1
Stereoselective Acetate Aldol Reactions

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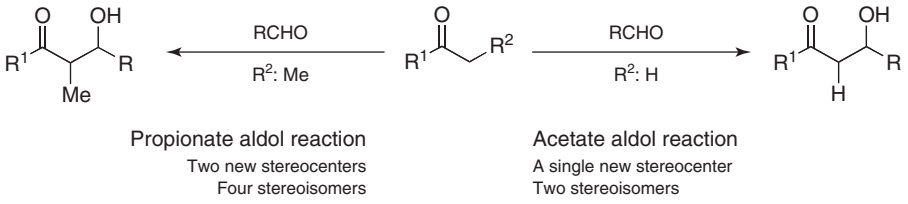
1.1
Introduction

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.

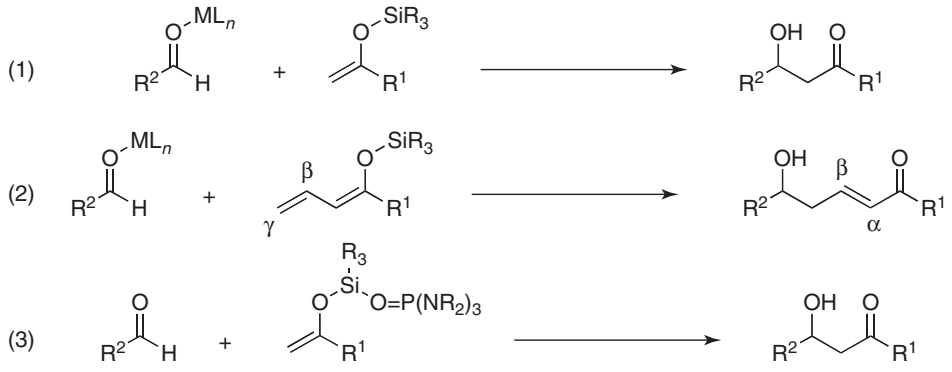
Modern Methods in Stereoselective Aldol Reactions, First Edition. Edited by Mahrwald, R.

1.2
Mukaiyama Aldol Reaction

1.2.1
Concept and Mechanism

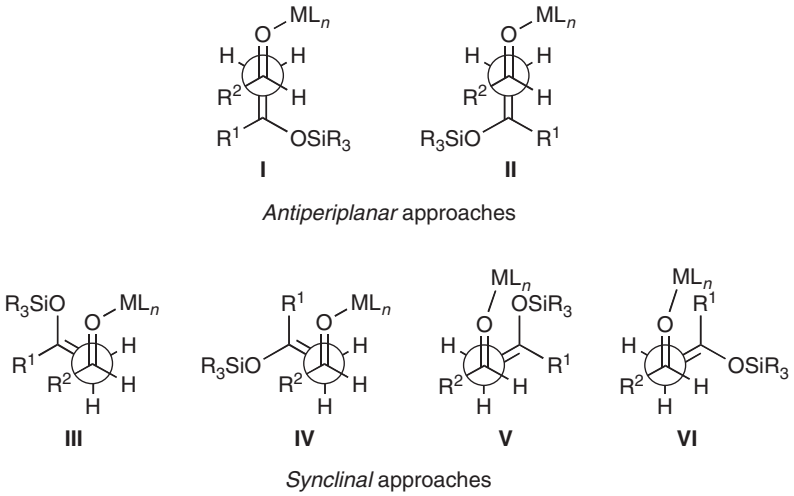
With some significant exceptions, enolsilanes are unreactive toward aldehydes.[1)] This lack of reactivity can be overcome by increasing the electrophilic character of aldehydes or the nucleophilicity of enolsilanes. The former option is achieved by coordination of Lewis acids (ML_n) to the carbonyl 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.

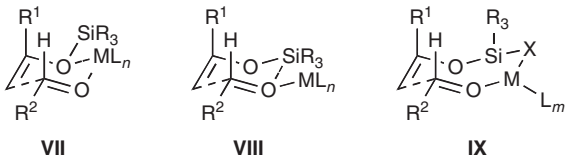


Scheme 1.3 Open transition states for Mukaiyama aldol reactions.

I–**VI** and the capacity to differentiate one from the other faces of the carbonyl bond.

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 becomes crucial to the turnover necessary for nonstoichiometric transformations [11].

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 all 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.

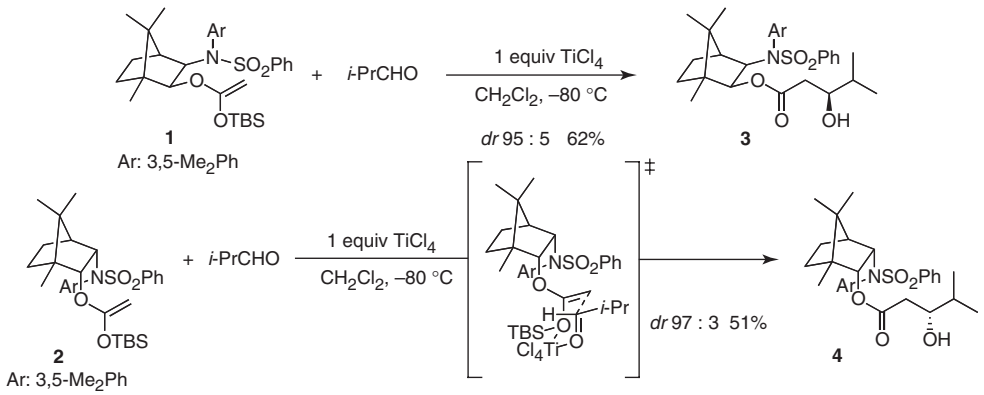


Scheme 1.4 Cyclic transition states for Mukaiyama aldol reactions.

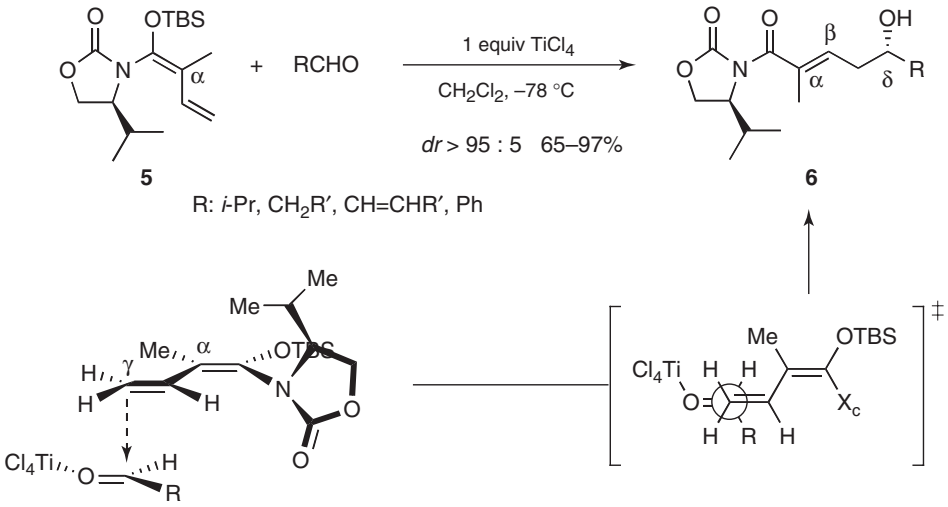
1.2.2
Chiral Auxiliaries

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.

This approach was quickly surpassed by alternative methodologies based on chiral aldehydes or 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, $TiCl_4$-mediated additions of α-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.

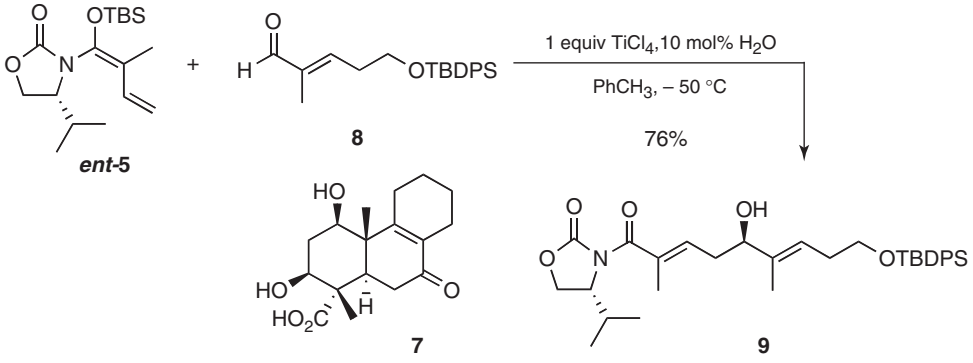


Scheme 1.5 Chiral auxiliary-based Mukaiyama aldol reactions.

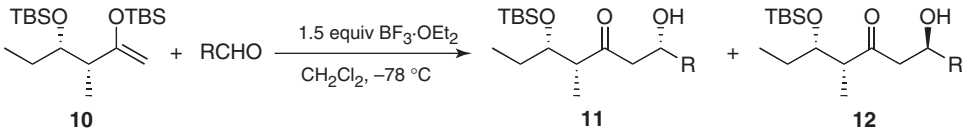


Scheme 1.6 Chiral auxiliary-based vinylogous Mukaiyama aldol reactions.

This methodology was used for the construction of the AB ring of fomitellic acids (**7**) (Scheme 1.7) [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 fomitellic acids.



10 **11** **12**

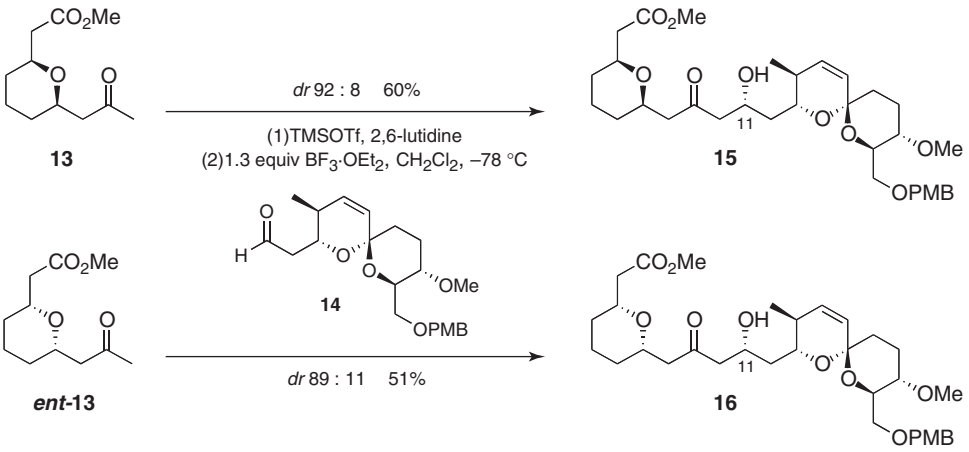
R	*dr* (**11 : 12**)
Ph	60 : 40
i-Pr	50 : 50
$PhCH_2CH_2$	36 : 64
PhCH=CH	33 : 67

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

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** or **12**, depends on the achiral aldehyde (Scheme 1.8) [18].

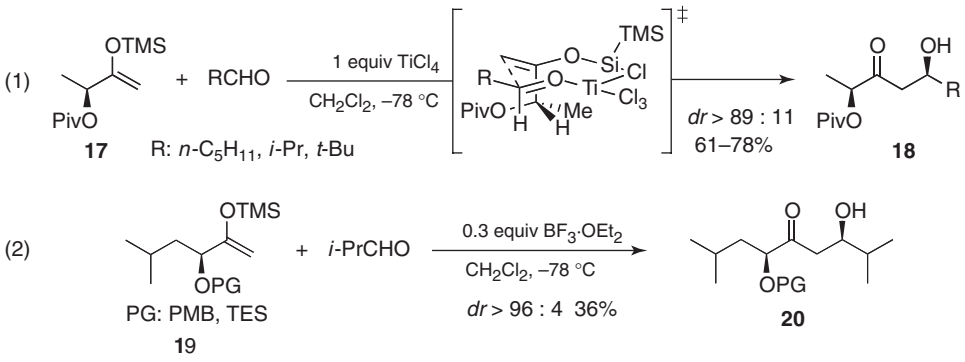
In a more complex framework, De Brabander also reported that silyl enol ethers from enantiomeric methyl ketones (**13**) and (***ent*-13**) underwent additions to chiral aldehyde (**14**) to afford the corresponding aldol adducts **15** and **16** in similar yields (Scheme 1.9) [19]. Considering that the new C11-stereocenters possess the same configuration in both adducts and that the diastereoselectivity is



13 **14** **15**

***ent*-13** **16**

Scheme 1.9 Chiral methyl ketones in stereoselective Mukaiyama aldol reactions.



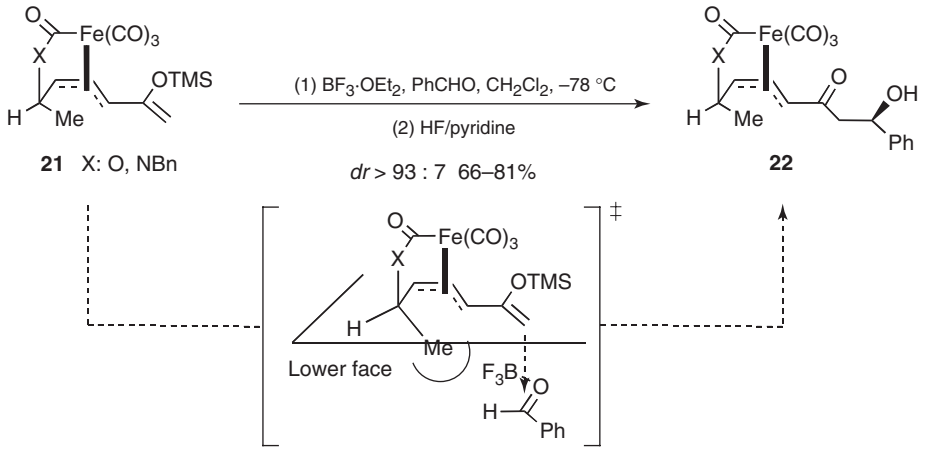
Scheme 1.10 Asymmetric induction imparted by chiral α-hydroxy methyl ketones in Mukaiyama aldol reactions.

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.

Lactate-derived and other α-hydroxy methyl ketones are exceptions to this trend. Thus, Trost found that $TiCl_4$-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 BF_3-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.

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-allyltricarbonyliron 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 these 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 sp^3-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.

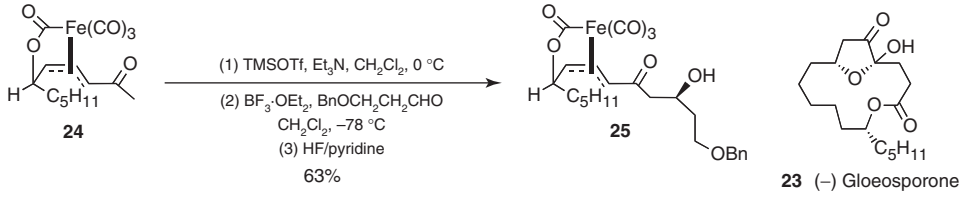
As the iron lactone and lactam (**22**) can be easily decomplexed to afford a rich array of stereodefined derivatives, this reaction may represent a powerful tool to the rapid construction of highly functionalized systems under *remote stereocontrol*. For instance, total synthesis of (−)-gloeosporone (**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].

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



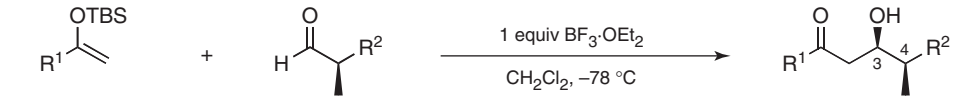
Scheme 1.12 Synthesis of (−)-gloeosporone.

(**28**) proceeded with high diastereofacial selectivity to favor 3,4-*syn* aldol adducts (**29**) (Scheme 1.13) [26].

As expected, the 1,2-asymmetric induction of such aldehydes was eroded when R^2 was sterically 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 2-methyl-3-phenylpropanal (Scheme 1.14). The stereochemical outcome of these reactions shows that 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 combinations of bulky nucleophiles and Lewis acids do not provide the expected results [27].

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).

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**)



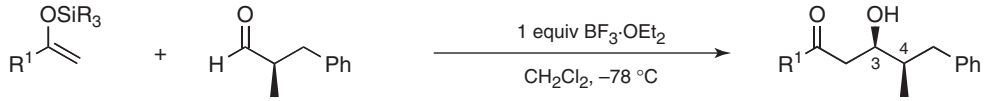
26 R^1: Me, *t*-Bu, **27** R^1: OMe, O*t*-Bu

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

dr 91 : 9 to 97 : 3 68–81%

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

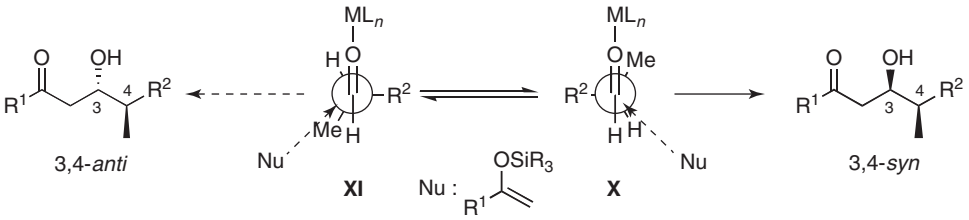
Scheme 1.13 Asymmetric induction imparted by chiral α-methyl aldehydes in Mukaiyama aldol reactions.



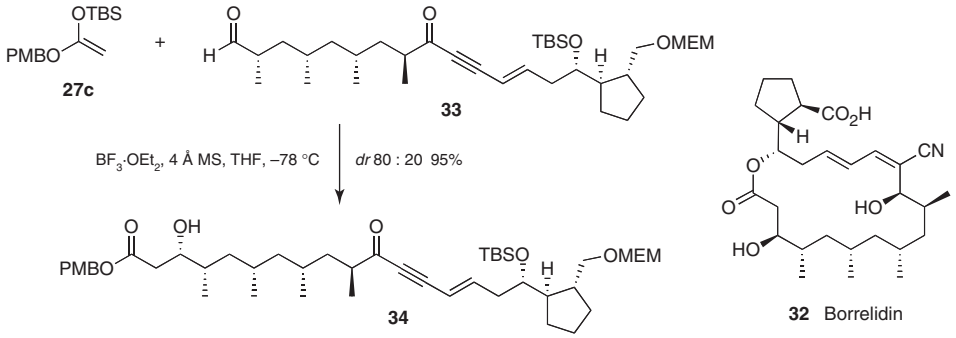
26, 27, 30 **28d** **31**

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

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



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

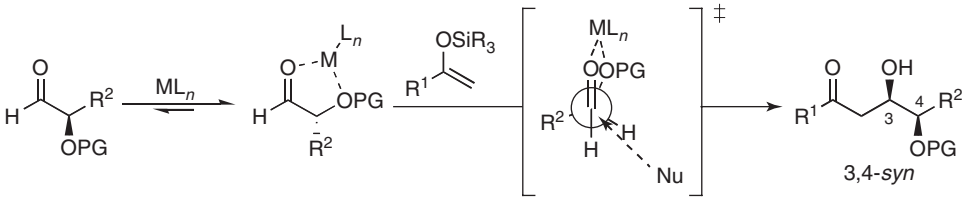


Scheme 1.16 Synthesis of borrelidin.

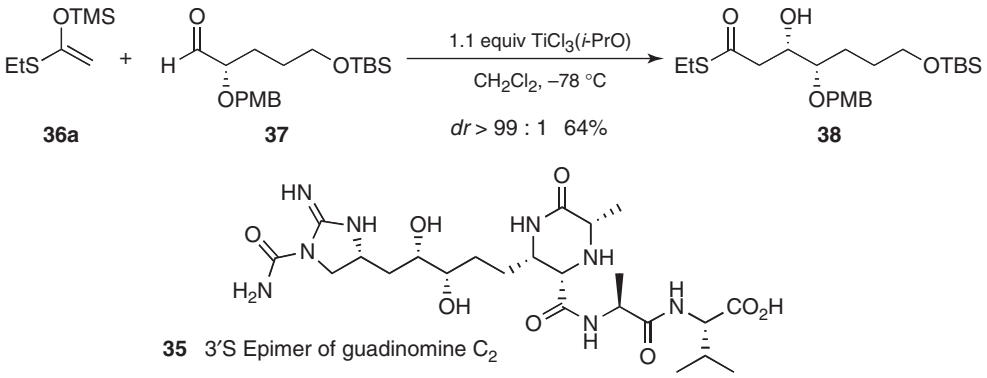
as a 80 : 20 mixture of diastereomers in a 95% combined yield, which demonstrates the π-facial selectivity provided by the α-stereocenter of aldehydes of this kind [30].

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).

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 C_2 (**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 $TiCl_3$(*i*-PrO) gave 3,4-*syn* aldol (**38**) with exceptional diastereoselectivity in 64% yield [32].

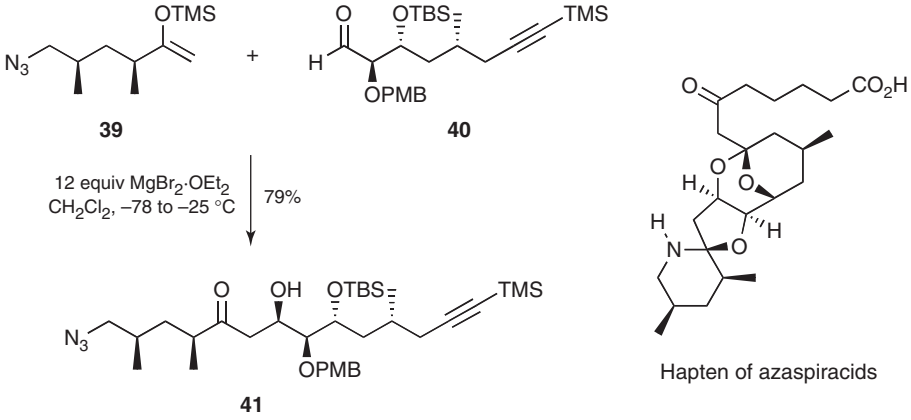


Scheme 1.17 *Cram* model for Mukaiyama aldol additions to chiral α-hydroxy aldehydes.



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 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].

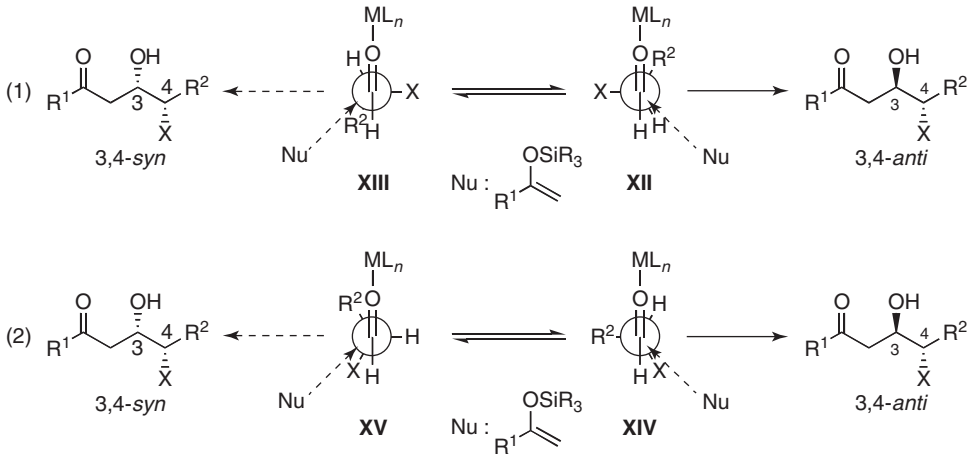


Scheme 1.19 Synthesis of a hapten for azaspiracids.

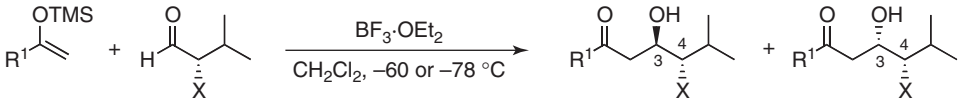
In the absence of chelated intermediates, nucleophilic additions to chiral aldehydes possessing an α-heteroatom are currently explained by the *polar Felkin–Anh* [36] and *Cornforth* models [37], which apply to conformations **XII**–**XV** arising from rotation about the C1–C2 bond of the aldehyde (Scheme 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). Then, the stereochemical outcome of these additions depends on the steric interactions between the nucleophile and the remaining α-substituents in alternative transition states. Application of both models to Mukaiyama aldol reactions predicts the preferential formation of 3,4-*anti* aldol adducts.

Most of the aldol reactions involving such aldehydes proceed in accordance with these expectations, but systematic studies on the addition of enolsilanes (**42**) to α-chloro, α-hydroxy, and α-amino aldehydes (**43**–**45**) revealed that their diastereoselectivity is dependent significantly on the α-heteroatom and the steric bulk of nucleophiles (Scheme 1.21) [38–40]. Thus, additions of acetone-derived enolsilane (**42a**) to aldehydes (**43**) and (**44**) possessing an electronegative α-heteroatom such as chlorine or oxygen afforded the corresponding 3,4-*anti* aldols (**46a**) and (**47a**) (dr 60 : 40 and 82 : 18, respectively), whereas more sterically hindered pinacolone-derived enolsilane (**42c**) gave under the same conditions 3,4-*syn* aldol (**46c**) or equimolar mixtures of 3,4-*anti* and *syn* diastereomers (**47c**). In turn, *N*-benzyl-*N*-tosyl protected valinal (**45**) always furnished 3,4-*anti* aldols (**48**) in modest to excellent diastereomeric ratios (Scheme 1.21).

In view of these and a few related studies on the influence of bulky Lewis acids, Somfai proposed that *N*-protected valinal (**45**) prefers the *polar Felkin–Anh*



Scheme 1.20 Models for Mukaiyama aldol additions to chiral aldehydes possessing an α-heteroatom.



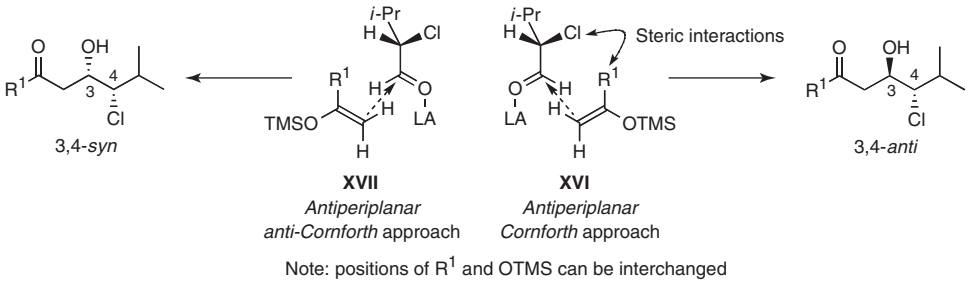
Enolsilane	R^1	Aldehyde	X	Aldols	*dr* (*anti/syn*)	Yield (%)
42a	Me	**43**	Cl	**46a**	60 : 40	94
42b	*i*-Pr		Cl	**46b**	65 : 35	92
42c	*t*-Bu		Cl	**46c**	16 : 84	99
42a	Me	**44**	OTBS	**47a**	82 : 18	66
42b	*i*-Pr		OTBS	**47b**	75 : 25	69
42c	*t*-Bu		OTBS	**47c**	50 : 50	66
42a	Me	**45**	NTsBn	**48a**	78 : 22	60
42b	*i*-Pr		NTsBn	**48b**	93 : 7	94
42c	*t*-Bu		NTsBn	**48c**	98 : 2	85

Scheme 1.21 Mukaiyama aldol additions to chiral aldehydes possessing an α-heteroatom.

