Stereoselective Synthesis

Stereoselective Reactions of Carbon–Carbon Double Bonds

Volume Editors
J. G. de Vries
P. A. Evans
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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 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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**Organizational Structure of Science of Synthesis**

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* A complete description of the full classification principles can be found in the Science of Synthesis Guidebook.
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) Advances, (3) Transformations, (4) Applications, (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
As the pace and breadth of research intensifies, organic synthesis is playing an increasing-ly central role in the discovery process within all imaginable areas of science: from pharmaceu-ticals, 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.

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

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July 2010
Remarkable advancements in stereoselective synthesis have occurred over the past half-century. For decades, the Diels–Alder reaction was perhaps the only reaction providing reliably high and predictable stereoselectivity with broadly applicable efficacy. Subsequent developments in catalytic asymmetric hydrogenations and oxidations of alkenes, asymmetric hydroboration, and diastereoselective/enantioselective aldol reactions, among others, opened the floodgates to a host of highly tuned reactions that provided access to compounds in stunningly high diastereo- and enantioselectivities. This evolution was alluded to in the preface to *Houben–Weyl, Vol. E 21 (Stereoselective Synthesis*, published in 1995), wherein Helmchen, Hoffmann, Mulzer, and Schaumann pointed to the enormous progress in stereoselectivity made in the 20 years prior to their extraordinary contribution.

In the intervening 15 years, one can see that further advancements have been, if anything, even more breathtakingly impressive. Whereas in the 1970s a 4:1 stereoselectivity in any given reaction might have been acceptable, if not remarkable, and in the 1990s the goal of 20:1 stereoselectivity was achieved in pockets of transformations of variable scope, in 2010 anything less than 20:1 stereoselectivity across a wide range of transformations and reacting partners is now decidedly unacceptable.

These many advancements called for an update that was timely, state-of-the-art, and focused on those modern methods likely to influence the course of organic synthesis for the foreseeable future. The result is *Stereoselective Synthesis*, a part of the *Science of Synthesis Reference Library*. *Stereoselective Synthesis* is a major reference work that critically reviews the status of the discipline and serves as a foundation to forge the future of the field. Although the original *Stereoselective Synthesis* focused largely on stoichiometric methods, the increasing significance of catalytic processes has transformed the field. This latest version of *Stereoselective Synthesis* reflects and highlights the stunning advancements in these many catalytic methods (metal-based, organocatalytic, or enzymatic), in addition to reemphasizing the importance of stoichiometric transformations.

Unlike other reference works, *Stereoselective Synthesis* is not a comprehensive review or treatise, but rather a critical selection of those synthetic methods that are viewed by distinguished experts as most significant. Typical or general experimental procedures for the methods have been carefully selected. In evaluating protocols for inclusion, the authors were asked to consider yields, selectivities, breadth of applicability, atom economy, robustness, scalability, and environmental impact. The result is a snapshot of the best, most useful synthetic methods available for constructing a wide range of important organic substructures.

The organization of *Stereoselective Synthesis* is based on synthetic methods, which are arranged according to the type of reaction. The contributions have been divided into three volumes. Volume 1 considers stereoselective reactions of carbon—carbon double bonds. In the second volume, stereoselective reactions of carbonyl and imine groups have been collected. The third volume discusses pericyclic reactions, cross-coupling reactions, and reactions taking place by C–H and C–X activation. Each chapter within these volumes covers a specific synthetic method.
The Editors have benefited tremendously from the expertise and dedicated efforts of all of the authors who have devoted their valuable time and energy to participate in this unique contribution. We thank all of these individuals, as well as the editorial staff in Stuttgart, for the outstanding efforts they have made throughout the entire publication process, making Stereoselective Synthesis a gold standard in Thieme’s Science of Synthesis reference series.

