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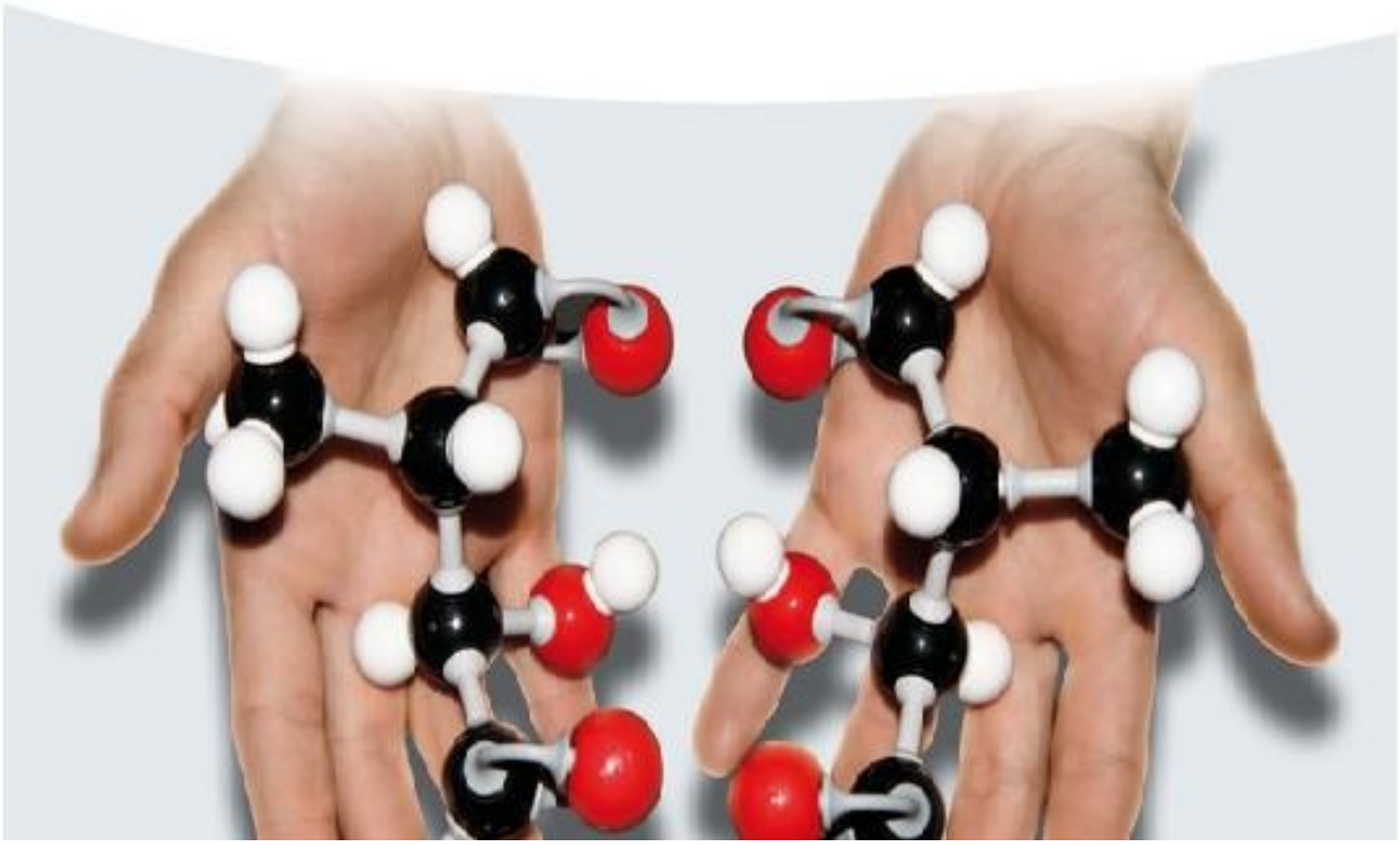
Modern Methods in Stereoselective Aldol Reactions



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Modern Methods in Stereoselective Aldol Reactions

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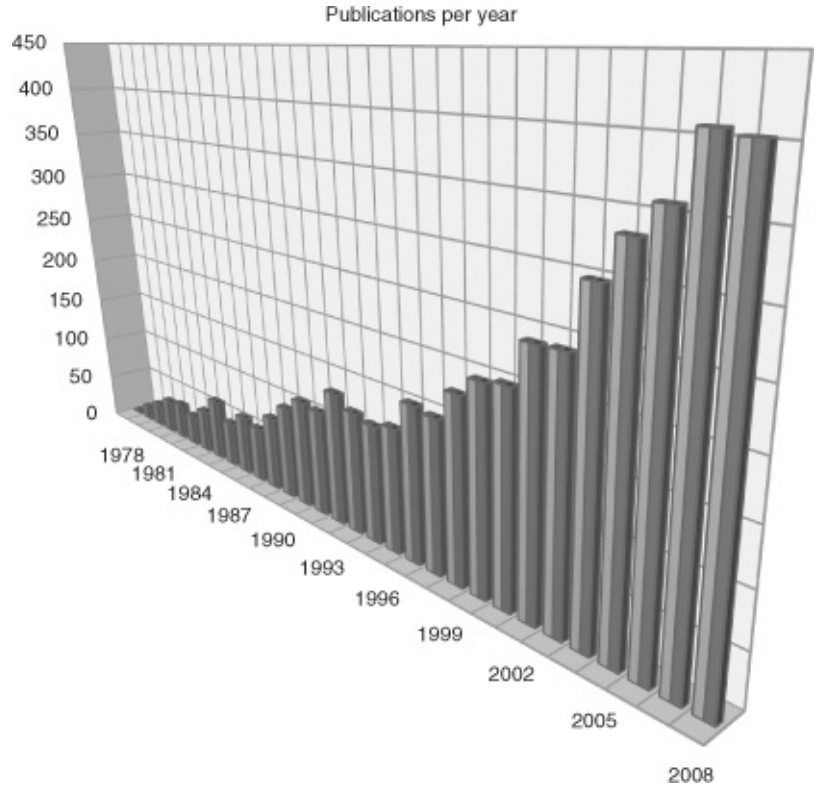
Preface

Stereoselectivity is one of the most important aspects for natural product chemists. Following th increasing possibility of detection and assignment of stereogenic centers, a tremendous increase stereoselective methods of organic reactions, particularly aldol reactions, has been noticed. In th beginning of this development, only sporadic examples of stereoselective aldol reactions we described, mostly in the context of total syntheses of natural products. An outstanding early examp is the R. B. Woodward's proline-catalyzed aldol addition in the total synthesis of erythronolide A a the Harvard University in 1981. In the following three decades, a vast arsenal of stereoselective ald 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 enantioselectivit Stereoselection is discussed under several different aspects. One aspect is the deployment of differe substrates – acetate or propionate aldol reactions. Another aspect is the mode of action includi metal enolate chemistry, Lewis acid as well as Lewis base catalysis, enzymatic catalysis, ar organocatalysis. There are some overlappings of these aspects in the chapters covering the cros cutting themes of vinyloguos Mukaiyama reaction or asymmetric inductions (e.g., compare Schem 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 th techniques for installing required configurations during aldol reactions. The utility of th corresponding methods is shown in the context of total syntheses of natural products. All chapters a 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 organiz and summarize this vast amount of material. It has been a great pleasure for me to work with this tea of authors at all times. Finally, my special thanks go to Elke Maase and Bernadette Gmeiner WILEY for their fine work in making this book a reality.

