

Edited by Rainer Mahrwald

Modern Methods in Stereoselective Aldol Reactions

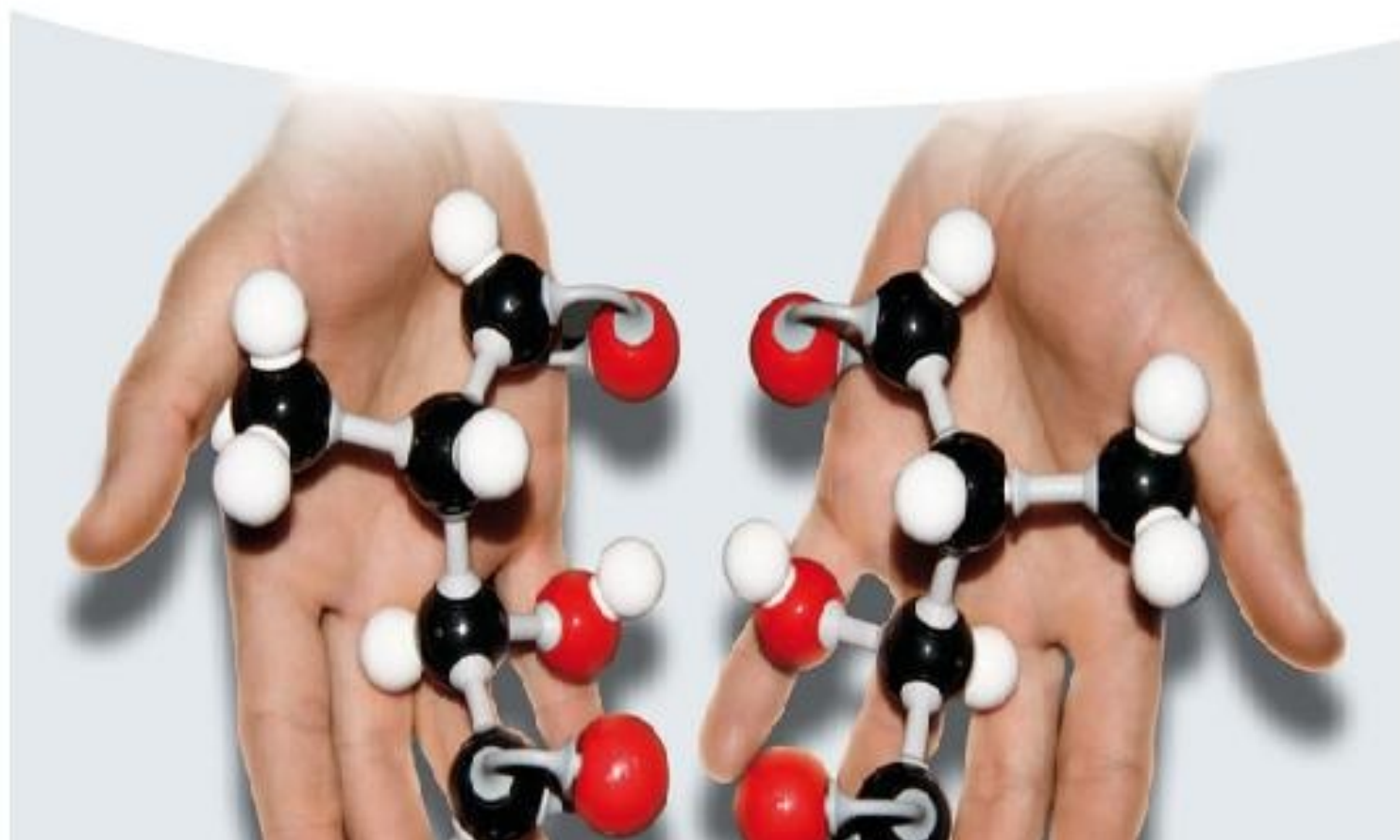


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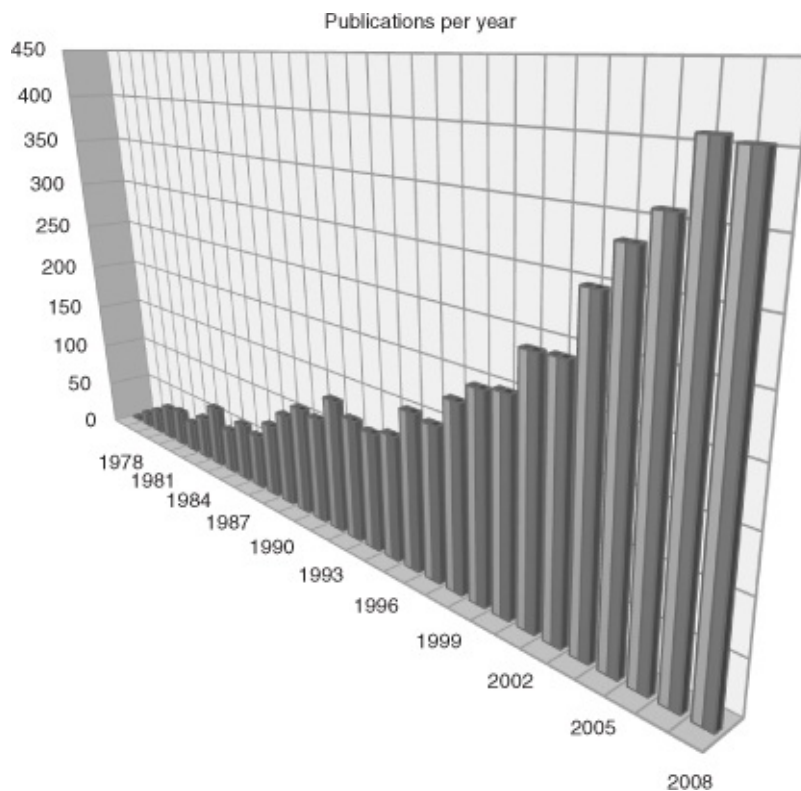
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Preface

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 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.

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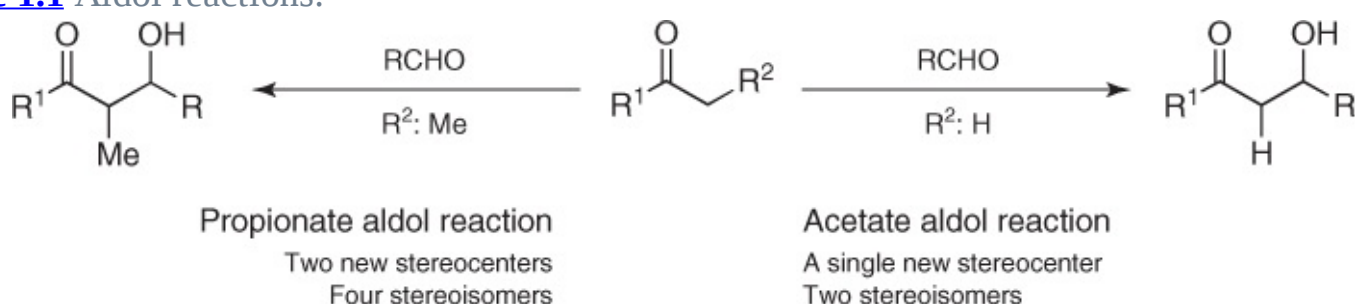
Stereoselective Acetate Aldol Reactions

Pedro Romea and Fèlix Urp

1.1 Introduction

The stereochemical control of aldol reactions from unsubstituted enol- or enolatelike species, what is 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 to 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.



