REVIEW

The control of remote asymmetric centres *via* reduction of acyclic carbonyl functions

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1 Introduction

Perhaps one of the most challenging problems in organic synthesis is the creation of new stereogenic centres in acyclic systems. To this end, a number of excellent methods have been developed for the generation of proximal stereocentres (1,2- and 1,3-relationships) in conformationally flexible molecules, with a high level of relative asymmetric induction.[1] However, establishing correct relationships between stereogenic centres separated by more than one atom node, *i.e.* achieving 1,*n*-stereocontrol ($n = >3$), is more difficult, and general effective approaches for this strategy are few.[2,3] In recent years there has been notable success in tackling the stereoselective construction of molecules containing remote stereogenic centres. Methods have been developed to enable remarkably efficient remote asymmetric induction, with examples published to date reaching 1,14-diastereocontrol.[4c]

Instances of remote acyclic stereocontrol have been reported for a variety of synthetic transformations.[4–19] In this review, remote asymmetric induction involving hydride addition to carbonyl groups and, in particular, the use of boron complexes in controlling these reactions is summarised. To our knowledge, all reported instances of remote asymmetric induction in hydride reductions involve carbonyl functional groups.

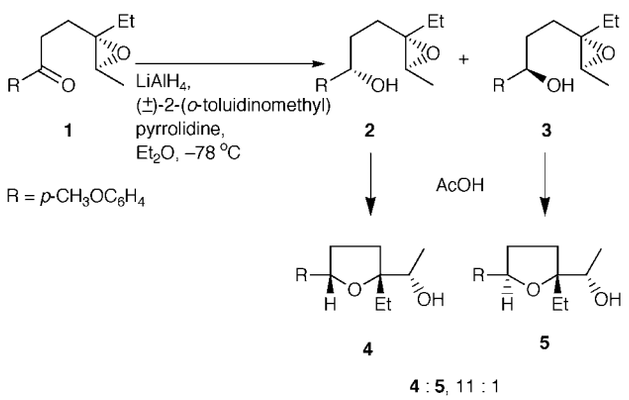
2 Hydride addition to carbonyl groups

The remote asymmetric reduction of carbonyl functional groups is an especially useful tool for the construction of optically active molecules, in particular, for the synthesis of ionophore, polyene and related macrolide antibiotics.[20]

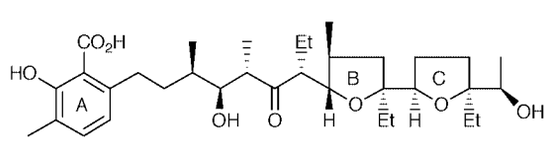
2.1 Early applications in natural product synthesis

In an early example of remote asymmetric induction, Kishi and co-workers achieved high 1,4-diastereocontrol in the reduction of an epoxy ketone **1** during studies directed towards polyether antibiotic synthesis[13a] (Scheme 1).

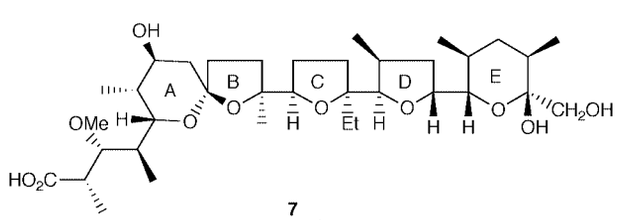
Reduction of keto epoxide **1** with lithium aluminium hydride in the presence of the diamine, (±)-2-(*o*-toluidinomethyl)pyrrolidine, afforded epoxide **2** as the major product. The stereoselectivity of the reaction was determined after acetic acid work-up, which produced tetrahydrofurans **4** and **5** (**4**:**5**, 11:1). Tetrahydrofuran **4** represents ring C of polyether antibiotics isolasalocid A **6** and monensin **7**.[21]



Scheme 1



6
isolasalocid A



7
monensin

Most methods used to construct molecules with remote stereogenic centres rely on chelate control or neighbouring group participation. Kishi suggested that coordination of aluminium to the epoxide and ketone oxygen atoms may explain the stereoselectivity observed in this reduction.

Matsumoto and co-workers subsequently exploited remote acyclic stereocontrol, employing both 1,3- and 1,5-asymmetric induction as key steps in the total synthesis of (+)-pedamide **9**,[22] one of the tetrahydropyran moieties of (+)-pederine **8**, a potent insect poison isolated from *Paedrus fuscipes*. The first total synthesis of **8**[23] was achieved by coupling amide **9** and (+)-acetylpederic acid **10** *via* an *N*-(1-methoxyalkyl)amide linkage (Scheme 2).

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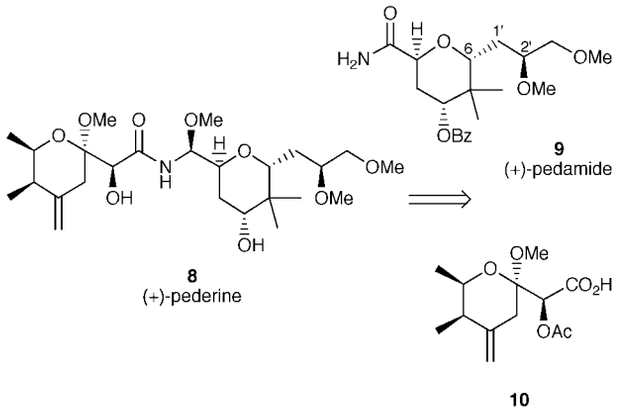
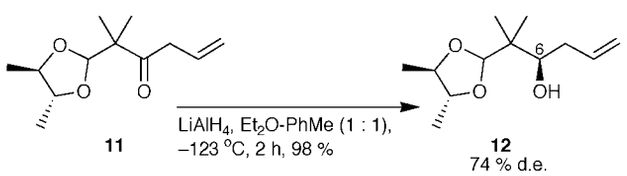


Scheme 2

Efficient 1,5-asymmetric induction was achieved by reduction of optically-active ketone **11** with $LiAlH_4$ in an ether–toluene mixture (1:1) at −123 °C. The alcohol **12**, possessing the required (6*R*)-stereochemistry was obtained in 74% diastereomeric excess (Scheme 3).



Scheme 3

Many effective strategies for stereocontrolled reactions in acyclic systems rely on metal-mediated cyclic transition states to limit the number of degrees of freedom available to the substrate, and therefore allow facial selectivity in the addition of nucleophiles. In this case, a fairly congested transition state which involved coordinated Li^+, with hydride attack from the least hindered face of the carbonyl group, was proposed to explain the selectivity observed in the reduction of **11** (Fig. 1).

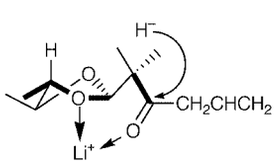
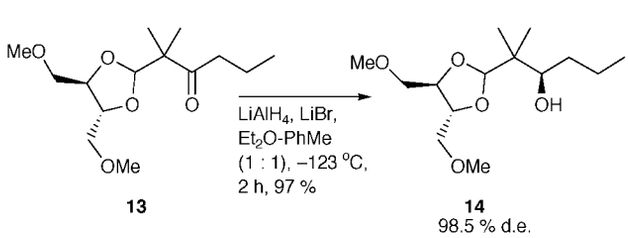


Fig. 1 The chelate involved in the reduction of **11**.

Further studies revealed increased optical yield (98.5% de) upon use of a different chiral source [(2*R*,3*R*)-1,4-dimethoxybutane-2,3-diol, in the presence of one equivalent of lithium bromide (Scheme 4)]. A highly organised rigid chelate structure was again proposed to explain this excellent selectivity, the nucleophile approaching from the less hindered face of the prochiral carbonyl function (Fig. 2).



Scheme 4

In ensuing studies, a reversal of stereoselectivity in the reduction of ketone **15a** with lithium aluminium hydride in the presence of one equivalent of magnesium bromide (Scheme 5), was produced [24] (Table 1, compare entries 1–3). Given this result, the reduction of a range of C_2-symmetric acetalketones **15b–e** was investigated. As expected, in all cases increased optical yield was observed upon addition of lithium bromide, confirming the importance of interaction between Li^+ and the substrate in this 1,5-asymmetric induction. However, it was found that the presence of magnesium bromide markedly influenced the reduction.

Table 1 Reduction of homochiral ketones **15a–e** with $LiAlH_4$

Entry	Ketone	R	Salt	**16**:**17**	De (%)
1	**15a**	H	—	80:20	60
2	**15a**	H	LiBr	83:17	66
3	**15a**	H	$MgBr_2$	22:78	56
4	**15b**	Ph	—	71:29	42
5	**15b**	Ph	LiBr	72:28	44
6	**15b**	Ph	$MgBr_2$	18:82	64
7	**15c**	OPh	—	67:33	34
8	**15c**	OPh	LiBr	72:28	44
9	**15c**	OPh	$MgBr_2$	9:91	82
10	**15d**	OBn	—	77:23	54
11	**15d**	OBn	LiBr	84:16	68
12	**15d**	OBn	$MgBr_2$	81:19	62
13	**15e**	OMe	—	83:17	66
14	**15e**	OMe	LiBr	92:8	84
15	**15e**	OMe	$MgBr_2$	79:21	58

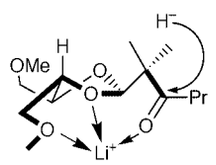
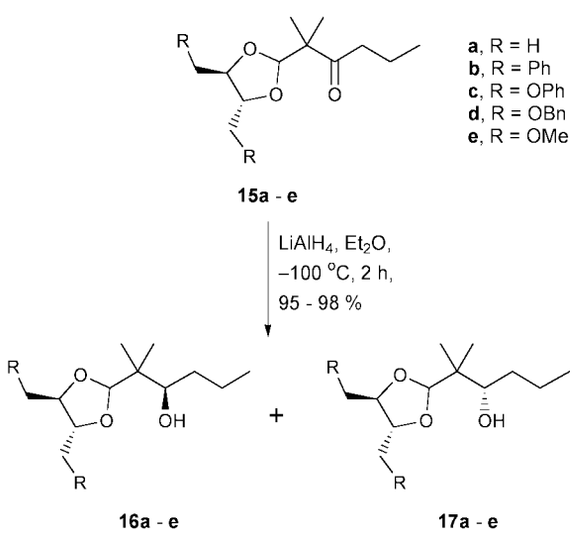


Fig. 2 The chelate involved in the reduction of **15e**.



Scheme 5

The reduction of **15b** and **15c** with $LiAlH_4$ in the presence of $MgBr_2$ again resulted in reversal of stereoselectivity, yielding the corresponding (*S*)-alcohols **17b** and **17c**, as the major epimers in good diastereomeric excess (Table 1, entries 6 and 9). Yet reversal of selectivity was *not* observed for the reduction of acetalketones **15d** and **15e** (Table 1, entries 12 and 15).

Following molecular mechanics calculation, and given the coordination geometry of the metals, transition states **18**, **19** and **20**, in which hydride attacks from the less hindered carbonyl face, were proposed to explain the selectivity of the reduction (Fig. 3). For bis(phenoxymethyl)dioxolane **15c** the reduction was thought to proceed *via* intermediate **19**. It was proposed that the steric hindrance of the phenoxy group hampered coordination of the metal cation to the dioxolane side-chain, hence explaining the reversal of selectivity observed for the reduction in this case.

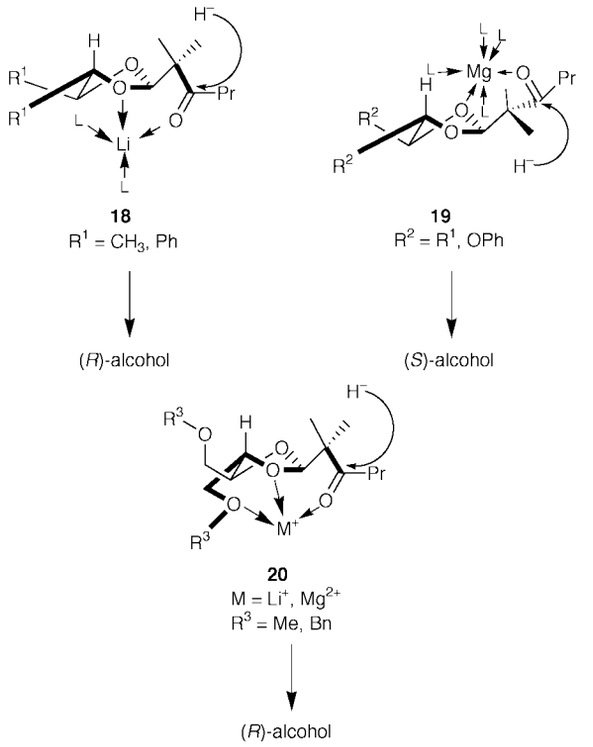
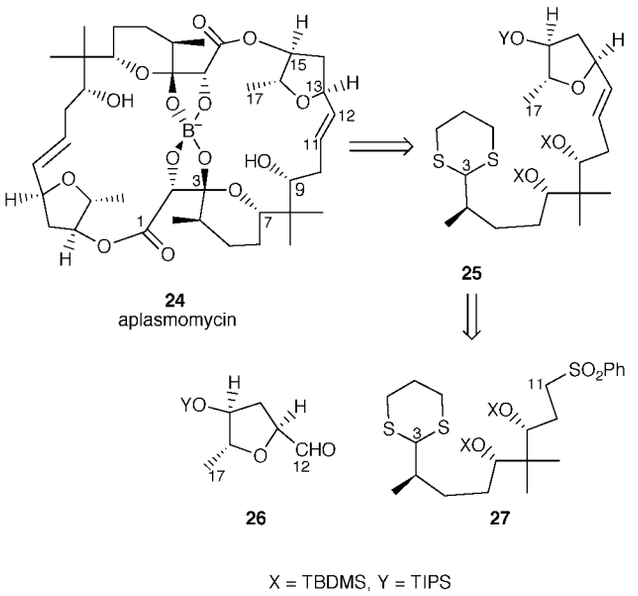


Fig. 3 Proposed chelates involved in the reduction of **18**, **19** and **20**.

In contrast to this 1,5-diastereocontrol, a more sterically hindered reagent resulted in more selective induction in the 1,3-hydride reduction of the β-alkoxy ketone **21** (Scheme 6).

The *syn*-alcohol **22** which possessed the desired (*S*)-configuration at the new chiral centre (C2′) was obtained as the major epimer. The highest selectivity (dr = >10 : 1) was obtained using $LiAlH(OtBu)_3$ in ether at −78 °C (Scheme 6). In this case, the selectivity of the reduction was explained by assuming a stable conformation **23**, with nucleophilic attack occurring at the less hindered carbonyl face. It was proposed that the steric bulk of the hydride reagent, rather than the interaction between metal cation and substrate, played an important role in this 1,3-asymmetric reduction.