Rainer Mahrwa

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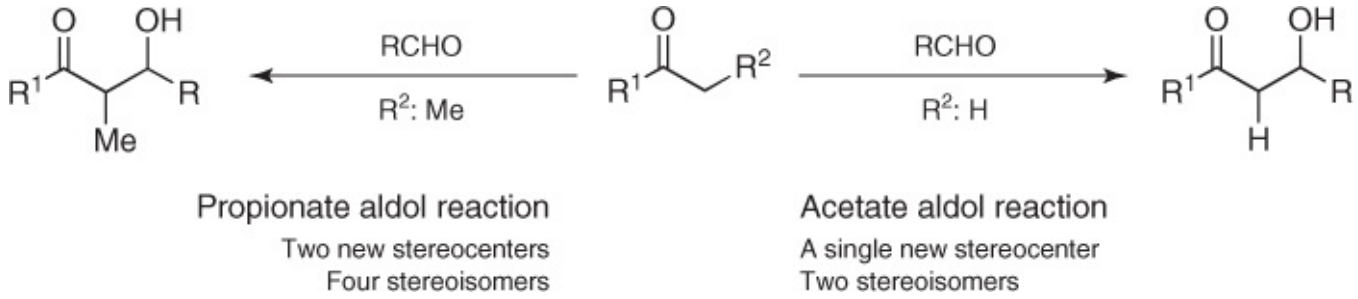
Stereoselective Acetate Aldol Reactions

Pedro Romea and Fèlix Urp

1.1 Introduction

The stereochemical control of aldol reactions from unsubstituted enol- or enolatelike species, what a known as *acetate aldol reactions*, has been a matter of concern for nearly 30 years [1, 2]. Indee pioneering studies soon recognized that the asymmetric installation of a single stereocenter in suc aldol reactions was much more demanding than the simultaneous construction of two ne stereocenters in the related *propionate* counterparts (Scheme 1.1) [3]. This challenge, together wi the ubiquitous presence of chiral β-hydroxy α-unsubstituted oxygenated structures in natural product has motivated the development of new concepts and strategies and a large number of high stereoselective methodologies. These involve Lewis-acid-mediated additions of enolsilane derivativ of carbonyl compounds to aldehydes (*Mukaiyama* aldol variant) [4, 5], a plethora of transformatio 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 f more powerful and selective methodologies and a better understanding of their intricate mechanism is an active area of research. Herein, we describe the most significant achievements in the field stereoselective *acetate aldol* reactions based on the Lewis-acid-mediated addition of enolsilanes an metal enolates to aldehydes, with particular attention to their application to the asymmetric synthes of natural products. Recent advances in parallel organocatalytic procedures are not discussed.

Scheme 1.1 Aldol reactions.



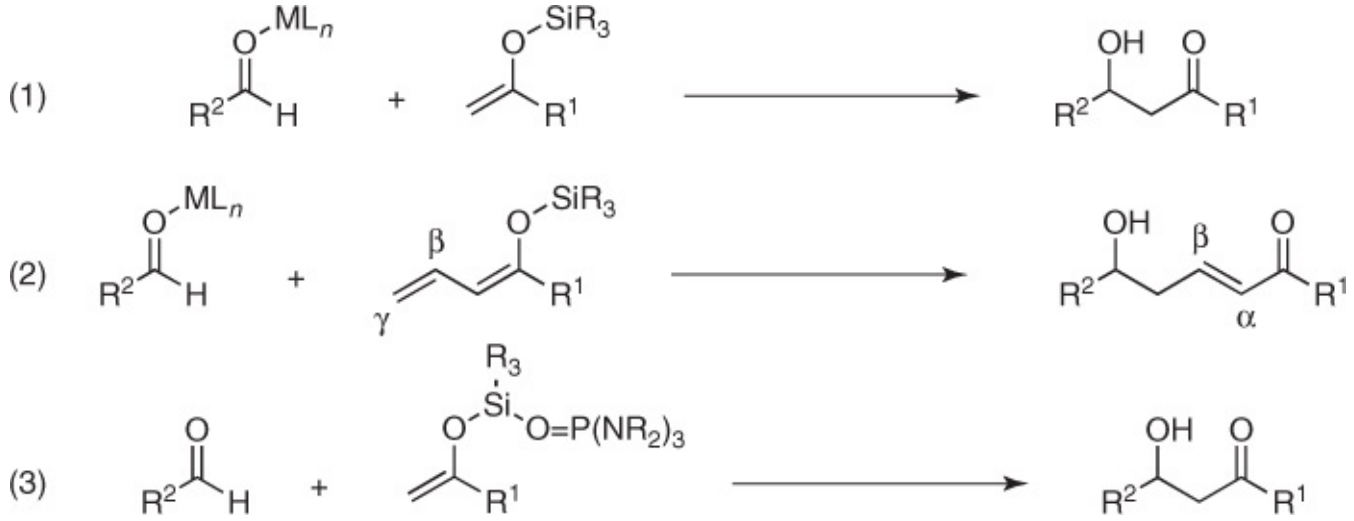
1.2 Mukaiyama Aldol Reaction

1.2.1 Concept and Mechanism

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

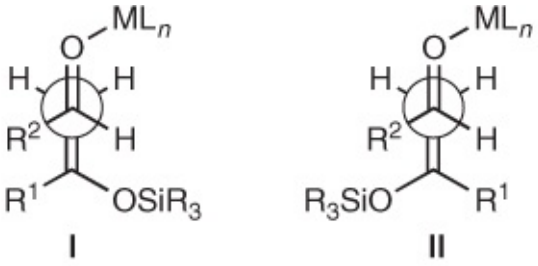
nucleophilicity of enolsilanes. The former option is achieved by coordination of Lewis acids (ML_n) the carbonyl group, which enhances the electrophilicity of the C—O bond and facilitates the attack enolsilanes. This represents the canonical Mukaiyama aldol variant ((1) in Scheme 1.2) [4, 5]. It als covers vinylogous aldol transformations, which involve the reactions of γ-unsubstituted β, conjugated enolsilanes ((2) in Scheme 1.2) [8]. In turn, the latter option takes advantage of th activation of the nucleophilic character of enolsilanes by binding of Lewis bases such phosphoramides ($O—P(NR_2)_3$) to the silicon atom ((3) in Scheme 1.2) [9].

Scheme 1.2 Mukaiyama aldol variants.

