Studies on the asymmetric reduction of β-oximino methyl ether boronates: reagent control, double diastereocontrol and transmitted remote asymmetric induction

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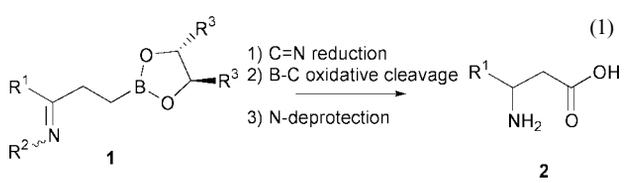
High asymmetric induction (94% ee) could be obtained in the reduction of the achiral *E*-oxime ether boronate **5** with a homochiral oxazaborolidine **13**–BH_3–THF complex. Application of this homochiral reducing agent system to non-aromatic oxime ethers **21** produced low to moderate asymmetric induction. Application of the same homochiral reducing agent system to reduction of homochiral boronate *E*-oximes **3** and **4** produced extreme double diastereoselection effects, *i.e.* 8 and 95% ee respectively, which demonstrated that remote asymmetry was being 'transmitted' by a suitable choice of a 'partner' molecule from the boronate moiety to the oxime during reduction. However, attempts to obtain direct remote asymmetric induction in the reduction of homochiral β-oximino boronate methyl ethers **3** and **4** to the corresponding amines produced zero, with for example BH_3–THF complex, up to 28% ee with an Et_3N–BH_3–THF mixture (after oxidative boronate ester cleavage).

Introduction

We recently reported the synthesis of a series of β-hydrazono, oximino methyl ether and imino chiral boronate esters of general type **1**.[1] The preparation of such derivatives was initiated in order to study the ability of the chiral boronate function of derivatives **1** in directing remote asymmetric reduction[2] of the C=N bond, *via* an activated complex as shown in Fig. 1, to provide a new route to β-amino acids [eqn. (1)].[3] In



(1)

1 **2**

this paper, we report the details of our unexpected results on the reduction of systems of oxime methyl ether derivatives of **1**, which include the indirect effects of the remote chiral ester[4] and chiral reagent controlled hydride reductions.

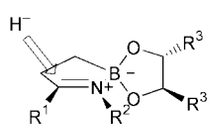
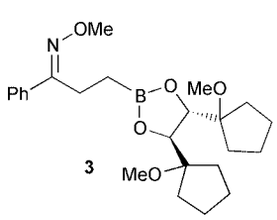


Fig. 1 Predicted trajectory of approach of a hydride-based reduced agent.



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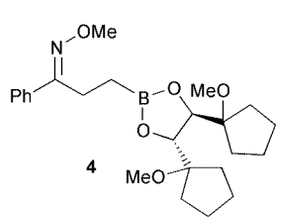

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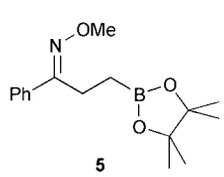

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Results and discussion

The synthesis of chiral β-boronate oxime ether (*S*,*S*)-**3** and its enantiomer (*R*,*R*)-**4** has been recently reported and their oxime ether geometries were shown to be *E*.[1] Consequently, C=N double bond reduction of these systems was investigated. In keeping with previous work from our laboratories concerning the reduction of β-keto boronate,[2a,b] initially model studies were undertaken concerning the reduction of achiral β-boronate *E*-*O*-methyloxime ether **5** with borane.[5]

It has been reported that facile borane reduction of oxime ethers occurs at room temperature to furnish the corresponding primary amines upon acidic or basic hydrolysis, with C=N bond reduction preceeding N–O bond reduction.[6] Achiral oxime ether **5** was therefore treated with an excess of borane–tetrahydrofuran complex in THF, followed by cleavage of the B–C bond with alkaline hydroperoxide and concomitant hydrolysis of the intermediate B–N complex, to yield the amino alcohol intermediate **6**. Direct diacetylation provided racemic derivative **7** (Scheme 1).[7]

In order to determine the asymmetric induction in subsequent reductions, it was necessary to develop an ee assessment method, preferably using chiral HPLC. Fortunately, enantiomeric separation of racemic acetate **7** was achieved using chiral HPLC analysis (Table 1, entry 1). The HPLC peaks were assigned by comparison with enantiopure (*S*)-**7** (Table 1, entry 2). A commercial sample of optically-pure γ-amino alcohol (*S*)-**6** was kindly donated by Chirotech; acetylation with acetic anhydride in pyridine yielded optically-pure (*S*)-diacetyl derivative (*S*)-**7** in 90% yield.

A similar synthetic protocol to that described for the reduction of achiral substrate **5** (*i.e.* as Scheme 1) was followed

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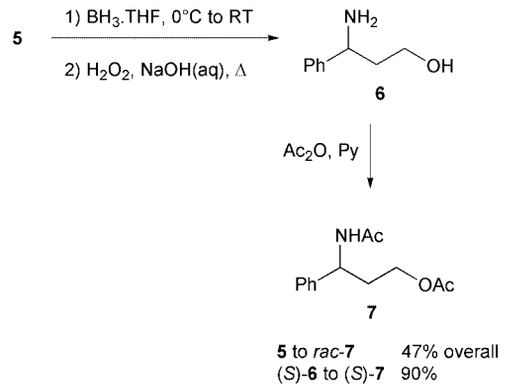
Table 1 Chiral HPLC analysis[a] of 1-acetoxy-3-acetylamino-3-phenylpropane **7**

		(*R*)-**7**		(*S*)-**7**	
Entry	Product	t_R/min	%	t_R/min	%
1	*rac*-**7**	5.06	49.7	8.01	50.3
2	(*S*)-**7**	5.04	0.9	7.97	99.1

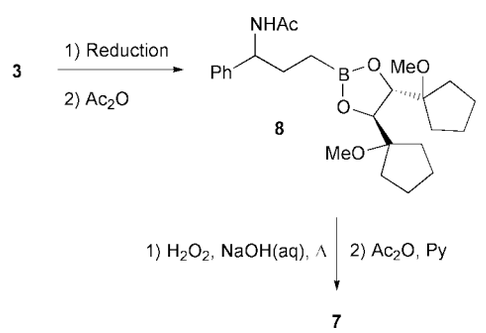
[a] Chiralpak AS, SFC, $\lambda = 205$ nm, 35 °C, 2.98 kpsi, 2 ml min^{-1}, 86% CO_2: 14% (isopropyl alcohol + 0.2% Et_2NH) elution.



Scheme 1

for the reduction of chiral β-boronate oxime ether (*S*,*S*)-**3** with borane–tetrahydrofuran complex, without isolation of intermediate **6**. Direct acetylation with acetic anhydride in pyridine provided **7** in 94% yield. Chiral HPLC analysis of the crude product **7** revealed that no asymmetric induction was obtained for the reduction.

In order to probe this reduction further, several additional reducing agents were screened for the reduction of this chiral β-boronate oxime ether (*S*,*S*)-**3**. The synthetic procedure was altered for these subsequent reductions, by directly quenching the reduction reactions with acetic anhydride to provide intermediate acetamide **8**, as shown in Scheme 2. This procedure was



Scheme 2

found to be more convenient, enabling determination of the diastereomeric excess of the resulting acetamide **8** by NMR. Subsequent oxidative cleavage of the C–B bond of **8** in the presence of alkaline hydrogen peroxide at room temperature followed by acetylation of the resulting primary alcohol, yielded the desired acetate **7** in good yield. Good yields were obtained following this synthetic route due to the decreased water-solubility of the intermediate *N*-acetylated product compared to that of the free amino alcohol **6** intermediate. Thus, chiral oxime ether (*S*,*S*)-**3** was successfully reduced with borane–dimethyl sulfide complex, borane–tetrahydrofuran complex and DIBAL-H, yielding acetamide **8** upon treatment with acetic anhydride. Reduction with L-Selectride® and lithium aluminium hydride was unsuccessful, and starting materials were recovered.

