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Edited by Rainer Mahrwald

Modern Methods in Stereoselective Aldol Reactions

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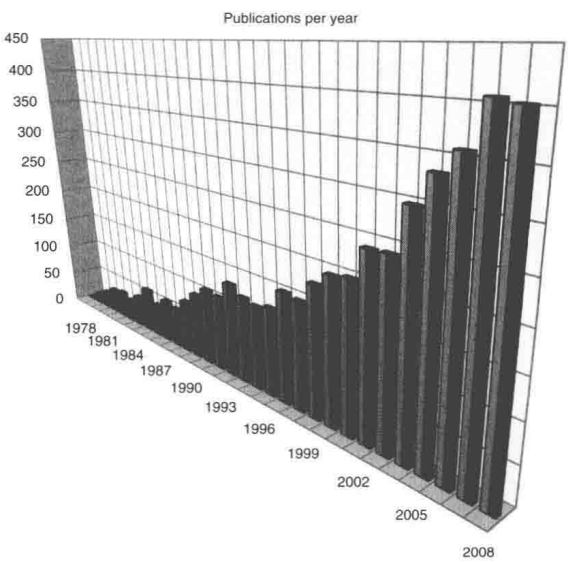
Preface

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 vinyloguos 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*

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Contents

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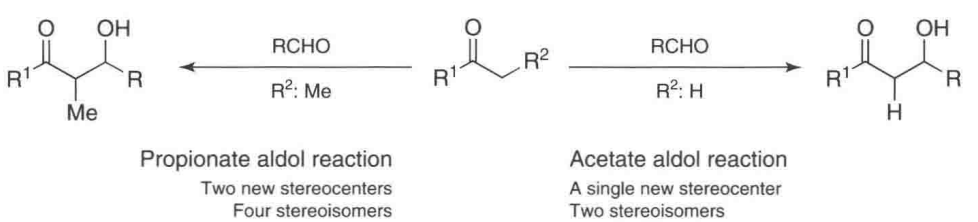
1
Stereoselective Acetate Aldol Reactions

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 β-hydroxy α-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.

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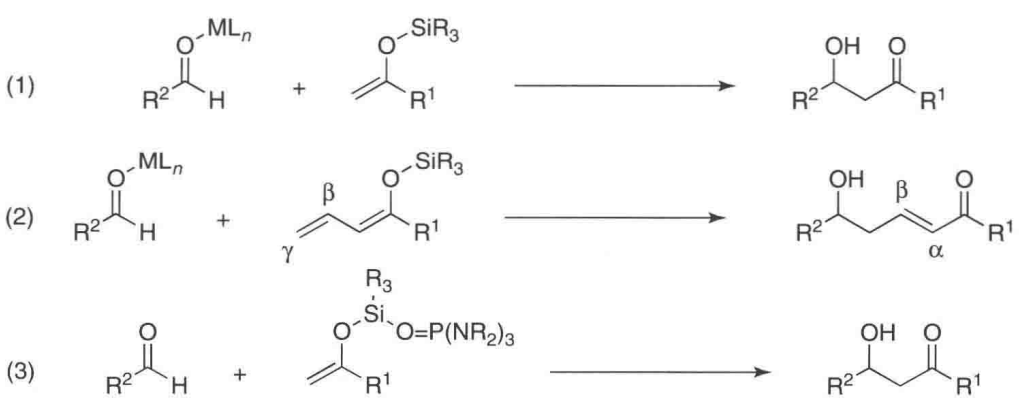
1.2
Mukaiyama Aldol Reaction

1.2.1
Concept and Mechanism

With some significant exceptions, enolsilanes are unreactive toward aldehydes.[1] 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 γ-unsubstituted β,γ-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.

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