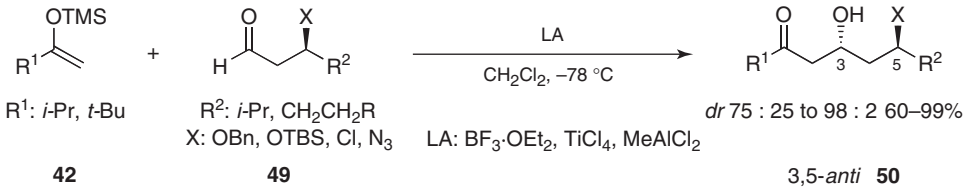
manifold, which is not seriously affected by the size of the nucleophile ((1) in Scheme 1.20) [39]. In turn, Mukaiyama aldol additions to α-chloro aldehyde (**43**) would proceed essentially through antiperiplanar *Cornforth* transition state **XVI** provided that R^1 is small enough to avoid serious steric interactions with chlorine (Scheme 1.22). Facing such deleterious interactions, sterically hindered silyl enol ethers would react through *antiperiplanar anti-Cornforth* transition state **XVII**. A similar rationale could be applied to α-silyloxy aldehyde (**44**).

1.2.4.2 1,3-Asymmetric Induction

Mukaiyama aldol additions to chiral α-unsubstituted aldehydes bearing a β-heteroatom usually proceed with significant levels of 1,3-*anti* asymmetric induction [41]. As illustrated in Scheme 1.23, most of the aldol reactions of silyl enol ethers (**42**) with β-hydroxy, β-chloro, and β-azido aldehydes (**49**) produce the



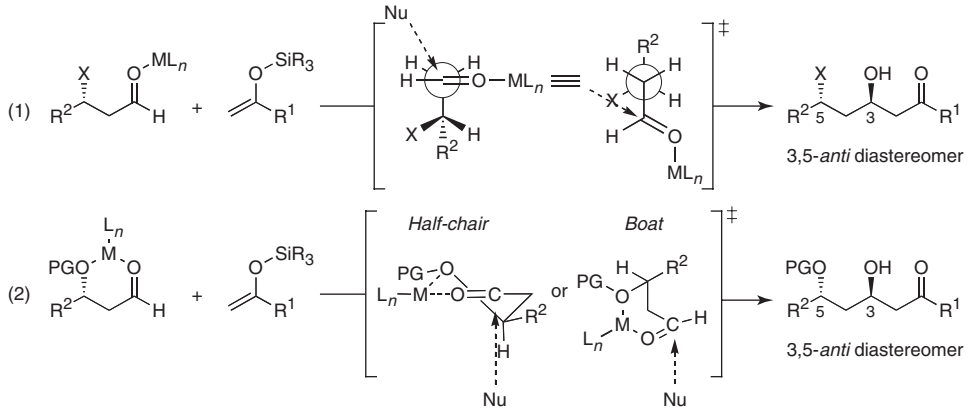
Scheme 1.22 *Cornforth* model for Mukaiyama aldol additions to (*S*) 2-chloro-3-methylbutanal.



Scheme 1.23 Asymmetric induction imparted by chiral α-unsubstituted aldehydes bearing a β-heteroatom in Mukaiyama aldol reactions.

corresponding 3,5-*anti* aldols (**50**) in high diastereomeric ratios regardless of the chelating ability of the Lewis acid and the hydroxyl protecting group [42–44].

The stereochemical outcome of these reactions may not be readily interpreted because both open-chain and chelation control lead to the same 3,5-*anti* diastereomer (**50**). Thus, Evans proposed, after a systematic and insightful study, a revised induction polar model and a chelate-controlled model to account for the high 1,3-asymmetric induction provided by such chiral aldehydes [43]. The former is an open-chain model ((1) in Scheme 1.24) derived from several assumptions common to the *Felkin–Anh* analysis for 1,2-asymmetric induction. First, it is assumed that torsional effects dictate that aldehyde transition state conformations adopt a staggered relationship between the forming bond and the aldehyde α-substituents. Second, it is also assumed that the principal diastereomer arises from the reactant-like transition state wherein the β-stereocenter is oriented *anti*, rather than *gauche*, to the forming bond because this geometry reduces nonbonded interactions between the aldehyde α-substituents and the incoming nucleophile. In turn, the chelate-controlled model applies to suitable β-hydroxy-protected aldehydes able to form stable six-membered chelates, which can subsequently react through transition states involving either boat or half-chair conformations ((2) in Scheme 1.24).

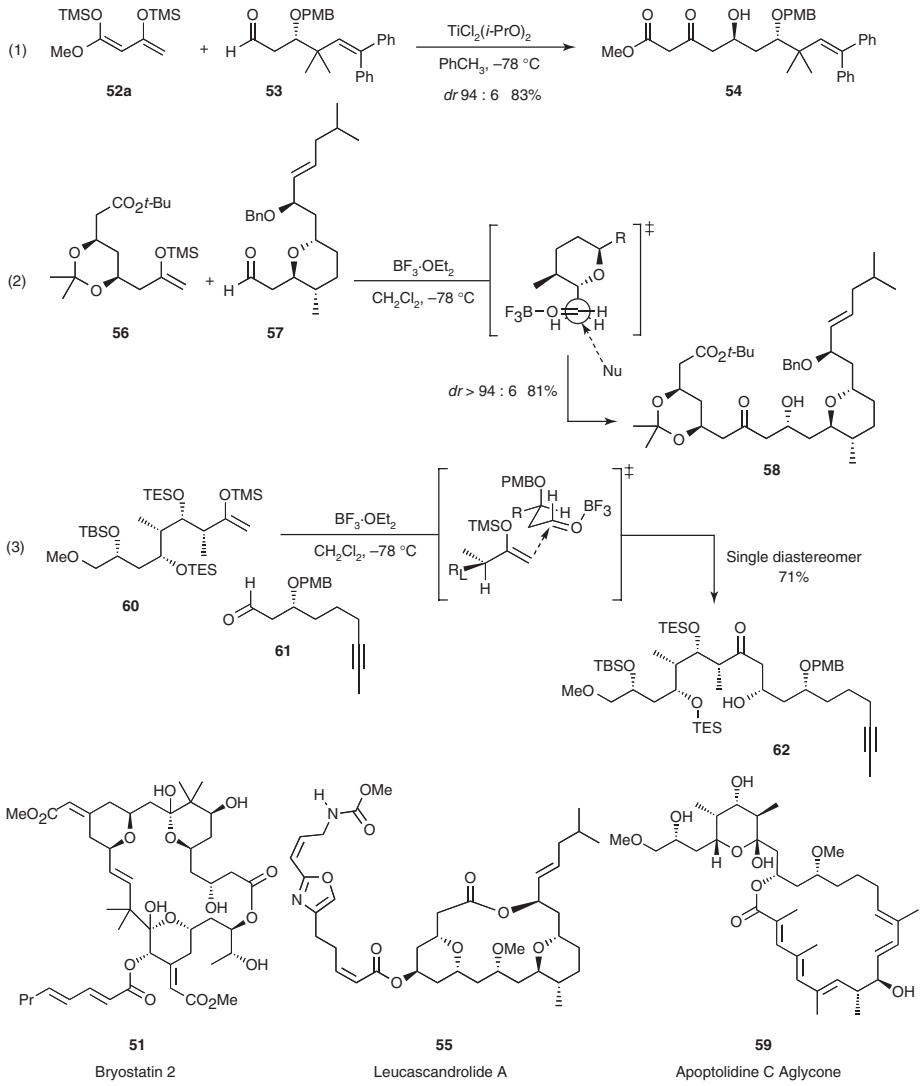


Scheme 1.24 *Evans* models for Mukaiyama aldol additions to chiral α-unsubstituted aldehydes bearing a β-heteroatom.

Regardless of mechanistic considerations, the predictable and high stereocontrol provided by these aldehydes has been used in many total syntheses. Evans reported in the total synthesis of bryostatin 2 (**51**) that aldol coupling of bis(trimethylsilyl)dienol ether (**52a**) with β-OPMB aldehyde (**53**) ((1) in Scheme 1.25) was only modestly stereoselective when it was carried out in the presence of $MgBr_2{\cdot}OEt_2$ or $BF_3{\cdot}OEt_2$, whereas strong Lewis acid ($TiCl_4$, $SnCl_4$) did not effect a clean transformation. Alternatively, mild $TiCl_2(i\text{-}PrO)_2$ in CH_2Cl_2 at $-78\,^{\circ}C$ delivered aldol (**54**) in a high-yielding and stereoselective manner (*dr* 86 : 14, 93%). Importantly, the diastereoselectivity was improved by using toluene (*dr* 94 : 6, 83%), a result that is consistent with the operation of electrostatic effects as the stereochemical control element [45]. In turn, Panek took advantage of the 1,3-asymmetric induction of β-alkoxy aldehydes in a challenging Mukaiyama aldol reaction to assemble an advanced intermediate in the total synthesis of leucascandrolide A (**55**) [46]. Indeed, the coupling of chiral silyl enol ether (**56**) and aldehyde (**57**) ((2) in Scheme 1.25) afforded the desired *anti* aldol (**58**) in 81% yield and excellent diastereomeric ratio (*dr* > 94 : 6). This, presumably occurred through an open transition state in which the β-stereocenter of the aldehyde determines the approach of the nucleophile to the carbonyl in accordance with the revised polar model described in (1) of Scheme 1.24. Finally, Nelson also used this reactivity in the total synthesis of the apoptolidine C aglycone (**59**) [47]. In this case, silyl enol ether (**60**) participated in a highly stereoselective addition to chiral aldehyde (**61**) ((3) in Scheme 1.25), affording aldol (**62**) as a single diastereomer in 71% yield. A matched pairing of aldehyde and enolsilane facial biases acting in the transition state shown in Scheme 1.25 was invoked to explain such outstanding stereoselectivity [48].

The aforementioned transformations show that the 1,3-*anti* asymmetric induction of protected β-hydroxy aldehydes can be very successful, but this control element should be used with caution because the diastereoselectivity drops when the steric bulk of the protecting group increases [49, 50]. Taking advantage of this trend, Yamamoto reported that the extremely bulky tris(trimethylsilyl)silyl group (TTMSS, $(Me_3Si)_3Si$), also known in the literature as the hypersilyl or super silyl group, confers to β-OTTMSS aldehydes an outstanding 1,3-*syn* asymmetric induction [51]. This silicon-protecting group is also remarkable because it permits acetaldehyde derived TTMSS enol ether to participate in highly diastereoselective Mukaiyama aldol additions to a large variety of aldehydes.[2)] Moreover, these additions can incorporate other TTMSS enol ethers in cascade aldol reactions with excellent levels of 1,2-*Felkin* and 1,3-*syn*-asymmetric induction. This is shown in the sequential addition of acetaldehyde- and acetophenone-derived TTMSS enol ethers to 2-phenylpropanal (Scheme 1.26) [51, 52]. On the basis of the open-chain model proposed by Evans ((1) in Scheme 1.24), the rationale for the observed 1,3-*syn* induction of β-OTTMSS aldehydes considers that the size of this silicon-protecting

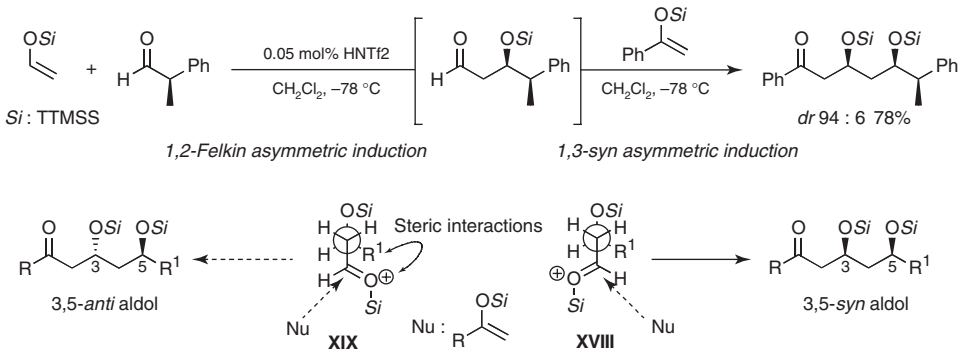
2) Mukaiyama aldol reactions involving silyl enol ethers from aldehydes are particularly troublesome, and a few examples have been reported.



Scheme 1.25 Use of 1,3-asymmetric induction imparted by chiral β-hydroxy aldehydes in Mukaiyama aldol reactions in the synthesis of natural products.

group now dictates that the carbonyl group is *antiperiplanar* to the OTTMSS substituent and far from the R^1 group, which avoids unfavorable steric interactions. Therefore, conformation **XVIII** is responsible to the predominant formation of the 3,5-*syn* aldol diastereomer.

As discussed in Section 1.3.6, this chemistry combined with lithium-mediated aldol reactions from β-OTTMSS methyl ketones provides new entries to efficient synthesis of natural products.



Scheme 1.26 Mukaiyama aldol reactions of tris(trimethylsilyl)silyl enolsilanes.

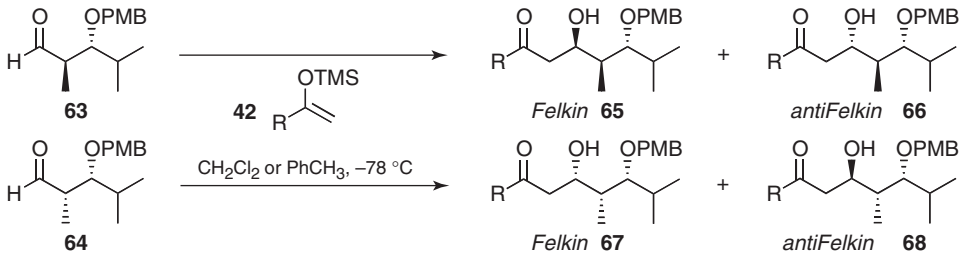
1.2.4.3 **Merged 1,2- and 1,3-Asymmetric Induction**

The high asymmetric induction imparted by α- and β-substituted aldehydes documented in previous sections raises the prospect that there might exist intrinsic stereochemical relationships between both substituents that are either mutually reinforcing or opposing. This is particularly true for α-methyl β-alkoxy aldehydes.

Indeed, the stereochemical outcome of Mukaiyama aldol additions to these chiral aldehydes under nonchelation conditions can be easily interpreted by invoking the 1,2-*Felkin* and 1,3-*anti* asymmetric induction provided by the α-methyl and the β-oxygenated substituent, respectively. Hence, it is not surprising that the BF_3-mediated additions of silyl enol ethers (**42**) to α-methyl-β-OPMB aldehydes (**63**) and (**64**) largely depend on the relative configuration of the aldehyde (Scheme 1.27). As the influences of the α-methyl and the β-OPMB substituents match in *anti*-substituted aldehyde (**63**), *Felkin* aldols (**65**) were virtually obtained as a single diastereomer, whereas *syn*-substituted aldehyde (**64**), in which those factors are opposing, gave mixtures of aldols (**67**) and (**68**) in variable diastereomeric ratios [53].

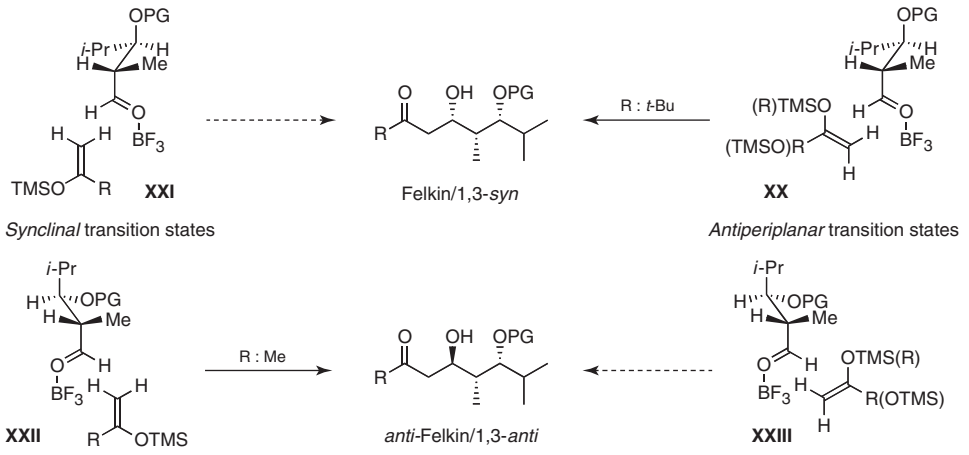
Interestingly, additions to **64** showed a turnover in carbonyl face selectivity (from *Felkin* to *anti-Felkin*) on decreasing the size of the enolsilane group R. This implies that the β-stereocenter becomes the dominant control element in the reactions with sterically nondemanding enolsilanes. Moreover, a decrease in the solvent polarity produced an increase of *anti-Felkin* diastereomer (**68**), which means that 1,3-induction is enhanced relative to 1,2-induction in nonpolar media. After a seminal analysis of these stereochemical data, Evans concluded that 1,2-stereoinduction is found in those reactions proceeding through an *antiperiplanar* open transition state such as **XX**, while dominant 1,3-stereoinduction is manifest from a *synclinal* open transition state such as **XXII**. Then, a subtle balance of stereoelectronic effects and steric interactions between the Lewis acid and the R group of the nucleophile on transition states **XX**–**XXIII** represented in Scheme 1.28 determines the stereochemical outcome of these reactions [53].

The consistently high stereocontrol provided by Mukaiyama aldol reactions of *anti* α-methyl β-oxygenated aldehydes has been successfully used in the synthesis of many natural products [54]. Evans reported that BF_3-mediated vinylogous



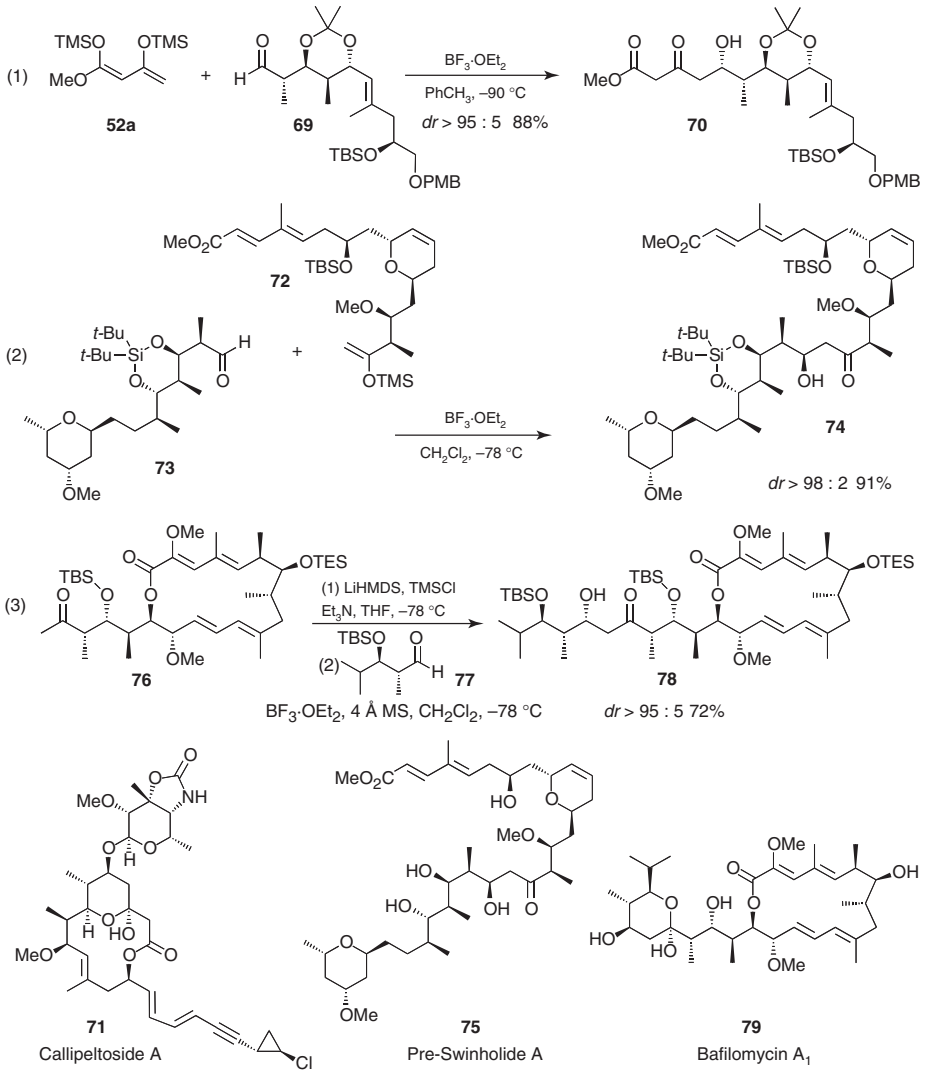
Enolsilane	R	Aldehyde	Solvent	65 : 66	67 : 68	Yield (%)
42a	Me	**63**	CH_2Cl_2	97 : 3		86
42b	*i*-Pr			98 : 2		98
42c	*t*-Bu			99 : 1		94
42a	Me	**64**	CH_2Cl_2		17 : 83	82
42b	*i*-Pr				56 : 44	98
42c	*t*-Bu				96 : 4	89
42a	Me	**64**	$PhCH_3$		6 : 94	92
42b	*i*-Pr				32 : 68	86
42c	*t*-Bu				88 : 12	75

Scheme 1.27 Mukaiyama aldol additions to α-methyl β-alkoxy aldehydes.



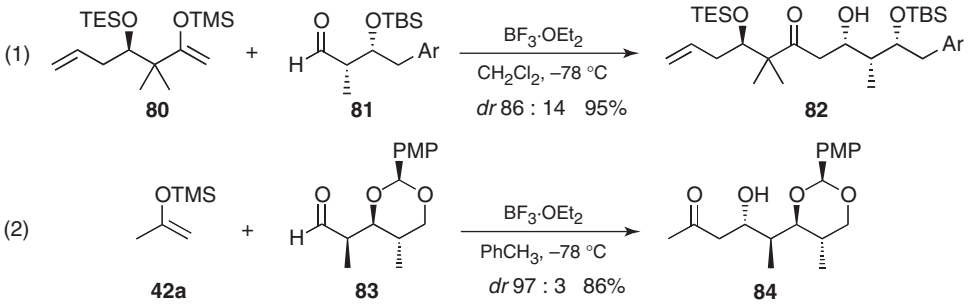
Scheme 1.28 *Evans* models for Mukaiyama aldol additions to *syn* α-methyl β-alkoxy aldehydes.

aldol addition of Chan's diene (**52a**) to chiral aldehyde (**69**) in toluene at −90 °C gave β-hydroxy ketone (**70**), an advanced intermediate in the total synthesis of callipeltoside A (**71**), with excellent stereocontrol ($dr > 95:5$) in 88% yield ((1) in Scheme 1.29) [55]. In turn, Paterson developed a highly efficient coupling of chiral silyl enol ether (**72**) and elaborate α-methyl β-oxygenated aldehyde (**73**) to



Scheme 1.29 Use of asymmetric induction imparted by *anti* α-methyl β-oxygenated aldehydes in Mukaiyama aldol reactions in the synthesis of natural products.

obtain aldol (**74**) as a single diastereomer in 91% yield, which was easily converted into preswinholide A (**75**) ((2) in Scheme 1.29) [56], the monomeric seco acid of swinholide A [57, 58]. Finally, the conversion of methyl ketone (**76**) into the corresponding silyl enol ether and subsequent BF_3-mediated addition to aldehyde (**77**) in the presence of 4 Å molecular sieves allowed Roush to generate aldol (**78**), the penultimate precursor of bafilomycin A_1 (**79**), with a high diastereoselectivity ($dr > 95:5$) in 72% yield ((3) in Scheme 1.29) [59].

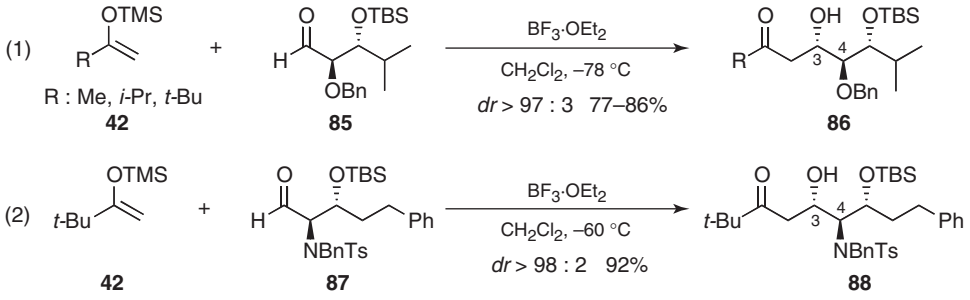


Scheme 1.30 Asymmetric induction imparted by *syn* α-methyl β-oxygenated aldehydes in Mukaiyama aldol reactions.

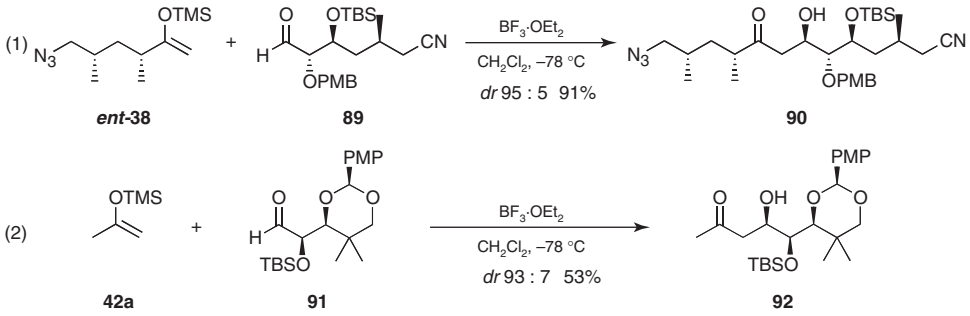
Parallel Mukaiyama aldol additions to *syn*-α-methyl β-oxygenated aldehydes have also been applied to the synthesis of natural products, but the uncertainty of their stereochemical outcome and the poorer diastereoselectivities often provided by these aldehydes have restricted their use compared to their *anti* counterparts. Remarkably, most of the examples found in the literature about these transformations involve *Felkin*-like reactions leading to *all syn* aldols. For instance, Floreancig reported the preparation of *Felkin* aldol (**82**) in excellent yield as an inseparable 86 : 14 mixture of diastereomers by addition of sterically hindered silyl enol ether (**80**) to chiral *syn*-α-methyl β-silyloxy aldehyde (**81**) ((1) in Scheme 1.30) [60, 61]. Furthermore, Kalesse described one of the few examples of substrate-controlled Mukaiyama aldol reaction in which the 1,3-induction of the β-oxygenated stereocenter prevailed over the *Felkin* induction imparted by the α-stereocenter [62]. This engaged the silyl enol ether (**42a**) addition to *syn*-aldehyde (**83**), which afforded aldol (**84**) with excellent diastereoselectivity (*dr* 97 : 3) in 86% yield ((2) in Scheme 1.30) [63].

Following these analyses, π-facial selectivity of chiral aldehydes possessing α- and β-heteroatoms could be expected to arise from the summation of the inductions imparted by both substituents. Unfortunately, α,β-bisalkoxy aldehydes do not fulfill such expectations. Mukaiyama aldol additions to *syn*-α,β-bisalkoxy aldehydes under nonchelating conditions are too reliant on the hydroxyl protecting groups and the steric encumbrance of the enolsilane and usually proceed with poor stereocontrol. The same occurs to *anti* diastereomers, but *anti*-configured α-OBn β-OTBS aldehyde (**85**) exhibited uniformly high selectivities toward 3,4-*anti* aldols (**86**) irrespective of the steric hindrance of silyl enol ethers (**42**) ((1) in Scheme 1.31) [38]. A similar trend was observed for α-amino β-alkoxy aldehydes [64]. In this case, addition of silyl enol ether (**42c**) to *anti* α-*N*-BnTs β-OTBS aldehyde (**87**) afforded 3,4-*anti* aldol (**88**) as a single diastereomer in 92% yield ((2) in Scheme 1.31).

The highly diastereoselective aldol reaction of silyl enol ether (***ent*-38**) and *anti*-aldehyde (**89**) affording *anti* aldol (**90**) is consistent with these features ((1) in Scheme 1.32). Moreover, alternative patterns occasionally proceed with excellent levels of diastereoselectivity. For instance, Paterson reported that silyl enol ether (**42a**) and *syn*-aldehyde (**91**) participated in a highly diastereoselective reaction (*dr* 93 : 7) toward *all syn*-aldol (**92**), thus indicating that the steric effect of the large



Scheme 1.31 Asymmetric induction imparted by chiral aldehydes possessing α- and β-heteroatoms in Mukaiyama aldol reactions.