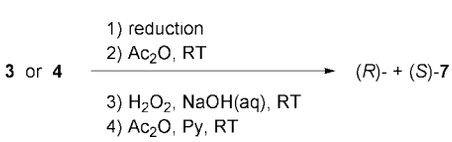
Table 2 Preparation of acetamide **8** *via* reduction of oxime ether (*S*,*S*)-**3**

Entry	Reduction (reagents and conditions)	Yield (%)	Dr of **8**
1	BH_3·SMe_2, THF, −15 °C–rt, 16 h	96	1 : 1
2	BH_3·THF, 0 °C–rt, 2 d	89	1 : 1
3	DIBAL-H, THF, rt, 2 d	87	1 : 1

Examination of the ^{13}C NMR spectrum of acetamide **8** could be used to determine the diastereomeric ratio. A 1 : 1 mixture of diastereomeric boronates was observed for all reducing agents (Table 2), as demonstrated by two peaks of equal intensity at δ 169.4 and 171.1 ppm, corresponding to the diastereomeric acetamide quaternary carbon atoms. Peaks of equal intensity at δ 55.0 and 55.2 ppm corresponding to the CHN methine tertiary carbon were also noted, confirming the presence of a 1 : 1 mixture of diastereomeric acetamides **8**. The lack of stereocontrol observed for the reductions of (*S*,*S*)-**3** was confirmed upon elaboration of the acetamide reduction product **8** to the diacetyl derivative **7** (Scheme 2). Chiral HPLC revealed that in each case, diacetyl derivative **7** was obtained in racemic form in all cases, confirming the results shown in Table 2.

The lack of asymmetric induction observed for the reduction of oxime ether **3** is likely be the result of the *E*-oxime ether stereochemistry of the substrate. B–N chelation in intermediate **3** is precluded, but could be replaced by B–O chelation as shown by the intramolecular flattened chair chelate **10** (Scheme 3). However, even if chelation does occur as shown by **10**, the remote chirality of the boronate ester is presumably too far from the oxime carbon to control asymmetric reduction. Hence, intermediate **10** should result in a 1 : 1 mixture of diastereoisomers **12** and hence **8** upon acetylation. In contrast, if oxime ether geometry **9** were accessible, B–N chelation could occur as shown by **11**, which in turn one would expect to direct asymmetric induction efficiently to provide **12**.

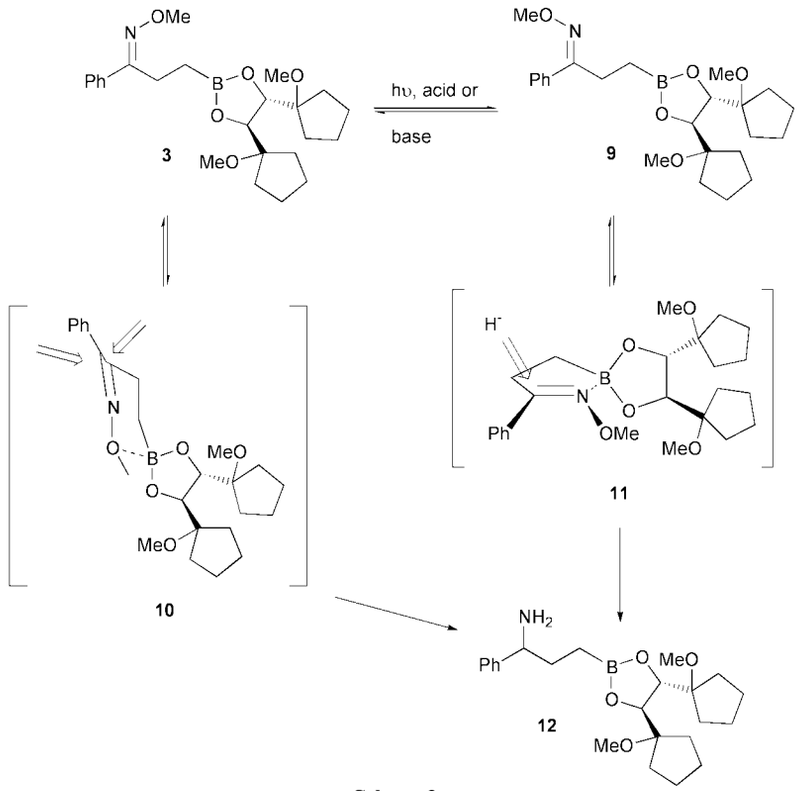
A solution to this problem would therefore be the design of a reducing system that either: a) allows reversible *E*–*Z* isomerisation in the reduction process, with the assumption that chelate **11** reduces more rapidly and selectively than chelate **10**; or b) oxime **3** could be irreversibly converted to oxime **9**. Previous studies[1] on these oxime ethers have shown that oxime **3** is stable, shows little sign of isomerisation and is clearly not reduced under the reaction conditions shown in eqn. (2) in a



(2)

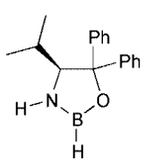
stereoselective manner. This allows us to conclude that the intramolecular boronate function of **3** is unable to effect isomerisation of the oxime and subsequently direct reduction. The alternative of "pushing" the equilibrium in favour of isomer **9** may be possible, since oxime ethers are susceptible to photochemical isomerisation,[8] as well as isomerisation under acidic or basic conditions,[9] but are stable to thermal isomerisation.[10] Unfortunately, such conditions are unlikely to be compatible with the desired reduction process outlined in the conversion of **9** to **12**.

In order to probe whether there was any further evidence for the intervention of the remote boronate functionality in the reduction of an oxime such as **3**, we decided to employ a homochiral reducing agent, since this would introduce the possibility of double-diastereoisomeric effects.[11] Such effects might be expected to be highly sensitive to the remote functionality and provide a much more sensitive probe for the possible effects of the remote boronate chirality. Whilst the asymmetric reduction of ketones has been intensively investigated,[12] the corresponding enantioselective reduction of C=N double bonds is much



Scheme 3

less studied, including asymmetric hydrogenation and hydrosilylation, as well as the use of chirally-modified reagents.[13] However, prochiral oxime ethers have been enantioselectively reduced using conditions reported by Itsuno *et al.*,[14] employing an *in situ* generated oxazaborolidine system **13** in the presence



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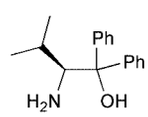

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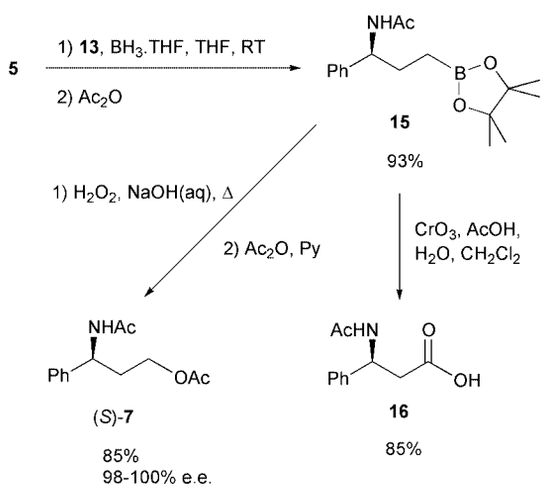
of excess borane to provide primary amines with an (*S*)-configuration. Sakito *et al.* subsequently reported the effect of oxime ether geometry on the enantioselectivity of oxazaborolidine-based reductions[15] using a (−)-norephedrine-derived reducing system and found that the prochiral carbon does not play a central role in the stereoselectivity of this reduction, with the preferred absolute configuration of the amine formed found to be dependent on the geometry of the oxime ether.

In order to test the compatibility of such oxazaborolidine reducing systems with the β-boronate oxime ethers, we examined the reduction of oxime ether **5**, initially using Itsuno's system under stoichiometric conditions. Thus, homochiral β-amino alcohol **14** was prepared by treating (*S*)-valine ethyl ester hydrochloride with an excess of phenylmagnesium bromide as reported.[16] Treatment of amino alcohol **14** in THF with excess borane–tetrahydrofuran complex at 0 °C for 6 hours, yielded the borane complex of **13** to which oxime ether **5** was added. The reaction was allowed to warm to room temperature overnight then quenched with acetic anhydride to afford acetamide **15** in 93% yield after column chromatography (Scheme 4).