In 1987 analogous methodology was successfully applied by Matsuda *et al.* to the stereoselective synthesis of the C3–C17 segment **25** of aplasmomycin **24**,[25] a boron-containing ionophoric antibiotic isolated from a marine-derived strain of *Streptomyces griseus* (Scheme 7). This synthesis involved the construction of aldehyde **26** (C12–C17) and dithiane **27** (C3–C11) based on 1,3- and 1,5-stereocontrolled reductions as key steps (Scheme 8) and their subsequent connection through a *trans*-double bond to furnish **25**. This C3–C17 segment **25** was a key intermediate used by Corey and co-workers in their total synthesis of aplasmomycin **24**.[26]



Scheme 7

Acetal auxiliaries have been used for a range of synthetic transformations.[27] In the above instance of 1,5-remote asymmetric induction described by Matsumoto and co-workers,[22–25] the cyclic acetal unit provides rigidity, hence facilitating the transfer of stereochemical information from the pre-existing stereocentre to the remote prochiral centre.

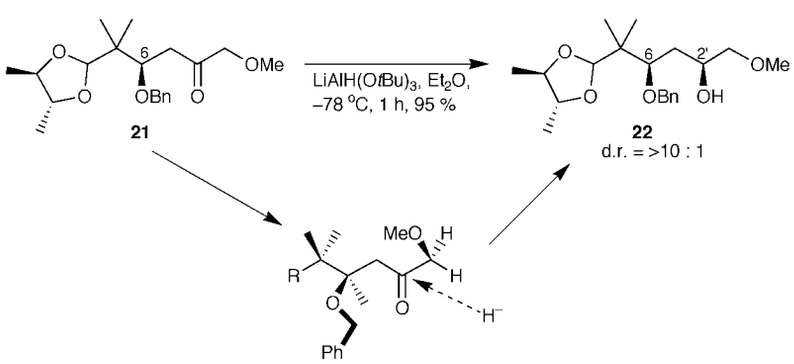
2.2 1,5-/1,6-Asymmetric induction in the reduction of acyclic hydroxy ketones

Maryanoff and co-workers first described a more recent example of high 1,5-asymmetric induction involving hydride reduction of a ketone in 1994.[28] In this example, the substrates are devoid of any conformationally rigidifying structural features, such as a cyclic array or an alkene group. A number of reducing agents were investigated for achieving stereoselective reduction of the conformationally flexible acyclic δ-hydroxy ketone **30a** (Scheme 9). The diol **31a** was a key intermediate required for the synthesis of **29**, an analogue of the cardiovascular drug nebivolol **28**.

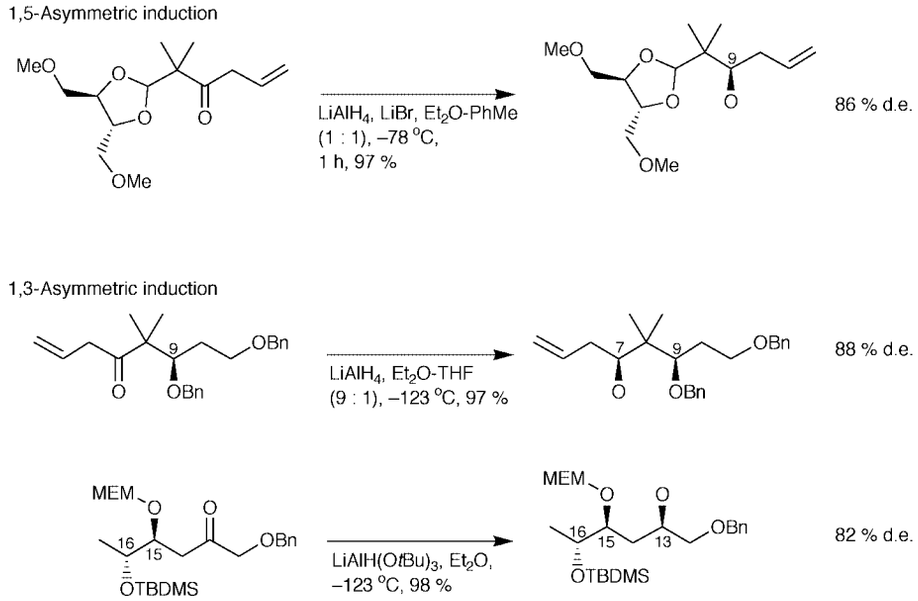
Only (*R*)-Alpine-Hydride® **33** was found to provide a useful level of 1,5-*anti*-diastereocontrol (**31a** : **32a**, 7 : 1) in the reduction of ketone **30a** (Table 2, entry 1). Modest asymmetric induction was obtained in the reduction of **30a** with $Zn(BH_4)_2$ and lithium thexyl-(*R*)-limonylborohydride† **34** (Table 2, entries 2 and 3).

The results obtained suggested that the reduction proceeded *via* a metal chelate intermediate with external hydride delivery.

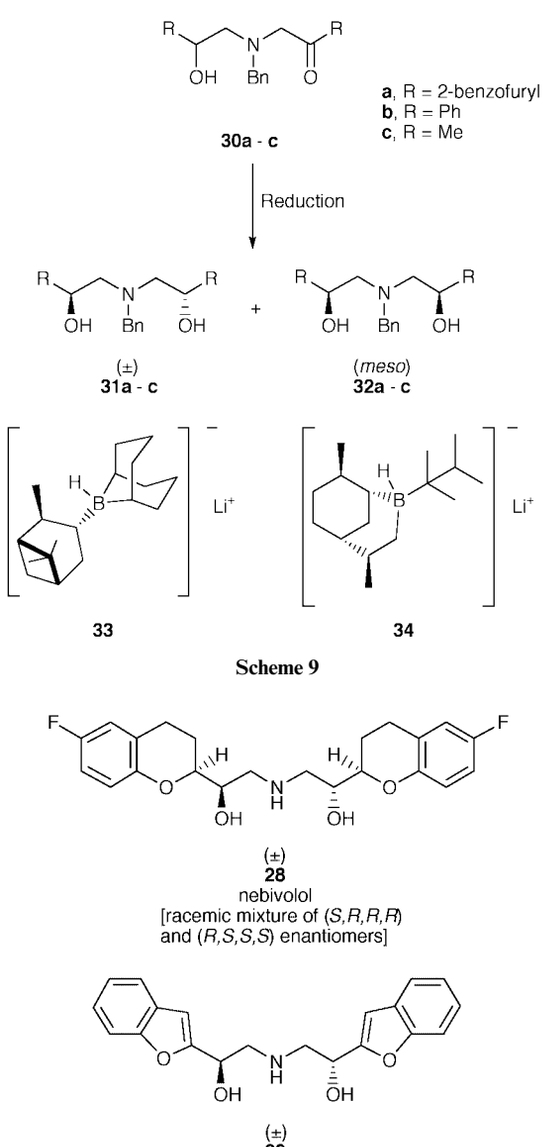
† IUPAC name for thexyl is 1,1,2-trimethylpropyl.



Scheme 6



Scheme 8



Scheme 9

Baker *et al.* had previously discussed such a mechanism for the 1,3-asymmetric reduction of a γ-hydroxy ketone **35** with lithium triethylborohydride, in the stereoselective synthesis of ancistrofuran **37**[29] (Scheme 10). They postulated the involvement of a chelate **38** to assist with locking the carbonyl orientation, to provide face selective hydride delivery. In view of the coordinative saturation of the triethylalkoxyborate function however, one cannot rule out lithium cation-mediated chelation as the actual source of efficient remote reduction. Consequently, in later studies, reaction conditions were modified to favour a rigid chelate species by the use of a less coordinating solvent such as dichloromethane, and lower reaction temperature (Table 2).

Table 2 Reduction of δ-hydroxy ketones **30a–c**

Entry	Ketone	Reducing agent	Solvent	Temp./ °C	Time/h	**31**:**32**
1	**30a**	**33**	THF	−98	18	7:1
2	**30a**	$Zn(BH_4)_2$	Et_2O	−78	18	2.5:1
3	**30a**	**34**	THF	−78	18	2:1
4	**30b**	**33**	THF	−98	16	6:1
5	**30b**	**33**	CH_2Cl_2 [a]	−78	26	10:1
6	**30b**	**33**	THF [b]	−40	5	4:1
7	**30b**	$Zn(BH_4)_2$	CH_2Cl_2 [b]	−78	26	13:1
8	**30b**	$LiBH_4$	CH_2Cl_2	−78	26	5:1
9	**30b**	$LiEt_3BH$	CH_2Cl_2 [a]	−78	26	8:1
10	**30c**	**33**	CH_2Cl_2 [a]	−78–0	20	7.8:1
11	**30c**	$LiBH_4$	CH_2Cl_2	−78–0	20	4:1

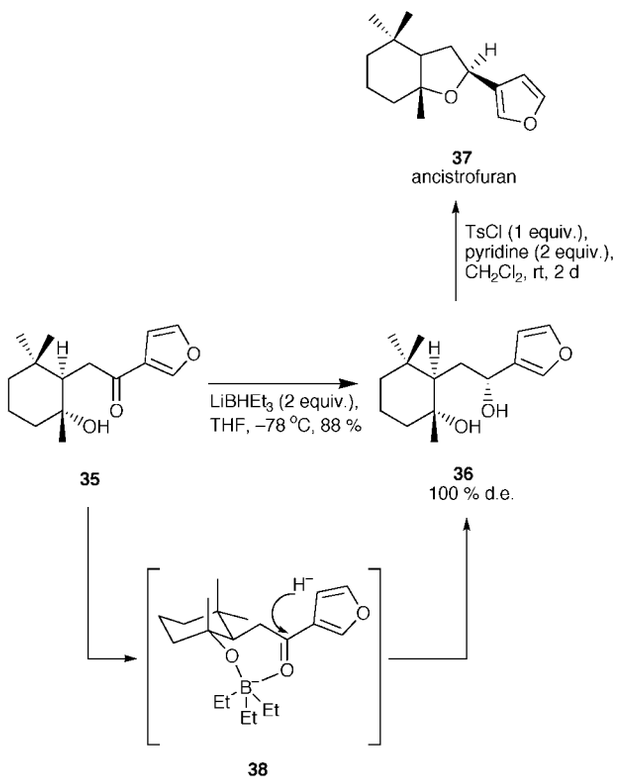
[a] Reaction contains 10–15% THF from the reducing agent. [b] Reaction contains 10–15% Et_2O from the reducing agent.

In ensuing investigations, the simpler, more readily available δ-hydroxy ketone **30b** was used. The highest 1,5-*anti*-selectivities for the reduction of diphenyl system **30b** were obtained using (*R*)-Alpine-Hydride® **33** in dichloromethane at −78 °C (**31b**:**32b**, 10:1) (Table 2, entry 5), and $Zn(BH_4)_2$ (**31b**:**32b**, 13:1) (Table 2, entry 7).

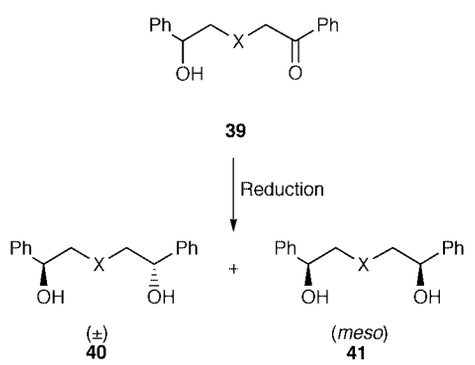
Similar diastereoselectivities to those obtained for the diphenyl substrate **30b** were observed for the reduction of the dimethyl analogue **30c** (Table 2, entries 11 and 12). However, it was found that the stereoelectronic character of the *N*-R unit played an important role in achieving high 1,5-diastereoselectivity. Replacement of the *N*-benzyl unit with carbon, sulfur or *N*-methyl groups led to poor diastereoselectivity in the analogous ketone **39** reductions[30] (Scheme 11, Table 3). To explain the results obtained, a 5,5-bicyclic structure **42** (Fig. 4) was initially proposed. Here, the lithium or zinc ion is coordinated to the hydroxy, amine and ketone groups, and attack by the hydride species is favoured from the less hindered *exo*-side of

Table 3 Reduction of ketones **39**

Entry	**39**, X	Reduction/reagent and conditions	**40**:**41**
1	CH_2	**33**, THF, −78 °C	1.2:1
2	CH_2	$Zn(BH_4)_2$, THF, −78 °C	1.2:1
3	S	**33**, THF, −78 °C	1.3:1
4	NMe	**33**, CH_2Cl_2, −78 °C	2.3:1



Scheme 10



Scheme 11

this conformationally rigid array, leading to *anti*-diols. This model however did *not* explain the stereodirecting effect of the nitrogen substituent (Table 3, entry 4). It was later suggested that the reduction proceeded *via* internal hydride delivery to an uncoordinated ketone carbonyl in monocyclic 5-membered chelate **43** (Fig. 4). The steric interaction between the *N*-benzyl and the carbonyl group was thought to force the ketone to adopt a suitable orientation to provide the *anti*-diol. It was reasoned that the smaller *N*-methyl group would have less influence on the orientation of the ketone, hence reducing the diastereoselectivity observed (Table 3, entry 4).

Given this unusually high 1,5-asymmetric induction, Maryanoff proceeded to study such chelation-based acyclic stereocontrol in related reductions of hydroxy ketones (Scheme 12). An impressive 1,6-*anti*-diastereoselectivity (12:1)

Table 4 Reduction of ketones **44a**–**e** at −78 °C in CH_2Cl_2

Entry	Ketone	R	Reagent	Time/h	**45**:**46**
1	**44a**	Bn	**33**	3	12:1
2	**44a**	Bn	$Zn(BH_4)_2$	3	7.5:1
3	**44a**	Bn	**34**	3	8:1
4	**44b**	H	**33**	4.5	2:1
5	**44c**	Me	**33**	4.5	3:1
6	**44d**	2,4,6-Trimethyl-benzyl	**33**	4.5	22:1
7	**44e**	Bz	**33**	20	1.5:1

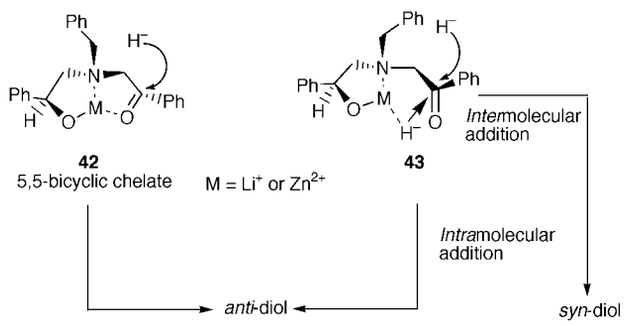
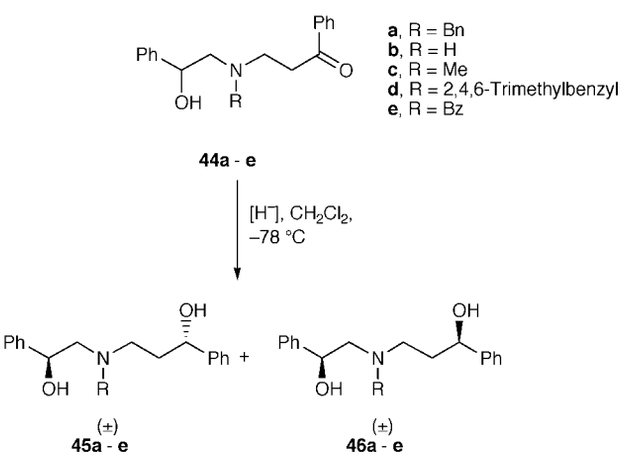


Fig. 4 Alternative chelates involved in the reduction of **30b**.



