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Stereoselective Acetate Aldol Reactions from Metal Enolates

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Dedicated to the memory of recently deceased Professor Rafael Suau.

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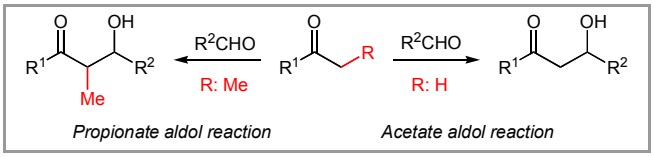
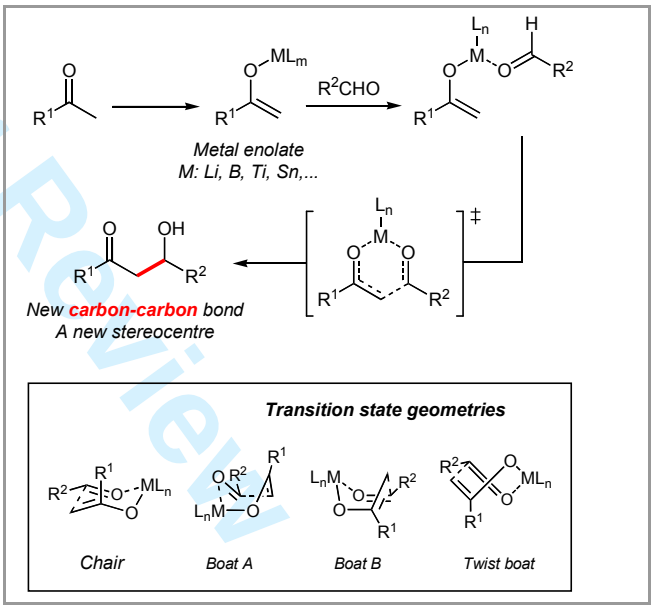
1 Introduction

The development of highly stereoselective aldol methodologies and their successful application to the synthesis of structurally complex natural products during the past decades have placed aldol reaction among the most important carbon–carbon bond forming processes.[1,2] In spite of these accomplishments, aldol reactions from unsubstituted chiral enolates are still matter of concern.[3] Indeed, pioneering studies early recognized that the stereochemical control on the *acetate* aldol reaction (R = H in Scheme 1)[4] was much more demanding than on the similar *propionate* counterpart (R = Me in Scheme 1).[5]



Scheme 1

This challenge has been usually met by Mukaiyama-like[6] and, more recently, by organocatalytic approaches.[7] Nowadays, there are successful examples of both methodologies, but the synthesis of natural products often contests their capability to install efficiently the required stereocentres. Hence, it has been always felt as highly desirable to achieve parallel transformations from metal enolates.[8] Unfortunately, *acetate* aldol reactions mediated by such intermediates can proceed through different six-membered cyclic transition states represented in Scheme 2, which hampers the proper differentiation of the two faces of the π C=O bond by the unsubstituted enolate.[3,9,10] Therefore, stereocontrol on these reactions relies on the appropriate choice of the metal and the chiral elements on the substrate, the aldehyde or the ligands (R^1, R^2, and L respectively in Scheme 2) to provide a single highly organized transition state.



Scheme 2

The scope of this overview is limited to the most significant methodologies on stereoselective *acetate* aldol additions of chiral metal enolates, that is, it describes the reactions in which the chiral elements are located on the substrate or the ligands bound to the metal of these intermediates. It does not intend to be an exhaustive coverage of the literature and crucial issues of these transformations, as the influence of the chirality of the aldehyde, are not specifically addressed.

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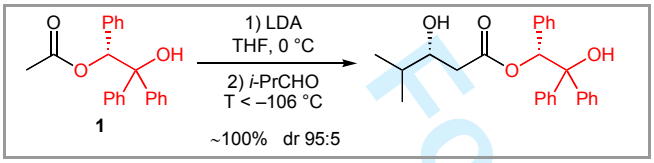
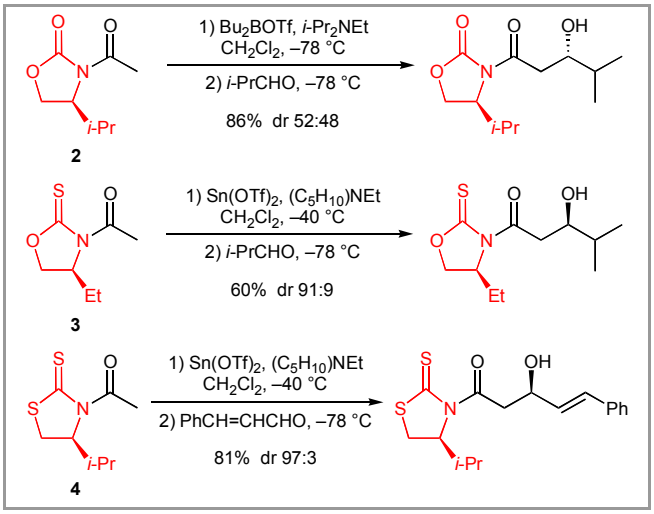
2 Chiral auxiliaries

The poor stereocontrol observed in preliminary studies on aldol reactions from unsubstituted enolates triggered an intense search for an efficient covalently bound chiral auxiliary.[3] Among the large number of reported auxiliaries, chiral 1,1,2-triphenylethanediol arising from mandelic esters, quickly achieved a prominent position.[11] Indeed, the lithium enolate from acetate **1** (Scheme 3) provides high yields and diastereoselectivities and has been successfully used in the synthesis of β–hydroxy carbonyl structures present in natural products.[11b,12]



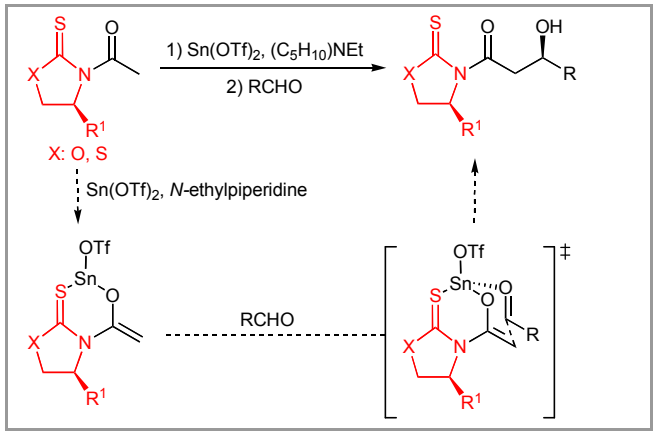
Scheme 3

However, the extremely low temperatures essential to attain high diastereoselectivities thwarted further applications and the quest for a more general approach remained active.[13] Thus, considering that boron enolates from *N*-acetyl oxazolidinone **2** (Scheme 4) afforded nearly 1:1 ratio of diastereomers,[5a,14,15] Nagao and Fujita findings on unprecedented stereocontrolled tin(II)–mediated aldol reactions from *N*-acetyl oxazolidinethione **3**[16] and thiazolidinethione **4**[17,18] were particularly outstanding (Scheme 4).



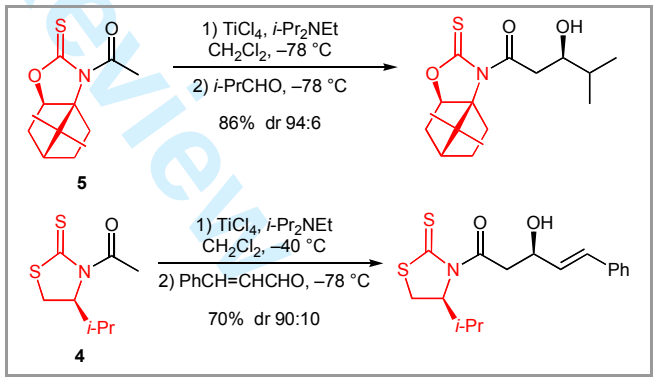
Scheme 4

The rationale for these highly stereoselective transformations placed four ligands on the tin(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 5). Eventually, a chair-like cyclic six membered transition state accounted for the configuration of the new stereocentre in the major diastereomer.