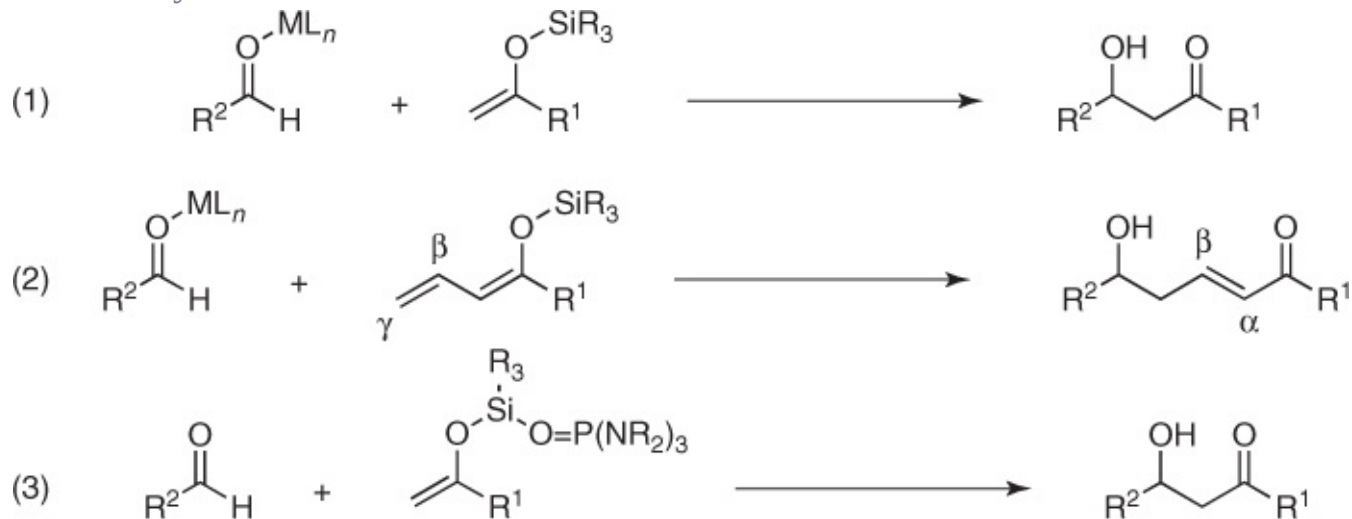
1.2 Mukaiyama Aldol Reaction

1.2.1 Concept and Mechanism

With some significant exceptions, enolsilanes are unreactive toward aldehydes.¹ This lack of reactivity can be overcome by increasing the electrophilic character of aldehydes or by

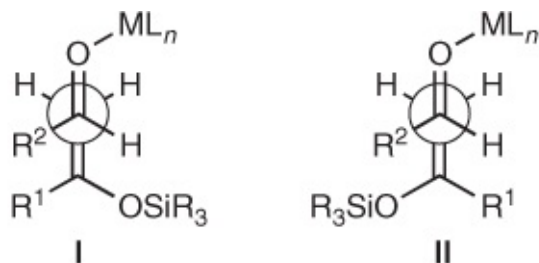
nucleophilicity of enolsilanes. The former option is achieved by coordination of Lewis acids (ML_n) to the carbonyl group, which enhances the electrophilicity of the C—O bond and facilitates the attack of enolsilanes. This represents the canonical Mukaiyama aldol variant ((1) in [Scheme 1.2](#)) [4, 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].

[Scheme 1.2](#) Mukaiyama aldol variants.

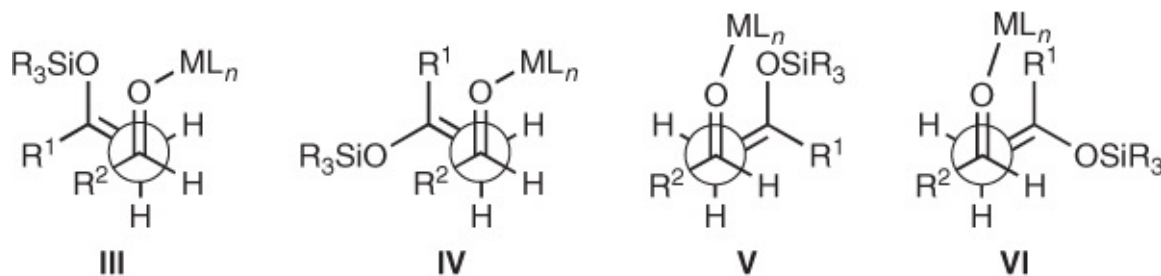


Early mechanistic analyses suggested that Lewis-acid-mediated aldol reactions represented in [Scheme 1.2](#) proceeded through open transition states [4, 5, 10]. This model assumes a *transo* geometry for the Lewis-acid-aldehyde complex, which the enolsilane attacks following *antiperiplanar* or *synclinal* 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 interaction 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 **I–VI** and the capacity to differentiate one from the other faces of the carbonyl bond.

[Scheme 1.3](#) Open transition states for Mukaiyama aldol reactions.



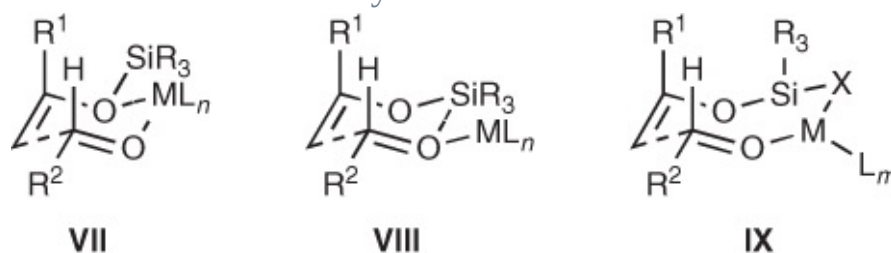
Antiperiplanar approaches



Synclinal approaches

Despite the importance and utility of this paradigm, it is probably an oversimplified model because it ignores the fate of the silyl group. In this respect, some models take into account the silicon moiety and suggest cyclic transition states **VII–IX**, as represented in [Scheme 1.4](#). Importantly, the role of the silyl group is not limited to influencing the nature of the transition state, because the silicon transfer from the enolsilane to the β -alkoxy position may be a key step in the overall mechanism and become crucial to the turnover necessary for nonstoichiometric transformations [11].

Scheme 1.4 Cyclic transition states for Mukaiyama aldol reactions.