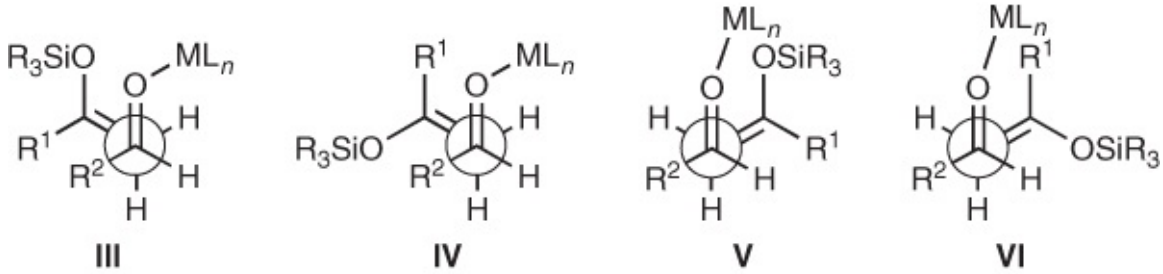


Early mechanistic analyses suggested that Lewis-acid-mediated aldol reactions represented Scheme 1.2 proceeded through open transition states [4, 5, 10]. This model assumes a *transo* geometry for the Lewis-acid-aldehyde complex, which the enolsilane attacks following *antiperiplan* or *synclinal* approaches,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



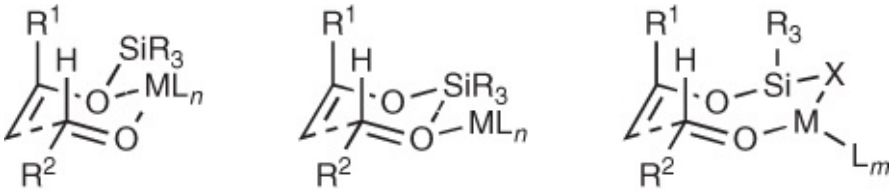
Antiperiplanar approaches



Synclinal approaches

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

Scheme 1.4 Cyclic transition states for Mukaiyama aldol reactions.

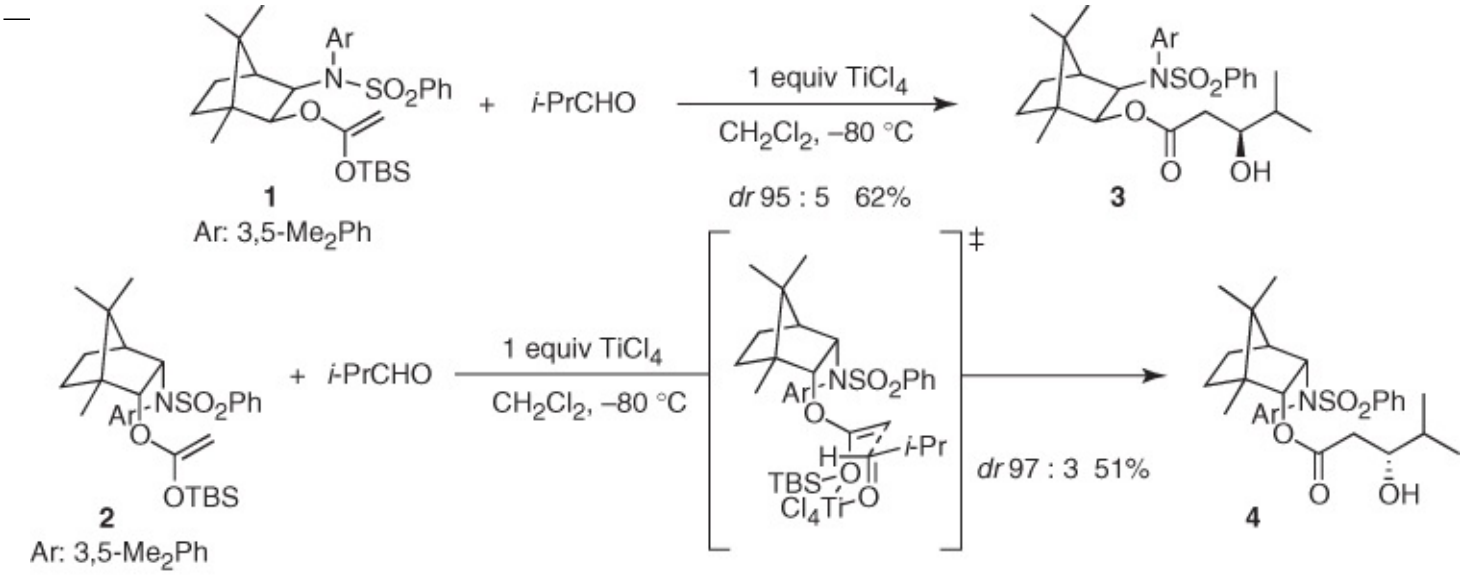


Irrespective of the mechanistic pathway, the asymmetric induction achieved by these Lewis-aci mediated aldol reactions depends on chiral elements on the enolsilane (the nucleophilic partner), th aldehyde (the electrophilic partner), or the Lewis acid (the activating element), so they must a cooperate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

