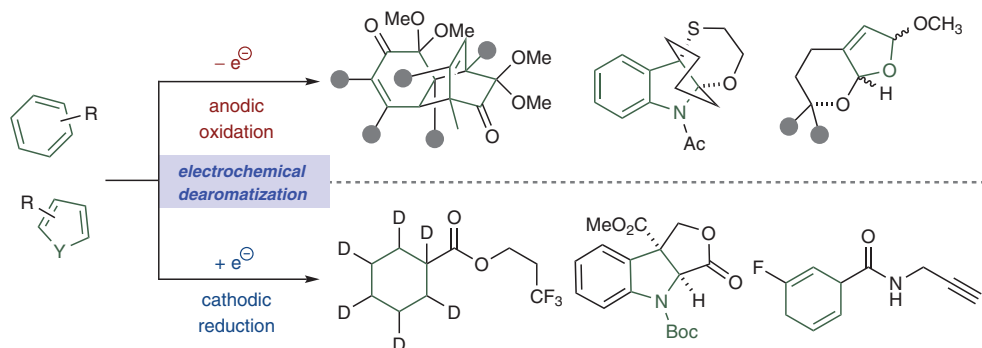


Keywords: biocatalysis · dearomatization · whole cells · dioxygenase · Rieske dioxygenase · flavin-dependent monooxygenase · 1,4-addition reactions · Diels–Alder cyclization · hydroxylation

8

Electrochemical DearomatizationsZ. Siddiqi 

The dearomatization of simple aromatics is one of the most direct strategies for preparing complex three-dimensional molecules from abundant chemical feedstocks. Electrochemistry serves as a powerful strategy that enables tunable control of redox potentials at the deeply oxidizing and reducing potentials required to disrupt aromaticity. Recent advances have demonstrated both increased atom efficiency in existing transformations and the preparation of unique scaffolds that cannot be prepared through traditional means. This review presents a summary of dearomative anodic oxidations and cathodic reductions, with an emphasis on recent developments in electrochemical methodology that have enabled the realization of these transformations.



Keywords: dearomatization · organic electrochemistry · anodic oxidation · cathodic reduction · cyclization · direct and indirect electrolysis

Dearomatizations

	Preface	V
	Abstracts	IX
	Table of Contents	XXIII
1	Introduction	
	D. Sarlah ^{ib}	1
2	Reduction of Arenes and Heteroarenes	3
2.1	Birch and Benkeser Reduction of Aromatic Hydrocarbons	
	M. S. Fogel ^{ib} , Z. S. Shellnutt ^{ib} , and K. Koide ^{ib}	3
2.2	Chemoselective Hydrogenation of Arenes	
	A. Shehzad, H. D. Vu, K. Devi, B. R. G. Bissinger, and M. P. Wiesenfeldt ^{ib}	55
2.3	Chemoselective Hydrogenation of Heteroarenes	
	Z. Nairoukh ^{ib} , H. Ding, and M. Hu	89
3	Oxidative Dearomatization of Phenols	117
3.1	Dearomatizations of Phenols Involving C—C Bond Formation	
	E. Guillet ^{ib} , C. Malenfant ^{ib} , and S. Canesi ^{ib}	117
3.2	Oxidative Dearomatizations of Phenols Involving Heteronucleophiles	
	E. Angelini and D. Sarlah ^{ib}	165
4	Photochemical Dearomatization of Arenes	203
4.1	Arenophile-Mediated Photochemical Dearomative Functionalization	
	M. Okumura	203
4.2	Photosensitized Dearomatization of (Hetero)Arenes	
	H. Cui, B. An, and X. Zhang ^{ib}	275
4.3	Nonsensitized Arene–Alkene Cycloadditions	
	C. G. Bochet ^{ib}	337
5	Additions to Activated Pyridines	359
5.1	Dearomatization of Activated Pyridines	
	Y. D. Boyko ^{ib} and S. L. Barlock ^{ib}	359
5.2	Asymmetric Dearomatization of Pyridinium Salts and Other N-Heteroarenes	
	R. K. Karimov ^{ib} and N. P. O'Hare	391

6	Transition-Metal-Catalyzed and -Mediated Dearomatizations	425
6.1	Palladium-Catalyzed Dearomative Functionalization of Arenes K. Muto ^{ib} and J. Yamaguchi ^{ib}	425
6.2	CADA Reactions Involving Palladium and Iridium Catalysis H. Song, Y.-M. Hou, and S.-L. You ^{ib}	447
6.3	Dearomatization of Metal-Bound Arenes M.-Y. Wang ^{ib} and W. Li ^{ib}	497
7	Enzymatic Oxidative Dearomatization Reactions J. Collins ^{ib}	533
8	Electrochemical Dearomatizations Z. Siddiqi ^{ib}	591
	Author Index	635
	Abbreviations	659