Volume Editors

J.G. de Vries (Geleen, the Netherlands)
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October 2010
Stereoselective Synthesis Volumes

Stereoselective Synthesis 1
**Stereoselective Reactions of Carbon—Carbon Double Bonds**
*Volume Editor: J. G. de Vries*

Stereoselective Synthesis 2
**Stereoselective Reactions of Carbonyl and Imino Groups**
*Volume Editor: G. A. Molander*

Stereoselective Synthesis 3
**Stereoselective Pericyclic Reactions, Cross Coupling, and C—H and C—X Activation**
*Volume Editor: P. A. Evans*
Abstracts

1.1 Dihydroxylation, Aminohydroxylation, Diamination, and Dibromination of Carbon—Carbon Double Bonds
K. Muñiz

Direct oxidative transformation of alkenes into the corresponding 1,2-difunctionalized derivatives represents a powerful tool for the introduction of heteroatoms. The formation of the two new C—X bonds can occur either within a concerted process or within stepwise transformations. In this review, standard procedures for oxidative alkene transformation, including dihydroxylation, ketohydroxylation, aminohydroxylation, and diamination, will be presented. Emphasis is placed on synthesis, and mechanistic details are only given in order to underline the conceptual background of a given transformation.

\[ \text{Os, Pd, or Cu reagent (cat.)} \]
\[ \text{co-oxidant, chiral ligand} \]

\[ X_1/X_2 = \text{OH/OH, OR}_5/\text{NHR}_6, \text{Br/Br, NR}_5^2/\text{NR}_6^2 \]

Keywords: alkenes • dihydroxylation • ketohydroxylation • dibromination • aminohydroxylation • diamination • 1,2-diols • \( \beta \)-amino alcohols • 1,2-diamines • osmium • oxidation • palladium • transition-metal catalysis • cinchona alkaloid ligands

1.2 Epoxidation of Carbon—Carbon Double Bonds
K. Matsumoto, T. Katsuki, and I. W. C. E. Arends

Catalytic enantioselective epoxidation of C=C bonds, including allylic alcohols and non-functionalized alkenes, using chiral transition-metal catalysts and organocatalysts as well as enzymes are reviewed in this chapter.

Keywords: alkenes • allylic alcohols • asymmetric catalysis • epoxidation • epoxy compounds • oxiranes • enzyme catalysis

1.3 Epoxidation of Enones by Nucleophilic Oxidation
S. Colonna and D. Perdicchia

Efficient asymmetric techniques for the epoxidation of \( \alpha,\beta \)-unsaturated ketones, in the presence of hydrogen peroxide, hypochlorite, or an organic peroxide as an oxygen source under basic conditions, are described. Considerable attention has been paid to asymmet-
ric variants of this epoxidation reaction using chiral metal-based or organic catalysts. The epoxidation of enones using nucleophilic oxidants is one of the most important reactions in organic synthesis because the corresponding enantiomerically enriched epoxides can be converted into a variety of useful enantioenriched intermediates.

**Keywords:** epoxidation of enones • $\alpha,\beta$-unsaturated ketones • hydrogen peroxide • alkyl peroxides • Weitz–Scheffer reaction • Julià–Colonna epoxidation • poly(amino acids) • enantioselectivity • diastereoselectivity • phase-transfer catalysis • scale-up • mechanistic considerations • chiral-ligand metal peroxide systems • organocatalyzed epoxidation • cinchona alkaloid based catalyst • chiral dioxiranes

### 1.4 Aziridination

*H. Muchalski and J. N. Johnston*

Aziridines are the smallest carbocycles containing one nitrogen atom. Due to their angle strain, they exhibit a synthetically useful balance between stability and reactivity. Thus, they are often employed as versatile intermediates. This chapter focuses on stereoselective synthesis of aziridines from alkenes using a variety of methods that include both stoichiometric and catalytic reactions.

**Keywords:** asymmetric catalysis • alkenes • azides • aziridination • aziridines • bis(4,5-di-hydrooxazole) ligands • chiral auxiliaries • metal complexes • diastereoselectivity • enantioselectivity • heterocycles • iminiodinanes • nitriles • nitrogen heterocycles • sulfonamides • three-membered rings • zeolites • organocatalysis • heterogeneous catalysis

### 1.5 Hydrogenation of Carbon–Carbon Double Bonds

*D. Ager*

The asymmetric hydrogenation of C=C bonds is an extremely powerful method to introduce a stereogenic center with high enantioselectivity. Although there is no general catalyst system, many types of functionalized and some nonfunctionalized alkenes can be reduced. The method has been used at industrial scale, as exemplified by the production of $\alpha$- and $\beta$-amino acid derivatives, and 2-substituted alkanoic acids. There are many catalyst systems available allowing for this green approach to be applied to a wide range of substrates.

**Keywords:** $\alpha$-amino acids • $\beta$-amino acids • asymmetric catalysis • amides • carboxylic acids • hydrogenation • rhodium catalysts • ruthenium catalysts • iridium catalysts