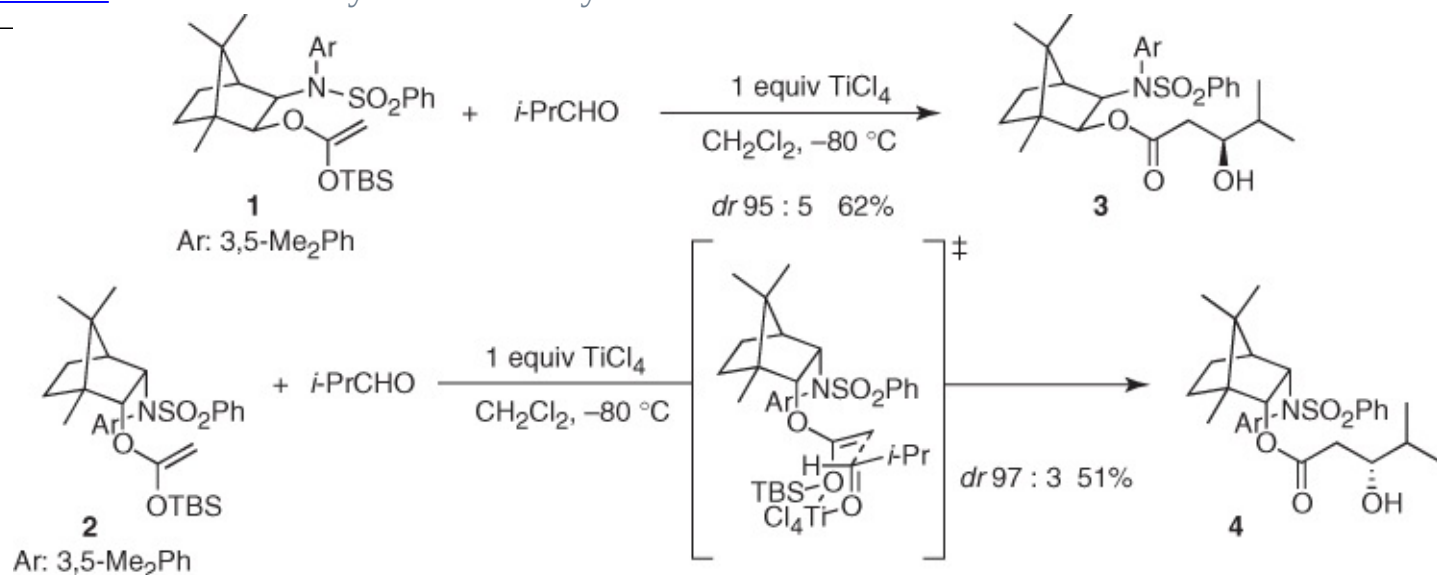


Irrespective of the mechanistic pathway, the asymmetric induction achieved by these Lewis-acid-mediated aldol reactions depends on chiral elements on the enolsilane (the nucleophilic partner), the aldehyde (the electrophilic partner), or the Lewis acid (the activating element), so they must cooperate to provide the appropriate face differentiation of the carbonyl bond in order to control the configuration of the new stereocenter. The influence of these elements is discussed in the following sections.

1.2.2 Chiral Auxiliaries

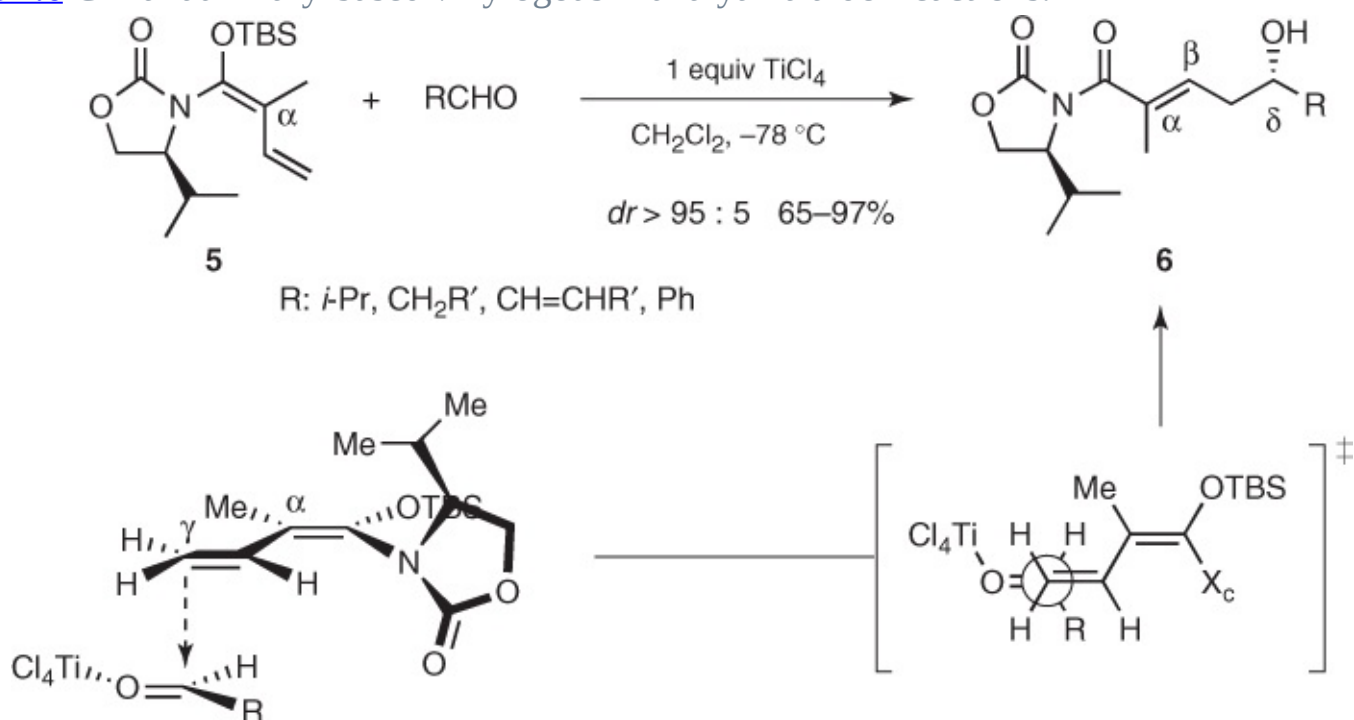
In the context of emergence of chiral auxiliaries as powerful platforms to achieve asymmetric transformations, Helmchen reported highly diastereoselective aldol reactions of chiral auxiliary-based silyl ketene acetals (**1**) and (**2**) [12, 13]. As shown in [Scheme 1.5](#), TiCl_4 -mediated additions of **1** and **2** to isobutyraldehyde afforded aldol adducts **3** and **4** in good yields and excellent diastereomeric ratios, presumably through a chairlike transition state in which the titanium atom is simultaneously coordinated to the carbonyl and the OTBS group. In turn, these adducts can be converted into the corresponding β -hydroxy acids in quantitative yield by simple treatment with KOH in methanol.

Scheme 1.5 Chiral auxiliary-based Mukaiyama aldol reactions.



This approach was quickly surpassed by alternative methodologies based on chiral aldehydes Lewis acids and bases (Sections 1.2.4–1.2.6). Nevertheless, new findings restored the interest in this sort of transformations a few years ago. Indeed, Kobayashi described highly stereoselective vinylogous Mukaiyama aldol reactions using silyl vinyl ketene *N,O*-acetals prepared from valine-derived 1,3-oxazolidin-2-ones [14]. As represented in Scheme 1.6, TiCl₄-mediated additions of methyl acetal (5) to aliphatic, α , β -unsaturated, and aromatic aldehydes afforded δ -hydroxy- α -methyl α , β -unsaturated imides (6) in excellent yields and diastereomeric ratios. Such outstanding remote asymmetric induction was believed to arise from a conformation in which the chiral heterocycle is almost perpendicular to the dienol plane and the isopropyl group overhangs the upper face of the dienol moiety. Then, the aldehyde approaches from the less hindered face through an open transition state in which the α -methyl group appears to be essential to achieve the observed high stereocontrol. Finally, the chiral auxiliary can be removed by well-known methodologies used for Evans auxiliaries.

