Stoichiometric Asymmetric Synthesis

*Stoichio*metric Asymmetric Synthesis

MARK A. RIZZACASA
School of Chemistry
The University of Melbourne
Victoria
Australia

and

MICHAEL PERKINS
Department of Chemistry
Flinders University
Adelaide
Australia

Blackwell
Science

First published 2000

Published by
Sheffield Academic Press Ltd
Mansion House, 19 Kingfield Road
Sheffield S11 9AS, England

ISBN 1-84127-111-X

Published in the U.S.A. and Canada (only) by
Blackwell Science, Inc.
Commerce Place
350 Main Street
Malden, MA 02148-5018, U.S.A.
Orders from the U.S.A. and Canada (only) to Blackwell Science, Inc.

Printed on acid-free paper in Great Britain by
Bookcraft Ltd, Midsomer Norton, Bath

British Library Cataloguing-in-Publication Data:
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data:
A catalog record for this book is available from the Library of Congress

Stoichiometric Asymmetric Synthesis

Postgraduate Chemistry Series

A series designed to provide a broad understanding of selected growth areas of chemistry at postgraduate student and research level. Volumes concentrate on material in advance of a normal undergraduate text, although the relevant background to a subject is included. Key discoveries and trends in current research are highlighted, and volumes are extensively referenced and cross-referenced. Detailed and effective indexes are an important feature of the series. In some universities, the series will also serve as a valuable reference for final year honours students.

Titles in the series:

Catalysis in Asymmetric Synthesis
Jonathan M.J. Williams

Protecting Groups in Organic Synthesis
James R. Hanson

Organic Synthesis with Carbohydrates
Geert-Jan Boons and Karl J. Hale

Organic Synthesis using Transition Metals
Roderick Bates

Stoichiometric Asymmetric Synthesis
Mark Rizzacasa and Michael Perkins

Foreword

by Dr Ian Paterson, Department of Chemistry, University of Cambridge, UK

The control of relative and absolute stereochemistry is an intellectually stimulating and challenging aspect of modern synthesis design. To understand the origins of stereoinduction, reaction pathways generally need to be evaluated in three dimensions, where competing transition states are energetically responsive to steric and electronic influences. Over the last three decades, powerful methods and strategies have been developed to synthesise organic compounds containing multiple stereocentres with high levels of diastereoselectivity and in enantiomerically pure form. Through appropriate use of substrate and reagent-based control of stereochemistry, chiral molecules having diverse functionality can now be synthesised in a practical and predictable fashion.

This book by Mark Rizzacasa and Michael Perkins does an admirable job of presenting, logically and systematically, the underlying stereochemical and mechanistic aspects associated with asymmetric synthesis. Both authors are active and skilled practitioners in stereocontrolled organic synthesis, so it is good to see their combined expertise and knowledge being made available to a wider audience. Emphasis is given to practical, stoichiometric methodology and the analysis of reaction transition states. There is a wealth of illustrative examples of stereocontrolled synthesis taken from the recent literature (including those involving radical reactions), accompanied by a useful bibliography for each chapter, including references to specialist reviews and research publications. The coverage is eminently suitable for graduate and advanced undergraduate courses concentrating on the synthesis of chiral organic compounds, and in addition it provides an up-to-date and authoritative overview of stereocontrolled transformations for synthetic chemists working in academia and industry.

Preface

This book focuses on the use of a stoichiometric amount of chirality to induce asymmetry in carbon-carbon bond-forming reactions. Stoichiometric asymmetric synthesis is widely used in the academic and industrial sectors for the synthesis of chiral molecules of biological importance. Although catalytic asymmetric synthesis is an alternative, the use of equimolar amounts of chirality usually provides high selectivities over a wider range of substrates, without extensive modifications of reaction conditions. This book is aimed primarily at graduate students, but postdoctoral researchers and teaching staff may also find it useful. It is not intended as a review of all the literature. However, the majority of the methods included are widely used and provide high selectivities. Those that are experimentally simple and well documented are highlighted.

Chapter 2 details additions to carbonyl compounds by simple nucleophiles, beginning with a description of the models used to predict facial selectivity. A section on the use of such additions in the synthesis of some important molecules is included. Chapter 3 discusses the asymmetric alkylation of enolates, including methods for stereoselective enolate formation. Chapters 4 and 5 show the strategies for one of the most important asymmetric C-C bond-forming reactions, the aldol condensation, while chapter 6 details the allyl and crotylmetal alternatives. Chapter 7 covers pericyclic reactions, while chapter 8 deals with asymmetric reactions of alkenes. The book concludes with chapter 9, which presents examples of asymmetric radical reactions.

