Recent developments in asymmetric aldol methodology

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Reviewing the literature published up to the end of 1993

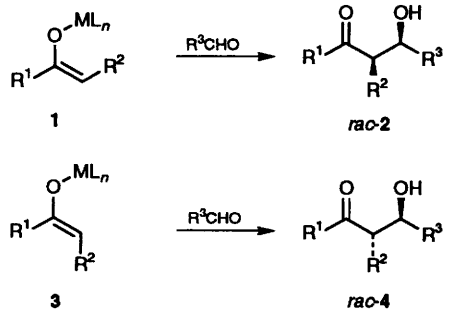
1 Introduction

The ability to form new carbon–carbon bonds in a regio-, stereo-, and enantio-selective fashion plays a fundamental role in modern organic synthesis. Over the last decade or so, the aldol reaction has been developed into one of the most powerful and versatile methods for the control of acyclic stereochemistry and the efficient assembly of complex natural products. Control of the absolute and relative stereochemistry of the aldol addition is possible using a range of techniques. A chiral auxiliary or reagent is frequently employed to direct enolization and π-face selectivity. More recently, chiral Lewis acids have been introduced to promote enantioselective Mukaiyama aldol additions. These methods rely on reagent control. An alternative strategy depends on substrate control using a chiral ketone or aldehyde component, where appropriate choice of the metal and the enolate geometry enables high levels of π-face selectivity to be attained in the absence of any auxiliary group.

This review provides an overview of the many generally applicable methods for absolute stereocontrol in the aldol reaction developed in recent years (predominantly 1990–1993).[1,2] While mechanistic issues and molecular modelling of aldol transition states are also active areas of current research,[3,4] they are not dealt with here. The reader is referred to some excellent comprehensive reviews on the aldol reaction, which provide an account of transition state models.[1] The emphasis of this review is given to those aldol methods which have seen some application in total synthesis, as well as state-of-the-art methods which appear to offer considerable potential for future development. In the latter case, an important area is catalytic aldol processes using sub-stoichiometric chiral Lewis acids. While aldolase enzymes have been used synthetically, particularly for carbohydrates, they are not covered in this particular review.[5]

1.1 Controlling factors in the stereochemical outcome of aldol additions to aldehydes

For the aldol reactions of substituted enolates with aldehydes, a fundamental consideration is the relationship between the two adjacent stereocentres created in the addition. Early work on lithium and boron enolates showed that the disastereoselectivity of aldol reactions performed under kinetic conditions is predominantly† dependent on the geometry of the enolate component.[6] Thus, *Z*-enolates **1** give rise to *syn* aldol products **2** whilst *E*-enolates **3** provide *anti* adducts **4** (**Scheme 1**).[7]



Scheme 1

More recently, extensive studies[8] have explored the factors governing the selective generation of *Z*- or *E*-enol borinates of ethyl ketones using electrophilic boron reagents of the type L_2BX and an amine base. In general, sterically demanding ligands (*e.g.* c-hex) and a

†Note that the diastereoselectivity of Mukaiyama aldol reactions of silyl enolates with aldehydes is frequently unaffected by their *E*/*Z* geometry.

poor leaving group on boron (*e.g.* Cl) combined with a small amine base (*e.g.* Et_3N) provide the *E*-enolate, whilst small ligands (*e.g.* Bu^n), a good leaving group (*e.g.*OTf) and a hindered amine (*e.g.* Pr^i_2NEt), give *Z*-selective enolization. Thus, selective access to *syn* or *anti* aldol adducts can often be obtained by appropriate choice of the boron reagent and enolization conditions. These trends have been rationalized by computer modelling of the intermediate ate complexes formed between the ketone carbonyl oxygen and the Lewis acidic boron reagent.[4]

Titanium(IV) enolates may be generated either by transmetallation of lithium enolates or, more simply, using the $TiCl_4/Pr^i_2NEt$ system developed by Evans *et al.*[9] both approaches give rise to *syn* products, often in higher yields than the boron counterpart. In general, boron performs better for simple unbranched or α-branched ethyl ketones, whilst titanium-mediated aldol reactions give improved selectivity for chiral ethyl ketones, particularly in auxiliary based systems.[10] Tin(II) enolates, generated using tin(II) triflate and an amine base, also afford *syn* aldol products with high selectivity.[11]

Asymmetric induction in aldol reactions represents a much greater challenge than the control of simple *syn/anti* diastereoselectivity, requiring significant stereodifferentiation of the π-faces of the enolate and the aldehyde. Three main strategies have been actively pursued:

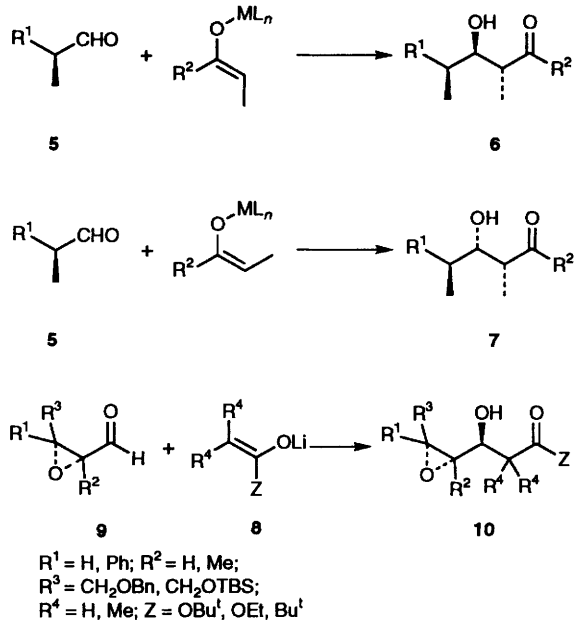
(i) Induction from the aldehyde component.
(ii) Induction from covalently-bound ligands or auxiliaries in the enolate component or, in its simplest form, inherent chirality in the ketone substrate.
(iii) Induction from a chiral Lewis acid in Mukaiyama aldol reactions.

Where the formation of new stereogenic centres may be influenced by two or more sources of induction, possibilities exist for both the enhancement and reduction of selectivity. Overall, when these influences are in the same stereochemical sense, this constitutes a 'matched' pair, leading to increased selectivity. However, those known to have opposing influences undergo 'mismatched' reactions with a concomitant reduction in overall selectivity.[12] Double (and triple) asymmetric induction effects are generally seen to be additive, however, reactants with a very high diastereofacial preference may control the stereochemical course of a reaction regardless of the influence of other components. It is important to stress that these are simple guidelines for what to expect and that, particularly in the combination of chiral reactants, interactions which do not play a significant role in simple systems may cause unforeseen selectivity.

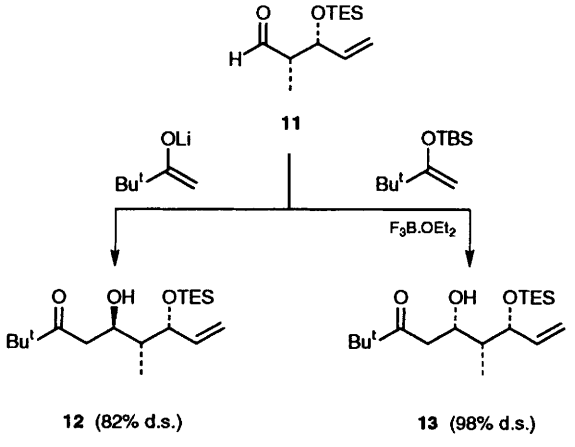
2 Asymmetric induction from the aldehyde

Aldol reactions between achiral enolates and α-chiral aldehydes provide the least general route to the diastereoselective synthesis of β-hydroxy carbonyl compounds. Although α-methyl, α-alkoxy, and α-amino aldehydes exhibit high diastereofacial preferences in Mukaiyama aldol reactions with enol silanes (*vide infra*),[13] additions of other metal enolates exhibit considerable variability.[14] The reaction of α-methyl aldehydes **5** with achiral *E*-enolates usually gives adduct **6** as predicted by the Felkin–Anh model (**Scheme 2**).[15] However, additions to *Z*-boron, lithium, and titanium enolates exhibit anti-Felkin facial selectivity, yielding **7**, provided the steric requirements of R^1 are greater than that of the α-methyl group, with an increase in selectivity observed for larger R^1.[16] High anti-Felkin selectivity is also observed in the reactions of α-methyl-β-alkoxy aldehydes with achiral *Z*-enolates. However, lithium enolates **8** add to α,β-epoxyaldehydes **9** with good diastereofacial selectivity to give **10** as predicted by the Felkin–Anh model.[17]

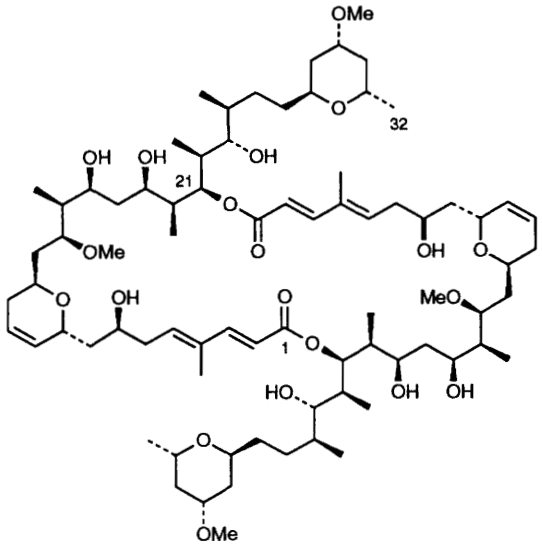
In studies directed towards the synthesis of calyculin A (**Scheme 3**), Evans *et al.* showed that



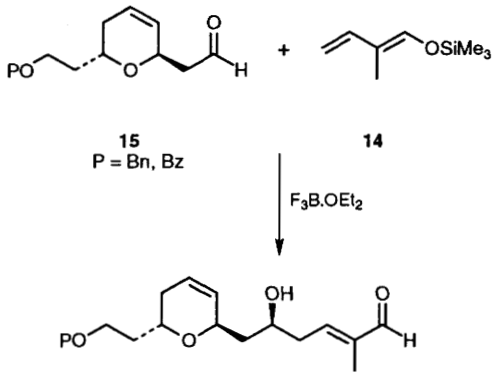
Scheme 2



Scheme 3



swinholide A



81 – 90% d.s.

Scheme 4

complementary 1,2-asymmetric induction may be obtained for the addition of pinacolone to aldehyde **11**.[18] The lithium enolate gives rise to anti-Felkin product **12**, whilst a Lewis acid mediated Mukaiyama addition using the silyl enol ether gives Felkin product **13**.

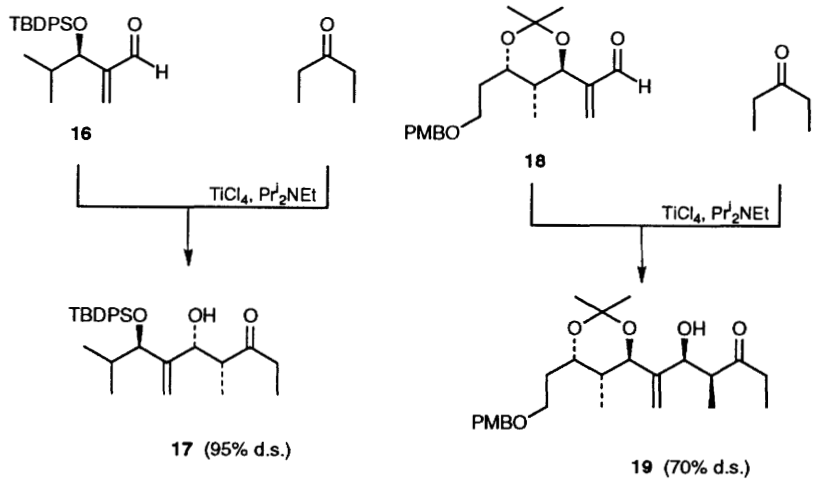
In certain cases, synthetically useful levels of 1,3-stereocontrol may be obtained in additions to β-chiral aldehydes, particularly where chelation can be exploited under Mukaiyama aldol conditions.[19] In studies directed towards the synthesis of swinholide A, Paterson *et al.* found that the vinylogous Mukaiyama aldol reaction of silyl dienol ether **14** with aldehyde **15** proceeded with high diastereoselectivity (**Scheme 4**).[20] However, here the best Lewis acid was boron trifluoride etherate, which precludes chelation by the dihydropyran oxygen. The stereoselectivity in aldol reactions of methyl and ethyl ketones with α-methylene-β-alkoxy aldehydes mediated by boron, tin(II), and titanium(IV) enolates have been examined.[21] Useful levels of 1,3-asymmetric induction from the aldehyde are possible, where the sense and level of induction varies with the nature of the enolate and the substitution in the aldehyde. For example, the titanium-mediated aldol addition of diethylketone to **16** gives adduct **17** with 95% d.s., whereas addition to **18** gives predominantly **19** (**Scheme 5**).