Scheme 12

was obtained in the (*R*)-Alpine-Hydride® **33** reduction of ε-hydroxy ketone **44a**[31] (Table 4, entry 1). Reduction of **44a** with $Zn(BH_4)_2$ (Table 4, entry 2) or with lithium thexyl-(*R*)-limonylborohydride **34** (Table 4, entry 3) also produced significant selectivity.

It was again found that the stereoelectronic character of the *N*-R subunit played a key role in obtaining high asymmetric induction (Table 4, entries 4–6). An exceptional *anti*:*syn* ratio (22:1) was obtained for the reduction of bulky *N*-2,4,6-trimethylbenzyl-substituted substrate **44d** with (*R*)-Alpine-Hydride® **33** (Table 4, entry 6). In contrast, for the reduction of ketone **44e**, comprising an electron-deficient nitrogen, little selectivity was observed (Table 4, entry 7). The rate of reduction of the 1,6-hydroxy ketones **44a**–**d** (Table 4) was found to be much greater than that of the corresponding 1,5-hydroxy ketones **30a**–**c** (Table 2). It was therefore proposed that the reduction of the more reactive 1,6-hydroxy ketones **44a**–**d** may proceed *via* a bicyclic intermediate in which the ketone carbonyl is activated towards reduction by metal complexation. External hydride addition to a 5,6-bicyclic chelate structure was suggested to rationalise the high 1,6-acyclic stereocontrol obtained (Fig. 5).

Analogous 1,7-hydroxy ketone reductions were also explored, however unremarkable stereocontrol was observed.[32] More recently, Maryanoff and co-workers reported high 1,5-

Table 5 Reduction of 1,6-hydroxy ketones **44a–c** and **44e** with K-Selectride®

Entry	Ketone	R	Lewis acid	Temp./°C	Time/h	**45**:**46**
1	**44a**	Bn	$Ti(OiPr)_4$	−78	0.25	>100:1
2	**44a**	Bn	$Ti(OiPr)_4$	−20	0.3	13.4:1
3	**44c**	Me	$Ti(OiPr)_4$	—	—	>100:1
4	**44b**	H	$Ti(OiPr)_4$	—	—	2:1
5	**44e**	Bz	$Ti(OiPr)_4$	—	—	1:1
6	**44a**	Bn	$Al(OEt)_3$	−78	—	1:7.1
7	**44a**	Bn	$Yb(OiPr)_3$	−78	—	1:4.3

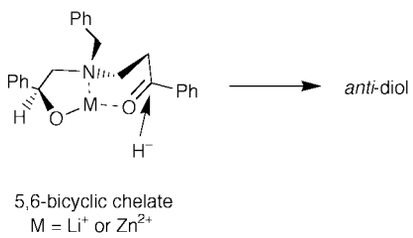
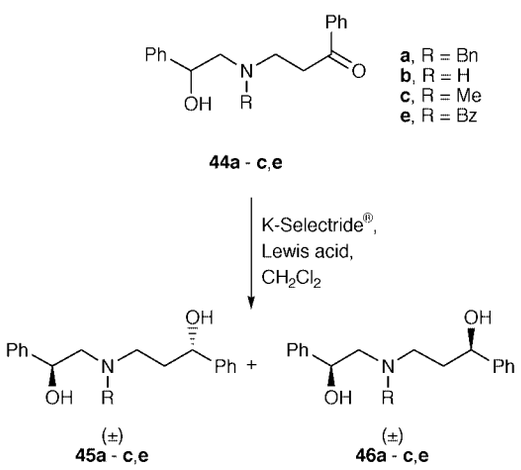


Fig. 5 Chelate involved in the reduction of **44a**.

and 1,6-diastereoselection in the reduction of 1,5- and 1,6-hydroxy ketones by sequential addition of a Lewis acid then a borohydride reagent.[33] Either *syn*- or *anti*-diol products were obtained depending on which Lewis acid pre-complexing agent was used.

When $Ti(OiPr)_4$ was used, extremely high *anti*-selectivity (>100:1) was observed for the K-Selectride® reduction of 1,6-hydroxy ketone **44a** at −78 °C (Scheme 13) (Table 5, entry 1). Perhaps surprisingly it was also found that, with the nitrogen as a tertiary amine, the size of the *N*-substituent had little effect on the diastereoselectivity observed (Table 5, entry 3, compare with Table 4, entry 5).



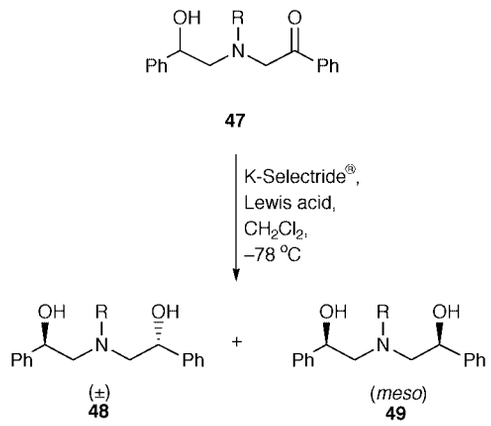
Scheme 13

These results were consistent with the 5,6-bicyclic metal chelate proposed earlier (Fig. 5), that experiences external hydride addition. However, it was found that the *syn*-isomer could be formed preferentially depending on which Lewis acid was used for pre-complexation (Table 5, entries 6 and 7). This was attributed to a change in coordination geometry with different Lewis acids.

In contrast, pre-coordination of 1,5-hydroxy amino ketones **47** with a Lewis acid followed by reduction with K-Selectride®, furnished the *syn*-isomers **49** with high selectivity (Scheme 14) (Table 6, entries 2–4). In this case the size of the substituent on nitrogen *did* have a substantial effect on diastereoselectivity obtained, with R = Me affording an *anti*:*syn* ratio of just 1:2.1 (Table 6, entry 5). The reduction was thought to proceed *via* the same type of 5-membered chelate **43** as described previously.

Table 6 Reduction of 1,5-hydroxy amino ketones **47** with K-Selectride®

Entry	R	Lewis acid	Time/h	**48**:**49**
1	Bn	$Ti(OiPr)_4$	21	1:1
2	Bn	$Mg(OTf)_2$	23	1:9
3	Bn	BuLi	23	1:11
4	Bn	$Al(OEt)_3$	23	1:18.5
5	Me	$Al(OEt)_3$	23	1:2.1



Scheme 14

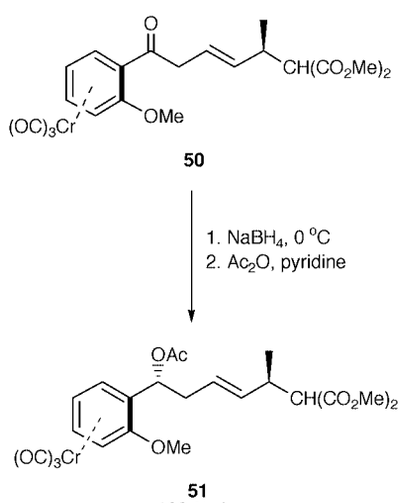
However, reduction would have to occur *via* intermolecular addition of hydride in chelate **43** to form the *syn*-diol **49** (Fig. 4).

2.3 Use of tricarbonylchromium complexes

Remote asymmetric inductions with tricarbonyliron complexes,[5g,10h,11a] organo-palladium substrates,[12b,n,19] zirconium complexes,[4r,10e,12i] (η^6-arene)tricarbonylchromium complexes[5l] and, in particular, organo-tin compounds[4d,g,p,8d] have also been published. Of these, to our knowledge, only chromium complexes have been successfully applied to the remote asymmetric reduction of carbonyl functions.

Uemura *et al.* reported asymmetric reduction of a ketone which utilised an (η^6-arene)tricarbonylchromium complex as a temporary template to relay stereochemical information into a flexible 1,5-system[34] (Scheme 15). It is noteworthy however, that the chiral chromium complex has a 1,2-relationship relative to the ketone function being reduced.

Reduction of the complex **50** with sodium borohydride in methanol at 0 °C, followed by acetylation gave a single diastereo-



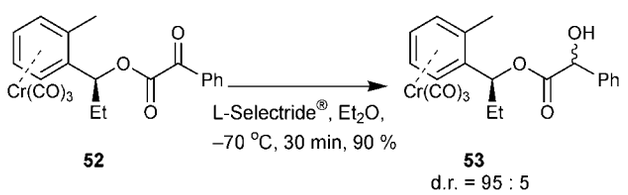
Scheme 15

Table 7 DIBAL-H reduction of ketones **54**

Entry	**54**, R	**55**, De (%)
1	Me	75
2	Ph	74
3	*i*Pr	92
4	*t*Bu	96

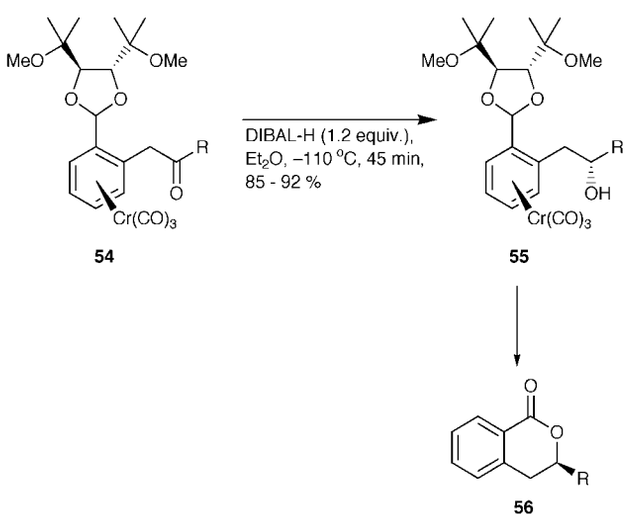
meric acetyl complex **51**, representing an interesting example of a ketone reduction in an acyclic system that proceeds with high 1,2-diastereocontrol. No evidence was presented to suggest that the 1,5-chiral centre controls the reduction process in preference to the chromium centre.

In another example of the use of an (η^6-arene)tricarbonylchromium complex, Solladié-Cavallo and Suffert reported high diastereoselectivity (90% de) in the 1,4-asymmetric reduction of α-keto ester substrate **52** with L-Selectride®, using a chromium complexed hydroxymethyl auxiliary[35] (Scheme 16).



Scheme 16

More recently, Thangarasa *et al.* reported high diastereoselectivity (up to 96% de) in the asymmetric reduction of homochiral (arene)tricarbonylchromium complexes of homobenzylic ketones **54**, to form the corresponding alcohols **55** as intermediates in dihydroisocoumarin **56** synthesis[36] (Scheme 17).



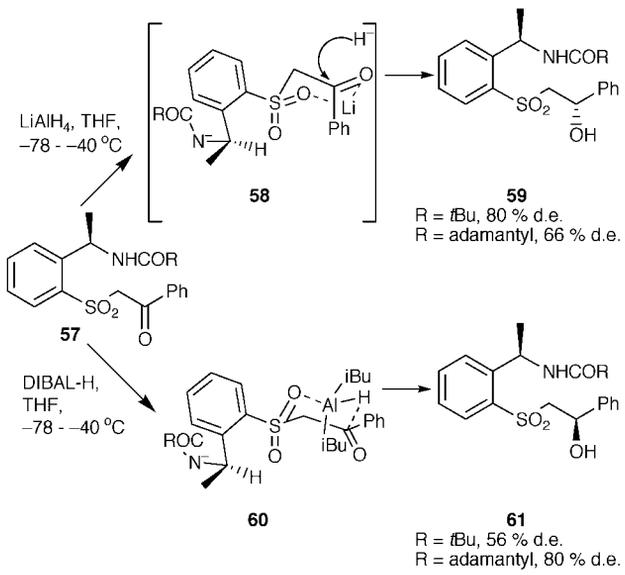
Scheme 17

Reduction of ketones **54** with diisobutylaluminium hydride in diethyl ether at −110 °C afforded the corresponding alcohols **55** with good diastereomeric excess (Table 7).

2.4 Transfer of chirality *via* a π-aryl system

Many examples of remote chiral induction have been reported for systems comprising an intervening rigidifying π-system.[3]

In 1996, Nájera and co-workers described 1,6-remote asymmetric induction in hydride addition to a prochiral carbonyl function separated from the inducing stereogenic centre by a π-aryl moiety.[37] 1,6-Asymmetric reduction of a chiral β-keto sulfone **57** derived from (*R*)-*N*-α-methylbenzylamine was reported (Scheme 18). Reduction of sulfone **57** with $LiAlH_4$ afforded (*R*,*S*)-β-hydroxy sulfone **59** in high diastereomeric excess. However, reduction with DIBAL-H yielded (*R*,*R*)-β-hydroxy sulfone **61** as the major diastereomer.

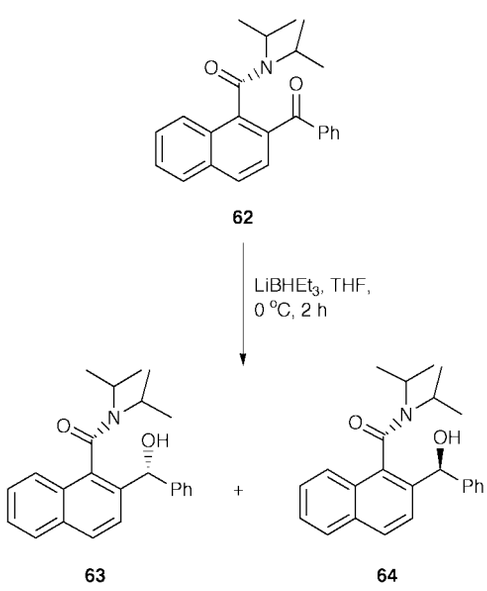


Scheme 18

Transition states **58** and **60** were proposed to explain the stereoselectivity of the reductions. In the case of the $LiAlH_4$ reduction, a chair-like transition state **58** was suggested in which the lithium cation is on the same side as the methyl group of the stereogenic centre. Hydride is delivered intermolecularly from the opposite side. Transition state **60**, in which the bulky hydride is positioned far from the methyl group and intramolecular hydride delivery, was thought to explain the stereoselectivity observed for the diisobutylaluminium hydride reduction.