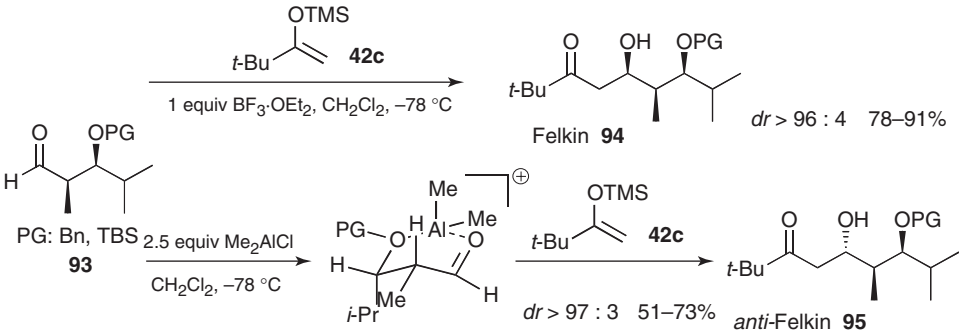


Scheme 1.32 Mukaiyama aldol reactions involving α,β-bisalkoxy aldehydes.

alkyl group overrode any electronic stereocontrol from the oxygenated substituents ((2) in Scheme 1.32) [65, 66]. In spite of these successful examples, most of the stereocontrolled aldol reactions of α, β-bisalkoxy aldehydes rely on the use of lithium enolates (Section 1.3.5).

The stereochemical outcome of all these Mukaiyama aldol reactions involving α, β-disubstituted aldehydes can be dramatically affected if they are carried out under chelating conditions. Particularly, Evans established that the choice of the Lewis acid was crucial to the control of the additions to *syn* α-methyl β-OPG (PG: Bn, TBS) aldehydes (**93**) (Scheme 1.33) [67].[3] Thus, BF_3-mediated additions of silyl enol ether (**42c**) to these aldehydes provided *Felkin* aldols (**94**) in excellent diastereomeric ratios (*dr* > 96 : 4), whereas opposite *anti-Felkin* aldols (**95**) were obtained with the same level of diastereoselectivity by using Me_2AlCl.[4] Further theoretical and spectroscopic studies revealed that these transformations proceed through a cationic dimethylaluminum chelate that preferentially adopts a boat conformation and directs the attack of the nucleophile to the *Si* face of the C=O bond (Scheme 1.33). From a general point of view, these results demonstrate

3) Related *anti* α-methyl β-oxygenated aldehydes do not display any remarkable stereocontrol in chelating-controlled reactions.
4) Similar results were obtained with $MeAlCl_2$.



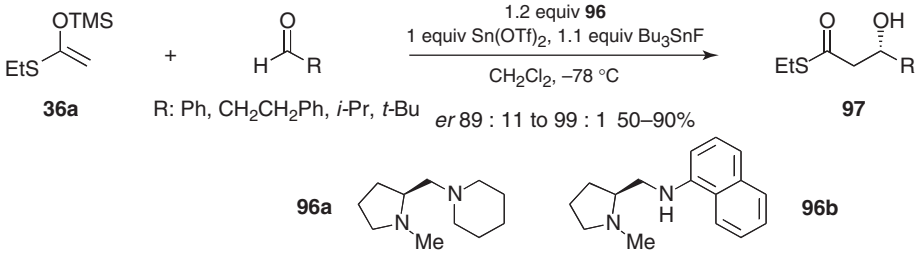
Scheme 1.33 Influence of Lewis acids on the stereochemical outcome of Mukaiyama aldol reactions of α-methyl β-alkoxy aldehydes.

the exceptional chelating ability of this aluminum Lewis acid and expand the stereochemical control provided by these aldehydes [68, 69].

1.2.5 Chiral Lewis Acids

Not surprisingly, the crucial role played by Lewis acids in Mukaiyama aldol reactions has stimulated the search for chiral ligands to dictate the stereochemical outcome of these transformations. The resultant chiral Lewis acids must increase the electrophilicity of aldehydes, create a suitable asymmetric environment around the carbonyl bond, and, as far as possible, facilitate catalytic turnover at the same time [5]. The following section describes how the intense efforts directed to this challenging objective have already provided highly enantioselective approaches, paying particular attention to those chiral Lewis acids used in the synthesis of natural products.

Mukaiyama and Kobayashi reported the first chiral complexes to provide stereocontrolled *acetate* Mukaiyama aldol reactions. These initially consisted of three pieces: $Sn(OTf)_2$, an optically active diamine, and a tin(IV) additive. Thus, stoichiometric amounts of $Sn(OTf)_2$, proline-derived diamines (**96**), and tributyltin



Scheme 1.34 Asymmetric Mukaiyama aldol reactions promoted by stoichiometric amounts of $Sn(OTf)_2$ and proline-derived diamines.

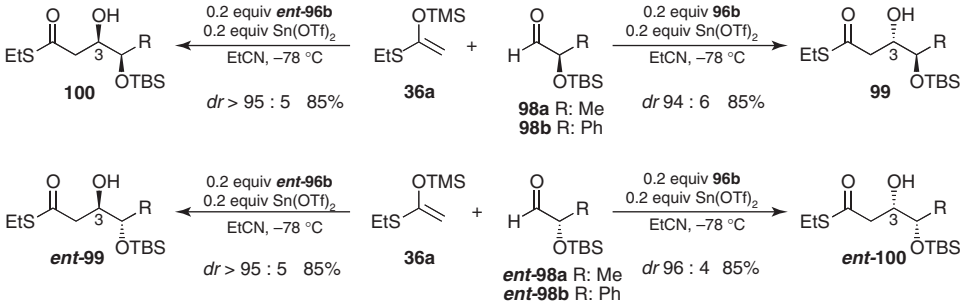
fluoride promoted highly enantioselective additions of silyl ketene *S,O*-acetal (**36a**) to representative aldehydes, leading to the corresponding β-hydroxy thioesters (**97**) (Scheme 1.34) [70]. Application of these conditions to the TBS ketene acetal from benzyl acetate furnished similar results [71].

Remarkably, these additions were also successful when using catalytic amounts of $Sn(OTf)_2$ and diamine (**96b**) without tributyltin fluoride provided that the reaction was carried out in propionitrile, and the enolsilane and the aldehyde were both added slowly to the reaction mixture [72]. The power of this methodology was demonstrated on the addition of **36a** to chiral α-OTBS aldehydes (**98**) and (***ent*-98**), in which the C3 stereocenter of aldols (**99**) and (**100**) was controlled by the diamine (**96**) regardless of the inherent diastereofacial preference of the chiral aldehydes (Scheme 1.35) [73, 74].

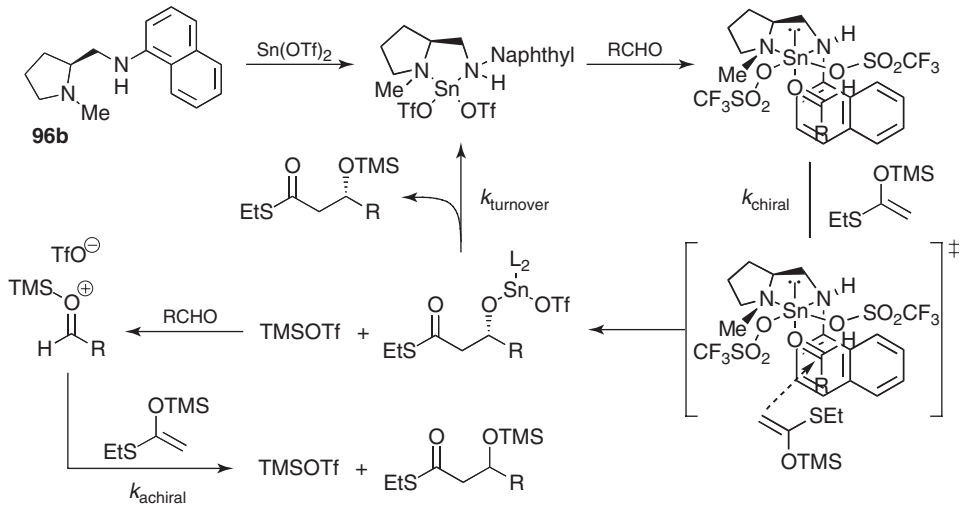
Mechanistic analyses of this reaction suggested that such excellent stereocontrol might arise from the approach of the enolsilane to the less hindered face of the aldehyde in the highly ordered complex shown in Scheme 1.36 [75]. Regarding the catalytic turnover, the metal exchange reaction with TMSOTf to regenerate the catalyst was identified as a crucial step, because TMSOTf can promote an alternative achiral route (Scheme 1.36) that erodes the enantioselectivity if the silyl transfer is slow ($k_{turnover} \approx k_{achiral}$). Thus, the need to minimize this side reaction led to the use of a more polar solvent such as propionitrile, which increases $k_{turnover}$, and to the slow addition of both the enolsilane and the aldehyde to the reaction mixture.

This methodology showed that catalytic asymmetric Mukaiyama aldol reactions were possible and could be used successfully in organic synthesis, but it suffered from the difficulty of handling $Sn(OTf)_2$ [76] and the need for the reagents to be added to the reaction mixture slowly.

In the early 1990s, some chiral catalysts derived from the easily available BINOL ligand emerged as candidates to overcome such limitations. Mukaiyama was the first to use a BINOL-derived titanium–oxo complex to catalyze the addition of silyl ketene *S,O*-acetals to a limited number of aldehydes with modest stereocontrol [77]. This was followed by Mikami's findings on highly enantioselective *ene* and aldol reactions catalyzed by BINOL–titanium complex (**101**). Remarkably, addition of silyl enol ether (**26a**) to methyl glyoxylate afforded α-hydroxy ester (**102**) as a



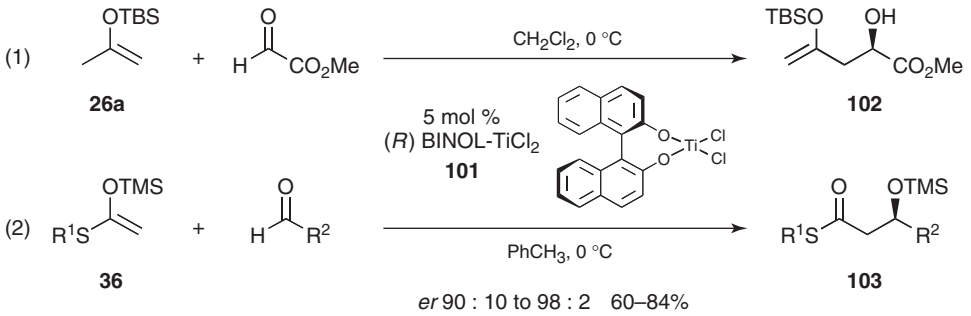
Scheme 1.35 Asymmetric Mukaiyama aldol reactions promoted by catalytic amounts of $Sn(OTf)_2$ and proline-derived diamines.



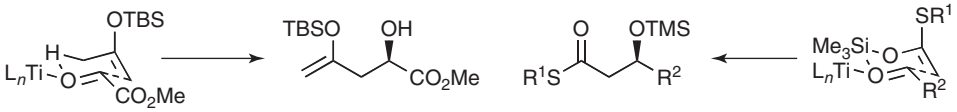
Scheme 1.36 Mechanism for the Mulaiyama aldol reaction catalyzed by $Sn(OTf)_2$ and a proline-derived diamine.

single enantiomer ((1) in Scheme 1.37) [78], whereas aldol reactions of silyl ketene *S,O*-acetals (**36**) and a wide array of aldehydes furnished thioesters (**103**) in good to high yields and enantiomeric ratios up to 98 : 2 ((2) in Scheme 1.37) [79].

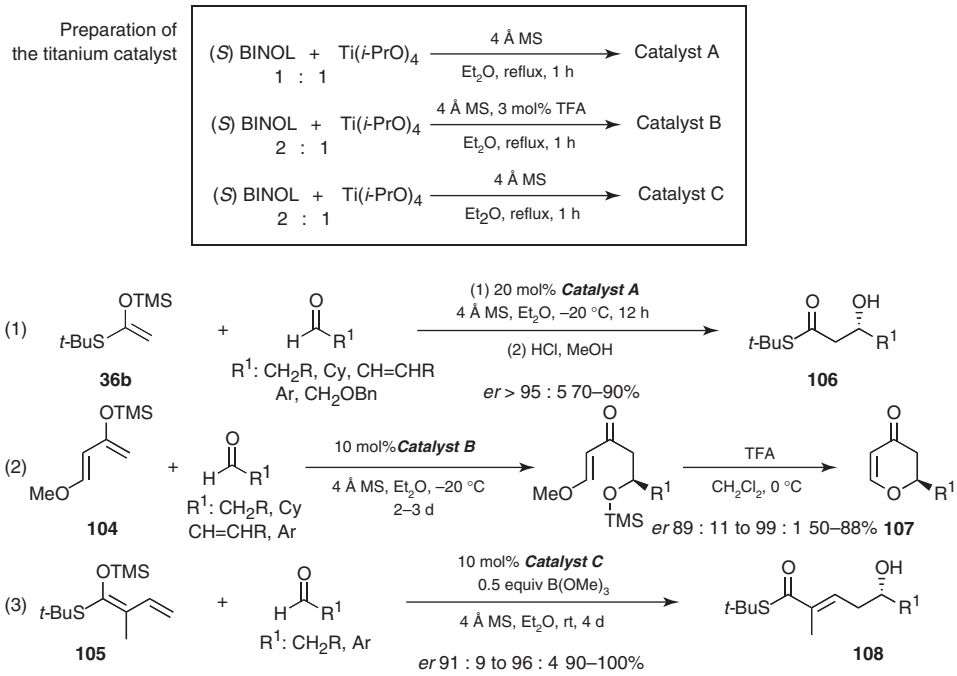
Crossover experiments and analyses of the stereochemical outcome of related reactions led to the suggestion of a cyclic six-membered transition state for these transformations, wherein the oxygen of the activated carbonyl bond interacts with the transferring group, H or SiR_3 for *ene* or aldol reactions, respectively (Scheme 1.38). Furthermore, the enantioselectivity was further improved by the addition of achiral ligands or by more bulky silicon groups, which suggests a more complex mechanism [80]. Irrespective of the mechanism, the synthetic potential of both transformations was demonstrated in two-directional *ene* processes [81] and aldol reactions involving chiral aldehydes by using a catalyst derived from BINOL and $TiCl_2(i\text{-PrO})_2$ [82].



Scheme 1.37 Asymmetric Mukaiyama aldol reactions catalyzed by BINOL-$TiCl_2$.



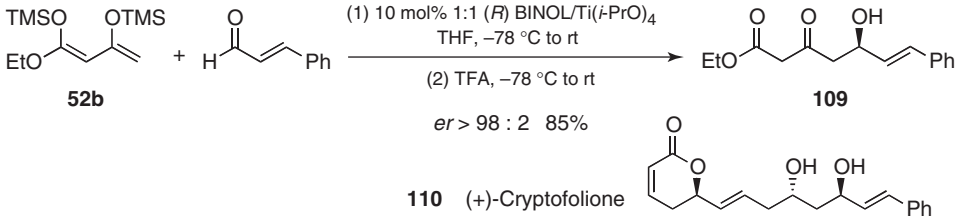
Scheme 1.38 Cyclic transition states for *ene* and aldol reactions.



Scheme 1.39 Asymmetric Mukaiyama aldol reactions catalyzed by BINOL/Ti(*i*-PrO)$_4$.

Keck reported a similar methodology in which the titanium catalyst was prepared by mixing BINOL ligand and Ti(*i*-PrO)$_4$ [83]. The stereocontrol was again excellent, but Keck warned about the unknown structure of the catalytic species and emphasized the pronounced sensitivity of these reactions to BINOL–metal stoichiometry and the presence of other additives. Indeed, the catalytic species can be prepared according to several protocols adapted to different nucleophiles. Therefore, these have been applied to reactions from silyl ketene *S,O*-acetal (**36b**) [83], diene (**104**) [84, 85], and vinyl ketene *S,O*-acetal (**105**) [86] leading to β-hydroxy thioesters (**106**), dihydropyrones (**107**), and β-hydroxy α,β-unsaturated thioesters (**108**) in a highly enantioselective manner ((1–3) in Scheme 1.39).

A thorough analysis and optimization of these transformations revealed the nonlinear effects and the dramatic influence of some additives [87, 88], which confirmed Keck's comments about the sensitivity of these reactions to structural and experimental modifications [89]. In spite of these limitations, these catalysts



Scheme 1.40 Synthesis of (+)-cryptofolione.

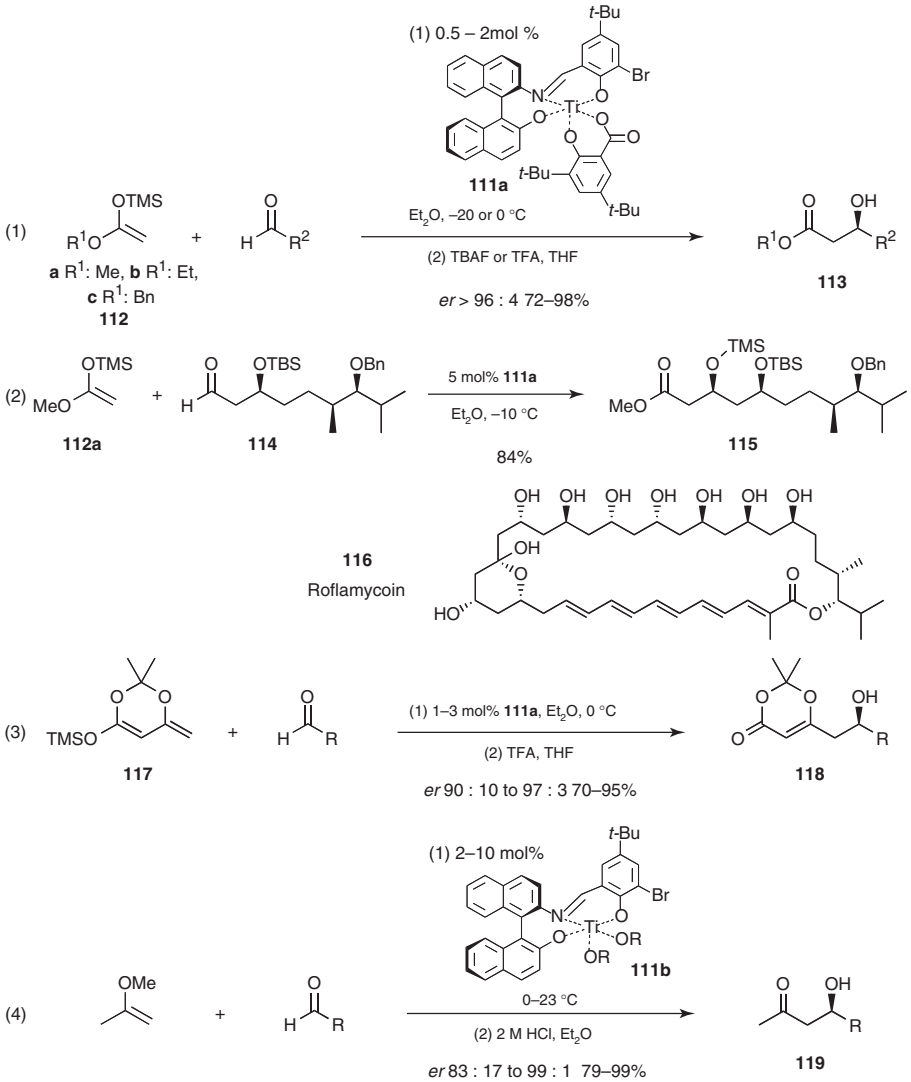
are an important tool for the stereocontrolled synthesis of natural products [90]. This is illustrated by the catalytic addition of Chan's diene (**52b**) to cinnamaldehyde affording aldol (**109**), an intermediate in the total synthesis of (+)-cryptofolione (**110**) described by Meshram (Scheme 1.40) [91].

At the same time that Mikami and Keck developed their BINOL-derived titanium catalysts, Carreira reported that mononuclear Ti(IV) complex (**111a**), generated from a chiral tridentate Schiff base, Ti(*i*-PrO)$_4$, and 3,5-di-*tert*-butylsalicylic acid, triggered extremely efficient reactions of silyl ketene acetals (**112**) and a wide range of aldehydes [92] including α, β-ynals [93] to yield β-hydroxy esters (**113**) with enantiomeric ratios up to 99 : 1 ((1) in Scheme 1.41). The stereocontrolled synthesis of ester (**115**) by addition of silyl ketene acetal (**112a**) to chiral aldehyde (**114**) in the total synthesis of roflamycoin (**116**), reported by Rychnovsky ((2) in Scheme 1.41) [94], is a convincing demonstration of the potential of this methodology [95]. This method was also applied to *O*-silyl dienolate (**117**), which yielded carbonyl adducts (**118**) in a stereocontrolled manner ((3) in Scheme 1.41) [96]. Furthermore, a parent chiral Ti(IV) complex (**111b**) prepared by mixing the chiral tridentate Schiff base and Ti(*i*-PrO)$_4$ (the structure of the active catalyst has not been determined yet) promoted the enantioselective addition of 2-methylpropene to aldehydes leading to β-hydroxy methyl ketones (**119**) ((4) in Scheme 1.41) [97].

The success of all these transformations is largely due to the effective transfer of the silyl group. As represented in Scheme 1.42, this transfer is understood to occur intramolecularly through an intermediate **XXIV**, wherein the ligand associated with the metal complex serves as a shuttle, transiently undergoing silylation. In this context, the replacement of isopropoxide groups by salicylic acid in catalyst (**111**) became crucial, as it facilitated the silyl transfer, which finally produced a strong increase of yields, enantioselectivities, and catalytic turnover.

The prominence of boron Lewis acids in metal-enolate-mediated aldol reactions (Section 1.3) often overshadows their contribution to the development of asymmetric Mukaiyama aldol counterparts. Nevertheless, oxazaborolidinone complexes readily prepared from α-amino acids are among the most successful chiral Lewis acids for highly stereocontrolled transformations [98].

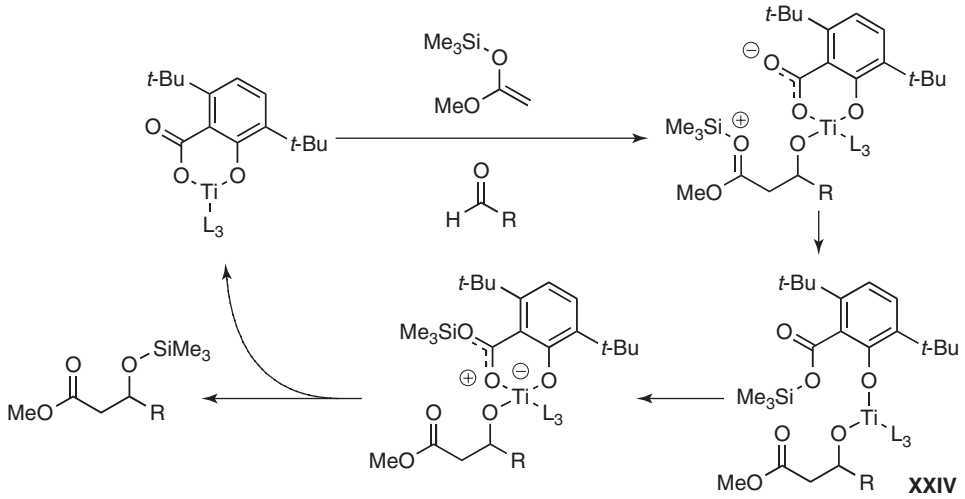
Introduced by Kiyooka, valine-derived *N*-tosyl oxazaborolidinone (**120**) was successfully engaged in stoichiometric Mukaiyama aldol reactions [99, 100]. Its ability as a chiral promoter was demonstrated in synthetic studies involving a wide array of



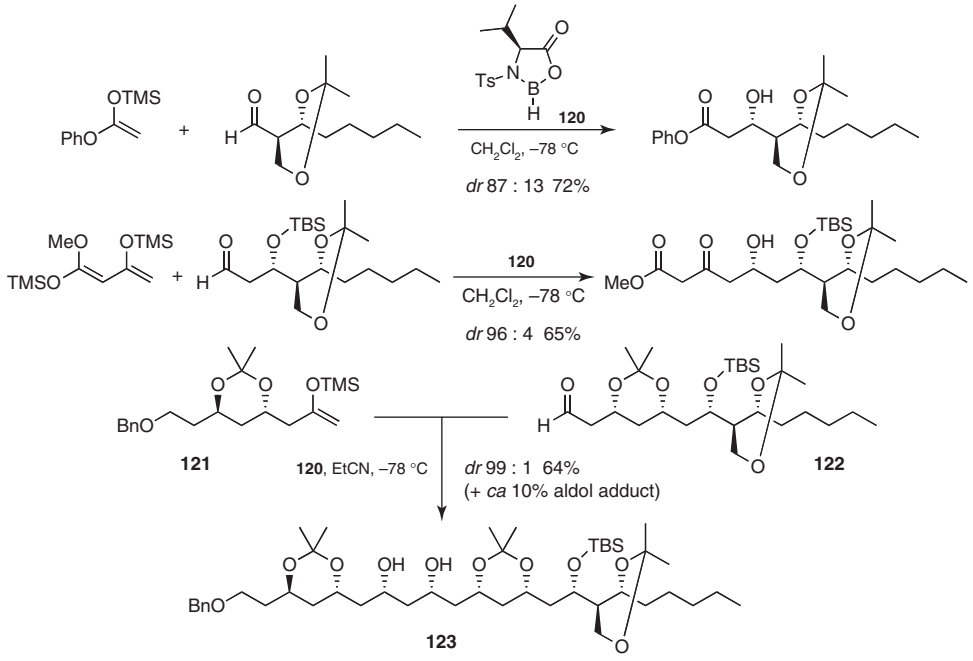
Scheme 1.41 Asymmetric Mukaiyama aldol reactions catalyzed by Carreira's titanium complex.

enolsilanes derived from phenyl acetate, methyl acetoacetate, and methyl ketones (Scheme 1.43) [101, 102]. Remarkably, **120** facilitated the addition of silyl enol ether (**121**) to chiral aldehyde (**122**) and the subsequent *syn* reduction of the resulting aldol adduct to give diol (**123**) with excellent diastereoselectivity in 64% yield.

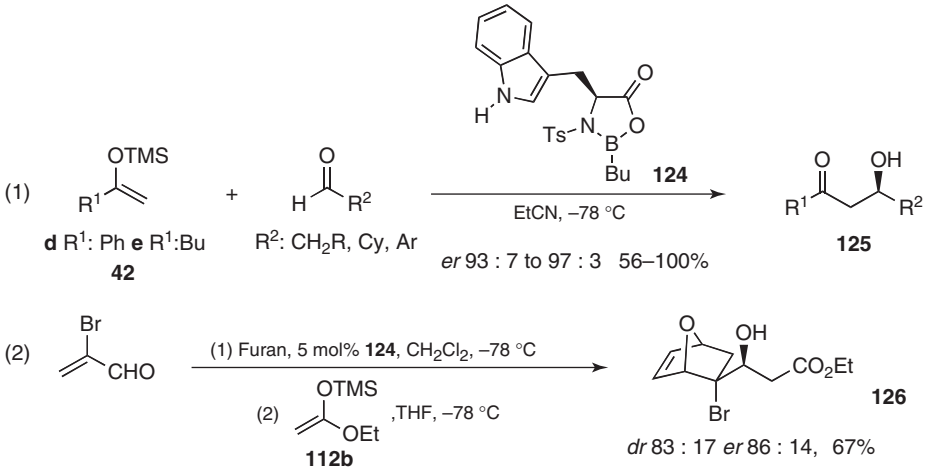
In turn, Corey reported that Mukaiyama aldol additions of silyl enol ethers (**42**) to representative aldehydes in the presence of catalytic amounts of tryptophan-derived chiral borane complex (**124**) furnished β-hydroxy ketones (**125**) enantioselectively



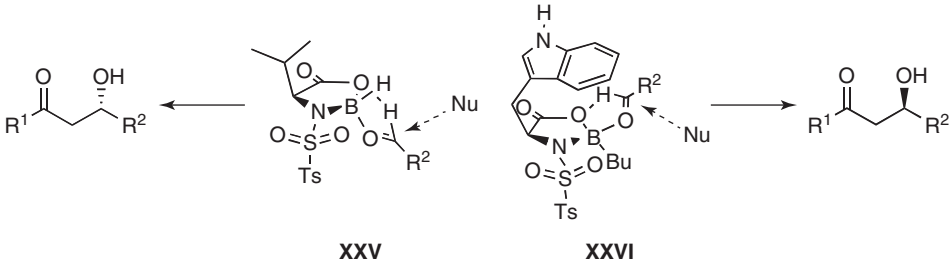
Scheme 1.42 Mechanism for the asymmetric Mukaiyama aldol reaction catalyzed by Carreira's titanium complex.