To show the origin of stereoselectivity, attention has been paid to the facial selectivities of reactions, and detailed transition states are included where appropriate. We hope that this text provides the researcher with a source of asymmetric reactions that can be utilised for the synthesis of chiral compounds.

We wish to thank the following for their invaluable assistance with the preparation of this volume: Dr Ian Paterson (Cambridge University), Ivona Czuba for indexing, Anthony Cuzzupe, Dr Mike Lilly, Mariana El Sous, Georgina Holloway and Robert Mann (all from the University of Melbourne).

Mark A. Rizzacasa
Michael Perkins

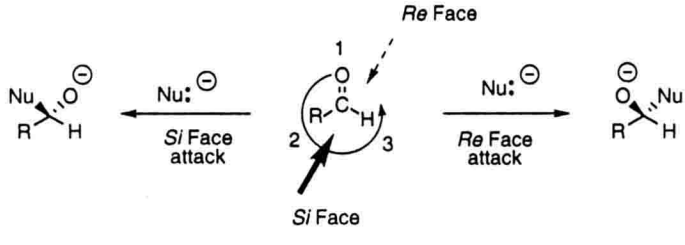
Contents

1 Introduction

1.1 Background

The past 20 years have been a renaissance period for asymmetric organic synthesis. The development of efficient methods for the enantiospecific synthesis of chiral molecules has intensified as more complex chiral natural products have been targeted.[1] The requirement that all chiral drugs must be produced in optically pure form has also driven research in asymmetric synthesis.[2,3] Currently, the most widely used general method for the production of chiral compounds is the stoichiometric approach where the chiral information is present in either the substrate or in the reagent. This book will outline the major methods of stoichiometric asymmetric synthesis, with the main focus being on the formation of carbon–carbon bonds.

Some key types of asymmetric carbon–carbon bond-forming reactions are shown in Tables 1.1 and 1.2. The reactions in Table 1.1 involve the generation of a new C—C bond along with the formation of an asymmetric centre at one or both of the carbon atoms involved in the process. The first example is the simple addition of carbon-based nucleophiles to aldehydes and ketones (Chapter 2) which can generate a new asymmetric centre. The nucleophile can attack either face of the sp^2 hybridised carbonyl carbon (trigonal planar) as shown in Scheme 1.1. These two faces can be described as either *Re* (if the



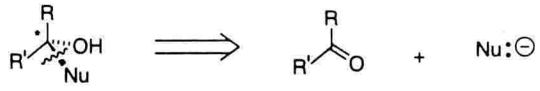
Scheme 1.1

three groups attached to the carbonyl are clockwise according to decreasing priority according to the Cahn–Ingold–Prelog system) or *Si* (if the three groups are anticlockwise).[4,5] The facial selectivity or topicity of the reaction must be controlled in order to produce the desired asymmetry at the newly formed stereogenic centre.

In the reactions of enolates and crotylmetal reagents, two new asymmetric centres can be formed simultaneously. One can now consider the topicity of

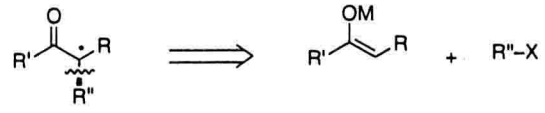
Table 1.1 Carbonyl additions

Simple carbon nucleophiles

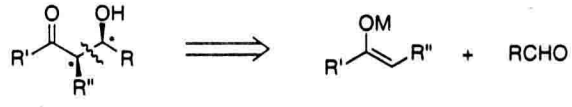


Enolates

akylations

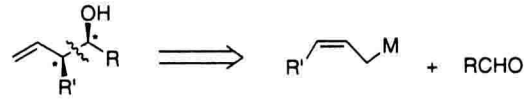


aldol reactions

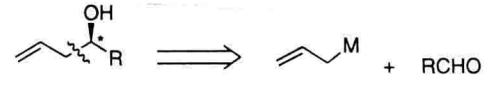


Crotylmetal and allyl nucleophiles

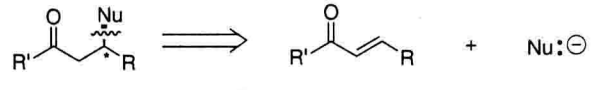
crotylmetallation



allylmetallation



Conjugate additions



*Ene reactions (pericyclic reactions)

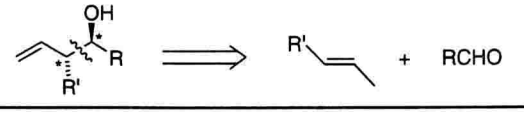
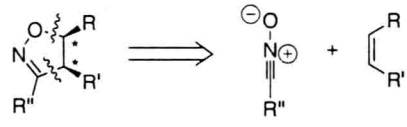