Clayden *et al.* used atropisomerism to control the reduction of ketones **62**[38] (Scheme 19). The chirality of the rotationally restricted amide unit is transmitted through a π-aryl system to the carbonyl function resulting in high 1,4-asymmetric induction in the reduction.

Reduction of ketone **62** with the bulky reducing agent $LiBHEt_3$ in diethyl ether at 0 °C afforded the *anti*-alcohol **63** as



Scheme 19

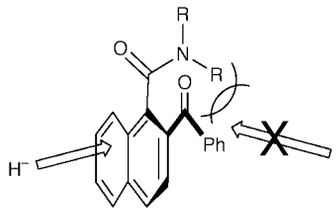


Fig. 6 Favoured direction of reduction of ketone **62**.

the major atropisomer with high stereoselectivity (99.3 : 0.7). This stereocontrol was explained by assuming a transition state in which nucleophilic attack occurs at the ketone face opposite to the NR_2 group (Fig. 6).

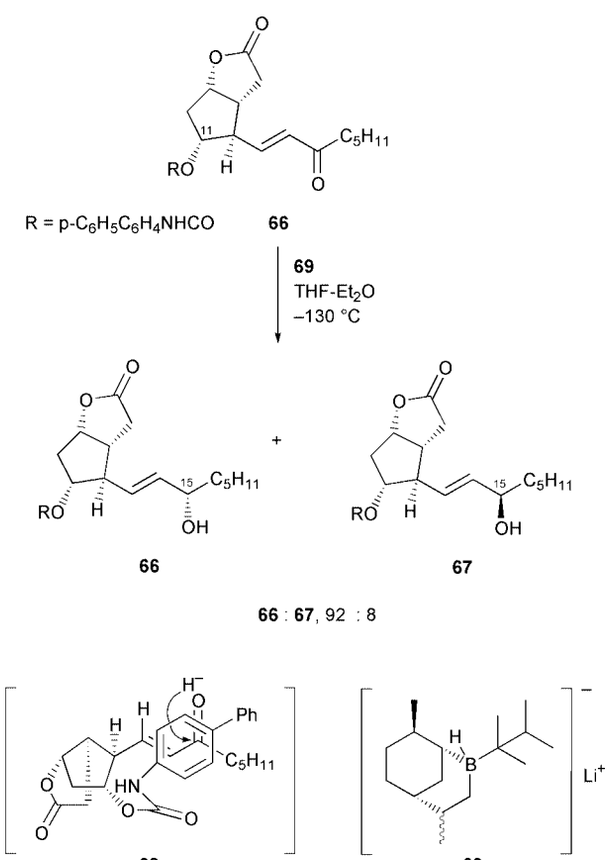
Similarly, high levels of 1,4-stereocontrol were obtained upon addition of organometallic reagents to such amide substrates. Analogous methodology was also applied to the 1,5-stereocontrolled addition to enolates.[12c]

2.5 Reduction of α,β-unsaturated ketones

Mitchell *et al.* have recently reviewed methods for the stereocontrolled synthesis of molecules with remote stereogenic centres across a double bond of fixed configuration.[3] Transfer of chirality in such systems is facilitated by a conformationally rigidifying alkene function.

Perhaps remote asymmetric induction in the reduction of enones has been illustrated most prominently in the control of the remote C15 chiral centre in prostaglandin synthesis. In 1972, Corey *et al.* reported high diastereoselectivity (84% de) in the quantitative reduction of α,β-unsaturated ketone **65** with *racemic* borohydride **69**, to afford the desired (15*S*)-alcohol **66**[39] (Scheme 20).

It was thought that the large carbamoyl protecting group at C11 on the *cis*-fused bicyclic system directed hydride attack

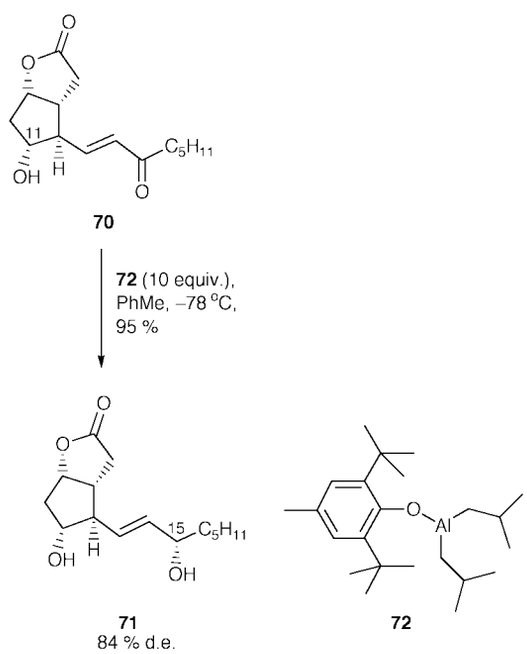


Scheme 20

Table 8 Reagent-controlled reduction of enones **73**

Entry	**73**, R	Reduction (reagents and conditions)	**74**:**75**	Reference
1	THP	(*S*)-**76** (3 equiv.), THF, −100 °C	99.5 : 0.5	42
2	THP	(*R*)-**76** (3 equiv.), THF, −100 °C	32 : 68	42
3	*p*-PhC$_6$H$_4$-CO	(*R*)-**77** (10 mol%), BH_3·THF (0.6 equiv.)	90 : 10	41
4	*p*-PhC$_6$H$_4$-CO	(*S*)-**77** (10 mol%), BH_3·THF (0.6 equiv.)	9 : 91	41

by blocking one face of the ketone in configuration **68**, in addition to controlling the required s-*cis*-enone conformation, to form preferentially (15*S*)-alcohol **66**. Excellent 1,4-diastereoselectivity was hence obtained in this instance of substrate-controlled reduction in the absence of a metal template. Similar selectivity was reported by Yamamoto and co-workers in the reduction of enone **70** with excess (2,6-di-*tert*-butyl-4-methylphenoxy)diisobutylaluminium **72** to form (15*S*)-alcohol **71**[40] (Scheme 21).



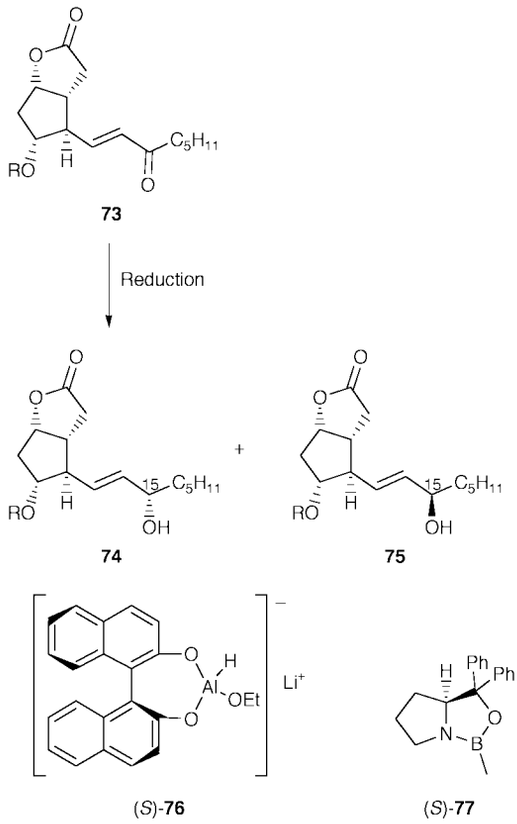
Scheme 21

In this case it was thought that the excess bulky aluminium reagent coordinates to the C11 hydroxy group. Hydride delivery and s-*cis*-enone conformation were therefore controlled, resulting in the high stereoselectivity observed.

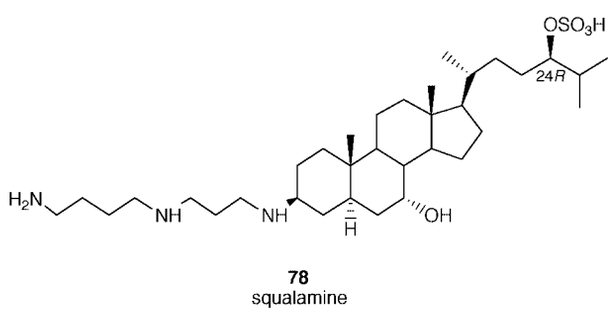
Corey[41] and Noyori and their co-workers[42] have since reported effective reagent-controlled techniques to control the C15 centre in prostaglandin synthesis (Scheme 22) (Table 8).

Reagent-controlled remote asymmetric induction has also been exploited in the reduction of α,β-unsaturated ketones to efficiently access (24*R*)-hydroxylated steroids. During studies directed towards the synthesis of aminosterol squalamine **78**, Rao *et al.* investigated the reduction of α,β-unsaturated ketones **79** and **81** using the *C*orey–*B*akshi–*S*hibata (CBS) oxazaborolidine-borane reagents[43] (Scheme 23).

Reduction of enone **79** with the (*R*)-**77**-based borane system afforded the corresponding (24*S*)-allylic alcohol **80** with excellent 1,4-diastereoselectivity (94–98% de). α,β-Ynone **81** was stereoselectively reduced in the presence of the (*S*)-**77** complex to produce (24*S*)-propargylic alcohol **82**. Hydrogenation of **80** and **82** gave the desired (24*R*)-hydroxylated product **83**. Similarly, application of the Noyori binaphthyl reducing system

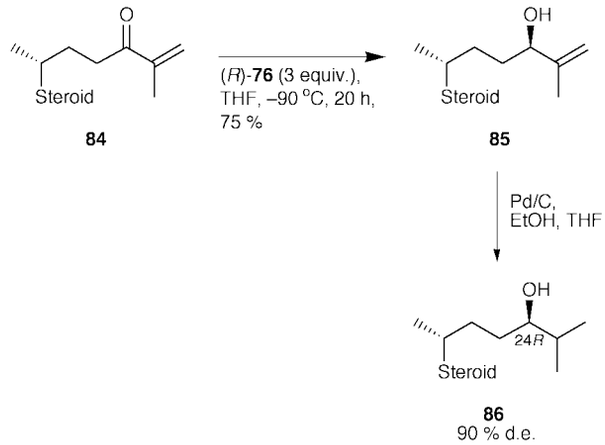


Scheme 22



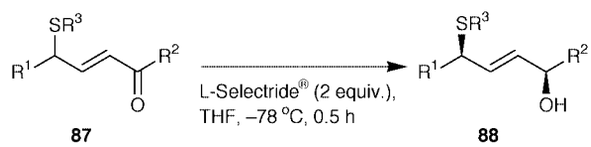
(*R*)-**76** to control C24 stereochemistry in the cholesterol side chain, has been successful[44] (Scheme 24).

Other substrate-controlled examples of remote acyclic 1,4-stereocontrol in the reduction of α,β-unsaturated ketones



Scheme 24

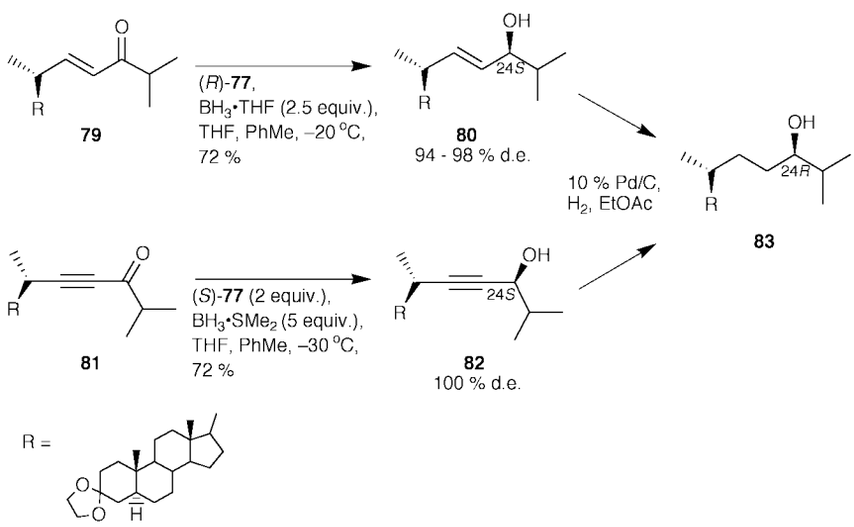
include work reported by Otera and co-workers on the stereoselective reduction of γ-sulfenyl α-enones **87** with L-Selectride®[45] (Scheme 25).



Scheme 25

Enones **87** were reduced with L-Selectride® in THF at −78 °C to yield *syn*-allylic alcohols **88** in high diastereomeric excess (up to 94% de) (Table 9). Hydride attack occurred from the opposite side to the sulfenyl group, however, steric effects did *not* explain this stereoselectivity since the smaller methylthio-substituted derivative (R^3 = Me) gave rise to a similar result to the bulkier phenyl-substituted compound (R^3 = Ph) (Table 9). A chelate-controlled mechanism was also found to be incompatible with the sense of the observed diastereoselectivities. It was therefore proposed that stereoelectronic effects controlled the facial selectivity of the reduction (Fig. 7).

A slight reduction in selectivity was observed with decreasing bulk of R^2 (Table 9, compare entries 1 and 3), again indicating the importance of the enone ground state geometry. A favourable configuration was proposed in which the electron-donating sulfenyl group is favourably situated orthogonal to the enone face, stabilising the s-*cis*-enal fragment through σ–π*



Scheme 23

Table 9 Reduction of γ-sulfenyl α-enones **87** with L-Selectride®

	87			
Entry	R^1	R^2	R^3	**88**, De (%)
1	*t*Bu	*t*Bu	Ph	94
2	Me	*t*Bu	Ph	90
3	*t*Bu	Me	Ph	82
4	nC_6H_{13}	*t*Bu	Ph	86
5	nC_6H_{13}	*t*Bu	Me	74

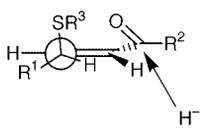
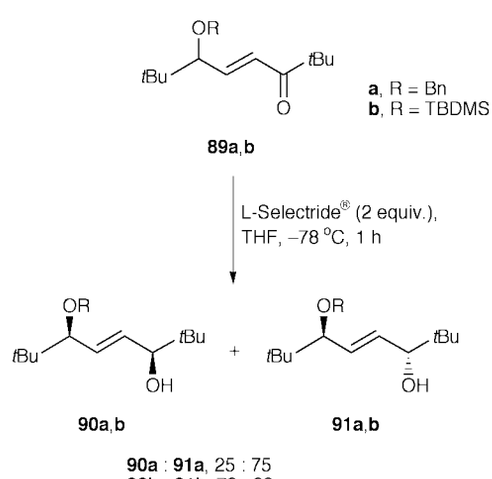


Fig. 7 Preferred direction of reduction of substrates **87**.

interaction, with nucleophilic attack then occurring from the opposite side (Fig. 7).