Scheme 5

Although this methodology has been largely used in the synthesis of natural products, $Sn(OTf)_2$ is not easy to handle.[19,20] Keeping in mind this drawback, it is not surprising that the attention was focused on the development of similar procedures using other Lewis acids. In this context, Yan took advantage of titanium(IV)-mediated aldol reactions from camphor-derived thioimide **5**,[21,22] whereas Urpí and Vilarrasa used *N*-acetyl thiazolidinethione **4** in parallel aldol additions to α,β-unsaturated aldehydes (Scheme 6).[23] Last approach was particularly inspiring since both enantiomers of the chiral auxiliary can be prepared from natural and unnatural α-amino acids[24] and $TiCl_4$ is an easily available Lewis acid.[25]



Scheme 6

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 **2** (see Scheme 4) gave good yields but poor diastereoselectivities,[26] whereas the stereochemical outcome from a close 5,5-disubstituted oxazolidinone turned out to be dramatically dependent on the metal of the enolate.[27] Thus, the most striking advances have come up from sulfur containing chiral auxiliaries. For instance,

boron and titanium enolates from *N*-acetyl oxazolidinethiones **6–7**[28,29] and thiazolidinethiones **8–10**[29–32] shown in Figure 1 provide high levels of stereocontrol and the chiral auxiliary can be easily removed using very mild conditions.[33]

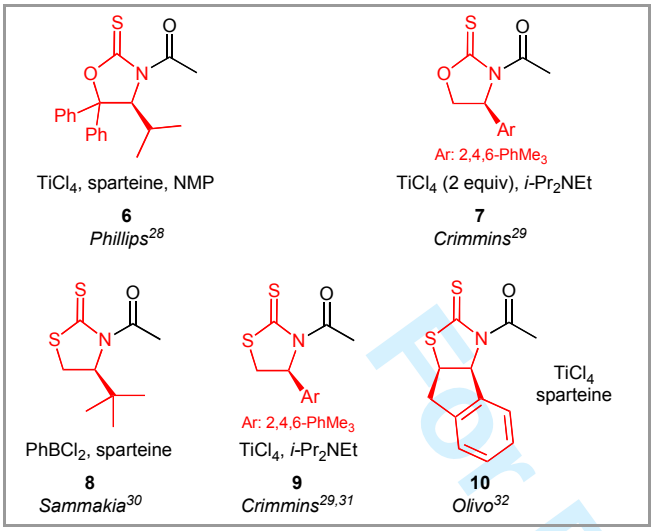
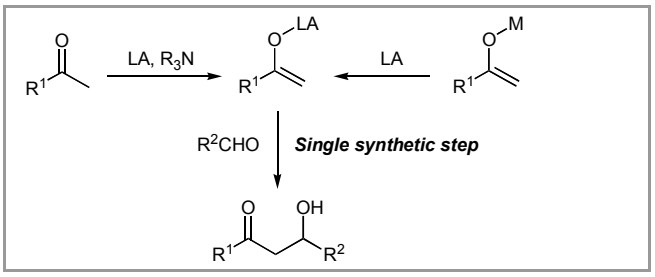


Figure 1

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 (LA in Scheme 7). 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 be also 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.



Scheme 7

The Lewis acids **11–16** represented in Figure 2 fulfill such requirements.[34–38] 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.[39] Isopinocampheylborane **14** (Ipc_2BCl) is the exception, since it participates in many double asymmetric aldol reactions from chiral ketones (see Section 5).

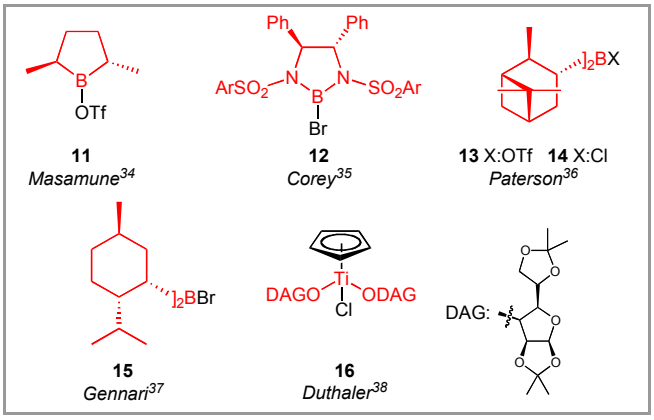
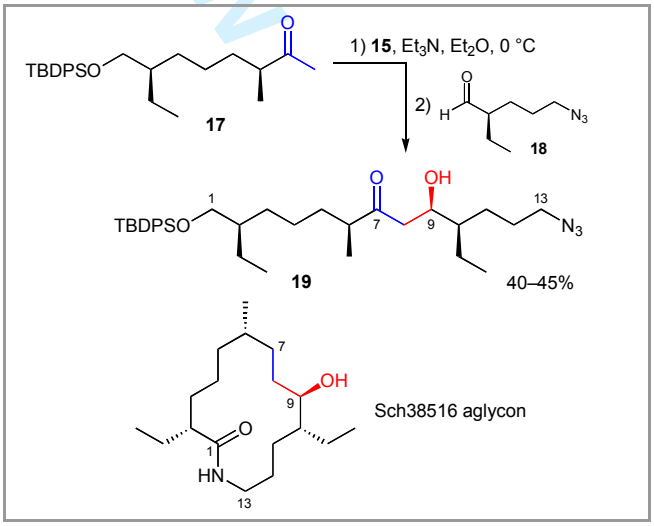


Figure 2

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 can not 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 (Scheme 8). While lithium, sodium or titanium enolates of chiral ketone **17** and aldehyde **18** delivered almost equimolar mixtures of both diastereomers, boryl bromide **15** provided a highly stereoselective aldol coupling (dr 20.6:1) and furnished pure aldol **19** in 40–45% yield after a simple chromatographic purification (Scheme 8).[39d]



Scheme 8

4 Catalytic Lewis Acids and Bases

As in other areas of synthetic chemistry, much efforts are being devoted to the search of new catalytic methodologies.[1,40] Early applications of metal catalysts in stereoselective aldol reactions involved Lewis acid-mediated addition of silyl enol ethers to aldehydes, the so-called Mukaiyama aldol reaction.[1,6] These processes take advantage of the increase of the electrophilic character of aldehydes by binding to chiral Lewis acids, which triggers the addition of a nucleophilic preformed silyl enolate through an open transition state. In turn, organocatalytic methodologies have blossomed during last years, since they allow *direct* aldol reactions in which nucleophilic and electrophilic roles are assigned by the catalytic species.[7]

Inspired by Nature, the attention was also focused on aldolases. Particularly, class II aldolases use zinc cations to activate the enolate partner (a *metal enolate*) as well as other centres on the enzyme assist to the activation of the incoming aldehyde. Considering such a mechanism, Shibasaki[41] and Trost[42] described the first direct aldol reactions from unmodified methyl ketones in the presence of multifunctional catalysts **20** and **21** (Figure 3).

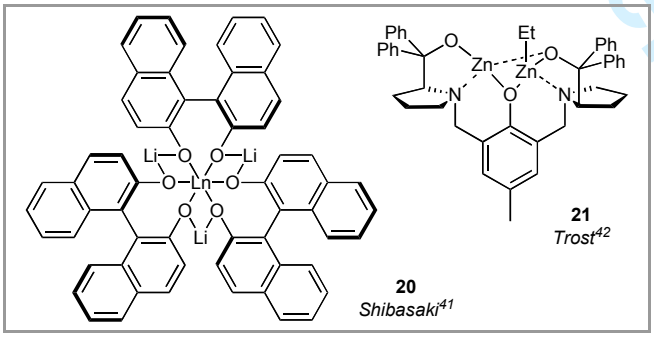
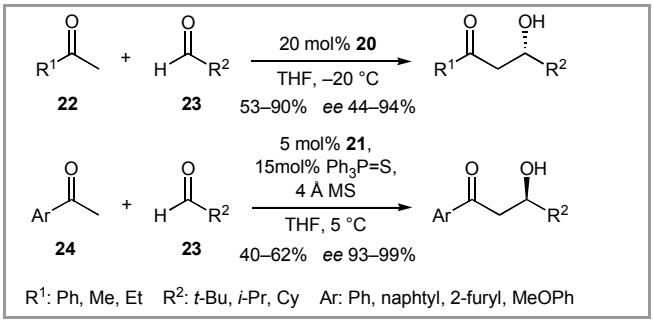


Figure 3

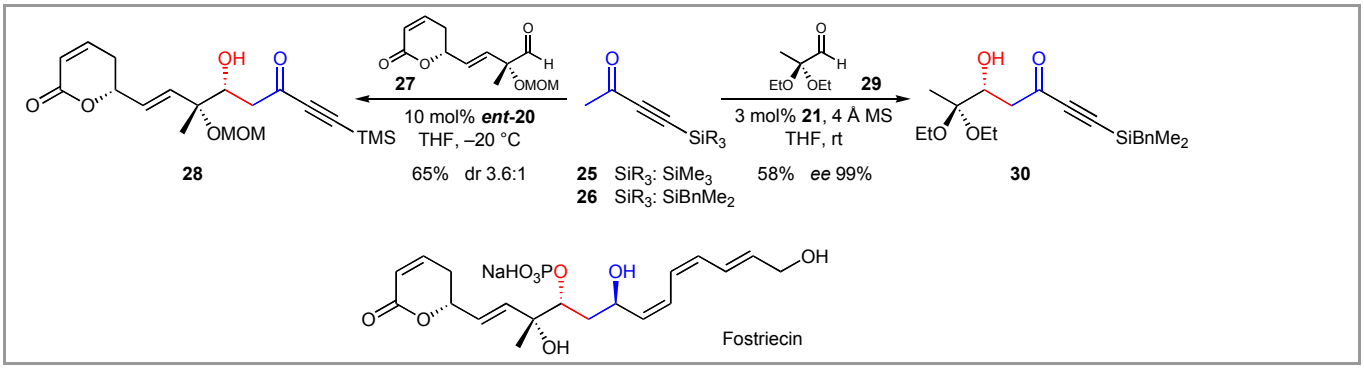
Heralding a new mechanistic paradigm, the central lanthanum(III) atom of **20** functions as a Lewis acid activating the aldehyde whereas the lithium binaphtoxide moiety acts as a Bronsted base. Thus, this catalyst mimics the enzymatic activity and permits efficient stereoselective aldol reactions from methyl ketones **22** and α-branched aldehydes **23** under mild conditions (Scheme 9).[43] In turn, Trost described that one of the zinc atoms of bimetallic catalyst **21** can form the metal enolate while the second one binds to the aldehyde acting as a Lewis acid centre. Then, aldol additions of aryl methyl ketones **24** to **23** proceed in good yields and outstanding enantioselectivities (Scheme 9). Further studies have expanded the scope of this procedure to other functionalizable ketones, such as methyl vinyl ketone, and the simple acetone.[44]