3 Asymmetric induction from the enolate

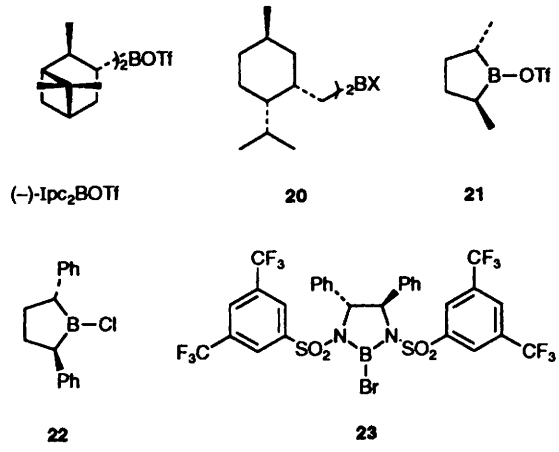
3.1 Ligand-mediated

The use of chiral ligands on the metal of an enolate provides a mean of differentiating the two diastereotopic π-faces. Work in this area has concentrated mainly on the use of chiral boron reagents for the enolization of simple ketones, esters, and thioesters [(−)-Ipc_2BOTf and **20–23**].

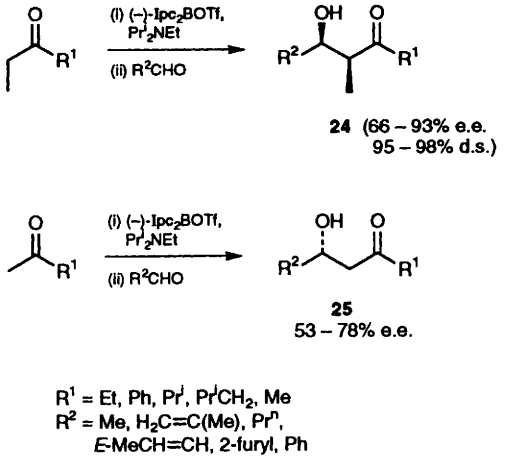
The α-pinene-derived reagents di-isopinocampheylboron triflate [(+)- or (−)-Ipc_2BOTf] have been shown by Paterson *et al.* to



Scheme 5

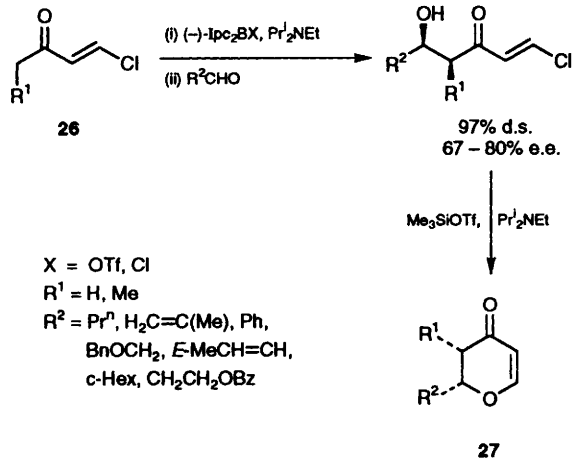


provide access to either enantiomer of *syn* aldol product **24** from the addition of ethyl ketones to sterically undemanding aldehydes (**Scheme 6**).[22] The use of enol di-isopinocampheyl borinates generated from the 1,4-addition of Ipc_2BH to *E*-α,β-unsaturated ketones in the synthesis of enantiomerically enriched *syn* aldols has also been reported.[23] This approach allows regioselective enolization of unsymmetrical ketones and gives exclusively the *syn* product in good enantiomeric purity (60–90% e.e.). Ipc_2BCl or Ipc_2BOTf can also be used for enantioselective aldol reactions of methyl ketones.[22] β-Hydroxyketones **25** are produced with reduced levels of enantioselectivity and with the opposite hydroxyl configuration to that observed in the ethyl ketone aldols for a given reagent configuration.



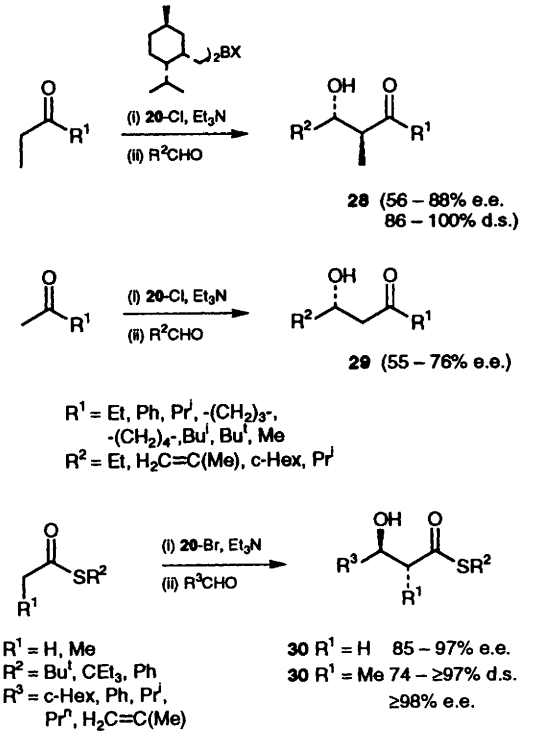
Scheme 6

An asymmetric synthesis of dihydropyrones **27** has been developed using the Ipc-controlled boron aldol reactions of β-chloroenones **26** with aldehydes, followed by cyclization (**Scheme 7**).[24] This method has been used in the synthesis of **27** ($R^2 = H$, $R^2 = CH_2CH_2OBz$), a key intermediate for the synthesis of swinholide A and scytophycin C.[20]



Scheme 7

The corresponding *anti* aldol reactions of *E*-enolates generated from ketones using Ipc_2BCl proceed with little enantioselectivity.[22] In contrast, the computer-designed boron reagent $[(menth)CH_2]_2BCl$ **20** (X = Cl) introduced by Gennari *et al.* has been shown[25] to enolize a range of cyclic and acyclic ketones leading to *anti* aldols **28** with high diastereoselectivity in good enantiomeric purity (**Scheme 8**). Methyl ketone derived enolates exhibit the same aldehyde enantioface preference (in contrast with the Ipc case) giving **29**, again with reduced enantioselectivity.

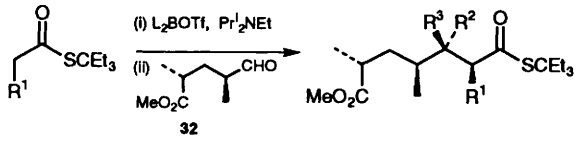


Scheme 8

This methodology has been extended to the enolization of thioacetates and thiopropionates by modification of the reagent to its bromo derivative (the

boron chloride was found to be ineffective for the enolization of thioesters).[26] Thioacetates give enantiomerically enriched β-hydroxythioesters **30** ($R^1 = H$) whilst the thiopropionates react with high enantio- and diastereo-selectivity. The reagent **24** (X = Br) was also shown to be marginally more *anti* selective than the corresponding chloride for the aldolization of ketones.

The two closely related chiral boranes **21** and **22** have been employed by the groups of Masamune and Reetz respectively for the enolization of ketones and thioesters. The diphenyl derivative **22** performs better in thioacetate aldols (92–> 95% e.e.)[27,28] whilst the dimethyl reagent **21** is superior for thiopropionate systems (98–100% e.e.)[29] although the differences are small. The reactions of thioesters with chiral α-amino aldehydes mediated by **22** have been shown to proceed with a high level of reagent control.[27] Reagent **21** follows the rules of double asymmetric induction (**Scheme 9**), thus the addition of thioester enolates **31** to chiral aldehyde **32** giving adducts **33–36** provides both matched and mismatched product ratios, although the reagent chirality dictates the overall facial selectivity.[29]



31 **32**

33 $R^1 = H$; $R^2 = OH$; $R^3 = H$
34 $R^1 = H$; $R^2 = H$; $R^3 = OH$

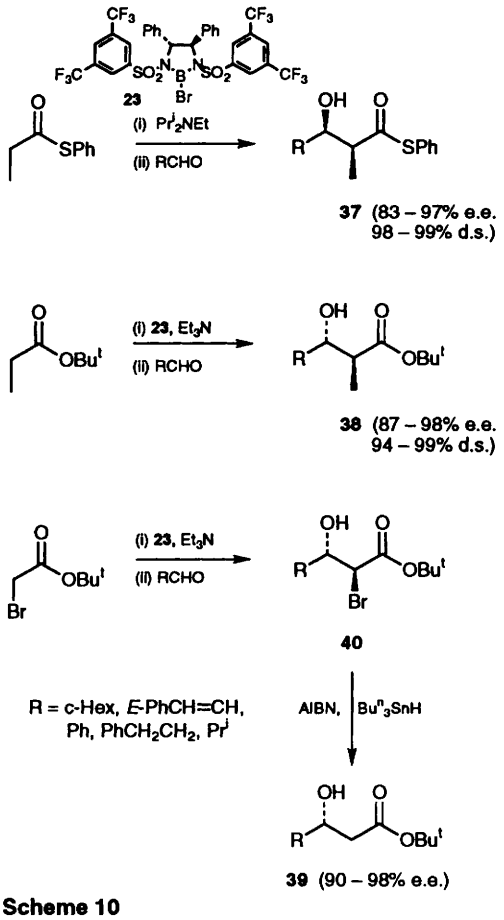
	33 : **34**
(*RR*)-**21**	13 : 1
(*SS*)-**21**	1 : 7

35 $R^1 = Me$; $R^2 = OH$; $R^3 = H$
36 $R^1 = Me$; $R^2 = H$; $R^3 = OH$

	35 : **36**
(*RR*)-**21**	>200 : 1
(*SS*)-**21**	1 : 55

Scheme 9

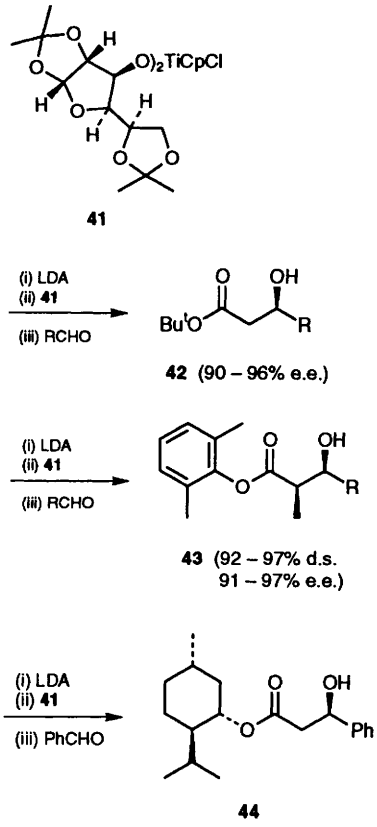
Corey *et al.* have employed bromoborane **23** in the enantioselective aldols of propionates and thioesters (**Scheme 10**).[30,31] Enolization of phenylthioesters with **23** and Pr^i_2NEt leads to *syn* products **37** whilst t-butyl esters and Et_3N as base give rise to *anti* isomers **38**. Acetate derivatives **39** can be accessed *via* t-butyl bromoacetate[32] with Bu^n_3SnH/AIBN being used for debromination of the initially formed *anti* bromohydrin **40**.