Modest diastereoselectivities were obtained in the hydride addition to γ-alkoxy or γ-siloxy α-enones **89a** and **89b** (Scheme 26). In this case it was found that the stereochemical outcome was dependent upon the oxygen function, with benzyl derivative **89a** preferably affording the *anti*-product **91a**, and siloxy analogue **89b** favouring production of the *syn*-isomer **90b**.



Scheme 26

γ-Benzyloxy α,β-unsaturated carbonyl compounds prefer to adopt a CH-eclipsed form, while the corresponding silyl ethers prefer the CO-eclipsed conformer. The configurations **92** and **93** were therefore proposed to explain the diastereoselectivities obtained (Fig. 8). As with the γ-sulfenyl substrates **87**, it was reasoned that the most electron-donating alkyl group lies perpendicular to the enone face, with hydride attack occurring from the opposite side.

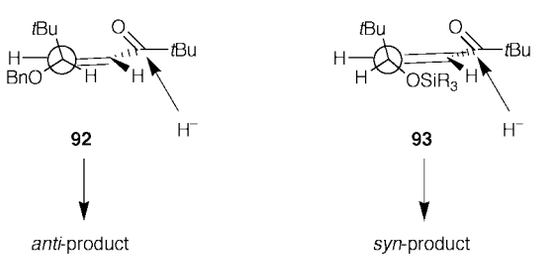
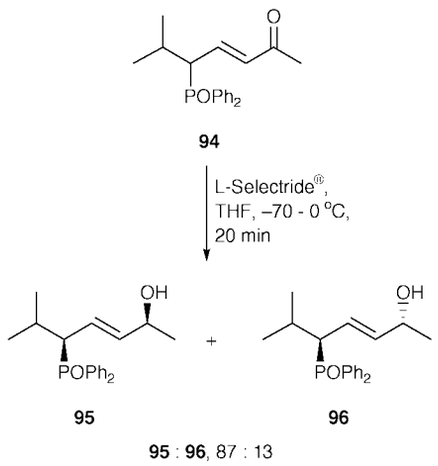


Fig. 8 Alternative modes of reduction for substrates **89a** *versus* **b**.

Warren and co-workers have also reported effective 1,4-diastereoselectivity across a *trans*-double bond in the diphenylphosphinoyl-directed reduction of enone **94** with L-Selectride® [46] (Scheme 27). In this case a steric argument was proposed to explain the high 1,4-*syn*-diastereoselectivities, with approach of the hydride from the enone face opposite to the large phosphorus-containing group being favoured (Fig. 9). This followed a "vinylogous Cram's rule" as discussed and sought by Fleming *et al.*[47]



Scheme 27

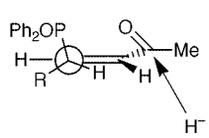
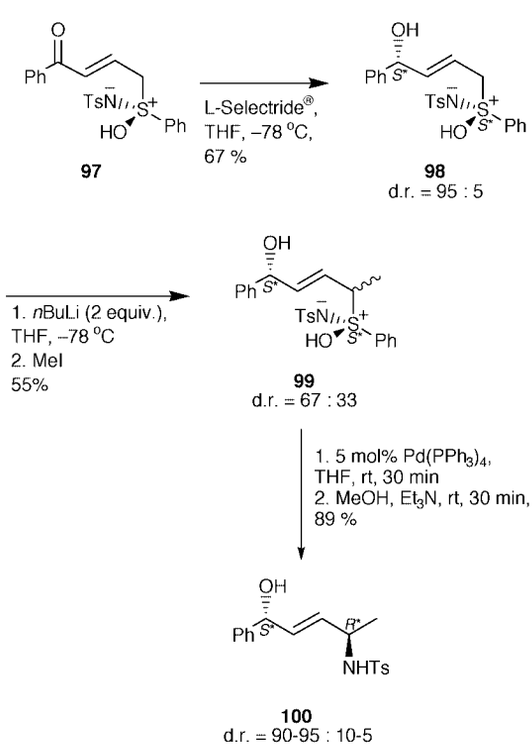


Fig. 9 Preferred direction of reduction of **94**.

In related studies, Pyne *et al*. recently demonstrated that high 1,5-diastereoselectivity could be achieved in the reduction of γ-keto-vinyl sulfoximine **97** with L-Selectride® [48] (Scheme 28).



Scheme 28

The high level of diastereoselectivity observed was attributed to the *N*-tosyl group on the sulfoximine moiety effectively shielding one face of the carbonyl group from attack

Table 10 Reduction of 1,4-diketones **101** with $LiAlH_4$ in Et_2O at 23 °C

Entry	**101**, R	Yield (%)	**102**, De (%)
1	Me	100	52
2	Ph	98	52
3	*p*-$MeOC_6H_4$	97	54

Table 11 Reduction of 1,5-diketones **104** with $LiAlH_4$ in Et_2O at 23 °C

Entry	**104**, R	Yield (%)	**105**, De (%)
1	Me	96	10
2	Ph	98	20
3	*p*-$MeOC_6H_4$	100	18

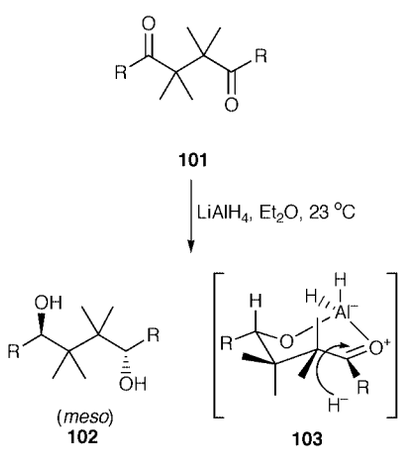
by hydride.[49] C-Methylation of **98** and diastereoselective palladium-catalysed rearrangement of **99** yielded the 1,4-amino alcohol **100** with excellent 1,4-*anti*-stereocontrol.

In summary, high levels of 1,4- and 1,5-diastereocontrol have been demonstrated in the reduction of acyclic α,β-unsaturated ketones, using both substrate- and reagent-controlled strategies.

2.6 Reduction of 1,*n*-diketones

In 1985 Maier *et al*. reported diastereocontrol in the reduction of 1,2-, 1,3-, 1,4- and 1,5-diketones with lithium aluminium hydride in diethyl ether at room temperature.[50] Mixtures of *meso*- and (±)-diols were observed in all cases, with the level of diastereoselectivity decreasing with increasing carbonyl group separation.

Maier *et al*. found that 1,4-diketones **101** afforded predominantly *meso*-diols **102** (Scheme 29, Table 10), whereas the 1,5-diketones **104** mostly led to (±)-isomers **105** (Scheme 30, Table 11). These alternating selectivities were explained by a stepwise reduction. It was suggested that complexes **103** and **106** were generated and attacked by excess hydride *via* a diastereofacial-differentiating mode, the ultimate stereochemistry being determined by the second reduction.



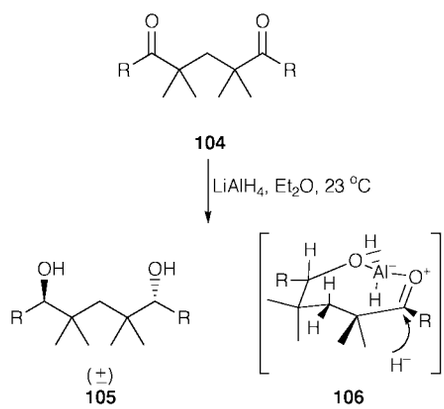
Scheme 29

The modest remote 1,4- and 1,5-stereocontrol observed by Maier *et al*. in the substrate-controlled reduction of 1,4- and 1,5-diketones **101** and **104** highlights the significance of the results obtained by Maryanoff and co-workers in the reduction of achiral 1,5- and 1,6-hydroxy ketones **30** and **44** (*vide supra*). Subsequently, Quallich *et al*. reported the reduction of 1,2-, 1,3-, 1,4-, 1,5- and 1,6-diketones **107** to the corresponding C_2-symmetric diols **109** with borane–dimethylsulfide complex in THF, in the presence of a chiral oxazaborolidine catalyst **108**[51] (Scheme 31).

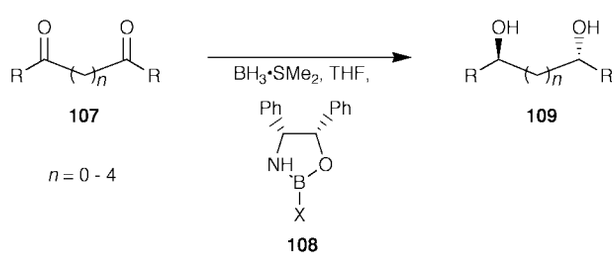
It was observed that the oxazaborolidine-catalysed reactions managed to override the *meso*-isomer preference observed in most of the uncatalysed borane reductions (Table 12). Employing stoichiometric oxazaborolidine **108** increased the enantiomeric excess and lowered the *meso*-isomer level. Increased (±)-selectivity was noted with increased separation of the reaction centres. This was thought to be reflective of the intrinsic reagent-based enantioselectivity, which appeared to be counteracted when the reaction centres were proximal.

Table 12 Reduction of 1,*n*-diketones **107**

	107		**108**		**109**	
Entry	R	*n*	X	Mol%	*Meso*:±	Ee (%)
1	Ph	0	—	—	83:17	—
2	Ph	0	H	5	59:41	86 (*R*,*R*)
3	Ph	0	H	10	48:52	85 (*R*,*R*)
4	Ph	0	Me	10	61:39	70 (*R*,*R*)
5	Me	2	—	—	43:57	—
6	Me	2	H	10	31:69	17 (*S*,*S*)
7	Ph	2	—	—	61:39	—
8	Ph	2	H	10	21:79	94 (*S*,*S*)
9	Ph	2	H	100	16:84	99 (*S*,*S*)
10	*t*Bu	2	—	—	67:33	—
11	*t*Bu	2	H	10	20:80	97 (*S*,*S*)
12	Ph	3	—	—	57:43	—
13	Ph	3	H	10	9:91	99 (*S*,*S*)
14	Ph	3	H	100	2:98	99 (*S*,*S*)
15	Ph	3	Me	10	16:84	96 (*S*,*S*)
16	Ph	4	—	—	50:50	—
17	Ph	4	H	10	12:88	94 (*S*,*S*)
18	Ph	4	Me	10	11:89	99 (*S*,*S*)



Scheme 30



Scheme 31

This enantioselective reduction of diketones provides a desirable route to C_2-symmetric diols, and an example of high 1,4-, 1,5- and 1,6-asymmetric induction in a reagent-controlled reaction.

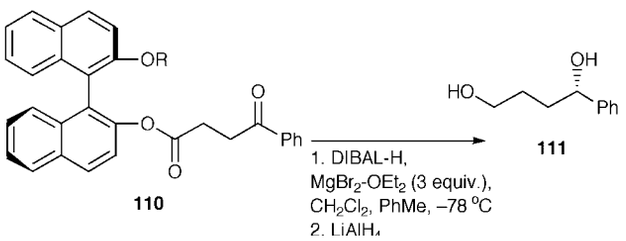
2.7 Reduction of keto esters and keto amides

One of the most popular and reliable methods for asymmetric synthesis is *via* chiral auxiliary-based methodology. A variety of chiral auxiliaries have been used to demonstrate 1,4-, 1,5-, 1,6- and 1,7-remote asymmetric induction for the reduction of keto esters.

Table 13 Reduction of γ-keto esters **110** with DIBAL-H

		111	
Entry	**110**, R	Yield (%)	Ee (%)
1	$(CH_2)_2OMe$	85	78
2	$(CH_2)_2O(CH_2)_2OMe$	82	82
3	$(CH_2)_3O(CH_2)_2OMe$	85	92

In 1991 Tamai and co-workers first reported an impressive example of high 1,7-asymmetric induction in the intermolecular reduction of γ-keto esters **110**[52] (Scheme 32).



Scheme 32

The DIBAL-H reduction of γ-keto esters of 1,1′-binaphthalen-2-ol derivatives **110** bearing an oligo-ether group in the C2′ position, in the presence of excess $MgBr_2{\cdot}OEt_2$, afforded 1,4-diol **111** with up to 92% enantiomeric excess (Table 13), following reduction of the corresponding diastereomeric hydroxy ester intermediate (Scheme 32).

The level of induction achieved in the reduction of keto ester substrates depends upon the level of diastereofacial selectivity imparted by the chiral auxiliary, and the degree of bias in the transition state for *cis*- or *trans*-orientation of the carbonyl groups. In this case, it was thought that the high 1,7-stereoselectivity observed was due to the formation of a *pseudo*-macrocyclic magnesium complex (Fig. 10). It was suggested that chelation of the oxygen atoms of the oxyethylene chain and the keto carbonyl function to the Lewis acid fixes the orientation of the carbonyl groups of the γ-keto esters. The oxyethylene chain therefore shields one face of the keto-carbonyl π-bond, hence hydride addition occurs from the opposite face.

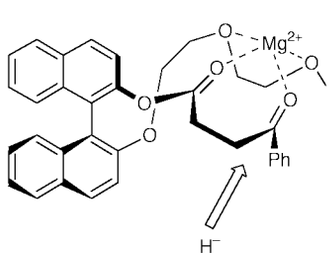


Fig. 10 Chelate involved in the reduction of **110** [R = $(CH_2)_2O(CH_2)_2OMe$].

Examples of high 1,5- to 1,12-asymmetric induction in the addition of Grignard reagents to analogous substrates have also been published by Tamai and co-workers.[5a,h,i]

Nair and co-workers have since reported instances of modest 1,7-asymmetric induction and high 1,6-stereocontrol in the reduction of keto esters **112** using a novel anhydrofuranoside chiral auxiliary.[53] This methodology was applied to the asymmetric synthesis of lactones **114** (Scheme 33) (Table 14).

It was proposed that the origin of the observed stereoselectivity was nucleophilic attack at the least hindered face of a wedge-shaped chelate intermediate, in which zinc is coordinated to the C5-hydroxy and carbonyl ketone groups (Fig. 11).