Scheme 1.43 Asymmetric Mukaiyama aldol reactions catalyzed by a valine-derived *N*-tosyl oxazaborolidinone.



Scheme 1.44 Asymmetric Mukaiyama aldol reactions catalyzed by a tryptophan-derived chiral borane complex.

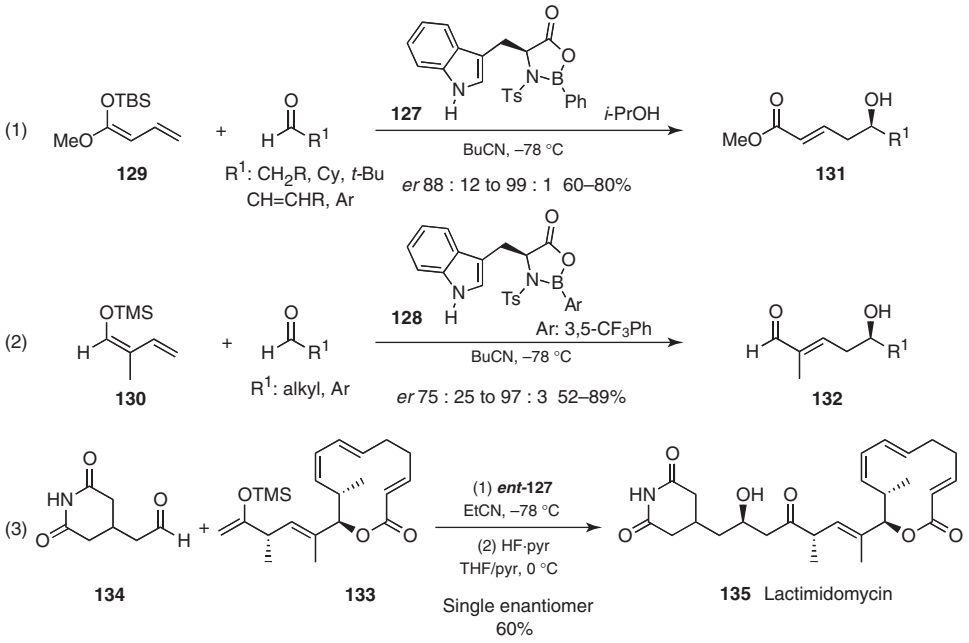


Scheme 1.45 Transition states for asymmetric Mukaiyama aldol reactions catalyzed by oxazaborolidinones.

((1) in Scheme 1.44) [103].[5] In a fine example of tandem catalysis, Carreira used this complex to construct the azabicyclononane core common to a family of biomolecules [104]. Thus, it catalyzed the Diels–Alder reaction of furan and bromoacrolein followed, on consumption of the educts, by aldol addition of silyl ketene acetal (**112b**), which led to the stereoselective formation of β-hydroxy ester (**126**) ((2) in Scheme 1.44) [105].

Mechanistic studies on these and other reactions and X-ray crystallographic evidence led to the suggestion that the stereocontrol achieved by these transformations arose from the assemblies shown in Scheme 1.45, wherein a hydrogen bond between formyl and oxygen came up as a crucial stereocontrol element [106]. Thus, pyramidalization of the sulfonamide due to a gearing interaction with the isopropyl substituent in Kiyooka's complex **XXV** orients the sulfonamide residue to shield the *Re* face of the aldehyde, which impels the nucleophile to approach the opposite

5) Oxazaborolidinone (**124**) also participated in stereocontrolled additions of diene (**104**) to aldehydes affording dihydropyrones, but the enantioselectivity was modest in this case.

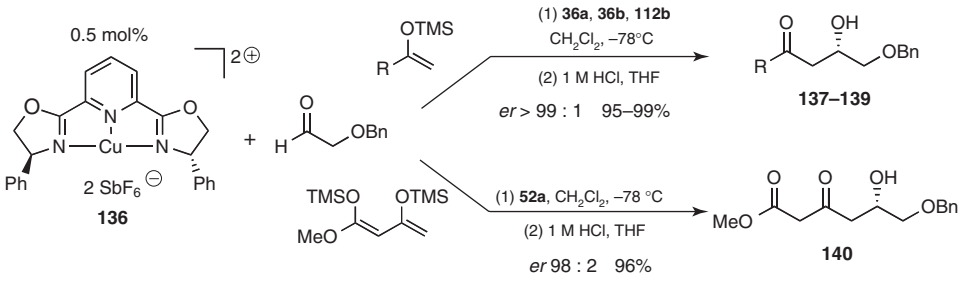


Scheme 1.46 Asymmetric Mukaiyama aldol reactions catalyzed by tryptophan-derived B-aryl oxazaborolidinones.

face. Conversely, attractive $\pi - \pi$ interaction in Corey's complex **XXVI** blocks the *Si* face of the aldehyde and favors the attack of the nucleophile on the less hindered *Re* face.

On the basis of these and other precedents [107], Kalesse reported that tryptophan-derived B-aryl oxazaborolidinones (**127**) and (**128**) underwent enantioselective vinylogous Mukaiyama aldol reactions from dienes (**129**) and (**130**), furnishing δ-hydroxy esters (**131**) or aldehydes (**132**) in high yields under stoichiometric conditions ((1) and (2) in Scheme 1.46). Importantly, the latter is the first asymmetric vinylogous Mukaiyama aldol reaction with aldehyde-derived silyl dienol ethers. Moreover, B-phenyl oxazaborolidinone (**127**) was successfully used by Fürstner to assemble silyl enol ether (**133**) and aldehyde (**134**) in the penultimate step of the total synthesis of lactimidomycin (**135**) ((3) in Scheme 1.46) [108]. In turn, Harada also found that an *allo*-threonine-derived B-phenyl oxazaborolidinone catalyzed the enantioselective addition of dimethylsilyl ketene *S,O*-acetals to acetophenone [109].

In addition to these Lewis acids, Evans disclosed that Cu(II), Sn(II), and Sc(III) complexes of chiral pyridine-bisoxazoline (pybox) and bisoxazoline (box) ligands catalyze the asymmetric Mukaiyama aldol reactions of chelating electrophiles. For instance, low catalyst loadings of Cu(II) pybox–complex (**136**) were enough to trigger the addition of several nucleophiles to benzyloxyacetaldehyde, affording the

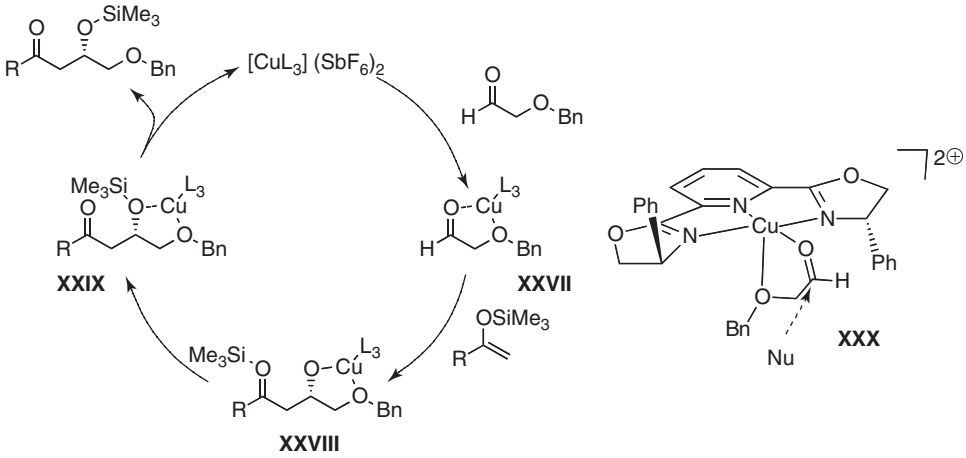


Scheme 1.47 Asymmetric Mukaiyama aldol reactions catalyzed by a pybox copper complex.

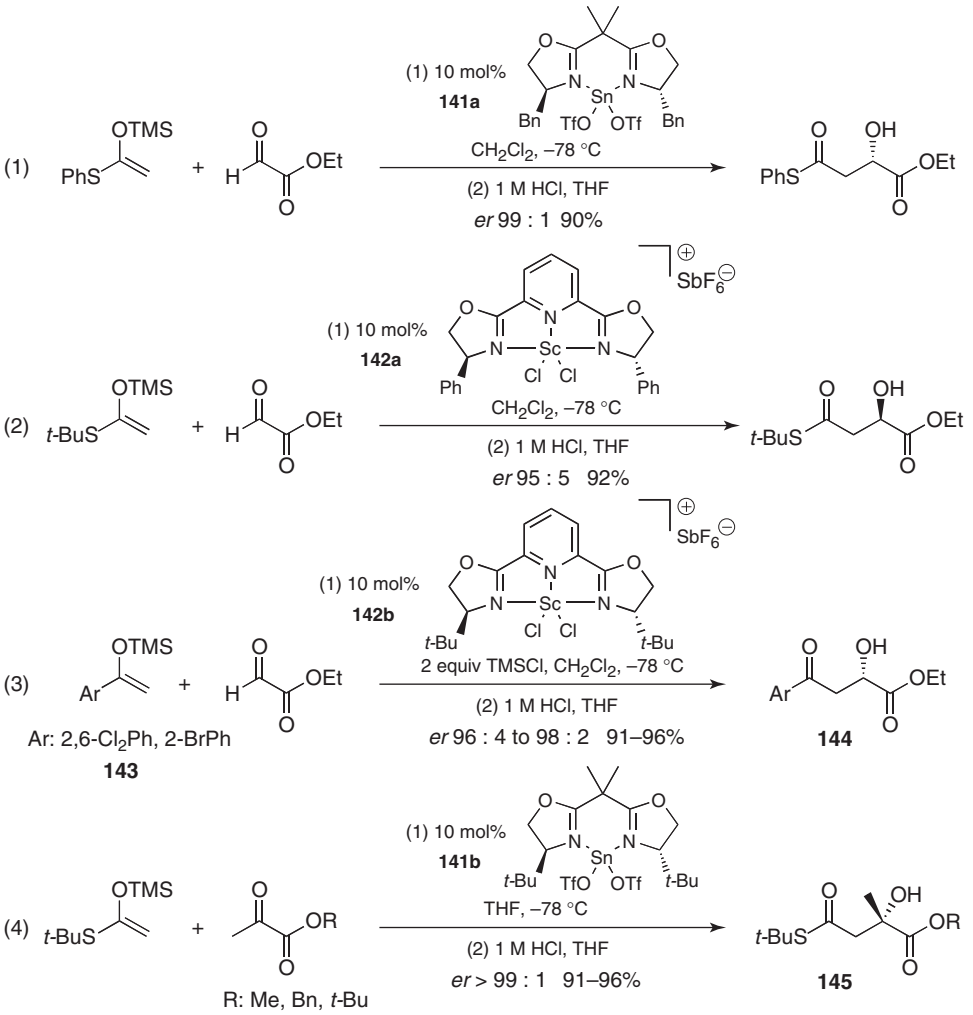
corresponding aldol adducts (**137–140**) in high yields and excellent stereocontrol (Scheme 1.47) [110].

The proposed catalytic cycle for these aldol reactions is outlined in Scheme 1.48. Coordination of the aldehyde to the Cu(II) center produces complex **XXVII**, which undergoes the nucleophilic addition to produce a copper aldolate **XXVIII**. Importantly, both intra- and intermolecular fast silyl transfers form **XXIX** and subsequent decomplexation affords the aldol adduct and regenerates catalyst (**136**). In turn, a stereochemical model **XXX** containing a chelated α-OBn aldehyde at the metal center, which forms a square pyramidal copper intermediate, accounts for the direction of the induction observed.

Unfortunately, only benzyloxy-like acetaldehydes participated in this highly enantioselective reaction. Other aldehydes capable of engaging in five-membered chelated complexes such as glyoxalate esters required Sn(II)-box or Sc(III)-pybox complexes (**141a** and **142a**, respectively) to react with silyl ketene *S,O*-acetals with similar levels of enantioselectivity ((1) and (2) in Scheme 1.49) [111, 112].



Scheme 1.48 Mechanism for asymmetric Mukaiyama aldol reactions catalyzed by a pybox copper complex.



Scheme 1.49 Asymmetric Mukaiyama aldol reactions catalyzed by box and pybox complexes.

Therefore, other enolsilanes were surveyed in an effort to expand the scope of this glyoxalate aldol process. It was found that the addition of silyl enol ethers (**143**) catalyzed by Sc(III)-pybox (**142b**) furnished α-hydroxy-γ-keto esters (**144**) in high yields and excellent enantioselectivity, provided that TMSCl was added to facilitate catalyst turnover ((3) in Scheme 1.49). Importantly, *t*-Bu-catalyst (**142b**) afforded the opposite direction of induction to that of **142a**. Steric factors within the chiral pocket affecting the location of the aldehyde carbonyl in the complex have been proposed to explain this different behavior. Furthermore, Evans reported in a brilliant study that Sn(II)-box (**141b**) catalyst promoted highly enantioselective additions of silyl ketene *S,O*-acetals to pyruvate esters affording functionalized hydroxysuccinate

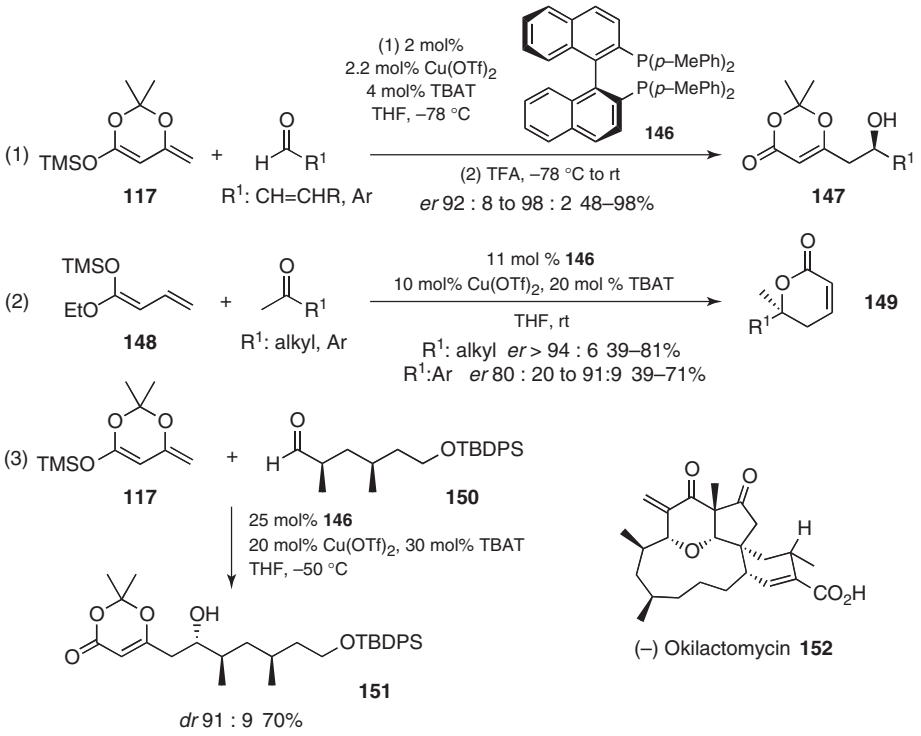
derivatives (**145**) with an absolute stereocontrol ((4) in Scheme 1.49) [113]. The scope of this reaction was further extended to include nucleophiles such as silyl enol ethers from methyl ketones and other electrophiles capable of providing five-membered chelated complexes such as 1,2-diketones. In spite of such advances, these transformations lack generality and can only be applied to a selected set of electrophiles, although their outstanding levels of enantioselectivity have allowed them to be widely used in the synthesis of natural products [114].

Beyond the results themselves, these studies had a profound impact on asymmetric reactions, because they introduced new concepts and chiral ligands suitable for Lewis-acid-mediated transformations based on aldehydes or ketones with chelating functional groups. Therefore, it is not surprising that a large amount of work has been devoted to surveying alternative box- and pybox-like ligands or to identifying other metals to catalyze such reactions [115–117]. Furthermore, they also inspired the development of new catalysts, such as C_1-symmetric aminosulfoximines reported by Bolm, which undergo Cu(II)-catalyzed reactions with pyruvate esters [118], or a peptide bearing a Schiff base disclosed by Hoveyda, which promotes highly successful and experimental friendly AgF_2-mediated stereocontrolled additions to a wide array of α-keto esters [119].

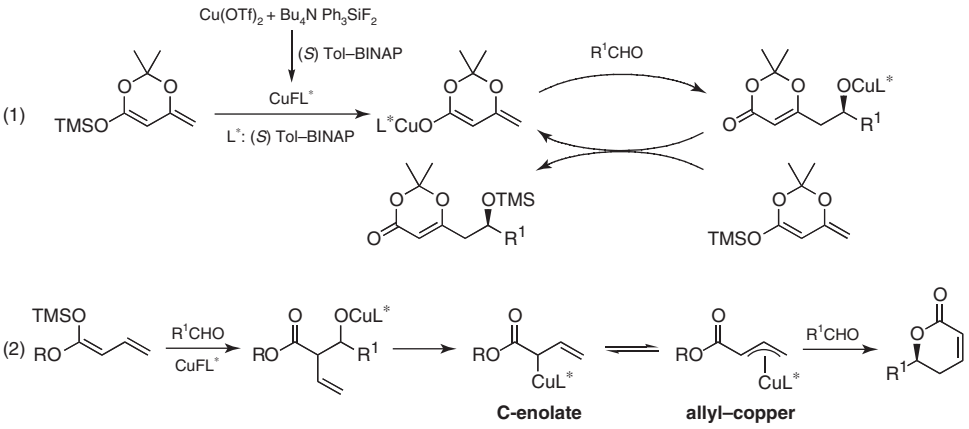
Regarding the use of copper-derived Lewis acids, Carreira devised a different way of taking advantage of the resultant chiral catalysts [120]. This involved the addition of *O*-silyl dienolate (**117**) to α, β-unsaturated and aromatic aldehydes catalyzed by a chiral copper complex generated *in situ* by mixing (*S*)-Tol-BINAP (**146**), $Cu(OTf)_2$, and $(Bu_4N)Ph_3SiF_2$ (TBAT), which afforded aldol adducts (**147**) with enantiomeric ratios up to 98 : 2 ((1) in Scheme 1.50). In turn, Campagne expanded the scope of this methodology to methyl ketones and diene (**148**), obtaining lactones (**149**) in modest to high yields in stereocontrolled way ((2) in Scheme 1.50) [121]. This reliable methodology has been often used in the synthesis of natural products. For instance, Scheidt used the diastereoselective reaction of **117** and chiral aldehyde (**150**) to prepare aldol (**151**), an important fragment of the total synthesis of (−)-okilactomycin (**152**) ((3) in Scheme 1.50) [122, 123].

Importantly, other Cu(I) sources served equally well as $Cu(OTf)_2$. This result, along with the known reduction of Cu(II) to Cu(I) by enolsilanes, suggested that a Cu(I) complex was the catalytic species. Further spectroscopic studies confirmed this hypothesis and also supported a mechanism in which a copper enolate acted as the reactive species ((1) in Scheme 1.51). Nevertheless, studies on related additions from dienes such as **148** led Campagne to point out that this model did not account for the origin of the enantioselectivity because the chiral copper center is far away from the aldehyde. Instead, the reaction might proceed through an initial nonselective α-aldol, followed by a retroaldol step, producing a *C*-enolate that would evolve toward an allyl-copper intermediate, which would finally undergo an asymmetric allylation ((2) in Scheme 1.51) [124].

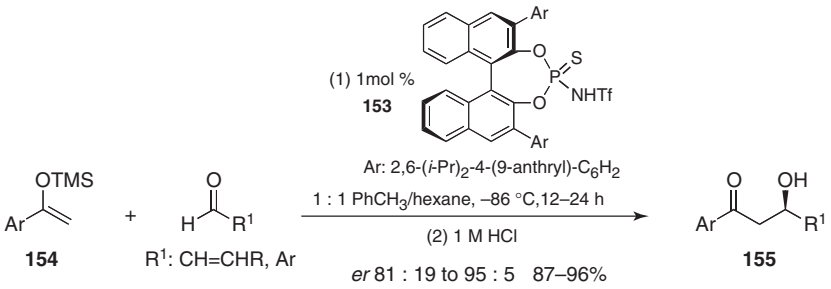
Finally, some studies have recently focused on the use of chiral Brønsted acids and other protic catalysts to control the stereochemical outcome of these reactions. Rawal described the first examples of hydrogen-bond-mediated enantioselective Mukaiyama acetate aldol reactions, which involved additions of *O*-silyl dienolates



Scheme 1.50 Asymmetric Mukaiyama aldol reactions catalyzed by a Tol-BINAP copper complex.



Scheme 1.51 Proposed mechanisms for Mukaiyama aldol reactions catalyzed by Tol-BINAP copper complexes.



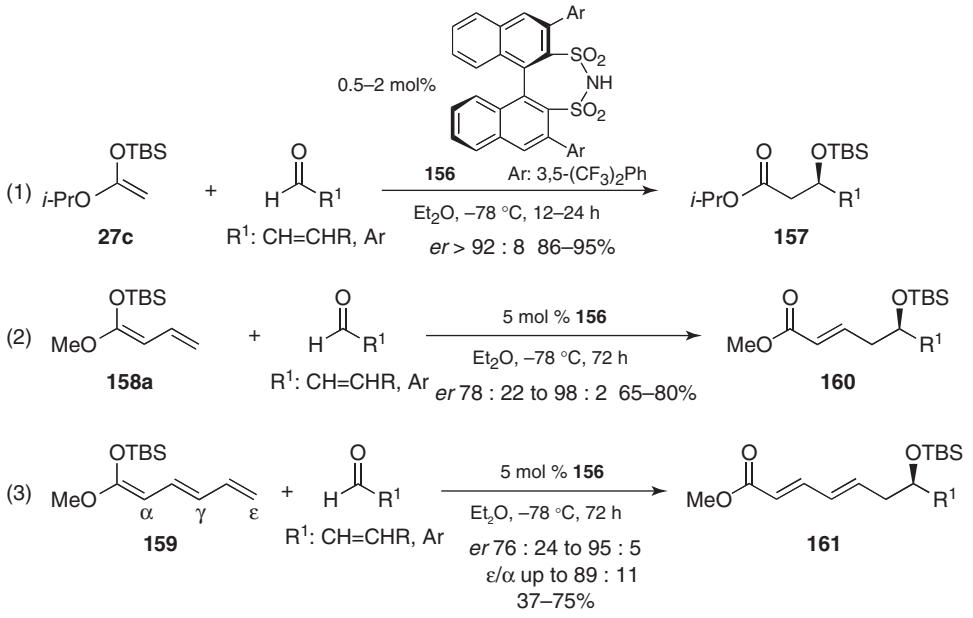
Scheme 1.52 Asymmetric Mukaiyama aldol reactions catalyzed by a chiral *N*-triflylthiophosphoramide.

to reactive aldehydes in the presence of diols as catalysts [125, 126]. Furthermore, Yamamoto found that catalytic amounts of *N*-triflylthiophosphoramide (**153**) promoted stereocontrolled additions of silyl enol ethers (**154**) from aryl methyl ketones to α, β-unsaturated and aromatic aldehydes, affording the corresponding β-hydroxy ketones (**155**) in high yields (Scheme 1.52) [127]. Importantly, mechanistic studies revealed that the actual catalyst was **153** itself rather than the silylated Brønsted acid.

In turn, List reported that chiral disulfonimide (**156**) was an efficient catalyst for different Mukaiyama aldol reactions. Indeed, tiny amounts of this chiral Brønsted acid triggered additions of silyl ketene acetal (**27c**) to nonenolizable aldehydes, producing β-OTBS isopropyl esters (**157**) in high yields and enantioselectivities ((1) in Scheme 1.53) [128]. This chemistry was further extended to vinylogous and bisvinylogous additions of (**158a**) and (**159**) to α, β-unsaturated and aromatic aldehydes, which afforded the corresponding methyl esters (**160**) and (**161**) in a regio and stereocontrolled manner ((2) and (3) in Scheme 1.53) [129]. The mechanism of these transformations is unknown, but it was proposed that **156** might be first silylated by the ketene acetal, providing an *N*-silyl disulfonimide that could activate the aldehyde through *O*-silylation. Thus, the asymmetric induction would occur by stereochemical communication within an ion pair consisting of the disulfonimide anion and the silylated oxonium cation. Irrespective of such mechanistic considerations, these findings have paved the way for the development of a new sort of transformations based on the appropriate choice of chiral hydrogen-bond donors [130].

1.2.6
Chiral Lewis Bases

In addition to the above-mentioned methodologies based on the increase of the electrophilicity of aldehydes by binding Lewis or Brønsted acids to the carbonyl group, Denmark developed a variant of the Mukaiyama aldol reaction that takes advantage of the Lewis acidic silicon atom of trichlorosilyl enolates. Thereby, association of these enolates with Lewis bases gives rise to a hypervalent silicon



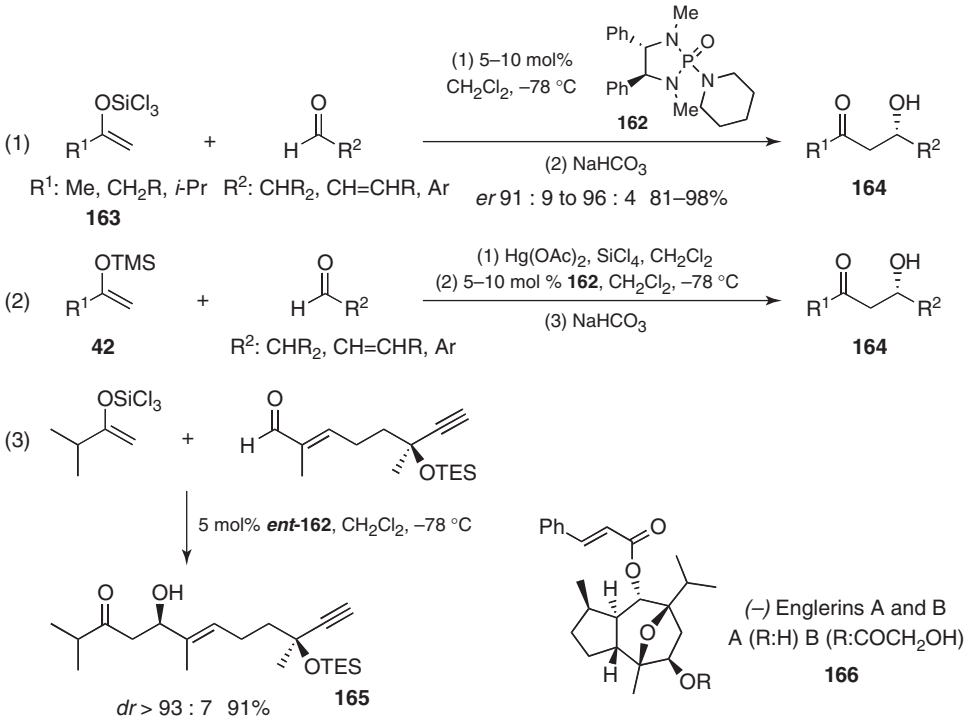
Scheme 1.53 Asymmetric Mukaiyama aldol reactions catalyzed by a chiral disulfonimide.

moiety characterized by enhanced Lewis acidity. Thus, such a reacting species is poised for activation of the carbonyl component, which allows it to participate in highly efficient aldol reactions (Scheme 1.2) [9].

