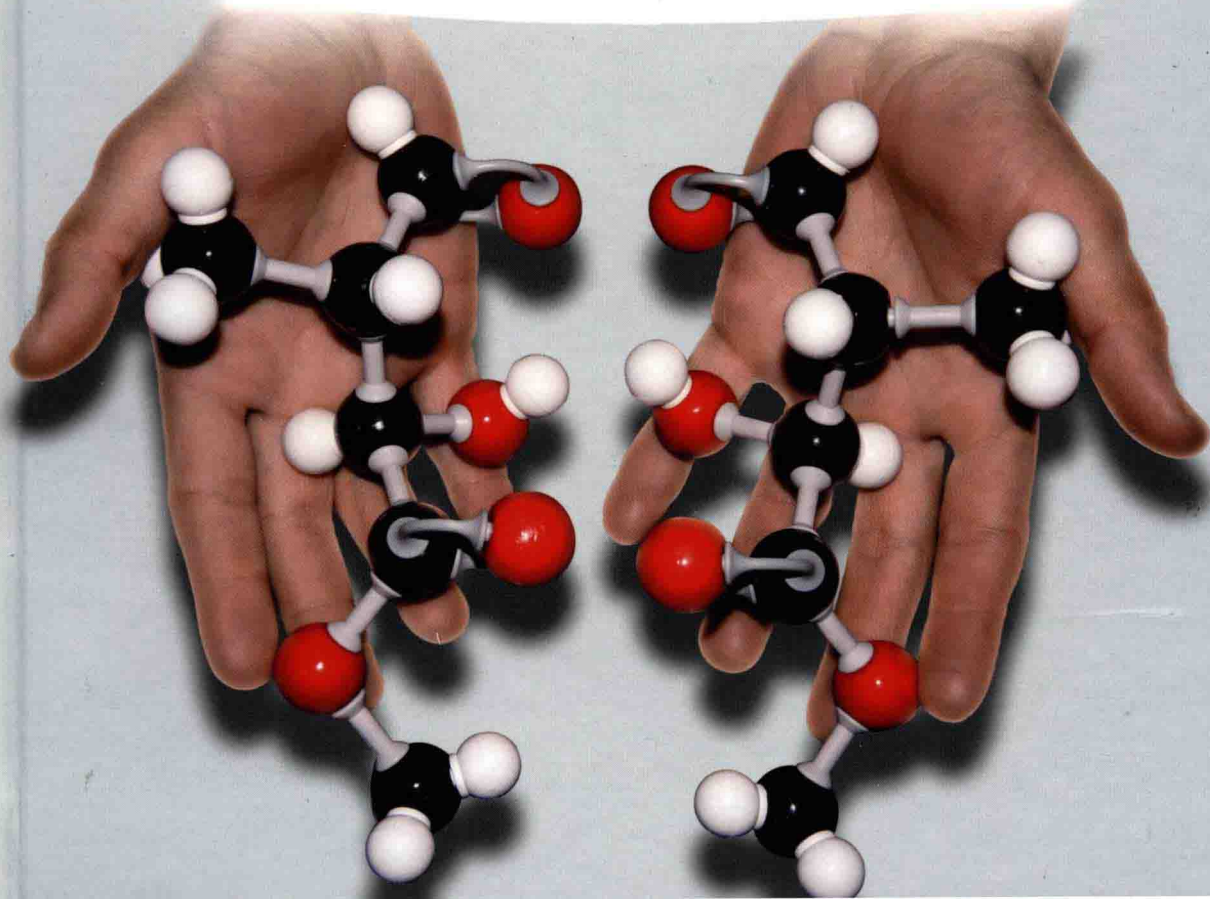


Edited by Rainer Mahrwald

# Modern Methods in Stereoselective Aldol Reactions



*Edited by Rainer Mahrwald*

## **Modern Methods in Stereoselective Aldol Reactions**



WILEY-VCH Verlag GmbH & Co. KGaA

## The Editor

**Prof. Dr. Rainer Mahrwald**  
Humboldt-Universität Berlin  
Institut für Chemie  
Brook-Taylor-Str. 2  
12489 Berlin

All books published by Wiley-VCH are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

**Library of Congress Card No.:** applied for

### **British Library Cataloguing-in-Publication Data**

A catalogue record for this book is available from the British Library.

### **Bibliographic information published by the Deutsche Nationalbibliothek**

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <<http://dnb.d-nb.de>>.