1.2.2 Chiral Auxiliaries

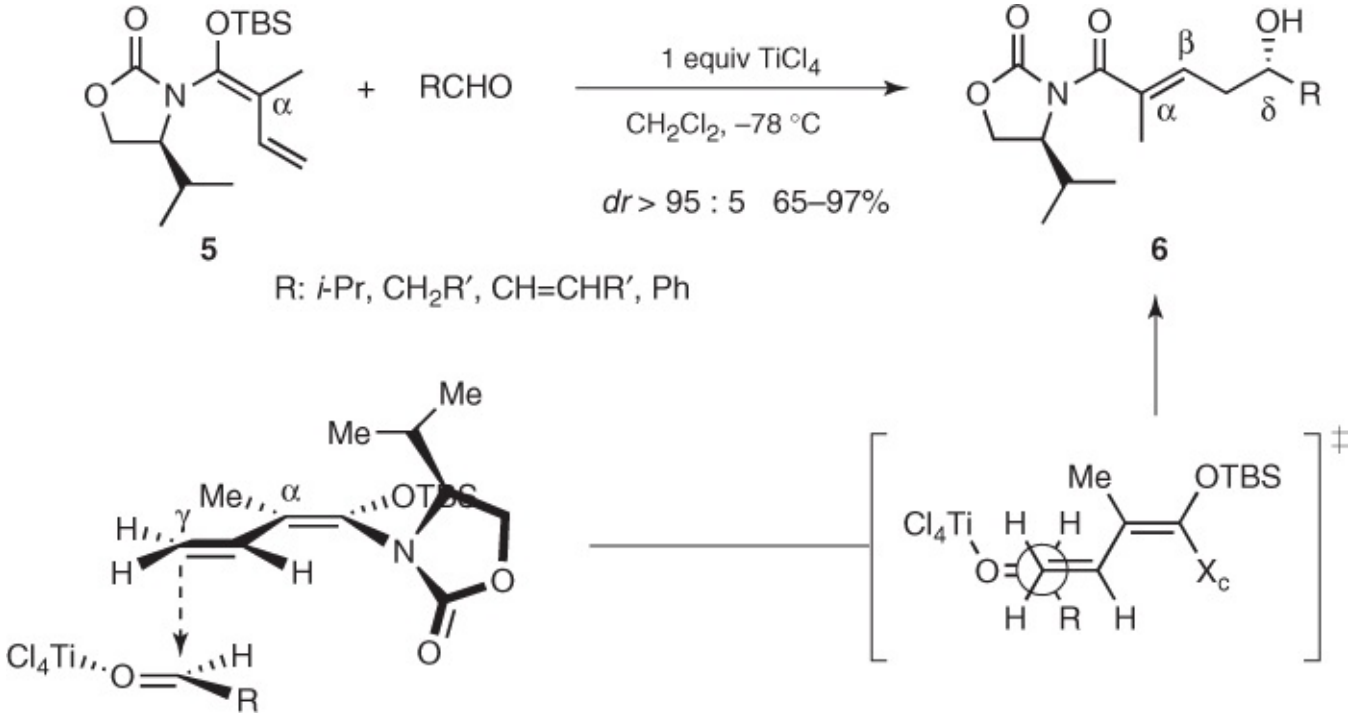
In the context of emergence of chiral auxiliaries as powerful platforms to achieve asymmetr transformations, Helmchen reported highly diastereoselective aldol reactions of chiral auxiliary-base silyl ketene acetals (**1**) and (**2**) [12, 13]. As shown in Scheme 1.5, $TiCl_4$-mediated additions of **1** and to isobutyraldehyde afforded aldol adducts **3** and **4** in good yields and excellent diastereomeric ratio presumably through a chairlike transition state in which the titanium atom is simultaneous coordinated to the carbonyl and the OTBS group. In turn, these adducts can be converted into th 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 th sort of transformations a few years ago. Indeed, Kobayashi described highly stereoselecti vinylogous Mukaiyama aldol reactions using silyl vinyl ketene *N,O*-acetals prepared from valin derived 1,3-oxazolidin-2-ones [14]. As represented in Scheme 1.6, $TiCl_4$-mediated additions of methyl acetal (**5**) to aliphatic, α, β-unsaturated, and aromatic aldehydes afforded δ-hydroxy-α-methy α, β-unsaturated imides (**6**) in excellent yields and diastereomeric ratios. Such outstanding remo asymmetric induction was believed to arise from a conformation in which the chiral heterocycle almost perpendicular to the dienol plane and the isopropyl group overhangs the upper face of t dienol moiety. Then, the aldehyde approaches from the less hindered face through an open transitio state in which the α-methyl group appears to be essential to achieve the observed high stereocontro Finally, the chiral auxiliary can be removed by well-known methodologies used for Evans auxiliaries

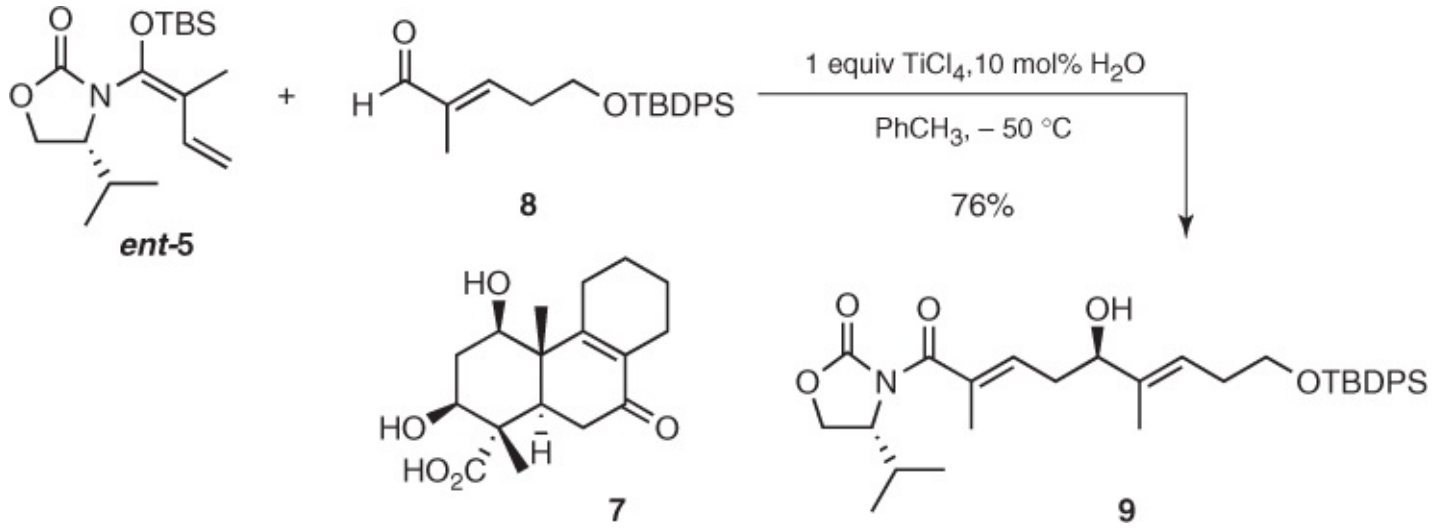
Scheme 1.6 Chiral auxiliary-based vinylogous Mukaiyama aldol reactions.



This methodology was used for the construction of the AB ring of fomitellic acids (**7**) (Scheme 1. [15]. Initially, application of the standard conditions to ***ent*-5** and enal (**8**) provided the desired ald

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

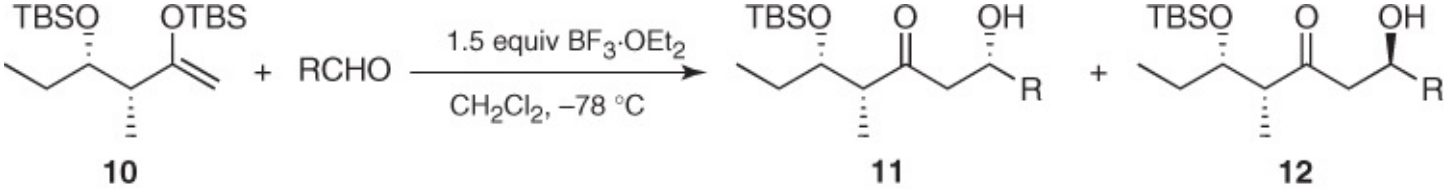
Scheme 1.7 Synthesis of the central ring of fomitellic acids.



1.2.3 Chiral Methyl Ketones

There are no systematic studies on the asymmetric induction imparted by chiral methyl ketone However, most of the examples reported so far suggest that substrate-controlled Mukaiyama ald reactions based on chiral methyl ketones are poorly stereoselective. This lack of stereocontrol is we illustrated by the aldol reaction of chiral silyl enol ether (**10**), in which the major diastereomer, **11** **12**, depends on the achiral aldehyde (Scheme 1.8) [18].

