SOS Science of Synthesis

Knowledge Updates 2020/2

Volume Editors
M. Christmann
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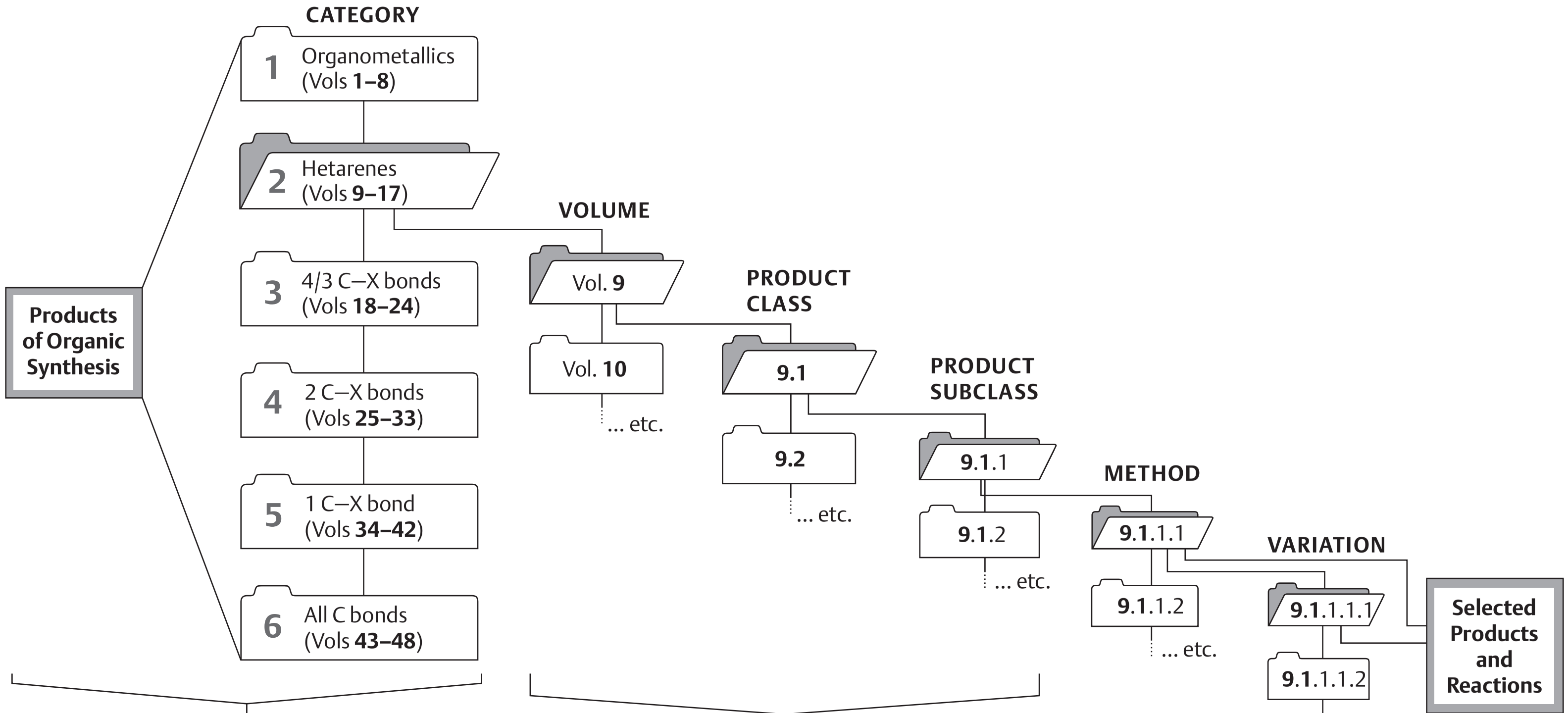
Organizational Structure of Science of Synthesis*



Classification is **based on the product**, with all products belonging to one of six broad-ranging categories. All products occupy a strict hierarchical position in Science of Synthesis, defined according to the classification principles*. Products in Categories 3–6 are organized according to oxidation state, with products containing the greatest number of carbon–heteroatom (C—X) or C—C π-bonds to a single carbon occupying the highest positions (e.g., carboxylates, enolates, and alcoholates are covered in Categories 3, 4, and 5, respectively).