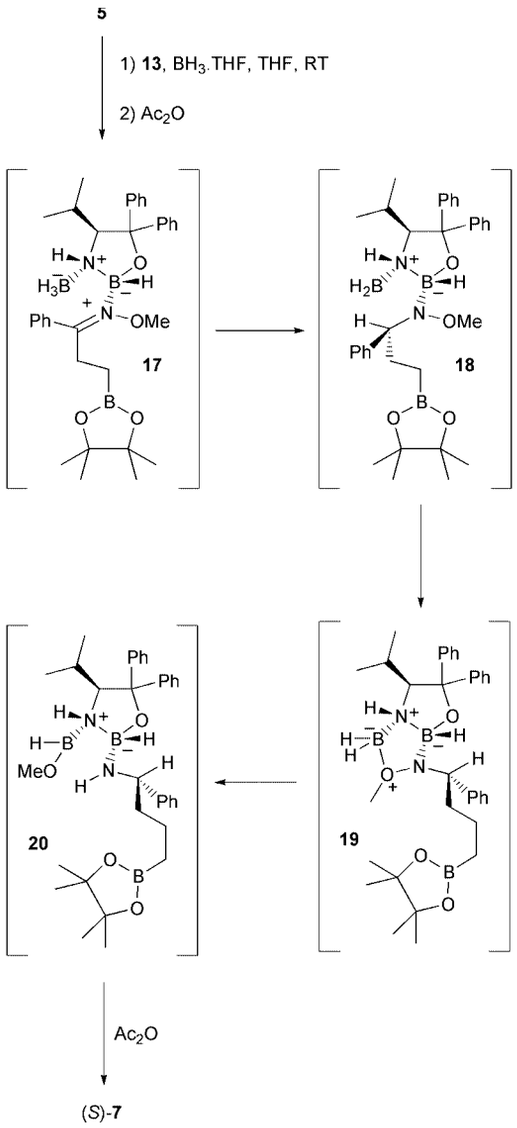
The stereoselectivity of the reduction was assessed by elaboration of boronate ester **15** to diacetyl derivative **7**. The major enantiomer formed was (*S*)-**7**, in 98–100% ee, which is comparable to that obtained by Itsuno for the reduction of acetophenone *O*-methyloxime.[14] Oxidation of the boronate unit of **15** was also accomplished using reported conditions,[17] to provide β-amino acid derivative **16** (Scheme 4).[18]



Scheme 4

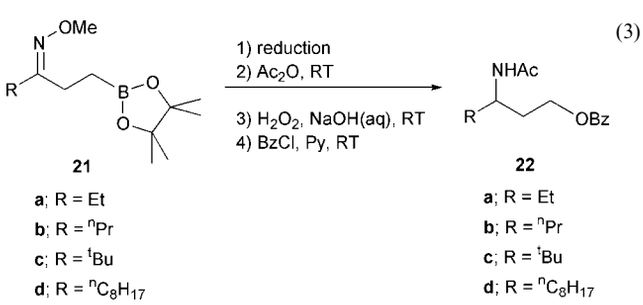
Oxazaborolidine **13** could also be used catalytically (25 mol%) for the borane–THF reduction of β-boronate oxime ether **5**, to provide (*S*)-**7** with reduced asymmetric induction, *i.e.* 85% ee, after *in situ* acetylation, peroxide-mediated C–B bond oxidation and acetylation (73% overall yield).

The excellent stereoselectivity obtained in the borane reduction of β-boronate oxime ether **5** in the presence of stoichiometric and catalytic oxazaborolidine **13**, can be explained by directly applying the mechanism proposed by Corey for the reduction of prochiral ketones.[19] Thus, complex **17** would be responsible for delivery of hydride to the oxime carbon, to provide intermediate **18** (Scheme 5). Since Itsuno and Sakito found[14,15] that the asymmetric reduction of ketone-derived oxime ethers to the corresponding primary amines using an oxazaborolidine reducing system required the presence of *one* equivalent of borane, whereas the corresponding reduction of aldehyde oxime ethers with borane only, required *two* equivalents of BH_3, one may conclude that cleavage of the N–O bond is likely to proceed *via* an intramolecular hydride delivery to intermediate **19** (Scheme 5). The resulting complex **20** is then quenched with acetic anhydride to provide final product **7**.



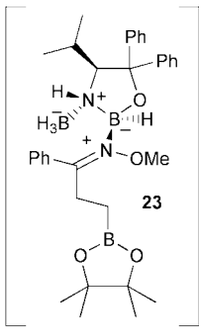
Scheme 5

The successful reduction of oxime **5** led us to examine other aliphatic oxime ethers **21**[1] in the presence of the Itsuno oxazaborolidine **13**. The reduction products were isolated as *O*-benzoyl derivatives **22**, as summarised in eqn. (3) and Table 3.



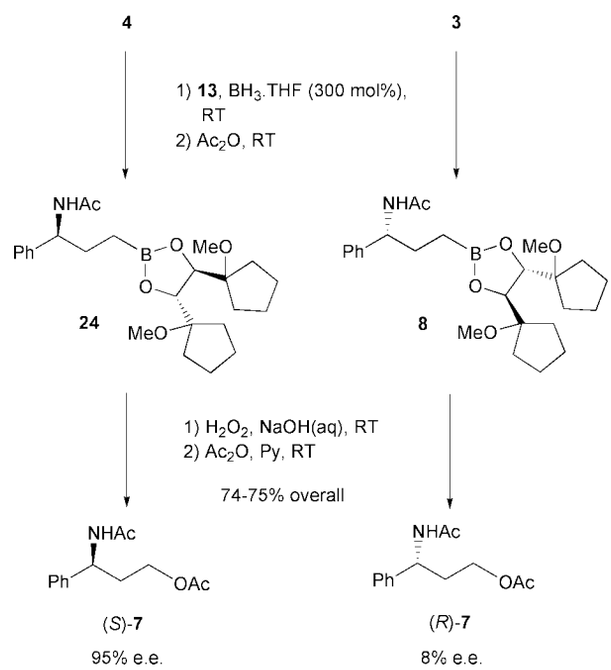
(3)

The magnitude of the stereoselectivity achieved for the oxime ether **21** reductions in the presence of oxazaborolidine **13**, was obtained by chiral HPLC analysis of the *O*-benzoylated reduction products **22**. The corresponding racemic compounds **22** were obtained *via* reduction of β-boronate oxime ethers **21** with borane–tetrahydrofuran complex. The absolute stereochemistry of the major enantiomers from the asymmetric reduction of oximes **21** were not determined, except based upon our knowledge of the starting material oxime ether C=N double bond geometry, from which a similar outcome to that demonstrated for α-phenyl oxime ether **5** may be predicted. Therefore, it is expected that the major enantiomers for **22a**, **b** and **d** would be (*R*), and **22c** would be (*S*). The low to modest enantiomeric excesses obtained for borane reduction of prochiral oxime ethers **21** in the presence of oxazaborolidine **13** may be due to the increased competition between intermolecular "B–H" addition, rather than intramolecular hydride attack *via* the sterically less favourable complex **23** (compare with complex **17**).[19]



Having demonstrated the high efficiency of catalyst **13** to reduce achiral oxime **5**, we turned to examine the potential for the boronate function in systems **3** and **4** at influencing the reduction process. If the reduction of both chiral systems **3** and **4** followed the mechanism outlined in Scheme 5, one would not expect to observe any double diastereoselective effects, thus confirming the redundant role of the boronate ester and the zero asymmetric induction observed for system **3**.

Treatment of (*S*)-valine-derived amino alcohol **14** in THF with 4 equivalents of borane–tetrahydrofuran complex at 0 °C for 6 hours, yielded a reducing mixture to which chiral β-boronate oxime ether (*R*,*R*)-**5** was slowly added. The reaction was allowed to warm to room temperature, then quenched with acetic anhydride. Oxidative cleavage of the C–B bond using alkaline hydrogen peroxide, followed by acetylation of the resulting primary alcohol, furnished diacetyl derivative (*S*)-**7** in 95% enantiomeric excess. The sense and magnitude of the asymmetric induction obtained in the borane reduction of chiral boronate (*R*,*R*)-**4** in the presence of oxazaborolidine **13**, was comparable to that obtained for the corresponding achiral oxime ether **5**. However, and in direct contrast, a similar reduction of enantiomer, (*S*,*S*)-**3** yielded the (*R*)-acetamide **7** in 8% enantiomeric excess (Scheme 6)!