© 2013 Wiley-VCH Verlag & Co. KGaA,  
Boschstr. 12, 69469 Weinheim, Germany

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

**Print ISBN:** 978-3-527-33205-2

**ePDF ISBN:** 978-3-527-65674-5

**ePub ISBN:** 978-3-527-65673-8

**mobi ISBN:** 978-3-527-65672-1

**oBook ISBN:** 978-3-527-65671-4

**Cover Design** Adam-Design, Weinheim

**Typesetting** Laserwords Private Limited,  
Chennai, India

**Printing and Binding** Markono Print Media  
Pte Ltd, Singapore

Printed on acid-free paper

*Edited by*  
*Rainer Mahrwald*

**Modern Methods in Stereoselective Aldol  
Reactions**

## ***Related Titles***

Majumdar, K. C., Chattopadhyay, S. K.  
(eds.)

### **Heterocycles in Natural Product Synthesis**

2011

ISBN: 978-3-527-32706-5

Poupon, E., Nay, B. (eds.)

### **Biomimetic Organic Synthesis**

2011

ISBN: 978-3-527-32580-1

Nicolaou, K. C., Chen, J. S.

### **Classics in Total Synthesis III Further Targets, Strategies, Methods**

2011

ISBN: 978-3-527-32958-8

Yang, J

### **Six-Membered Transition States in Organic Synthesis**

2010

ISBN: 978-0-470-65258-9

Joule, J. A., Mills, K.

### **Heterocyclic Chemistry**

2010

ISBN: 978-0-470-68597-6

Zabicky, J. (ed.)

### **The Chemistry of Metal Enolates**

2009

ISBN: 978-0-470-06168-8

Carreira, E. M., Kvaerno, L.

### **Classics in Stereoselective Synthesis**

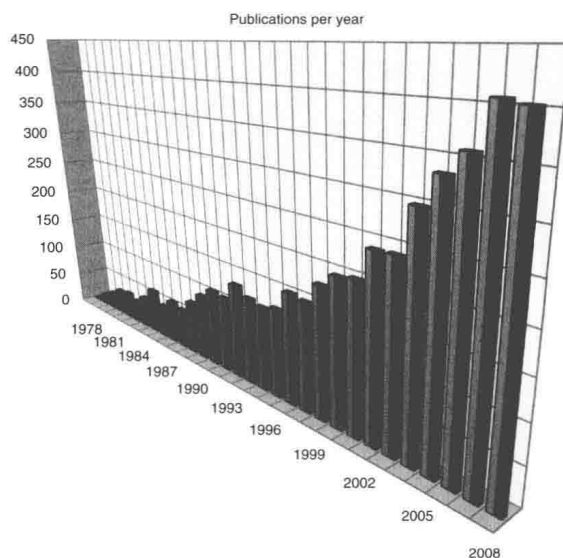
2009

ISBN: 978-3-527-32452-1

## Preface

Stereoselectivity is one of the most important aspects for natural product chemists. Following the increasing possibility of detection and assignment of stereogenic centers, a tremendous increase in stereoselective methods of organic reactions, particularly aldol reactions, has been noticed. In the beginning of this development, only sporadic examples of stereoselective aldol reactions were described, mostly in the context of total syntheses of natural products. An outstanding early example is the R. B. Woodward's proline-catalyzed aldol addition in the total synthesis of erythronolide A at the Harvard University in 1981. In the following three decades, a vast arsenal of stereoselective aldol additions has been developed (see Figure).

This book provides a comprehensive review of modern aldol reactions, especially in the aspect of how to achieve high stereoselectivity – diastereoselectivity as well as enantioselectivity. Stereoselection is discussed under several different aspects. One aspect is the deployment of different substrates – acetate or propionate aldol reactions. Another aspect is the mode of action including metal enolate chemistry, Lewis acid as well as Lewis base catalysis, enzymatic catalysis, and organocatalysis. There are some overlappings of these aspects in the chapters covering the cross-cutting themes of vinylogous Mukaiyama reaction or asymmetric inductions (e.g., compare Scheme 1.50 with Scheme 2.59) or total synthesis of dolastatin 19 – (compare Scheme 1.82 with Scheme 5.8). These overlappings, however, are intentional in order to give a comprehensive insight into the techniques for installing required configurations during aldol reactions. The utility of the corresponding methods is shown in the context of total syntheses of natural products. All chapters are thoroughly well written by experts in the respective fields.