Each category is subdivided into volumes (see opposing page), each of which is devoted to discrete groupings of compounds called **product classes** (e.g., “Thiophenes” is Product Class 10 of Volume 9). Product classes may be further subdivided into **product subclasses**, (e.g., “Thiophene 1,1-Dioxides” is Product Subclass 3 of Product Class 10 of Volume 9). Consequently, the relationship between heading name and heading number varies below product class level within individual volumes.

For each product class or subclass, a number of methods are described for synthesizing the general product type. Often there are variations on a method given. Both methods and variations contain experimental procedures with relevant background information and literature references. **Selected products and reactions** display the scope and limitations of the methods.

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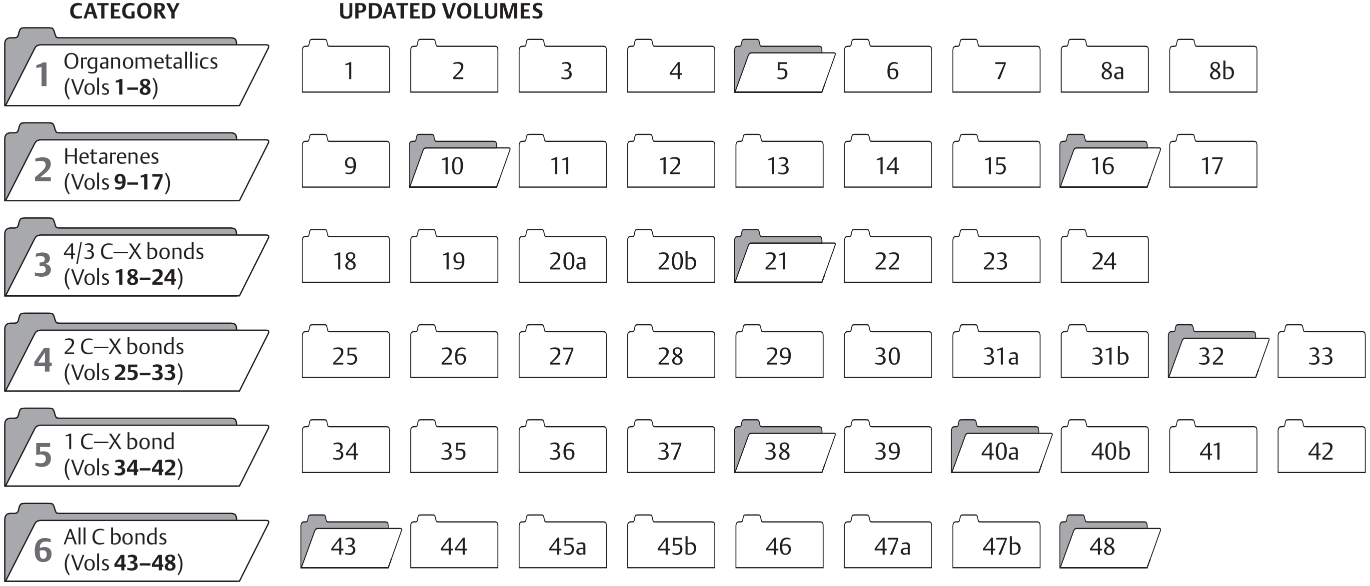
* A complete description of the full classification principles can be found in the **Science of Synthesis Guidebook.**



CATEGORY	UPDATED VOLUMES									
1 Organometallics (Vols **1–8**)	1	2	3	4	5	6	7	8a	8b	
2 Hetarenes (Vols **9–17**)	9	10	11	12	13	14	15	16	17	
3 4/3 C—X bonds (Vols **18–24**)	18	19	20a	20b	21	22	23	24		
4 2 C—X bonds (Vols **25–33**)	25	26	27	28	29	30	31a	31b	32	33
5 1 C—X bond (Vols **34–42**)	34	35	36	37	38	39	40a	40b	41	42
6 All C bonds (Vols **43–48**)	43	44	45a	45b	46	47a	47b	48		

5	Compounds of Group 14 (Ge, Sn, Pb)
10	Fused Five-Membered Hetarenes with One Heteroatom
16	Six-Membered Hetarenes with Two Identical Heteroatoms
21	Three Carbon—Heteroatom Bonds: Amides and Derivatives; Peptides; Lactams
32	X—Ene—X (X = F, Cl, Br, I, O, S, Se, Te, N, P), Ene—Hal, and Ene—O Compounds
38	Peroxides
40a	Amines and Ammonium Salts
43	Polyynes, Arynes, Enynes, and Alkynes
48	Alkanes

* Detailed listings of product classes and subclasses, methods, and variations can be found in the **Table of Contents** sections of every volume.