Scheme 6

Table 3 Borane reduction of oxime ethers **21**

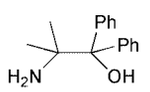
Entry	Oxime ether	R	Reduction (reducing agent and conditions)	Ee of **22** (%)
1	**21a**	Et	BH_3–THF, THF, rt, 14 h	—
2	**21a**	Et	**13**, BH_3–THF (300 mol%), THF, 2 d	26
3	**21b**	*n*Pr	BH_3–THF, THF, rt, 2 h	—
4	**21b**	*n*Pr	**13**, BH_3–THF (300 mol%), THF, 2 d	62
5	**21c**	*t*Bu	BH_3–THF, THF, rt, 6 d	—
6	**21c**	*t*Bu	**13**, BH_3–THF (300 mol%), THF, 6 d	47
7	**21d**	nC_8H_{17}	BH_3–THF, THF, rt, 16 h	—
8	**21d**	nC_8H_{17}	**13**, BH_3–THF (300 mol%), THF, 16 h	16

Table 4 Borane reduction of chiral β-boronate oxime ethers (*S*,*S*)-**3** and (*R*,*R*)-**4** in the presence of achiral "N–B"-type additives

			(*S*) *versus* (*R*)-**7**		
Entry	Oxime	Reduction (reagents and conditions)	Yield (%)	Ee (%)	Absolute configuration
1	(*S*,*S*)-**3**	BH_3–pyridine (100 mol%), BH_3–THF (400 mol%), rt, 14 h	90	1.4	*R*
2	(*S*,*S*)-**3**	Et_3N (100 mol%), BH_3–THF (400 mol%), rt, 14 h	81	0	—
3	(*S*,*S*)-**3**	Et_3N (100 mol%), BH_3–THF (100 mol%), rt, 20 h; BH_3–THF (300 mol%), rt, 5 d	82	28	*R*
4	(*S*,*S*)-**3**	Et_3N (100 mol%), BH_3–THF (250 mol%), rt, 2 d; BH_3–THF (150 mol%), rt, 4 d	83	3	*R*
5	(*S*,*S*)-**3**	**25** (100 mol%), BH_3–THF (400 mol%), rt, 14 h	67	2.2	*R*
6	(*S*,*S*)-**3**	**25** (100 mol%), BH_3–THF (250 mol%), rt, 2 d; BH_3–THF (350 mol%), rt, 6 d	96	13	*S*
7	(*R*,*R*)-**4**	Ethanolamine (100 mol%), BH_3–THF (400 mol%), rt, 14 h	69	0	—
8	(*S*,*S*)-**3**	Ethanolamine (100 mol%), BH_3–THF (250 mol%), rt, 2 d; BH_3–THF (350 mol%), rt, 6 d	95	2	*S*

Clearly the chiral boronate functionalities of oximes **3** and **4** are capable of influencing the C=N double bond reduction as summarised in Scheme 6, resulting in extreme double diastereoselection effects when coupled with the oxazaborolidine **13**-based reducing system. The matched reducing agent–boronate ester stereochemistry of **4** produces unperturbed, high asymmetric induction, similar to that obtained for the reduction of achiral boronate **5**. However, the use of the corresponding mismatched system of **3** and **13** and borane produced low asymmetric induction, with reversal of the sense of asymmetric induction. These results show that remote asymmetric effects can be "transmitted" by a suitable choice of "partner" molecule. In the present example, it would seem that oxazaborolidine **13**, presumably as its borane adduct, destructively transmits stereochemical information from the homochiral boronate moiety to the remote C=N double bond in oxime ether (*S*,*S*)-**3**. These effects are manifest despite the remote position of the boronate ester and are contrary to the previous indications that boronate ester of either **3**, **4** or **5** play no part in their respective reductions. Clearly, if oxazaborolidine system **13** could exert such an effect, one might expect other, achiral, systems to behave similarly. Hence, controlling the remote asymmetric induction would become a matter of carefully matching the structure of the reducing agent to these boronate ester systems. To this end, further investigations of a range of achiral additives, in place of the chiral catalyst oxazaborolidine **13**, for the borane-based reducing system were undertaken to more fully probe the nature of these transmitted remote asymmetric interaction effects as shown in eqn. (2) and Table 4.

Negligible stereocontrol was observed in the reduction of homochiral β-boronate ester (*S*,*S*)-**3** with excess borane–tetrahydrofuran complex, in the presence of one equivalent of borane–pyridine complex (Table 4, entry 1) or borane–triethylamine complex (Table 4, entries 2 and 4). Indeed, borane–pyridine complex alone did not effect reduction of oxime ether **3**. However, the reduction in the presence of the borane–triethylamine complex additive proved interesting. When oxime ether (*S*,*S*)-**3** was stirred at room temperature overnight with one equivalent of borane–triethylamine complex (prepared *in situ* by treatment of triethylamine with borane–tetrahydrofuran complex), then treated with 3 further equivalents of borane–tetrahydrofuran followed by acylation and elaboration to the diacetyl derivative **7**, chiral HPLC analysis revealed the formation of (*R*)-**7** in 28% ee (Table 4, entry 3). No asymmetric induction was observed for the reduction of oxime ethers **3** or **4** in the presence of complexes prepared from β-amino alcohol **25** and ethanolamine with



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excess borane (Table 4, entries 5 and 7), *i.e.* achiral analogues of the Itsuno's oxazaborolidine **13** reducing system.

Asymmetric induction *was*, however, observed when oxime ether **3** was slowly added to one equivalent of the complex prepared by treatment of amino alcohol **25** with 2.5 equivalents of borane–tetrahydrofuran complex (Table 4, entry 6). After 2 days at room temperature, stepwise addition of 3.5 equivalents of borane–tetrahydrofuran was carried out. Upon conversion to the diacetate **7**, chiral HPLC analysis showed that (*S*)-**7** was present in 13% ee. However, application of an identical reaction procedure using diethanolamine in place of **25** resulted in very low asymmetric induction (Table 4, entry 8).

Given these results, it is difficult to draw firm conclusions as to the mechanism of the reduction in the presence of "N–B"-type additives and borane–tetrahydrofuran complex. However, given the dependence of the stereocontrol obtained in the borane reduction of oxime ethers (*R*,*R*)-**4** and (*S*,*S*)-**5** in the presence of the chiral Itsuno oxazaborolidine **13**, on the chirality of the boronate ester moiety, it is unlikely that the reaction proceeds *via* the simple mechanistic route first proposed for achiral boronate **5** outlined in Scheme 5. In order to influence the stereoselectivity of the reduction, the remote chiral boronate must be brought into proximity with the prochiral oxime ether unit. It can be envisaged that in the presence of oxazaborolidine **13**–borane complex, oxime ether **4** could form a half-chair boron–methoxy chelate of type **26** (Fig. 2). This results in formation of the matched system, intramolecular hydride delivery occurs to the *Re*-face and results in formation

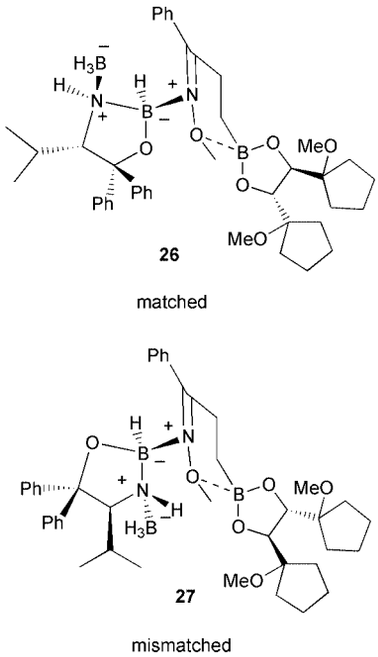

Fig. 2 Possible oxime ether–oxaborolidine chelates involved in the reduction of **4** (top) and **3** (bottom).

of the (*S*)-**7**. In the mismatched system, shown by structure **27**, hydride delivery to the oxime carbon occurs predominantly to the *Si*-face, but only marginally, presumably due to an insufficient energy difference between the conformation shown by structure **27** and the conformation that would result from 180° rotation around the oxime-N–oxazaborolidine-B bond. Such an analysis is compatible with the notion that chelate **10** does intervene in the borane reduction (*vide infra*) of **3**, and that the explanation for the lack of asymmetric induction in that case lies in the remoteness of the chiral centres of the boronate ester due to the boronate-B–O-oxime chelation, as opposed to boronate-B–N-oxime chelation, which would be expected to be a more efficient directing system, *i.e.* system **11**.