Scheme 10

Duthaler *et al.* have used the chiral titanium reagent **41** to transmetallate acetate[33] and propionate[34] ester lithium enolates, leading to significant levels of enantioselectivity in their reactions with aldehydes to give **42** and **43** (**Scheme 11**). The same species has been used in the aldol additions of menthyl acetate enolates to give **44**, where the influence of the ligands on the titanium is dominant in determining the facial selectivity.[35]

The use of chiral lithium amides as enantioselective deprotonation agents for ketones provides potential access to optically active aldol products. Although

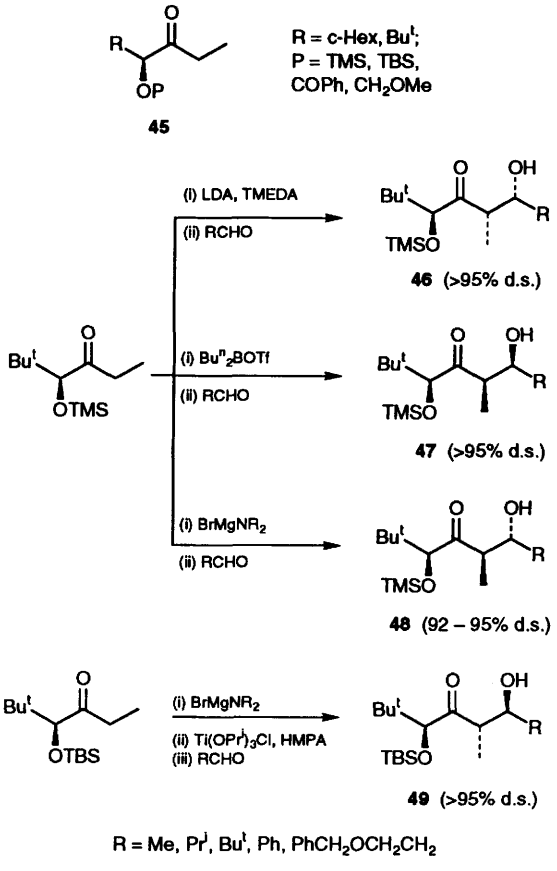


Scheme 11

good enantiomeric excesses (up to 86% e.e.) have been achieved, the origins of selectivity in these reactions are not well understood, limiting their application at the present time to a few, specific systems based on sterically demanding acyclic and cyclic ketones.[36]

3.2 Auxiliary-mediated

A common means of controlling asymmetric aldol additions is through the use of a chiral auxiliary attached to the enolate component. These must be readily synthesized, impart a high level of stereocontrol, and be easily cleaved, under high yielding and mild conditions, without loss of stereochemical integrity at the newly formed centres. The initial formation of diastereomeric products in these reactions should allow facile separation prior to cleavage to essentially enantiopure products.

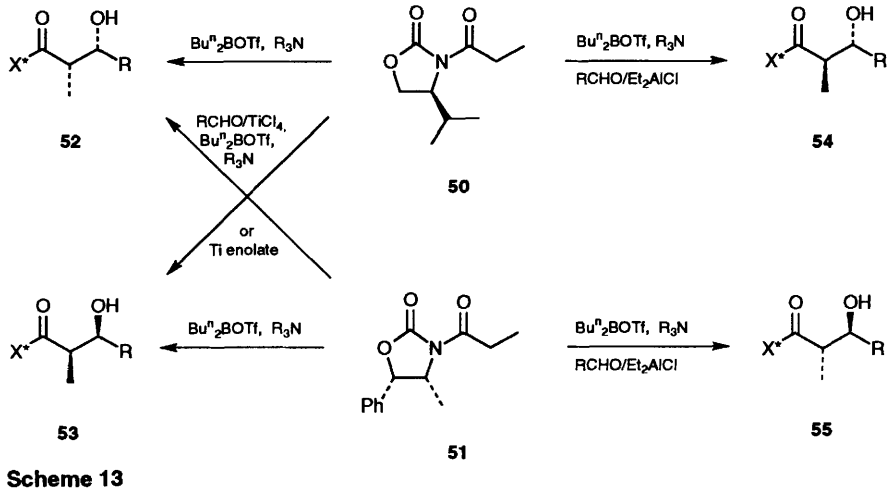


Scheme 12

Perhaps the simplest chiral auxiliary system consists of the protected α-hydroxy ketones **45** (**Scheme 12**) where aldol addition, deprotection, and periodate cleavage yields the corresponding α-methyl-β-hydroxy carboxylic acid.[37] Heathcock *et al.* have shown that all four possible diastereoisomers **46–49** are available from one enantiomer of **45** (R = Bu^t, P = TMS or TBS) by appropriate choice of enolization conditions.[38]

The *N*-propionyl imides **50** and **51**, derived from (*S*)-valine and (1*S*, 2*R*)-norephedrine respectively were introduced by Evans *et al.* in 1981 and allow highly enantiocontrolled synthesis of both *syn* and *anti* aldol products (**Scheme 13**).

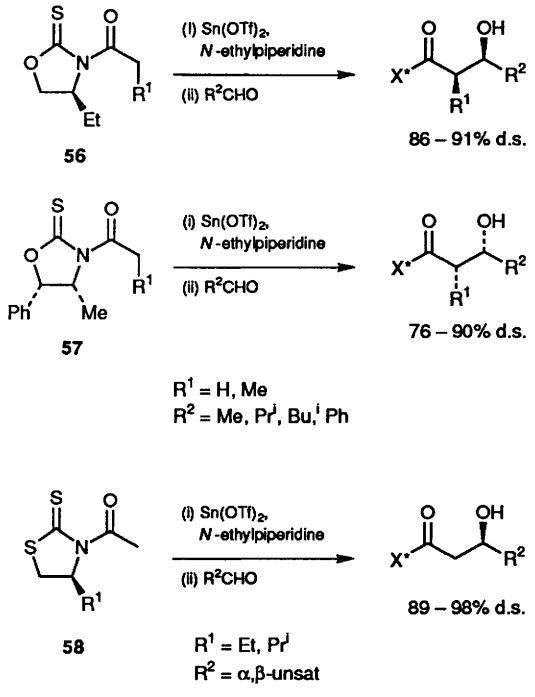
The *Z*-enol borinate of **50**, generated using di-n-butylboron triflate, reacts with aldehydes to give *syn* aldol **52**. Similarly, the *Z*-boron enolate of **51** gives *syn* isomer **53** arising from complementary asymmetric induction. In both cases, treatment with sodium methoxide in methanol gives the corresponding methyl ester in > 99% enantiomeric purity.[39] Alternatively, access to the second *syn* isomer from a given auxiliary is possible *via* the titanium enolate. Transmetallation of the lithium enolate of **50** with $ClTi(OPr^i)_3$ and subsequent addition of aldehyde gives the 'non-Evans' *syn* product **53** (85–92% d.s.).[40] Direct generation of the more reactive chlorotitanium enolates by deprotonation of the $TiCl_4$-complexed imide with di-isopropylethylamine simplifies this approach.[9] Addition of $TiCl_4$ to the preformed boron enolate prior to reaction with the aldehyde also gives the 'non-Evans' *syn* product **53** in 87–94% d.s.[41] A more significant application of Lewis acid additives developed by Heathcock *et al.* gives *anti* isomers **54** or **55** with good diastereoselectivity (74:26–95:5) from the addition of the boron enolates of **50** or **51** to aldehydes precomplexed with Et_2AlCl. Again the two auxiliaries exhibit opposite facial selectivities.[41]



Scheme 13

Reversal of the simple *syn* selectivity of these boron enolates to give both *anti* and 'non-Evans' *syn* products has also been observed in a small number of substrate-specific cases, particularly in the presence of excess di-*n*-butylboron triflate.[42]

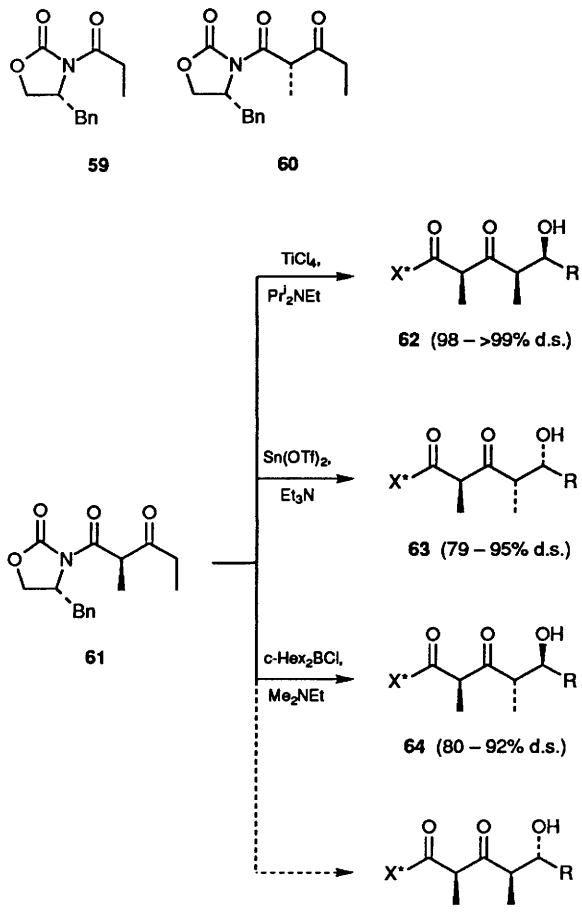
The corresponding acetate aldol reactions of these oxazolidinone systems have proved disappointing. However, Nagao *et al.* have shown that the closely related thiocarbonyl species **56** and **57** induce diastereoselectivity in both propionate ($R^1 = Me$) and acetate ($R^1 = H$) aldol additions *via* their tin(II) enolates, whilst **58** functions solely as an acetate equivalent (**Scheme 14**).[43]



Scheme 14

Stereocontrolled acylation of **59** to give β-ketoimides **60** and **61**[44] provides further opportunities for directing aldol additions, leading to dipropionate units. Evans *et al.* have shown that three of the four possible stereochemical courses of the aldol additions of these substrates can be achieved by variation of the enolization conditions (**Scheme 15**). Titanium(IV) chloride/di-isopropylethylamine enolization of **61** leads to the all *syn* product **62**, whilst the second *syn* aldol isomer **63** is available using tin(II) triflate/triethylamine.[45] The *anti* isomer **64** arises from reaction of the *E*-enol borinate, generated from **61** using dicyclohexylboron chloride and dimethylethylamine, with aldehydes.[46] Reactions of these β-ketoimides with α-chiral aldehydes have been shown to follow the rules of double asymmetric induction.

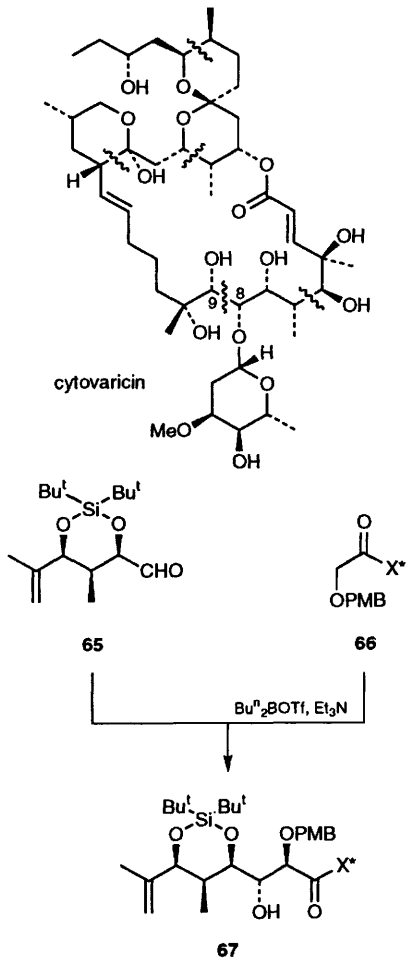
A number of possibilities for auxiliary cleavage beyond simple hydrolysis (which may also be performed under milder conditions with LiOOH) exist, allowing ready access to aldehydes, Weinreb amides,[47] thioesters, benzyl esters, and alcohols,



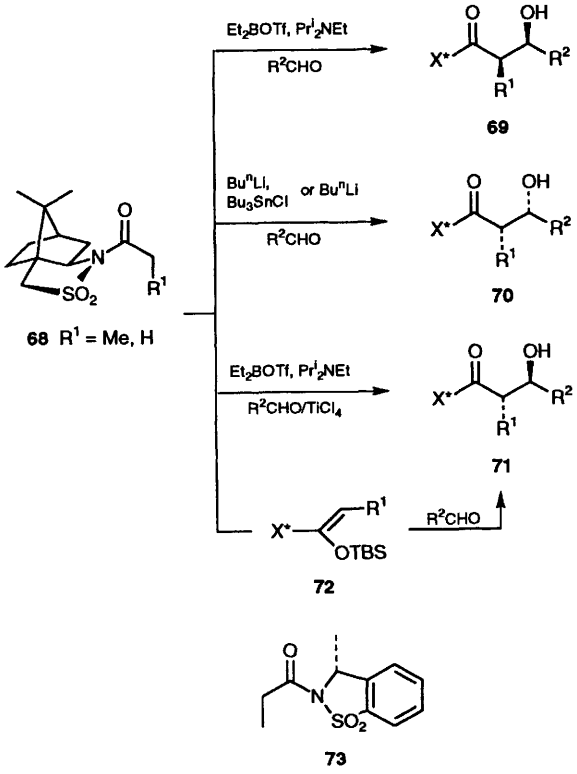
Scheme 15

facilitating further functionalization. Numerous examples of the use of these highly effective auxiliaries in the synthesis of complex targets have been reported, particularly those containing polypropionate fragments.[48–50] Often a large proportion of the stereocentres are introduced by asymmetric aldol reactions with further induction by these centres then playing an important role in subsequent steps. One such synthesis is that of cytovaricin from the Evans group.[51] Here, a total of five aldol connections were made (**Scheme 16**). It should also be noted that the aldol addition of **65** to **66** (C_8–C_9) proceeded with unprecedented *anti* selectivity to give **67**, apparently due to the high π-facial bias of the aldehyde component.