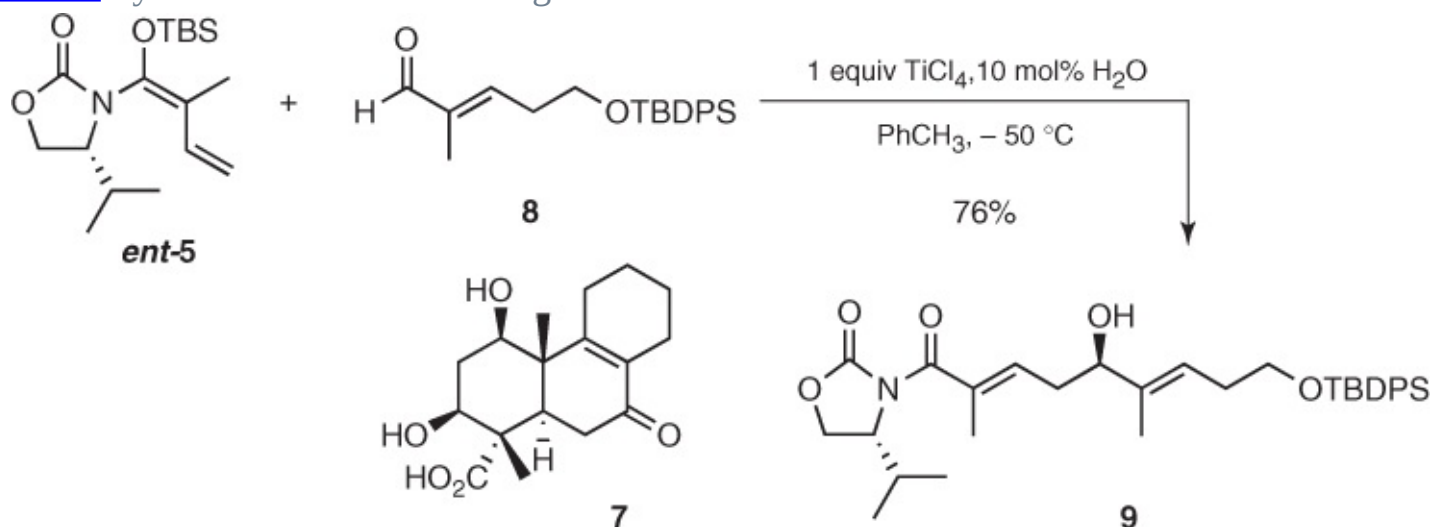
Scheme 1.6 Chiral auxiliary-based vinylogous Mukaiyama aldol reactions.



This methodology was used for the construction of the AB ring of fomitelic acids (7) (Scheme 1.7) [15]. Initially, application of the standard conditions to *ent*-5 and enal (8) provided the desired aldol

(9), but the reaction was slow and hard to reproduce. Then, a thorough study of this particular reaction uncovered significant rate enhancements by adding catalytic amounts of water in toluene, which permitted to obtain aldol (9) in 76% yield as a single diastereomer in a straightforward and consistent way [16]. The origin of this catalytic effect remains unclear, but it has proved to be general and has been successfully applied to other aldehydes [17].

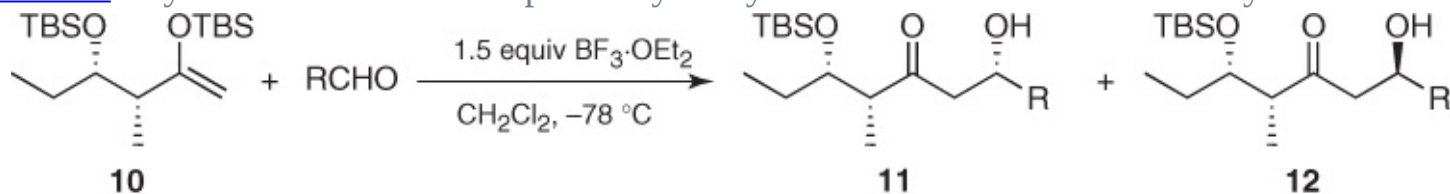
Scheme 1.7 Synthesis of the central ring of fomitelic acids.



1.2.3 Chiral Methyl Ketones

There are no systematic studies on the asymmetric induction imparted by chiral methyl ketones. However, most of the examples reported so far suggest that substrate-controlled Mukaiyama aldol reactions based on chiral methyl ketones are poorly stereoselective. This lack of stereocontrol is well illustrated by the aldol reaction of chiral silyl enol ether (10), in which the major diastereomer, 11, depends on the achiral aldehyde (Scheme 1.8) [18].

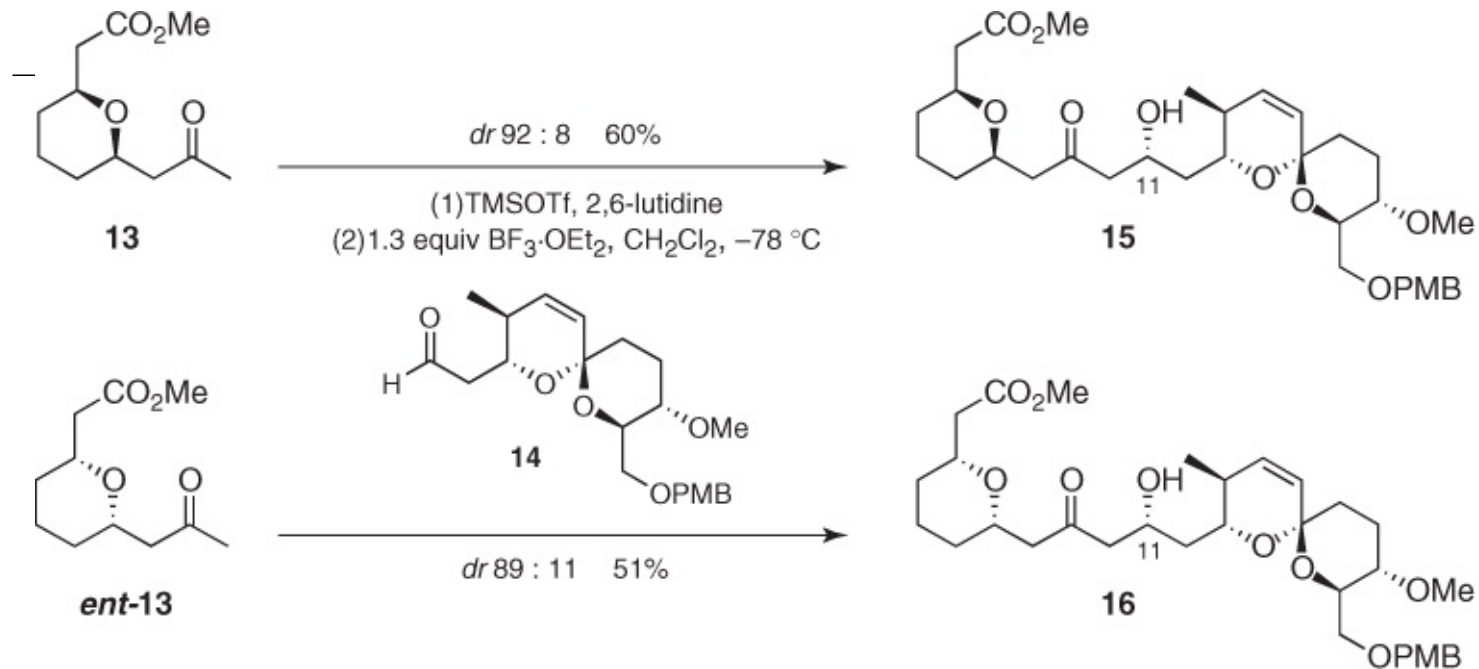
Scheme 1.8 Asymmetric induction imparted by a silyl enol ether from a chiral methyl ketone.



| R | dr (11 : 12) |
|-----------------------------------|--------------|
| Ph | 60 : 40 |
| <i>i</i> -Pr | 50 : 50 |
| PhCH ₂ CH ₂ | 36 : 64 |
| PhCH=CH | 33 : 67 |

