Science of Synthesis

Knowledge Updates 2021/3

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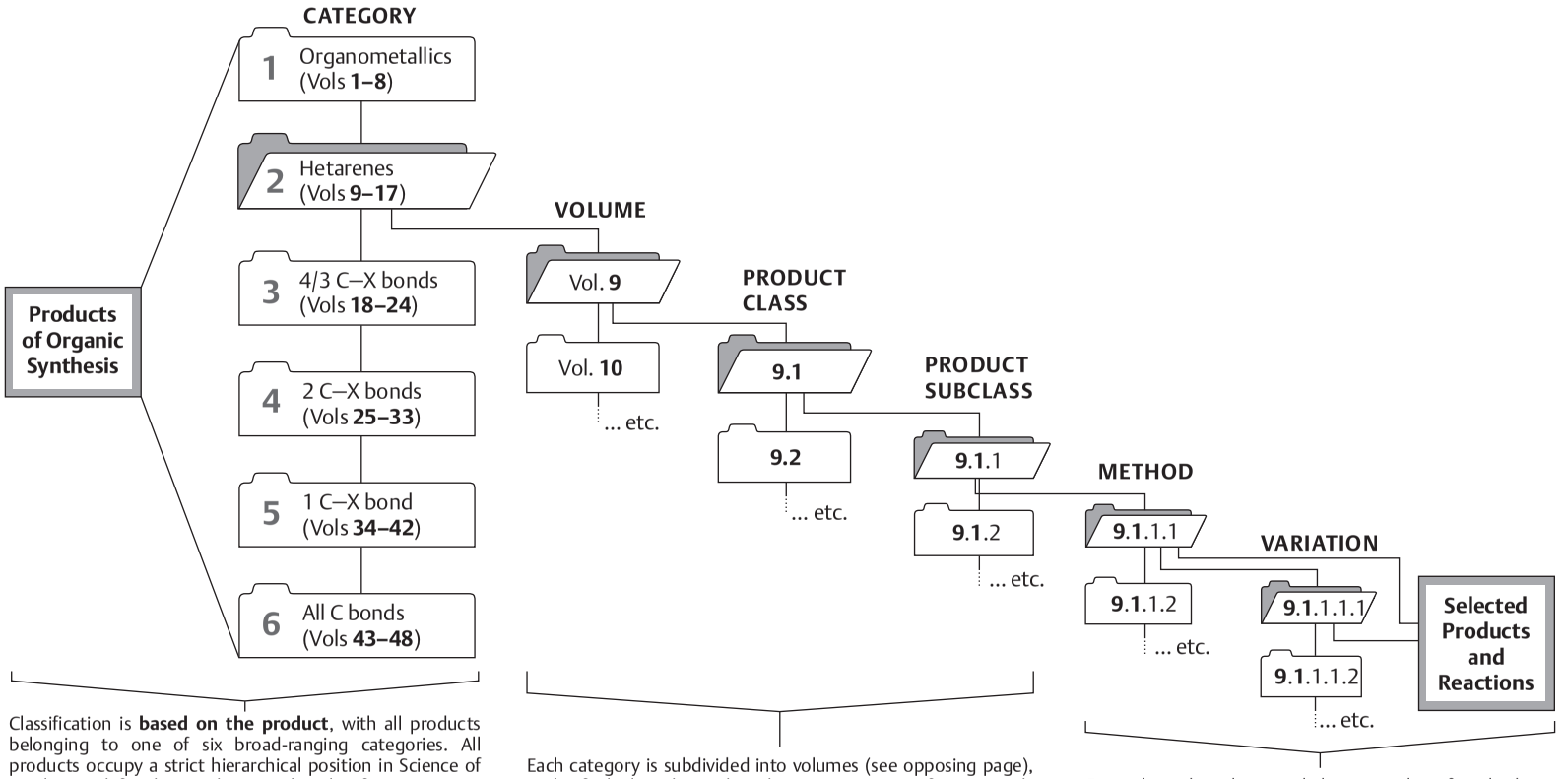
Organizational Structure of Science of Synthesis*