In 1987 Taber *et al.* reported high 1,5-asymmetric induction in the reduction of a chiral β-keto ester **115**, with application to

Table 14 Reduction of keto esters **112**

		114	
Entry	**112**, *n*	Yield (%)	Ee (%)
1	1	82	93
2	2	76	53

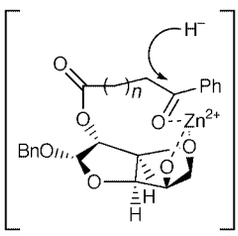
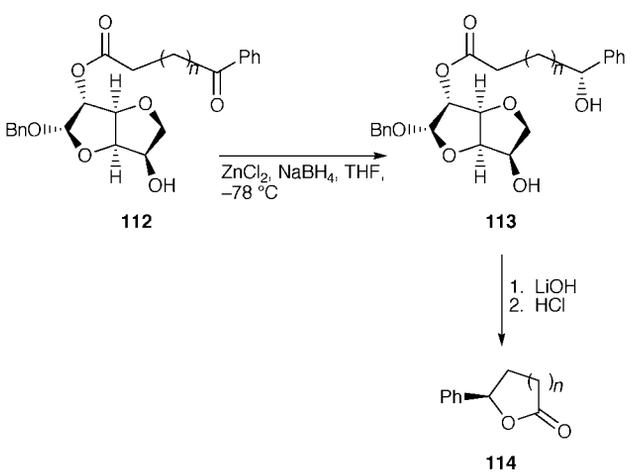


Fig. 11 Chelate involved in the reduction of **112**.



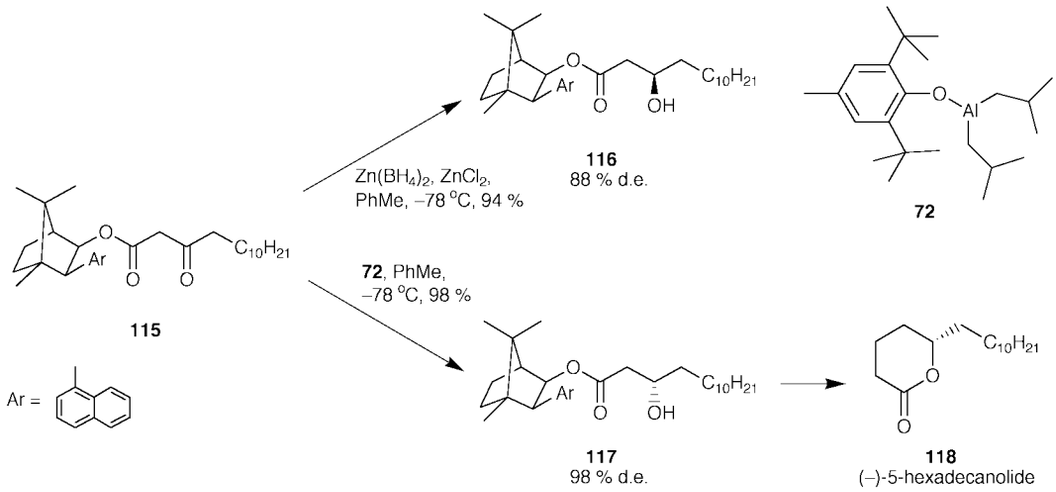
Scheme 33

the enantioselective synthesis of cyclic ether **118**[54] (Scheme 34). By careful choice of an appropriate reducing system, and design of chiral auxiliary, Taber *et al.* were able to access alcohols **116** and **117** with a high degree of stereocontrol. Reduction of ketone **115** with $Zn(BH_4)_2$ in the presence of $ZnCl_2$, afforded (*R*)-alcohol **116** in 88% diastereomeric excess. Hydride reduction was thought to proceed *via* a transition state in which the carbonyls are *syn*, where ketone **115** is activated by complexation with a bidentate zinc metal ion. The chiral auxiliary used contained an arene group which blocked one face of the ketone, hydride therefore attacked from the opposite carbonyl face. Reduction with (2,6-di-*tert*-butyl-4-methylphenoxy)diisobutylaluminium **72**, afforded diastereomeric (*S*)-alcohol **117** as the major product. This reduction was thought to proceed *via* the alternative transition state in which the carbonyls are *anti*, due to the sterically-demanding monodentate metal centre.

Similar types of auxiliaries derived from β-pinene have since been studied for the 1,5-asymmetric reduction of β-keto esters **119**[55] (Scheme 35). However, in this case only modest diastereoselectivities were achieved in the reduction with zinc borohydride.

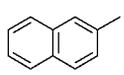
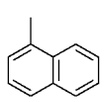
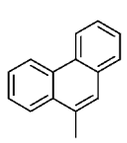
Again it was proposed that the zinc ion blocks the *syn*-conformation of the carbonyl groups, and the attack of hydride therefore takes place preferentially from the less hindered face of this chelate ring. The level of 1,5-diastereoselectivity was found to be proportional to the shielding ability of the aromatic moiety present in the chiral auxiliary (Table 15).

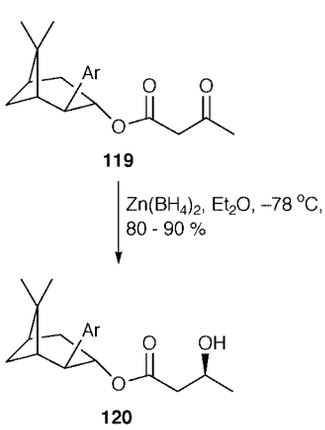
The above chiral auxiliary-based methodology, requires remote asymmetric induction over at least a 1,4-relationship,



Scheme 34

Table 15 Reduction of β-keto esters **119**

Entry	**119**, Ar	**120**, De (%)
1	Ph	2
2		2
3		54
4		70



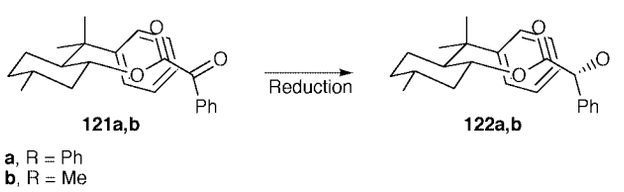
Scheme 35

even in the reduction of α-keto acid derivatives. A number of examples of 1,4-stereocontrol have therefore been reported in the reduction of keto esters[56] and indeed keto amides, and are briefly reviewed.

Following the successful use of chromium-complexed hydroxymethyl auxiliaries for the reduction of α-keto esters (Scheme 16),[35] Solladié-Cavallo and Bencheqroun reported high diastereoselectivity in the asymmetric reduction of 8-phenylmenthol-derived phenylglyoxylate **121a** with potassium tributylborohydride[57] (Scheme 36) (Table 16, entry 2). Previously Whitesell *et al.* had only achieved a modest 50% de for the reduction of α-phenyl ketone **121a** using potassium triisopropoxyborohydride (Table 16, entry 1). High diastereo-

Table 16 Reduction of α-keto esters **121a** and **b**

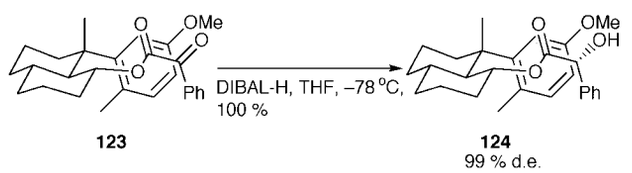
Entry	Ketone	R	Reduction (reagents and conditions)	**122** Yield	**122** De (%)
1	**121a**	Ph	$K(OiPr)_3BH$, THF, −78 °C	—	50
2	**121a**	Ph	$KBHBu_3$, THF, −78 °C	>95	94
3	**121b**	Me	$K(OiPr)_3BH$, THF, −78 °C	90	90



Scheme 36

selectivity was however obtained in the reduction of the α-methyl substrate **121b**[58] (Table 16, entry 3).

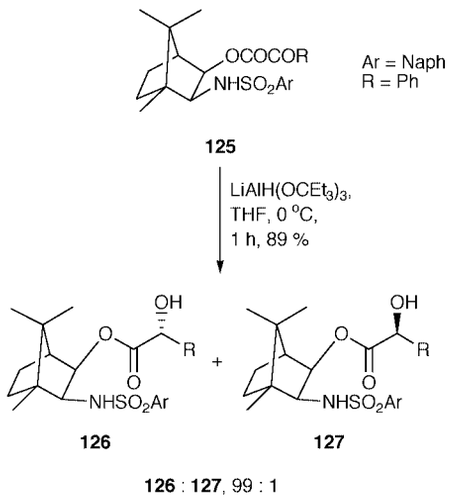
Massy-Westropp and co-workers subsequently developed a conformationally restricted perhydronaphthalenol auxiliary which proved to be more efficient than 8-phenylmenthol in the DIBAL-H reduction of the phenylglyoxylate ester **123**[59] (Scheme 37).



Scheme 37

α-(Arylsulfonamido)borneol derivatives have also been successfully used as chiral auxiliaries for this transformation[60] (Scheme 38).

In the above examples of 1,4-asymmetric induction, the stereoselectivities observed were consistent with hydride addition from the less hindered face of a metal chelate that favours *syn*-conformation of the carbonyl groups. Akiyama *et al.* were first to report the diastereoselective reduction of a chiral α-keto ester **128** derived from L-quebrachitol, which afforded both diastereomeric alcohols **131** and **132**, from treatment with a single metal hydride and an appropriate choice of additive[61] (Scheme 39).



Scheme 38

Reduction of keto ester **128** with K-Selectride® in ether was thought to proceed *via Re*-face attack at the metal–ketone complex **129** with high diastereoselectivity, to give alcohol **131**. By using 18-crown-6 or HMPA, which efficiently sequester metal cations, formation of the 5-membered chelated complex **129** was less favoured, and the s-*trans* isomer **130** predominated, to produce alcohol **132**. Similar trends have been described in the effective 1,4-asymmetric reduction of *cis*-1-arylsulfonamidoindan-2-ol-derived α-keto esters **134**[62] (Scheme 40).

1,4-Asymmetric reduction of chiral α-keto amides has also been investigated, but perhaps to a lesser extent than their keto ester analogues. For example, Soai and co-workers have used proline esters as chiral amine components in the complex metal hydride reduction of α-keto amides **139**[63] (Scheme 41).

Other instances include the use of *trans*-2,5-disubstituted pyrrolidines[64] (Scheme 42), and imidazolidinones[65] (Scheme 43, Table 17), for 1,4-asymmetric reduction of α-keto amides **144** and **147** respectively.

In both instances hydride attacks from the less hindered face of the α-carbonyl group of the preferred *trans*-coplanar conformer.

Table 17 Reduction of α-keto amide **147**

Entry	Reduction (reagents and conditions)	**148**:**149**
1	$NaBH_4$ (0.75 equiv.), DME, 25 °C	90.5:9.5
2	$HSiMe_2Ph$ (4 equiv.), CsF (5 mol%), 18-crown-6 (5 mol%), CH_2Cl_2, 25 °C	100:0

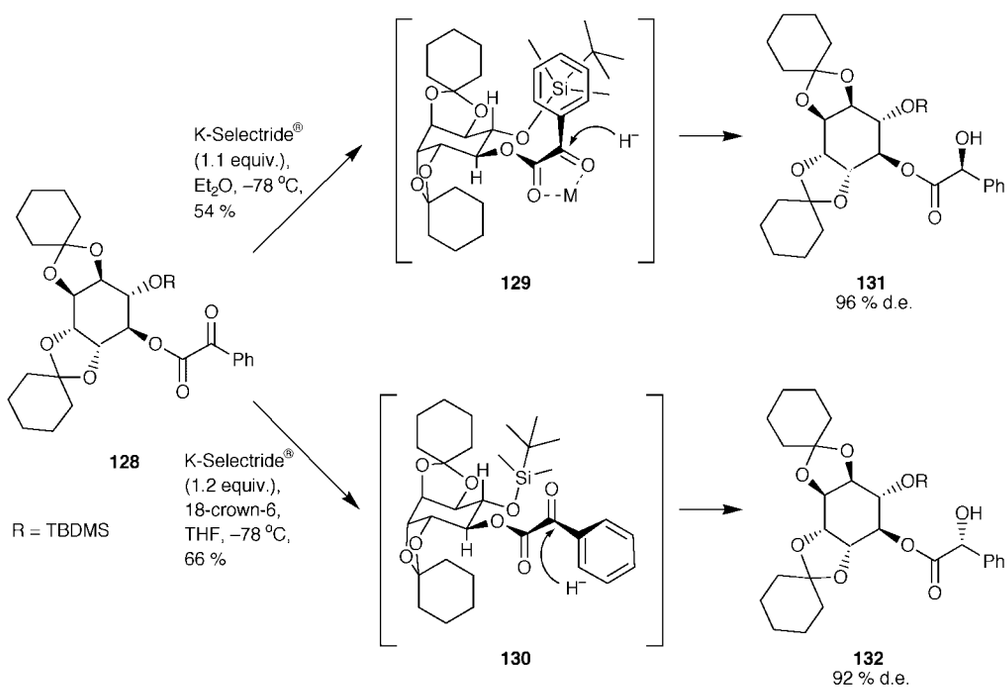
2.8 Use of boron complexes

Cases of remote asymmetric induction involving boron complexes have been reported for aldol,[11d] and cyclic hydroboration reactions.[18] However, the application of borinates, borates and, in particular, boronate esters in controlling the reduction of remote asymmetric centres has been especially effective.