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

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Knowledge Updates 2020/2

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2020
Georg Thieme Verlag KG
Stuttgart · New York · Delhi ·
Rio de Janeiro · Beijing

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Rüdigerstrasse 14
70469 Stuttgart, Germany
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General Partner: Dr. Albrecht Hauff

VAT ID number: DE 147 638 607

Legal structure: Limited Partnership
Domicile and Commercial Register:
Stuttgart, HRA 3499

Printed in Germany

Typesetting: 3w+p GmbH, Ketteler Strasse 5–11,
97222 Rimpar, Germany

Printing and Binding: AZ Druck und Datentechnik
GmbH, Heisinger Strasse 16, 87437 Kempten,
Germany

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 <http://dnb.ddb.de>

Library of Congress Cataloging in Publication Data

Science of synthesis : **Houben–Weyl** methods of
molecular transformations.
p. cm.
Includes bibliographical references.
Contents: Science of Synthesis Knowledge Updates
2020/2 / volume editors, M. Christmann, Z. Huang,
J. A. Joule, C.-J. Li, J. J. Li, C. Marschner, E. J. Petersson,
H.-U. Reissig, A. O. Terent'ev
ISBN 978-3-13-243561-2
1. Organic compounds–Synthesis. I. Title: **Houben–Weyl** methods of molecular transformations.
QD262 .S35 2000
547'.2–dc21
00-061560

(**Houben–Weyl methods of organic chemistry**)

British Library Cataloguing in Publication Data

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

ISSN (print) 2510-5469
ISSN (online) 2566-7297

ISBN (print) 978-3-13-243561-2
ISBN (PDF) 978-3-13-243562-9
DOI 10.1055/b000000103

Structure searchable version available at:
sos.thieme.com

Date of publication: July 8, 2020

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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 September 2018

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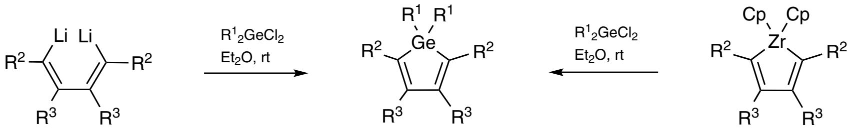
Abstracts

New — p 1

5.1.28 Product Subclass 28: Germoles

T. Müller

This chapter provides an overview of methods for the synthesis of 1*H*-germoles. It covers the literature from 1959 until 2020. Classical methods involve the cyclization of 1,4-dilithiobuta-1,3-dienes and zirconium/germanium exchange in zirconacyclopentadienes, but more-recent approaches such as catalytic double hydrogermylations of butadiynes are included as well. Finally, methods for the preparation of alkali metal salts of 1*H*-germol-1-ides and 1*H*-germole-1,1-diides are summarized.



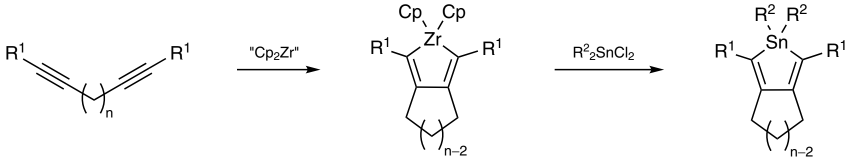
Keywords: germoles · anionic reagents · alkynes · butadienes · butadiynes · germanium compounds · germanes · iodo compounds · lithium compounds · zirconocenes

New — p 31

5.2.30 Product Subclass 30: Stannoles

I.-M. Ramirez y Medina, W. Kipke, J. Makow, and A. Staubitz

This chapter gives an overview of different methods for the synthesis of classical stannoles and related compounds such as ring-fused stannoles and stannoles containing further heteroatoms. It represents a review of the literature from 1959 to 2019.