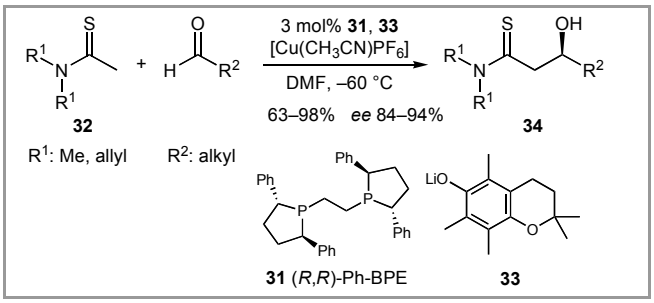
Scheme 9

Both methodologies have been applied to the synthesis of fostriecin using methyl ynones **25** and **26** as the active methylene partners (Scheme 10). Thereby, aldol addition of **25** to chiral aldehyde **27** in the presence of catalyst ***ent*-20** gave aldol **28** in 65% yield and 3.6:1 diastereomeric ratio.[45] In turn, catalyst **21** promoted the reaction of ynone **26** and α-ketal aldehyde **29** to produce aldol **30** as a single enantiomer in 58% yield.[46,47]

More recently, Shibasaki has reported a new direct catalytic asymmetric aldol process inspired in the biosynthesis of 1,3-diols.[48] This new procedure takes advantage of the high chemoselectivity of $[Cu(CH_3CN)PF_6]$ and biphosphine **31** (PhBPE) for the nucleophilic activation of thioamides **32** (Scheme 11). Then, the addition of lithium salt **33** to aliphatic aldehydes in the presence of such a catalytic system produces enantioselectively aldols **34** in high yields.



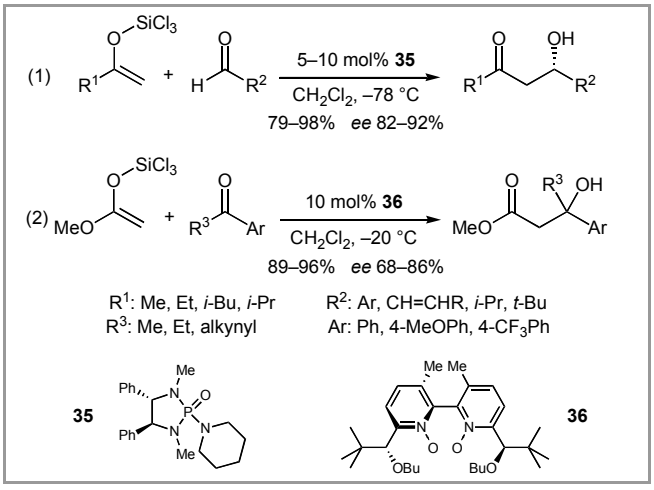
Scheme 10



Scheme 11

Other metal catalysts have been also reported,[49] 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.

In contrast to the abovementioned methodologies, an alternative approach devised by Denmark uses chiral Lewis bases to catalyze the stereoselective addition of trichlorosilyl enolates to aldehydes and ketones.[50,51] These species act as metal enolates in such a way that the binding of chiral phosphoramide **35** to the silicon atom promotes aldol reactions proceeding through cyclic six-membered transition states. Unsaturated aldehydes react quickly and cleanly with ketone-derived trichlorosilyl enolates to provide enantioselectively the corresponding adducts. In turn, branched aliphatic aldehydes require longer reaction times but unbranched ones do not afford aldol products (eq 1 in Scheme 12).[50,52] Alternatively, *N*-oxide **36** catalyzes the parallel addition of the silyl enolate of methyl acetate to aryl ketones (eq 2 in Scheme 12).[51]



Scheme 12

5 Substrate-controlled Aldol Reactions

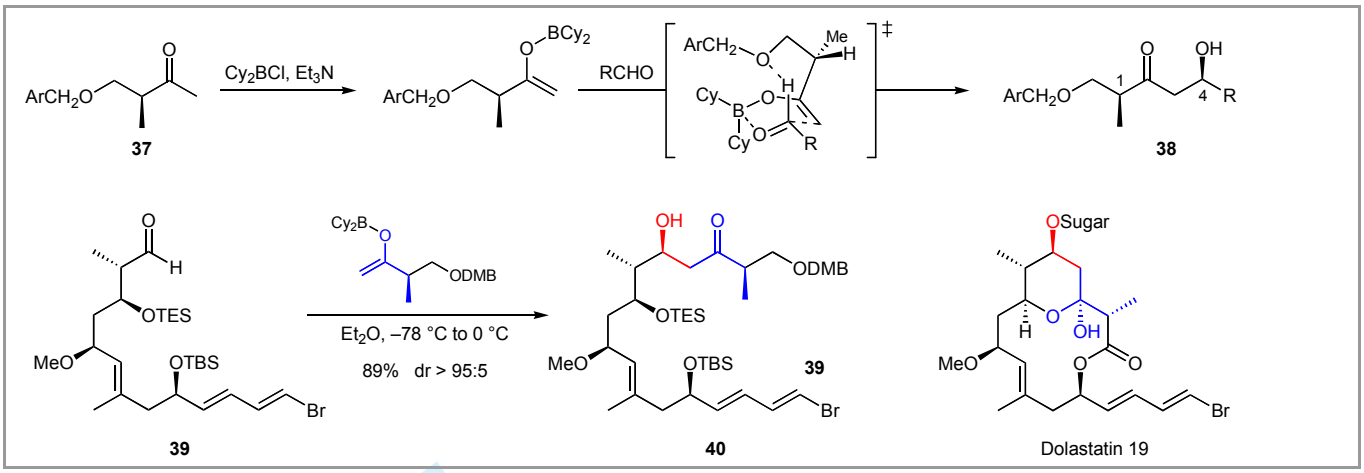
An important set of transformations employ metal enolates in substrate-controlled aldol reactions from chiral methyl ketones, which are especially useful in advanced steps of the synthesis of natural products. Unfortunately, the clear understanding of these reactions is frequently challenged by the broad scope of substrates that can support them and the different sort of elements controlling their stereochemical outcome. Thus, examples reported in the literature 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 the β-position to the carbonyl.

5.1 α-Methyl Ketones

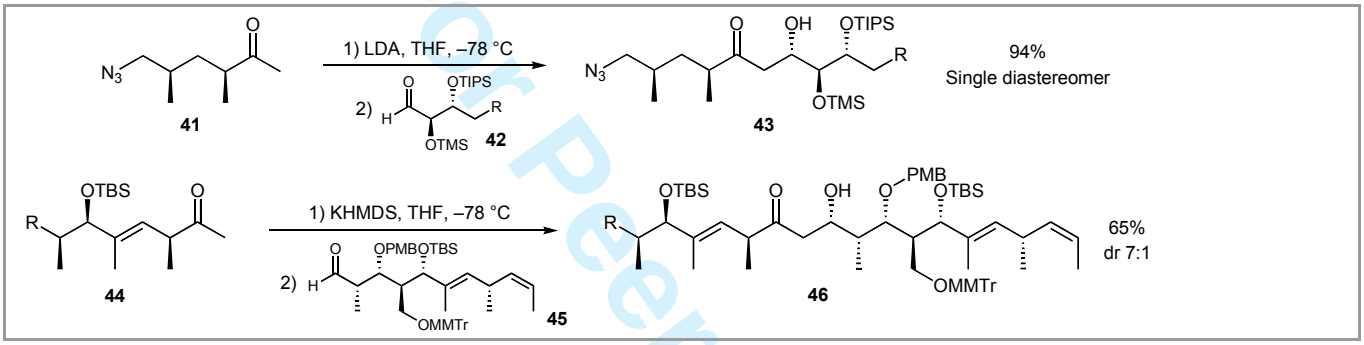
There are no systematic studies on *acetate* aldol reactions based on chiral α-methyl ketones, since the structure of the ketone and the aldehyde partners seems to play a crucial role on the stereochemical outcome of these reactions. For instance, chiral α-methyl ketones derived from Roche ester have proved to be an excellent platform to provide highly stereoselective aldol reactions.[1b] Particularly, dicyclohexyl borinates from benzyl protected ketones **37** furnish 1,4-*syn* aldols **38** with a remarkable stereocontrol (Scheme 13).[53,54] Theoretical calculations suggest 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 **38**.[55] This procedure turns out to be particularly valuable in the addition to chiral aldehydes leading to the 1,4-*syn* Felkin adducts,[56] as for the conversion of chiral aldehyde **39** into aldol **40** in the total synthesis of dolastatin 19 (Scheme 13).[56b]