The possible existence of complexes **26** and **27**, and therefore by implication **10** (*vide supra*) in equilibrium with their open-chain versions **3** and **4**, makes the picture clearer as to why zero-low asymmetric induction is observed for the achiral reducing systems reported in Table 4. Activation of the C=N bond towards "B–H"-addition *via* a chelated species, may be necessary for reduction with borane–triethylamine complex, whereas in the presence of the more reactive borane–tetrahydrofuran species, oxime reduction may proceed *via* the unactivated open-chain species resulting in no asymmetric induction. In the presence of one equivalent of borane–triethylamine complex the reduction of oxime ether **3** proceeded slowly (Table 4, entry 3), possibly *via* B–O chelate **10** in which borane is delivered to the *Si*-face of the oxime. The fact that asymmetric induction is observed in this case, is presumably because the triethylamine–borane complex is sufficiently sterically encumbered that it can experience some level of steric repulsion from the rather remote boronate ester. The reduction of oxime ether **4**, in the presence of the oxazaborolidine complex derived from β-amino alcohol **25** and borane–tetrahydrofuran complex results in (*S*)-**7** in 13% ee (Table 4, entry 6). This hindered oxazaborolidine has low reactivity and hence slow external borane reduction of the oxime may result in racemic product; some level of efficient directed N-chelated oxazaborolidine-mediated reduction from the same face as the chiral system, *i.e.* similar to complex **26**, would result in the observed asymmetric induction. The low stereoselectivity obtained for the corresponding diethanolamine-based reduction of **4** suggests that the resulting oxazaborolidine complex does not discriminate between hydride delivery to either of the oxime faces.

Summary

β-*E*-Oximino ether boronates such as **3**, **4**, **5**, and **21** are easily accessed by simple lithiation methods and can be readily converted to γ-amino alcohol or β-amino acid derivatives by an oxime ether reduction, oxidative boronate ester cleavage sequence. It is not possible to utilise a remote homochiral boronate ester to directly control the asymmetric reduction of the oxime ether functions with BH_3–THF alone, *e.g.* in esters **3** and **4**, due to the incorrect oxime ether geometry required for boronate activation of the oxime nitrogen. However, probing the application of a homochiral reducing system, *i.e.* **13**–BH_3–THF, to the reduction of homochiral boronate esters **3** and **4** did demonstrate that remote asymmetric centres could influence the oxime ether reduction *if* a suitable reducing agent was selected. Hence, subsequent examination of different BH_3–THF–achiral amine reducing agent systems can effect remote asymmetric reduction of ester **3** and **4** (albeit only 28% ee to date), despite the unfavourable oxime ether geometry and effectively greater distance between the remote chiral centres and the oxime ether being reduced. Further studies on the application of 'partner' molecules for transmitting remote asymmetric information over more extreme distances are underway.

Experimental

(*S*)-3-Amino-3-phenylpropan-1-ol was donated by Chirotech. All other reagents were obtained from Acros, Aldrich or Lancaster. Dimethyl sulfoxide and ethanolamine were stored under argon, over activated 3 Å molecular sieves. Dry tetrahydrofuran was freshly distilled from sodium and benzophenone immediately prior to use. Dry dichloromethane was distilled from calcium hydride. Bromobenzene and triethylamine were distilled from calcium hydride before use. Distillations were carried out under an argon atmosphere. Flash column chromatography was achieved using Acros silica gel, pore size 60 Å, or Lancaster silica gel 60, 0.060–0.2 mm (70–230 mesh). Thin layer chromatography was performed on Merck plastic or aluminium sheets coated with silica gel 60 F_{254} (Art. 5735). Chromatograms were initially examined under UV light and then developed by spraying with either phosphomolybdic acid (6 g in 125 ml of ethanol) or aqueous potassium permanganate, followed by heating. All anhydrous reactions were carried out in oven-dried (120 °C) glassware which was cooled under a stream of argon. Organic extracts were dried over $MgSO_4$ before evaporation. Evaporations were achieved using a Büchi rotary evaporator followed by drying at *ca.* 5 mmHg using a vacuum pump. Bulb-to-bulb distillations were carried out using a Büchi GKR-51 Kugelrohr apparatus. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded using Bruker NMR spectrometers. ^{1}H NMR and ^{13}C NMR spectra were recorded using $CHCl_3$ and $CDCl_3$ respectively, as internal standards. Resonances for ^{11}B NMR spectra are quoted relative to BF_3–Et_2O (δ ^{11}B = 0.00 ppm) as external standard. Chemical shift values (δ) are given in ppm, coupling constants (J) are given in Hz, and NMR peaks are described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Infra-red (IR) spectra were recorded on a Perkin-Elmer 298 spectrophotometer or a Matson Unicam FTIR spectrometer. Electron impact (EI) (70 eV) and chemical ionisation (CI) were recorded with a Kratos MS50 or a Finnigan MAT 95S spectrometer. Fast atom bombardment (FAB) spectra were recorded on a Kratos MS50 using an *m*-nitrobenzyl alcohol matrix. Accurate mass determinations were carried out on a Kratos Concept IS spectrometer. Microanalyses were performed using a Carlo-Erba 1106 elemental analyser. Optical rotation values [*a*] were determined using a Perkin-Elmer Model 241 or an Optical Activity AA-1000 polarimeter, and are recorded in

units of 10^{-1} deg cm^2 g^{-1}. High performance liquid chromatography (HPLC) was carried out using a Shimadzu Class VP model equipped with an autosampler and UV detector, or a Gilson SF3 instrument. Chiralpak (AD, AS) and Chiralcel (OD, OB, OJ) columns, dimensions 250 × 4.6 mm, were used.

Preparation of racemic 1-acetoxy-3-acetylamino-3-phenylpropane 7

To a stirred solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propiophenone *O*-methyloxime **5** (0.11 g, 0.38 mmol) in dry THF (10 ml) at 0 °C under argon, borane–tetrahydrofuran complex (4.00 ml of a 1.0 M solution in THF, 4.00 mmol) was slowly added. After 2 hours the reaction was allowed to warm to room temperature and stirred overnight. The solution was then cooled to 0 °C, and treated with NaOH (aq.) (5.00 ml of a 1.0 M solution, 5.00 mmol) and H_2O_2 (aq.) (0.33 ml of a 40% w/v solution, 3.90 mmol). Heating at reflux for 1 hour yielded a colourless solution. This solution was partitioned between dichloromethane and saturated NaCl (aq.). The combined organic phases were dried and evaporated, affording a cloudy oil which was re-dissolved in pyridine (2 ml). Acetic anhydride (1.00 ml, 10.60 mmol) was added. Stirring at room temperature for 24 hours afforded an orange solution which was cooled in an ice bath. Saturated $NaHCO_3$ (aq.) was then carefully added until no further effervescence was observed. Extraction with ethyl acetate (3 × 10 ml), followed by washing of the combined organic phases with 10% HCl (aq.) (30 ml), then water (30 ml), and drying, yielded a pale yellow oil upon evaporation. Trituration with cold diethyl ether furnished the title compound racemic **7** (0.042 g, 0.18 mmol, 47%) as a white solid upon filtration: mp 102–103 °C (lit.,[7] 84–85 °C, Et_2O); HPLC [SFC, Chiralpak AS, 35 °C, 3000 psi, $\lambda = 215$ nm, 2 ml min^{-1}, 86% CO_2: 14% (isopropyl alcohol (IPA) + 0.2% Et_2NH) elution] t_R/min 5.06 (49.7%), 8.01 (50.3%) (Found: C, 65.9; H, 7.4; N, 5.6. $C_{13}H_{17}NO_3$ requires C, 66.4; H, 7.3; N, 6.0%); ν_{max} (KBr)/cm^{-1} 3300, 3060, 3029, 2972, 2924, 1732, 1642, 1548, 1468, 1420, 1244, 1052; δ_H (250 MHz; $CDCl_3$) 2.00 (3 H, s, CH_3C=ON), 2.01 (3 H, s, CH_3C=OO), 2.08–2.20 (2 H, m, C*H*$_2$CHN), 4.01–4.11 (2 H, m, CH_2O), 5.08–5.17 (1 H, m, CH_2CHN), 5.76 (1 H, br s, NH), 7.27–7.34 (5 H, m, H aromatic) (addition of D_2O caused peak at δ 5.76 to disappear, and that at δ 5.08–5.17 to collapse to a triplet, J 7.2, δ 5.12); δ_C (62.9 MHz; $CDCl_3$) 20.9 (*C*H$_3$C=ON), 23.4 (*C*H$_3$C=OO), 34.7 (*C*H$_2$CHN), 50.7 (CH_2*C*HN), 61.4 (CH_2O), 126.5, 127.7, 128.8, 141.1 (C aromatic), 169.2 (CH_3*C*=ON), 171.0 (CH_3*C*=OO); *m*/*z* (CI, NH_3) 236 $(M + H)^+$, 471 $(2M + H)^+$ [Found (HRMS): *m*/*z* 235.1216. $C_{13}H_{17}NO_3$ requires M^+ 235.1208].

