

Science of Synthesis

Volume Editors
Shengming Ma
Shuanhu Gao





Science of Synthesis

Metal-Catalyzed Cyclization Reactions 2

Volume Editors

S. Ma

S. Gao

Authors

U. Bora

G. Domínguez

H. Du

L. K. B. Garve

M. Harmata

W. Hu

D. E. Jones

D. Lee

X. Li

M. Mondal

J. Pérez-Castells

V. Reddy Sabbasani

Y. Shibata

K. Tanaka

W. Tang

D. B. Werz

F. Xia

X. Xu

S. Ye



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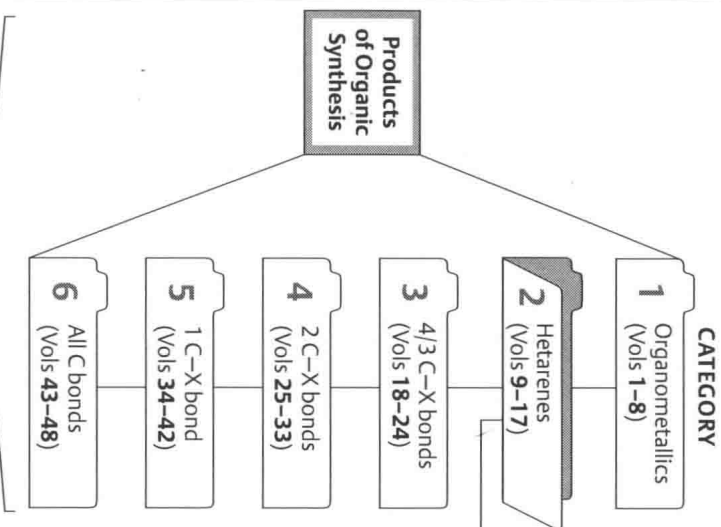
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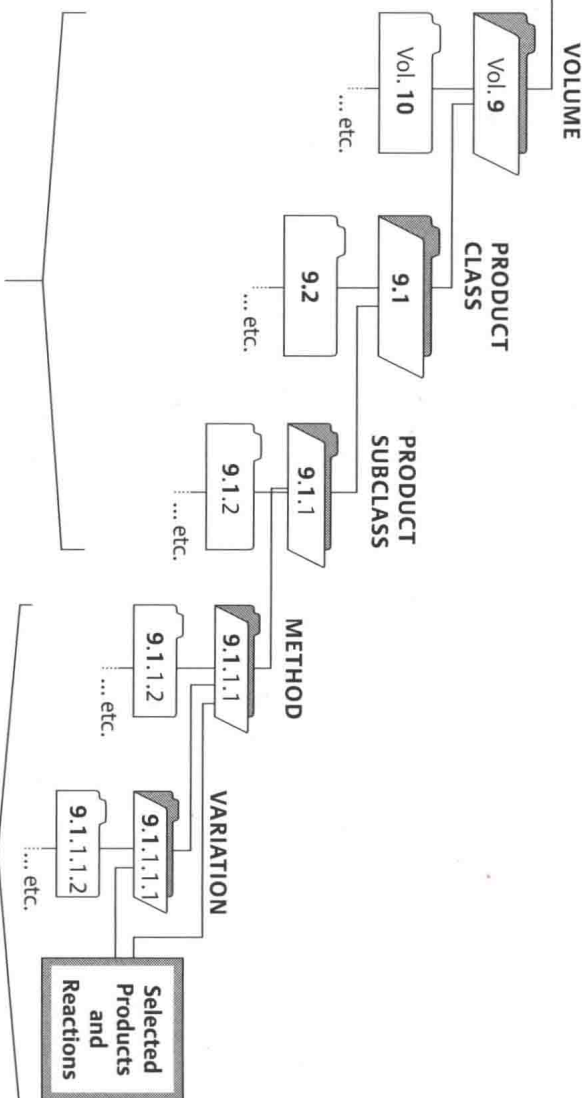
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Classification is **based on the product**, with all products belonging to one of six broad-ranging categories. All products occupy a strict hierarchical position in Science of Synthesis, defined according to the classification principles*. Products 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 alcohols are covered in Categories 3, 4, and 5, respectively).

