Handbook of Chiral Chemicals

Handbook of CHIRAL CHEMICALS

edited by

David J. Ager

NSC Technologies
Mount Prospect, Illinois

MARCEL DEKKER, INC. NEW YORK · BASEL

ISBN: 0-8247-1058-4

This book is printed on acid-free paper.

Headquarters
Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution
Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 44-61-261-8482; fax: 44-61-261-8896

World Wide Web
http://www.dekker.com

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Handbook of CHIRAL CHEMICALS

Preface

The purpose of this book is to highlight the problems associated with the production of chiral compounds on a commercial scale. With the movement by pharmaceutical companies to develop single enantiomers as drug candidates, the focus has turned to problems associated with this subclass of organic synthesis. The major classes of natural products are also discussed since the stereogenic center can be derived from nature through the use of "chiral pool" starting materials.

Despite the explosion of asymmetric methods over the past 20 years, very few can be performed at scale due to limitations in cost, thermodynamics, or equipment. The major reactions that have been used are covered in this volume. Resolution, whether chemical or enzymatic, still holds a key position. This is highlighted by a short discussion of the best-selling compounds of 1996. Many are obtained either by resolution or by fermentation methods.

The most mature chemical method is asymmetric reductions and hydrogenations. This is highlighted by chapters on the uses of new ligands for hydrogenation and hydride-reducing agents. Although we have made considerable advances in this area, the general catalyst is still elusive. The struggle goes on to identify the ultimate hydrogenation catalyst; for example, the use of enzymes and biological systems for the production of chiral compounds continues to increase at an almost explosive rate. Now that we have learned to manipulate nature's catalysts, this area will continue to grow and become more important.

The chapter on amino acid derivatives is the result of a considerable amount of research on the new methods for the preparation of unnatural amino acids and derivatives at scale. Their findings carry over into other classes of compounds, but the principles are highlighted exclusively within this field.

The chapters are grouped by topic. The first three are an introduction and discussion of the requirements of sourcing chiral intermediates. Another chapter presents an overview of the current large-volume chiral compounds and how they are synthesized.

The next three chapters discuss how the key subclasses of the chiral pool

are obtained. The amino acid chapter is specific to the chiral pool materials as there are more examples of amino acid syntheses contained within other chapters.

The next eight chapters cover methods that can be used to introduce or control stereogenic centers. In some cases, such as asymmetric hydrogenations, the approach is well established and has been employed for the large-scale synthesis of a number of commercially important compounds. In other cases, such as pericyclic reactions, the potential exists, but has not yet been used. One chapter covers enzymatic methods, an area that seems to be becoming more important as we learn how to manipulate enzymes by allowing them to catalyze new reactions or take new substrates. The rush to market for pharmaceutical companies is forcing the chemical development time to be minimized. This is leading to large-scale usage of chiral auxiliaries.

The chapter on resolutions has a number of examples as illustrations showing that this methodology is still important to obtain chiral compounds. Although, ultimately, it may not be the most cost-effective method, it can provide material in a rapid manner, and can usually be scaled up. The introduction of large-scale chromatographic techniques, as well as the availability of a large number of enzymes that can be used to perform reactions on only one enantiomer, will ensure that this approach remains a useful tool in the future.

The remaining chapters discuss various examples and topics to augment other chapters and provide a perspective of the different methods available.

I would like to thank all the authors who contributed to this book and who have worked on it with me for the past few years. I would especially like to thank my colleagues at NSC Technologies for writing a number of the chapters and for having supplied numerous suggestions and ideas. Not only have they developed new methodology, but they have also proceeded to use it at scale within a very short timeframe. They continue to inspire me, as do many others working in the arena of asymmetric synthetic methodology.

David J. Ager

Contributors

DAVID J. AGER, PH.D. Fellow, NSC Technologies, Mount Prospect, Illinois

DAVID R. ALLEN, B.S. Senior Process Chemist, NSC Technologies, Mount Prospect, Illinois

MICHEL BULLIARD, PH.D. Research and Development Manager, PPG-SIPSY, Avrille, France

MARK J. BURK, PH.D. Head, ChiroTech Technology Limited, Chiroscience PIC., Cambridge, United Kingdom

MICHAEL B. EAST, PH.D. Senior Research Scientist, NSC Technologies, Mount Prospect, Illinois

IAN G. FOTHERINGHAM, PH.D. NSC Technologies, Mount Prospect, Illinois

SCOTT A. LANEMAN, PH.D. Senior Research Scientist, NSC Technologies, Mount Prospect, Illinois

WEIGUO LIU, PH.D. Senior Research Scientist, NSC Technologies, Mount Prospect, Illinois

DAVID P. PANTALEONE, PH.D. Group Leader, Protein Biochemistry, NSC Technologies, Mount Prospect, Illinois

DAVID R. SCHAAD, PH.D. Senior Research Scientist, Department of Chemical Process Development, NSC Technologies, Mount Prospect, Illinois

PAUL P. TAYLOR, PH.D. NSC Technologies, Mount Prospect, Illinois

GRAHAM J. TUCKER, B.SC. The R-S Directory, Kenley Chemicals, Kenley, Surrey, United Kingdom

BASIL J. WAKEFIELD, PH.D., D.SC. Chemicals Director, Ultrafine Chemicals, UFC Pharma, Manchester, United Kingdom

Contents

1

Introduction

DAVID J. AGER
NSC Technologies, Mount Prospect, Illinois

This book discusses various aspects of chiral fine chemicals, including their synthesis and uses at scale. There is an increasing awareness of the importance of chirality in biological molecules, as the two enantiomers can sometimes have different effects. [1–4].