Bornane-sultam **68** ($R^1 = Me$) has been employed by Oppolzer *et al.* for asymmetric aldol reactions (**Scheme 17**). Enolization of **68** ($R^1 = Me$) with diethylboron triflate and di-isopropylethylamine followed by addition of aldehyde gives the *syn* aldol product **69**. In contrast, the lithium or tin(IV) enolates of **68** ($R^1 = Me$) react with aldehydes to give the other *syn* isomer **70**.[52] *anti*-Aldols **71** can be accessed either *via* ketene acetal **72**[53], or directly by addition of $TiCl_4$-complexed aldehyde to the boron enolate of **68** ($R^1 = Me$).[54] In all cases, products are obtained in > 99% d.s. after recrystallization.



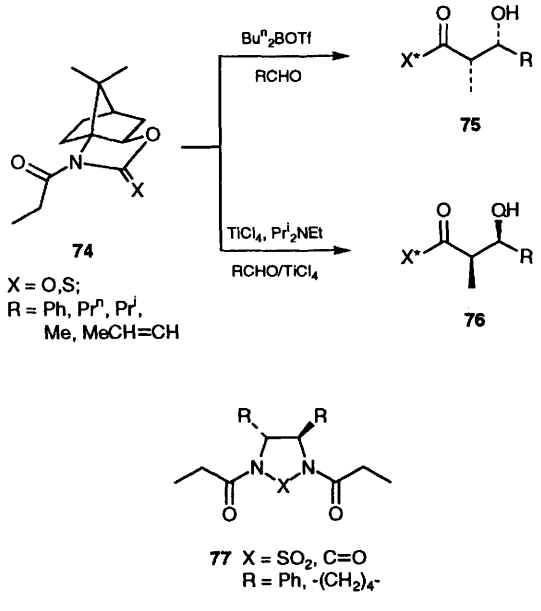
Scheme 16



Scheme 17

The corresponding acetate aldols of **68** (R^1 = H) again proceed *via* the ketene acetal **72** (R^1 = H) although selectivities are lower (79:21–95:5) than the corresponding propionate systems.[55] Cleavage of recrystallized aldol products occurs readily with alkaline peroxide,[53] allyl alcohol/$Ti(OPr^i)_4$,[56] or dilithiated methyl phenyl sulfone[57] to give enantiopure β-hydroxy carbonyl derivatives. The *anti* and *syn* selective aldols of **68** (R^1 = Me) and sultam **73**[58] respectively have been used in the asymmetric synthesis of serricorole.[59]

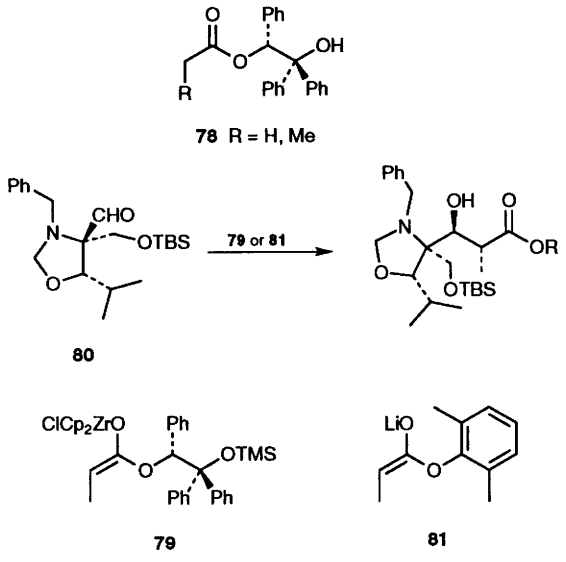
The camphor-derived *N*-propionyloxazolidine **74** has also been used in asymmetric aldol reactions (**Scheme 18**). The boron enolate of **74** (X = O or S) gives *syn* isomer **75**[60] whilst the second *syn* isomer **76** is the product of addition of $TiCl_4$-complexed aldehyde to the chlorotitanium enolate of **74** (X = S).[61] The asymmetric *syn* aldols of a range of other *N*-propionyl derivatives have been reported with other chiral amine[62] or camphor[63] based auxiliaries. Di-*N*-propionyl derivatives of the general type **77** have also been employed, providing access to two identical aldol fragments from a single chiral source.[64]



Scheme 18

Chiral esters have been shown to provide ready access to asymmetric aldol products, often in an *anti* selective sense.[65] Of particular note in this area is **78** which was introduced by Braun *et al.*[66] and has been used, as its TMS ether, by Corey *et al.* in a synthesis of lactacystin. The *anti* aldol of zirconium enolate **79** with aldehyde **80** proceeded with 86% d.s., whilst that of the achiral lithium enolate **81** showed only 60% d.s. (**Scheme 19**).[67]

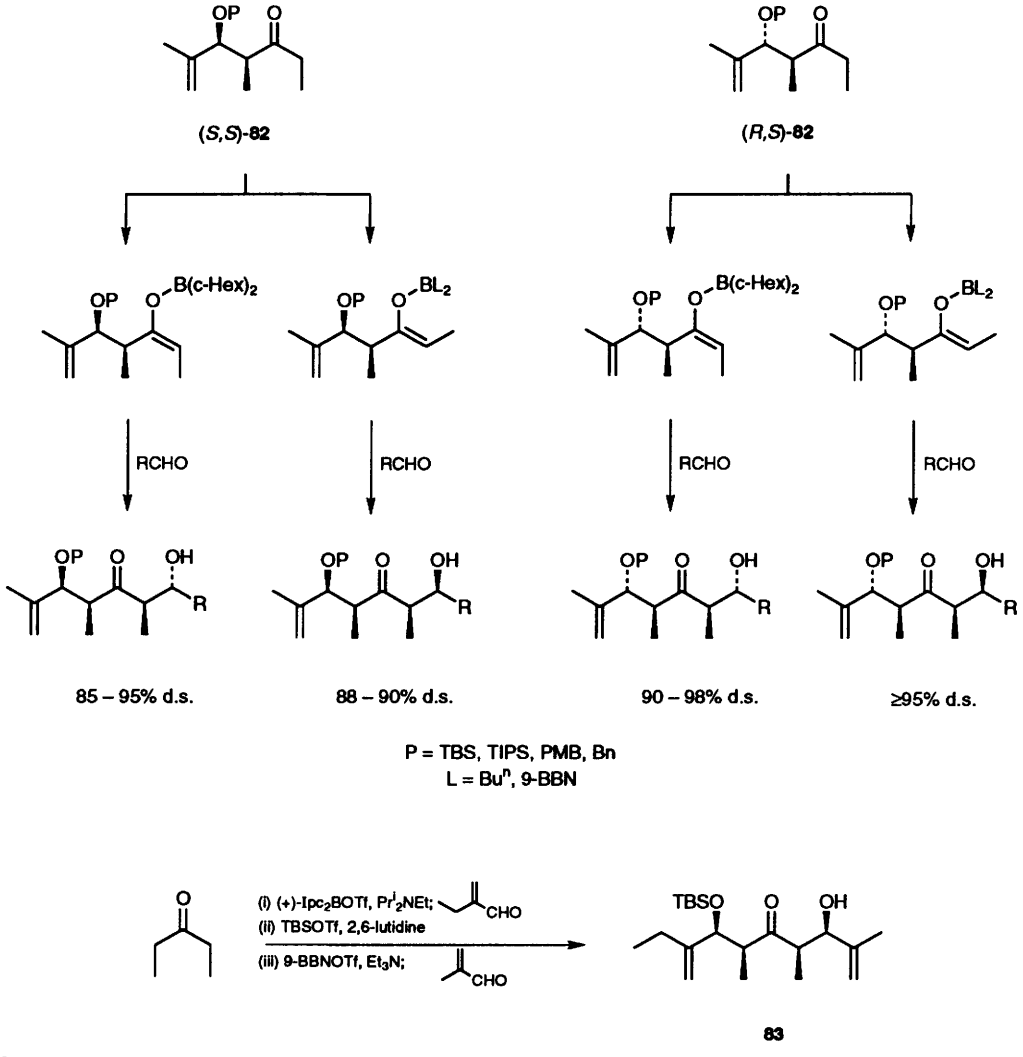
Other auxiliary-based approaches have employed chiral amides,[68] sulfoxides,[69] hydrazones,[70] and oxazaphosphites[71] to induce asymmetry in aldol reactions.[1]



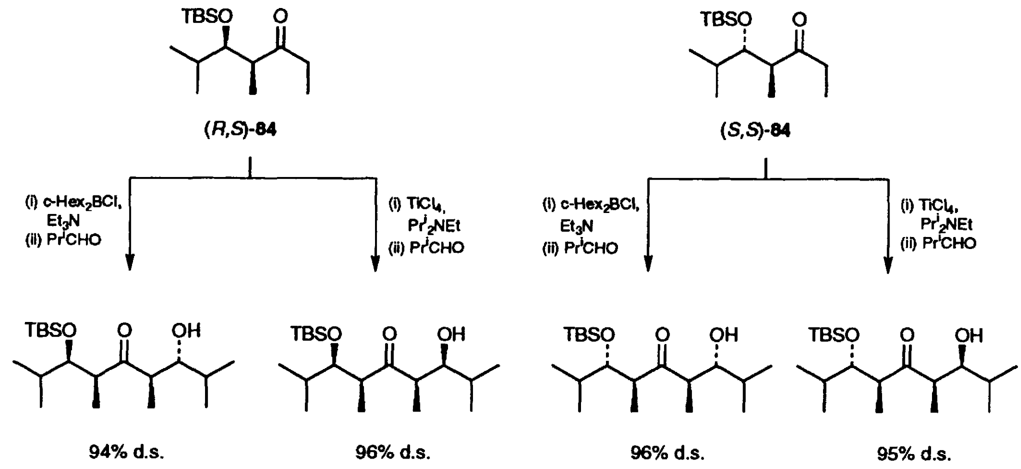
Scheme 19

3.3 Substrate-mediated using chiral ketones

In certain cases, the inherent chirality of an α- or β-substituted ketone leads to useful π-facial discrimination of its enolate without the requirement for a temporary chiral auxiliary or enolization reagent. Despite the potential for asymmetric induction in the aldol additions of α-chiral ethyl ketones, systematic study in this area has been limited to relatively few specific substrates. The α,β-substituted ketones **82** undergo diastereoselective boron-mediated additions to aldehydes (**Scheme 20**) and function as tripropionate equivalents.[72–74] This approach has been applied to the asymmetric synthesis of ebelactone A and B, where the key intermediate **83** was obtained by sequential aldol reactions on diethylketone.[75] The reactions of the structurally related ethyl ketones **84** have been reported by Evans *et al.*[10,46] with improved diastereoselectivities for the *syn* isomers, in the same stereochemical sense as boron, being obtained *via* their chlorotitanium enolates (**Scheme 21**).