In spite of these achievements, the search for better diastereoselectivities and the use of silicon protecting groups on the Roche-derived methyl ketones have encouraged the assistance of a chiral boron Lewis acid as Ipc_2BCl (**14** in Figure 2) in matched pairs of double asymmetric aldol reactions.[57]

Otherwise, 1,4-*anti* adducts have been prepared using lithium[58] and potassium[59] enolates. For instance, addition of lithium enolate of methyl ketone **41** to chiral aldehyde **42** furnishes a single diastereomer of 1,4-*anti* aldol **43** in 94% yield. In turn, coupling of methyl ketone **44** and aldehyde **45** produces diastereoselectively aldol **46** when KHMDS is used as the base (Scheme 14).[59,60]



Scheme 13

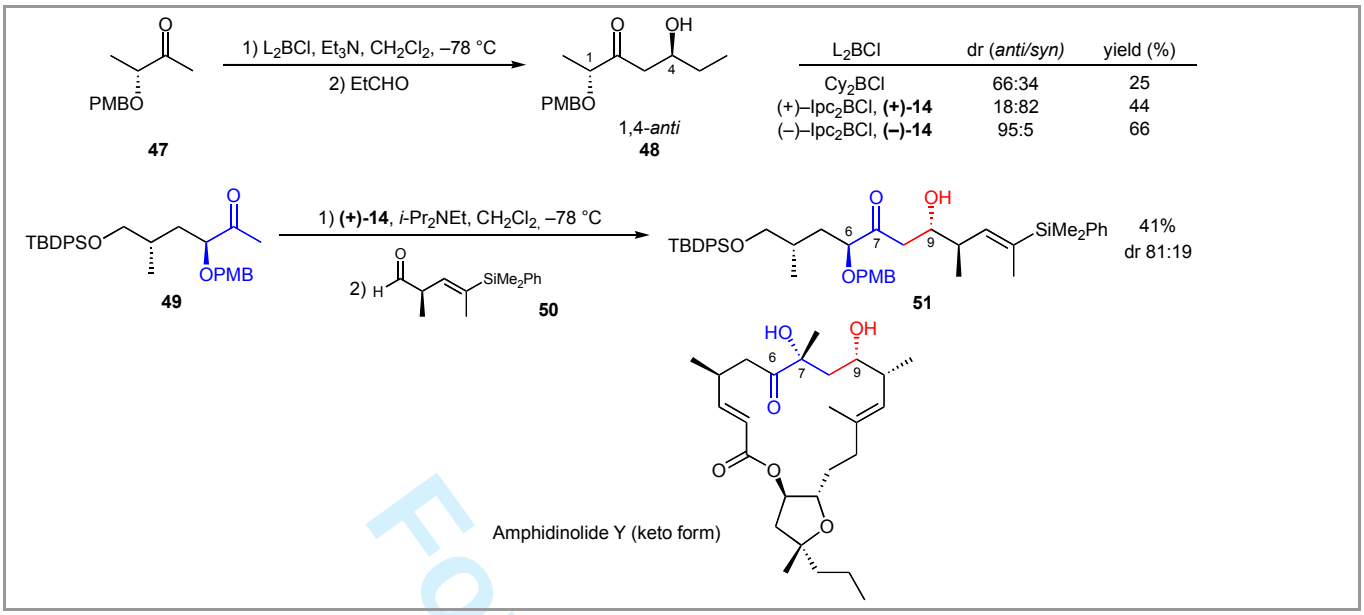


Scheme 14

5.2 α-Hydroxy Ketones

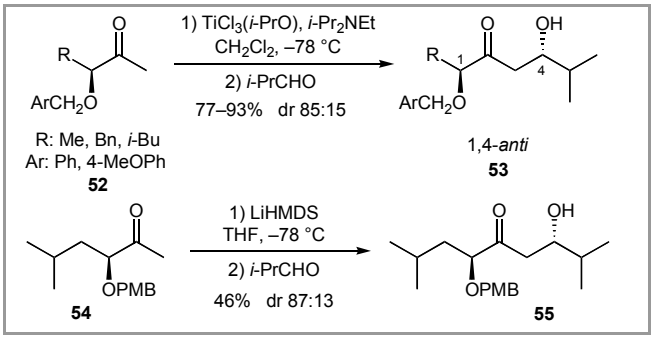
The lack of stereocontrol imparted by borinates from mandelic acid-derived α-*tert*-butyldimethylsilyloxy methyl ketone observed in early studies on asymmetric aldol reactions suggested that such systems might be unsuitable for these transformations.[5c] However, Trost proved that the appropriate choice of the Lewis acid and the hydroxy protecting group on lactate-derived methyl ketones could allow highly stereoselective processes.[61]

Thereby, a remarkable 1,4-*anti* induction can be expected from α-alkoxy methyl ketones provided that the proper boron Lewis acid is used. Evans reported that the addition of the dicyclohexyl borinate from lactate-derived methyl ketone **47** to propanal furnishes 1,4-*anti* aldol **48** in a low diastereomeric ratio, whereas it is considerably improved by using **(–)-14** (Scheme 15).[62] Fürstner has also employed this methodology in one of the key steps of the synthesis of amphidinolide Y.[63] As shown in Scheme 15, boron-mediated aldol addition of α-OPMB methyl ketone **49** to chiral aldehyde **50** furnished 1,4-*anti* aldol **51** in moderate yield and good diastereoselectivity.



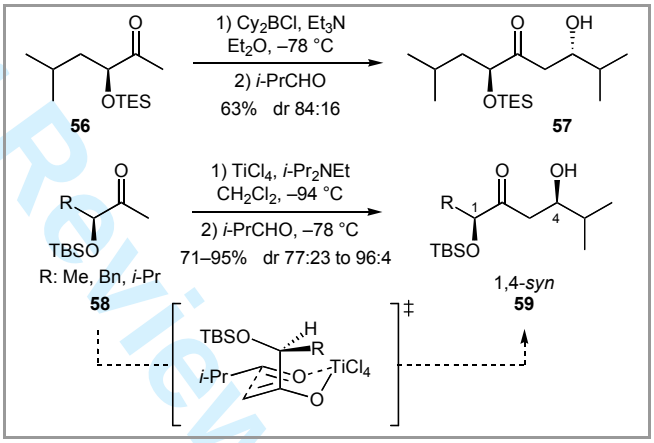
Scheme 15

Parallel trends have been observed in other transformations from α-benzyloxy methyl ketones. For instance, $TiCl_3$(*i*-PrO)-mediated aldol additions of methyl ketones **52** to isobutyraldehyde afford the corresponding 1,4-*anti* adducts **53** in yields up to 93% and 85:15 diastereomeric ratio (Scheme 16).[64,65] In turn, lithium counterpart from ketone **54** gives aldol **55** in similar diastereoselectivity.[66,67]