In many respects, chiral compounds have been regarded as special entities within the fine chemical community. As we will see, the possession of chirality does not, in many respects, make the compound significantly more expensive to obtain. Methods for the preparation of optically active compounds have been known for well over 100 years (many based on biological processes). The basic chemistry to a substrate on which an asymmetric transformation is then performed can offer more challenges in terms of chemistry and cost optimization than the "exalted" asymmetric step.

1.1. CHIRALITY

The presence of a stereogenic center within a molecule can give rise to chirality. Unless a chemist performs an asymmetric synthesis, equal amounts of the two antipodes will be produced. To separate these, or to perform an asymmetric synthesis, a chiral agent has to be employed. This can increase the degree of complexity in obtaining a chiral compound in a pure form. However, nature has been kind and does provide some chiral compounds in relatively large amounts. Chirality does provide an additional problem that is sometimes not appreciated by those who work outside of the field: analysis of the final compound is often not a trivial undertaking.

1.2. CHIRAL POOL

Nature has provided a wide variety of chiral materials, some in great abundance. The functionality ranges from amino acids to carbohydrates to terpenes (Chapters 4–6). All of these classes of compounds are discussed in this book. Despite the breadth of functionality available from natural sources, very few compounds are available in optically pure form at large scale. Thus, incorporation of a "chiral pool" material into a synthesis can result in a multistep sequence. However, with the advent of synthetic methods that can be used at scale, new compounds are being added to the chiral pool, although they are only available in bulk by synthesis. When a chiral pool material is available at large scale, it is usually inexpensive. An example is provided by L-aspartic acid (Chapter 16), where the chiral material can be cheaper than the racemate (see also Chapter 15).

How some of these chiral pool materials have been incorporated into synthesis of biologically active compounds is illustrated in this book. In addition, chiral pool materials are often incorporated, albeit in derivatized form, into chiral reagents and ligands that allow for the transfer of chirality from a natural source into the desired target molecule.

1.3. CHIRAL REAGENTS

Chiral reagents allow for the transfer of chirality from the reagent to the prochiral substrate. Almost all of these reactions involve the conversion of an sp^2 carbon to an sp^3 center. For example, reductions of carbonyl compounds (Chapter 11), asymmetric hydrogenations (Chapter 9), and asymmetric oxidations of alkenes (Chapter 12) are all of this type. The reagents can be catalytic for the transformation they bring about, or stoichiometric. The former is usually preferred because it allows for chiral multiplication during the reaction—the original stereogenic center gives rise to many product stereocenters. This allows for the cost of an expensive catalyst to be spread over a large number of product molecules.

1.4. CHIRAL CATALYSTS

Considerable resources are being expended in the quest for new asymmetric catalysts for a wide variety of reactions (Chapter 9). In many cases, these catalysts are based on transition metals, where the ligands provide the chiral environment. However, as our understanding of biotransformations increases, coupled with our ability to produce mutant enzymes at scale, biocatalysts are beginning to become key components of our asymmetric synthetic tool box (Chapters 13 and 15).

1.4.1. Chemical Catalysts

The development of transition metal catalysts for the asymmetric reduction of functionalized alkenes allowed synthetic chemists to perform reactions with a stereochemical fidelity approaching that of nature (Chapter 9). We now have a number of reactions at our disposal that can be performed with chemical catalysts, and the number continues to grow. However, there are still problems associated with this approach because many catalysts have specific substrates requirements, often involving just one alkene isomer of the substrate. The chiral multiplication associated with use of a chiral catalyst often makes for attractive economical advantages. However, the discovery and development of a chemical catalyst to perform a specific transformation is often tedious, time consuming, and expensive. There are many reports of chiral ligands in the literature, for example, to perform asymmetric hydrogenation, yet very few have been used at scale (Chapter 9). This highlights the problem that there are few catalysts that can be considered general. As previously mentioned, the preparation of the substrate is often the expensive part of a sequence, especially with catalysts that have high turnover numbers and can be recycled.

1.4.2. Biological Catalysts

Biological catalysts have been used for asymmetric transformations in specific cases for a considerable period of time, excluding the chiral pool materials. However, until recently, the emphasis has been on resolutions with enzymes rather than asymmetric transformations (Chapter 13). With our increasing ability to produce mutant enzymes that have different or broad-spectrum activities compared with the wild types, the development of biological catalysts is poised for major development. In addition to high stereospecificities, an organism can be persuaded to perform more than one step in the overall reaction sequence, and may even make the substrate (Chapter 15).

Unlike the design of a chemical catalyst, which has to be semi-empirical in nature and is therefore very difficult to apply to a completely different transformation, screening for an enzyme that performs a similar reaction is relatively straightforward and often gives the necessary lead for the development of a potent biological catalyst. The use of molecular biology, site-specific mutagenesis, and enzymology all contribute to the development of such a catalyst. This approach is often ignored because these methods are outside of traditional chemical methodologies.

There are a large number of reports of abzymes, or catalytic antibodies, in the literature [5–10]. Although catalysis has been observed in a large number of examples, the problems associated with the production of large amounts of abzymes, compounded by the low turnover numbers often observed, makes this