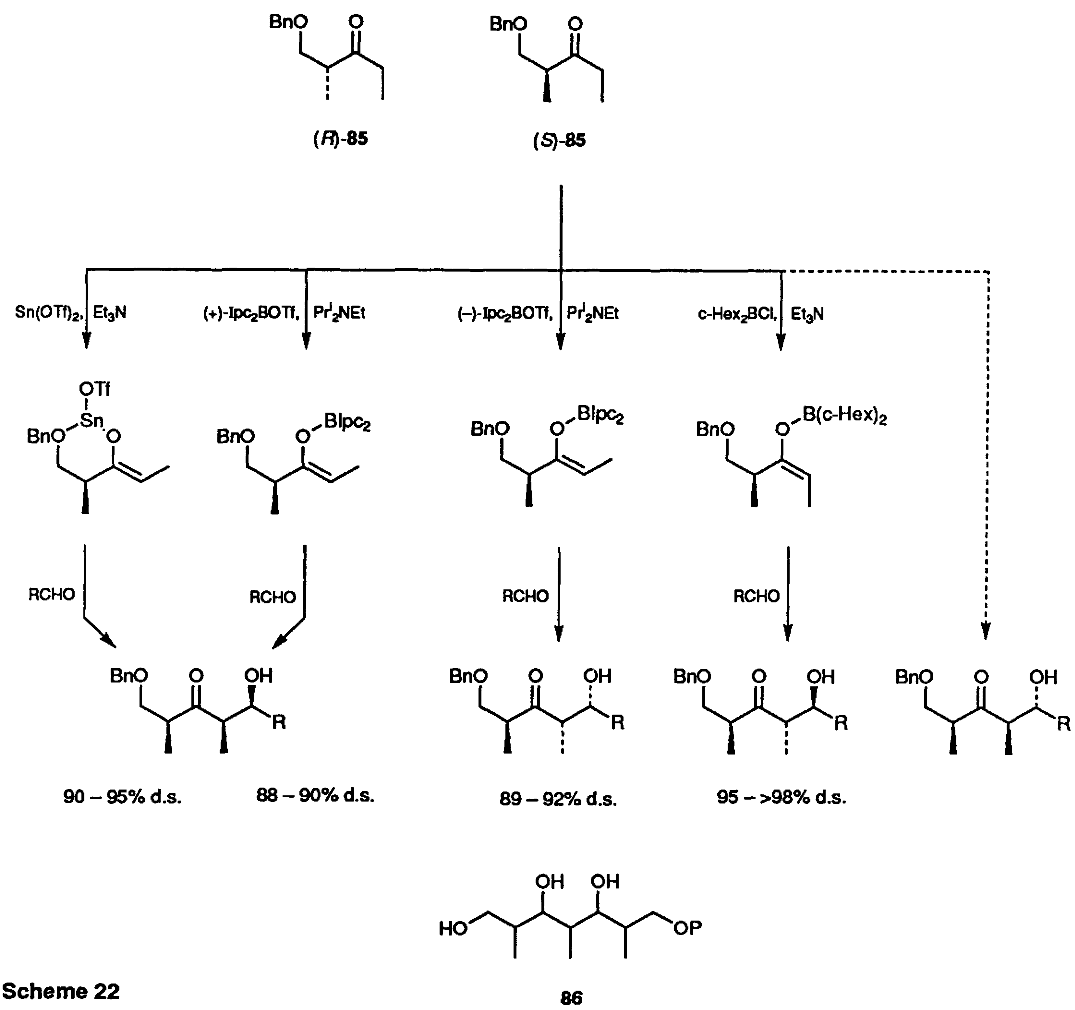


Scheme 20

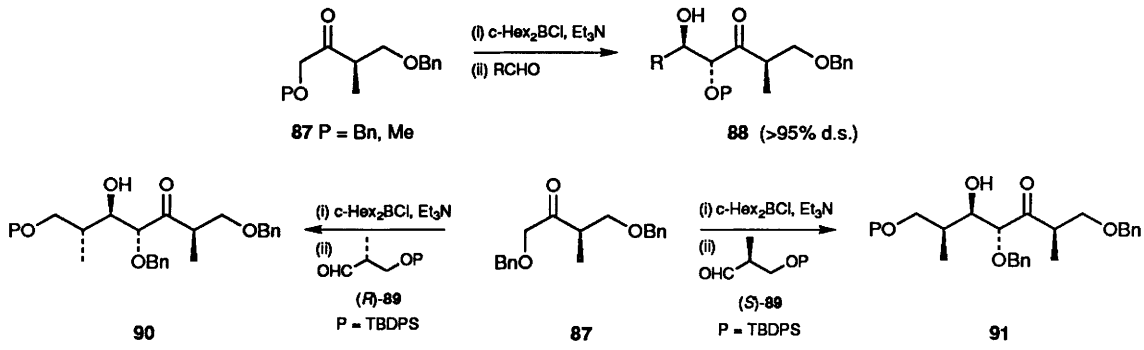


Scheme 21

Ketones (*R*)- and (*S*)-**85** have been introduced by Paterson *et al.* as versatile dipropionate equivalents for the construction of polyketide natural products (**Scheme 22**).[73] Three out of the four diastereomeric aldol adducts can be obtained selectively for any aldehyde by using appropriate boron[76,77] or tin(II) enolates.[78] The chiral ketones **85** have been widely used in the synthesis of complex polypropionate targets with the majority of the stereocentres being introduced by appropriate asymmetric aldol reactions.[79] Induction by these centres may then influence the selectivity of subsequent reactions: selective access to all possible (32) stereoisomers of the stereopentad sequence **86** may be achieved by



Scheme 22

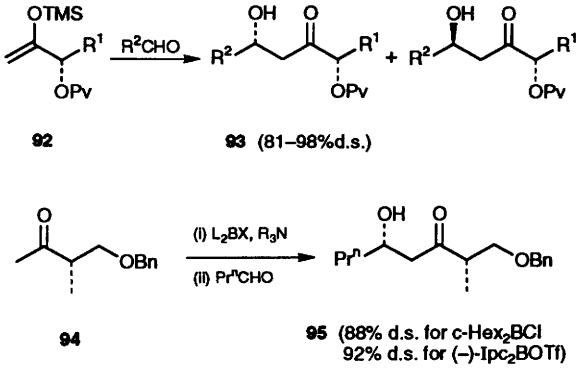


Scheme 23

stereoselective reduction and hydroboration of the appropriate aldol adducts of **85** and methacrolein.[80]

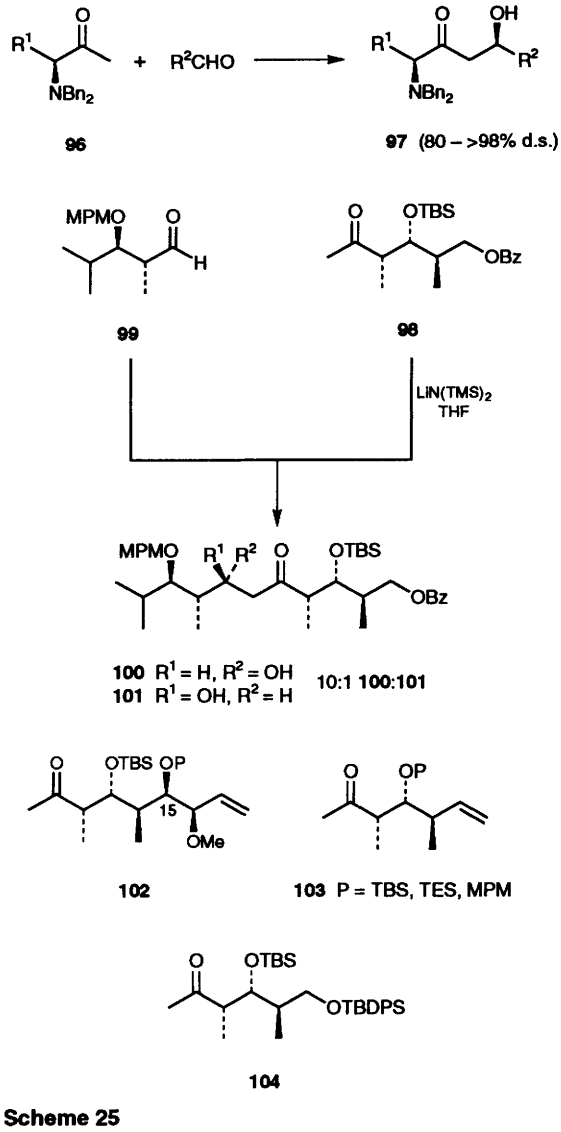
The *anti* aldol reactions of chiral alkoxymethyl ketones have also been studied.[81] Simple aldehydes react with the *E*-enol borinate of **87** to give adduct **88** (**Scheme 23**). The enolate exhibits high π-facial selectivity in its reactions with (*R*)- and (*S*)-**89** overriding any Felkin–Anh type influence from the aldehyde stereocentre to give the respective adducts **90** and **91** with 80% (mismatched) and 95% (matched) diastereoselectivity. This approach has been used in the synthesis of a polypropionate fragment of rapamycin.

As in other approaches to asymmetric aldol reactions, methyl ketone aldols often provide a greater challenge than ethyl or higher alkyl ketones. The silyl enol ethers **92** of α-pivaloyloxy ketones react with aldehydes in the presence of a Lewis acid with good selectivity for **93**,[82] which has been used in the synthesis of ipsenol (**Scheme 24**).[83] The chiral methyl ketone **94** undergoes boron-mediated aldol reactions to give predominantly **95** with useful levels of induction, which can be further enhanced by using appropriate Ipc ligands.[77]



Scheme 24

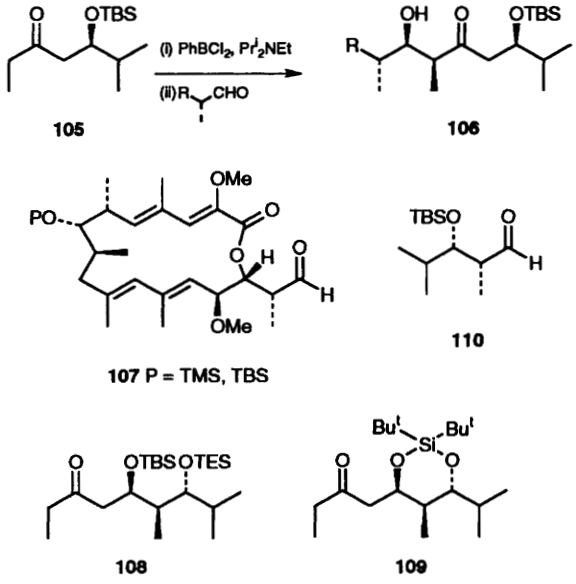
In certain cases, the key to obtaining useful levels of selectivity in α-chiral methyl ketone aldol reactions appears to be additional chelation by a suitably positioned heteroatom. For example, the lithium enolates of α-(*N*,*N*-dibenzylamino)alkyl methyl ketones **96** add to aldehydes with high selectivity in favour of **97** (**Scheme 25**).[84] Remote chelation has also been shown to play a role in determining the stereoselectivity of methyl ketone aldol reactions. During studies on the synthesis of bafilomycin A_1, Roush *et al.* found that methyl ketone **98** underwent a selective addition to aldehyde **99**, to yield **100** and **101**, only as its lithium enolate and in the absence of chelating solvent additives.[85] Further studies[86]



Scheme 25

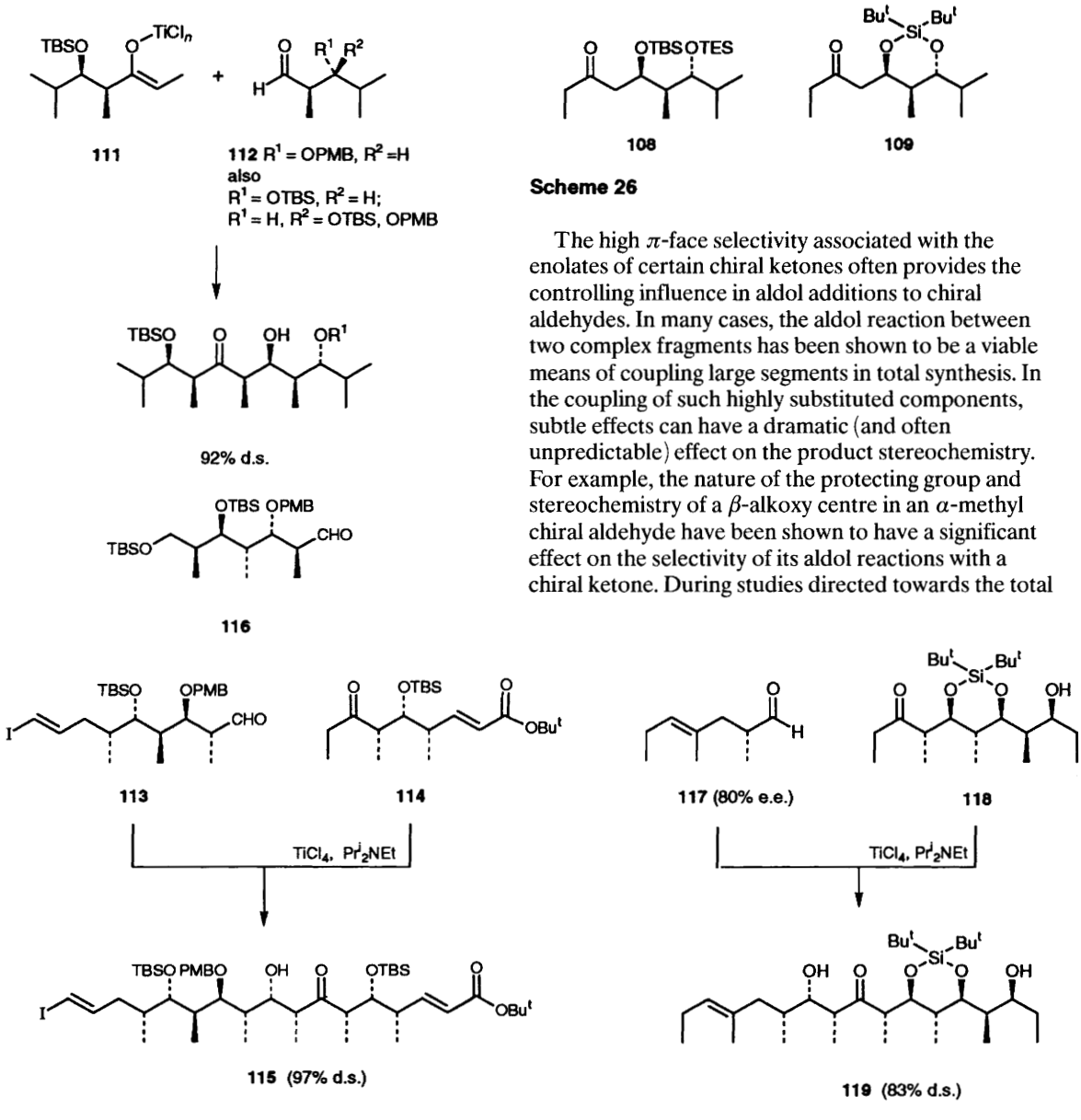
indicated that this selectivity was probably due to chelation by the C_{15} alkoxy substituent, with ketones of type **102** (P = MOM) reacting selectively (8:1), whilst those of type **102** (P = TES), **103**, and **104** gave little selectivity (1.2:1–3:1). However, these chelation effects appear to be insignificant in the aldol reactions of the corresponding chlorotitanium enolates, with **102** (P = TES, Bz) undergoing highly selective (≥ 96% d.s.) reactions.