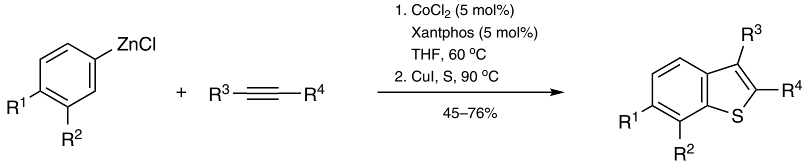
Keywords: carbon—tin bonds · coupling reactions · cyclization · five-membered rings · fused-ring systems · heterocycles · hydrostannation · lithiation · tin compounds · transmetalation · organoboration · stannoles

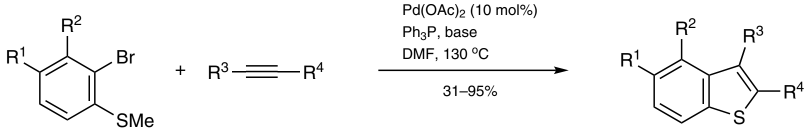
2020 — p 53

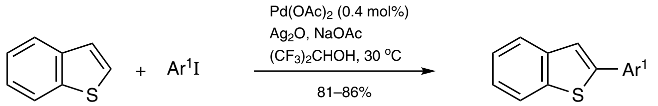
10.4 Product Class 4: Benzo[*b*]thiophenes

N. Yoshikai, C. M. Rayner, and M. A. Graham

This chapter is a revision of the earlier *Science of Synthesis* Section 10.4. It describes methods for the synthesis of benzo[*b*]thiophenes and related compounds by ring closure or by modification of existing substituent(s) on the benzo[*b*]thiophene skeleton. Ring-closure methods typically involve the formation of the five-membered ring starting from benzene derivatives bearing substituents such as halogen, alkenyl, alkynyl, or sulfanyl groups at appropriate positions. Ring closure to form the benzene ring can also be achieved using suitably substituted thiophene derivatives. In particular, a number of new methods involving metal-catalyzed C—C and C–S bond formation that have been developed since the previous review are included. Recent years have also witnessed substantial progress in the methods available to directly introduce new substituents to the 2- and 3-positions of benzo[*b*]thiophenes through metal-catalyzed C—H bond functionalization, and these are included in this chapter.







Keywords: benzo compounds · benzo[*b*]thiophenes · thiophenes · sulfides · alkenes · alkynes · halo compounds · carbonyl compounds · palladium catalysis · copper catalysis · organolithium compounds · cyclization · ring closure · annulation · cross-coupling reactions · C—H activation reactions

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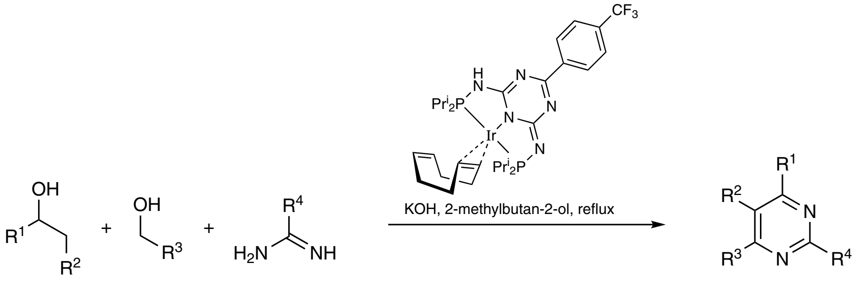
16.12.5 Pyrimidines

J. M. Campagne and E. Leclerc

This chapter is an update to the earlier *Science of Synthesis* contribution (Section 16.12) covering the synthesis and substituent modification of pyrimidines. It focuses on the literature published in the period 2012–2019, gathering all the methods reported in this period, but with a particular emphasis on transition-metal-catalyzed synthetic processes.



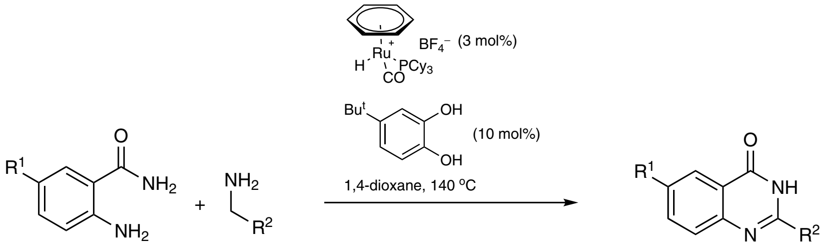
Keywords: pyrimidines · heterocycles · transition-metal catalysis · cyclization · cycloadditions · metalation · substitution

2020 p 185

16.13.6 Quinazolines

J. M. Campagne and E. Leclerc

This chapter is an update to the earlier *Science of Synthesis* contributions (Sections 16.13 and 16.13.5) covering the synthesis of quinazolines. It focuses on the literature published in the period 2012–2019, gathering all the methods reported in this period, but with a particular emphasis on transition-metal-catalyzed synthetic processes.