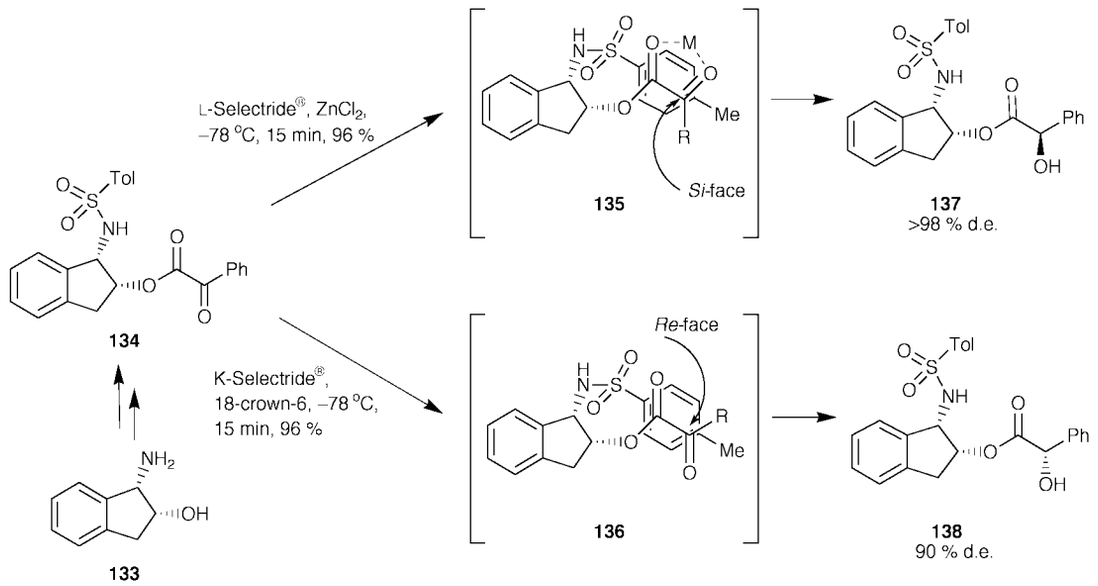
Boron chelate intermediates have been found to be effective in the reduction of hydroxy ketones. Highly selective asymmetric induction in the 1,3-asymmetric reduction of a γ-hydroxy ketone **35** *via* a boron complex **38**[29] (Scheme 10) has already been discussed (*vide supra*). Narasaka and Pai, however, reported some of the earliest work in this area.[66] They have described a highly stereoselective reduction of acyclic β-hydroxy ketones *via* borinic esters (Scheme 44).

syn-1,3-Diol **152** was prepared with excellent diastereoselectivity by treatment of β-hydroxy ketone **150** with tributylborane, and successive reduction with sodium borohydride (Scheme 44). The *syn*-stereochemistry observed was assumed to be a consequence of chelate-controlled intermolecular axial attack of hydride to a stable *pseudo*-chair conformation **151**. Similarly, Narasaka and co-workers achieved high 1,3-asymmetric induction in the reduction of oxime ether analogues **153**[67] (Scheme 45). The reduction of *O*-benzyloximes **153** with lithium aluminium hydride in the presence of sodium methoxide was found to result in the preferential formation of *syn*-1,3-amino alcohols **154**. In this case, *inter*molecular hydride addition to sodium-complexed chair-like conformation **156** of *trans*-oxime isomer, and *intra*molecular reduction of the *cis*-oxime *via* an aluminium-complexed transition state **157**, were proposed to explain the observed diastereoselectivity.

Evans *et al.* have reported effective 1,3-*anti*-stereocontrol (up to 92% de) in the reduction of acyclic β-hydroxy ketones **158** with tetramethylammonium triacetoxyborohydride *via* *intra*molecular hydride delivery[68] (Scheme 46).



Scheme 39

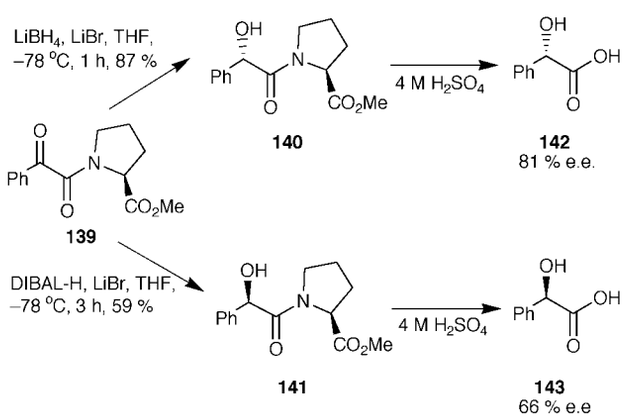


Scheme 40

Table 18 Hydroboration–carbonyl reduction of enones **165a–f** with $ThexBH_2$

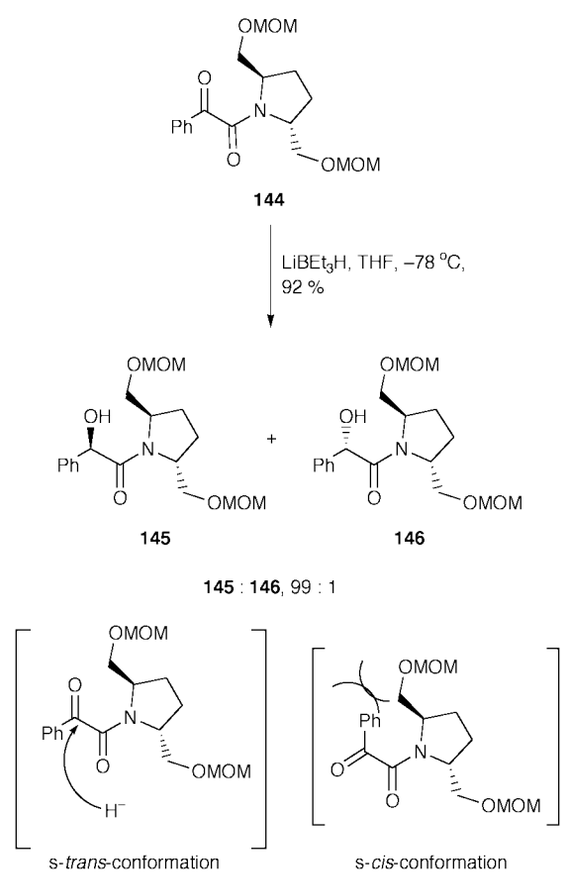
Entry	Ketone	R^1	R^2	*n*	Yield (%)	**166**:**167**
1	**165a**	H	H	1	84	15:1
2	**165b**	Me	H	1	78	19:1
3	**165c**	H	Me	1	32	1:8.5
4	**165d**	H	H	0	49	2.5:1 [a]
5	**165e**	H	H	2	86	6.6:1
6	**165f**	H	H	3	57	1.2:1 [a]

[a] Relative stereochemistry of the major product was not determined.



Scheme 41

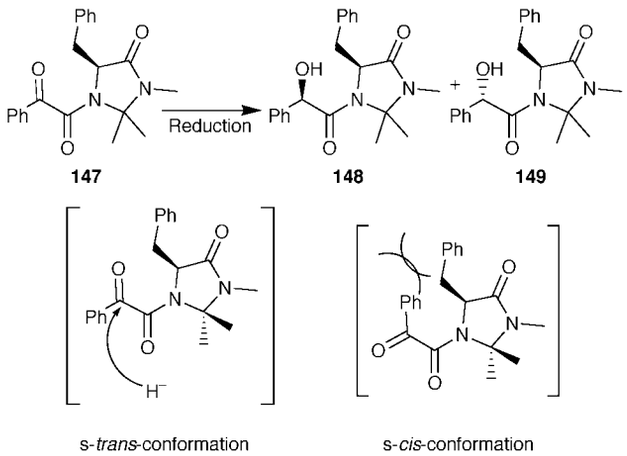
The mechanism of this reaction was thought to involve the acid-promoted ligand exchange of acetate for substrate alcohol by the triacetoxyborohydride. It was postulated that the resultant hydride intermediate then reduces proximal ketones by intramolecular hydride delivery *via* a cyclic borate *pseudo*-chair transition state **159**. Pansare and Ravi have since described a similar substrate-directed intramolecular addition mechanism in the reduction of α-keto amides **161a** and **161b**, with tetramethylammonium triacetoxyborohydride, which proceeded with good selectivity[69] (Scheme 47). The observed 1,4-diastereoselectivity for the reduction was reported to be consistent with a transition state **164**. A coplanar *syn*-amide–*anti*-α-dicarbonyl conformation was assumed, with intramolecular reduction from the *Si*-face of the ketone.



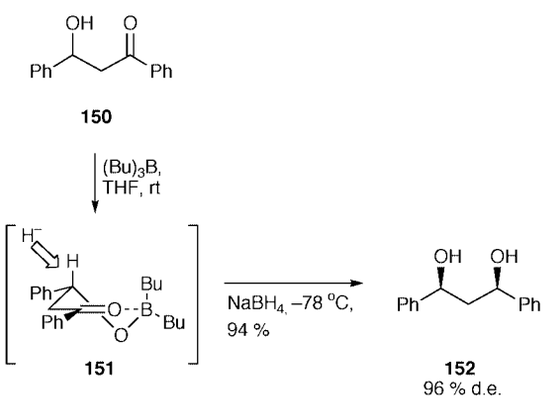
Scheme 42

Harada *et al*. have also reported the application of boron-complexed intermediates in efficient 1,4- and 1,5-diastereocontrolled hydroboration–carbonyl reduction reactions[70] (Scheme 48).

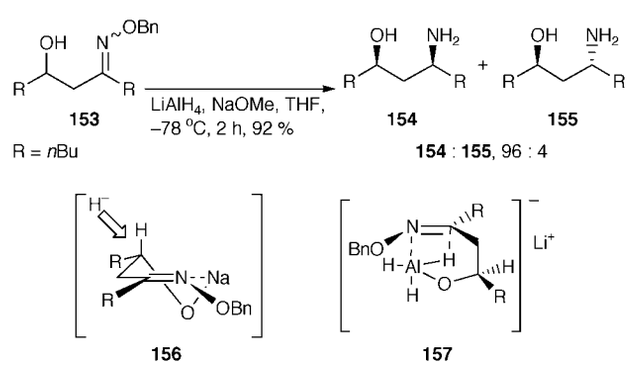
Reaction of ketones **165a** and **165b** with $ThexBH_2$ (Thex = 1,1,2-trimethylpropyl) proceeded with high 1,4-*syn*-diastereoselectivity affording diols **166a** and **166b** respectively (Table 18, entries 1 and 2). In contrast, the reaction of $ThexBH_2$ with *Z*-enone **165c** proceeded with high 1,4-*anti*-stereocontrol, to yield a 8.5:1 mixture of **167c** and **166c** diastereomers (Table 18, entry 3). High levels of 1,5-asymmetric induction were also achieved in the hydroboration–reduction reaction of enone



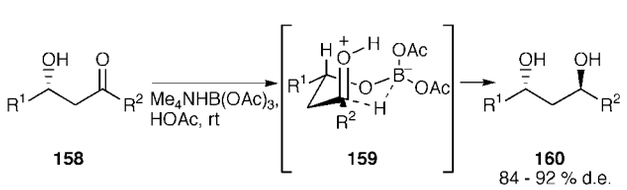
Scheme 43



Scheme 44



Scheme 45



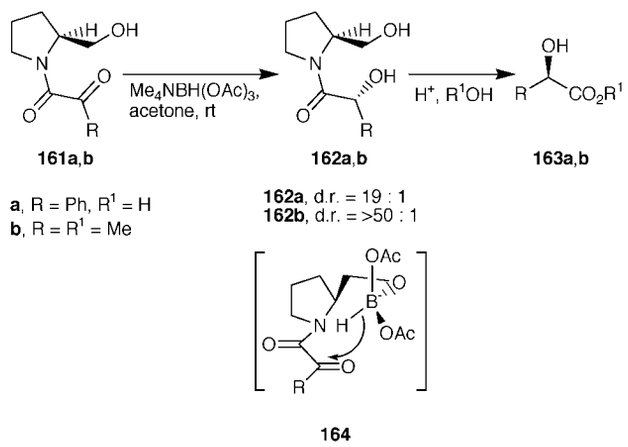
Scheme 46

165e (Table 18, entry 5). However, levels of 1,3- and 1,6-diastereocontrol were low for analogous systems **165d** and **165f** (Table 18, entries 4 and 6).

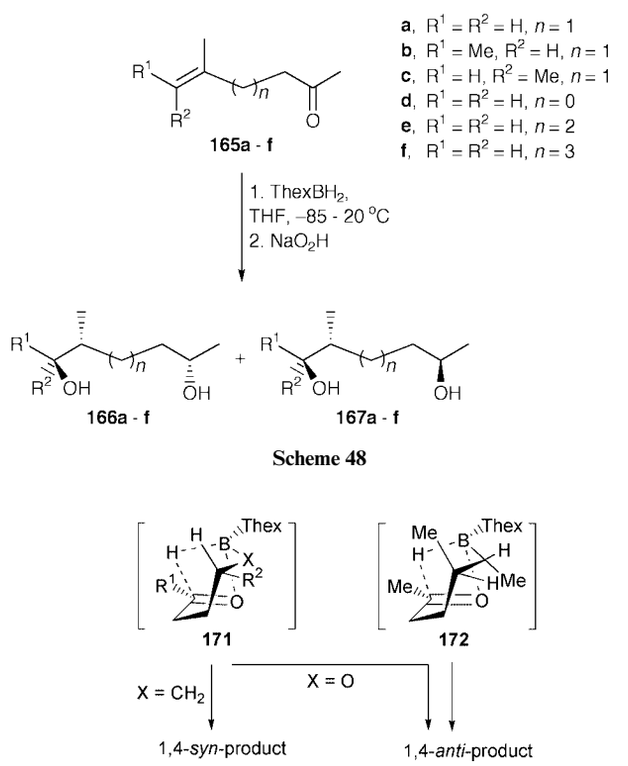
It was proposed that intermolecular hydroboration precedes intramolecular carbonyl reduction. The reducing agent is therefore incorporated in the reactant, and the reduction was thought to progress *via* an intramolecularly constrained cyclic transition state such as **171**, in which R^2 takes a *pseudo*-equatorial position (Fig. 12). The 1,4-*anti*-diastereoselectivity

Table 19 Reduction of diketones **168a–e**

Entry	Diketone	R^1	R^2	R^3	*n*	Yield (%)	**169**:**170**
1	**168a**	Ph	Ph	H	1	59	47:1
2	**168b**	Me	Me	H	1	92	11:1
3	**168c**	*i*Pr	*i*Pr	H	1	78	8.1:1
4	**168d**	Ph	Me	H	1	89	17:1
5	**168e**	Me	Me	Me	0	39	6.1:1



Scheme 47



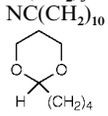
Scheme 48

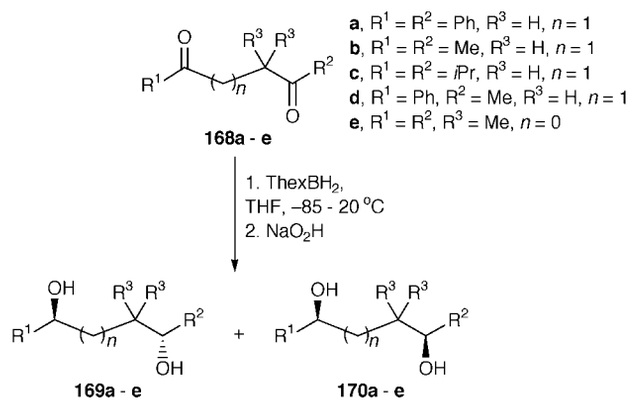
Fig. 12 Possible cyclic transition states involved in the reduction of compounds **165**.

observed in the reaction of **165c** was thought to be due to a *pseudo*-diaxial transition state **172** in which an unfavourable *gauche* interaction between the methyl group and the bulky thexyl group is avoided (Fig. 12).