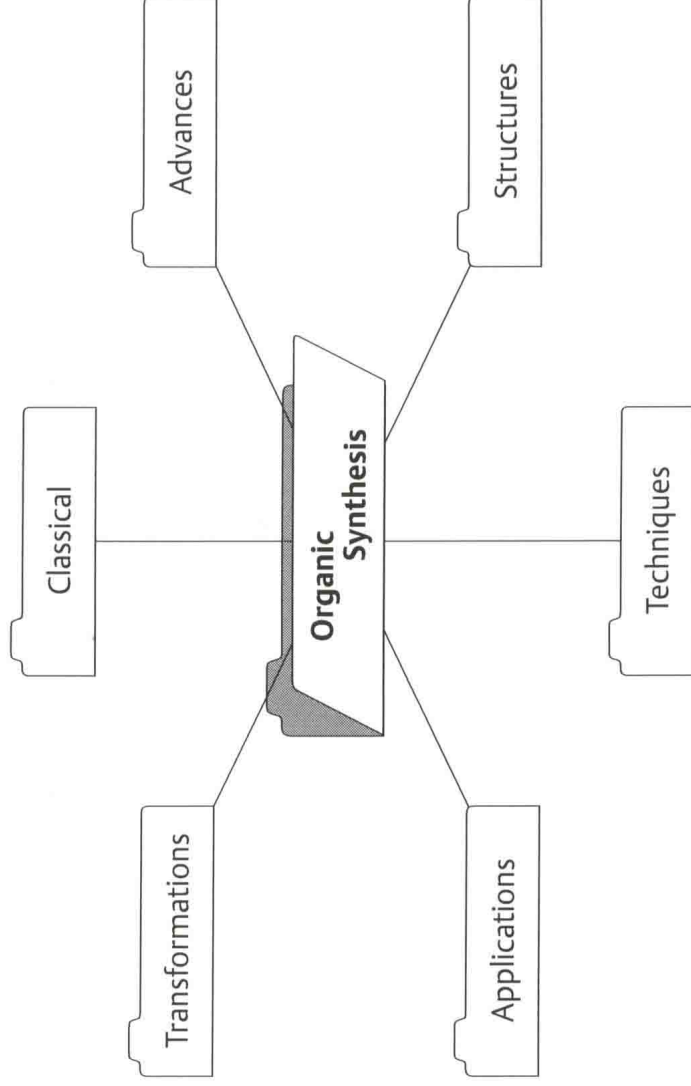


Each category is subdivided into volumes (see opposing page), each of which is devoted to discrete groupings of compounds called **product classes** (e.g., "Thiophenes" is Product Class 10 of Volume 9). Product classes may be further subdivided into **product subclasses**, (e.g., "Thiophene 1,1-Dioxides" 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.

Science of Synthesis Reference Library

The **Science of Synthesis Reference Library** comprises volumes covering special topics of organic chemistry in a modular fashion, with six main classifications: (1) Classical, (2) Transformations, (4) Advances, (5) Structures, and (6) Techniques. Volumes in the **Science of Synthesis Reference Library** focus on subjects of particular current interest with content that is evaluated by experts in their field. **Science of Synthesis**, including the **Knowledge Updates** and the **Reference Library**, is the complete information source for the modern synthetic chemist.



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

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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.

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Science of Synthesis Reference Library

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.)

Volume Editors' Preface

Metal-catalyzed reactions, especially cyclizations, remain the most useful methods for the efficient construction of cyclic compounds and thus have continuously attracted attention. These methodologies have also been comprehensively applied as the key steps in various novel strategies for the synthesis of natural products and drug molecules. Many new discoveries and advances have been reported, which provide new tools for synthetic organic chemists, medicinal chemists, and even materials chemists. A timely summary is now required of the well-established advances that will shape the future development of this field and its application. On the basis of these considerations, the Editorial Board of *Science of Synthesis* planned two volumes in the Reference Library that focus on metal-catalyzed cyclization reactions. After a careful selection made by the Volume Editors, some of the most significant and practical metal-catalyzed reactions for modern organic synthesis are presented. The organization of these two volumes is based on the types of reaction, which mainly include metal-catalyzed C—C, C—O, and C—N bond formations, as well as epoxidation, aziridination, cyclopropanation, Pauson–Khand reactions, cycloadditions, radical reactions, and metathesis. We hope that these volumes can serve as a reference work for chemists in related areas to inspire future research and the development of new applications.

We would like to take this opportunity to express our sincere thanks for the support and contributions from all of the outstanding authors; without their dedication and professionalism, this project would not have been possible. We are also grateful to Alex Russell and Joe P. Richmond, scientific editors at *Science of Synthesis*, who solved a lot of problems to enable the project to proceed smoothly over the past two and a half years. It has been a very pleasant journey to work with the editorial team at Thieme, especially Michaela Frey and Guido F. Herrmann. We appreciate the professional spirit and passion of all members of this team, which have brought the manuscripts together into a two-volume set.

Volume Editors

Shengming Ma and Shuanhu Gao

Shanghai, May 2016

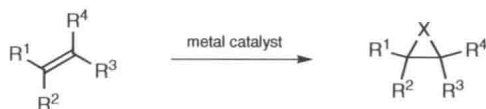
Abstracts

p 1

2.1 Epoxidation and Aziridination Reactions

F. Xia and S. Ye

Due to the strain associated with three-membered rings, epoxides and aziridines react with various nucleophiles to give 1,2-difunctionalized products. This makes them valuable intermediates in organic synthesis, including in the synthesis of bioactive natural and nonnatural compounds. This chapter summarizes recent advances in metal-catalyzed epoxidation and aziridination reactions of alkenes, as well as their synthetic applications.