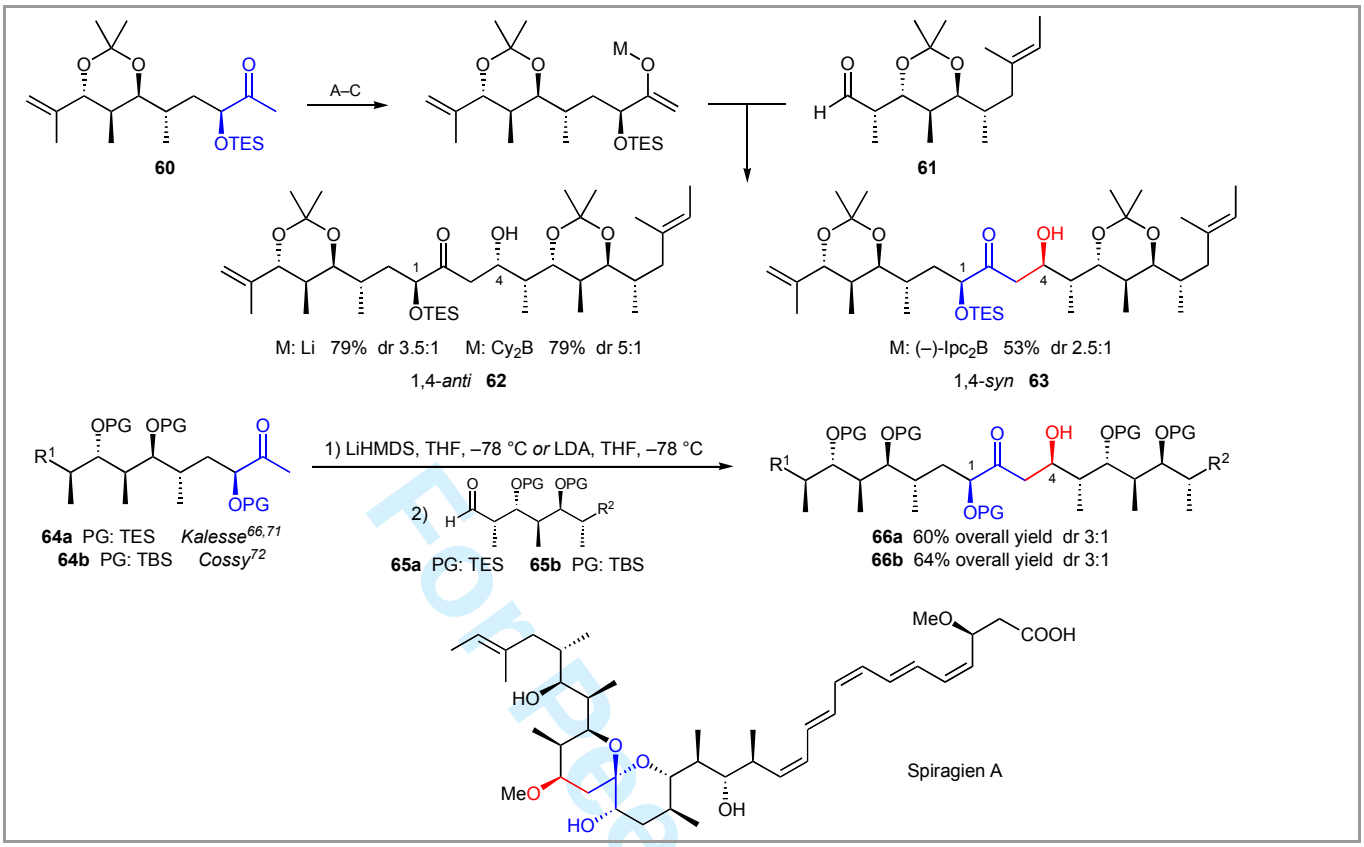
Scheme 16

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 has been also assessed. As for benzyl protected ketones, addition of the dicyclohexyl borinate of α-triethylsilyloxy methyl ketone **56** to isobutyraldehyde gives 1,4-*anti* aldol **57** in good yield and high diastereomeric ratio (Scheme 17).[66] However, the diastereoselectivity is dramatically eroded for alkaline enolates,[66] whereas enolization of α-*tert*-butyldimethylsilyloxy ketones **58** with $TiCl_4$/*i*-Pr_2NEt and subsequent addition to isobutyraldehyde give access to 1,4-*syn* aldols **59**.[68] The rationale for this result is based on a six-membered chair-like transition state in which the antiperiplanar distribution of both TBSO–C and C–OTi bonds would act as the key element to determine the *syn* configuration (Scheme 17).[69]



Scheme 17

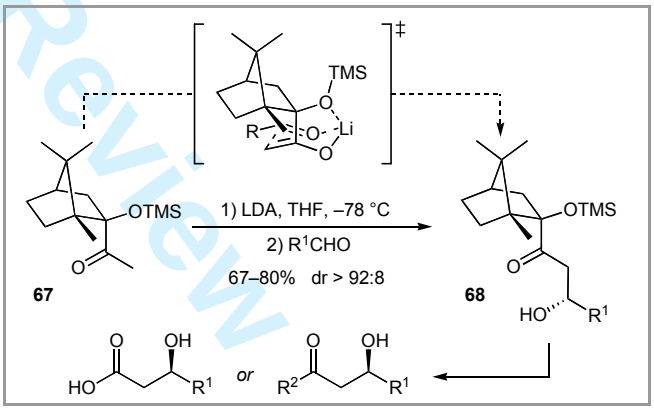
A nice account on the intricacy of these aldol reactions can be found in the synthesis of the spiroketal core of spirangien A. Paterson reported that the stereoselectivity of the aldol addition of the α-OTES methyl ketone **60** to chiral aldehyde **61** was very sensitive to the enolization procedure. Preliminary studies using LDA or Cy_2BCl/Et_3N furnished *anti* aldol **62**, but this inherent diastereoselectivity in the undesired direction was eventually overturned by employing chiral Ipc ligands to afford 1,4-*syn* aldol **63** (Scheme 18).[70] Therefore, boron Lewis acid **(–)-14** determines the stereochemical outcome of this transformation and prevails over the induction imparted by the ketone **60** and aldehyde **61**. Moreover, Kalesse[71] and Cossy[72] have established that aldol reactions of lithium enolates from α-silyloxy methyl ketones **64** and chiral aldehydes **65** afford the



Scheme 18

desired 1,4-*syn* aldols **66** in 3:1 diastereomeric ratio (Scheme 18), which proves that subtle changes on the metal and the structure of the aldehyde partner can dramatically affect to the stereochemical outcome of these aldol reactions.

At last, it is worth mentioning that the lithium enolate of the camphor-based α-trimethylsilyloxy methyl ketone **67** affords the corresponding aldol adducts **68** with a remarkable high diastereoselectivity.[73] As shown in Scheme 19, the aldol addition proceeds through a chelated six-membered chair-like transition state in which the bulky camphor backbone determines the approach of the aldehyde. From a conceptual point of view, the camphor acts as a chiral auxiliary in such a way that the removal of the silicon protecting group of **68** and the appropriate manipulation of the resultant hydroxy ketones yield enantiopure β-hydroxy acids or ketones (Scheme 19).

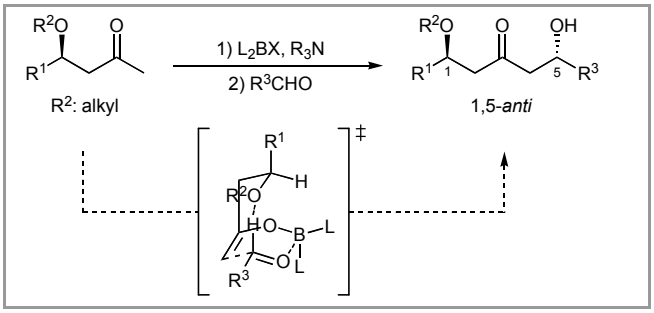


Scheme 19

5.3 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 with boron Lewis acids (X: Cl, OTf in Scheme 20) and tertiary amines (Et_3N or *i*-Pr_2NEt) yields the less substituted enolborinate that participates in highly diastereoselective 1,5-*anti* aldol reactions, whereas other metals and protecting groups provide remarkably lower diastereoselectivity.[74,75] As previously pointed for related transformations, a theoretical model that accounts for such a high stereocontrol is based on a

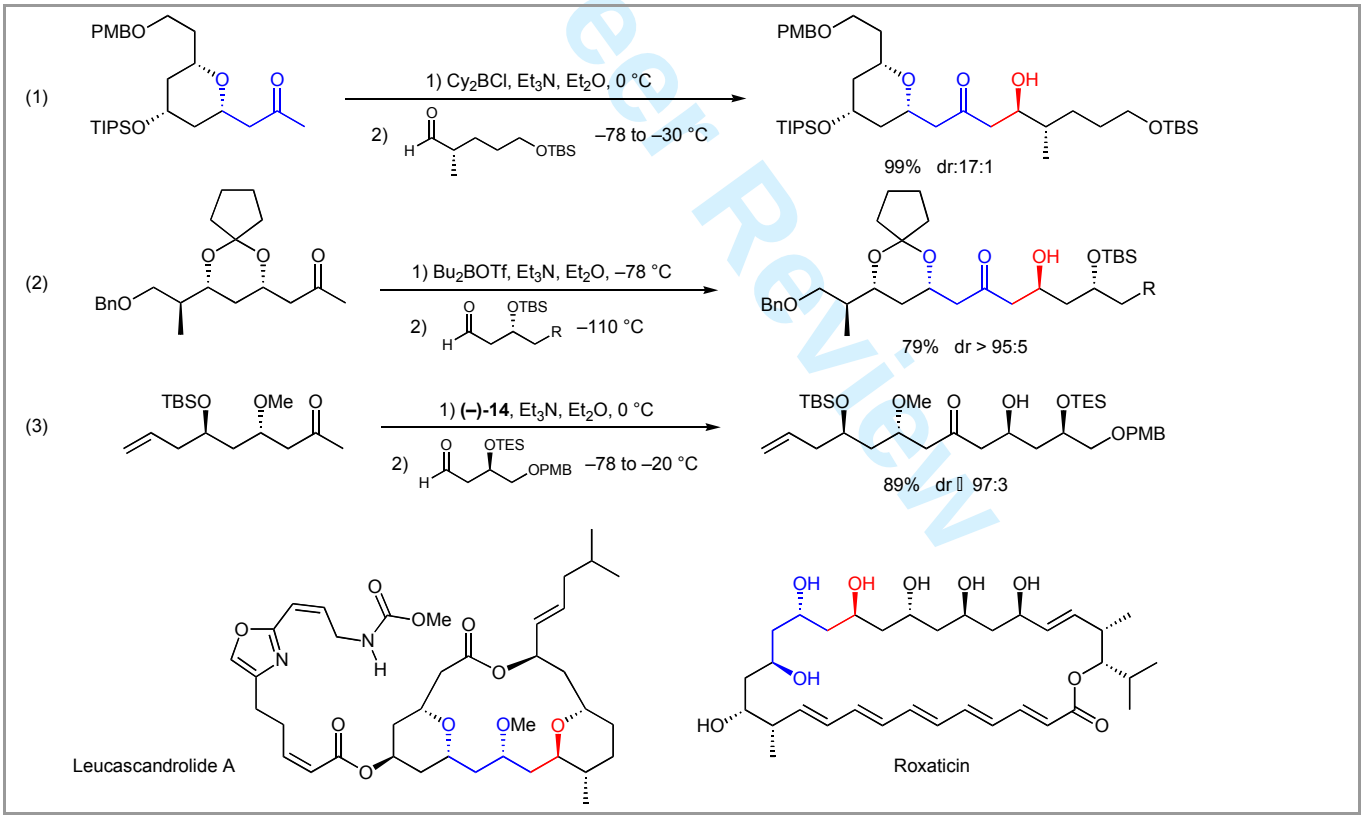
boat-shaped transition structure in which a stabilizing formyl hydrogen bond exists between the alkoxy oxygen and the aldehyde proton.[55]