Preparation of (*S*)-1-acetoxy-3-acetylamino-3-phenylpropane (*S*)-7

Acetic anhydride (0.50 ml, 5.30 mmol) was added to a solution of (*S*)-3-amino-3-phenylpropan-1-ol (*S*)-**6** (0.050 g, 0.33 mmol) in pyridine (0.50 ml). The solution was stirred at room temperature for 24 hours, then partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic phases were washed with 10% HCl (aq.) (20 ml), then water (20 ml), and dried. Evaporation yielded the title compound (*S*)-**7** (0.070 g, 0.301 mmol, 90%) as a white solid: mp 103 °C; $[\alpha]_D^{23}$ −72.4 (*c* 0.468, MeOH); HPLC [SFC, Chiralpak AS, 35 °C, 3000 psi, $\lambda = 215$ nm, 2 ml min^{-1}, 86% CO_2: 14% (IPA + 0.2% Et_2NH) elution] t_R/min 5.04 (0.9%), 7.97 (99.1%); all other spectroscopic properties were identical to those reported above.

Preparation of diacetyl derivative 7 *via* reduction of (*S*,*S*)-3 with borane–tetrahydrofuran complex

To a solution of boronate ester (*S*,*S*)-**3** (0.16 g, 0.37 mmol) in dry THF (5 ml) at 0 °C under argon, borane–tetrahydrofuran complex (3.70 ml of a 1.0 M solution in THF, 3.70 mmol) was slowly added. The solution was maintained at 0 °C for a further 2 hours, then allowed to warm to room temperature overnight. The colourless solution formed was cooled in an ice bath and NaOH (aq.) (3.70 ml of a 2.0 M solution, 7.40 mmol) and H_2O_2 (aq.) (0.63 ml of a 40% w/v solution, 7.40 mmol) added dropwise. A cloudy solution was formed which was heated at reflux for 1 hour, then partitioned between dichloromethane and saturated NaCl (aq.). The organic layers were combined and evaporated, affording a cloudy oil which was re-dissolved in pyridine (5 ml). Acetic anhydride (0.71 ml, 7.50 mmol) was added and the solution was stirred at room temperature for 2 days yielding an orange solution. Saturated $NaHCO_3$ (aq.) was carefully added to this solution until no further effervescence was observed. Extraction with ethyl acetate (3 × 10 ml), washing of the combined organic phases with 1.6 M HCl (aq.) (20 ml), then water (20 ml), and drying, yielded crude 1-acetoxy-3-acetylamino-3-phenylpropane **7** (0.082 g, 0.35 mmol, 94%), as a yellow oil upon evaporation: HPLC [SFC, Chiralpak AS, 35 °C, 3000 psi, $\lambda = 215$ nm, 2 ml min^{-1}, 86% CO_2: 14% (IPA + 0.2% Et_2NH) elution] t_R/min 5.03 (49.5%), 8.02 (50.3%); all spectroscopic and analytical properties were identical to those reported above.

Preparation of *N*-{3-[(4*S*,5*S*)-4,5-bis(1-methoxycyclopentyl)-1,3,2-dioxaborolan-2-yl]-1-phenylpropyl}acetamide 8 *via* reduction of (*S*,*S*)-3 with borane–dimethyl sulfide complex

To a stirred solution of 3-[(4*S*,5*S*)-4,5-bis(1-methoxycyclopentyl)-1,3,2-dioxaborolan-2-yl]propiophenone *O*-methyloxime (*S*,*S*)-**3** (0.096 g, 0.22 mmol) in dry THF (0.50 ml) at −15 °C under argon, borane–dimethyl sulfide complex (1.10 ml of a 2.0 M solution in THF, 2.20 mmol) was added dropwise. The reaction was then allowed to warm to room temperature and stirred for 16 hours. Quenching the reaction at 0 °C with acetic anhydride (0.42 ml, 4.40 mmol), then stirring at room temperature for 2 days afforded a yellow solution and a white precipitate. This mixture was cooled in an ice bath and saturated $NaHCO_3$ (aq.) was carefully added until no further effervescence was observed. Extraction with ethyl acetate (3 × 10 ml), washing the combined organic extracts with water (20 ml) and drying, yielded a very pale yellow oil upon evaporation. Flash column chromatography [3:2, ethyl acetate–petroleum ether (40–60 °C) as eluent] yielded acetamide **8** (0.094 g, 0.21 mmol, 96%) as a 1:1 mixture of diastereoisomers: $[\alpha]_D^{27.5}$ +13 (*c* 0.15, $CHCl_3$); ν_{max} (film)/cm^{-1} 3460–3274, 2931, 2855, 1741, 1239, 1075, 1046; δ_H (300 MHz; $CDCl_3$) 0.68–0.89 (2 H, m, CH_2B), 1.56–1.94 (18 H, m, CH_2 cyclopentyl, C*H*$_2$CH$_2$B), 1.98 (3 H, s, CH_3C=O), 3.23 (6 H, s, 2 × OCH_3), 4.28 (1 H, s, CHO), 4.30 (1 H, s, CHO), 4.87–4.99 (1 H, m, C*H*NH), 5.96 (1 H, br d, *J* 8.0, NH), 7.21–7.34 (5 H, m, H aromatic) (addition of D_2O caused the peak at δ 5.96 to disappear); δ_C (75.5 MHz; $CDCl_3$), 1:1 mixture of diastereomers, 20.9 (*C*H$_2$CH$_2$B), 23.3 (C=O*C*H$_3$), 24.4, 25.2, 30.4, 30.6, 31.1, 31.2 (CH_2 cyclopentyl), 50.3, 50.4 (OCH_3), 55.0, 55.2 (CHNH), 63.9 (*C*H$_2$CH), 81.0 (CHO), 87.8, 87.9 (*C*OCH$_3$), 126.4, 126.5, 127.1, 128.5, 142.1, 142.4 (C aromatic), 169.4, 171.1 (N*C*=OCH$_3$); δ_B (64.2 MHz; $CDCl_3$) +34.2; *m*/*z* (FAB) 444 $(M + H)^+$ [Found (HRMS): *m*/*z* 444.2922. $C_{25}H_{38}BNO_5$ requires $(M + H)^+$ 444.2921].

Preparation of acetamide 8 *via* reduction of (*S*,*S*)-3 with borane–tetrahydrofuran complex

To a stirred solution of β-boronate *O*-methyloxime (*S*,*S*)-**3** (0.014 g, 0.033 mmol) in dry THF (0.50 ml) at 0 °C under Ar, borane–tetrahydrofuran complex (0.33 ml of a 1.0 M solution in THF, 0.33 mmol) was slowly added. The solution was allowed to warm to room temperature and stirred for 2 days. The reaction was then quenched at 0 °C with acetic anhydride (0.062 ml, 0.66 mmol) and stirred overnight at room temper-

ature. The solution was cooled in an ice bath and saturated $NaHCO_3$ (aq.) was added dropwise until no further effervescence was observed. Extraction with ethyl acetate (3 × 10 ml), washing the combined organic phases with water (20 ml), and drying, yielded crude acetamide **8** (0.013 g, 0.029 mmol, 89%) upon evaporation, as a 1:1 mixture of diastereomers by ^{13}C NMR: all spectroscopic and analytical properties were identical to those reported above.