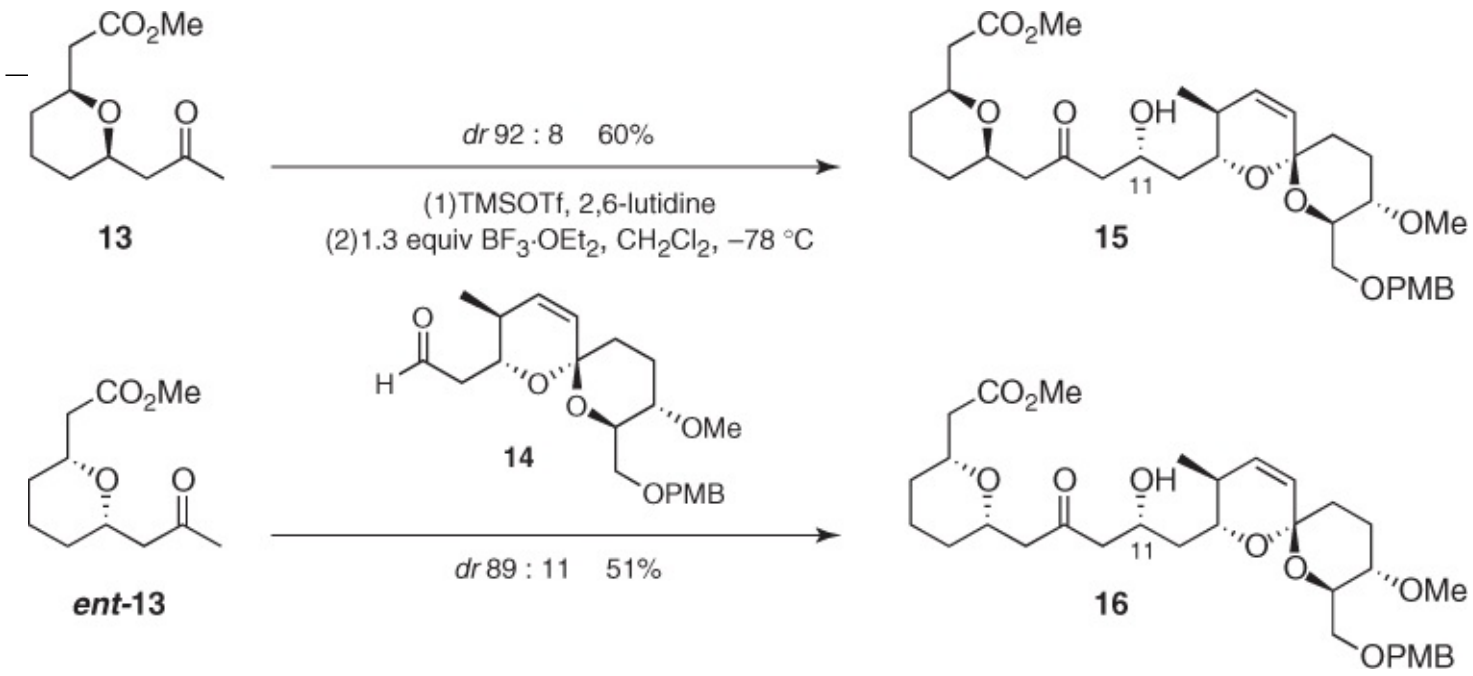
Scheme 1.8 Asymmetric induction imparted by a silyl enol ether from a chiral methyl ketone.



R	*dr* (**11** : **12**)
Ph	60 : 40
i-Pr	50 : 50
$PhCH_2CH_2$	36 : 64
PhCH=CH	33 : 67

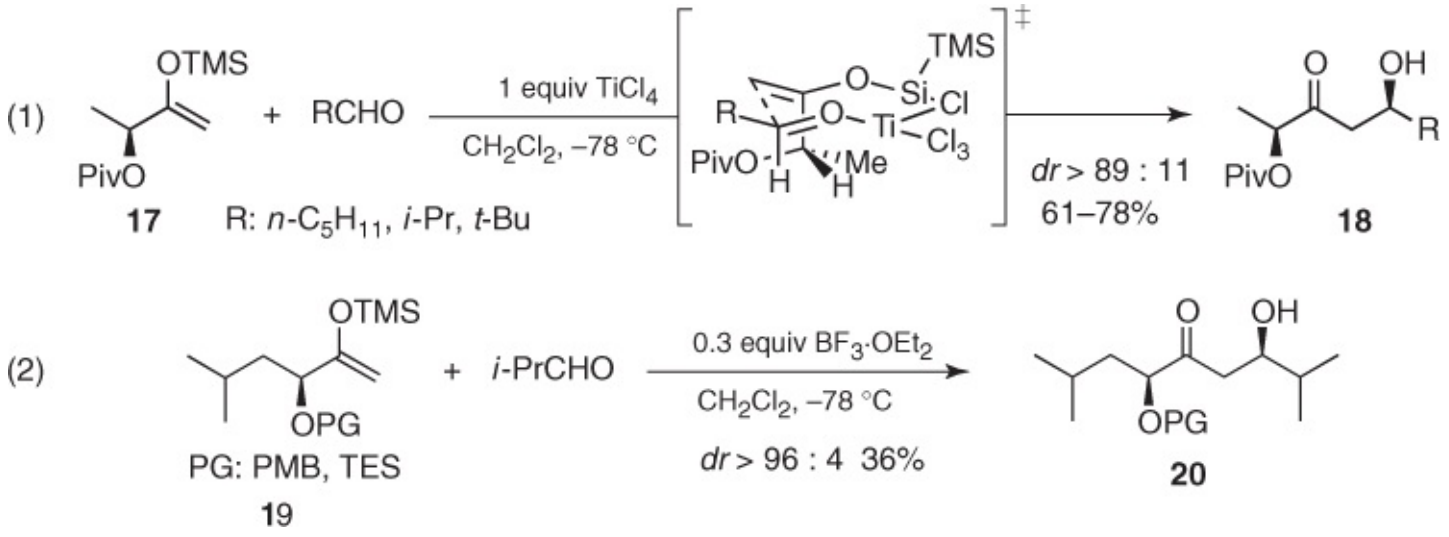
In a more complex framework, De Brabander also reported that silyl enol ethers from enantiomer methyl ketones (**13**) and (***ent*-13**) underwent additions to chiral aldehyde (**14**) to afford th corresponding aldol adducts **15** and **16** in similar yields (Scheme 1.9) [19]. Considering that the ne C11-stereocenters possess the same configuration in both adducts and that the diastereoselectivity comparable for both processes, it can be concluded that the asymmetric induction provided by th 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 four that $TiCl_4$-mediated aldol reactions of pivaloyl-protected silyl enol ether (**17**) afforded β-hydrox ketones (**18**) in high yields and diastereomeric ratios up to 98 : 2 [20]. This was assumed to l achieved through an eight-membered cyclic transition state in which the titanium is simultaneous bound to the aldehyde and the enolsilane ((1) in Scheme 1.10). Importantly, dipole–dipole interactio are understood to favor the *antiperiplanar* arrangement of the C–OPiv and the C–OSi bonds and imp the aldehyde toward the less hindered face of the enolsilane. Moreover, Kalesse reported that parall BF_3-catalyzed additions of silyl enol ethers (**19**) to isobutyraldehyde afforded the correspondi aldols (**20**) with excellent diastereoselectivity but in low yield ((2) in Scheme 1.10) [21]. The origin such remarkable stereocontrol is unclear.