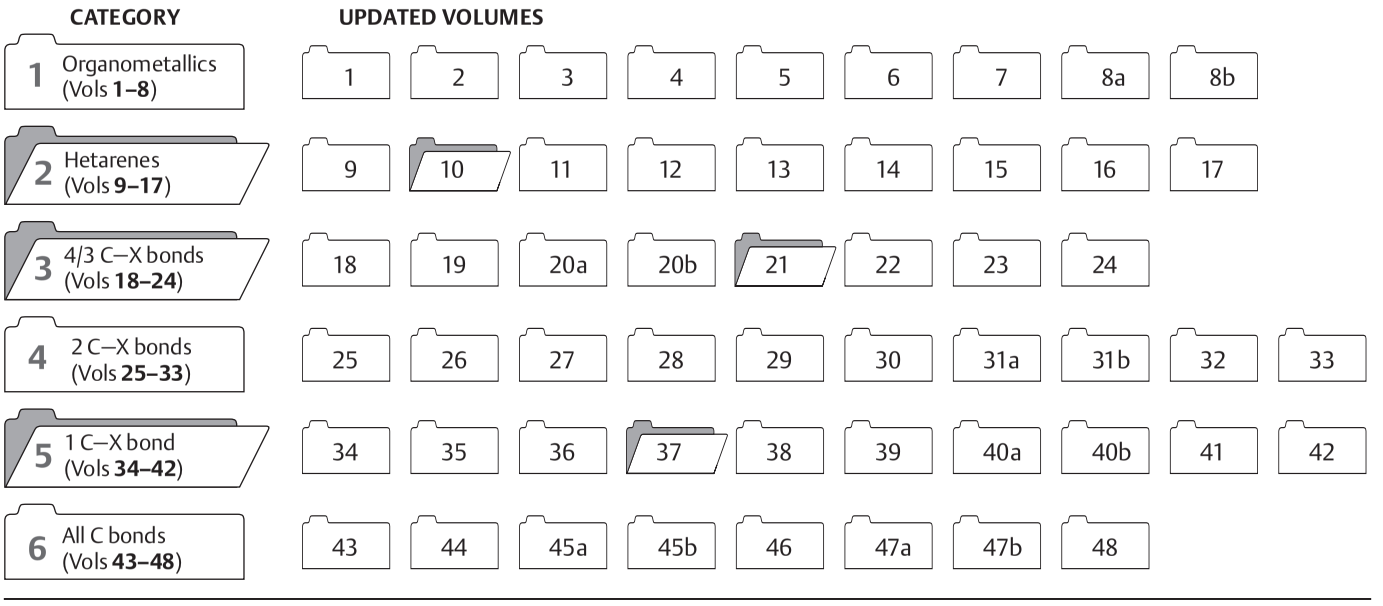
* A complete description of the full classification principles can be found in the **Science of Synthesis Guidebook.**



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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37 Ethers

* 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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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.

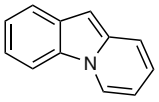
The Editorial Board September 2018

Abstracts

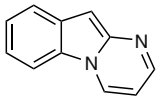
New p 1

10.24 **Product Class 24: Pyrido[1,2-*a*]indoles and Azapyrido[1,2-*a*]indoles**
P. A. Harris

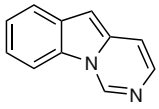
This introductory chapter describes the various pyrido[1,2-*a*]indole and azapyrido[1,2-*a*]indole ring systems that will be covered in subsequent chapters. Biologically active indole alkaloids containing these structural motifs are also detailed, the most well-known of which is the toxic alkaloid strychnine.



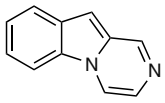
pyrido[1,2-*a*]indole



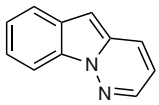
pyrimido[1,2-*a*]indole



pyrimido[1,6-*a*]indole



pyrazino[1,2-*a*]indole



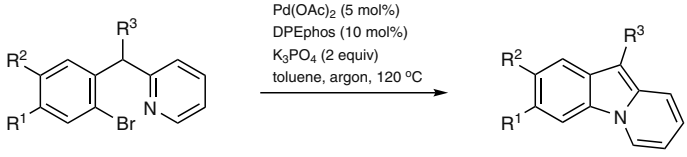
pyridazino[1,6-*a*]indole

Keywords: pyrido[1,2-*a*]indoles · pyrimido[1,2-*a*]indoles · pyrimido[1,6-*a*]indoles · pyrazino[1,2-*a*]indoles · pyridazino[1,6-*a*]indoles

New p 5

10.24.1 **Product Subclass 1: Pyrido[1,2-*a*]indoles and Related Benzo-Fused Ring Systems**
P. A. Harris

This review describes methods for the synthesis of pyrido[1,2-*a*]indoles, as well as the related benzo-fused ring systems indolo[1,2-*a*]quinolines, indolo[1,2-*b*]isoquinolines, indolo[2,1-*a*]isoquinolines, and indolo[1,2-*f*]phenanthridines. The most common routes to access these ring systems involve a variety of transition-metal-catalyzed cyclizations, but alternative approaches are also covered.