Systematic investigation on aldol reactions of trichlorosilyl enolates revealed that chiral phosphoramide (**162**) triggered highly enantioselective additions of methyl ketone-derived enolates (**163**) to branched aliphatic, α, β-unsaturated, and aromatic aldehydes, affording β-hydroxy ketones (**164**) in high yields ((1) in Scheme 1.54). Importantly, the Hg(II)-catalyzed transilylation of TMS enol ethers (**42**) with $SiCl_4$ provided an entry to a one-pot method for the generation and reaction of these enolates with similar yields and enantioselectivities ((2) in Scheme 1.54) [131]. Echavarren used this method to prepare β-hydroxy ketone (**165**), an intermediate in the enantioselective synthesis of (−)-englerins A and B (**166**) ((3) in Scheme 1.54) [132].

This method was further tested on chiral substrates with different results. For instance, the additions of trichlorosilyl enolate from lactate-derived silyl enol ether (**167**) to benzaldehyde catalyzed by **162** or ***ent*-162** produced the same 1,4-*syn* aldol (**168**) in both cases ((1) in Scheme 1.55). Conversely, parallel aldol additions of trichlorosilyl enolates from β-silyloxy silyl enol ethers (**169**) and (**170**) produced the corresponding aldol adducts (**171**–**174**) depending on the phosphoramide ((2) and (3) in Scheme 1.55) [133].

The mechanism of all these reactions is rather complex. Indeed, exhaustive studies established that the process takes place via the simultaneous operation of two mechanistic pathways involving one or two phosphoramides bound to



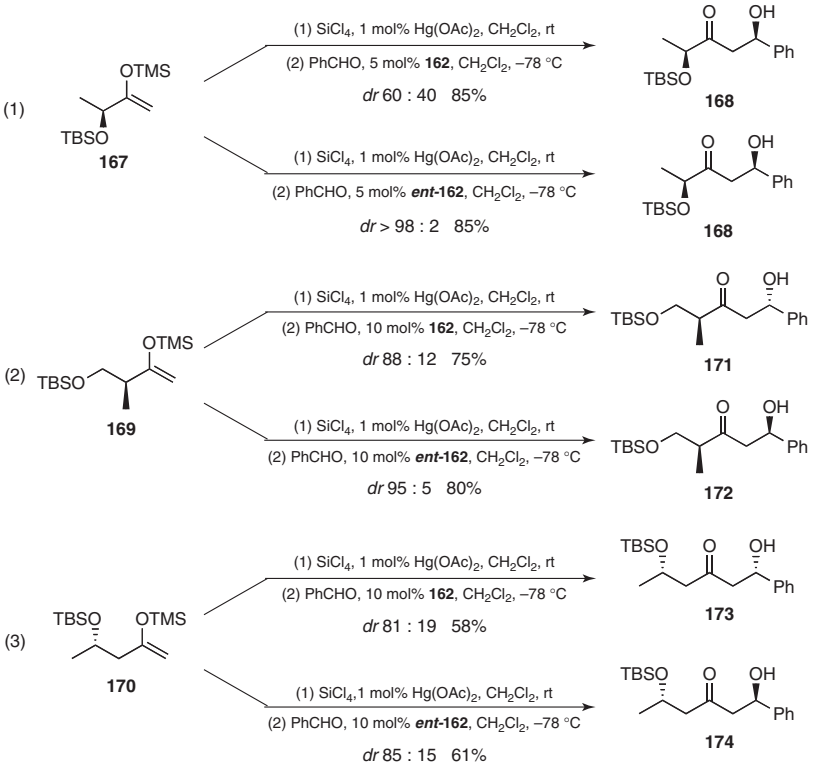
Scheme 1.54 Asymmetric Mukaiyama aldol reactions catalyzed by chiral phosphoramides.

the silicon atom in cationic complexes **XXXI** and **XXXII** (Scheme 1.56). Their subsequent association with the aldehyde leads to a reversible albeit unfavorable formation of an activated complex, which evolves through cyclic transition states **XXXIII** or **XXXIV**. The rate of this cycle determines the turnover as well as the stereochemical outcome of the aldol reaction [134]. Thus, the achievement of highly stereocontrolled transformations requires that the aldol reaction mainly proceeds through one of these competitive pathways.

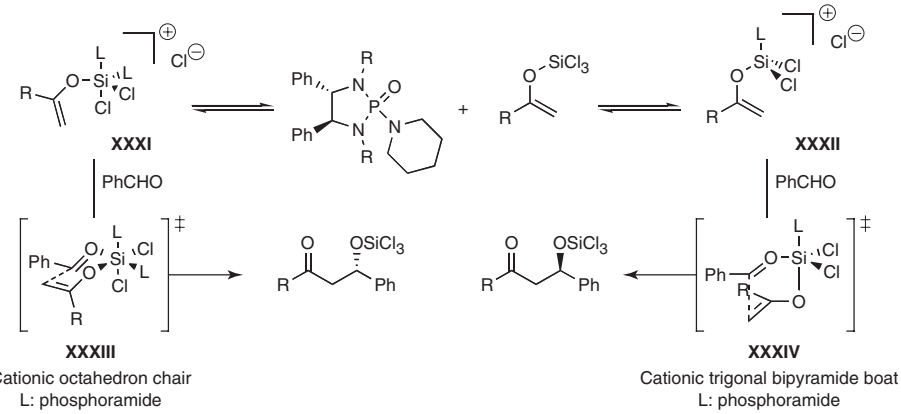
A second type of Lewis base catalysis involves activation of weakly acidic $SiCl_4$ by binding of strong Lewis basic chiral phosphoramide (**175**), which leads to the formation of a chiral Lewis acid *in situ*. This species has been shown to be a competent catalyst for Mukaiyama aldol additions of achiral and chiral silyl enol ethers to α, β-unsaturated and aromatic aldehydes (Scheme 1.57) [133, 135].

Furthermore, these procedures were also successful for the additions of silyl ketene acetal (**27a**) and vinylogous systems (**158b**) and (**176**) to a broad scope of aldehydes, affording β- and δ-hydroxy esters (**177–179**) in high yields and exceptional levels of regio- and enantioselectivity, which expanded the synthetic potential of this methodology (Scheme 1.58) [136–138].

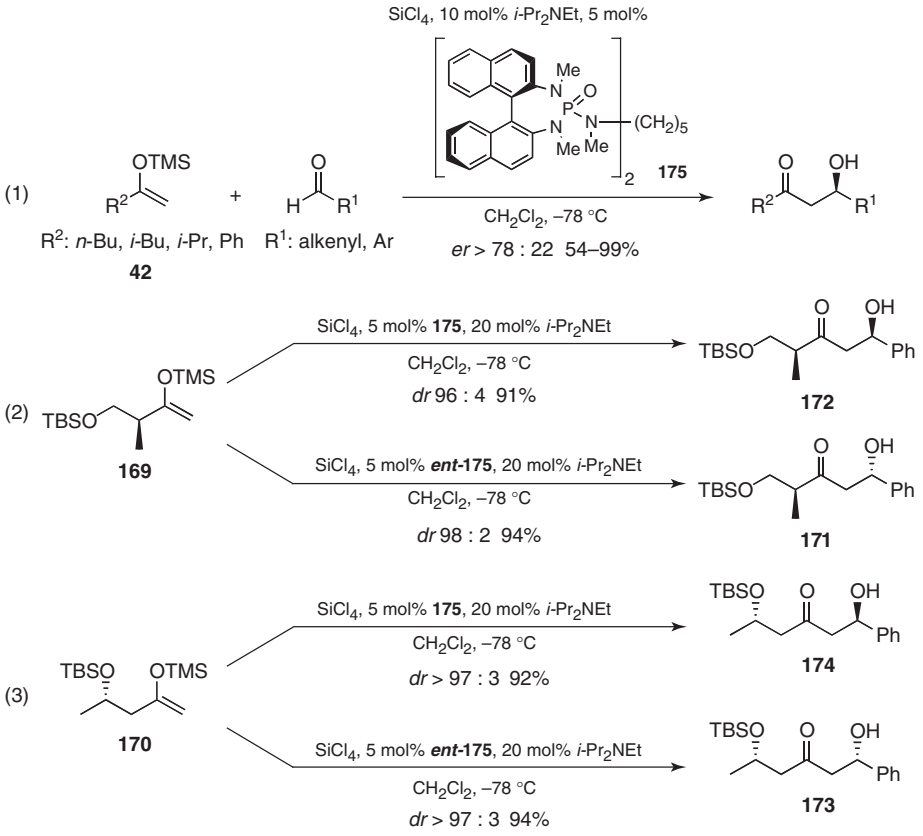
Although the origin of the observed enantioselectivity is still unclear, spectroscopic and mechanistic studies of these reactions suggested that the catalytic



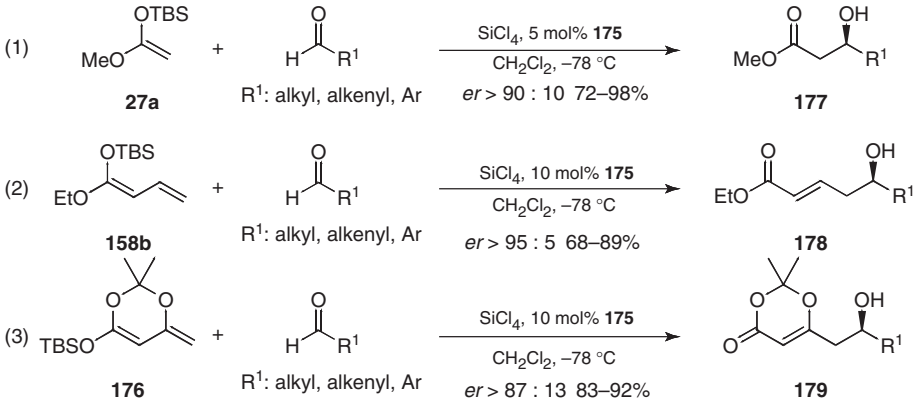
Scheme 1.55 Mukaiyama aldol reactions of chiral trichlorosilyl enolates catalyzed by chiral phosphoramides.



Scheme 1.56 Mechanistic profile adapted from the original proposed for the trichlorosilyl enolate from cyclohexanone.



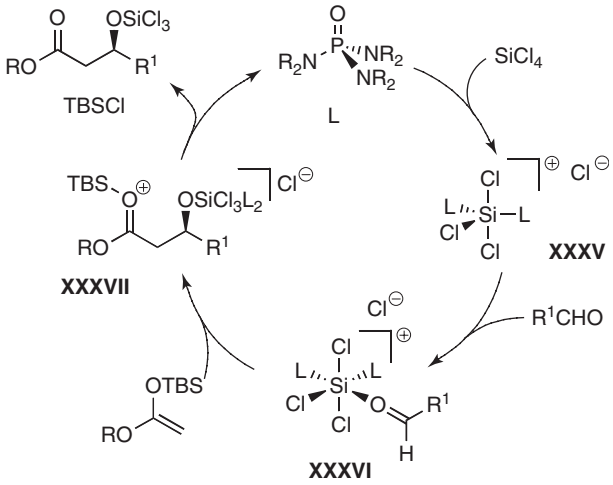
Scheme 1.57 $SiCl_4$-mediated Mukaiyama aldol reactions of silyl enol ethers catalyzed by chiral phosphoramides.



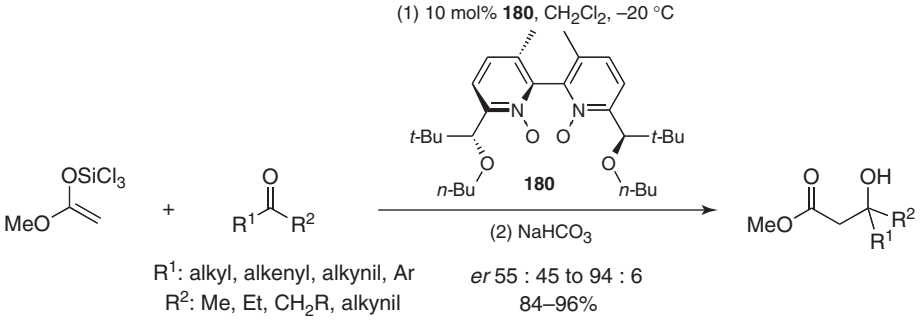
Scheme 1.58 $SiCl_4$-mediated Mukaiyama aldol reactions catalyzed by chiral phosphoramides.

cycle involved a highly electrophilic, phosphoramide-bound silyl cation **XXXV** (Scheme 1.59). This species could then bind the aldehyde to form complex **XXXVI**, which would undergo the addition of the enolsilane through an open transition state. After cleavage of the silyl group and dissociation of the catalyst, the resultant aldolate **XXXVII** would give a trichlorosilyl ether (Scheme 1.59) [136, 139].

Finally, Denmark also reported that bis *N*-oxide (**180**), a Lewis base, catalyzed the aldol addition of methyl trichlorosilyl ketene acetal to a wide range of nonactivated ketones (Scheme 1.60). The resultant β-*tert*-hydroxy esters were obtained in excellent yields with enantioselectivities highly dependent on the structure of the ketone [140]. From a mechanistic point of view, this reaction is understood to proceed through a six-membered boatlike transition state organized around a cationic silicon center, in a way similar to the aldol additions to aldehydes described in Scheme 1.56.



Scheme 1.59 Mechanism for the $SiCl_4$-asymmetric Mukaiyama aldol reactions catalyzed by chiral phosphoramides.



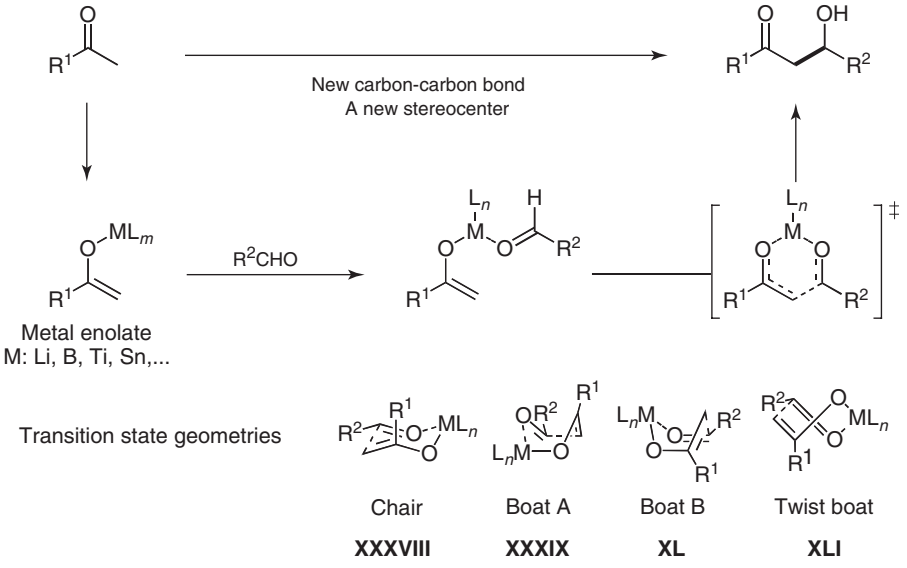
Scheme 1.60 Asymmetric Mukaiyama aldol reactions catalyzed by a chiral bis *N*-oxide.

1.3
Metal Enolates

1.3.1
Concept and Mechanism

The enolization of a parent carbonyl compound with a strong base, a suitable combination of a Lewis acid and a tertiary amine, or by simple transmetallation affords metal enolates from nearly every element of the periodic table [141], which suggests that any element could participate in asymmetric aldol reactions. Nevertheless, only a narrow group of elements including lithium, boron, titanium, or tin fulfill the required conditions to undergo stereocontrolled aldol transformations. In essence, the configurationally stable *O*-enolates of these elements allow the aldol reactions to proceed through cyclic and highly organized transition states. Such transition states provide the appropriate environment to control the new stereocenters provided that the appropriate chiral elements are placed on the substrate, the aldehyde, or the ligands bound to the metal. Unfortunately, *acetate* aldol reactions mediated by such intermediates can evolve through different six-membered cyclic transition states **XXXVIII–XLI** (Scheme 1.61), which hampers the proper differentiation of the two faces of the carbonyl bond by the unsubstituted enolate.

Indeed, pioneering studies soon recognized that the stereochemical control on the metal-enolate-mediated *acetate* aldol reaction ($R^2 = H$ in Scheme 1.1) was much more demanding than control on the similar *propionate* counterpart ($R^2 = Me$ in Scheme 1.1). Hence, this challenging transformation has attracted much attention in recent decades. At present, a wide range of highly stereoselective *acetate* aldol



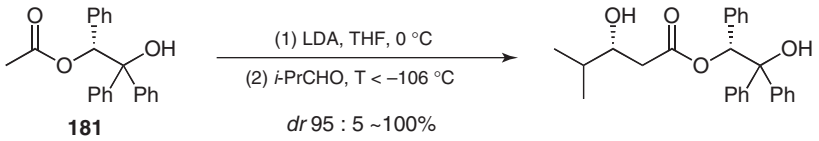
Scheme 1.61 Metal-enolate-mediated *acetate* aldol reactions.

reactions based on metal enolates from chiral auxiliaries, chiral Lewis acids, and chiral ketones complement the accomplishments described in the previous section.

1.3.2 Chiral Auxiliaries

The poor stereocontrol observed in preliminary studies on aldol reactions from unsubstituted enolates triggered an intense search for an efficient covalently bound chiral auxiliary. Among the large number of reported auxiliaries, chiral 1,1,2-triphenylethanediol arising from mandelic esters quickly achieved a prominent position [142]. Indeed, the lithium enolate from acetate (**181**) (Scheme 1.62) provides high yields and diastereoselectivities and has been successfully used in the synthesis of β-hydroxy carbonyl structures present in natural products [142b, 143].

However, the extremely low temperatures essential to attain high diastereoselectivities thwarted further applications and the quest for a more general approach remained active [144, 145]. Thus, considering that boron enolates from *N*-acetyl oxazolidinone (**182**) (Scheme 1.63) afforded nearly equimolar mixture of diastereomers [3a, 146, 147], Nagao and Fujita findings on unprecedented stereocontrolled



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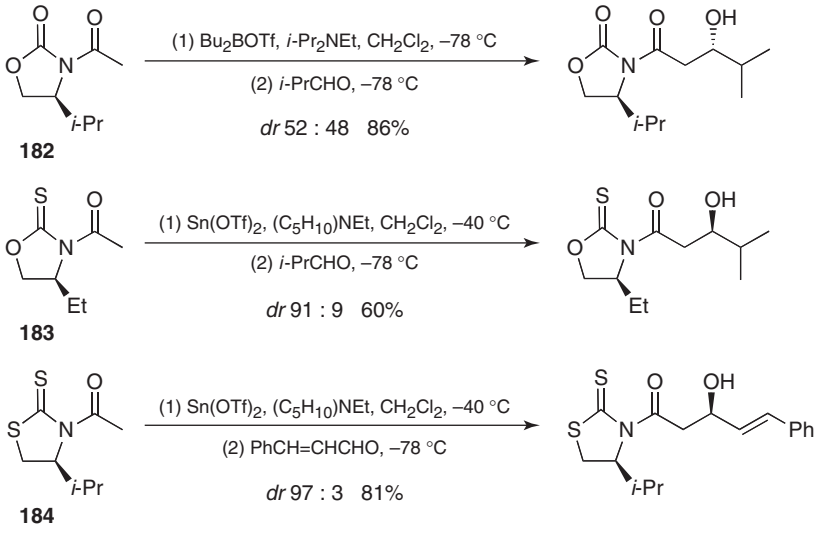
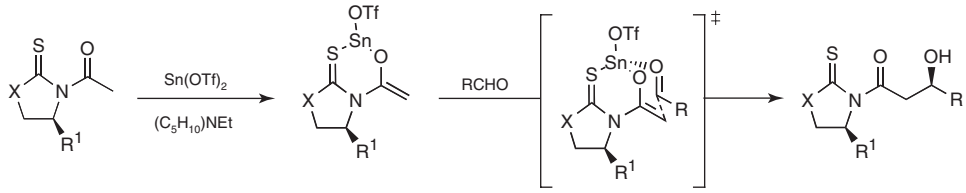
Scheme 1.62 Chiral auxiliary-based lithium-mediated stereoselective aldol reaction.



182 **183** **184**

Scheme 1.63 Chiral auxiliary-based tin(II)-mediated stereoselective aldol reactions.



Scheme 1.64 Mechanism for tin(II)-mediated aldol reactions.

Sn(II)-mediated aldol reactions from *N*-acetyl oxazolidinethione (**183**) [148] and thiazolidinethione (**184**) [149][6] were particularly outstanding (Scheme 1.63).

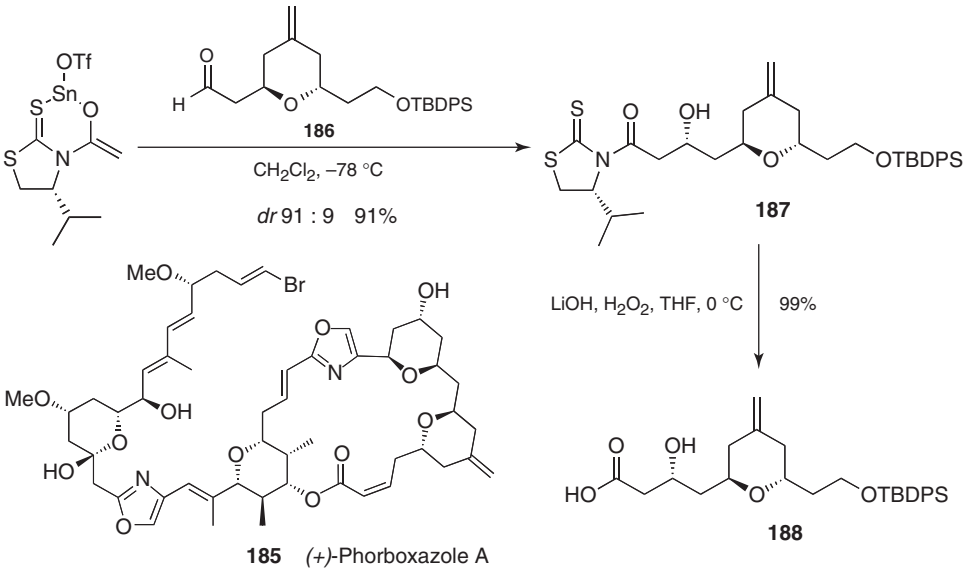
The rationale for these highly stereoselective transformations placed four ligands on the Sn(II) atom in the transition state. Hence, the exocyclic sulfur atom was responsible for the lasting chelated tin enolate and the coordination of the incoming aldehyde far from the R^1 group of the chiral auxiliary (Scheme 1.64). Eventually, a chairlike cyclic six-membered transition state accounted for the configuration of the new stereocenter in the major diastereomer.

This methodology has been largely used in the synthesis of natural products [150]. Its synthetic potential can be illustrated by the syntheses of (+)-phorboxazole A (**185**), reported by Smith *et al.* [151], in which the highly diastereoselective addition of the Sn(II)–enolate from ***ent*-184** to chiral aldehyde (**186**) followed by the easy removal of the chiral auxiliary of the resultant aldol (**187**) furnished the desired β-hydroxy acid (**188**) in excellent overall yield (Scheme 1.65).

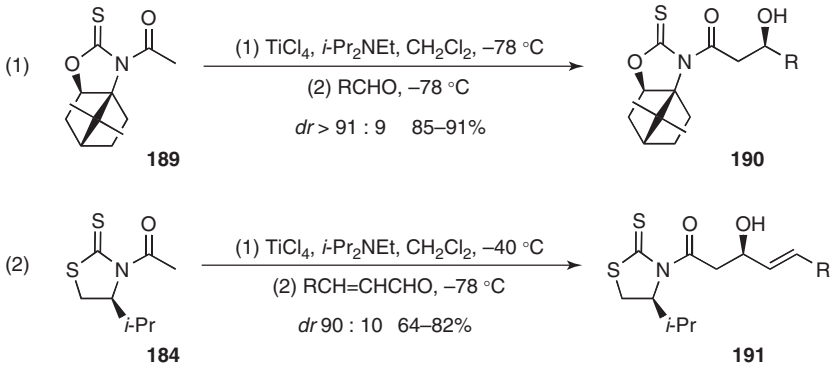
Despite these successes, the attention was focused on the development of similar procedures using other Lewis acids. In this context, Yan took advantage of Ti(IV)-mediated aldol reactions from camphor-derived thioimide (**189**) with representative aldehydes to obtain adducts **190** in excellent yields and diastereoselectivities ((1) in Scheme 1.66) [152][7] whereas Urpí and Vilarrasa used *N*-acetyl thiazolidinethione (**184**) in parallel aldol additions to α,β-unsaturated aldehydes to yield aldols (**191**) in high diastereomeric ratios ((2) in Scheme 1.66) [153]. Last approach was particularly inspiring because both enantiomers of the chiral auxiliary can be prepared from natural and unnatural α-amino acids [154], $TiCl_4$ is an easily available Lewis acid, and permitted the isolation of pure diastereomers **191** in higher yields than the Sn(II)-based methodology.

Then, the stage was set for further developments in this area. The crucial role of the exocyclic C=S bond was well established through careful analyses of aldol reactions involving *N*-acetyl oxazolidinones. As for boron enolates, titanium-mediated aldol reaction from *N*-acetyl-4-isopropyl-1,3-oxazolidin-2-one (**182**) (Scheme 1.63) gave good yields but poor diastereoselectivities [155], whereas the stereochemical outcome from a close 5,5-disubstituted oxazolidinone turned out to be dramatically dependent on the metal of the enolate [156]. Thus, the most striking advances came up from sulfur-containing chiral auxiliaries. Indeed, Phillips [157] and Crimmins

6) Oxazolidinethiones turned out to be slightly less stereoselective than the corresponding thiazolidinethiones for α, β-unsaturated aldehydes.
7) Boron enolates afforded lower diastereomeric ratios.



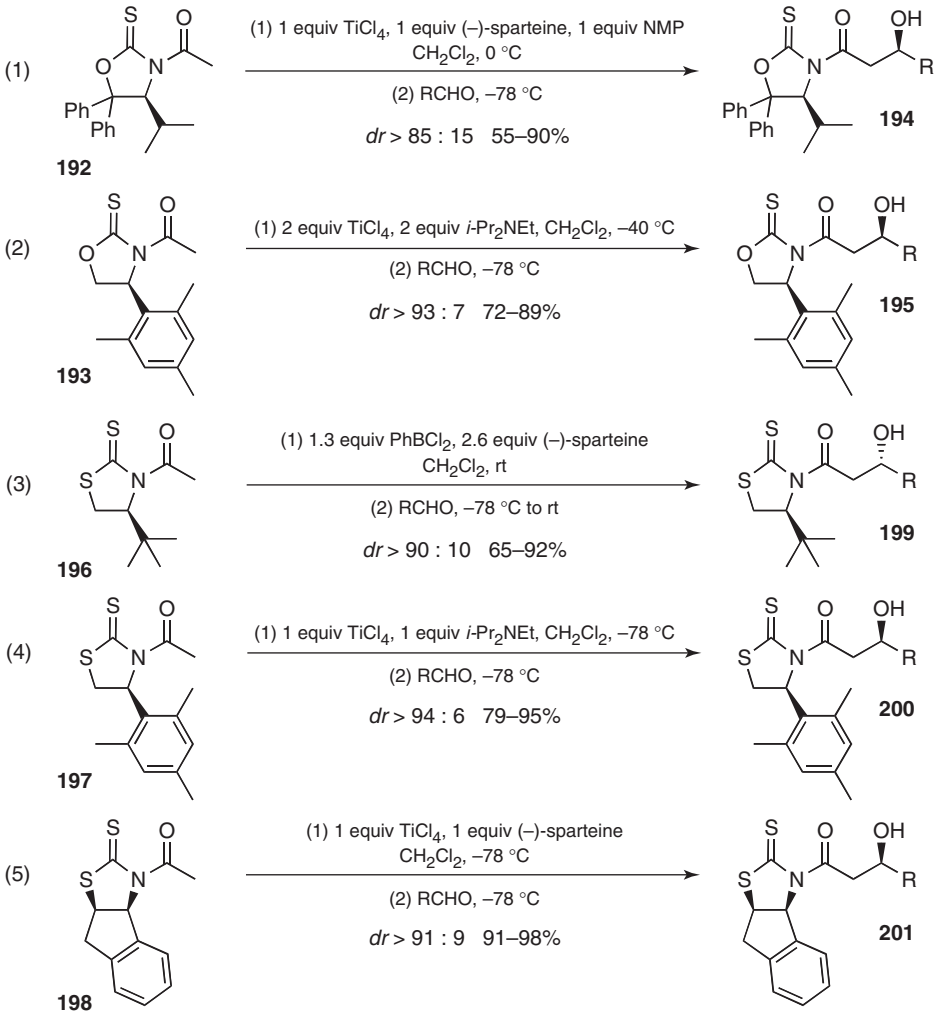
Scheme 1.65 Synthesis of (+)-phorboxazole A.