Keywords: quinazolines · heterocycles · pyrimidines · transition-metal catalysis · cyclization · cycloadditions · metalation

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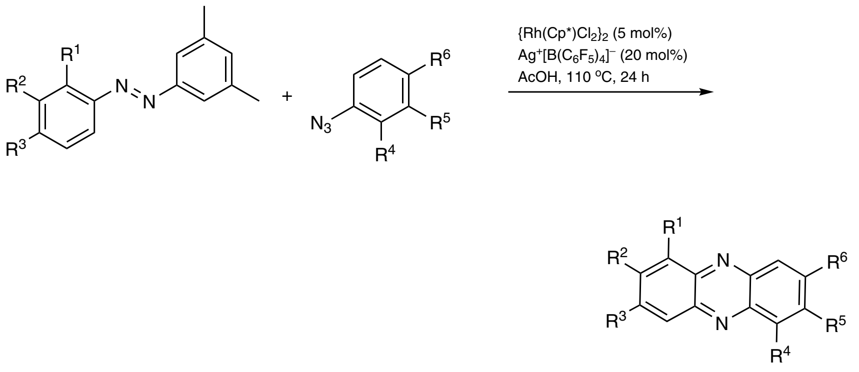
16.16.5 Phenazines

N. B. Ambhaikar

Phenazines are an interesting class of nitrogen-containing heterocycles present in many natural products. This update describes the construction of phenazines through some newer practical synthetic methods that have been reported since the first review on phenazines in *Science of Synthesis* (Section 16.16). For the most part, standard ways of synthesizing phenazine and its derivatives have employed traditional approaches or their variations along the lines of the Wohl–Aue reaction and the Beirut reaction. The current account focuses on modern synthetic tools to construct the phenazine core and includes some of the newer approaches, with recent key methods that have been developed between 2004 and 2019.



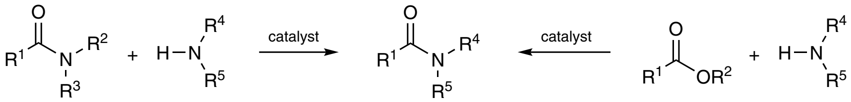
Keywords: phenazines · phenazine *N*-oxides · electrochemical reduction · C—H activation · oxidative coupling · Fischer carbenes · cyclization · quinoxalines

New p 219

21.1.8 Synthesis of Amides by Transamidation and Amidation of Activated Amides and Esters

G. Li and M. Szostak

This chapter provides a summary of the recent advances in direct transamidation and amidation reactions of activated amides and esters via transition-metal-catalyzed and transition-metal-free C(acyl)—N and C(acyl)—O bond cleavage as a new disconnection for the synthesis of amide bonds.



Keywords: amides · esters · transamidation · amidation · N—C cleavage · O—C cleavage · tetrahedral intermediates · nucleophilic addition · cross coupling · palladium–NHC catalysis · nickel catalysis · nitroarenes · anilines · chemoselectivity · reductive coupling · twisted amides · ground-state destabilization · electronic activation

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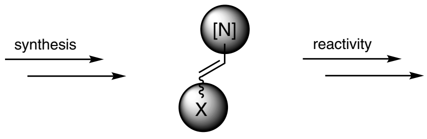
32.3.4.2 1-Nitrogen-Functionalized 2-Haloalkenes

M. L. Tong, K. Kunz, M. Jaschinski, K. Holzschneider, I. E. Celik, and S. F. Kirsch

This chapter is an update to the earlier *Science of Synthesis* contribution (Section 32.3.4) describing general synthetic methods to access 1-nitrogen-functionalized 2-haloalkenes. It puts a new focus on recent synthetic developments for this rather broad class of compounds, covering the literature from 2008 until 2018. The contents are broadly categorized by discussing methods of synthesis first, followed by specific reactivities. The synthetic methods section is arranged according to the number of substituents attached to the alkene core. Due to the vast number of examples in the literature, the current overview represents a selection of methods. In particular, when describing reactivities with 1-nitrogen-functionalized 2-haloalkenes, only archetypical examples are shown, while explicit variants are omitted.