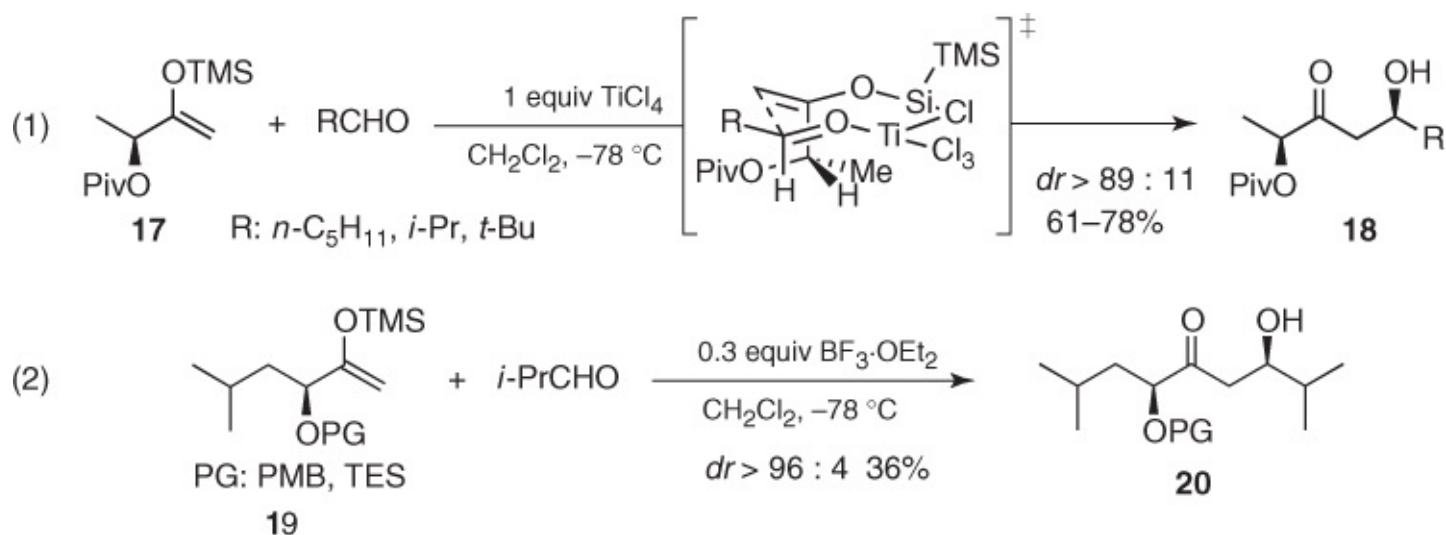
In a more complex framework, De Brabander also reported that silyl enol ethers from enantiomeric methyl ketones (13) and (*ent*-13) underwent additions to chiral aldehyde (14) to afford the corresponding aldol adducts 15 and 16 in similar yields (Scheme 1.9) [19]. Considering that the new C11-stereocenters possess the same configuration in both adducts and that the diastereoselectivity is comparable for both processes, it can be concluded that the asymmetric induction provided by the aldehyde is much more important than that provided by the ketone.

Scheme 1.9 Chiral methyl ketones in stereoselective Mukaiyama aldol reactions.



Lactate-derived and other α -hydroxy methyl ketones are exceptions to this trend. Thus, Trost found that TiCl₄-mediated aldol reactions of pivaloyl-protected silyl enol ether (**17**) afforded β -hydroxy ketones (**18**) in high yields and diastereomeric ratios up to 98 : 2 [20]. This was assumed to be achieved through an eight-membered cyclic transition state in which the titanium is simultaneously bound to the aldehyde and the enolsilane ((1) in [Scheme 1.10](#)). Importantly, dipole–dipole interactions are understood to favor the *antiperiplanar* arrangement of the C–OPiv and the C–OSi bonds and impel the aldehyde toward the less hindered face of the enolsilane. Moreover, Kalesse reported that parallel BF₃-catalyzed additions of silyl enol ethers (**19**) to isobutyraldehyde afforded the corresponding aldols (**20**) with excellent diastereoselectivity but in low yield ((2) in [Scheme 1.10](#)) [21]. The origin of such remarkable stereocontrol is unclear.

Scheme 1.10 Asymmetric induction imparted by chiral α -hydroxy methyl ketones in Mukaiyama aldol reactions.

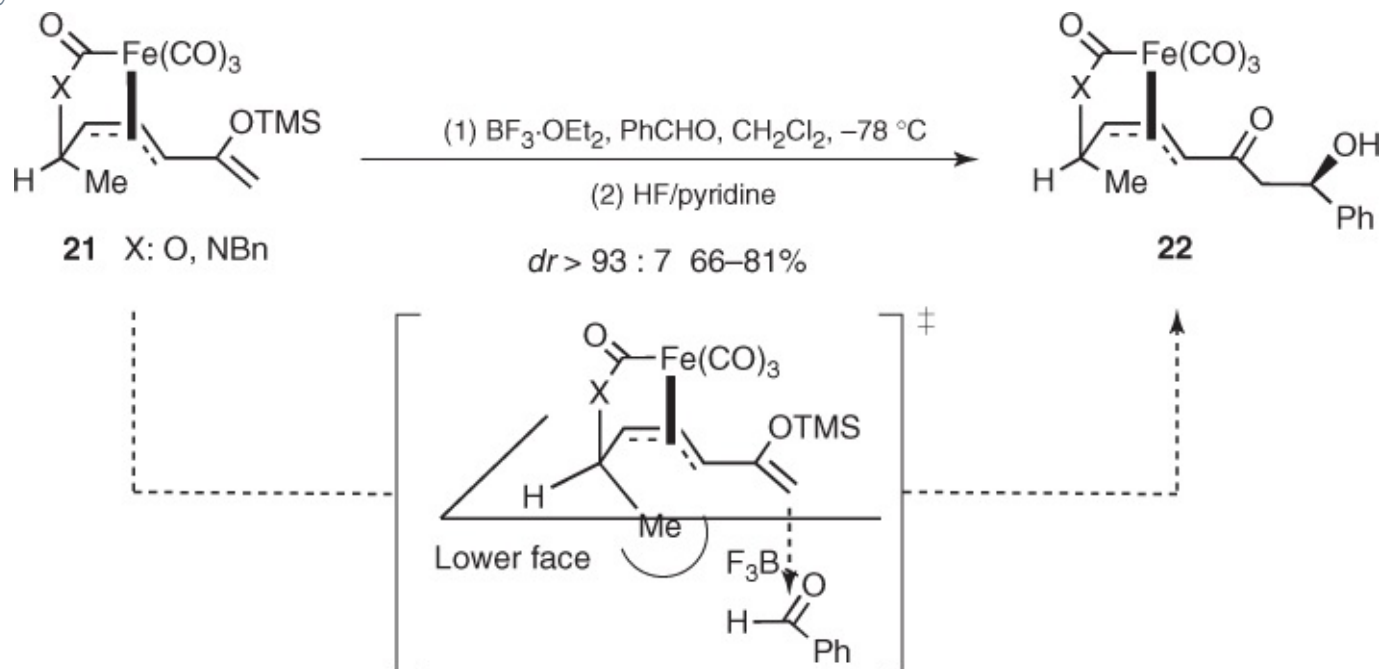


At this point, it is worth mentioning that Yamamoto has also reported highly diastereoselective Mukaiyama aldol reactions based on chiral β -tris(trimethylsilyl)silyloxy methyl ketones containing a single stereocenter at the β -position [22]. This chemistry is discussed in connection with parallel methodologies (Sections 1.2.4 and 1.3.6).