Scheme 1.66 Chiral auxiliary-based titanium(IV)-mediated stereoselective aldol reactions.

[158] reported that *N*-acetyl oxazolidinethiones (**192**) and (**193**) underwent highly diastereoselective additions to aliphatic, α, β-unsaturated, and aromatic aldehydes, affording aldols (**194**) and (**195**) in high yields and diastereoselectivities ((1) and (2) in Scheme 1.67), whereas Sammakia [159], Crimmins [158, 160], and Olivo [161] described that boron and titanium enolates from *N*-acetyl thiazolidinethiones (**196**–**198**) provided high levels of stereocontrol with a wide range of aldehydes, affording aldols (**199**–**201**) in high yields ((3–5) in Scheme 1.67) [162].

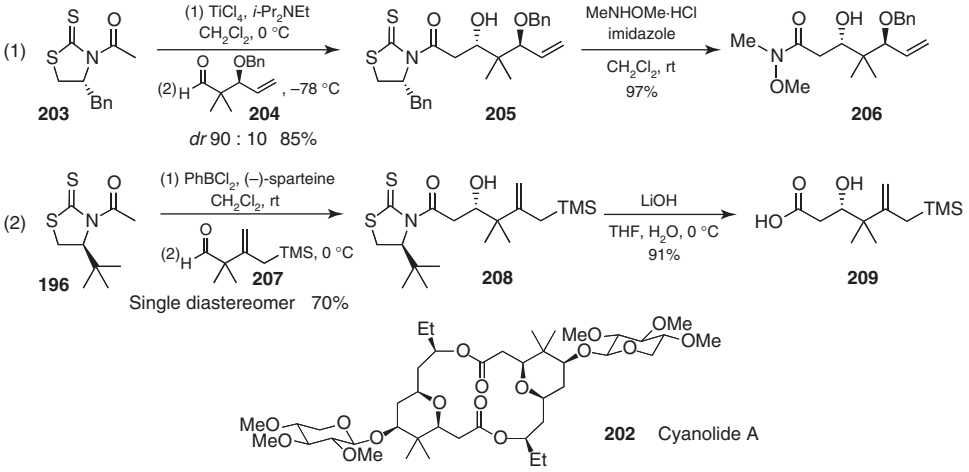
This chemistry has been widely applied to the synthesis of natural products [163], as can be illustrated by two concurrent reports on the total synthesis of cyanolide A (**202**). Thereby, Pabbaraja took advantage of a highly diastereoselective



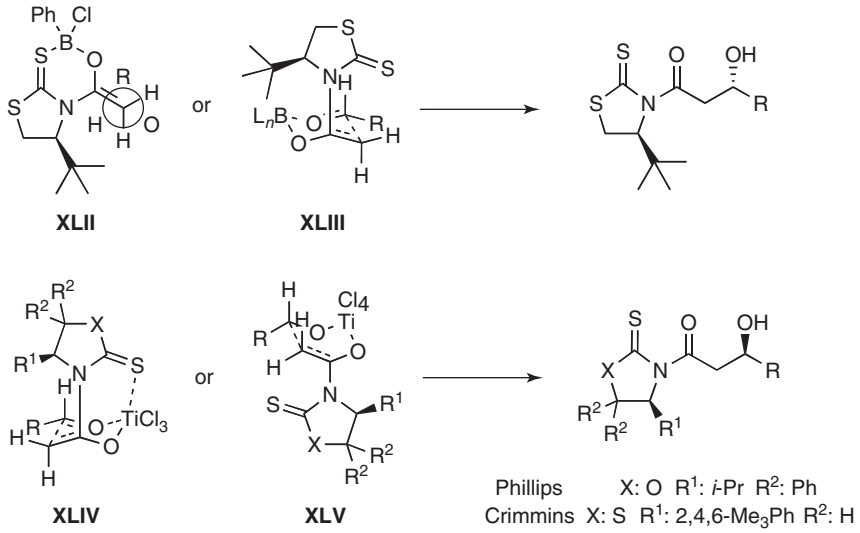
Scheme 1.67 Oxazolidinethione- and thiazoldinethione-based stereoselective aldol reactions.

titanium-mediated aldol reaction of *N*-acetyl thiazolidinethione (**203**) and aldehyde (**204**) to prepare aldol (**205**), which was subsequently treated with MeNHOMe·HCl to remove the chiral auxiliary and produce Weinreb amide (**206**) in an excellent yield ((1) in Scheme 1.68) [164]. In turn, Rychnovsky claimed that similar titanium- and tin-based methodologies on aldehyde (**207**) led exclusively to the protodesilylated product, but the reaction proceeded smoothly using boron-mediated Sammakia's conditions to provide aldol adduct **208** as a single diastereomer, which was easily converted into carboxylic acid (**209**) ((2) in Scheme 1.68) [165].

The mechanism of these transformations is poorly understood, and alternative models are often proposed. This is the case of thiazolidinethione (**196**). As



Scheme 1.68 Synthesis of cyanolide A.

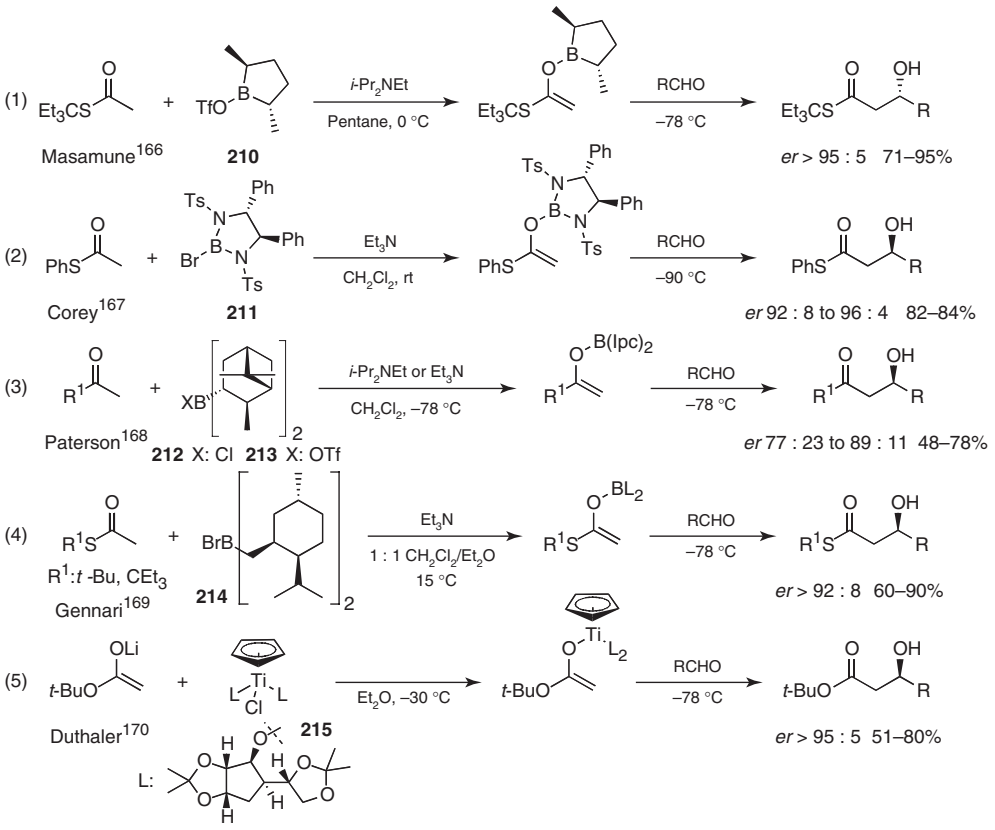


Scheme 1.69 Transition states for oxazolidinethione- and thiazolidinethione-based aldol reactions.

Evans oxazolidinone auxiliary fails to give high selectivities in *acetate* aldol reactions, Sammakia speculated that the boron-mediated reaction from **196** ((3) in Scheme 1.67) proceeded through an open transition state, but a more common cyclic chairlike transition state was not ruled out (**XLII** and **XLIII**, respectively, in Scheme 1.69) [159a]. On the other hand, the opposite stereochemistry obtained in the titanium-mediated reactions led Phillips [157a] and Crimmins [158] to propose a chelated chairlike or a non-chelated boatlike transition states (**XLIV** and **XLV**, respectively, in Scheme 1.69) to account for the observed stereocontrol.

1.3.3
Stoichiometric Lewis Acids

Simultaneously to the search for a covalently bound chiral auxiliary, many efforts were invested in the development of chiral Lewis acids. Thereby, the coordination of a Lewis acid to a carbonyl should enhance its acidity and allow the formation of the corresponding enolate by simple addition of a tertiary amine. Alternatively, it could also be introduced by transmetallation of a preformed enolate. In any case, chiral ligands on these Lewis acids should provide the source for a proper discrimination of the two faces of the C=O bond of the aldehyde in such a way that the stereoselective carbon–carbon bond formation would render the desired aldol adduct without the need of further synthetic steps. Therefore, this approach would avoid the introduction and the removal of the chiral auxiliary, increasing the efficiency of the process. The Lewis acids (**210**–**215**) represented in Scheme 1.70 fulfilled such requirements and afforded the corresponding aldol products in excellent enantioselectivities [166–170].

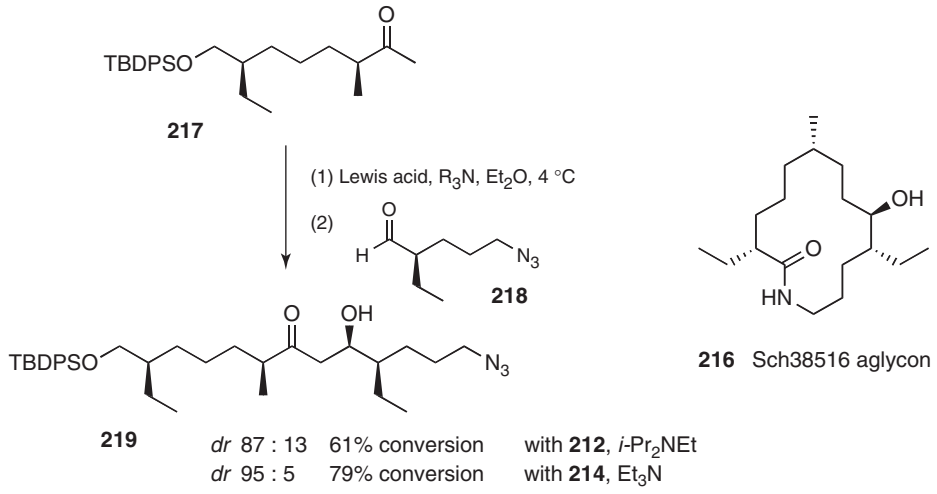


Scheme 1.70 Chiral Lewis acids in asymmetric aldol reactions.

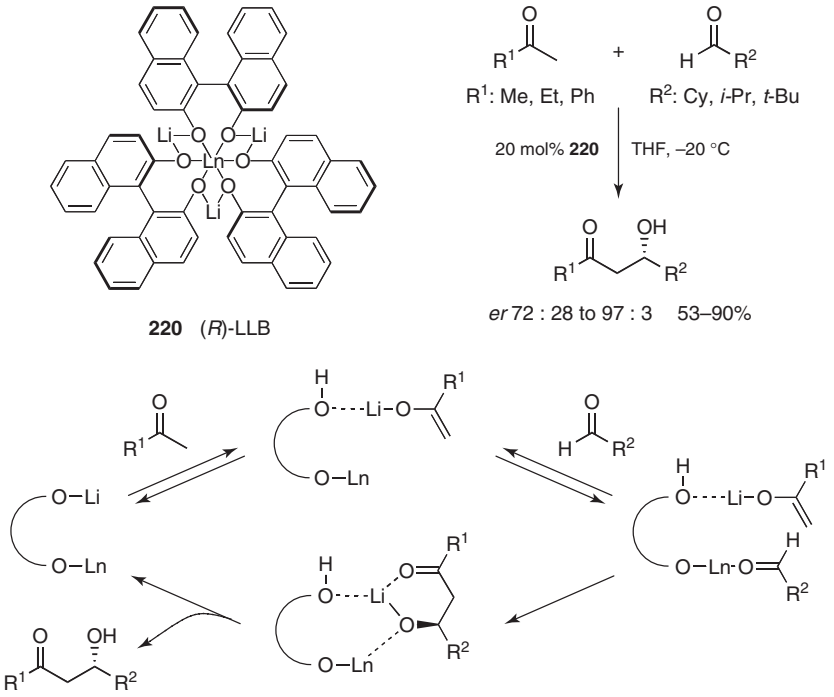
Unfortunately, most of them have been scarcely used in the synthesis of natural products and a short number of applications can be found in the literature [171]. Commercially available isopinocampheylborane chloride (**212**) (Ipc_2BCl) is the exception, because it participates in many double asymmetric aldol reactions from chiral ketones (Section 1.3.6) [1b, 168]. This failure is occasionally due to the troublesome preparation of some of these Lewis acids, but the Achilles heel of the overall strategy lies on the purification of the resulting products. Indeed, these Lewis acids must provide high stereoselective transformations, because mixtures of enantiomers cannot be easily purified and they come across the whole synthetic sequence. Thus, this strategy becomes synthetically useful when the aldol reaction proceeds in a highly stereoselective manner or is applied to chiral substrates, as occurs in the synthesis of Sch38516 aglycon (**216**) (Scheme 1.71). While lithium, sodium, or titanium enolates of chiral ketone (**217**) and aldehyde (**218**) delivered almost equimolar mixtures of both diastereomers, boryl bromide (**214**) provided a highly stereoselective aldol coupling (*dr* 95 : 5) and furnished pure aldol (**219**) in 40–45% yield after a simple chromatographic purification (Scheme 1.71) [171d].

1.3.4
Catalytic Lewis Acids

Inspired by Nature, the attention was also focused on class II aldolases that use zinc cations to activate the enolate partner (a *metal enolate*) as well as other centers on the enzyme assist to the activation of the incoming aldehyde. Considering such a mechanism, Shibasaki and Trost described the first direct aldol reactions from unmodified methyl ketones in the presence of multifunctional catalysts.



Scheme 1.71 Synthesis of Sch38516 aglycon.

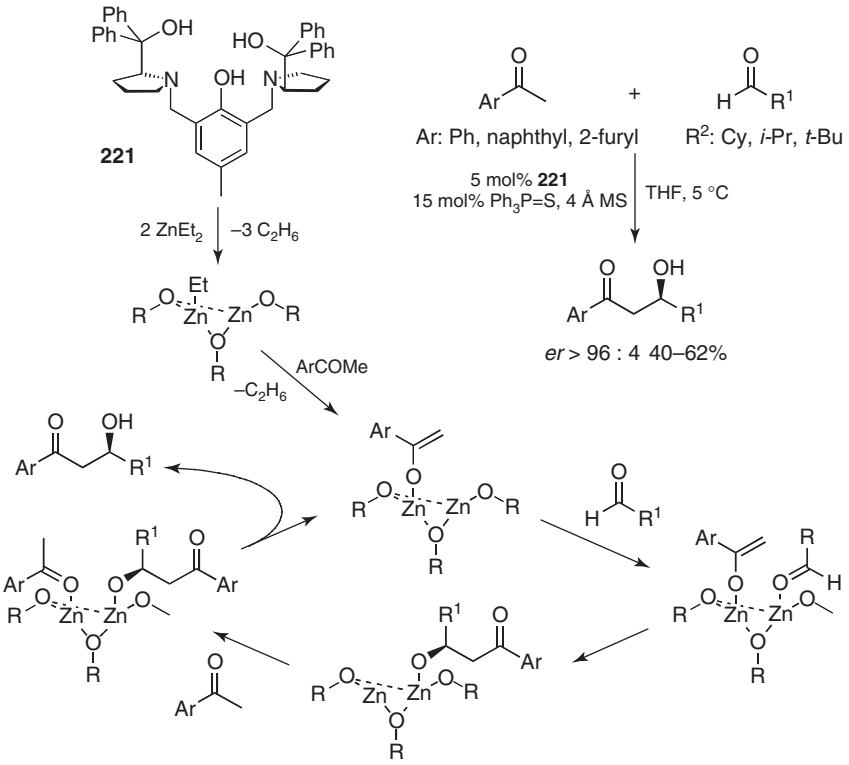


Scheme 1.72 Asymmetric aldol reactions of methyl ketones catalyzed by $LnLi_3$ tris(binaphthoxide).

Shibasaki reported that $LnLi_3$ tris(binaphthoxide) (**220**) triggered direct catalytic asymmetric aldol reactions of methyl ketones and α-branched aldehydes under mild conditions in good to high yields (Scheme 1.72) [172, 173]. Heralding a new mechanistic paradigm, Shibasaki speculated that the central lanthanum(III) atom of **220** functions as a Lewis acid activating the aldehyde, whereas the lithium binaphthoxide moiety acts as a Brønsted base. Thus, this catalyst mimicked the enzymatic activity and permitted the efficient stereoselective aldol reactions represented in Scheme 1.72 [174].

In turn, Trost described that one of the zinc atoms of bimetallic catalyst (**221**) could form the metal enolate while the second one bound to the aldehyde acting as a Lewis acid center. Then, aldol additions of aryl methyl ketones to α-branched aldehydes proceeded in good yields and outstanding enantioselectivities (Scheme 1.73) [175]. Furthermore, studies have expanded the scope of this procedure to other functionalizable ketones, such as methyl vinyl ketone, and the simple acetone [176].

Both methodologies were applied to the synthesis of fostriecin (**222**), using methyl ynones (**223**) as the active methylene partners (Scheme 1.74). Thereby, aldol addition of **223a** to chiral aldehyde (**224**) in the presence of catalyst ent-220 gave aldol (**225**) in 65% yield and 78 : 22 diastereomeric ratio [177]. In turn, **221** catalyzed the reaction of **223b** and α-ketal aldehyde (**226**) to produce aldol (**227**) as a single enantiomer in 58% yield [178, 179].



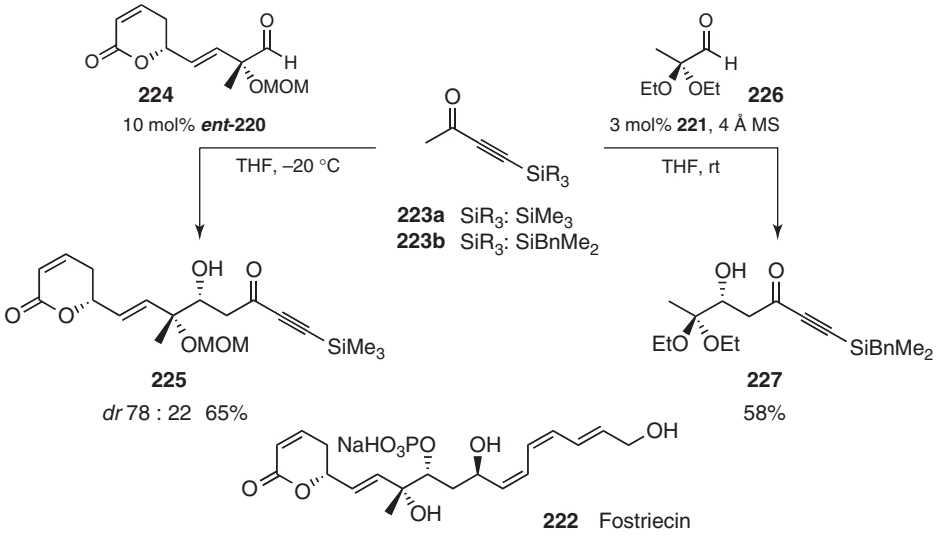
Scheme 1.73 Asymmetric aldol reactions of methyl ketones catalyzed by a zinc bimetallic complex.

More recently, Shibasaki has reported a new direct catalytic asymmetric aldol process inspired in the biosynthesis of 1,3-diols. This procedure takes advantage of a soft Lewis acid/hard Brønsted base cooperative catalyst comprising biphosphine (**228**) and $[Cu(CH_3CN)]PF_6$/LiOAr to promote enantioselective aldol additions of thioamides (**229**) to aliphatic aldehydes, affording aldols (**230**) in high yields (Scheme 1.75) [180].

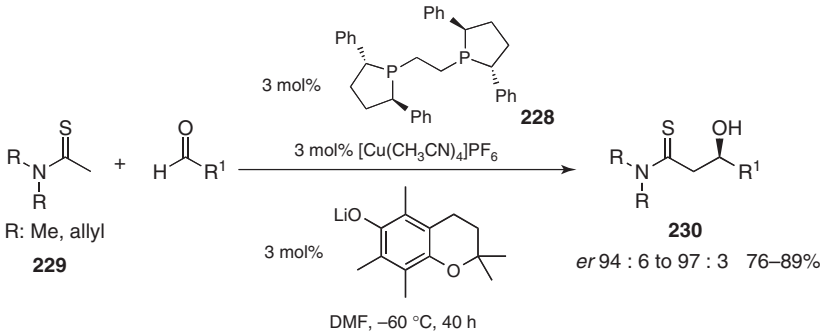
These examples have stimulated the development of new metal catalysts, which proves the interest on this kind of reactions. Regrettably, most of them can be used on a reduced range of substrates or show a low reactivity, which restrict their synthetic scope [181].

1.3.5
Chiral Aldehydes

The asymmetric induction imparted by chiral aldehydes in aldol reactions involving achiral unsubstituted metal enolates is usually low. This is the case of chiral aldehydes bearing a Cα stereocenter. Indeed, pioneering studies revealed that

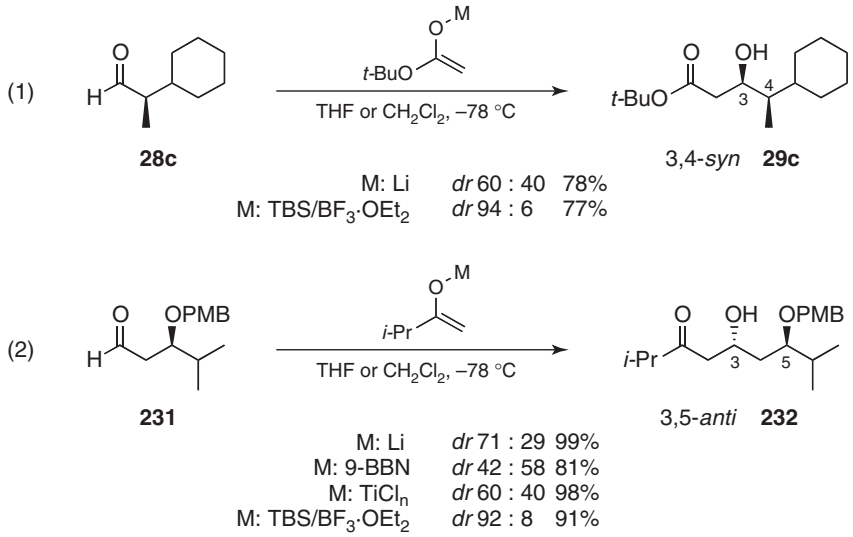


Scheme 1.74 Synthesis of fostriecin.



Scheme 1.75 Asymmetric aldol reactions of thioamides catalyzed by a copper biphosphine complex.

aldol additions of lithium, boron, and titanium enolates to these aldehydes led to the *Felkin* product with a simple 1,2-diastereoselection often insufficient to be synthetically useful. For instance, the addition of lithium enolate from *tert*-butyl acetate to chiral aldehyde (**28c**) afforded *Felkin* 3,4-*syn* adduct (**29c**) in good yield but low diastereoselectivity ((1) in Scheme 1.76), much lower than that attained under Mukaiyama conditions [26, 182] (Schemes 1.13 and 1.14). This trend was also observed in chiral aldehydes possessing alkoxy groups at the Cβ position. Thereby, aldol additions of metal enolates from isopropyl methyl ketone to aldehyde (**231**) bearing a Cβ–OPMB group (or Cβ–OTBS) mainly gave 3,5-*anti* aldols (**232**) in excellent yields but low stereocontrol ((2) in Scheme 1.76) [43, 183], much poorer

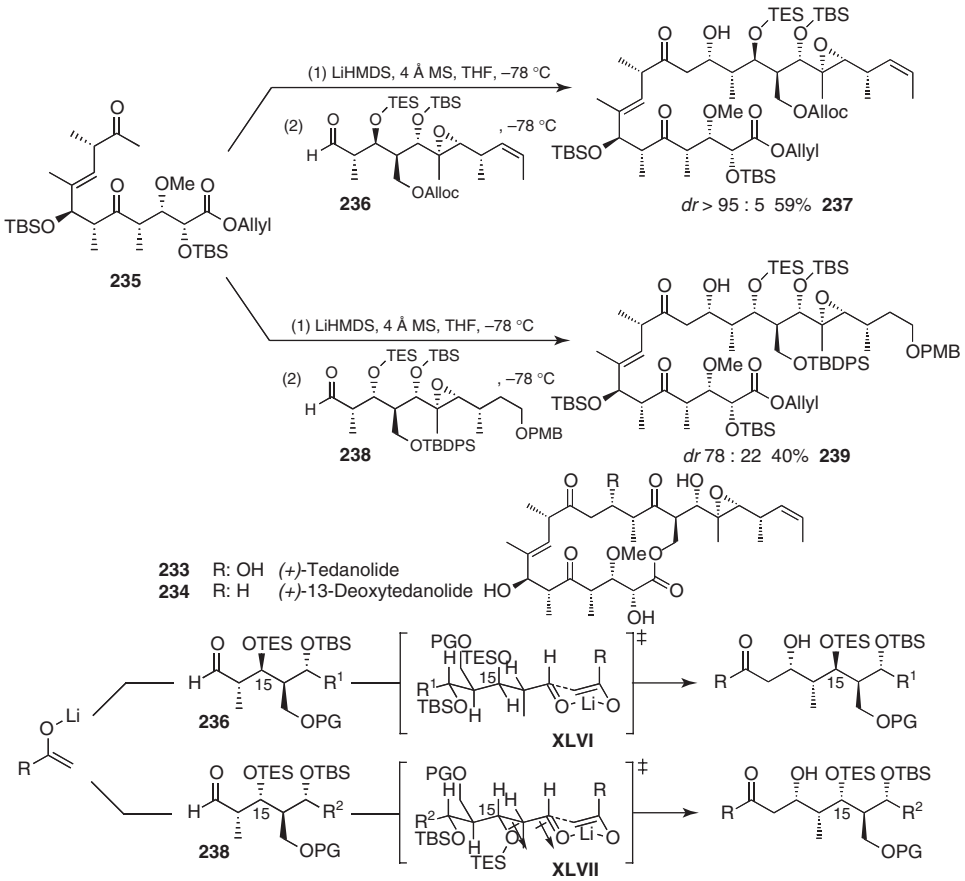


Scheme 1.76 Asymmetric induction imparted by chiral aldehydes in aldol reactions involving metal enolates.

than that provided by the Mukaiyama variant (Scheme 1.23). Interestingly, the best results were achieved with lithium enolates under conditions in which chelate organization was unlikely.