$X = O, NR^1$

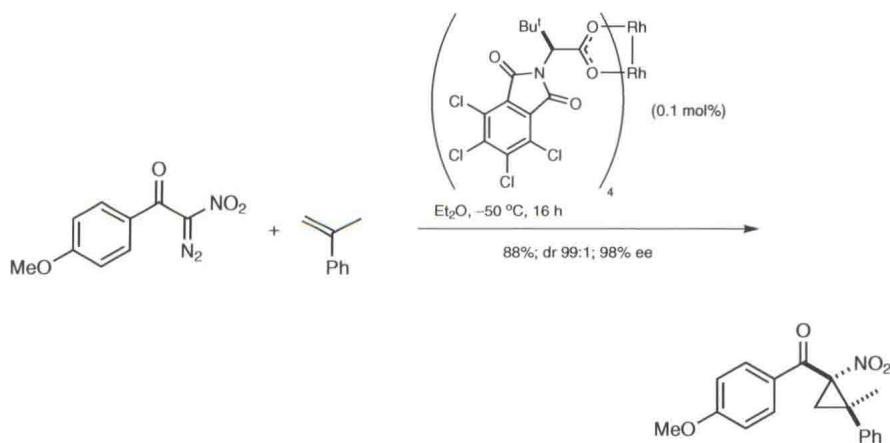
Keywords: epoxidation • aziridination • epoxides • aziridines • alkenes • metal catalysis • cyclization • enantioselectivity • diastereoselectivity • asymmetric synthesis

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2.2 Metal-Catalyzed Cyclopropanation

L. K. B. Garve and D. B. Werz

This chapter describes the most important metal-catalyzed methods to generate cyclopropanes, the smallest class of cycloalkanes. In the past fifty years, the use of metals in combination with chiral ligands for diastereo- and enantiodiscrimination in cyclopropane synthesis has been intensively studied. Two main approaches have emerged. Utilizing carbenes in the form of metal-carbene complexes has led to a renaissance of three-membered-rings in organic synthesis. In another approach, metal cations such as gold(I) and platinum(II) interact with alkynes, forming novel cyclopropane motifs. Finally, further metal-catalyzed cyclopropanations are mentioned.



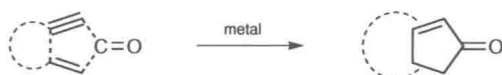
Keywords: cyclopropanes • three-membered rings • metal-catalyzed cyclopropanation • asymmetric cyclopropanation • carbenes • metal-carbene complexes • Kulinkovich cyclopropanation • enynes • copper • rhodium • cobalt • iridium • ruthenium • iron • palladium • gold • platinum • titanium • bicyclic molecules

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2.3 Pauson–Khand Reactions

G. Domínguez and J. Pérez-Castells

The Pauson–Khand (2+2+1) cycloaddition (PKR) is one of the best ways to construct a cyclopentenone. In this review, standard procedures to perform both stoichiometric and catalytic Pauson–Khand reactions are presented. These include the use of homo- and heterogeneous catalysts as well as different promoters. Asymmetric versions are described, as are cascade processes where the Pauson–Khand reaction is combined with other transformations. The chapter ends with a summary of representative total syntheses of natural products where a Pauson–Khand reaction is used as the key step.



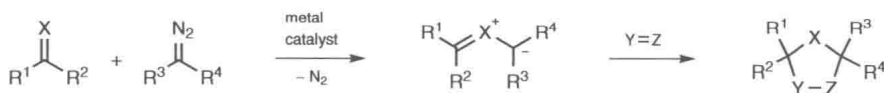
Keywords: Pauson–Khand • cycloaddition • transition-metal catalysis • stereoselectivity • asymmetric synthesis • cobalt • rhodium • iridium • heterogeneous catalysis • cascade synthesis • total synthesis

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2.4 1,3-Dipolar Cycloadditions Involving Carbonyl or Azomethine Ylides

X. Xu and W. Hu

Carbonyl ylides, which behave as active 1,3-dipole species, have found numerous applications in organic synthesis, especially in the formation of five-membered heterocycles. Among the versatile transformations of carbonyl ylides, 1,3-dipolar cycloadditions with π -bonds, including (3+2)-cycloaddition reactions with carbon–carbon π -bonds, aldehydes, and imines, are ubiquitous and important reactions. This chapter focuses on recent advances in these catalytic (3+2)-cycloaddition reactions and the examples presented emphasize the chemo-, diastereo-, and enantiocontrol that can be achieved. Also described are selected examples of cycloaddition reactions with azomethine ylides, which behave with similar reactivity to carbonyl ylides, to give the corresponding N-heterocycles. In addition, some selected applications of these (3+2)-cycloaddition reactions in natural product synthesis are highlighted.



X = O, NR⁵; Y = Z = aldehyde, ketone, alkene, alkyne, imine, etc.

Keywords: (3+2) cycloaddition • carbonyl ylides • azomethine ylides • 1,3-dipoles • diazo compounds • chiral dirhodium carboxylates • heterocycles • five-membered rings • natural product synthesis • asymmetric catalysis