It is my pleasure to express profound gratitude to the 15 authors for their huge endeavor to organize and summarize this vast amount of material. It has been a great pleasure for me to work with this team of authors at all times. Finally, my special thanks go to Elke Maase and Bernadette Gmeiner at WILEY for their fine work in making this book a reality.

Berlin, Autumn 2012

*Rainer Mahrwald*

## List of Contributors

### ***Patrick B. Brady***

The University of Chicago  
Department of Chemistry  
5735 S. Ellis Ave. (GHJ 409)  
Chicago  
Illinois 60637  
USA

### ***Pere Clapès***

Instituto de Química Avanzada de  
Cataluña  
Consejo Superior de  
Investigaciones Científicas  
(IQAC-CSIC)  
Departamento de Química  
Biológica y Modelización  
Molecular  
Jordi Girona 18-26  
08034 Barcelona  
Spain

### ***Martin Cordes***

Leibniz Universität Hannover  
Center for Biomolecular Drug  
Research  
Schneiderberg 1 B  
30167 Hannover  
Germany

### ***Michael T. Crimmins***

University of North Carolina at  
Chapel Hill  
Kenan Laboratories  
Chapel Hill  
NC 27599  
USA

### ***Luiz C. Dias***

University of Campinas  
UNICAMP  
Institute of Chemistry  
C.P. 6154  
13083-970 Campinas  
São Paulo  
Brazil

### ***Marco A. B. Ferreira***

University of Campinas  
UNICAMP  
Institute of Chemistry  
C.P. 6154  
13083-970 Campinas  
São Paulo  
Brazil



**Gabriela Guillena**

Universidad de Alicante  
Instituto de Síntesis Orgánica  
Departamento de Química  
Orgánica  
Apdo 99  
03080 Alicante  
Spain

**Jesús Joglar**

Instituto de Química Avanzada de  
Cataluña  
Consejo Superior de  
Investigaciones Científicas  
(IQAC-CSIC)  
Departamento de Química  
Biológica y Modelización  
Molecular  
Jordi Girona 18-26  
08034 Barcelona  
Spain

**Markus Kalesse**

Leibniz Universität Hannover  
Center for Biomolecular Drug  
Research  
Schneiderberg 1 B  
30167 Hannover  
Germany

**Emílio C. de Lucca Jr.**

University of Campinas  
UNICAMP  
Institute of Chemistry  
C.P. 6154  
13083-970 Campinas  
São Paulo  
Brazil

**Ellen C. Polo**

University of Campinas  
UNICAMP  
Institute of Chemistry  
C.P. 6154  
13083-970 Campinas  
São Paulo  
Brazil

**Pedro Romea**

Universitat de Barcelona  
Departament de Química  
Orgànica  
Martí i Franqués 1–11  
08028 Barcelona  
Catalonia  
Spain

**Fèlix Urpí**

Universitat de Barcelona  
Departament de Química  
Orgànica  
Martí i Franqués 1–11  
08028 Barcelona  
Catalonia  
Spain

**Dale E. Ward**

University of Saskatchewan  
Department of Chemistry  
110 Science Place  
Saskatoon  
SK S7N 5C9  
Canada

**Hisashi Yamamoto**

The University of Chicago  
Department of Chemistry  
5735 S. Ellis Ave. (GHJ 409)  
Chicago  
Illinois 60637  
USA

## Contents

**Preface** XI

**List of Contributors** XIII

<b>1</b>	<b>Stereoselective Acetate Aldol Reactions</b>	<b>1</b>
	<i>Pedro Romea and Félix Urpí</i>	
1.1	Introduction	1
1.2	Mukaiyama Aldol Reaction	2
1.2.1	Concept and Mechanism	2
1.2.2	Chiral Auxiliaries	4
1.2.3	Chiral Methyl Ketones	6
1.2.4	Chiral Aldehydes	8
1.2.4.1	1,2-Asymmetric Induction	8
1.2.4.2	1,3-Asymmetric Induction	13
1.2.4.3	Merged 1,2- and 1,3-Asymmetric Induction	17
1.2.5	Chiral Lewis Acids	22
1.2.6	Chiral Lewis Bases	35
1.3	Metal Enolates	41
1.3.1	Concept and Mechanism	41
1.3.2	Chiral Auxiliaries	42
1.3.3	Stoichiometric Lewis Acids	47
1.3.4	Catalytic Lewis Acids	48
1.3.5	Chiral Aldehydes	50
1.3.6	Chiral Methyl Ketones	55
1.3.6.1	$\alpha$ -Methyl Ketones	56
1.3.6.2	$\alpha$ -Hydroxy Ketones	57
1.3.6.3	$\beta$ -Hydroxy Ketones	60
1.3.6.4	$\beta$ -Hydroxy $\alpha$ -Methyl Ketones	63
1.3.6.5	$\alpha,\beta$ -Dihydroxy Ketones	64
1.3.6.6	Remote Stereocontrol	67
1.4	Conclusions	68
	References	69