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

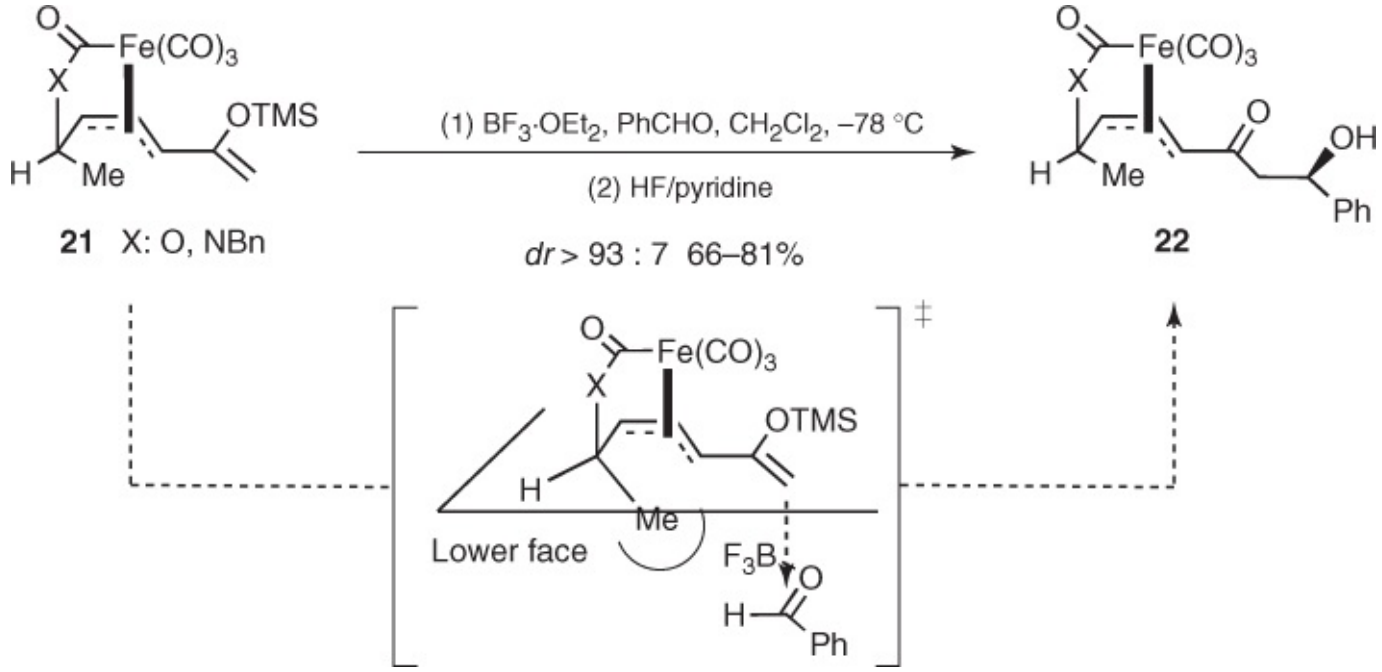


At this point, it is worth mentioning that Yamamoto has also reported highly diastereoselectiv Mukaiyama aldol reactions based on chiral β-tris(trimethylsilyl)silyloxy methyl ketones containing single stereocenter at the β-position [22]. This chemistry is discussed in connection with parall methodologies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

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

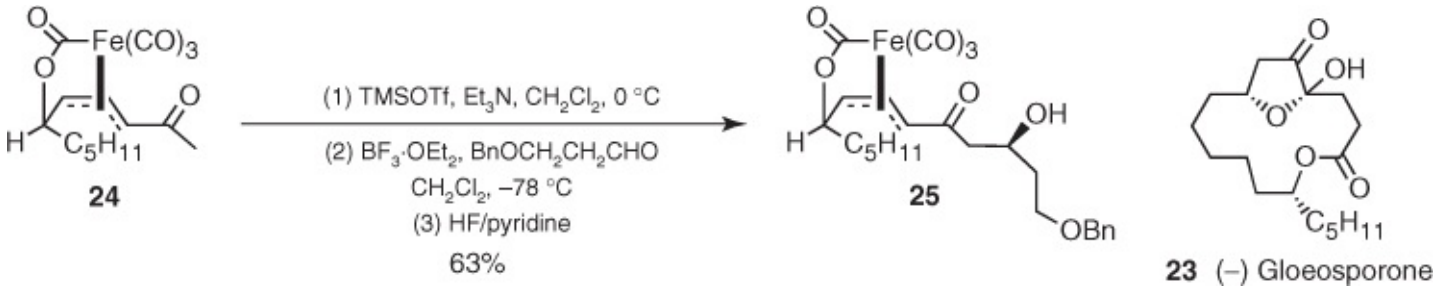
BF_3-mediated addition of complexes **21** to benzaldehyde furnishing β-hydroxy ketones (**22**) wi excellent diastereomeric ratios (Scheme 1.11). The remarkable 1,7-induction provided by the substrates is due to the chiral environment created on the lower face of the silyl enol ether (the upp face is blocked by the tricarbonyliron moiety) by the *endo*-oriented methyl substituent at the sp stereocenter. Then, the incoming activated aldehyde approaches in a *synclinal* arrangement in whi 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 stereodefined derivatives, this reaction may represent a powerful tool to the rapid construction highly functionalized systems under *remote stereocontrol*. For instance, total synthesis of (− gloeosporone (**23**) commenced with the addition of silyl enol ether from methyl ketone (**24**) benzyloxypropanal, which afforded aldol (**25**) as a single diastereomer in a 63% yield (Scheme 1.1 [24].

Scheme 1.12 Synthesis of (−)-gloeosporone.



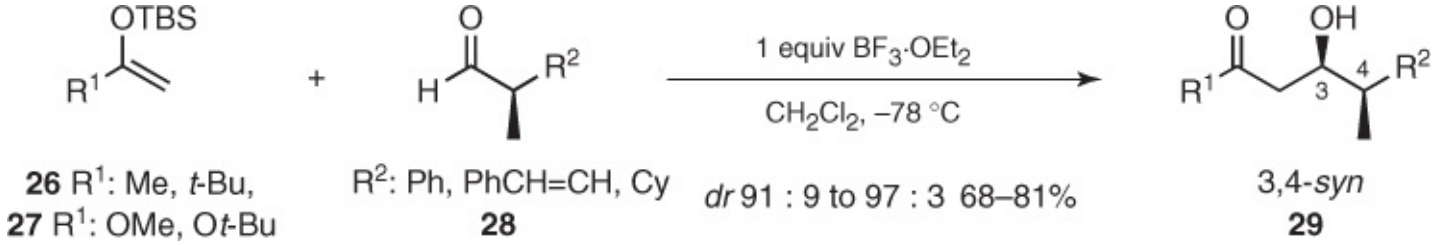
1.2.4 Chiral Aldehydes

The asymmetric induction of chiral aldehydes in Mukaiyama aldol reactions is much more importa and has stimulated the formulation of increasingly more refined models to predict the π-faci selectivity in nucleophilic additions to the carbonyl bond [25]. Therefore, the influence of α- and 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 enolsilane derivatives (**26**) and (**27**) to chiral α-methyl aldehydes (**28**) proceeded with hig 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.