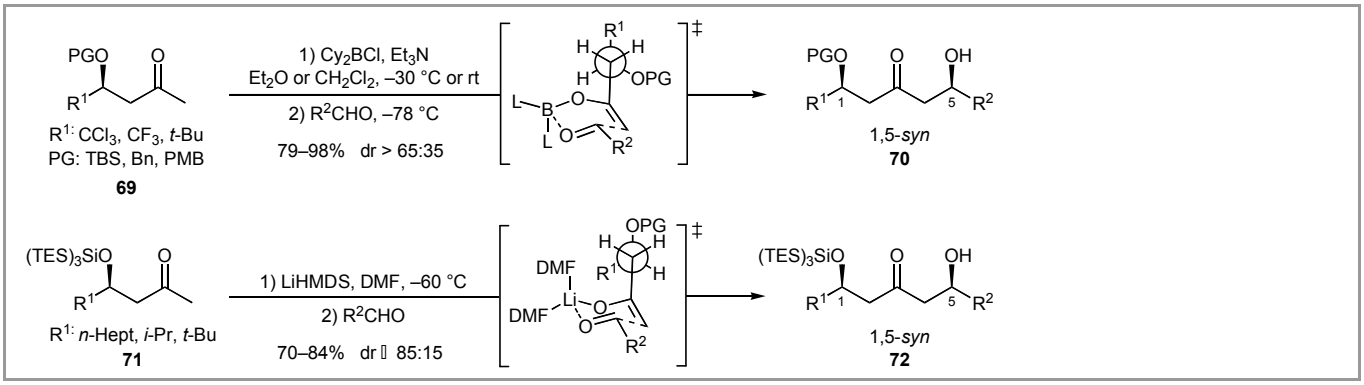
Scheme 20

This powerful transformation has been successfully applied to the synthesis of natural products as leucascandrolide A (eq 1 in Scheme 21),[76] roxaticin (eq 2 in Scheme 21),[77] spongistatin 1 (eq 3 in Scheme 21)[78] and many others.[75,79]

The dominant 1,5-*anti* trend observed for these transformations has been occasionally overriden by the influence of remote stereocentres, functional groups or chiral boron Lewis acids.[80] In this context, Dias has established that good levels of substrate-controlled 1,5-*syn* stereoinduction are obtained in boron-mediated aldol reactions of β-trihalomethyl- as well as β-*tert*-butyl-β-hydroxy methyl ketones **69** possessing different hydroxy protecting groups (Scheme 22).[81,82] Theoretical calculations on the competing pathways involved in these reactions suggest that a boat-like transition state lacking the formyl hydrogen bond is the most stable one and leads to 1,5-*syn* aldol adducts **70** (Scheme 22). Moreover, Yamamoto has recently reported that lithium enolates of β-*super* silyloxy methyl ketones **71** add to aliphatic, α,β-unsaturated and aromatic aldehydes in DMF to provide 1,5-*syn* aldols **72** in outstanding diastereoselectivities.[83] In this case, a chair-like transition state that minimizes unfavorable steric interactions has been invoked to rationalize the observed *syn* induction.



Scheme 21

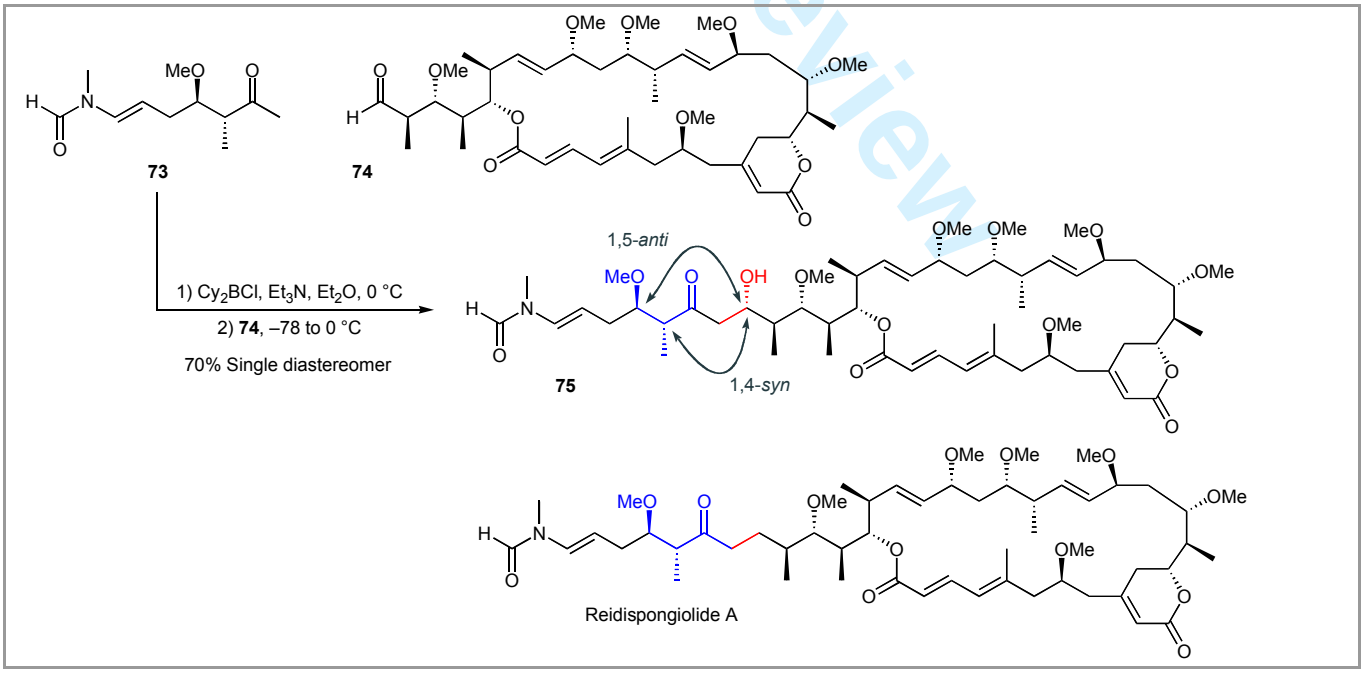


Scheme 22

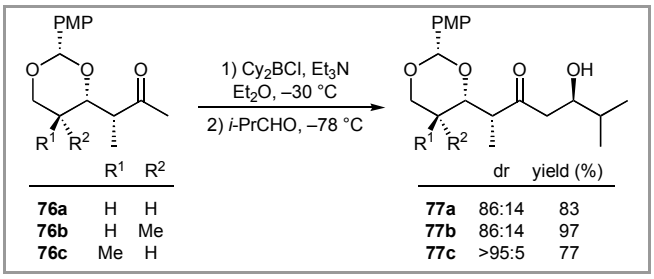
5.4 β-Hydroxy α-Methyl Ketones

Most of the examples reported in the literature on substrate-controlled aldol additions of β-hydroxy-α-methyl 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 (see Scheme 20 and 13). 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 involves the aldol addition of the dicyclohexyl borinate of methyl ketone **73** to chiral aldehyde **74** that furnishes aldol **75**, an advanced intermediate in the total synthesis of reidispongiolide A, as a single diastereomer in 70% yield (Scheme 23).[57e,84]

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 stereocentre 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 **76** has established that the prevailing 1,5-*anti* induction imparted by the β-alkoxy leads to the adducts **77** (Scheme 24).[85] These studies have also proved that even the configuration of the γ-stereocentre plays a significant role on the stereochemical outcome of these reactions, as occurs for ketone **76c**.[86] However, it is worth keeping in mind that these transformations are not completely well understood and unexpected effects can play a crucial role.[86]