Table 1.2 Pericyclic reactions

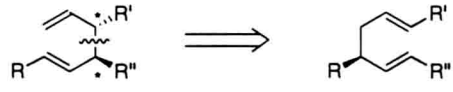
[4 + 2] Diels–Alder reactions

[3 + 2] Dipolar cycloadditions

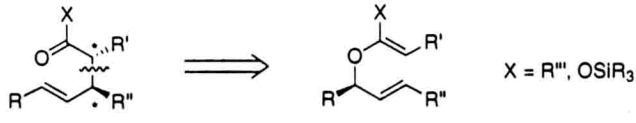


[3,3] Rearrangements

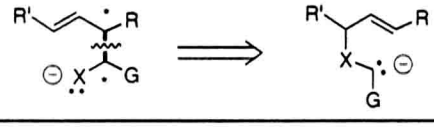
Cope rearrangements



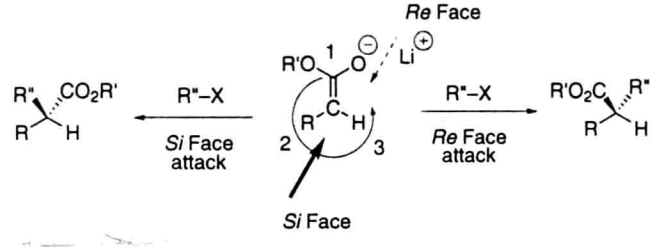
Claisen rearrangements



2,3-Wittig rearrangements



the reaction of the enolate and designate *Re* and *Si* faces of the sp^2 hybridised enolate carbon (R = alkyl group) by the orientation of the three substituents, as is shown in Scheme 1.2 for the alkylation of an ester enolate (Chapter 3).



Scheme 1.2

In the case of a propionate type aldol reaction (see Chapter 4) the topicity of the enolate and aldehyde must both be considered and there are several stereochemical outcomes, an enantiomeric *syn* pair (OH and Me on the same side of the 'zigzag' carbon chain) and an *anti* pair (OH and Me on opposite sides) (Figure 1.1).[5,6] This type of nomenclature will be used throughout this book

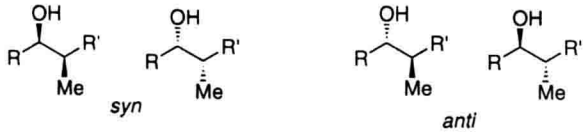


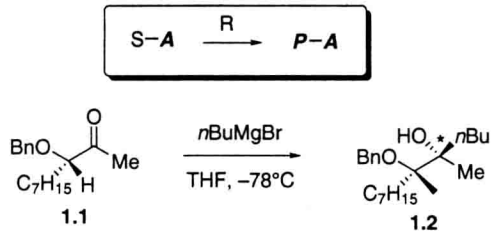
Figure 1.1

in preference to the older *threo* and *erythro* designation of the stereochemical relationship between two asymmetric adjacent centres. Asymmetric crotylmetallation (Chapter 6) and ene type reactions (Chapter 7) can also provide either *syn* or *anti* type products with stereocontrol similar to that for aldol reactions. Conjugate additions to α,β-unsaturated carbonyl compounds (Chapter 8) is the other method of asymmetric carbon–carbon bond formation presented where both simple and enolate type nucleophiles can be utilised.

In some pericyclic reactions (Table 1.2), formation of two σ-bonds results in the introduction of several stereocentres simultaneously. Stereocontrol in these reactions can be high since they are concerted processes that proceed via highly ordered transition states (Chapter 7). Cycloaddition reactions can often result in the formation of more than two new asymmetric centres while rearrangements involve the formation of a new σ-bond and the 'transfer' of chirality from one stereogenic centre to another.