[N] = NR^1_2, N_3, NO_2, $NR^1(SO_2R^2)$; X = F, Cl, Br, I

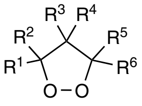
Keywords: alkenes · enamines · haloalkenes · halogenation · cross coupling · elimination reactions · Michael addition · metathesis · Wittig alkenation

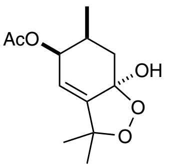
New — p 277

38.8.3.2 Stable and Unstable 1,2-Dioxolanes: Origin, Synthesis, and Biological Activities

V. M. Dembitsky and I. A. Yaremenko

This chapter describes 1,2-dioxolanes, with confirmed biological activity, isolated from various natural sources . The key steps in the formation of the 1,2-dioxolane ring in the total synthesis of some natural peroxides as well as interesting modern procedures for the synthesis of 1,2-dioxolanes are also presented.





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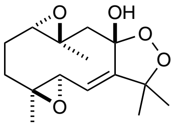

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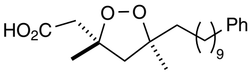

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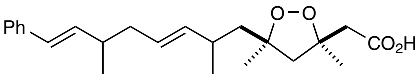

plakinic acid A

Keywords: 1,2-dioxolanes · peroxides · oxidation · oxygen · hydrogen peroxide · hydroperoxides · cyclopropanes · acetylenes · carbonyl compounds · ketones · alkenes · enones · ketals · acetals · epoxides · allenes · nitrosoarenes · ozonolysis · antimalarial · antifungal · antiviral · anticancer

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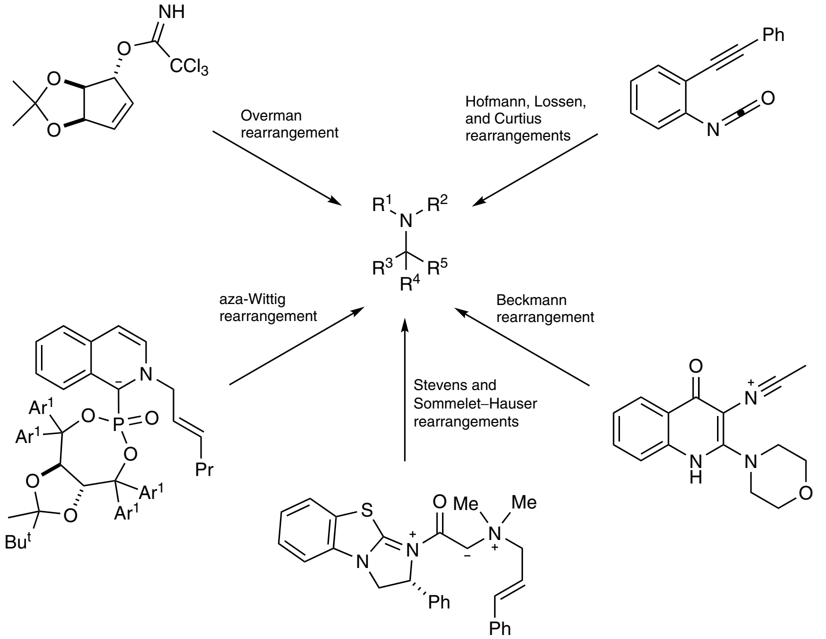
40.1.1.4.3 Synthesis of Amines by Rearrangement

C. I. Ochoa and U. K. Tambar

The synthesis of amines is one of the most important areas of research in organic chemistry due to the prevalence of nitrogen atoms in many functional molecules, including natural products, pharmaceutical drugs, and agrochemicals. The synthesis of amines through rearrangement reactions has been heavily researched and discussed over the past few decades. One of the most comprehensive reviews of this topic was included in *Science of Synthesis* (Section 40.1.1.4). The purpose of this review is to provide an up-to-date account of new methods and synthetic developments in amine rearrangement reactions within the last decade. Over this period of time, new chemistry has been developed which was not discussed in any particular section in the original account on this topic. Thus, this chapter serves as a supplementary document to the earlier review but is also a source of new synthetic strategies not discussed previously. The chapter is arranged in two sections: rearrangements from carbon to nitrogen, and rearrangements from nitrogen to carbon.