Preparation of acetamide 8 *via* reduction of (*S*,*S*)-3 with diisobutylaluminium hydride

To a stirred solution of boronate *O*-methyloxime (*S*,*S*)-**3** (0.11 g, 0.26 mmol) in dry THF (5 ml) at 0 °C under Ar, diisobutylaluminium hydride (2.60 ml of a 1.0 M solution in THF, 2.60 mmol) was slowly added. The solution was allowed to warm to room temperature and stirred for 2 days. The reaction was then quenched at 0 °C with acetic anhydride (0.47 ml, 5.00 mmol) and stirred overnight at room temperature. The solution was cooled in an ice bath and saturated $NaHCO_3$ (aq.) was added dropwise until no further effervescence was observed. Extraction with ethyl acetate (3 × 10 ml), washing the combined organic phases with water (20 ml) and drying, yielded crude acetamide **8** (0.10 g, 0.23 mmol, 87%) as a colourless oil upon evaporation: 1:1 mixture of diastereomers by ^{13}C NMR; all spectroscopic and analytical properties were identical to those reported above.

Preparation of acetate 7 from acetamide 8

Acetamide **8** (1:1 mixture of diastereoisomers) (0.022 g, 0.050 mmol) was dissolved in THF (1 ml) and treated with H_2O_2 (0.10 ml of a 40% w/v solution, 1.18 mmol) and NaOH (aq.) (0.60 ml of a 2.0 M solution, 1.20 mmol). The cloudy solution was stirred at room temperature for 2 days, then extracted with dichloromethane (3 × 10 ml). The combined organic phases were washed with water (20 ml) and dried. Evaporation yielded a colourless oil which was re-dissolved in pyridine (0.50 ml). Acetic anhydride (0.50 ml, 5.30 mmol) was added and the reaction mixture stirred overnight at room temperature. After cooling in an ice bath, saturated $NaHCO_3$ (aq.) was carefully added until no further effervescence was observed, and the solution was then extracted with dichloromethane (3 × 10 ml). The combined organic layers were washed with 10% HCl (aq.) (20 ml), then water (20 ml), and dried. Evaporation yielded crude acetate **7** (9 mg, 0.038 mmol, 77%) as an off-white solid: HPLC [SFC, Chiralpak AS, 35 °C, 3000 psi, $\lambda = 215$ nm, 2 ml min^{-1}, 86% CO_2: 14% (IPA + 0.2% Et_2NH) elution] t_R/min 5.03 (49.5%), 8.02 (50.3%); all spectroscopic and analytical properties were identical to those reported above.

Preparation of (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol 14

Bromobenzene (9.28 ml, 0.088 mol) was carefully added dropwise to magnesium turnings (2.56 g, 0.11 mol) and iodine (1 crystal) in anhydrous diethyl ether (80 ml) under Ar. When reaction was initiated, the solution was cooled in an ice bath until addition of the aryl bromide was complete. The solution was allowed to warm to room temperature then heated at reflux for 2 hours. The reaction was again cooled in an ice bath and L-valine ethyl ester hydrochloride (2.00 g, 0.011 mol) carefully added. After refluxing for a further 5 hours, the reaction was quenched by pouring onto ice (50 ml), and concentrated HCl (aq.) (1 ml) was slowly added. The mixture was left to stand at room temperature for 1 hour, then the ether layer was separated. The aqueous phase was basified (pH = 10) with 35% NH_4OH (aq.) and extracted with diethyl ether (3 × 25 ml). The combined organic phases were dried and evaporated to furnish **14** (1.10 g, 4.31 mmol, 39%) as a white solid after flash column chromatography (1:20, methanol–dichloromethane as eluent): mp 89–91 °C (lit.,[14a] 94–95 °C); $[\alpha]_D^{27}$ −121 (*c* 1.2, $CHCl_3$) [lit.,[10] $[\alpha]_D^{25}$ −127.7 (*c* 0.639, $CHCl_3$)]; δ_H (300 MHz; $CDCl_3$) 0.91 [3 H, d, *J* 6.8, $(CH_3)CH_3CH$], 0.95 [3 H, d, *J* 7.1, $(CH_3)CH_3CH$], 1.72–1.85 [1 H, m, $(CH_3)_2CH$], 3.87 (1 H, d, *J* 1.9, CHN), 7.16–7.36 (6 H, m, H aromatic), 7.50–7.53 (2 H, m, H aromatic), 7.62–7.66 (2 H, m, H aromatic); ^{13}C NMR and IR were as reported in the literature;[16] *m*/*z* (CI, NH_3) 256 $(M + H)^+$ [Found (HRMS): *m*/*z* 256.1700. $C_{17}H_{21}NO$ requires $(M + H)^+$ 256.1701].

Preparation of *N*-[(*S*)-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl]acetamide 15 *via* borane reduction of 5 in the presence of oxazaborolidine 13

To a stirred solution of homochiral amino alcohol **13** (0.041 g, 0.16 mmol) in dry THF (2 ml) at 0 °C under Ar, borane–tetrahydrofuran complex (0.64 ml of a 1.0 M solution in THF, 0.64 mmol) was slowly added. After 6 hours, oxime ether **5** (0.046 g, 0.16 mmol) in THF (1 ml) was added, and the solution allowed to warm to room temperature overnight. A colourless solution was formed which was treated with acetic anhydride (0.30 ml, 3.20 mmol) at 0 °C. After stirring at room temperature for a further 1 hour, the THF was removed by rotary evaporation. The cloudy residue was partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic phases were dried and evaporated yielding a very viscous colourless oil. Flash column chromatography [1:1, ethyl acetate–petroleum ether (40–60 °C) as eluent] afforded **15** (0.045 g, 0.15 mmol, 93%) as a very viscous cloudy oil: $[\alpha]_D^{27.5}$ −54 (*c* 0.92, $CHCl_3$); ν_{max} (film)/cm^{-1} 3050, 2980, 1665, 1415, 1370, 1260, 1140; δ_H (300 MHz; $CDCl_3$) 0.73–0.82 (2 H, m, CH_2B), 1.24 [12 H, s, 2 × $(CH_3)_2C$], 1.84–1.92 (2 H, m, CH_2CH_2B), 1.98 (3 H, s, $CH_3C{=}O$), 4.89 (1 H, q, *J* 7.5, CHNH), 5.96 (1 H, br d, *J* 7.2, NH) (addition of D_2O caused peak at δ 5.96 to disappear, and that at δ 4.89 to collapse to a triplet, *J* 7.2, δ 4.88); δ_C (100.6 MHz; $CDCl_3$) 7.9 (br, CH_2B), 23.3 ($CH_3C{=}O$), 24.7 [$(CH_3)_2C$], 24.8 [$(CH_3)_2C$], 30.4 (CH_2CHN), 55.2 (CHN), 83.2 [$(CH_3)_2C$], 126.4, 127.0, 128.4, 142.3 (C aromatic), 169.2 (C=O); δ_B (64.2 MHz; $CDCl_3$) +34.0; *m*/*z* (FAB) 304 $(M + H)^+$ [Found (HRMS): *m*/*z* 304.2091. $C_{17}H_{26}BNO_3$ requires $(M + H)^+$ 304.2084].

Preparation of acetate (*S*)-7 from acetamide 15

Acetamide **15** (0.045 g, 0.15 mmol) was dissolved in THF (2 ml) and H_2O_2 (aq.) (0.15 ml of a 40% w/v solution, 1.76 mmol) and NaOH (aq.) (1.00 ml of a 2.0 M solution, 2.00 mmol) were added. A cloudy solution was formed which was stirred at room temperature for 2 hours then extracted with ethyl acetate (3 × 10 ml). Drying and evaporating the combined organic extracts yielded a residue which was treated with acetic anhydride (0.15 ml, 1.60 mmol) in the presence of pyridine (2 ml) at room temperature for 2 hours. An orange solution was formed which was partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic extracts were washed with 10% HCl (aq.) (20 ml), dried and evaporated to afford acetate (*S*)-**7** (0.030 g, 0.13 mmol, 85%) after chromatography [1:1, ethyl acetate–petroleum ether (40–60 °C) as eluent]: HPLC [Chiralpak AS, SFC, 35 °C, 3000 psi, $\lambda = 218$ nm, 2 ml min^{-1}, 90% CO_2: 10% (IPA + 0.2% Et_2NH) elution] t_R/min 6.23 (1.2%), 8.92 (98.8%); all spectroscopic and analytical properties were as reported above.