Unfortunately, these studies did not permit a clear identification of the dominant element governing the aldol reactions of chiral β-alkoxy α-methyl aldehydes. Thus, any prediction of the stereochemical outcome of such reactions must take into account the complete architecture of the substrates. A good example of these difficulties was described by Roush in the synthesis of (+)-tedanolide and (+)-13-deoxytedanolide (**233** and **234**, respectively, in Scheme 1.77). Indeed, lithium enolate derived from structurally complex methyl ketone (**235**) reacted with *anti* β-silyloxy α-methyl aldehyde (**236**) to give 3,4-*syn* aldol (**237**) in good yield and excellent diastereoselectivity (Scheme 1.77), whereas the parallel addition to *syn* β-silyloxy α-methyl aldehyde (**238**) provided a 78 : 22 mixture of diasteromers (**239**) in 40% yield (Scheme 1.77). Roush suggested that the diminished diastereoselectivity observed for the latter was due to a mismatched induction imparted by the *syn*-aldehyde (**238**), because the transition state **XLVII** for this aldol reaction was destabilized relative to the transition state **XLVI** from *anti*-aldehyde (**236**) because of the stereoelectronic repulsion of interacting dipole of the aldehyde carbonyl and the C15 OTES group [184, 185].

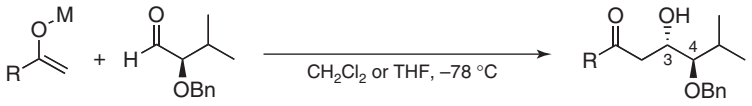
Chiral aldehydes bearing a Cα heteroatom are the exception to this rule, and some of them give access to highly stereocontrolled transformations. A systematic study of aldol additions to chiral α-alkoxy aldehydes carried out by Evans demonstrated that the stereocontrol provided by lithium enolates was superior to that obtained from the corresponding enolsilane nucleophiles. The levels of asymmetric induction are relatively insensitive to both the α-oxygen protecting group and the steric



Scheme 1.77 Syntheses of (+)-tedanolide and(+)-13-deoxytedanolide.

hindrance of the enolate, but they depend to some extent on the nature of the β-alkyl substituent. Thereby, aldol additions of lithium enolates from alkyl methyl ketones to α-OBn aldehyde (**240**) furnished 3,4-*anti* aldols (**241**) in high yields and excellent diastereoselectivities (Scheme 1.78) [38, 186].

Remarkable levels of stereocontrol can also be attained with chiral aldehydes possessing two alkoxy groups at Cα and Cβ positions, wherein the π-facial selectivity depends on their relative configuration and the metal enolate. Thus, *anti*-α,β-bisalkoxy aldehydes (**242**) reacted with methyl ketone-derived lithium enolates to give consistently 3,4-*anti* aldols (**243**) in excellent yields irrespective of both protecting groups ((1) in Scheme 1.79), whereas *syn*-α,β-bisalkoxy aldehydes resulted more sensitive and only the additions of related enolborinates to *syn*-α,β-OTBS aldehyde (**244**) provided the corresponding 3,4-*syn* aldols (**245**) in high yields and diastereoselectivities ((2) in Scheme 1.79) [38]. Satake and Tachibana described that a related transformation involving a chiral bisalkoxy aldehyde played a crucial role in the total synthesis of (−)-brevisin (**246**). Thereby, aldol addition of

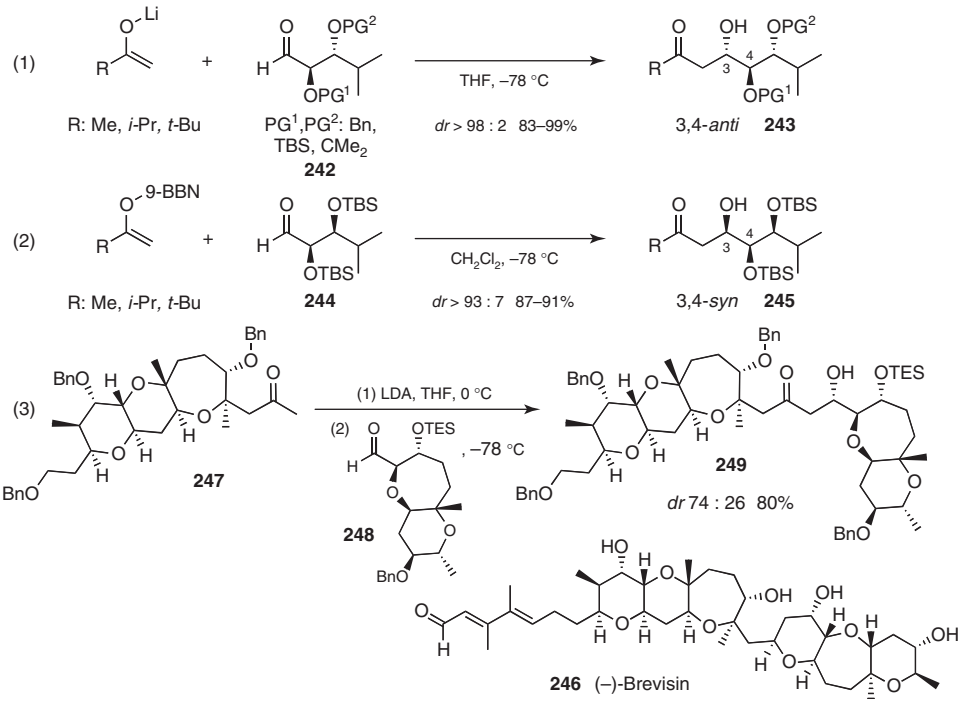


R: Me, *i*-Pr, *t*-Bu **240**

	M: TMS/BF_3·OEt_2		M: Li	
R: Me	*dr* 80 : 20	67%	*dr* 94 : 6	88%
R: *i*-Pr	*dr* 53 : 47	60%	*dr* 91 : 9	84%
R: *t*-Bu	*dr* 64 : 36	65%	*dr* 89 : 11	76%

3,4-*anti* **241**

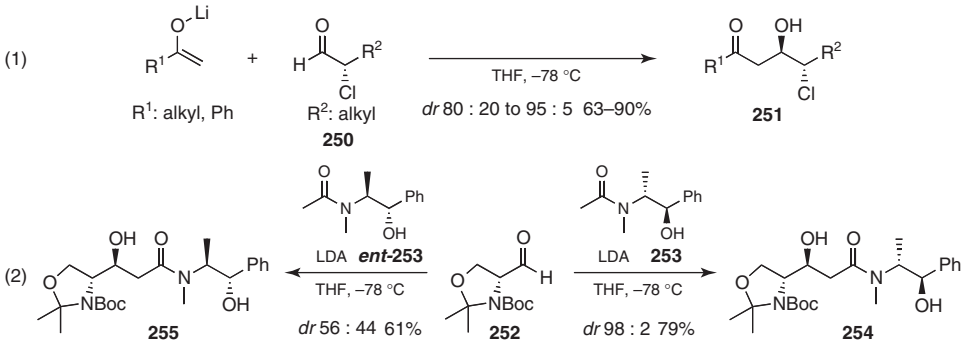
Scheme 1.78 Asymmetric induction imparted by (*R*)-2-benzyloxy-3-methylbutanal.



Scheme 1.79 Asymmetric induction imparted by α, β-bisalkoxy aldehydes in aldol reactions involving metal enolates.

lithium enolate from structurally complex methyl ketone (**247**) to *anti*-α, β-bisalkoxy aldehyde (**248**) led to the construction (*dr* 74 : 26) of polycyclic core **249** in 80% yield ((3) in Scheme 1.79), which suggests that the stereochemical outcome might be due to the above-mentioned trend [187, 188].

Aldol additions of lithium enolates to other chiral α-heterosubstituted aldehydes also show a similar trend favoring the 3,4-*anti* diastereomer. Thus, Britton observed that lithium enolates of methyl ketones reacted with α-chloro aldehydes (**250**) to provide the corresponding *anti* aldols (**251**) in good to high yields and diastereoselectivities up to 95 : 5 ((1) in Scheme 1.80) [189]. In turn, Carrillo and Badia reported

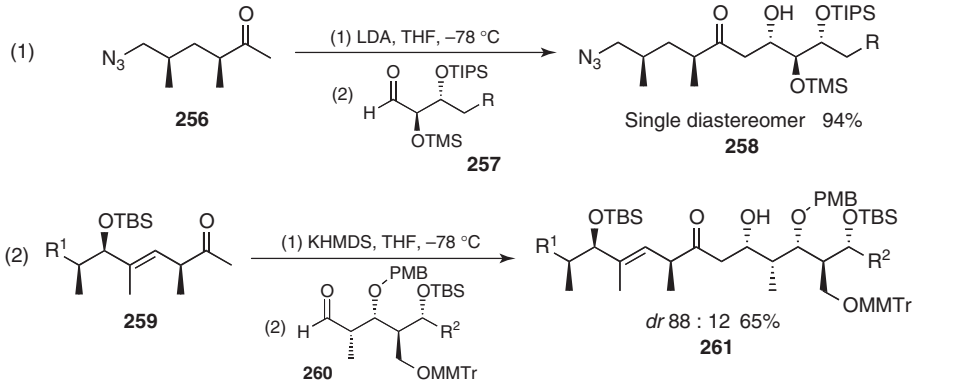


Scheme 1.80 Asymmetric induction imparted by α-heterosubstituted aldehydes in aldol reactions involving metal enolates.

that Garner's aldehyde (**252**) underwent double asymmetric lithium-mediated aldol reactions with pseudoephedrine chiral auxiliaries (**253**), affording *anti* diastereomers **254** and **255** both for the matched and mismatched case ((2) in Scheme 1.80) [190].

1.3.6
Chiral Methyl Ketones

Unlike what happens with aldehydes, metal enolates from chiral methyl ketones are an important source of substrate-controlled aldol reactions, which are especially useful in advanced steps of the synthesis of natural products. Unfortunately, the clear understanding of these reactions is frequently challenged by the broad scope of substrates that can support them and the different sort of elements controlling their stereochemical outcome. Facing this problem and aiming to shed light to such intricate structural diversity, examples reported in the literature



Scheme 1.81 Stereoselective aldol reactions of metal enolates from chiral ketones.

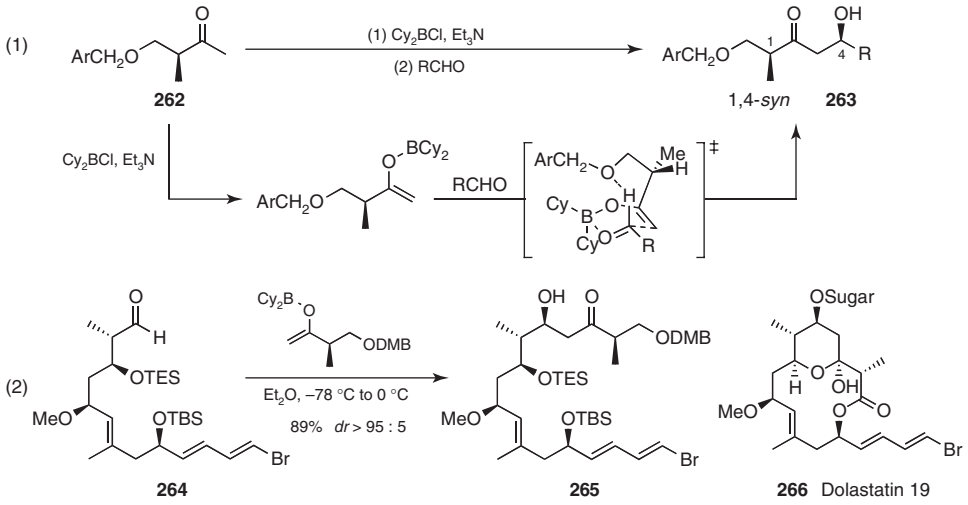
have been organized according to the structure of the ketone, namely, the sort of substituents (alkyl or hydroxy groups) on chiral centers at the α- or β-position to the carbonyl.

1.3.6.1 α-Methyl Ketones

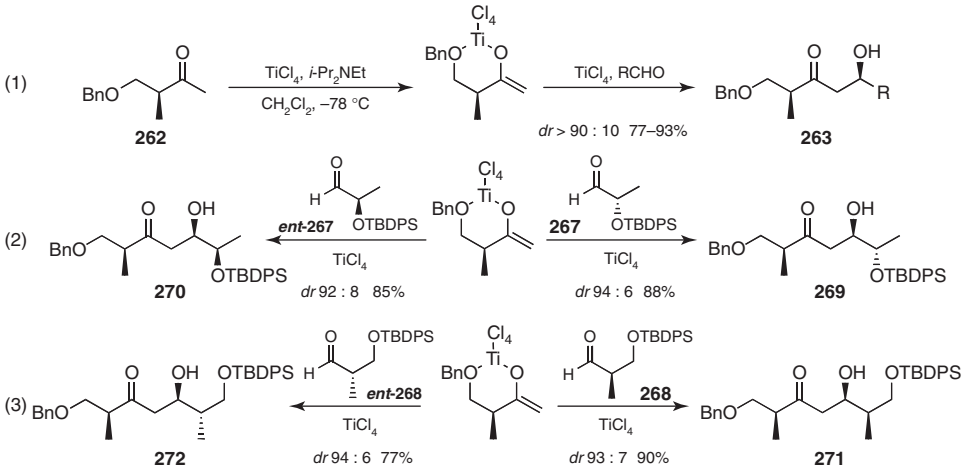
There are no systematic studies on *acetate* aldol reactions based on chiral α-methyl ketones and most of the reported examples involve chiral aldehydes, so it is usually difficult to recognize the contribution of each partner to the control of the new stereocenter.

Lithium and potassium enolates have been reported to furnish 1,4-*anti* adducts in double stereodifferentiating processes. For instance, Carter described that the reaction of lithium enolate of methyl ketone (**256**) and chiral *anti* α,β-bisalkoxy aldehydes (**257**) afforded a single diastereomer of 1,4-*anti* aldols (**258**) in 94% yield ((1) in Scheme 1.81) [191], likely as a result of the asymmetric induction provided by the aldehyde (Scheme 1.79). In turn, Kalesse reported that coupling of methyl ketone (**259**) and aldehyde (**260**) produced diastereoselectively aldol (**261**) when KHMDS was used as the base ((2) in Scheme 1.81) [192].

Otherwise, chiral α-methyl ketones derived from Roche ester have proved to be an excellent platform to provide highly stereoselective aldol reactions. Particularly, Paterson reported that dicyclohexyl borinates from benzyl-protected ketones (**262**) furnished 1,4-*syn* aldols (**263**) with a remarkable stereocontrol ((1) in Scheme 1.82) [1b, 35a, 193]. Theoretical calculations have suggested that these additions proceed through a highly ordered transition state in which a hydrogen bond between the benzyl ether and the incoming aldehyde ($ArCH_2O \cdots H–C{=}O$) determines the diastereoselective formation of **263** [194]. This procedure turned out to be



Scheme 1.82 Stereoselective aldol reactions of boron enolates from chiral Roche ester-derived methyl ketones.



Scheme 1.83 Stereoselective aldol reactions of titanium enolates from (*S*) 4-benzyloxy-3-methyl-2-butanone.

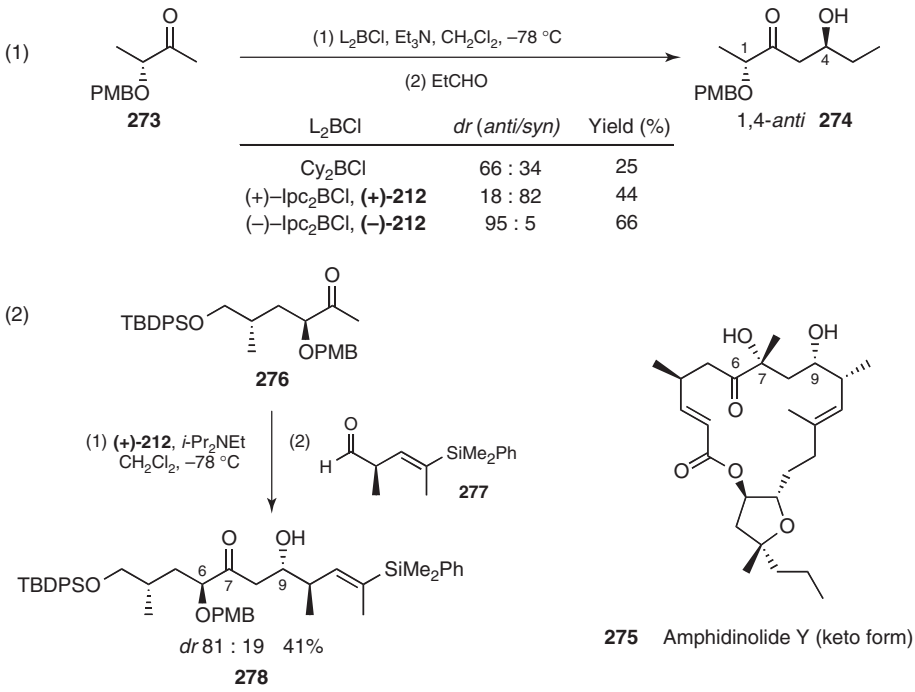
particularly valuable in the addition to chiral aldehydes leading to the 1,4-*syn* Felkin adducts [195], as for the conversion of chiral aldehyde (**264**) into aldol (**265**) in the total synthesis of dolastatin 19 (**266**) ((2) in Scheme 1.82) [195b]. Higher diastereoselectivities were further achieved by using chiral boron Lewis acid as Ipc_2BCl (**212**, see Scheme 1.70) in matched pairs of double asymmetric aldol reactions, which expanded the scope of this methodology to silicon-protected Roche-derived methyl ketones with great success [196].

In turn, Romea and Urpí took advantage of the chelating capability of benzyloxy group of these Roche-derived methyl ketones to disclose highly sterecontrolled titanium-mediated reactions with a wide array of aliphatic, α,β-unsaturated, and aromatic aldehydes, affording *syn* aldols (**263**) in high yields and diastereoselectivity without needing other sources of chirality ((1) in Scheme 1.83) [197]. Furthermore, double asymmetric aldol additions to protected lactaldehydes ((2) in Scheme 1.83) and Roche ester-derived chiral aldehydes ((3) in Scheme 1.83) provided the corresponding 1,4-*syn* aldols (**269**–**272**) in high yields and excellent diastereomeric ratios ($dr \geq 92 : 8$).

1.3.6.2 α-Hydroxy Ketones

The lack of stereocontrol imparted by borinates from mandelic-acid-derived α-OTBS methyl ketone observed in early studies on asymmetric aldol reactions suggested that such systems might be unsuitable for these transformations [3c]. However, Trost proved that the appropriate choice of the Lewis acid and the hydroxy protecting group on lactate-derived methyl ketones allowed highly stereoselective processes ((1) in Scheme 1.10) [20].

Thereby, a remarkable 1,4-*anti* induction could be expected from α-alkoxy methyl ketones provided that the proper boron Lewis acid was used. Evans reported that

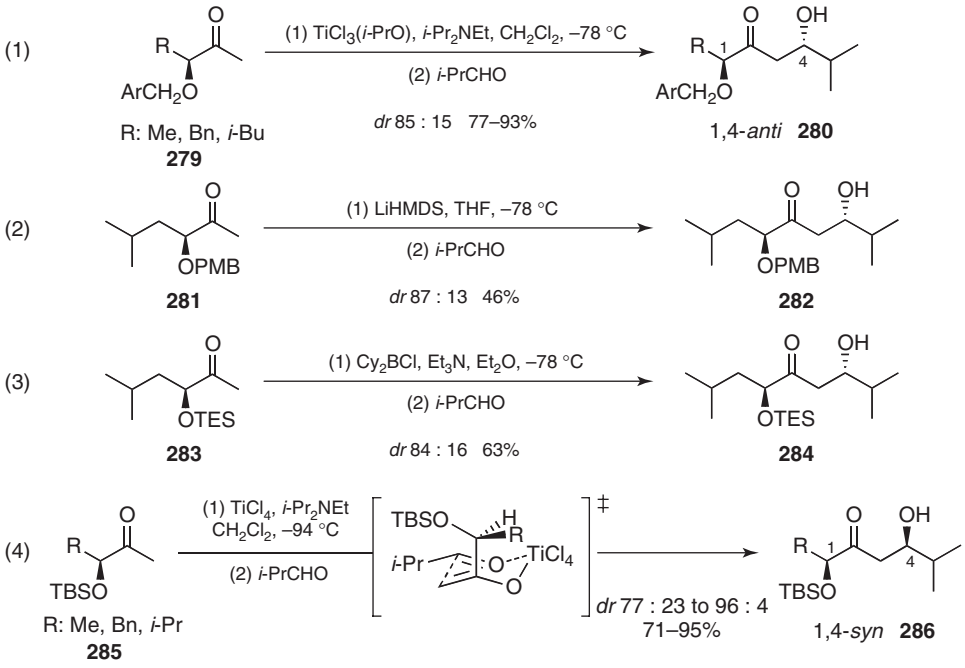


Scheme 1.84 Stereoselective aldol reactions of boron enolates from chiral α-hydroxy methyl ketones.

the addition of the dicyclohexyl borinate from lactate-derived methyl ketone (**273**) to propanal furnished 1,4-*anti* aldol (**274**) in a low diastereomeric ratio, whereas it was considerably improved by using (−)-**212** ((1) in Scheme 1.84) [45]. Fürstner also employed this method in one of the key steps of the synthesis of amphidinolide Y (**275**) (Scheme 1.84) [198]. Thus, boron-mediated aldol addition of α-OPMB methyl ketone (**276**) to chiral aldehyde (**277**) furnished *anti* aldol (**278**) in moderate yield and good diastereoselectivity ((2) in Scheme 1.84).

Parallel trends have been observed in other transformations from α-OBn methyl ketones. For instance, $TiCl_3$(*i*-PrO)-mediated aldol additions of methyl ketones (**279**) to isobutyraldehyde afforded the corresponding 1,4-*anti* adducts (**280**) in yields up to 93% and 85 : 15 diastereomeric ratio ((1) in Scheme 1.85) [199].[8] In turn, lithium counterpart from ketone (**281**) gave aldol (**282**) in similar diastereoselectivity ((2) in Scheme 1.85) [21, 200]. Foreseeing the influence of the protecting group of these ketones on the stereochemical outcome of this sort of reactions, the reactivity of α-silyloxy ketones was also assessed. As for benzyl-protected ketones, addition of the dicyclohexyl borinate of α-OTES methyl ketone (**283**) to isobutyraldehyde gave 1,4-*anti* aldol (**284**) in good yield and high diastereomeric ratio ((3) in Scheme 1.85) [21]. However, the diastereoselectivity was dramatically eroded for

8) Similar results are obtained with other aliphatic, α, β-unsaturated, and aromatic aldehydes.



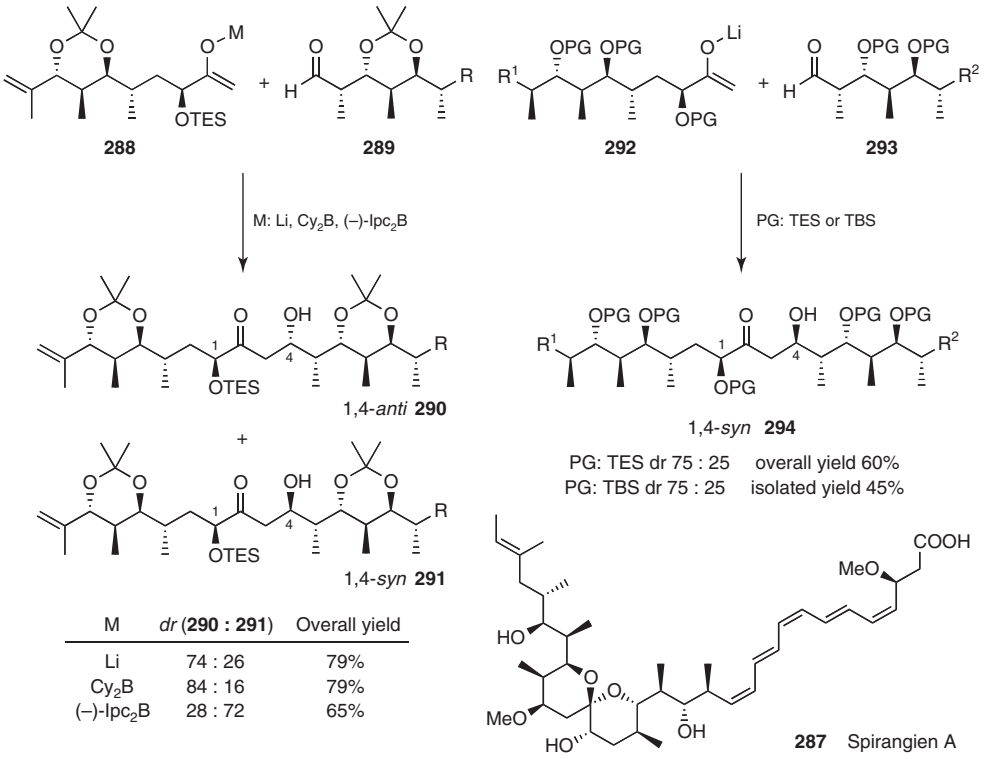
Scheme 1.85 Stereoselective aldol reactions of metal enolates from chiral α-hydroxy methyl ketones.

alkaline enolates [21], whereas the enolization of α-OTBS ketones (**285**) with $TiCl_4$/*i*-Pr_2NEt and subsequent addition to isobutyraldehyde provided 1,4-*syn* aldols (**286**) ((4) in Scheme 1.85) [201]. The rationale for this result was based on a six-membered chairlike transition state in which the antiperiplanar distribution of both TBSO–C and C–OTi bonds acted as the key element to determine the *syn* configuration.[9)]

The synthesis of the spiroketal core of spirangien A (**287**) (Scheme 1.86) is a good example of the intricacy of these aldol reactions. Paterson reported that the stereochemical outcome of the aldol addition of boron and lithium enolates from α-OTES methyl ketone (**288**) to chiral aldehyde (**289**) was very sensitive to the enolization procedure. Preliminary studies using LDA or Cy_2BCl/Et_3N furnished 1,4-*anti* aldol (**290**), but this inherent diastereoselectivity in the undesired direction was eventually overturned by using (−)-Ipc_2BCl to afford 1,4-*syn* aldol (**291**) (Scheme 1.86) [202]. Therefore, boron Lewis acid determined the stereochemical outcome of this transformation and prevailed over the induction imparted by ketone enolates (**288**) and aldehyde (**289**). Surprisingly, Kalesse [203] and Cossy [204][10)]

9) In support for this theoretical model, it has been observed that the more sterically bulky the R group (Me to *i*-Pr) the better the diastereoselectivity is for aliphatic as well as α,β-unsaturated and aromatic aldehydes.

10) Importantly, no reaction was observed when the starting TBS-protected ketone was treated with (−)-Ipc_2BCl/Et_3N.



M	*dr* (**290 : 291**)	Overall yield
Li	74 : 26	79%
Cy_2B	84 : 16	79%
(–)-Ipc_2B	28 : 72	65%

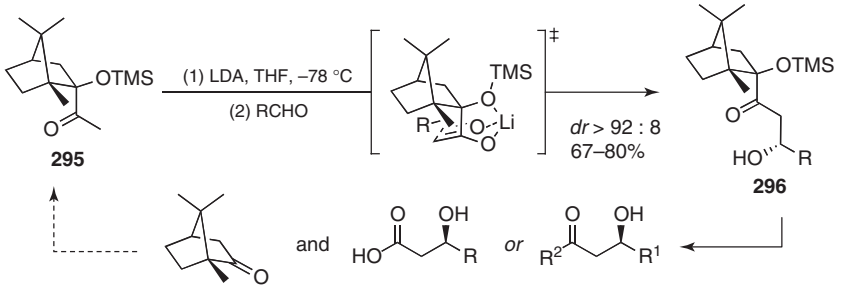
Scheme 1.86 Synthesis of spirangien A.

established that lithium-mediated aldol reactions from fully silylated enolates (**292**) (PG: TES or TBS) and aldehydes (**293**) (PG: TES or TBS) afforded the desired 1,4-*syn* aldols (**294**) in 75 : 25 diastereomeric ratio (Scheme 1.86), which proved that subtle changes on the metal and the structure of the reactant partners can dramatically affect the stereochemical outcome of these aldol reactions.

Finally, it is worth mentioning that the lithium enolate of the camphor-based α-OTMS methyl ketone (**295**) afforded the corresponding aldol adducts (**296**) with a remarkable high diastereoselectivity [205]. As shown in Scheme 1.87, the aldol addition proceeded through a chelated six-membered chairlike transition state in which the bulky camphor backbone determined the approach of the aldehyde. From a conceptual point of view, the camphor acted as a chiral auxiliary in such a way that the removal of the silicon-protecting group of **293** and the appropriate manipulation of the resultant hydroxy ketones yielded enantiopure β-hydroxy acids or ketones and camphor (Scheme 1.87).