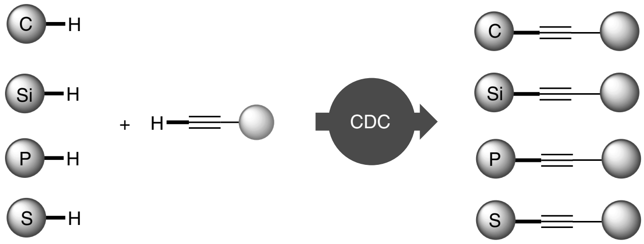
Keywords: amines · rearrangements · Stevens rearrangement · Sommelet–Hauser rearrangement · aza-Wittig rearrangement · Overman rearrangement · Beckmann rearrangement · Hofmann rearrangement · Lossen rearrangement · Curtius rearrangement

New p 375

43.10 Cross-Dehydrogenative Coupling of Terminal Alkynes

T. Tian and Z. Li

The construction of C—C and C—X bonds via cross-dehydrogenative coupling (CDC) reactions has made remarkable progress, and the methods developed have reached excellent levels of versatility, selectivity, and efficiency over the past few decades. The oxidative coupling of various C—H or X—H substrates to terminal alkynes can complement the coupling reactions of functionalized starting materials and can minimize waste and allow faster access to functionalized product molecules. These reactions represent a historic breakthrough in alkynylation chemistry and have greatly expanded the synthetic routes available for the efficient construction of alkynyl compounds.



Keywords: cross-dehydrogenative coupling · terminal alkynes · alkynylation · C—C bond formation · C—X bond formation

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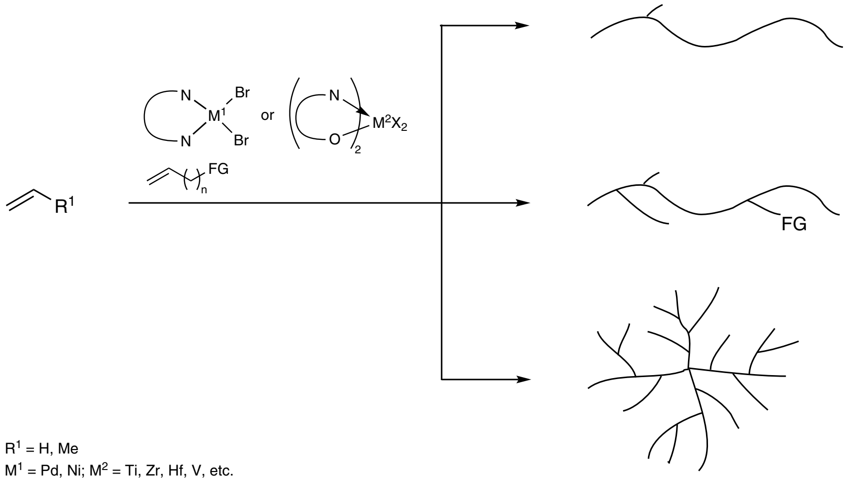
48.5.5 Hydrocarbon Polymers

X.-Y. Wang and X.-L. Sun

X.-Y. Wang and X.-L. SunThis review is an update to the original *Science of Synthesis* chapter (Section 48.5) on hydrocarbon polymers, published in 2009. This update focuses on the typical methods for the synthesis of polyethene and polypropene reported over the past two decades. In addition, it has been supplemented with some general synthesis procedures for copolymers of ethene or propene with polar vinyl monomers as well as typical synthetic methods for other polyalk-1-ene [poly(α-olefin), PAO] products. The methods covered are mainly based on early-transition-metal, non-metallocene catalysts and late-transition-metal catalysts.



R^1 = H, Me
M^1 = Pd, Ni; M^2 = Ti, Zr, Hf, V, etc.
FG = OH, CO_2H, CO_2R^2, Cl, CN

Keywords: coordination polymerization · catalysis · polyalkenes · polyolefins · polymers · copolymers · structure · non-metallocene catalysts · late-transition-metal catalysts

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