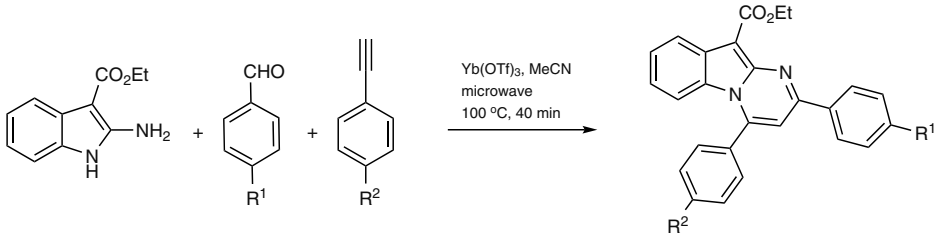
Keywords: pyrido[1,2-*a*]indoles · indolo[1,2-*a*]quinolines · indolo[1,2-*b*]isoquinolines · indolo[2,1-*a*]isoquinolines · indolo[1,2-*f*]phenanthridines · cyclization

New p 85

10.24.2 **Product Subclass 2: Pyrimido[1,2-*a*]indoles and Related Benzo-Fused Ring Systems**

P. A. Harris

Methods for the synthesis of pyrimido[1,2-*a*]indoles and the related indolo[1,2-*a*]quinazoline and indolo[2,1-*b*]quinazoline ring systems are reviewed in this chapter. Although limited reports have been published to date, a variety of differing approaches to these heterocycles have been described.



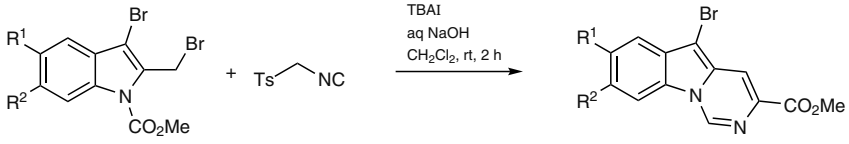
Keywords: pyrimido[1,2-*a*]indoles · indolo[1,2-*a*]quinazolines · indolo[2,1-*b*]quinazolines · cyclization

New p 109

10.24.3 **Product Subclass 3: Pyrimido[1,6-*a*]indoles and Related Benzo-Fused Ring Systems**

P. A. Harris

Methods for the synthesis of pyrimido[1,6-*a*]indoles, indolo[1,2-*c*]quinazolines, and the less-common pyrido[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-ium ring systems are reviewed in this chapter. Indolo[1,2-*c*]quinazolines are the most represented in the literature, most often being accessed via cyclization of either 2-(2-aminoaryl)indoles or 2-(2-haloaryl)indoles, although a variety of additional approaches are described.



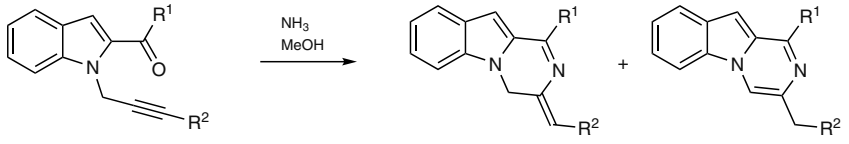
Keywords: pyrimido[1,6-*a*]indoles · indolo[1,2-*c*]quinazolines · pyrido[2′,1′:2,3]pyrimido[1,6-*a*]indol-5-ium salts · cyclization

New p 145

10.24.4 **Product Subclass 4: Pyrazino[1,2-*a*]indoles and Related Benzo-Fused Ring Systems**

P. A. Harris

The synthesis of pyrazino[1,2-*a*]indoles and related indolo[1,2-*a*]quinoxalines and pyrido[2′,1′:3,4]pyrazino[1,2-*a*]indol-5-ium salts are reviewed in this chapter. The most common routes to pyrazino[1,2-*a*]indoles involve cyclization of indole derivatives containing a formyl, keto, ester, or nitrile function at the 2-position. Indolo[1,2-*a*]quinoxalines are most readily accessed via cyclization of 1-(aryl)-1*H*-indoles, where the aryl group is substituted at the 2-position by either amino, iodo, or nitro functionality.