The reduction of diketone substrates **168a–e** was also explored (Scheme 49). Excellent *anti*-stereoselectivity (47:1) was obtained in the reduction of symmetrical 1,4-diketone **168a** with $ThexBH_2$ (Table 19, entry 1). High 1,4-stereocontrol was also observed in the preparation of C_2-symmetric diols **169b** and **169c** (Table 19, entries 2 and 3), and *anti*-diol **169d** (Table 19, entry 4). However, reduced selectivity was noted in the

Table 20 Reduction of keto boronate esters **177**

177, R	Yield (%)	**180**, Ee (%)
CH_3	83	85
nC_5H_{11}	87	92
C_6H_{11}	85	>98
Ph	95	97
$Cl(CH_2)_3$	97	93
$NC(CH_2)_{10}$	81	97
	89	98
$CH_3O_2C(CH_2)_4$	95	>96



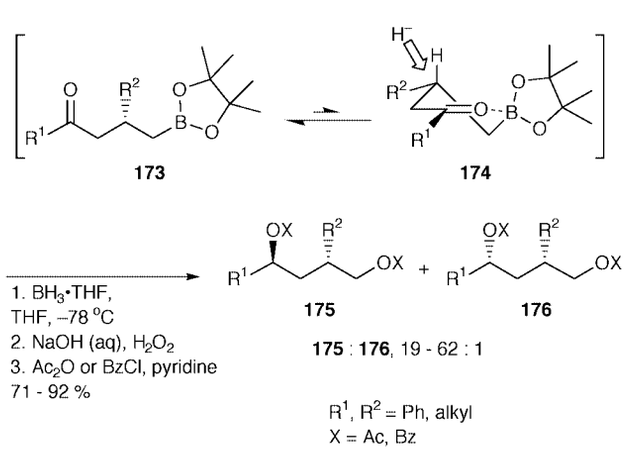
Scheme 49

reduction of 1,3-diketone **168e** (Table 19, entry 5). A staggered transition state **171** was again proposed to explain the high 1,4-diastereoselectivity observed (Fig. 12).

Examples of substrate-directed mechanisms involving aluminium complexes, and reagent-controlled asymmetric induction, in the reduction of diketones, have been discussed (*vide supra*).

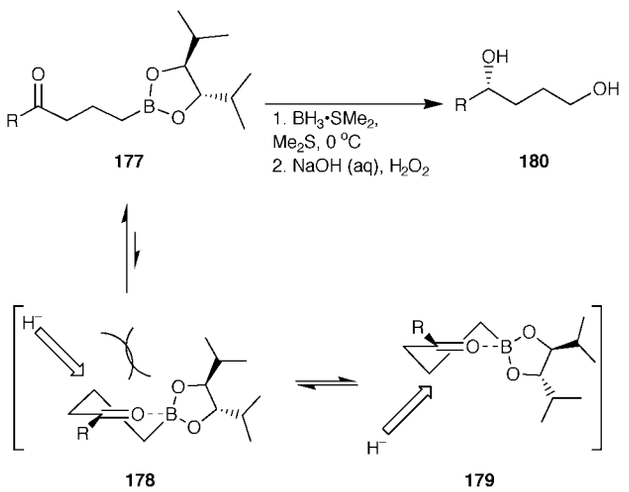
The use of boronate esters has been particularly successful in achieving high remote asymmetric induction in hydride additions to carbonyl groups, with examples ranging up to 1,7-stereocontrol.

In 1992, Molander *et al.* observed high diastereoselectivities upon the 1,3-reduction of a range of keto boronate compounds of type **173** with borane–tetrahydrofuran complex[71] (Scheme 50). The high diastereoselectivities obtained for the reduction of these γ-boronate ketone substrates **173** was presumed to be a result of stereoelectronically preferred axial attack to a boron-complexed substrate such as **174**. This synthetic method



Scheme 50

represented the first use of a carbon-bound organometallic–ketone intramolecular complex as a conformational device in diastereoselective carbonyl addition reactions. Molander and Bobbitt subsequently reported an impressive example of 1,7-asymmetric induction in the borane–dimethyl sulfide reduction of a keto boronate substrate of type **177**[72] (Scheme 51). In this case a chiral ligand attached to boron was used.

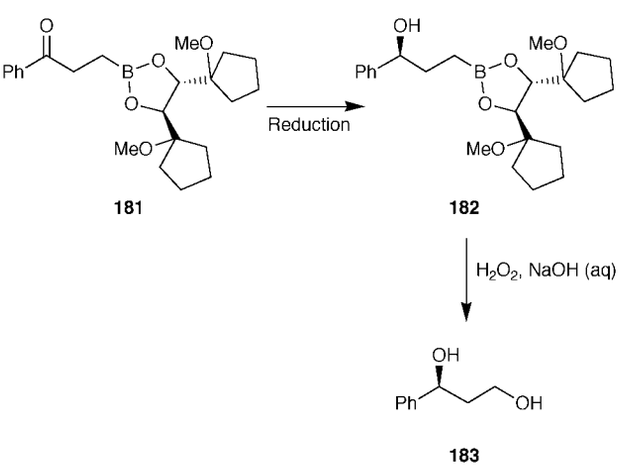


Scheme 51

Given the extraordinarily high enantiomeric excesses observed for a variety of substrates (Table 20), a highly ordered transition state was suggested. The origin of the diastereoselection was thought to be steric interaction between the isopropyl group of the boronate and the incoming nucleophile in complexed transition states such as **178** and **179**.

This example of 1,7-stereocontrol represents a useful method for the synthesis of simple, enantiomerically enriched secondary alcohols, in which there is little steric or electronic difference between the groups adjacent to the prochiral carbonyl unit in the substrate.

Previous work by Whiting and co-workers has focused on the application of β-boronate carbonyl compounds for controlling the stereochemistry of aldol reactions.[73,74] More recently, directed remote 1,6-asymmetric induction in the reduction of a ketone *via* a homochiral boronate ester was reported[75] (Scheme 52). Excellent 1,6-stereocontrol was achieved in the reduction of β-keto boronate ester **181** with borane–tetrahydrofuran complex in dichloromethane at −45 °C, yielding (*S*)-alcohol **183** in 89% enantiomeric excess (Table 21, entry 2).



Scheme 52

Table 21 Reduction of keto boronate ester **181**

Entry	Reduction (reagents and conditions)	183	
		Yield (%)	Ee (%)
1	BH_3·SMe_2, THF, −45 °C	81	55
2	BH_3·THF, CH_2Cl_2, −45 °C	87	89
3	L-Selectride®, THF, −78 °C	76	0

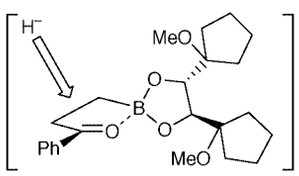
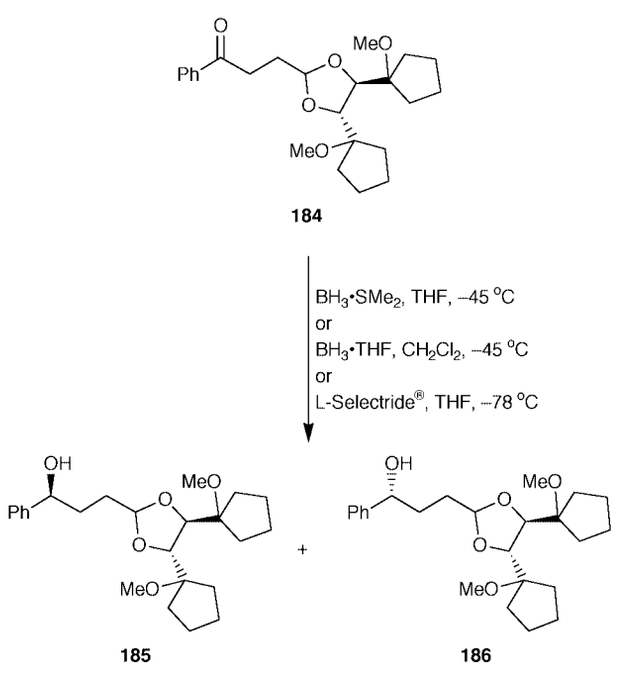


Fig. 13 Favoured direction of reduction of ketone **181**.

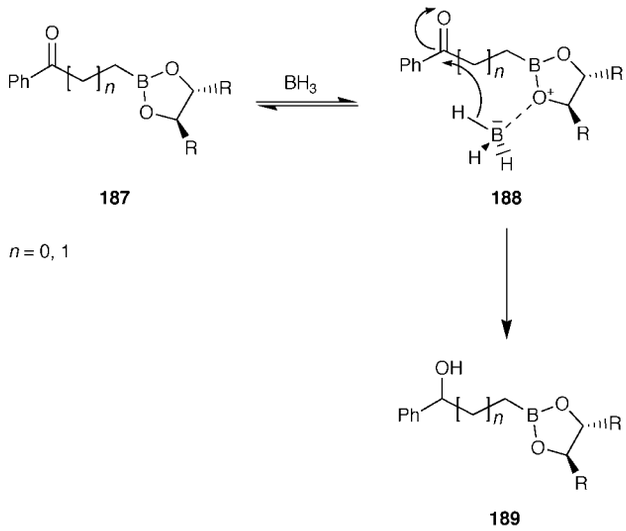
Again, the asymmetric induction observed in this reduction was rationalised by assuming carbonyl group activation *via* chelation to the boronate ester group. In this model, the boronate ester blocks the addition of 'B–H' from the *Si*-face of the substrate (Fig. 13).

When borane–dimethyl sulfide complex was used, a decreased level of stereoselectivity was observed for the reduction of homochiral ketone **181** (Table 21, entry 1). In this case, it was thought that dimethyl sulfide competes for chelation of the boronate group resulting in reduced 1,6-diastereocontrol. Reduction with L-Selectride® at −78 °C gave no asymmetric induction (Table 21, entry 3) which suggested that L-Selectride® did *not* require boronate activation by chelation in order to reduce the carbonyl group. However, whilst the mechanistic interpretation agreed with the experimental results obtained, it was not possible to detect the postulated boronate–ketone intramolecular complex spectroscopically. However, the existence of an intramolecular boron–oxygen chelate transition state in these keto boronate reductions has been since reinforced by recent work[76] (Scheme 53).



Scheme 53

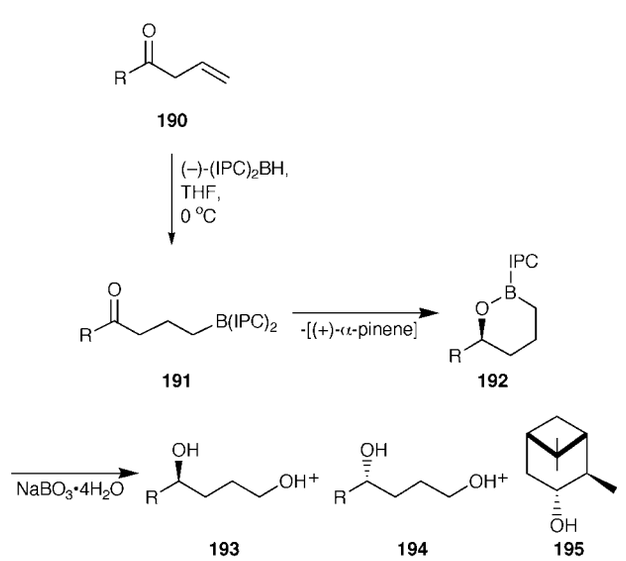
No stereoselection was observed in the borane and L-Selectride® reductions of the non-boron containing ketone analogue **184** (Scheme 53). It was therefore concluded that the presence of the boronate centre was essential for the control of the asymmetric borane reduction of the carbonyl group. These results also confirmed that in the case of the acetal **184**, neither the dioxolane ring oxygen atoms, nor the methoxy functions were able to direct asymmetric induction by a borane–oxygen chelating system such as **188** (Scheme 54).



Scheme 54

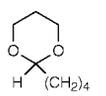
Further evidence for the asymmetric reduction of keto boronate esters of the type **177** and **181**, *via* boron–oxygen chelate intermediates, was provided by the study of MM2 force field parameters developed for boronate esters and their carbonyl complexes.[77]

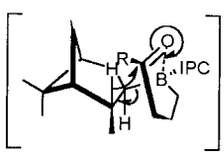
Finally, in an attempt to increase the likelihood of observing an intramolecular boron–carbonyl oxygen complex, replacement of the boronate ester by a stronger Lewis acid such as a trialkylborane was considered by Molander and Bobbitt.[78] However, it was found that hydroboration of β,γ-unsaturated ketones **190** with (−)-diisopinocamphenylborane, [(−)-$(IPC)_2$-BH], followed by sodium perborate oxidation resulted in the formation of (*R*)-secondary alcohols **193** in high enantiomeric excess (Scheme 55).



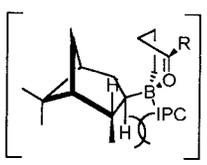
Scheme 55

Table 22 Hydroboration/intramolecular reduction of allyl ketones **190**

190, R	Yield (%)	**193**, Ee (%)
nC_5H_{11}	98	96
C_6H_{11}	91	87
Ph	86	94
$Cl(CH_2)_3$	85	98
$NC(CH_2)_{10}$	98	75
	88	86
$CH_3O_2C(CH_2)_4$	94	88



196



197

Fig. 14 Mode of intramolecular reduction of ketone **191**.

This unexpected result was explained by a concerted intramolecular reduction of the carbonyl group with release of (+)-α-pinene **195**. A favoured intermediate **196** which minimises steric interactions, and also provides close approach of the hydride to the carbonyl centre, was postulated to rationalise the high selectivity observed in these particular reactions (Fig. 14).

3 Summary and conclusion

In recent years, there have been many major advances for the absolute stereochemical control of asymmetric centres using a wide range of methodologies. Remote asymmetric control is one of these methods, which can prove highly efficient under certain circumstances. Effecting stereocontrolled reduction over centres which are disposed between 1,2 and 1,4 relative to another centre, tends not be difficult to achieve, however, more remote stereocontrol (1,5 upwards) is more difficult. It is possible to specifically design molecules which contain functions which enable either chelation of the carbonyl group intramolecularly (sometimes involving formation of a reactive intermediate), or chelation of the reducing agent intermolecularly, to achieve efficient remote carbonyl reduction. As our ability to model multi-functional systems in which both intra- and intermolecular interactions play a role improves, one can expect more efficient examples of greater than 1,5-asymmetric reduction processes to be reported. There is clearly great scope for the application of such remote stereocontrolled processes in natural product synthesis.

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