Recent work by the Evans group has shown that asymmetric induction by a β-chiral centre in the ketone may also play a role in certain substrates. The aldol additions of α-unsubstituted-β-silyloxy ethyl ketones to α-methyl aldehydes have been studied as part of a synthetic approach to bafilomycin A_1 (**Scheme 26**).[87] Best results were obtained with the enol borinate prepared using dichlorophenylborane.[88] Ketone **105** reacted with high selectivity in favour of **106** (87% d.s. with Pr^{i}CHO, 79% d.s. with **107**). However, the nature of the silyl protecting group in the ketone proved crucial. Low selectivity was observed with **108** whilst silylene-protected **109** gave excellent diastereoselection (> 99:1 for Pr^{i}CHO and **110**, > 95:5 for **107**).



Scheme 26

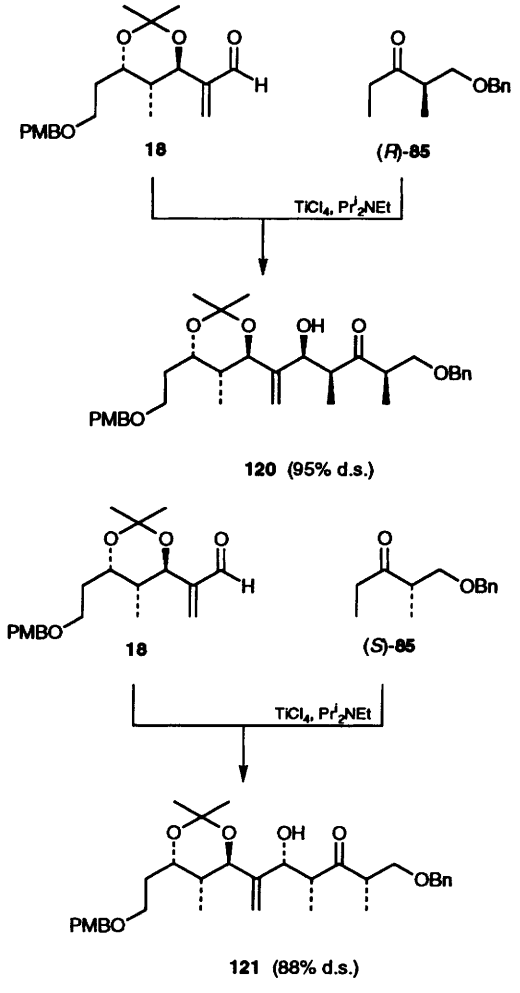
The high π-face selectivity associated with the enolates of certain chiral ketones often provides the controlling influence in aldol additions to chiral aldehydes. In many cases, the aldol reaction between two complex fragments has been shown to be a viable means of coupling large segments in total synthesis. In the coupling of such highly substituted components, subtle effects can have a dramatic (and often unpredictable) effect on the product stereochemistry. For example, the nature of the protecting group and stereochemistry of a β-alkoxy centre in an α-methyl chiral aldehyde have been shown to have a significant effect on the selectivity of its aldol reactions with a chiral ketone. During studies directed towards the total



Scheme 27

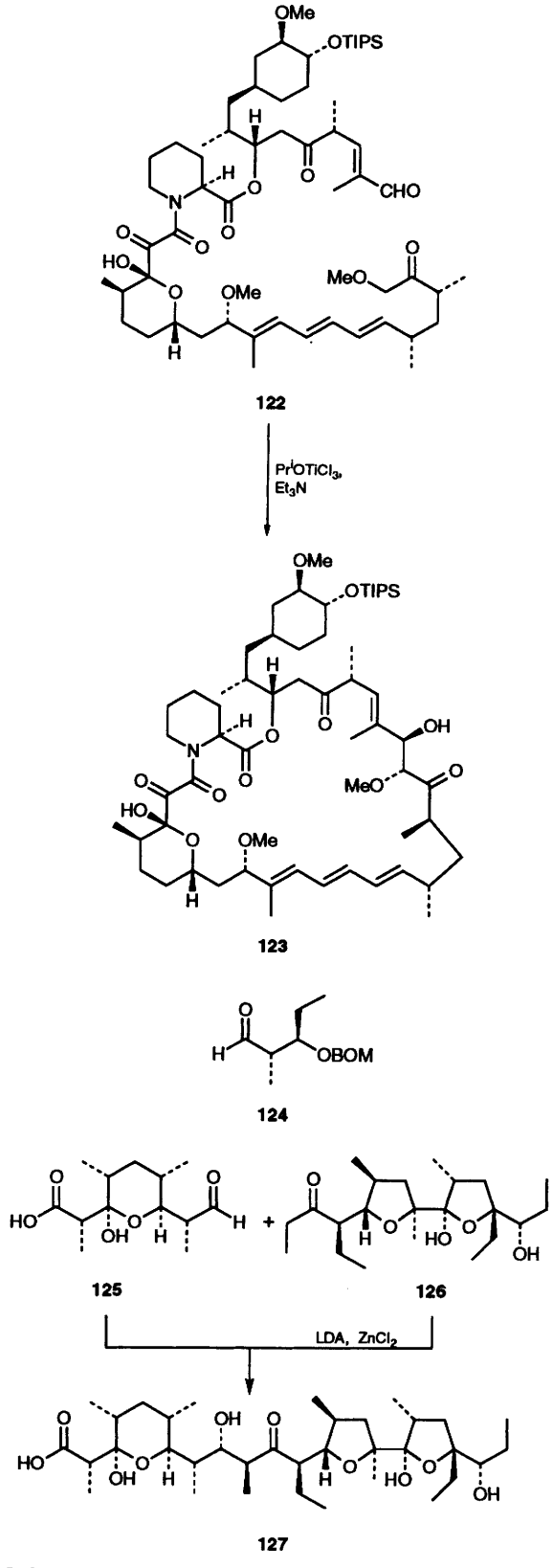
synthesis of rutamycin B, Evans *et al.* found that only the coupling of **111** and **112** proceeded with high diastereoselectivity (**Scheme 27**).[49]
The corresponding titanium-mediated coupling of fragments **113** and **114** also proceeded with high selectivity to give **115** despite apparently constituting a mismatched reaction.[89] Similar selectivity (> 93:7) has been observed by White *et al.* with the closely related aldehyde **116**.[90] A related mismatched aldol coupling between **117** and **118**, reported by Paterson *et al.*, proceeds with high diastereoselectivity to give adduct **119**, leading to the stereocontrolled synthesis of denticulatin B.[91]

The titanium-mediated aldol addition of the ketones (*R*)- and (*S*)-**85** to aldehyde **18** have also been explored (**Scheme 28**).[21] Unexpectedly high diastereoselectivities were obtained based on the low intrinsic facial biases of the two reactants. Thus, the matched pair gave adduct **120** with 95% d.s., while the mismatched pair gave **121** with 88% d.s. Here the chlorotitanium enolate from (*S*)-**85**, which shows a small preference (*ca.* 2:1) for *re*-face attack on aldehydes, completely overrides the low (*ca.* 70:30) *si*-facial bias of **18**. These results demonstrate that the accurate prediction of the product stereochemistry in such complex coupling situations remains largely elusive.



Scheme 28

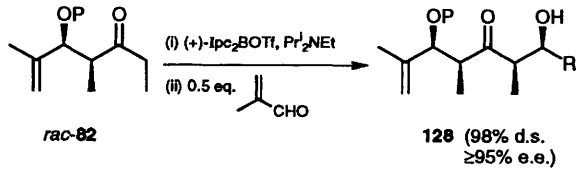
Frequently, the selection of the metal in the enolate has a significant effect on the stereochemical course of the aldol reaction. During studies on an aldol-macrocyclization approach to rapamycin (**Scheme 29**), Danishefsky *et al.* found that only a



Scheme 29

titanium-mediated reaction of **122** provided the desired product **123**, albeit in low yield (11%), despite investigating lithium, boron, tin, zinc, zirconium, and cerium enolates as alternatives.[92] Martin *et al.* have noted that the diastereoselectivity of the aldol reactions of α-methyl aldehyde **124** with α-chiral ethyl ketones is dependent on the nature of the metal counter-ion.[93] Similarly, Evans *et al.* completed the synthesis of ferensimycin B by the addition of aldehyde **125** to the zinc enolate of **126** to give **127** in preference to the lithium- or magnesium-mediated reactions.[94]

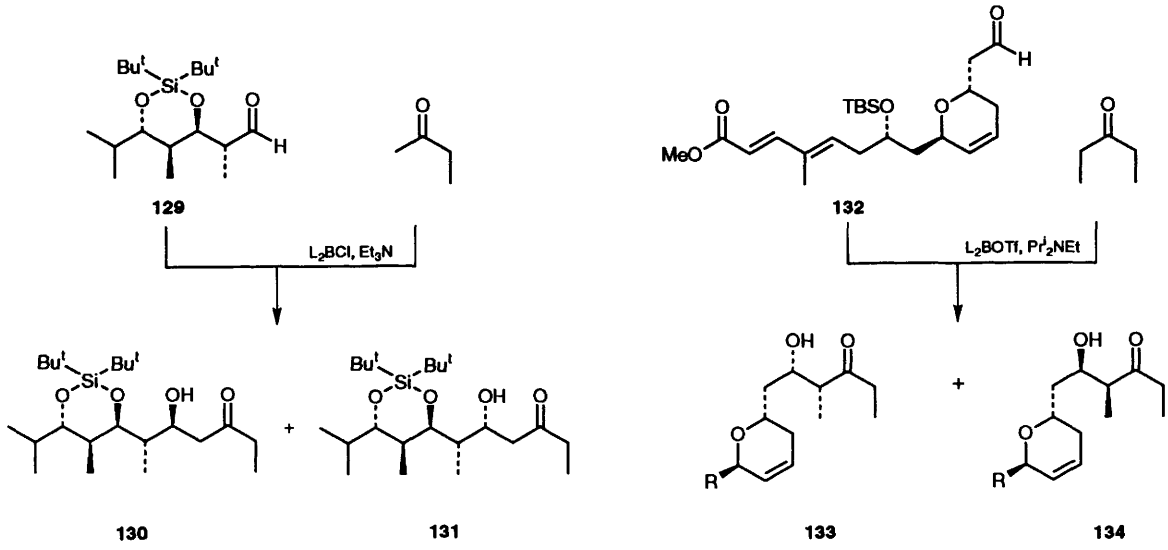
The Ipc boron aldol reaction has been used in double asymmetric induction situations, in enhancing substrate-based stereoselectivity in the aldol reactions both of chiral ketones with achiral aldehydes and of achiral ketones with chiral aldehydes. In the former case, kinetic resolution in the aldol reactions of certain ethyl ketones has been demonstrated, where *syn* aldol **128** was obtained with high enantio- and diastereo-selectivity by starting from *rac*-**82** (**Scheme 30**).[95] This was converted into an ansa chain segment for the synthesis of rifamycin S.



rac-**82** — **128** (98% d.s. ≥95% e.e.)