Table of Contents

1	Introduction D. Sarlah 	
1	Introduction	1
2	Reduction of Arenes and Heteroarenes	
2.1	Birch and Benkeser Reduction of Aromatic Hydrocarbons M. S. Fogel  , Z. S. Shellnutt  , and K. Koide 	
2.1	Birch and Benkeser Reduction of Aromatic Hydrocarbons	3
2.1.1	Monoaromatic Systems	4
2.1.1.1	Reduction of Alkyl- and Alkoxybenzenes	4
2.1.1.2	Reduction of Benzoic Acid Derivatives	15
2.1.2	Polyaromatic Systems	29
2.1.2.1	Reduction of Biphenyls	30
2.1.2.2	Reduction of Naphthalenes	39
2.1.2.3	Reduction of Anthracenes and Other Polyaryls	46
2.1.3	Conclusions	52
2.2	Chemoselective Hydrogenation of Arenes A. Shehzad, H. D. Vu, K. Devi, B. R. G. Bissinger, and M. P. Wiesenfeldt 	
2.2	Chemoselective Hydrogenation of Arenes	55
2.2.1	Transition-Metal Catalysts for Arene Hydrogenation Reactions	56
2.2.2	Transition-Metal-Free Catalysts for Arene Hydrogenation Reactions	58
2.2.3	Analysis of Scope and Limitations	59
2.2.4	Accessible Ring Systems	60
2.2.5	Functional-Group Tolerance	64
2.2.5.1	Tolerance of Coordinating Functional Groups	67
2.2.5.2	Tolerance of Reducible Functional Groups	68
2.2.5.3	Tolerance of Directly Attached Functional Groups	71
2.2.6	Arene-Selective Hydrogenation of Benzene Rings	75
2.2.6.1	Preferential Hydrogenation of Benzene Rings in the Presence of Less-Aromatic (Hetero)Arenes	75
2.2.6.2	Preferential Hydrogenation of the Carbocyclic Rings In Annulated Heteroarenes	78

2.2.7	Hydrogenation of Multisubstituted Arenes	81
2.2.8	Conclusions	83
2.3	Chemoselective Hydrogenation of Heteroarenes Z. Nairoukh  , H. Ding, and M. Hu	
2.3	Chemoselective Hydrogenation of Heteroarenes	89
2.3.1	Hydrogenation of Heteroarenes in the Presence of Reducible Moieties	89
2.3.1.1	Synthesis of Functionalized Piperidines	89
2.3.1.1.1	Rhodium-Catalyzed Chemoselective Reduction of Pyridines	89
2.3.1.1.2	Tris(pentafluorophenyl)borane-Catalyzed Cascade Reduction of Pyridines	90
2.3.1.2	Synthesis of Piperidinones	92
2.3.1.2.1	Iridium-Catalyzed Chemoselective Hydrogenation of 3-Hydroxypyridinium Salts	92
2.3.1.2.2	Palladium-Catalyzed Chemoselective Hydrogenation of Oxazolidinone-Substituted Pyridines	92
2.3.1.3	Synthesis of 2-Substituted Indolines	93
2.3.1.4	Synthesis of Substituted 1,2,3,4-Tetrahydroquinolines	95
2.3.1.5	Synthesis of Substituted Indolizidines	96
2.3.2	Hydrogenation of Heteroarenes with Directly Attached Labile Functional Groups	97
2.3.2.1	Synthesis of <i>cis</i> -(Multi)Fluorinated Piperidines	97
2.3.2.1.1	One-Pot Dearomatization/Hydrogenation Reaction of Fluoropyridines	97
2.3.2.1.2	Hydrogenation of Fluoropyridines Using a Heterogeneous Catalyst	99
2.3.2.2	Synthesis of Silylated Aliphatic Heterocycles	100
2.3.2.3	Synthesis of Borylated Aliphatic Heterocycles	101
2.3.2.4	Synthesis of Germanylated Aliphatic Heterocycles	102
2.3.2.5	Synthesis of 4-Substituted Piperidines	103
2.3.2.6	Synthesis of Substituted Octahydrobenzofurans	104
2.3.3	Hydrogenation of Heteroarenes Featuring Other Aromatic Moieties	106
2.3.3.1	Chemoselective Hydrogenation of Indoles	106
2.3.3.2	Chemoselective Hydrogenation of Quinolines, Isoquinolines, Acridines, and Phenazines	107
2.3.3.3	Chemoselective Hydrogenation of Quinoxalines	111
2.3.3.4	Chemoselective Hydrogenation of Indolizines and [1,2,3]Triazolo[1,5- <i>a</i>]pyridines	112
2.3.4	Conclusions	114

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 ₂ N(CH ₂) ₂ OH	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-tetrahydro-pyrimidin-2(1 <i>H</i>)-one	DMPU	DMPU
ethyl diazoacetate	EDA	EDA
ethylenediaminetetraacetic acid	edta	edta
hexamethylphosphoric triamide	HMPA	HMPA
hexamethylphosphorous triamide	HMPT	HMPT
iodomethane	MeI	MeI
<i>N</i> -iodosuccinimide	NIS	NIS
lithium diisopropylamide	LDA	LDA
lithium hexamethyldisilazane	LiHMDS	LiHMDS
lithium isopropylcyclohexylamide	LICA	LICA
lithium 2,2,6,6-tetramethylpiperidine	LTMP	LTMP
lutidine	lut	lut
methylaluminum bis(2,6-di- <i>tert</i> -butyl-4-methylphenoxide)	MAD	MAD
methyl ethyl ketone	MEK	methyl ethyl ketone
methylmaleimide	NMM	NMM
4-methylmorpholine <i>N</i> -oxide	NMO	NMO
1-methylpyrrolidin-2-one	NMP	NMP
methyl vinyl ketone	MVK	methyl vinyl ketone
petroleum ether	PE ^a	petroleum ether
<i>N</i> -phenylmaleimide	NPM	NPM
polyphosphoric acid	PPA	PPA
polyphosphate ester	PPE	polyphosphate ester
potassium hexamethyldisilazane	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
tetrabutylammonium bromide	TBAB	TBAB

^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 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 <i>N</i> -oxide	TMANO	trimethylamine <i>N</i> -oxide
<i>N,N,N',N'</i> -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	lpc
2,3- <i>O</i> -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
<i>tert</i> -butoxycarbonyl	Boc
butyl	Bu
<i>sec</i> -butyl	<i>s</i> -Bu
<i>tert</i> -butyl	<i>t</i> -Bu
<i>tert</i> -butyldimethylsilyl	TBDMS
<i>tert</i> -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	<i>J</i>
day	<i>d</i>
density	<i>d</i>
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