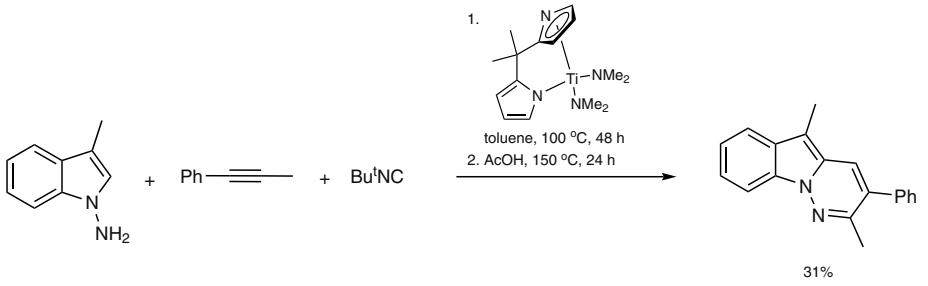
Keywords: pyrazino[1,2-*a*]indoles · indolo[1,2-*a*]quinoxalines · pyrido[2′,1′:3,4]pyrazino[1,2-*a*]indol-5-ium salts · annulation · cyclization

New p 181

10.24.5 **Product Subclass 5: Pyridazino[1,6-*a*]indoles and Related Benzo-Fused Ring Systems**

P. A. Harris

The synthesis of pyridazino[1,6-*a*]indoles, as well as the related indolo[1,2-*b*]cinnolines and indolo[2,1-*a*]phthalazines, are reviewed in this chapter. The most utilized methods to access pyridazino[1,6-*a*]indoles involve annulation of 1*H*-indol-1-amine derivatives.



Keywords: pyridazino[1,6-*a*]indoles · indolo[1,2-*b*]cinnolines · indolo[2,1-*a*]phthalazines · annulation · cyclization

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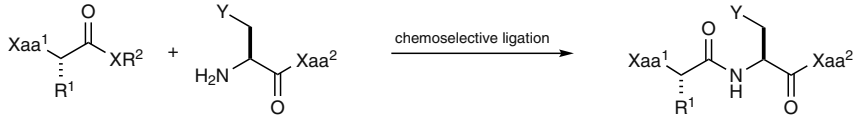
21.11.7 **Chemoselective Ligation Methods Based on the Concept of Native Chemical Ligation**

L. R. Malins and R. J. Payne

This chapter extends from the earlier *Science of Synthesis* contribution on peptide synthesis (Section 21.11) and focuses on recent developments in chemoselective ligation chemistry based on the logic of native chemical ligation. Synthetic strategies that broaden the scope and versatility of the ligation reaction and that have been widely adopted for the preparation of homogeneous peptides and proteins are highlighted. Methods enabling the efficient preparation of peptide ligation precursors are also included in this chapter.



X = S, Se; Y = SH, SeH, –Se-Se–

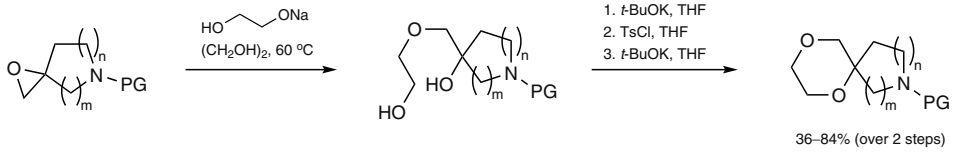
Keywords: ligation · cysteine · selenocysteine · desulfurization · deselenization · acyl shift · peptides · proteins · amides · solid-phase peptide synthesis · peptide coupling

New p 243

37.9 **Product Class 9: 1,4-Dioxanes**

B. V. Vashchenko and O. O. Grygorenko

In this chapter, the synthesis of substituted 1,4-dioxanes and their saturated bridged, fused, and spirocyclic derivatives is discussed for the first time in *Science of Synthesis*. Partially unsaturated compounds, in particular benzo, 2-oxo, and related derivatives, are excluded from this review. Methods based on the construction of the 1,4-dioxane core, as well as on functionalization of the parent 1,4-dioxane and 2,3-dihydro-1,4-dioxine are presented.



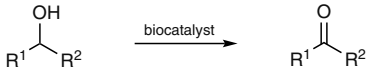
Keywords: 1,4-dioxanes · ethers · oxygen heterocycles · carbon—oxygen bonds · oxiranes · diols · cyclization · Williamson ether synthesis · radical reactions · acetalization · cycloaddition · halogen addition reactions

New p 429

3.3.4 **Biocatalytic Oxidation of Alcohols: An Overview**

F. Hollmann

This chapter provides a representative, but non-exhaustive, overview of biocatalytic methods for the oxidation of alcohols to the corresponding carbonyl products. Enzymes represent an attractive alternative to established oxidation catalysts, especially if mild reaction conditions are needed or if regio- or stereoselectivity are desirable.



Keywords: alcohol dehydrogenases · alcohol oxidases · alcohol oxidation · aldehyde synthesis · biocatalysis · carboxylate synthesis · ketone synthesis · oxidative kinetic resolution · regioselective oxidation · stereoselective oxidation

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P. A. Harris

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10.24.5 **Product Subclass 5: Pyridazino[1,6-*a*]indoles and Related Benzo-Fused Ring Systems** New
P. A. Harris

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