<b>2</b>	<b>The Vinylogous Mukaiyama Aldol Reaction in Natural Product Synthesis</b>	<b>83</b>
	<i>Martin Cordes and Markus Kalesse</i>	
2.1	Introduction	83
2.2	Aldehyde-Derived Silyl Dienol Ethers	84
2.2.1	Aldehyde-Derived Silyl Dienol Ethers – Diastereoselective Processes	84
2.2.2	Aldehyde-Derived Silyl Dienol Ethers – Enantioselective Processes	87
2.3	Ester-Derived Silyl Dienol Ethers	90
2.3.1	Ester-Derived Silyl Dienol Ethers – Diastereoselective Processes	90
2.3.2	Ester-Derived Silyl Dienol Ethers – Enantioselective Processes	96
2.3.3	Ester-Derived Silyl Dienol Ethers – Enantioselective and Substrate-Controlled Processes	105
2.4	Amide-Derived Silyl Dienol Ethers – Vinylketene Silyl <i>N,O</i> -Acetals	108
2.4.1	Model Systems – Kobayashi's Pioneering Studies	108
2.4.2	Total Syntheses	109
2.5	Acyclic Acetoacetate-Derived Silyl Dienolates – Chan's Diene	117
2.5.1	Chan's Diene in Diastereoselective Processes	117
2.5.2	Chan's Diene in Enantioselective Processes	121
2.5.3	Chan's Diene in Enantioselective and Substrate-Controlled Processes	122
2.6	Cyclic Acetoacetate-Derived Dienolates	124
2.6.1	Cyclic Acetoacetate-Derived Dienolates – Diastereoselective Processes	124
2.6.2	Cyclic Acetoacetate-Derived Dienolates – Enantioselective Processes	126
2.6.3	Cyclic Acetoacetate-Derived Dienolates – Enantioselective and Substrate-Controlled Processes	132
2.7	Furan-Derived Silyloxy Dienes	133
2.7.1	Furan-Derived Silyloxy Dienes – Diastereoselective Processes	133
2.7.2	Furan-Derived Silyloxy Dienes – Enantioselective Processes	138
2.7.3	Furan-Derived Silyloxy Dienes – Enantioselective and Substrate-Controlled Processes	141
2.8	Pyrrole-Based 2-Silyloxy Dienes	142
2.9	Comparison with Other Methods	148
	References	151
<b>3</b>	<b>Organocatalyzed Aldol Reactions</b>	<b>155</b>
	<i>Gabriela Guillena</i>	
3.1	Introduction	155
3.2	Proline as Organocatalyst	156
3.2.1	Intramolecular Reactions	156
3.2.1.1	Intramolecular Proposed Mechanism	159
3.2.1.2	Application to Natural Product Synthesis	161
3.2.2	Intermolecular Reactions	163