Finally, Ley reported that reactions of silyl enol ethers from chiral π -allyltricarboxyliron lactone or lactam complexes proceeded with a significant remote stereocontrol [23]. This is illustrated by the

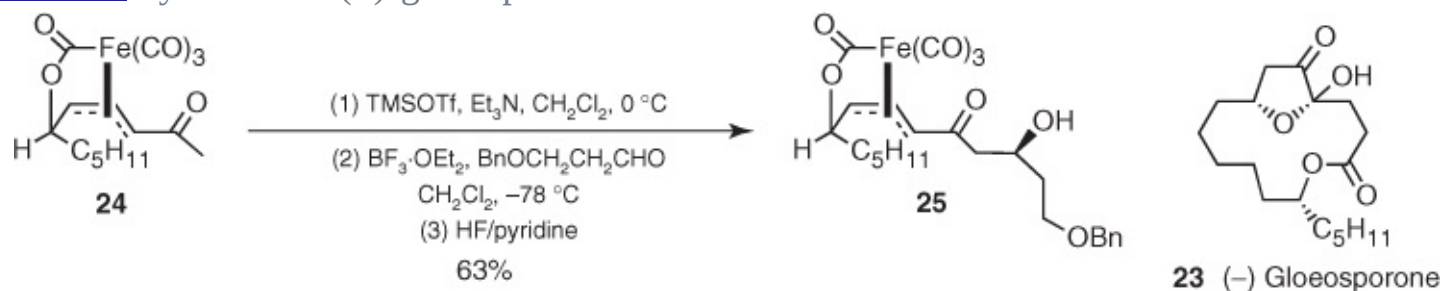
BF_3 -mediated addition of complexes **21** to benzaldehyde furnishing β -hydroxy ketones (**22**) with excellent diastereomeric ratios ([Scheme 1.11](#)). The remarkable 1,7-induction provided by the substrates is due to the chiral environment created on the lower face of the silyl enol ether (the upper face is blocked by the tricarbonyliron moiety) by the *endo*-oriented methyl substituent at the sp³ stereocenter. Then, the incoming activated aldehyde approaches in a *synclinal* arrangement in which unfavorable steric interactions are minimized.

[Scheme 1.11](#) Asymmetric induction imparted by chiral π -allyltricarbonyl iron complexes in Mukaiyama aldol reactions.



As the iron lactone and lactam (**22**) can be easily decomplexed to afford a rich array of stereodefined derivatives, this reaction may represent a powerful tool to the rapid construction of highly functionalized systems under *remote stereocontrol*. For instance, the total synthesis of (–)-gloeosporone (**23**) commenced with the addition of silyl enol ether from methyl ketone (**24**) to benzyloxypropanal, which afforded aldol (**25**) as a single diastereomer in a 63% yield ([Scheme 1.12](#)) [24].

[Scheme 1.12](#) Synthesis of (–)-gloeosporone.



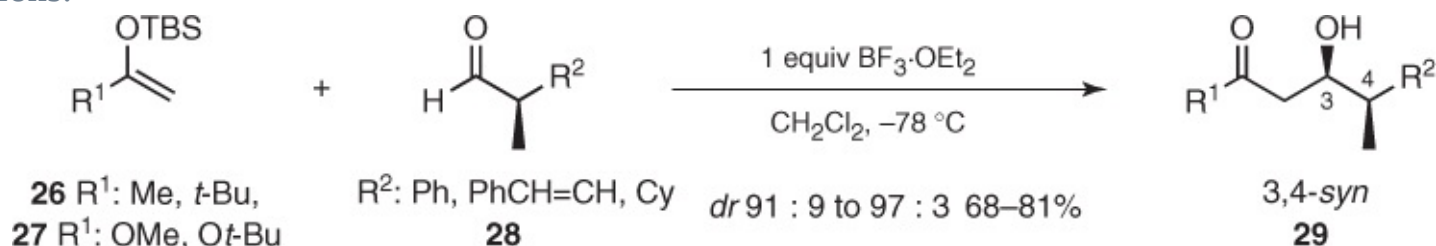
1.2.4 Chiral Aldehydes

The asymmetric induction of chiral aldehydes in Mukaiyama aldol reactions is much more important and has stimulated the formulation of increasingly more refined models to predict the π -facial selectivity in nucleophilic additions to the carbonyl bond [25]. Therefore, the influence of α - and β -substituents has received particular attention and is described in detail in the following sections.

1.2.4.1 1,2-Asymmetric Induction

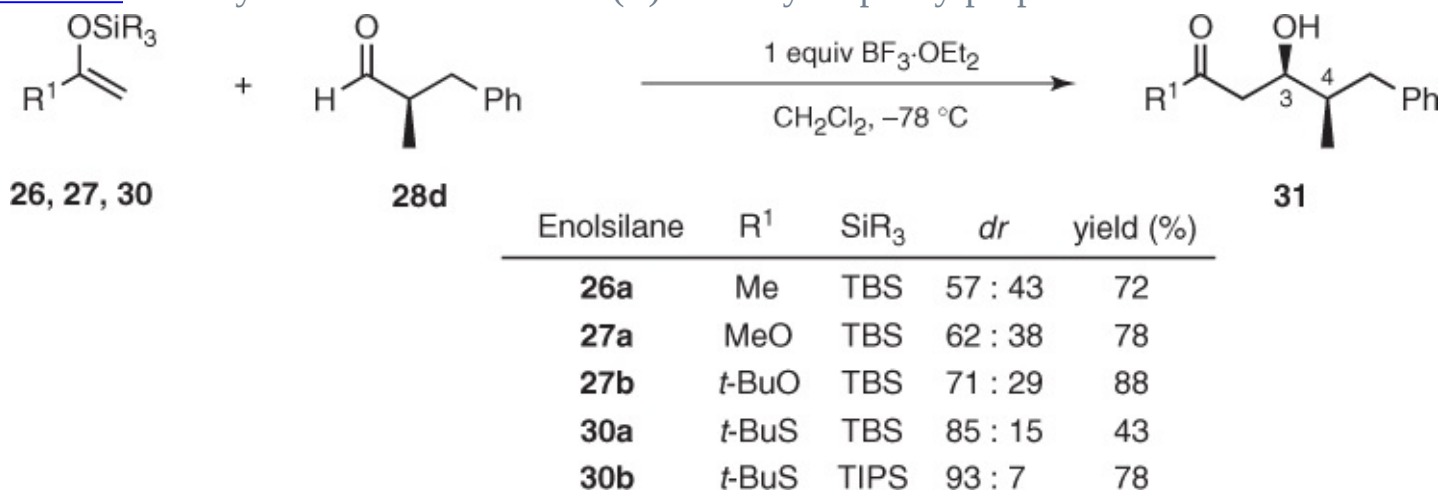
Pioneering studies on acyclic stereoselection established that Mukaiyama *acetate* aldol additions of enolsilane derivatives (**26**) and (**27**) to chiral α -methyl aldehydes (**28**) proceeded with high diastereofacial selectivity to favor 3,4-*syn* aldol adducts (**29**) (Scheme 1.13) [26].

Scheme 1.13 Asymmetric induction imparted by chiral α -methyl aldehydes in Mukaiyama aldol reactions.