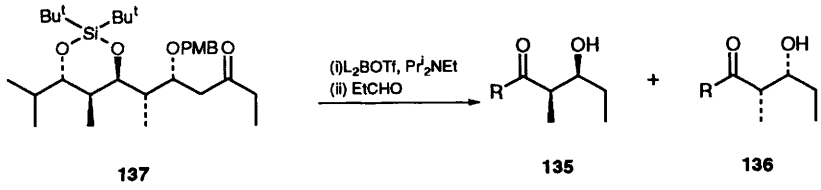
Scheme 30

In studies directed towards the synthesis of swinholide A, Paterson *et al.* examined the Ipc-mediated boron aldol reactions of methyl and ethyl ketones with chiral α-methyl and β-alkoxy aldehydes (**Scheme 31**).[96] The anti-Felkin selectivity obtained in enol borinate addition to **129** could be increased to > 95% d.s. for **130** by using the appropriate Ipc_2BCl reagent. Note that use of the enantiomeric reagent failed to reduce the substrate-induced face selectivity from this particular aldehyde. β-Alkoxy aldehyde **132** showed significant π-facial bias in favour of **134** in its reactions with *Z*-enol borinates, which could be overturned using (+)-Ipc_2BOTf. In a further example, reagent



	130 : 131
c-Hex_2BCl	70 : 30
(+)-Ipc_2BCl	>95 : <5
(–)-Ipc_2BCl	77 : 23

	133 : 134
Bu^n_2BOTf	16 : 84
(+)-Ipc_2BOTf	75 : 25



	135 : 136
Bu^n_2BOTf	33 : 67
(+)-Ipc_2BOTf	88 : 12
(–)-Ipc_2BOTf	8 : 92

Scheme 31

control was demonstrated for the selective formation of either **135** or **136** from the ethyl ketone **137**.

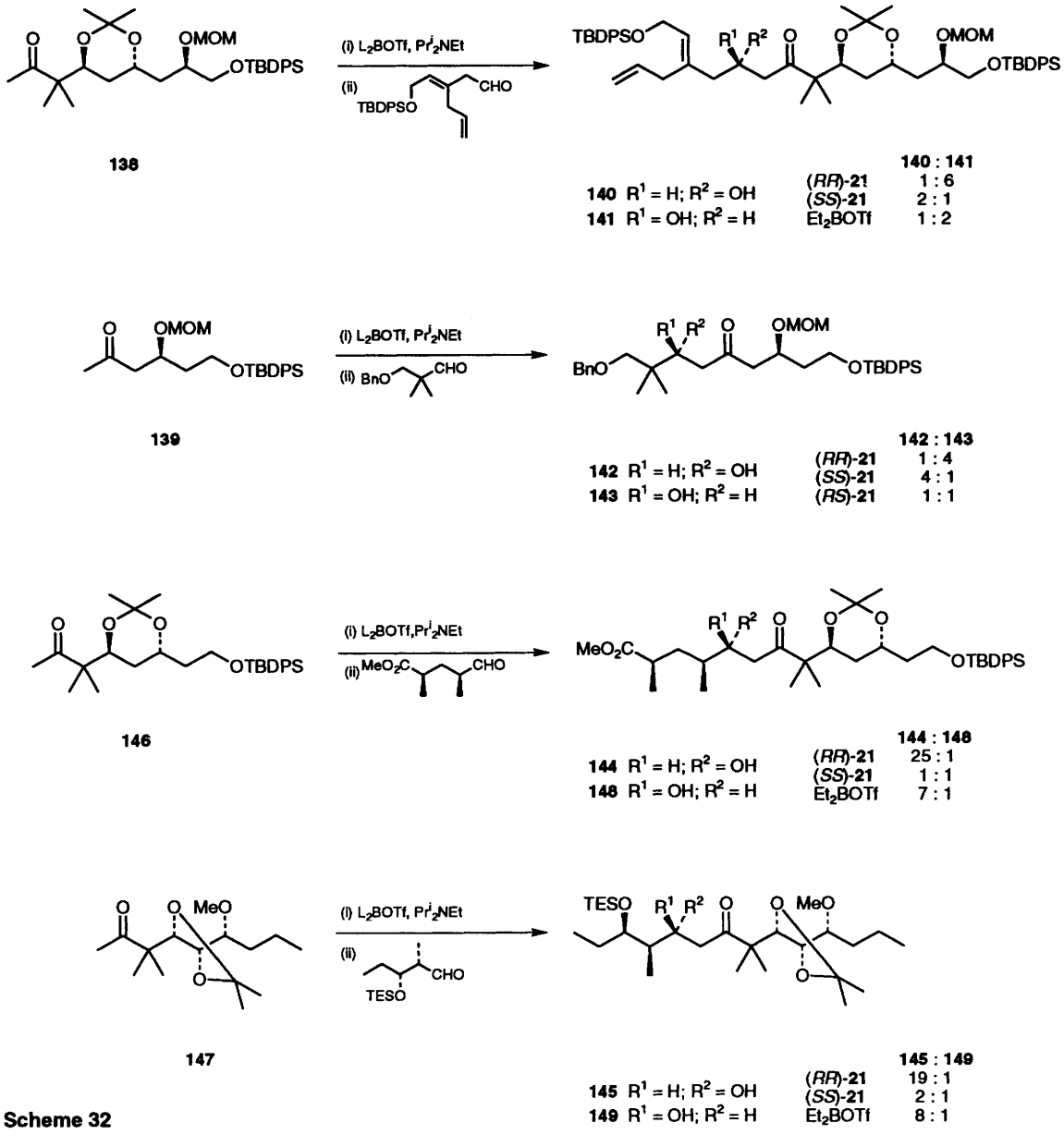
Work by Masamune *et al.* on the bryostatins and calyculins has provided examples of both double and triple asymmetric induction. The use of both enantiomers of boron triflate **21** in the coupling reactions of chiral aldehydes and chiral ketones leads to significant variation in selectivity compared to the corresponding achiral boron reagent mediated additions.[97] In the aldol coupling of methyl ketones **138** and **139** with achiral aldehydes a useful level of reagent control is possible (**Scheme 32**).
The substrate-based selectivity in favour of **144** and **145** in the aldol coupling of chiral methyl ketones **146** and **147** with chiral aldehydes can be enhanced by use of the appropriate chiral reagent, (*RR*)-**21**. However, in these triple asymmetric induction situations, the chiral reagent is largely ineffective for overturning the substrate-based selectivity.

4 Asymmetric induction in Mukaiyama aldol reactions from the Lewis acid

The Lewis acid mediated addition of a silyl enol ether to an aldehyde or ketone, the Mukaiyama aldol reaction, came to prominence as a useful asymmetric reaction in the 1980s. While the use of chiral silyl enol ethers and α-chiral aldehydes has been extensively explored,[13,98] the opportunities presented by variation of the Lewis acid catalyst have only been exploited more recently. Work has been focused on the design of new chiral Lewis acids for asymmetric Mukaiyama reactions with emphasis being placed on the ability of reagents to act in sub-stoichiometric quantities.

4.1 Boron Lewis acids

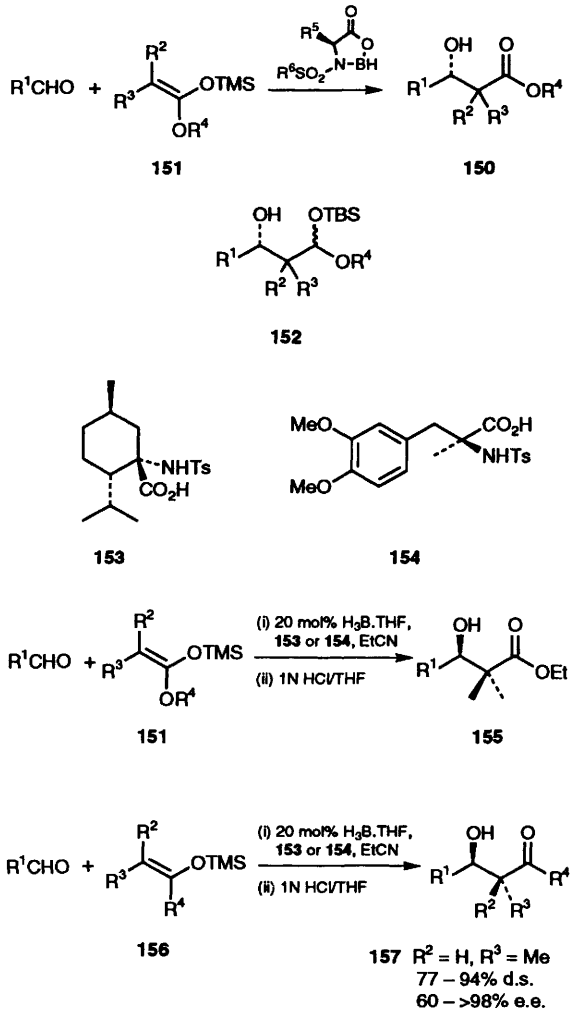
Kiyooka *et al.* have used chiral boron Lewis acids prepared from the sulfonamides of α-amino acids to



Scheme 32

promote the reaction of silyl ketene acetals and aldehydes (**Scheme 33**). Initial studies[99] demonstrated that a variety of boranes, when used stoichiometrically, promoted the formation of β-hydroxyesters **150** in 85–93% e.e. from silyl ketene acetal **151** ($R^2 = R^3 = Me$, $R^4 = Et$). Use of the analogous TBS ketene acetal gave improved enantioselectivities (92–98% e.e.) but led to the formation of acetal **152**, apparently from the reduction of an intermediate ester by hydride transfer from the borane. Use of nitroethane as solvent in place of dichloromethane allowed the catalyst to be employed in sub-stoichiometric quantities without any reduction in enantioselectivity.[100] β-Hydroxyesters **150** were obtained in 81–96% e.e. in reactions promoted by 20 mol% of borane ($R^5 = Pr^i$, $R^6 = p\text{-}NO_2Ph$). An alternative approach employed by Masamune *et al.* uses a boron Lewis acid prepared from α,α-disubstituted glycine arenesulfonamides **153** and **154** in the reactions of **151** ($R^2 = R^3 = Me$, $R^4 = Et$) to give β-hydroxyesters **155** of > 97% e.e. with typical primary aldehydes and 84–96% e.e. with secondary aldehydes.[101]

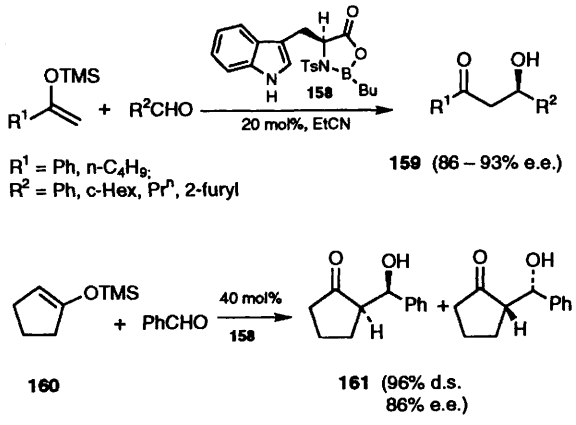
This approach can be extended to unsubstituted and monosubstituted ketene acetals[102] which give lower enantio-[99] or diastereo-selectivity[103] for similar



Scheme 33

Lewis acids. When ligand **153** was used to form the chiral catalyst in addition of unsubstituted ketene acetals **156** ($R^2 = R^3 = H$, R^4 = SEt, SBu^t, OPh) with a variety of aldehydes, the reactions proceeded with high enantioselection (81–93% e.e.). The reaction of monosubstituted ketene acetals **156** ($R^2 = H$, $R^3 = Me$, R^4 = SEt, SBu^t, OPh) with aromatic and α,β-unsaturated aldehydes proceeded well in the presence of ligand **153**, whilst **154** was found to be superior for primary aldehydes. In all cases *anti* products **157** were favoured† with both isomers being formed with good enantioselection.