3.2.2.1	Ketones as Source of Nucleophile	163
3.2.2.2	Aldehydes as Source of Nucleophile	171
3.2.2.3	Intermolecular Reaction Mechanism	175
3.2.2.4	Application to Natural Product Synthesis	177
3.3	Proline Derivatives as Organocatalysts	179
3.3.1	Prolinamide Derivatives	180
3.3.1.1	Ketones as Source of Nucleophile	180
3.3.1.2	Aldehydes as Source of Nucleophile	197
3.3.1.3	Application to Natural Product Synthesis	197
3.3.2	Proline Peptide Derivatives	199
3.3.2.1	Ketones as Source of Nucleophile	199
3.3.3	Hydroxyproline Derivatives	205
3.3.3.1	Intramolecular Reactions	205
3.3.3.2	Intermolecular Reactions	207
3.3.4	Sulfonimide Proline Derivatives	216
3.3.4.1	Ketones as Source of Nucleophile	216
3.3.4.2	Application to Natural Product Synthesis	219
3.3.5	Other Proline Derivatives	220
3.3.5.1	Intramolecular Reactions	220
3.3.5.2	Intermolecular Reactions	221
3.3.5.3	Application to Natural Product Synthesis	231
3.3.6	Other Organocatalysts	233
3.3.6.1	Intramolecular Reactions	233
3.3.6.2	Intermolecular Reactions	235
3.3.7	Phase-Transfer Catalysis	251
3.4	Conclusions and Outlook	253
	References	253
<b>4</b>	<b>Supersilyl Protective Groups in Aldol Reactions</b>	<b>269</b>
	<i>Patrick B. Brady and Hisashi Yamamoto</i>	
4.1	Introduction	269
4.2	Aldol Addition with Acetaldehyde-Derived Super Silyl Enol Ether (1)	270
4.3	$\alpha$ -Substituted Silyl Enol Ethers Derived from Aldehydes	270
4.4	Aldol Addition to Chiral Aldehydes	272
4.5	One-Pot Sequential Aldol Reactions	274
4.6	Sequential Aldol–Aldol Reactions of Acetaldehyde	275
4.6.1	Acetaldehyde Double Aldol Reactions	275
4.6.2	Acetaldehyde Triple Aldol Reactions	275
4.6.3	Mixed Sequential Aldol–Aldol Reactions	277
4.7	Double Aldol Reactions with $\alpha$ -Substituted Silyl Enol Ethers	277
4.7.1	Sequential Aldol–Aldol Reactions with Mixed SEEs	277
4.7.2	Propionaldehyde Aldol–Aldol Cascade Reactions	279
4.7.3	Haloacetaldehyde Aldol–Aldol Cascades	280
4.8	Stereochemical Considerations	281

4.9	Aldol Reactions of $\beta$ -Supersiloxy Methyl Ketones	282
4.10	Total Synthesis of Natural Products Using Supersilyl Aldol Reactions	285
4.11	Conclusion and Outlook	288
	References	288
<b>5</b>	<b>Asymmetric Induction in Aldol Additions</b>	<b>293</b>
	<i>Luiz C. Dias, Ellen C. Polo, Emílio C. de Lucca Jr, and Marco A.B. Ferreira</i>	
5.1	Introduction	293
5.2	Asymmetric Induction Using Chiral Ketones	295
5.2.1	1,4-Asymmetric Induction Using $\alpha$ -Alkyl Ketones	296
5.2.2	1,4-Asymmetric Induction Using $\alpha$ -Methyl- $\beta$ -Branched Ketones	302
5.2.3	1,4-Asymmetric Induction Using $\alpha$ -Alkoxy Ketones	305
5.2.4	1,5-Asymmetric Induction Using $\beta$ -Alkoxy Methyl Ketones	313
5.2.5	1,6-Asymmetric Induction Using Chiral Methyl Ketones	317
5.3	Asymmetric Induction Using Chiral Aldehydes	317
5.3.1	1,2-Asymmetric Induction Using Chiral Aldehydes	317
5.3.2	1,3-Asymmetric Induction Using Chiral Aldehydes	335
5.3.3	Asymmetric Induction Using $\alpha$ -Methyl- $\beta$ -Alkoxy Aldehydes	342
5.3.4	Asymmetric Induction Using $\alpha,\beta$ -Bisalkoxy Aldehydes	357
5.4	Asymmetric Induction in the Aldol Addition of Chiral Enolates to Chiral Aldehydes	360
	References	371
<b>6</b>	<b>Polypropionate Synthesis via Substrate-Controlled Stereoselective Aldol Couplings of Chiral Fragments</b>	<b>377</b>
	<i>Dale E. Ward</i>	
6.1	Introduction	377
6.2	Principles of Stereoselective Aldol Reactions	378
6.2.1	Relative Topicity	378
6.2.2	Chiral Reactants	381
6.2.2.1	Diastereoface Selectivity of Chiral Ethyl Ketones	381
6.2.2.2	Diastereoface Selectivity of Chiral Aldehydes	386
6.2.2.3	Multiplicativity Rule	394
6.3	Stereoselective Aldol Coupling of Chiral Reactants	398
6.3.1	2-Alkoxy-1-Methylethyl Ethyl Ketones: Paterson's Dipropionate Equivalent	398
6.3.1.1	Reactions with Achiral Aldehydes	398
6.3.1.2	Reactions with Chiral Aldehydes	400
6.3.2	1-Methylalkyl Ethyl Ketones: 3-Deoxy Polypropionate Equivalents	402
6.4	2-Alkoxyalkyl Ethyl Ketones: 2-Desmethyl Polypropionate Equivalents	406
6.4.1	2-Alkoxy-1-Methylalkyl Ethyl Ketones: Polypropionate Equivalents	409
6.4.1.1	(E) Boron Enolates	411
6.4.1.2	(Z) Boron Enolates	412

