Knowledge Updates 2012/1

Volume Editors
J. J. Li
I. Marek
M. North
M. Oestreich
E. Schaumann
S. M. Weinreb
M. Yus

Editorial Board
E. M. Carreira
C. P. Decicco
A. Fuerstner
G. A. Molander
P. J. Reider
E. Schaumann
M. Shibasaki
E. J. Thomas
B. M. Trost
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. For example, "Thiophenes" is Product Class 10 of Volume 9. Product classes may be further subdivided into product subclasses. For example, "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.

Selected description of the full classification principles can be found in the Science of Synthesis Guidebook.
### Table of Contents

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>UPDATED VOLUMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Organometallics (Vols 1–8)</td>
</tr>
<tr>
<td>2</td>
<td>Hetarenes (Vols 9–17)</td>
</tr>
<tr>
<td>3</td>
<td>4/3 C–X bonds (Vols 18–24)</td>
</tr>
<tr>
<td>4</td>
<td>2 C–X bonds (Vols 25–33)</td>
</tr>
<tr>
<td>5</td>
<td>1 C–X bond (Vols 34–42)</td>
</tr>
<tr>
<td>6</td>
<td>All C bonds (Vols 43–48)</td>
</tr>
</tbody>
</table>

1. Organometallics (Vols 1–8)
2. Hetarenes (Vols 9–17)
3. 4/3 C–X bonds (Vols 18–24)
4. 2 C–X bonds (Vols 25–33)
5. 1 C–X bond (Vols 34–42)
6. All C bonds (Vols 43–48)

2. Compounds of Groups 7–3 (Mn⋯, Cr⋯, V⋯, Ti⋯, Sc⋯, La⋯, Ac⋯)
4. Compounds of Group 15 (As, Sb, Bi) and Silicon Compounds
8a. Compounds of Group 1 (Li⋯, Cs)
16. Six-Membered Hetarenes with Two Identical Heteroatoms
17. Six-Membered Hetarenes with Two Unlike or More than Two Heteroatoms and Fully Unsaturated Larger-Ring Heterocycles
19. Three Carbon–Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives
27. Heteroatom Analogues of Aldehydes and Ketones

* 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
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.

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**

E. M. Carreira (Zurich, Switzerland)  
C. P. Decicco (Princeton, USA)  
A. Fuerstner (Muelheim, Germany)  
G. A. Molander (Philadelphia, USA)  
P. J. Reider (Princeton, USA)  
E. Schaumann (Clausthal-Zellerfeld, Germany)  
M. Shibasaki (Tokyo, Japan)  
E. J. Thomas (Manchester, UK)  
B. M. Trost (Stanford, USA)

July 2010
Organometallic Complexes of Titanium (Update 1)
P. Bertus, F. Boeda, and M. S. M. Pearson-Long

This chapter is an update to the earlier Science of Synthesis contribution describing the synthesis and application of titanium complexes in organic synthesis. This update focuses on the synthesis of cyclopropane derivatives using titanium reagents, with particular emphasis on the preparation of cyclopropanols from carboxylic esters (Kulinkovich reaction) and cyclopropylamines from carboxylic amides or nitriles.

Keywords: amides · bicyclic compounds · carbonates · cyclopropanes · cyclopropanols · cyclopropylamines · esters · Grignard reagents · imides · magnesium · nitriles · titanium
4.4.1 **Product Subclass 1: Disilenes**  
A. Meltzer and D. Scheschkewitz

The syntheses of stable and marginally stable compounds with Si=Si bonds, i.e. linear and cyclic disilenes as well as tetrasilabutadienes, are reviewed. Typical procedures are described including detailed special requirements and precautions.

**Keywords:** alkene analogues · coupling reactions · cyclic compounds · dehalogenation · disilenes · disilenides · disilynes · photolysis · reductive coupling · silanes · silicon compounds · silylenes · silyl halides · unsaturated compounds

---

8.1.31 **Functionalized Organolithiums by Ring Opening of Heterocycles**  
M. Yus and F. Foubelo

This manuscript describes the preparation of functionalized organolithium compounds by reductive opening of heterocycles and further reaction of these intermediates with electrophiles.