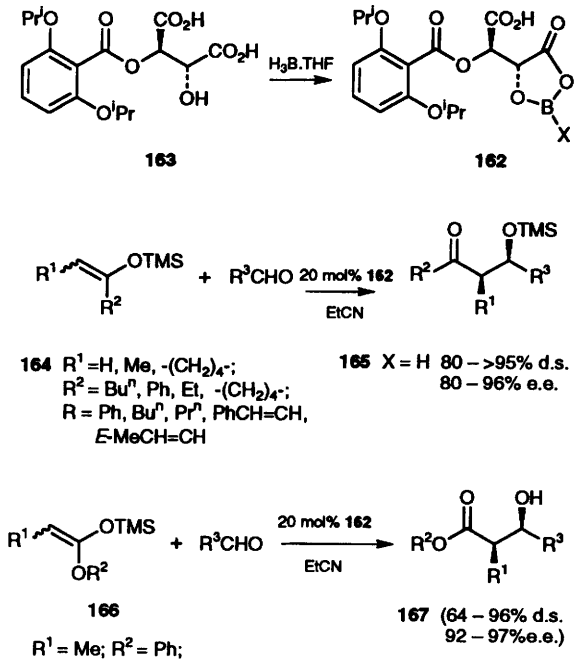
The tryptophan-derived oxazaborolidine **158** has been employed by Corey *et al.* as a catalyst in the asymmetric Mukaiyama aldol reaction (**Scheme 34**).[104] This catalyst performed best with terminal trimethylsilyl enol ethers derived from methyl ketones and a range of aldehydes giving **159**. The more substituted silyl enol ether **160** was found to react with benzaldehyde in the presence of 40 mol% of **158** to give predominantly **161**. However, silyl ketene acetals were found to react with poor enantioselectivity under these catalytic conditions.



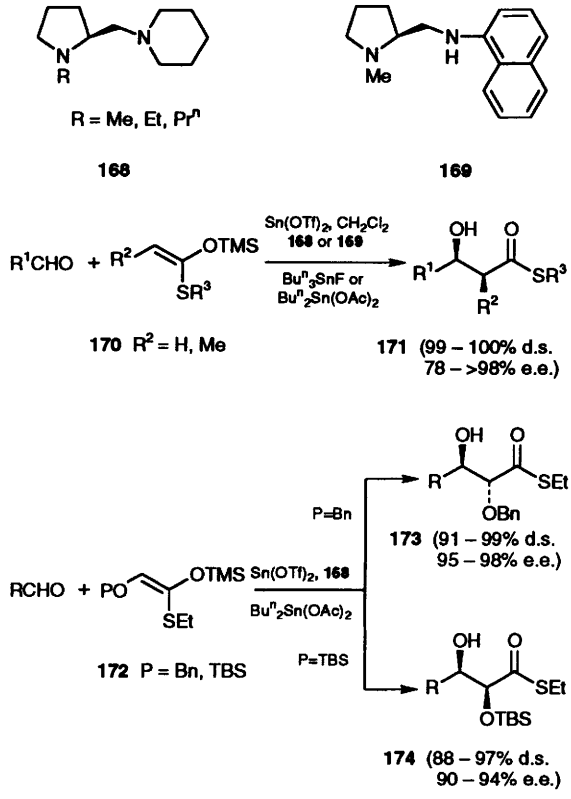
Scheme 34

The chiral (acyloxy)borane complex **162** (X = H), derived *in situ* from tartaric acid derivative **163** and $H_3B.THF$ (**Scheme 35**) promotes the Mukaiyama aldol reaction of silyl enol ethers and ketene acetals with various aldehydes when present in catalytic amounts (20 mol%). Using this catalyst system, Yamamoto *et al.* have established that silyl enol ethers **164** derived from ketones lead to aldol adducts **165** with high diastereo- and enantio-selectivity.[105] Improved diastereoselectivities (91–99% d.s.) were observed in the analogous reactions of **162** (X = 3,5-bistrifluoromethylphenyl) with ethyl ketones, whilst **162** (X = *o*-phenoxyphenyl) led to increased enantioselectivity (88–94% e.e. *versus* 80–85% e.e.) with methyl ketones.[106] Only phenyl ester derived silyl ketene acetals **166** gave reasonable levels of diastereoselectivity in the formation of **167**, with α,β-unsaturated aldehydes providing the best results.[103]

†Note that this *anti* selectivity is in contrast to the *syn* selectivity observed by Yamamoto *et al.*.[105]



Scheme 35



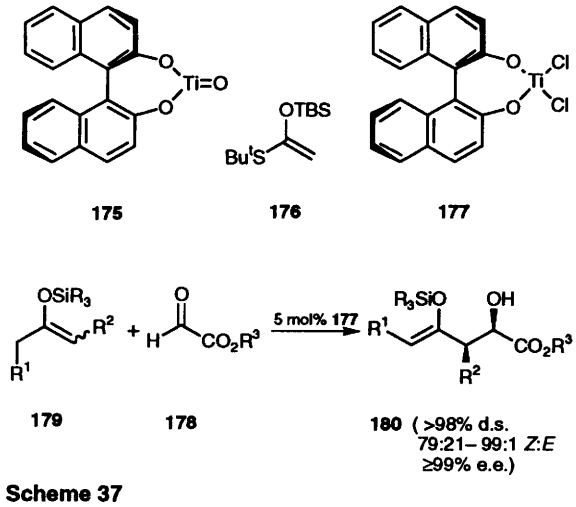
Scheme 36

4.2 Tin(II) Lewis acids

The use of a tin(II) triflate/diamine based system as a chiral promoter has been the subject of extensive study by Mukaiyama and Kobayashi *et al.* (**Scheme 36**). Early work involved the use of stoichiometric amounts of a three-component system consisting of tin(II) triflate, tributyltin fluoride,[107] or dibutyltin diacetate[108] and diamine **168** or **169**. This was shown to promote the reaction of aldehydes with ketene silyl acetals derived from acetic acid esters[109] and thioesters of acetic and propionic acids.[110] In all cases, the reactions proceeded with high enantioselectivity. The enol silanes of propionate thioesters **170** reacted with high diastereoselectivity to give the *syn* isomer **171**. Selective synthesis of both *syn* and *anti* α,β-dihydroxyester derivatives can be achieved by variation of protecting group, where **172** (P = Bn) gives *anti* products **173**[111] whilst the corresponding TBS ether **172** (P = TBS) gives *syn* products **174**.[112] Catalyst turnover in these reactions occurs in propionitrile[113] in the presence of 20 mol% tin(II) triflate and chiral diamine. Enol silanes derived from both acetate[114] and propionate[115] thioesters react with a range of aldehydes in a highly enantio- and diastereo-selective manner (68–97% e.e., 86:14–100:0 *syn*:*anti*). The selectivity of the reaction of α-chiral aldehydes with thioacetate derived enol silanes has also been investigated.[116] It was found that the stereochemistry of the aldol addition is almost completely controlled by the chiral catalyst regardless of the inherent diastereofacial preference of the aldehyde with ≥ 94% d.s. in all cases. These reactions provide a highly selective approach to the asymmetric synthesis of polyoxygenated 'sugar' derivatives from achiral starting materials.[117]

4.3 Other Lewis acids

Although titanium(IV) chloride is one of the most commonly used Lewis acid catalysts in Mukaiyama aldol reactions, relatively few examples of chiral titanium derived catalysts exist. Binapthol-derived catalysts have been employed, where the oxide **175** catalyses the addition of silyl enol ether **176** to α,β-unsaturated aldehydes (60–85% e.e., 20 mol% in toluene)[118] whilst the dichloro species **177** catalyses the addition of glyoxylates **178** to ketone silyl enol ethers **179**, giving **180** *via* an ene mechanism (**Scheme 37**).[119] The latter reactions proceed with high selectivity. The use of lanthanide derived catalysts has

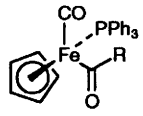


Scheme 37

also been explored with $Ln(dppm)_3$ and $Ln(fod)_3$ (Ln = Eu, Pr), inducing stereoselectivity in additions to α-chiral systems.[120]

5 Asymmetric induction by transition metal complexation

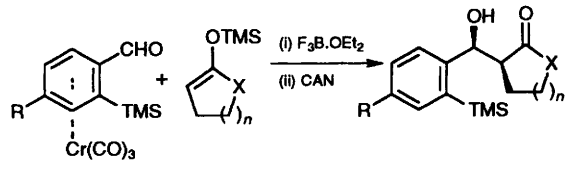
Metal complexation can provide asymmetry in either the aldehyde or enolate component in an aldol addition, with later decomplexation providing the free β-hydroxy carbonyl compound. Acyclic acyl iron complexes **181**, developed independently by the groups of Davies and Liebeskind, may be employed as ketone equivalents with their diethylaluminium and tin(II) enolates providing high, complementary, levels of π-face selectivity for acetate systems (R = Me).



181 R = Me, Et

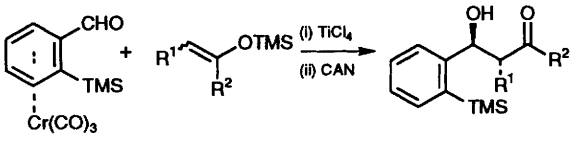
Aluminium and copper(I) enolates induce *anti* and *syn* selectivity respectively in propionate (R = Et) aldol reactions.[121] In reactions with chiral aldehydes, the high diastereofacial bias of the iron chiral auxiliary overrides the inherent selectivity of the aldehyde, allowing access to all possible diastereomers by variation of the auxiliary configuration and the enolate counter-ion.[122]

Tricarbonyl (η^6-arene) chromium complexes derived from substituted aromatic aldehydes are readily resolved,[123] giving access to enantiomerically pure aldehydes with potential for exceptional π-facial selectivity (**Scheme 38**).



182 R = H, OMe, Cl

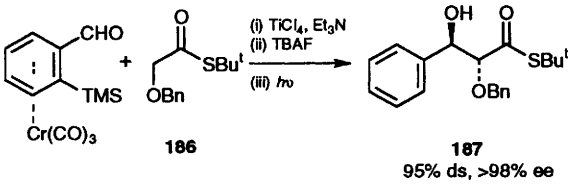
183 (n = 1,2,3;
X = CH_2 90 – >98% d.s.
X = O 85 – 90% d.s.
90 – >98% e.e.)



182

184 R^1 = Me, Et;
R^2 = SBu^t, SPh

185 (73 – 96% d.s.
92 – >98% e.e.)

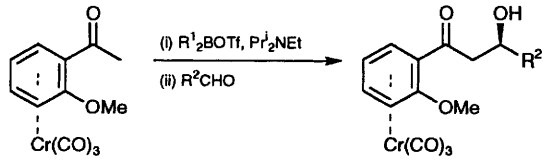


186

187
95% ds, >98% ee

Scheme 38

The boron trifluoride mediated reaction of *o*-trimethylsilyl benzaldehyde complexes **182** with cyclic silyl enol ethers[124] and ketene silyl acetals[125] leads to *syn* products **183**. The corresponding reaction of enol silanes with (+)- or (−)-**182** gives **183** or *ent*-**183** in high e.e.[126] The titanium tetrachloride mediated reaction of **182** (R = H), with enol silanes **184** proceeds with *anti* selectivity towards **185** irrespective of the initial double bond geometry.[127] Reactions with resolved **182** give products of high enantiomeric excess after metal decomplexation. This general approach has been applied to the synthesis of a taxol side chain analogue, where the titanium enolate of thioester **186** gave the *anti* product **187** ready for further elaboration.[128] Chromium complexation to an aromatic enolate component also influences aldol selectivity, where complex **188** undergoes aldol reactions *via* its enol borinate to give **189** (**Scheme 39**).[129]



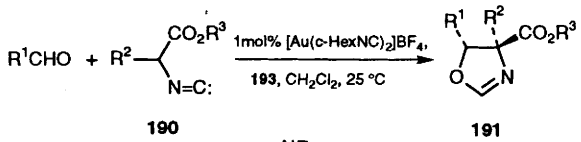
188

189 (86 – 95% d.s.)

Scheme 39

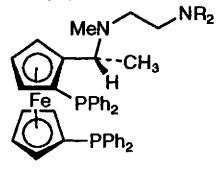
6 Aldol reactions of α-isocyanocarboxylates

The asymmetric aldol addition between isocyanoacetates **190** and aldehydes mediated by chiral gold(I) complexes was first reported in 1986.[130] The reaction proceeds with high diastereoselectivity to give *trans*-oxazolines **191** which may be converted into the corresponding *syn* β-hydroxy-α-amino acids **192** upon hydrolysis (**Scheme 40**). Detailed studies have been carried out on the effects of substitution patterns (R^1, R^2, R^3) within the substrates and on the nature of the terminal tertiary amino group in the ligand side chain of **193**, which is believed to play a key role in transition state coordination. The factors influencing gold(I) asymmetric aldol reactions (and their silver(I) counterparts) have recently been reviewed by Sawamura and Ito.[131]

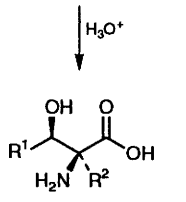


190

191



193



192

Scheme 40

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