6.4.1.3	Silyl Enolates	413
6.4.1.4	Lithium Enolates	414
6.4.1.5	Titanium Enolates	416
6.4.1.6	Tin Enolates	419
6.5	Conclusions	420
	References	424
<b>7</b>	<b>Application of Oxazolidinethiones and Thiazolidinethiones in Aldol Additions</b>	<b>431</b>
	<i>Michael T. Crimmins</i>	
7.1	Introduction	431
7.2	Preparation of Oxazolidinethione and Thiazolidinethione Chiral Auxiliaries	431
7.3	Acylation of Oxazolidinethione and Thiazolidinethione Chiral Auxiliaries	433
7.4	Propionate Aldol Additions	434
7.5	Acetate Aldol Additions	437
7.6	Glycolate Aldol Additions	443
7.6.1	Synthetic Applications of Aldol Additions of <i>N</i> -Propionyl Oxazolidinethiones and Thiazolidinethiones and Their Substituted Variants	443
7.6.2	Synthetic Applications of Aldol Additions of <i>N</i> -Acetyloxazolidinethiones and Thiazolidinethiones	461
7.6.3	Synthetic Applications of anti-Aldol Additions of <i>N</i> -Glycolyloxazolidinethiones	466
	References	471
<b>8</b>	<b>Enzyme-Catalyzed Aldol Additions</b>	<b>475</b>
	<i>Pere Clapés and Jesús Joglar</i>	
8.1	Introduction	475
8.2	Pyruvate Aldolases	477
8.3	<i>N</i> -Acetylneuraminic Acid Aldolase (NeuA)	478
8.3.1	Novel NeuA Biocatalyst by Protein Engineering	482
8.3.2	Large-Scale Process	486
8.3.3	Related Pyruvate Aldolases/2-Oxobutyrate Aldolases	487
8.4	Dihydroxyacetone Phosphate (DHAP) Aldolases	494
8.4.1	Structure and Mechanism	500
8.4.2	L-Rhamnulose-1-Phosphate Aldolase as a DHA-Dependent Aldolase	502
8.5	D-Fructose-6-Phosphate Aldolase and Transaldolase B Phe178Tyr: FSA-Like Aldolases	503
8.6	2-Deoxy-D-Ribose-5-Phosphate Aldolase (RibA or DERA; EC 4.1.2.4)	510
8.7	Glycine/Alanine Aldolases	514
8.8	Aldol Reactions Catalyzed by Non aldolases	520

8.9	Conclusions and Perspectives	520
8.9.1	Substrate Tolerance/Stereoselectivity	521
8.9.2	Future Perspectives	521
	References	522

<b>Index</b>	529
--------------	-----

## 1

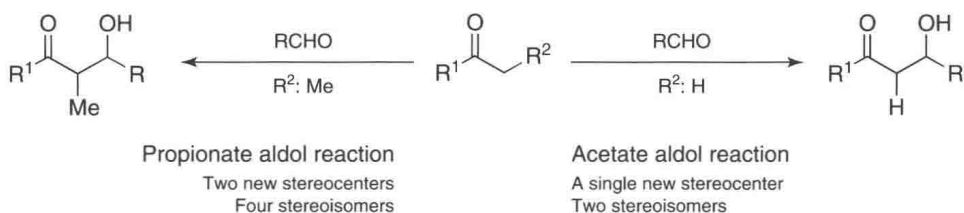
## Stereoselective Acetate Aldol Reactions