Scheme 23

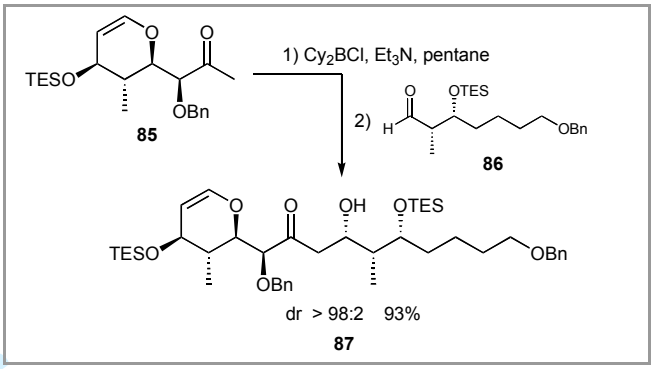


Scheme 24

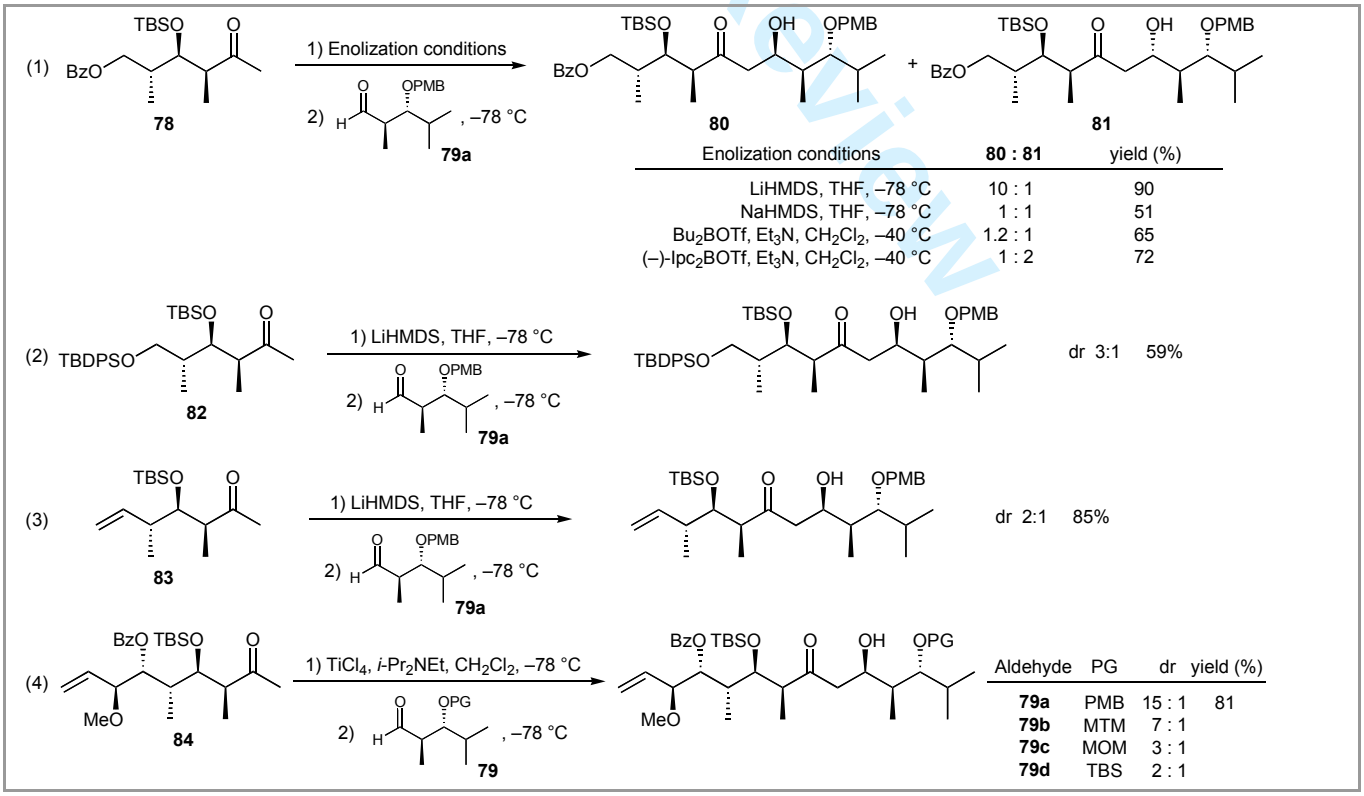
Other metal enolates have been also used in these reactions, but it is rather difficult to predict their stereochemical induction. For instance, a thorough analysis reported by Roush on the addition of the *syn* β-*tert*-butyldimethylsilyloxy-α-methyl ketone **78** to the chiral aldehyde **79a** has established the dependence of the aldol stereoselectivity on metal enolate (eq 1 in Scheme 25). Furthermore, the moderate and low diastereoselectivity observed for related ketones **82** and **83** (see eq 2 and eq 3 in Scheme 25) suggests that the presence of a chelating group at δ position is crucial to attain a high stereocontrol and proves that these aldol reactions are governed by several subtle structural details.[87] In turn, parallel studies on the titanium-mediated aldol reactions of ketone **84** have unveiled a close dependence of diastereoselectivity on the protecting group of the aldehyde **79**, which is a new proof of the sensitivity of these substrate-controlled transformations (see eq 4 in Scheme 25).[88]

5.5 α,β-Dihydroxy Ketones

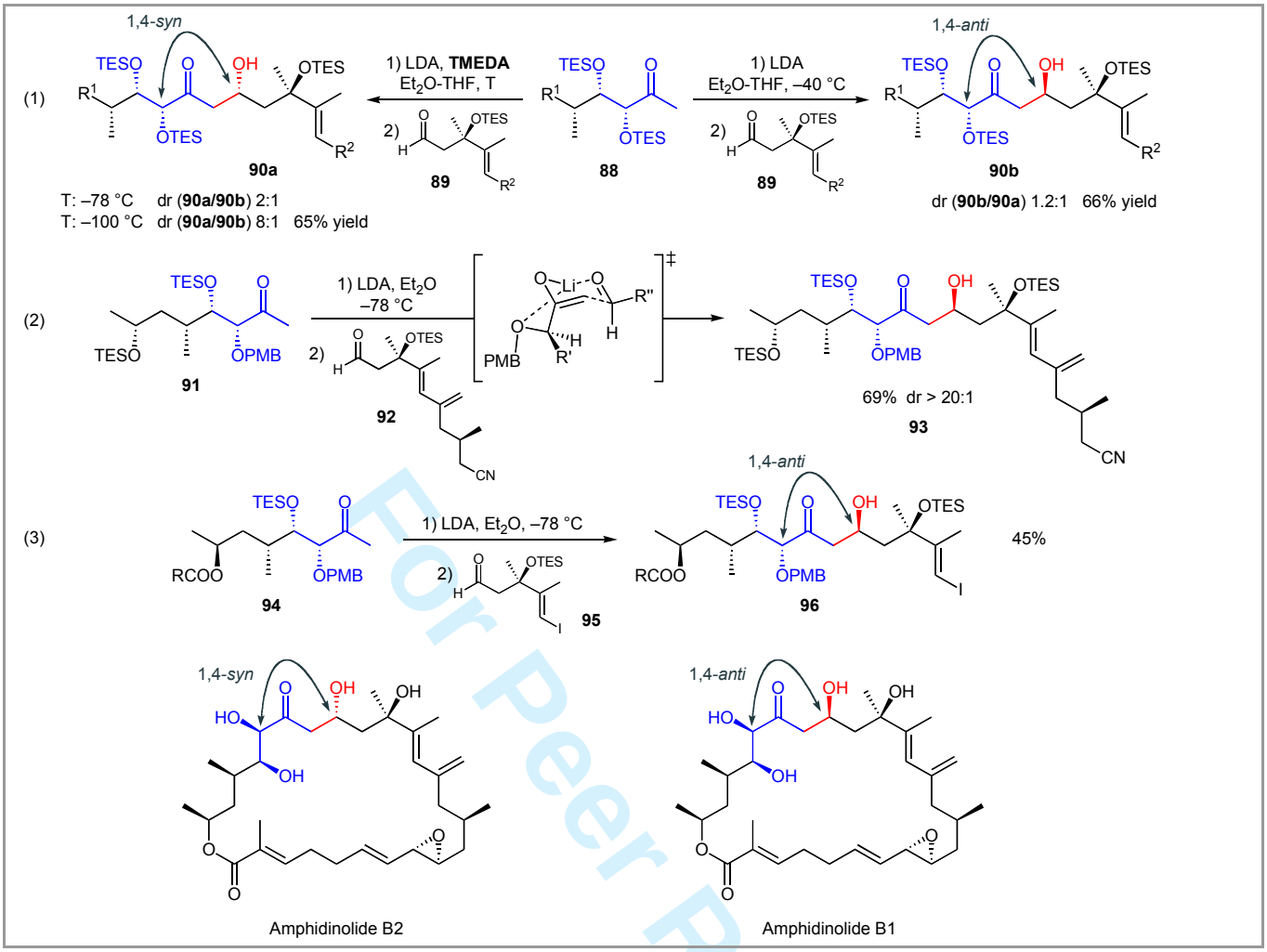
The diastereoselectivity of substrate-controlled aldol reactions from α,β-dihydroxy methyl ketones depends on the metal enolate, the configuration of α- and β-stereocentres and the hydroxy protecting groups. In this context, the remarkable 1,5-*anti* induction of boron-mediated aldol reactions of β-alkoxy methyl ketones (Scheme 20) also operates in these systems and may be assisted by the parallel 1,4-*anti* bias observed in related α-hydroxy methyl ketones (Scheme 15). Therefore, it is not surprising that the addition of the dicyclohexyl borinate of the α,β-dialkoxy methyl ketone **85** to aldehyde **86** led to the isolation of a single diastereomeric aldol adduct **87** in 93% yield (Scheme 26).[89,90]