1.2 Strategies

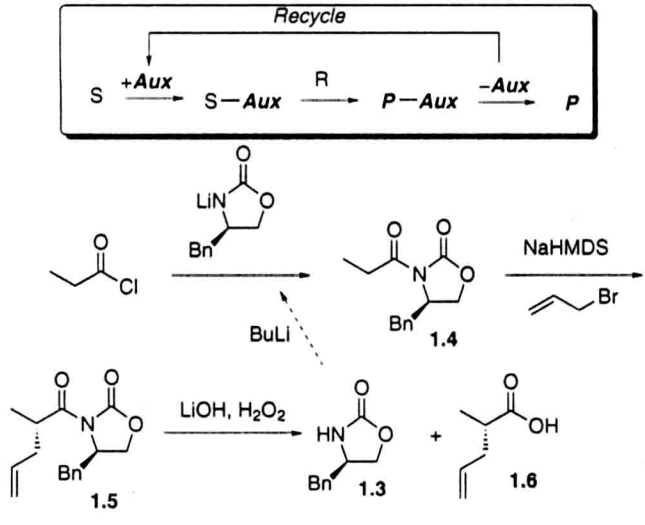
There are a number of stoichiometric strategies that can be utilised to generate new asymmetric centres in molecules and these can be divided into three main types: (1) substrate control, (2) auxiliary control and (3) reagent control.[7] These strategies are explained in detail below and will be the main ones covered in this volume. A representative substrate-controlled asymmetric reaction is shown in Scheme 1.3. Otherwise known as a 'first generation method',[7] this approach involves the use of an achiral substrate or portion of a molecule (S) with a chiral group or asymmetric centre (***A***) covalently attached nearby. The chiral influence is close enough so that the subsequent reaction with an achiral reagent (R) is effectively controlled by ***A*** which induces asymmetry in the substrate portion (S) of the molecule to provide the product (***P***) with the new stereogenic



Scheme 1.3

centre(s) present. The chiral group ***A*** is retained in this process and, in most cases, throughout the synthesis. In the example shown in Scheme 1.3, the chiral ketone **1.1** is converted into the alcohol **1.2** by a simple nucleophilic addition to a carbonyl group (Chapter 2). In this reaction, the stereogenic centre marked is introduced with good control.

The second method, auxiliary control, is shown in Scheme 1.4. In this case a temporary chiral influence or 'chiral auxiliary' (***Aux***) is covalently bound to the

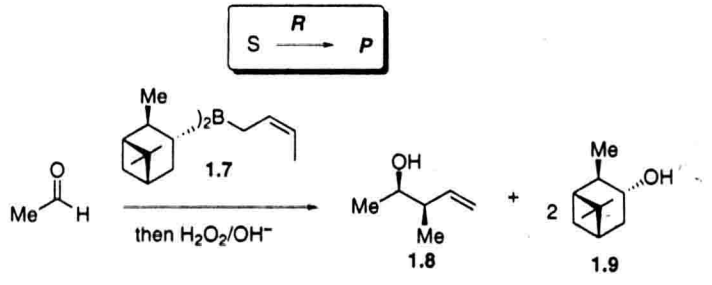


Scheme 1.4

substrate (S), normally by a weaker C—O or C—N bond which can be cleaved in a later step. The substrate–auxiliary (S—***Aux***) molecule is then treated with an achiral reagent, and an asymmetric reaction occurs, controlled by the auxiliary, to give the product (***P***) which now contains asymmetry and is still attached. The chiral auxiliary (***Aux***) is then removed in a subsequent step to give the desired product and the auxiliary, which can be recycled by attachment to more of the substrate. In the example shown in Scheme 1.4, the chiral

auxiliary is the oxazolidinone **1.3** derived from an amino acid. The achiral substrate is attached to give the substrate–auxiliary intermediate **1.4** which undergoes an asymmetric alkylation to provide product **1.5**; the auxiliary is then removed by hydrolysis to give the acid product **1.6** and neutral auxiliary **1.3** ready to recycle.

The final type of method is reagent control where a chiral reagent (***R***) is allowed to react with an achiral substrate (S) to produce a chiral product (***P***) (Scheme 1.5). In this method, the chirality of the reagent is transferred to the



Scheme 1.5

substrate. The chiral crotyl metal reagent **1.7** (Chapter 7) attacks acetaldehyde exclusively from the *Si* face while the double bond geometry dictates the relative stereochemical outcome (Scheme 1.5). This results in the production of the *syn*-propionate product **1.8** as well as two molar equivalents of alcohol **1.9** derived from the chiral auxiliary part of the reagent.

1.3 Chiral sources

The chiral sources from which auxiliaries and reagents can be synthesised for use in asymmetric synthesis can be divided into a number of main natural product groups (Table 1.3). Terpenes are inexpensive and readily available chiral precursors which have been used extensively in both auxiliary-based and reagent-based methods. Amino and hydroxy acids are useful as chiral starting materials for the production of heterocyclic chiral auxiliaries. Amino acids, in particular, have a wide range of hydrocarbon side-chains which are effective bulky substituents. Carbohydrates are also useful chiral materials and are relatively inexpensive. However, the large number of similar hydroxy groups and stereogenic centres in these compounds makes their use as chiral auxiliaries somewhat limited. Alkaloids and amines are effective chiral sources and can also be used for the classical resolution of racemic mixtures to provide non-natural optically pure compounds.