Pedro Romea and Fèlix Urpí

## 1.1

## Introduction

The stereochemical control of aldol reactions from unsubstituted enol- or enolate-like species, what are known as *acetate aldol reactions*, has been a matter of concern for nearly 30 years [1, 2]. Indeed, pioneering studies soon recognized that the asymmetric installation of a single stereocenter in such aldol reactions was much more demanding than the simultaneous construction of two new stereocenters in the related *propionate* counterparts (Scheme 1.1) [3]. This challenge, together with the ubiquitous presence of chiral  $\beta$ -hydroxy  $\alpha$ -unsubstituted oxygenated structures in natural products, has motivated the development of new concepts and strategies and a large number of highly stereoselective methodologies. These involve Lewis-acid-mediated additions of enolsilane derivatives of carbonyl compounds to aldehydes (*Mukaiyama* aldol variant) [4, 5], a plethora of transformations that take advantage of the reactivity of boron, titanium(IV), and tin(II) enolates (*metal enolates*) [6], and some insightful organocatalytic approaches [7]. In spite of these accomplishments, the quest for more powerful and selective methodologies and a better understanding of their intricate mechanisms is an active area of research. Herein, we describe the most significant achievements in the field of stereoselective *acetate aldol* reactions based on the Lewis-acid-mediated addition of enolsilanes and metal enolates to aldehydes, with particular attention to their application to the asymmetric synthesis of natural products. Recent advances in parallel organocatalytic procedures are not discussed.



Scheme 1.1 Aldol reactions.



## 1.2

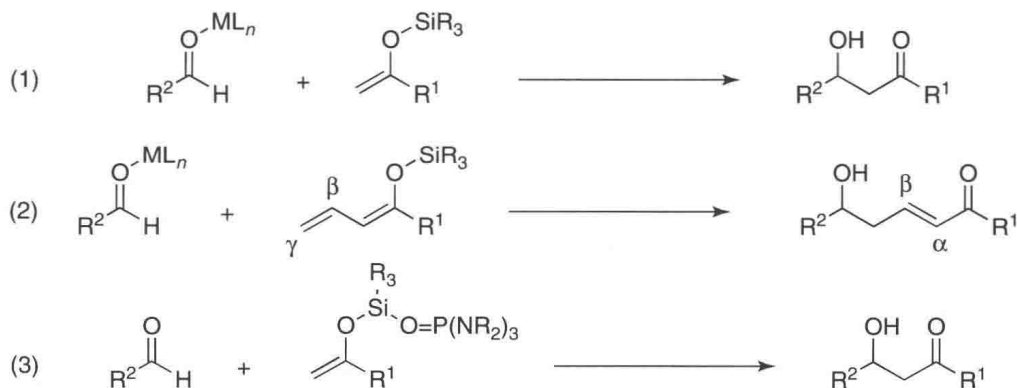
## Mukaiyama Aldol Reaction

## 1.2.1

## Concept and Mechanism

With some significant exceptions, enolsilanes are unreactive toward aldehydes.<sup>1)</sup> This lack of reactivity can be overcome by increasing the electrophilic character of aldehydes or the nucleophilicity of enolsilanes. The former option is achieved by coordination of Lewis acids ( $ML_n$ ) to the carbonyl group, which enhances the electrophilicity of the  $C=O$  bond and facilitates the attack of enolsilanes. This represents the canonical Mukaiyama aldol variant ((1) in Scheme 1.2) [4, 5]. It also covers vinylogous aldol transformations, which involve the reactions of  $\gamma$ -unsubstituted  $\beta, \gamma$ -conjugated enolsilanes ((2) in Scheme 1.2) [8]. In turn, the latter option takes advantage of the activation of the nucleophilic character of enolsilanes by binding of Lewis bases such as phosphoramides ( $O=P(NR_2)_3$ ) to the silicon atom ((3) in Scheme 1.2) [9].

Early mechanistic analyses suggested that Lewis-acid-mediated aldol reactions represented in Scheme 1.2 proceeded through open transition states [4, 5, 10]. This model assumes a *transoid* geometry for the Lewis-acid-aldehyde complex, which the enolsilane attacks following *antiperiplanar* or *synclinal* approaches, as represented in Scheme 1.3. *Antiperiplanar* transition states **I** and **II** are usually more favorable because of the minimization of dipolar interactions, the steric interactions between the enolsilane ( $R^1$  or  $R_3SiO$  groups) and the aldehyde ( $R^2$  group) being the main source of instability. Similar steric interactions arise in *synclinal* transition states **III** and **IV**, whereas **V** and **VI** are characterized by a destabilizing interaction between the enolsilane and the Lewis acid coordinated to the carbonyl oxygen. Then, steric and stereoelectronic interactions determine the relative stability of



**Scheme 1.2** Mukaiyama aldol variants.

1) As silyl enolates derived from amides and trihalosilyl enolates.