Scheme 26



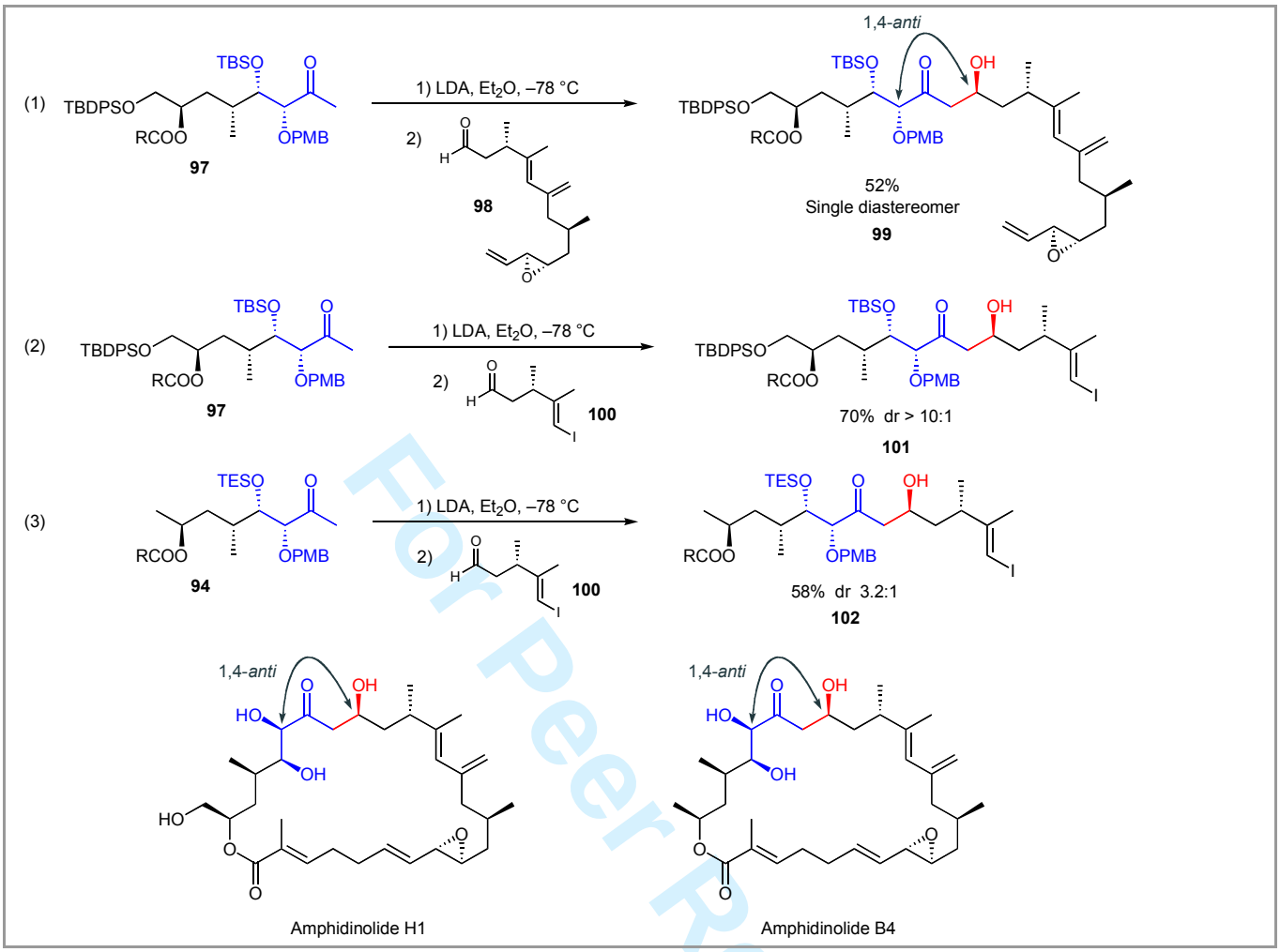
Scheme 25



Scheme 27

In spite of these accomplishments, most of the examples reported in the literature about substrate-controlled aldol reactions from α,β-dihydroxy methyl ketones take advantage of the high nucleophilicity of alkaline enolates. Particularly, alkaline-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 on the stereochemical outcome of such additions. Unfortunately, these aldol reactions 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 is well documented that silicon protecting groups provide poor stereocontrolled additions,[91] but Carter has recently reported that TMEDA increases the reactivity of the lithium enolate of α,β-disilyloxy methyl ketone **88**, produces a stereochemical reversal on the aldol addition to aldehyde **89** and the bias favoring 1,4-*syn* **90a** can be even improved by cooling to –100 °C (eq 1 in Scheme 27).[92] Interestingly, Carter also found that the aldol addition of β-OPMB α-OTES methyl ketone **91** to aldehyde **92** gives aldol **93** in 69% yield as a single diastereomer through a chelated transition state (eq 2 in Scheme 27),[93] which obviously makes the most of the chelating ability of the benzyl-like protecting group placed at the α-position.[94] Moreover, Fürstner found that the lithium-mediated aldol addition of β-OPMB α-OTES methyl ketone **94** to aldehyde **95** afforded 1,4-*anti* aldol **96** in 45% yield (eq 3 in Scheme 27).[91d] A quick glance to Scheme 27 reveals that ketones **88** and **91** and aldehydes **89**, **92** and **95** are pretty similar, but lithium enolates from **91** and **94** impart a much better stereocontrol than the parallel enolate from **88**, which proves how important protecting groups can be on the diastereoselectivity of these reactions.

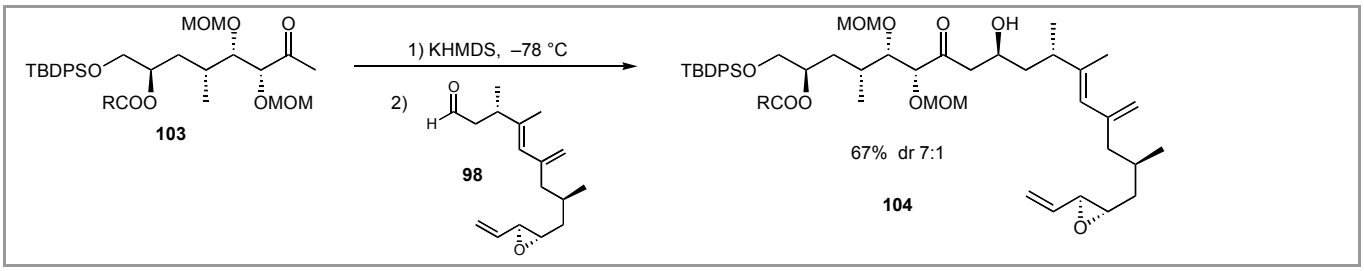
As anticipated by these results, α-alkoxy-β-silyloxy methyl ketones have been involved in much more stereoselective transformations. In the abovementioned analysis on the reactivity of alkaline enolates from *syn* α,β-dihydroxy methyl ketones, Fürstner also described that the addition of the lithium enolate from α-OPMB-β-OTBS methyl ketone **97** to aldehyde **98** affords aldol **99** as a single diastereomer in 52% yield (eq 1 in Scheme 28).[91d] The excellent diastereoselectivity was adscribed to the 1,4-*anti* directing effect imparted by the α-alkoxy group (see Scheme 16). This hypothesis



Scheme 28

was corroborated by the fact that the related disilyloxy ketone furnished a poor 2:1 mixture of the two possible diastereomers. However, minor changes on the aldehyde and the ketone were responsible of significant differences on the diastereoselectivity. For instance, a less elaborated aldehyde as **100** delivered the *anti* aldol **101** in 70% yield and a slightly lower diastereomeric ratio (dr > 10:1, compare eq 1 and eq 2 in Scheme 28). However, the diastereoselectivity was seriously eroded when the reaction was carried out on ketone **94** lacking remote OTBDPS group, which afforded aldol **102** in a modest diastereomeric ratio (compare eq 2 and eq 3 in Scheme 28).[91d] The reason why this particular reaction shows a significantly lower selectivity is unclear, but it is also instructive to realize the dramatic influence of the aldehyde partner by comparing eq 3 in Scheme 27 and eq 3 in Scheme 28.

Finally, other protecting groups have been also used in these transformations.[95] For instance, Zhao reported that the diastereoselective addition of the potassium enolate from α,β-diMOM protected methyl ketone **103** to aldehyde **98** in an advanced step of the total synthesis of amphidinolide H1 (Scheme 28) produces diastereoselectively 1,4-*anti* aldol **104** in 67% yield (Scheme 29).[95b]



Scheme 29

6 Conclusions

In spite of early reports, 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 metal enolates 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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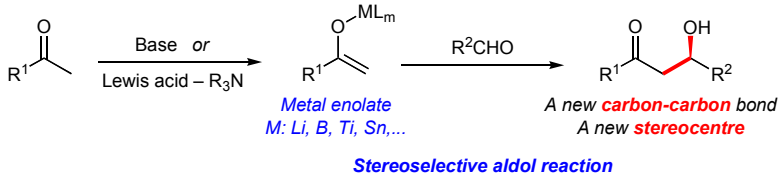
Stereoselective Acetate Aldol Reactions rom Metal Enolates



Graphical Abstract