26 R^1: Me, *t*-Bu, **27** R^1: OMe, O*t*-Bu

R^2: Ph, PhCH=CH, Cy **28**

dr 91 : 9 to 97 : 3 68–81%

3,4-*syn* **29**

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 bull 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 th enhancement of the steric hindrance of R^1 and SiR_3 groups gives the corresponding 3,4-*syn* aldols (**3** in higher diastereomeric ratios [26, 27]. A parallel improvement can also be attained by employin more bulky Lewis acids, but steric influences must be analyzed carefully because some combinatio of bulky nucleophiles and Lewis acids do not provide the expected results [27].

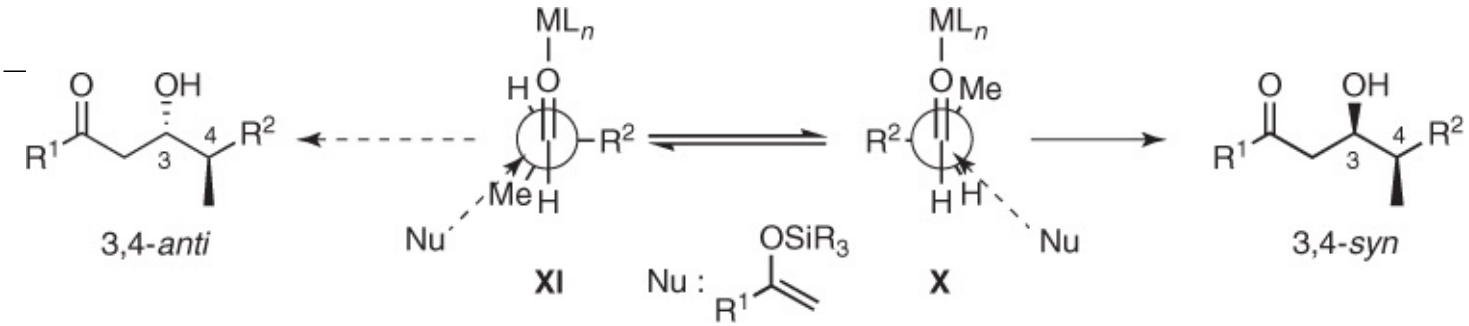
Scheme 1.14 Mukaiyama aldol additions to (*R*) 2-methyl-3-phenylpropanal.

26, 27, 30 **28d** **31**

Enolsilane	R^1	SiR_3	*dr*	yield (%)
26a	Me	TBS	57 : 43	72
27a	MeO	TBS	62 : 38	78
27b	*t*-BuO	TBS	71 : 29	88
30a	*t*-BuS	TBS	85 : 15	43
30b	*t*-BuS	TIPS	93 : 7	78

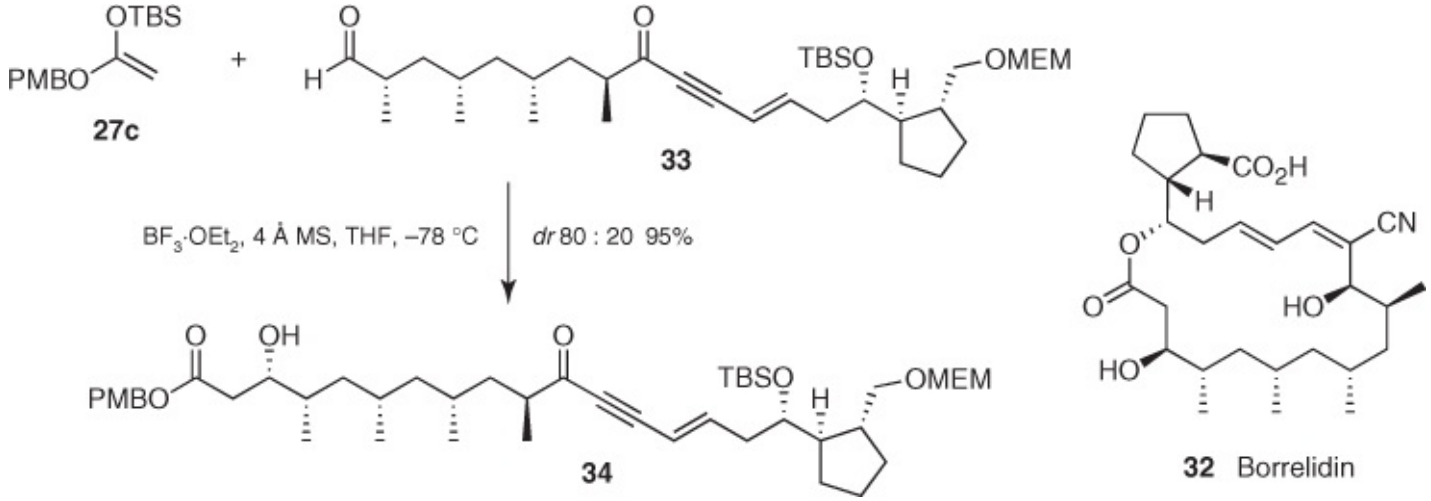
The *Felkin–Anh* model [25, 28] is usually invoked to account for the asymmetric induction observe in the Mukaiyama aldol additions to these chiral α-methyl aldehydes. Thus, once the methyl group h been identified as the *medium size* group, the major 3,4-*syn* diastereomer is obtained by bringing th enolsilane close to the face of the C—O bond in which the steric interactions between the nucleophi 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.



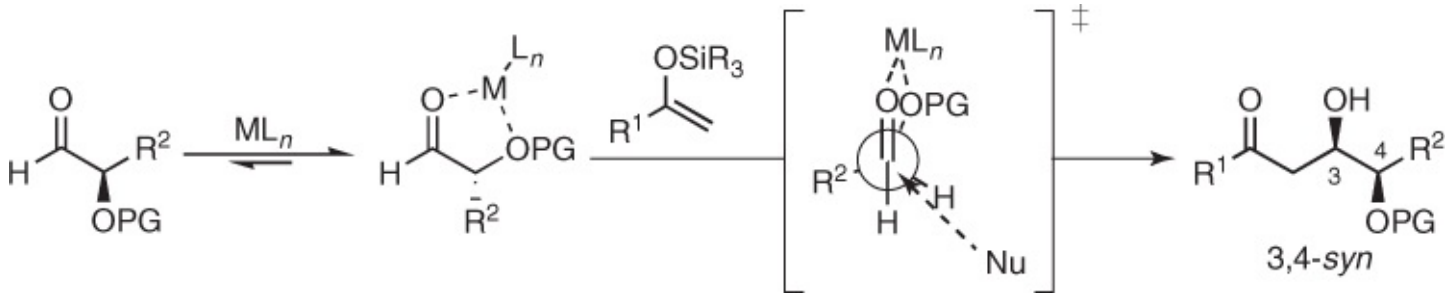
The total synthesis of borrelidin (**32**) reported by Theodorakis contains a good example stereocontrol based on the asymmetric induction imparted by such chiral aldehydes [29]. A represented in Scheme 1.16, the Mukaiyama aldol addition of silyl ketene acetal (**27c**) to α-meth aldehyde (**33**) produced 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 aldehydes of this kind [30].