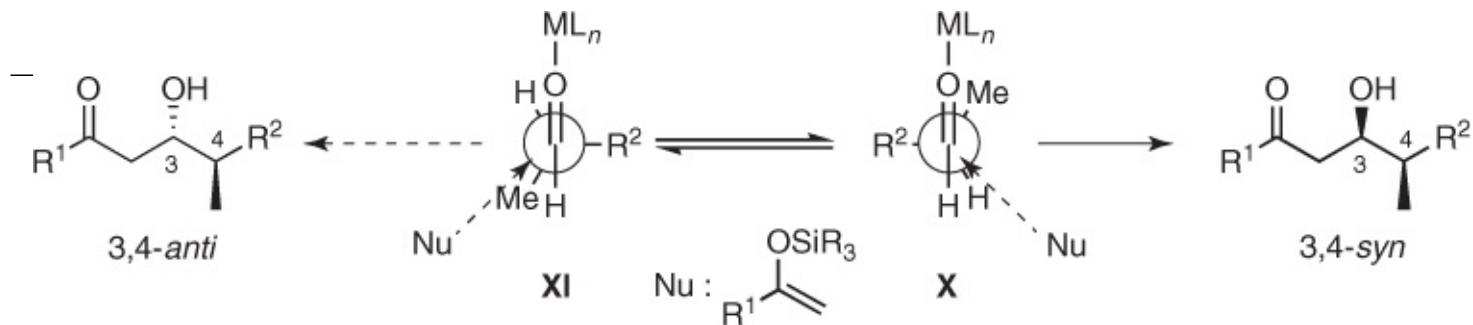
As expected, the 1,2-asymmetric induction of such aldehydes was eroded when R^2 was sterical similar to the α -methyl. The challenge posed by these transformations can be met by using more bulky nucleophiles, as has been observed in the aldol additions of enolsilanes (**26**), (**27**), and (**30**) to methyl-3-phenylpropanal (Scheme 1.14). The stereochemical outcome of these reactions shows the enhancement of the steric hindrance of R^1 and SiR_3 groups gives the corresponding 3,4-*syn* aldols (**31**) in higher diastereomeric ratios [26, 27]. A parallel improvement can also be attained by employing more bulky Lewis acids, but steric influences must be analyzed carefully because some combination of bulky nucleophiles and Lewis acids do not provide the expected results [27].

Scheme 1.14 Mukaiyama aldol additions to (*R*) 2-methyl-3-phenylpropanal.



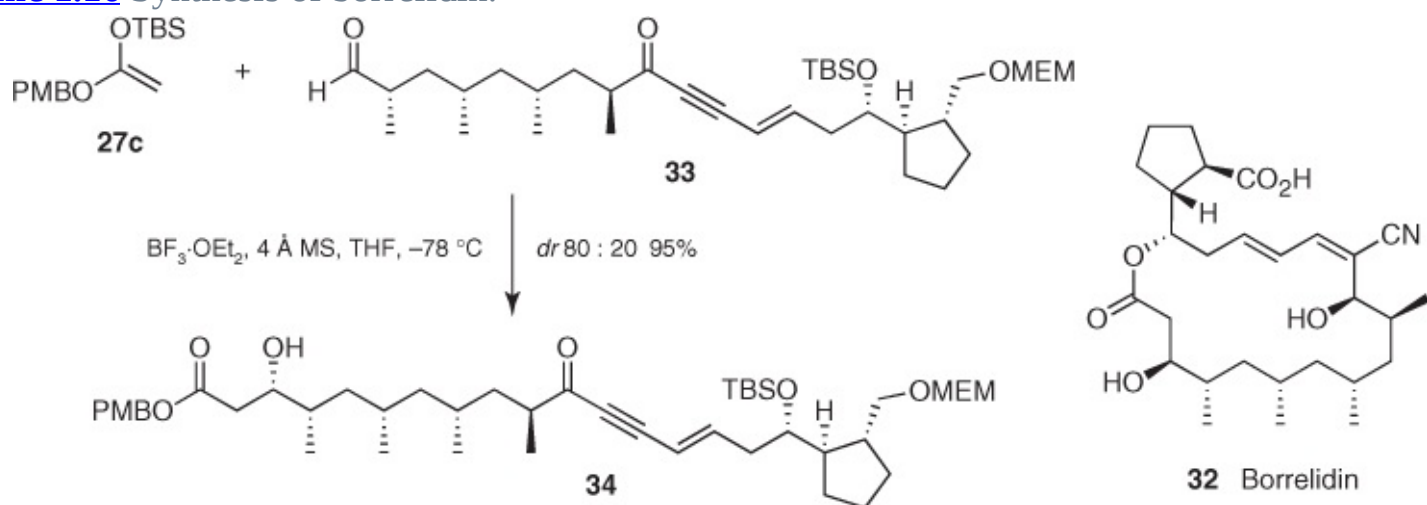
The *Felkin–Anh* model [25, 28] is usually invoked to account for the asymmetric induction observed in the Mukaiyama aldol additions to these chiral α -methyl aldehydes. Thus, once the methyl group has been identified as the *medium size* group, the major 3,4-*syn* diastereomer is obtained by bringing the enolsilane close to the face of the C—O bond in which the steric interactions between the nucleophile and the α -substituent (H vs Me) are weaker (X in Scheme 1.15).

Scheme 1.15 The *Felkin–Anh* model for Mukaiyama aldol additions to chiral α -methyl aldehydes.



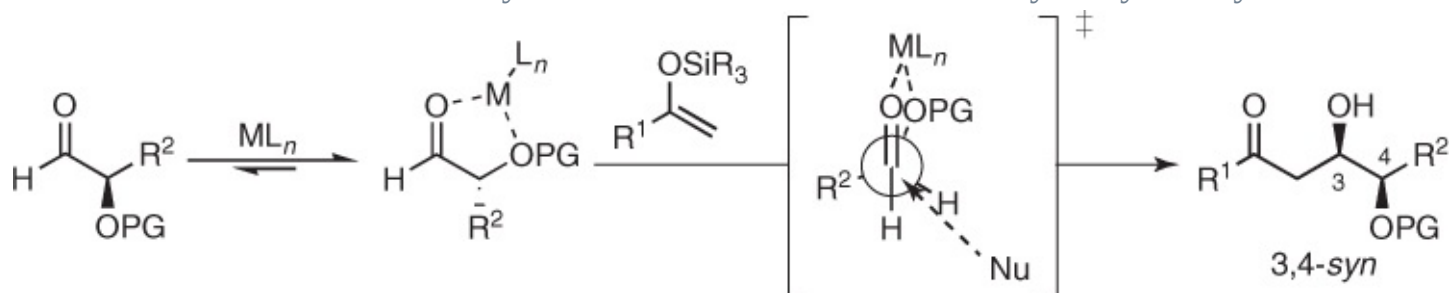
The total synthesis of borrelidin (**32**) reported by Theodorakis contains a good example of stereocontrol based on the asymmetric induction imparted by such chiral aldehydes [29]. As represented in [Scheme 1.16](#), the Mukaiyama aldol addition of silyl ketene acetal (**27c**) to α -methyl aldehyde (**33**) produced the desired ester (**34**) as a 80 : 20 mixture of diastereomers in a 95% combined yield, which demonstrates the π -facial selectivity provided by the α -stereocenter of aldehydes of this kind [30].

Scheme 1.16 Synthesis of borrelidin.



The substitution of the methyl group by a heteroatom affects these transformations dramatically. Indeed, a tenet in asymmetric synthesis states that nucleophilic additions to chiral aldehydes bearing an α -heteroatom attain outstanding levels of stereocontrol provided that the reaction is carried out under conditions in which chelate organization is favored. In this context, the *Cram* model [25, 31] accounts for the stereochemical outcome of chelate-controlled Mukaiyama aldol reactions. According to this model, the appropriate choice of the Lewis acid and the protecting group of α -hydroxy aldehydes permits the formation of stable five-membered chelated complexes and gives the corresponding 3,4-*syn* aldol adducts in a highly diastereoselective manner, presumably through an open transition state in which the nucleophile approaches the less hindered face of the chelated carbonyl group ([Scheme 1.17](#)).