1.3.6.3 β-Hydroxy Ketones

Aldol reactions of β-hydroxy methyl ketones are very sensitive to the metal of the enolate and the hydroxy protecting group. Indeed, enolization of β-alkoxy ketones

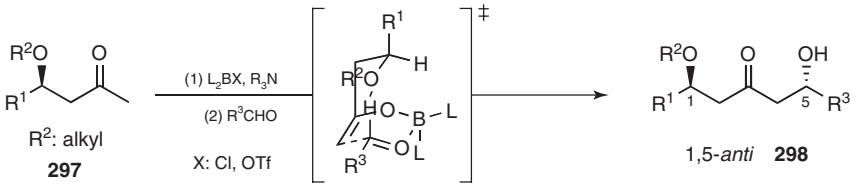


Scheme 1.87 Stereoselective aldol reactions of lithium enolates from a camphor-based α-OTMS methyl ketone.

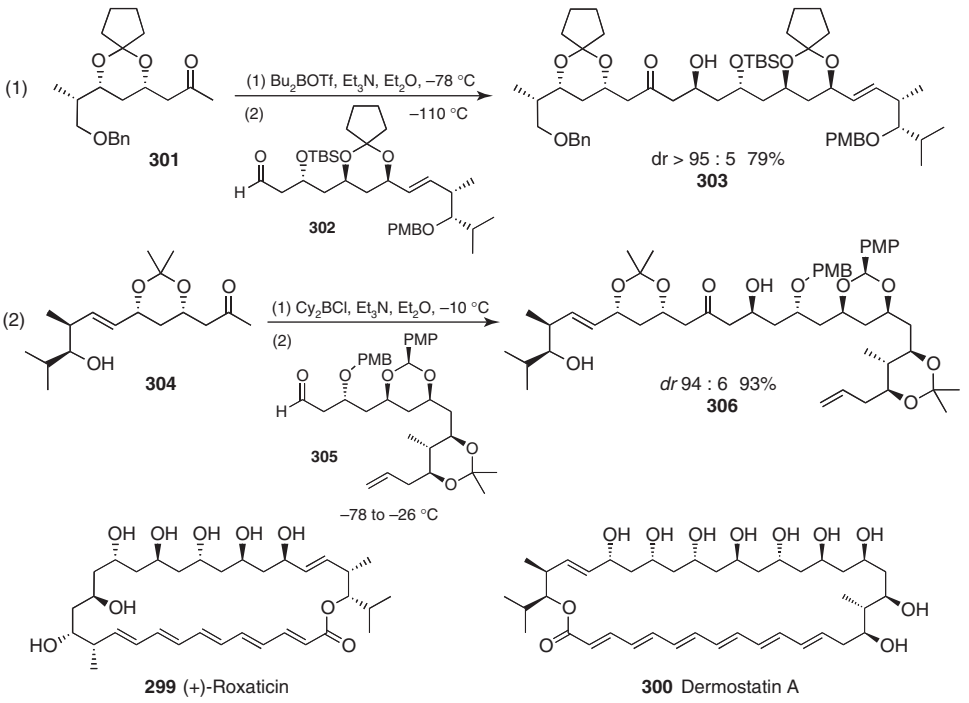
(**297**) with boron Lewis acids and tertiary amines yielded the less substituted enolborinate that participated in highly stereocontrolled reactions, affording 1,5-*anti* aldols (**298**) with excellent diastereoselectivity (Scheme 1.88). Instead, other metals and protecting groups provided poorer results [206, 207]. As previously pointed for related transformations (Scheme 1.82), a theoretical model that accounts for such a high stereocontrol is based on a boat-shaped transition structure in which a stabilizing formyl hydrogen bond exists between the alkoxy oxygen and the aldehyde proton [194].

Evans and Sammakia applied this powerful transformation in crucial steps of the total syntheses of oxopolyene macrolides roxaticin and dermostatin A (**299** and **300**, respectively, in Scheme 1.89). Thereby, Evans described that treatment of β-alkoxy methyl ketone (**301**) with Bu_2BOTf/Et_3N produced a boron enolate that reacted with β-OTBS aldehyde (**302**), affording *anti* aldol (**303**) as a single diastereomer (*dr* > 95 : 5) in 79% yield ((1) in Scheme 1.89) [114c]. In turn, Sammakia reported that coupling of dicyclohexylborinate from β-alkoxy methyl ketone (**304**) and β-benzyloxy aldehyde (**305**) provided *anti* aldol product (**306**) in excellent yield and diastereoselectivity ((2) in Scheme 1.89) [159d, 208].

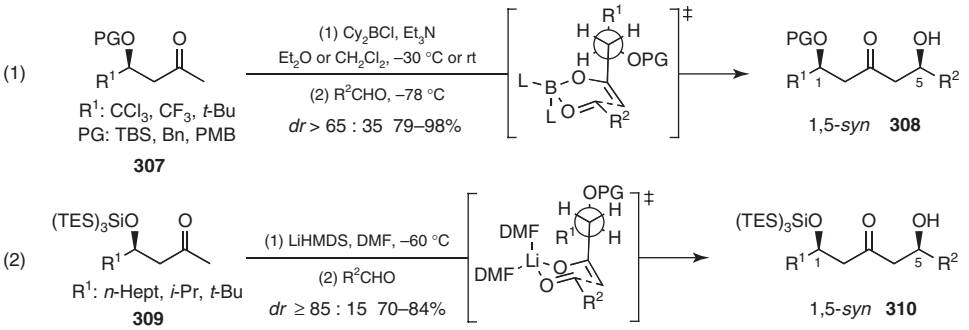
The dominant 1,5-*anti* trend observed for these transformations has been occasionally overridden by the influence of remote stereocenters, functional groups, or chiral boron Lewis acids [209]. In this context, Dias established that good levels of substrate-controlled 1,5-*syn* stereoinduction were obtained in boron-mediated aldol reactions of β-trihalomethyl- as well as β-*tert*-butyl-β-hydroxy methyl ketones (**307**) possessing different hydroxy protecting groups ((1) in Scheme 1.90) [210, 211].



Scheme 1.88 Stereoselective aldol reactions of boron enolates from chiral β-hydroxy methyl ketones.



Scheme 1.89 Examples of 1,5-*anti* asymmetric induction imparted by boron enolates from chiral β-hydroxy methyl ketones in the synthesis of natural products.



Scheme 1.90 1,5-*syn* Asymmetric induction of metal enolates from chiral β-hydroxy methyl ketones.

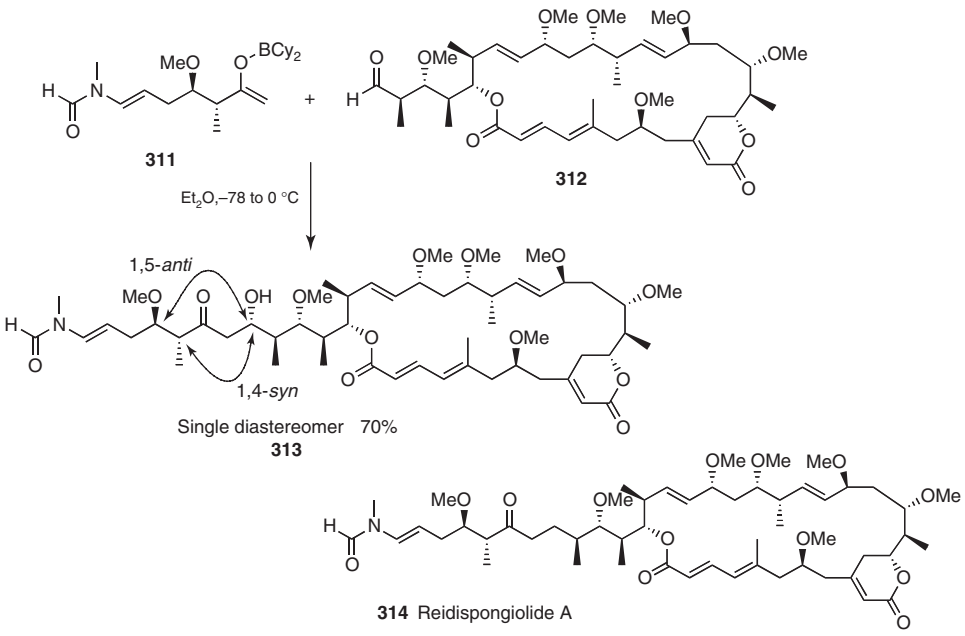
Theoretical calculations on the competing pathways involved in these reactions suggested that a boatlike transition state lacking the formyl hydrogen bond is the most stable one and led to 1,5-*syn* aldol adducts (**308**) (Scheme 1.90). Moreover, Yamamoto reported that lithium enolates of β-*super* silyloxy methyl ketones (**309**) added to aliphatic, α, β-unsaturated, and aromatic aldehydes in DMF to provide 1,5-*syn* aldols (**310**) in outstanding diastereoselectivities ((2) in Scheme 1.90) [22].

In this case, a chairlike transition state that minimizes the unfavorable steric interactions was invoked to rationalize the observed *syn* induction.

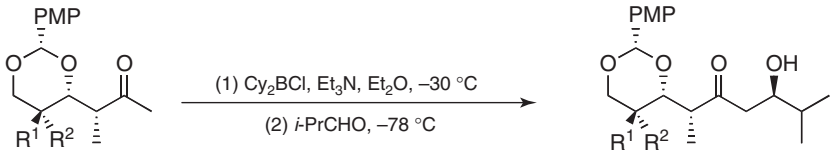
1.3.6.4 β-Hydroxy α-Methyl Ketones

Most of the examples reported in the literature on substrate-controlled acetate aldol additions of β-hydroxy-α-methyl ketones involve boron enolates. Thus, the stereochemical outcome of these reactions depends on the 1,5-*anti* and 1,4-*syn* inductions imparted by the β-hydroxy and the α-methyl groups, respectively (Schemes 1.82 and 1.88). In this scenario, an *anti*-β-hydroxy-α-methyl array corresponds to a matched case and the resultant aldol reactions usually proceed in excellent diastereoselectivities. An exceptional example of this sort of reactions involved the aldol addition of the dicyclohexyl borinate of methyl ketone (**311**) to chiral aldehyde (**312**) that furnished aldol (**313**), an advanced intermediate in the total synthesis of reidispongiolide A (**314**), as a single diastereomer in 70% yield (Scheme 1.91) [61d, 212].

Otherwise, the diastereoselectivity of *syn* β-hydroxy-α-methyl mismatched pairs is very sensitive to the structure of the methyl ketone, although the configuration of the new stereocenter is used to be ruled by the β-hydroxy group. For instance, a systematic study carried out by Dias on the boron-mediated aldol reactions of methyl ketones (**315**) established that the prevailing 1,5-*anti* induction imparted by the β-alkoxy led to the adducts **316** (Scheme 1.92) [213]. These studies also



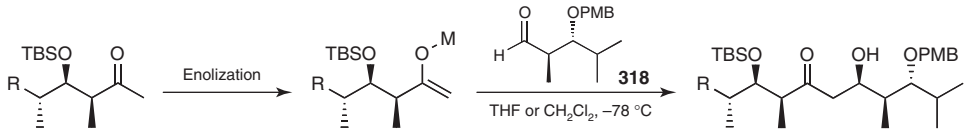
Scheme 1.91 Synthesis of reidispongiolide A.



315 316

Ketone	R^1	R^2	Aldol	dr	Yield (%)
315a	H	H	**316a**	86 : 14	83
315b	H	Me	**316b**	86 : 14	97
315c	Me	H	**316c**	> 95 : 5	77

Scheme 1.92 Stereoselective *acetate* aldol reactions of boron enolates from β-hydroxy α-methyl ketones.



317 319

Ketone	R	Enolization conditions	Aldol	*dr*	Yield (%)
317a	$BzOCH_2$	LiHMDS, THF, –78 °C	**319a**	91 : 9	90
		NaHMDS, THF, –78 °C		50 : 50	51
		Bu_2BOTf, Et_3N, CH_2Cl_2, –40 °C		55 : 45	65
317b	$TBDPSOCH_2$	LiHMDS, THF, –78 °C	**319b**	75 : 25	59
317c	$H_2C{=}CH$	LiHMDS, THF, –78 °C	**319c**	67 : 33	85

Scheme 1.93 Stereoselective *acetate* aldol reactions of metal enolates from β-hydroxy α-methyl ketones.

proved that even the configuration of the γ-stereocenter plays a significant role on the stereochemical outcome of these reactions, as occurs for ketone (**315c**) [214]. However, it is worth keeping in mind that these transformations are not completely well understood and unexpected effects can play a crucial role.

Other metal enolates have also been used in these reactions, but it is difficult to predict their stereochemical induction. For instance, Roush found that the diastereoselectivity of the reaction of *syn* β-OTBS-α-methyl ketone (**317a**) and the chiral aldehyde (**318**) producing aldol (**319a**) was strongly dependent on the metal enolate (Scheme 1.93). Furthermore, the moderate and low diastereoselectivity observed for related ketones (**317b**) and (**317c**) suggests that the presence of a chelating group at δ-position was crucial to attain a high stereocontrol and proves that these aldol reactions are governed by subtle structural details [215].

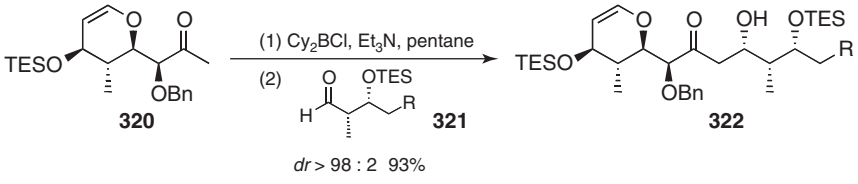
1.3.6.5 α,β-Dihydroxy Ketones

The diastereoselectivity of substrate-controlled aldol reactions from α,β-dihydroxy methyl ketones depends on the metal enolate, the configuration of α- and β-stereocenters, and the hydroxy protecting groups. In this context, the remarkable

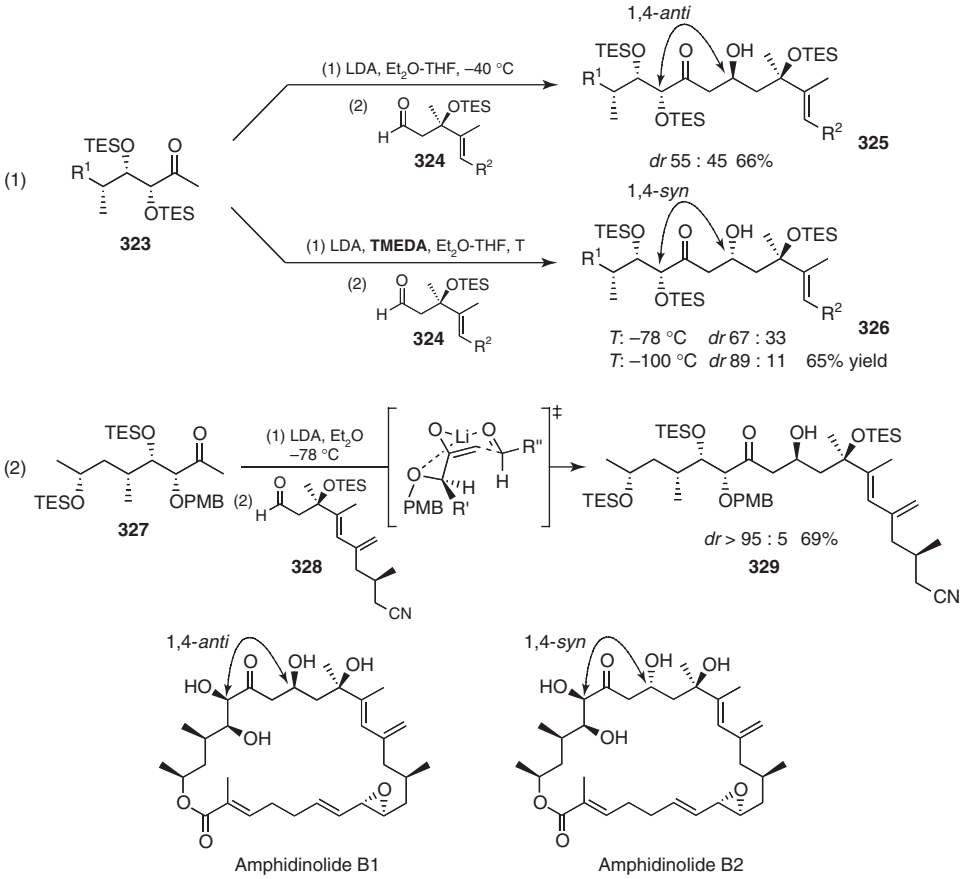
1,5-*anti* induction of boron-mediated aldol reactions of β-alkoxy methyl ketones (Scheme 1.88) also operates in these systems and may be assisted by the parallel 1,4-*anti* bias observed in related α-hydroxy methyl ketones (Scheme 1.84). Therefore, it is not surprising that the addition of the dicyclohexyl borinate of the α, β-dialkoxy methyl ketone (**320**) to aldehyde (**321**) led to the isolation of a single diastereomeric aldol adduct **322** in 93% yield (Scheme 1.94) [216].

In spite of these accomplishments, most of the substrate-controlled aldol reactions from α, β-dihydroxy methyl ketones reported in the literature take advantage of the high nucleophilicity of alkaline enolates. Particularly, lithium-mediated aldol reactions from chiral *syn*-α, β-dihydroxy methyl ketones have been thoroughly assessed along the syntheses of amphidinolides. These studies have proved that the protecting groups play a crucial role in the stereochemical outcome of such additions. Unfortunately, they are very sensitive to the structure of the reactive partners and the whole reaction conditions, which makes difficult to foresee the stereochemical outcome of a particular transformation. For instance, it was well documented that silicon-protecting groups provided poor stereocontrolled reactions [217], so it was usual that the lithium-mediated addition of α, β-disilyloxy methyl ketone (**323**) to chiral aldehyde (**324**) gave *anti*-aldol (**325**) in a very poor diastereomeric ratio ((1) in Scheme 1.95). Nevertheless, Carter found that TMEDA increased the reactivity of the lithium enolate of methyl ketone (**323**), produced a stereochemical reversal on the aldol addition to aldehyde (**324**), and the bias favoring 1,4-*syn* (**326**) was even improved by cooling to −100 °C ((1) in Scheme 1.95) [218]. Furthermore, the protection of the Cα hydroxyl with a chelating group modifies the stereoselectivity of these reactions dramatically. Indeed, α-OPMB ketone (**327**), structurally close to **323**, reacted with aldehyde (**328**) to afford aldol (**329**) in 69% yield as a single diastereomer through a chelated transition state ((2) in Scheme 1.95) [219], which obviously makes the most of the chelating ability of the benzyl-like protecting group placed at the α-position.

As anticipated by these results, α-alkoxy-β-silyloxy methyl ketones have been involved in much more stereoselective transformations. In a thorough analysis on the reactivity of alkaline enolates from *syn* α, β-dihydroxy methyl ketones, Fürstner described that the addition of the lithium enolate from α-OPMB-β-OTBS methyl ketone (**330**) to aldehyde (**331**) afforded aldol (**332**) as a single diastereomer in 52% yield ((1) in Scheme 1.96) [217d, 220]. The excellent diastereoselectivity was ascribed to the 1,4-*anti* directing effect imparted by the α-alkoxy group (Scheme 1.84). This hypothesis was corroborated by the fact that the related disilyloxy ketone furnished



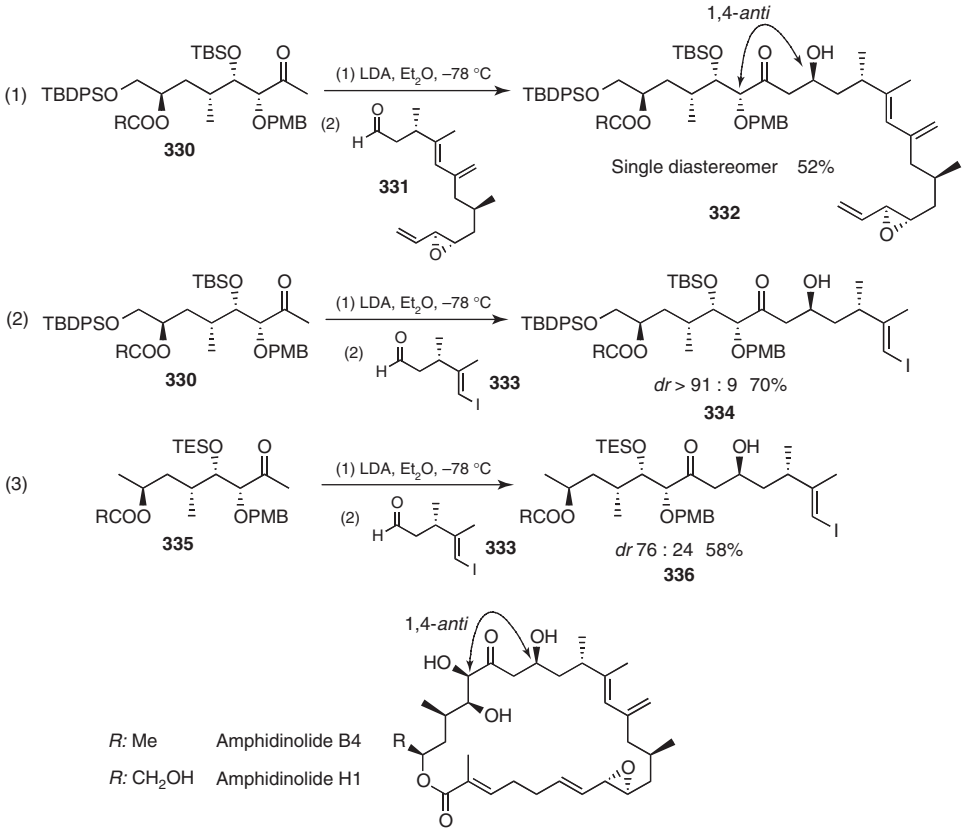
Scheme 1.94 Stereoselective aldol reactions of boron enolates from α,β-dihydroxy methyl ketones.



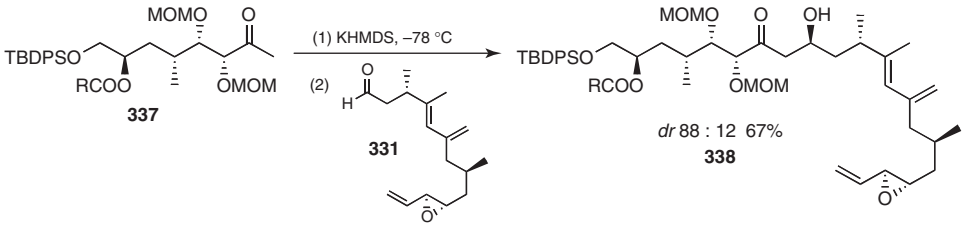
Scheme 1.95 Syntheses of amphidinolide B1 and B2.

a poor 67 : 33 mixture of the two possible diastereomers. However, minor changes on the aldehyde and the ketone were responsible for significant differences on the diastereoselectivity. For instance, a less elaborate aldehyde as **333** delivered the *anti* aldol (**334**) in 70% yield and a slightly lower diastereomeric ratio (compare (1) and (2) in Scheme 1.96). Moreover, the diastereoselectivity was seriously eroded when the reaction was carried out on ketone (**335**) lacking remote OTBDPS group, which afforded aldol (**336**) in a modest diastereomeric ratio (compare (2) and (3) in Scheme 1.96) [217d]. The reason why this particular reaction shows a significantly lower selectivity is unclear, and it is also instructive to realize the dramatic influence of the ketone partner.

Other protecting groups have also been used in these transformations [221]. For instance, Zhao reported that the diastereoselective addition of the potassium enolate from α,β-diMOM protected methyl ketone (**337**) to aldehyde (**331**) in an advanced step of the total synthesis of amphidinolide H1 (Scheme 1.97) produced diastereoselectively 1,4-*anti*-aldol (**338**) in 67% yield (Scheme 1.97) [221b].



Scheme 1.96 Syntheses of amphidinolide B4 and H1.

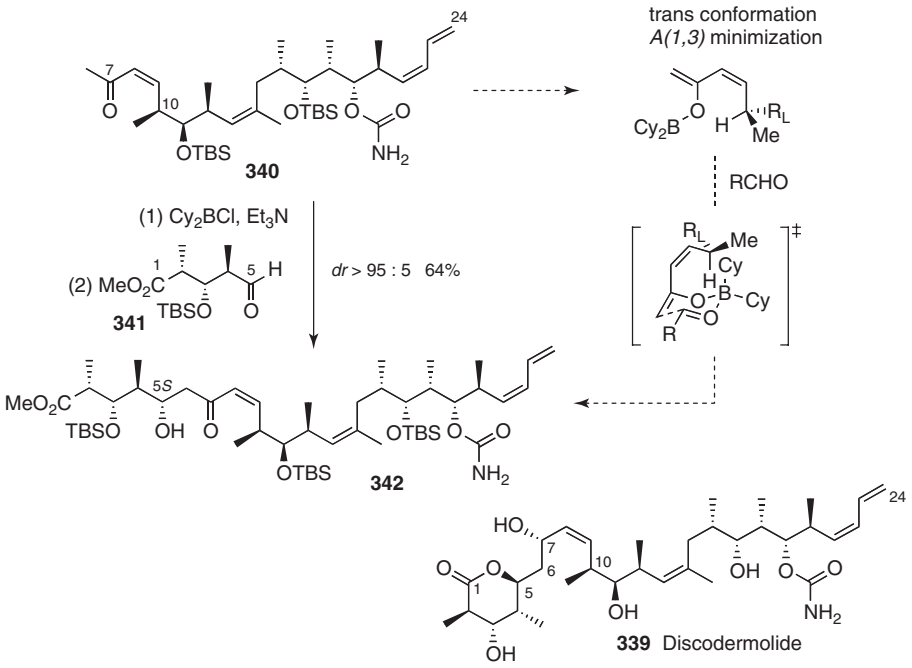


Scheme 1.97 Synthesis of amphidinolide H1.

1.3.6.6 **Remote Stereocontrol**

Rarely, other unusual arrangements can come into action and provide insightful synthetic approaches. This is the case of 1,6-asymmetric induction disclosed by Paterson for the synthesis of (+)-discodermolide (**339**) (Scheme 1.98) [222].

The second-generation approach on the total synthesis of (+)-discodermolide was based on the assembly of methyl *Z*-enone (**340**) (C6–C24 fragment) and aldehyde



Scheme 1.98 Synthesis of discodermolide.

(**341**) (C1–C5 fragment) [223]. As shown in Scheme 1.98, a boron-mediated aldol reaction of both fragments afforded the required 5*S* product **342** in 64% yield and an outstanding diastereomeric ratio (*dr* > 95 : 5). The rationale for this unparalleled remote stereocontrol invoked a chairlike transition state in which the dienolate was constrained in the lower energy *trans* conformation, allylic strain A(1,3) was minimized, and other steric clashes were avoided. Thus, all these elements were combined in such a way that the remote C10 γ-stereocenter of **340** provided an unprecedented 1,6-asymmetric induction. Irrespective of the mechanistic pathway followed by this transformation, it is a proof of the power of substrate-controlled aldol reactions provided that the appropriate structural elements are identified and placed at the right position.

1.4 Conclusions

In spite of early reports, enolsilanes and metal enolates have emerged as highly valuable intermediates for stereoselective *acetate* aldol reactions. Recent advances in this area have delivered highly stereoselective methodologies based on Mukaiyama and metal enolate-mediated aldol reactions from chiral auxiliaries, stoichiometric and catalytic Lewis acids and bases, or acting in substrate-controlled reactions,

which facilitate the synthesis of structurally complex natural products. Unfortunately, the structural and reactive elements that determine the configuration of the resultant aldol adducts are sometimes unclear and a proper understanding of the transition states involved in many of these transformations is still lacking. Thus, more insightful, simple, and reliable methodologies, as well as a better knowledge of their mechanisms, would be truly welcome.

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