Scheme 1.16 Synthesis of borrelidin.



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

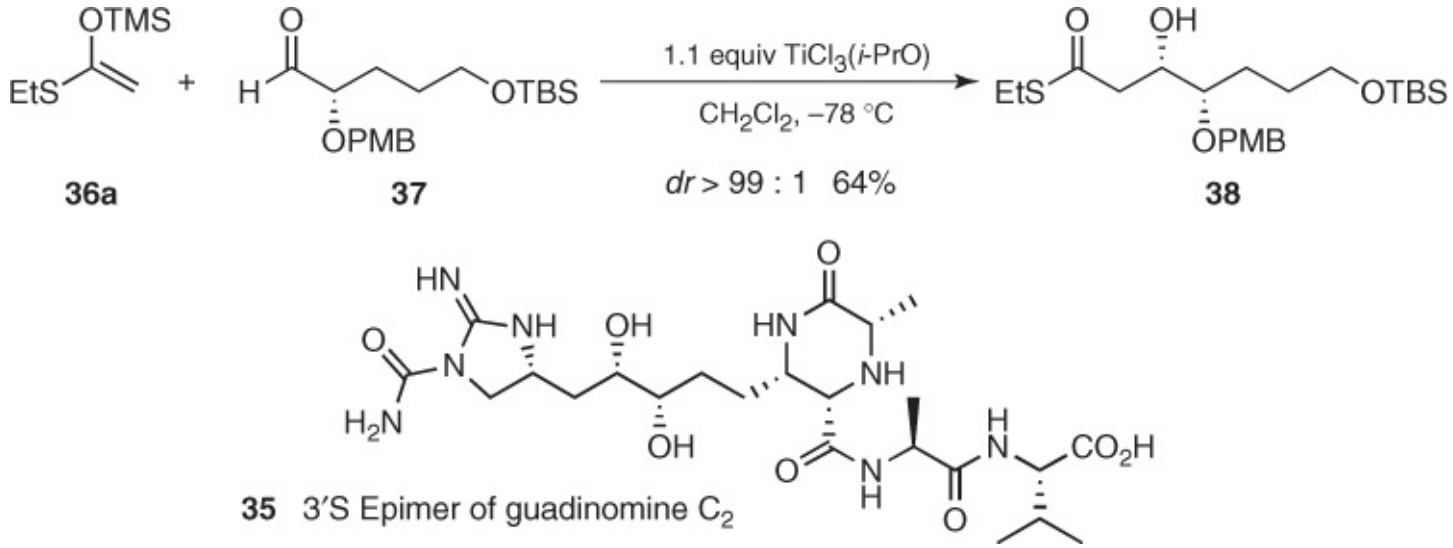
Scheme 1.17 *Cram* model for Mukaiyama aldol additions to chiral α-hydroxy aldehydes.



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

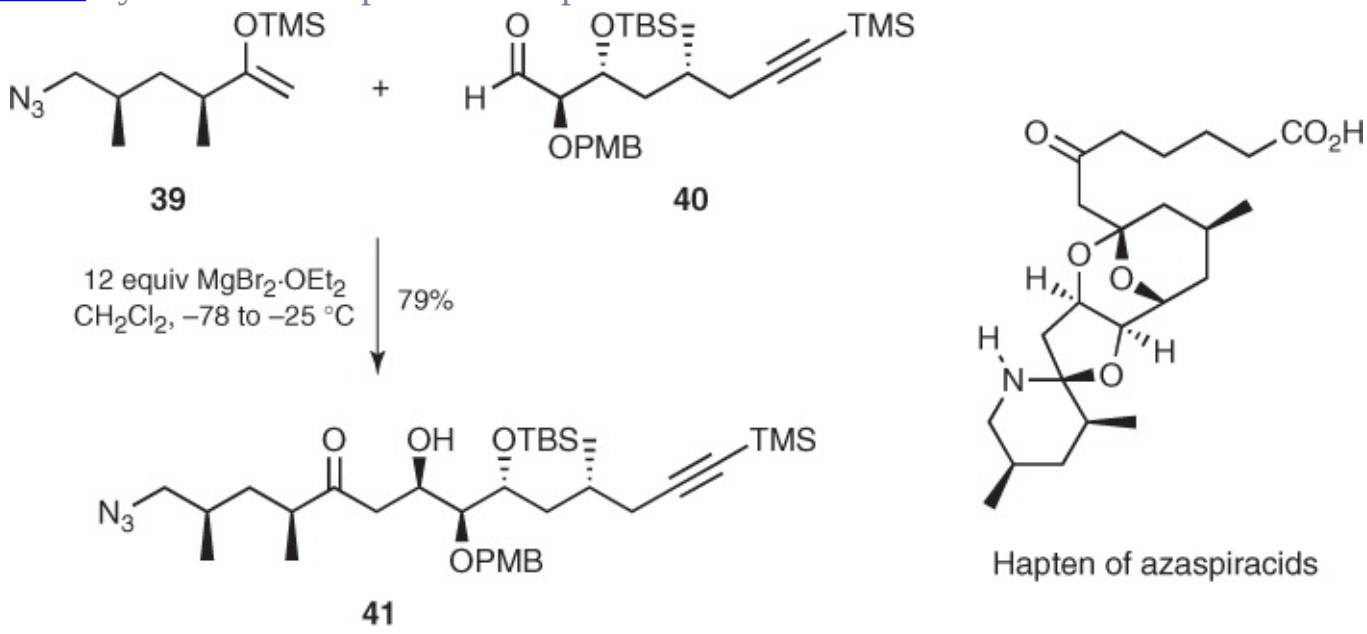
synthesis of natural products. For instance, Sunazuka and Omura used a chelate-controlle Mukaiyama aldol reaction for the total synthesis of an epimer of guadinomine C_2 (**35**). As shown Scheme 1.18, addition of silyl ketene *S,O*-acetal (**36a**) to chiral α-OPMB aldehyde (**37**) in the presen of 1.1 equiv of $TiCl_3(i\text{-PrO})$ gave 3,4-*syn* aldol (**38**) with exceptional diastereoselectivity in 64% yie [32].

Scheme 1.18 Synthesis of (3′*S*) epimer of guadinomine C_2.



Moreover, Forsyth reported that the addition of mild Lewis acid $MgBr_2 \cdot OEt_2$ to a mixture of chir silyl enol ether (**39**) and α-OPMB aldehyde (**40**) triggered a smooth aldol reaction that furnish 3,4-*syn* aldol (**41**) as a single diastereomer in 79% yield, which was further elaborated to a hapten f 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], whi apply to conformations **XII**–**XV** arising from rotation about the C1–C2 bond of the aldehyde (Schen 1.20) [25]. The *polar Felkin–Anh* model is based on the premise that staggered transition stat positioning the C–X bond perpendicularly to the carbonyl bond are preferred ((1) in Scheme 1.20). turn, the *Cornforth* model embraces the assumption that electrostatic effects are instrumental dictating a nearly antiparallel relationship between the carbonyl and the C–X bond ((2) in Schen