**Keywords:** activation of C—O bonds · alkali metal compounds · carbanions · carbon—metal bonds · heterocycles · lithiation · lithium compounds · radical ions · reductive cleavage

---

8.1.32 **Syntheses Mediated by α-Lithiated Epoxides and Aziridines**  
L. Degennaro, F. M. Perna, and S. Florio

Three-membered ring heterocycles such as epoxides and aziridines, whose structural motif occurs frequently in natural products and biologically active substances, are an uncommon combination of reactivity, synthetic flexibility, and atom economy. Readily accessible, also in enantioenriched form, they are mainly used as electrophiles, undergoing
highly regioselective ring-opening reactions when reacted with nucleophiles. There are, however, many other less conventional but useful reactions these small-ring heterocycles may undergo. This chapter surveys a selection of the most recent advances in the chemistry of α-lithiated epoxides and aziridines, which can be simply generated by treatment of the parent epoxide or aziridine with strong bases such as organolithiums or lithium amides. Such lithiated species are relatively stable and can be captured with a number of electrophiles to give more functionalized oxiranes and aziridines or undergo other transformations including 1,2-organo shifts to enolates, eliminative dimerization, β-elimination, intramolecular cyclopropanation onto a double bond (C=C insertion), transannular C—H insertion, and reductive alkylation.

Keywords: oxiranes · aziridines · small-ring heterocycles · α-lithiation · carbenoids · organolithiums · configurational stability · asymmetric synthesis
Transition-metal-catalyzed reactions with organolithiums are a useful tool for the formation of carbon–carbon bonds. This chapter covers reactions with organolithium compounds catalyzed by various transition metals such as copper, palladium, or iron.

**Keywords:** lithium compounds · cross coupling · copper catalysis · palladium catalysis · iron catalysis · carbolithiation · asymmetric catalysis

1,4-Dioxins and Benzo- and Dibenzo-Fused Derivatives

This manuscript concerns three types of compound: 1,4-dioxins, 1,4-benzodioxins, and dibenzo[b,e][1,4]dioxins, and covers recent syntheses of these substrates that have not previously been highlighted in Section 16.2 of *Science of Synthesis*.

**Keywords:** aromatization · base-induced coupling · 1,4-benzodioxins · Diels–Alder reaction · 1,4-dioxins · dibenzo[b,e][1,4]dioxins · lithium–halogen exchange · ring-closing metathesis · ring-closure reactions · Stille coupling · substituent modification · Vilsmeier reaction

1,2-Dithiins

1,2-Dithiins are six-membered rings with two double bonds and two sulfur atoms within the ring. Related compounds include 3,6-dihydro-1,2-dithiins, 1,4-dihydrobenzo[d][1,2]dithiins, and dibenzo[c,e][1,2]dithiins. A wide variety of compounds observed in nature are found to contain the dithiin motif and the group is implicated in a wide range of biological activity. 1,2-Dithiins have also been used in other fields, for example as organic tran-
sistors and ligands for transition metals. This section updates previously published material in *Science of Synthesis* and in particular focuses on synthesis by ring-closure reactions and applications of the group in reactions with transition metals, Lewis acids, diazo compounds, alkynes, and enzymes.

Keywords: cyclization · diazo compounds · dibenzo[c,e][1,2]dithiins · Diels–Alder reaction · 1,4-dihydrobenzo[d][1,2]dithiins · 3,6-dihydro-1,2-dithiins · dimerization · 1,2-dithianes · 1,2-dithiins · enzymes · Lewis acids · phase-transfer catalysis · photolysis · ring-closing metathesis · ring-closure reactions · sulfonation · transition metals

**17.4.5 Oxepins**  
*J. Hong*

This manuscript is an update to the earlier *Science of Synthesis* contribution describing methods for the synthesis of oxepins. It focuses on the literature published in the period 2003–2011.

Keywords: cycloaddition · dehydrogenation · isomerization · Michael addition · nucleophilic substitution · ring expansion
17.4.5. Benzoxepins

J. Hong

This manuscript is an update to the earlier Science of Synthesis contribution describing methods for the synthesis of benzoxepins. It focuses on the literature published in the period 2003–2011.

Keywords: annulation · condensation reactions · cyclization · cyclocondensation · rearrangement · ring closure · ring expansion · transition metals

17.4.5.5 Azepines, Cyclopentazepines, and Phosphorus Analogues

J. E. Camp

This manuscript is an update of the earlier Science of Synthesis contribution describing methods for the synthesis of fully unsaturated azepines, cyclopentazepines, and their phosphorus analogues. It focuses on the literature published between 2003 and 2010.

Keywords: azepines · cyclopentazepines · electrocyclization · Diels–Alder · photolytic decomposition · rearrangement · C-amination · C-alkoxylation · Friedel–Crafts · azepinium ion