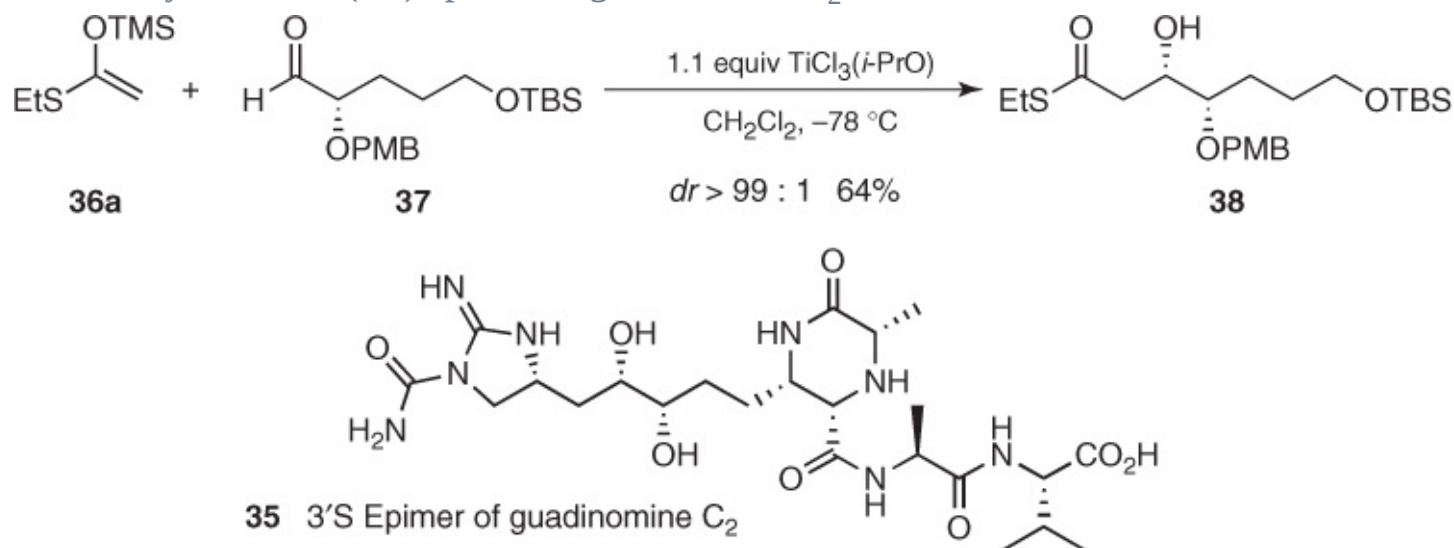
Scheme 1.17 *Cram* model for Mukaiyama aldol additions to chiral α -hydroxy aldehydes.



This highly reliable and powerful element of stereocontrol has been widely exploited in the

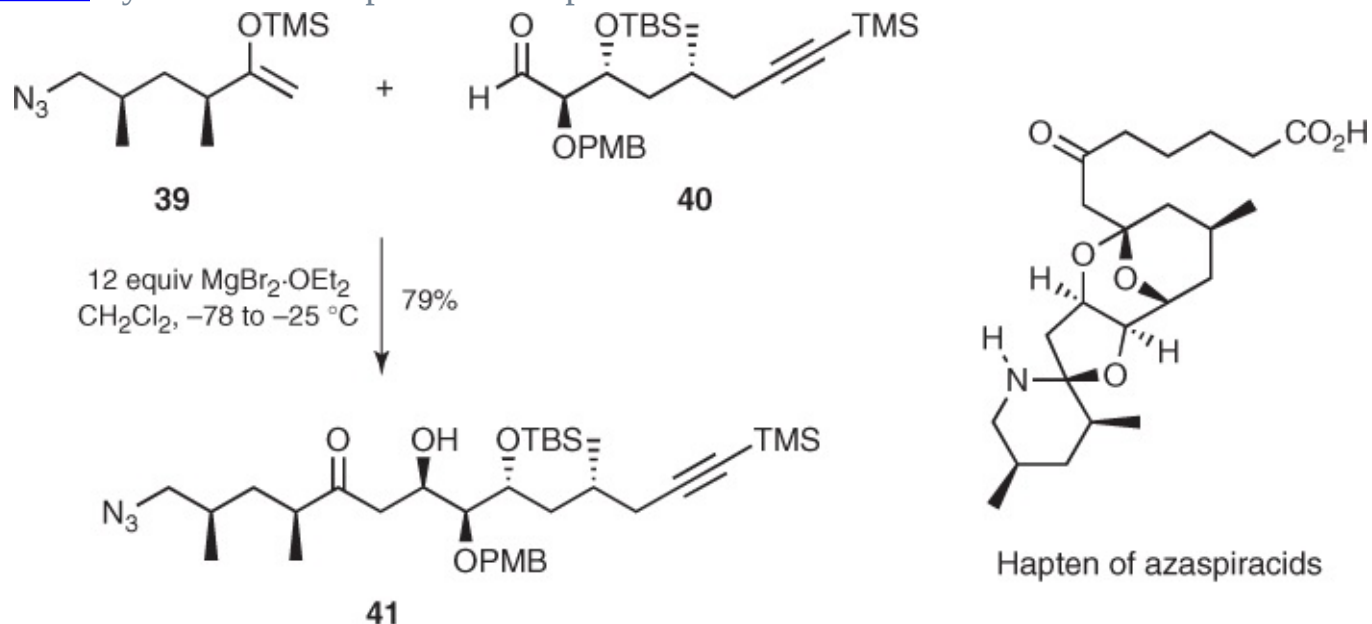
synthesis of natural products. For instance, Sunazuka and Omura used a chelate-controlled Mukaiyama aldol reaction for the total synthesis of an epimer of guadinomine C₂ (**35**). As shown in [Scheme 1.18](#), addition of silyl ketene S,O-acetal (**36a**) to chiral α-OPMB aldehyde (**37**) in the presence of 1.1 equiv of TiCl₃(*i*-PrO) gave 3,4-*syn* aldol (**38**) with exceptional diastereoselectivity in 64% yield [32].

Scheme 1.18 Synthesis of (3′S) epimer of guadinomine C₂.



Moreover, Forsyth reported that the addition of mild Lewis acid MgBr₂ · OEt₂ to a mixture of chiral silyl enol ether (**39**) and α-OPMB aldehyde (**40**) triggered a smooth aldol reaction that furnished 3,4-*syn* aldol (**41**) as a single diastereomer in 79% yield, which was further elaborated to a hapten for azaspiracids ([Scheme 1.19](#)) [33]. A very similar transformation was also reported by Evans [34, 35].

Scheme 1.19 Synthesis of a hapten for azaspiracids.



In the absence of chelated intermediates, nucleophilic additions to chiral aldehydes possessing an heteroatom are currently explained by the *polar Felkin–Anh* [36] and *Cornforth* models [37], which apply to conformations **XII–XV** arising from rotation about the C1–C2 bond of the aldehyde ([Scheme 1.20](#)) [25]. The *polar Felkin–Anh* model is based on the premise that staggered transition states positioning the C–X bond perpendicularly to the carbonyl bond are preferred ((1) in [Scheme 1.20](#)). In turn, the *Cornforth* model embraces the assumption that electrostatic effects are instrumental in dictating a nearly antiparallel relationship between the carbonyl and the C–X bond ((2) in [Scheme 1.20](#)).

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