Preparation of (*S*)-7 *via* borane reduction of 5 in the presence of a catalytic amount of oxazaborolidine 13

To a solution of homochiral amino alcohol **14** (0.021 g, 0.082 mmol) in dry THF (0.30 ml) at 0 °C under argon, borane–tetrahydrofuran complex (0.64 ml of a 1.0 M solution in THF, 0.64 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 14 hours, then cooled in an ice bath. Boronate ester **5** (0.094 g, 0.325 mmol)

in THF (0.50 ml) was added slowly and the reaction allowed to warm to room temperature. The solution was stirred for 20 hours at ambient temperature, then cooled to 0 °C and treated with acetic anhydride (0.30 ml, 3.20 mmol). This mixture was stirred at room temperature for 1 hour then the THF was evaporated. The cloudy residue was partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic extracts were dried, evaporated, and the residue dissolved in THF (5 ml) and treated with H_2O_2 (aq.) (0.30 ml of a 40% w/v solution, 3.52 mmol) and NaOH (aq.) (2.0 ml of a 2.0 M solution, 4.0 mmol). This cloudy solution was stirred at room temperature for 2 hours then extracted with ethyl acetate (3 × 10 ml). The combined organic phases were dried and evaporated. The residue was treated with acetic anhydride (0.30 ml, 3.20 mmol) in pyridine (4 ml) at room temperature for 2 hours, then partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The organic extracts were combined, washed with 10% HCl (aq.) (50 ml) then dried. Evaporation yielded **15** (0.055 g, 0.23 mmol, 73%) after purification by column chromatography [1 : 1, ethyl acetate–petroleum ether (40–60 °C) as eluent]: HPLC [Chiralpak AS, SFC, 35 °C, 3000 psi, $\lambda = 218$ nm, 2 ml min^{-1}, 90% CO_2: 10% (IPA + 0.2% Et_2NH) elution] t_R/min 6.57 (7.1%), 10.04 (88.1%); all other spectroscopic and analytical properties were as reported above.

Preparation of (*S*)-3-acetylamino-3-phenylpropionic acid 16 *via* oxidation of acetamide 15

To a solution of chromium trioxide (0.012 g, 0.12 mmol) in glacial acetic acid (0.45 ml) and water (0.05 ml), acetamide **15** (0.012 g, 0.040 mmol) in dichloromethane (0.50 ml) was added dropwise. The solution was stirred at room temperature for 4 hours, then extracted with dichloromethane (3 × 5 ml). The organic phases were combined and evaporated to yield **16** (7 mg, 0.034 mmol, 85%) as a white solid after triturating with cold chloroform: IR was as reported in the literature;[18] δ_H [300 MHz; $(CD_3)_2CO$] 1.90 (3 H, s, CH_3C=O), 2.81–2.87 (2 H, m CH_2C=OOH), 5.37–5.44 (1 H, m, CHNH), 7.22–7.42 (5 H, m, H aromatic), 7.55 (1 H, br d, *J* 6.0, NH), 10.80 (1 H, br s, OH) (addition of D_2O caused peaks at δ 7.55 and δ 10.80 to disappear, and multiplet at δ 5.37–5.44 to collapse to a triplet, *J* 7.4, δ 5.32); δ_C [100.6 MHz; $(CD_3)_2CO$] 22.5 (CH_3C=O), 40.6 (CH_2C=O), 50.2 (CHNH), 127.4, 128.7, 132.9, 142.9 (C aromatic), 168.6 (NC=O), 171.5 (C=OOH); *m*/*z* (CI, NH_3) 208 $(M + H)^+$ [Found (HRMS): *m*/*z* 208.0967. $C_{11}H_{13}NO_3$ requires $(M + H)^+$ 208.0974].

General procedure for the preparation of racemic *O*-benzoyl derivatives 22

To a solution of oxime ether **21** (0.18 mmol) in dry THF (0.30 ml) at 0 °C under Ar, borane–tetrahydrofuran complex (1.80 ml of a 1.0 M solution in THF, 1.80 mmol) is added dropwise. The reaction is allowed to warm to room temperature. When reduction is complete, the solution is cooled in an ice bath, treated with acetic anhydride (0.34 ml, 3.60 mmol), then stirred at room temperature for 1 hour. The THF is removed by rotary evaporation and the residue partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic phases are dried and evaporated. The resulting acetamide is dissolved in THF (1 ml) and treated with NaOH (aq.) (1.50 ml of a 2.0 M solution, 3.00 mmol) and H_2O_2 (aq.) (0.20 ml of a 40% w/v solution, 2.35 mmol). After stirring at room temperature for 2 hours the solution is extracted with ethyl acetate (3 × 10 ml). The organic extracts are combined, dried and evaporated, yielding crude alcohol. The crude alcohol is dissolved in pyridine (1 ml), treated with benzoyl chloride (0.10 ml, 0.90 mmol) and stirred at room temperature for 2 hours. The resulting solution is partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic phases are dried and evaporated yielding crude *O*-benzoylated product **22** which is then purified by flash column chromatography [1 : 4, ethyl acetate–petroleum ether (40–60 °C) as eluent].

(a) Preparation of racemic benzoate 22a. The general procedure outlined above was followed on a 0.12 mmol scale. The reduction was complete after 14 hours, yielding racemic acetamide **22a** (0.010 g, 0.040 mmol, 33%) as a cloudy viscous oil after column chromatography: HPLC (Chiralcel OJ, $\lambda = 254$ nm, 0.5 ml min^{-1}, 90% hexane: 10% IPA elution) t_R/min 18.46 (52.2%), 20.31 (49.8%); δ_H (300 MHz; $CDCl_3$) 0.94 (3 H, t, *J* 7.4, CH_3CH_2), 1.44–2.00 (4 H, m, CH_3CH_2, CH_2CH), 1.98 (3 H, s, CH_3C=O), 4.05–4.11 (1 H, m, CHNH), 4.29–4.45 (2 H, m, CH_2O), 5.35 (1 H, br d, *J* 7.5, NH), 7.42–7.48 (2 H, m, H *meta*), 7.52–7.59 (1 H, m, H *para*), 8.01–8.07 (2 H, m, H *ortho*) (addition of D_2O caused peak at δ 5.35 to disappear); *m*/*z* (FAB) 250 $(M + H)^+$ [Found (HRMS): *m*/*z* 250.1439. $C_{14}H_{19}NO_3$ requires $(M + H)^+$ 250.1443].

(b) Preparation of racemic benzoate 22b. The general procedure outlined above was followed on a 0.47 mmol scale. Reduction was complete after 48 hours, yielding racemic acetamide **22b** (0.031 g, 0.12 mmol, 25%): HPLC (Chiralcel OJ, $\lambda = 254$ nm, 1 ml min^{-1}, 95% hexane: 5% IPA elution) t_R/min 16.77 (48.6%), 18.38 (51.4%); δ_H (300 MHz; $CDCl_3$) 0.91 (3 H, t, *J* 7.0, CH_3CH_2), 1.23–1.57 (4 H, m, $(CH_2)_2CH_3$), 1.97 (3 H, s, CH_3C=O), 1.76–2.05 (2 H, m, CH_2CH_2O), 4.10–4.15 (1 H, m, CHNH), 4.31–4.44 (2 H, m, CH_2O), 5.44 (1 H, br d, *J* 8.3, NH), 7.41–7.47 (2 H, m, H *meta*), 7.53–7.58 (1 H, m, H *para*), 8.02–8.05 (2 H, m, H *ortho*) (addition of D_2O caused peak at δ 5.44 to disappear); *m*/*z* (FAB) 264 $(M + H)^+$ [Found (HRMS): *m*/*z* 264.1605. $C_{15}H_{21}NO_3$ requires $(M + H)^+$ 264.1600].

(c) Preparation of racemic benzoate 22c. The general procedure described above was followed on a 0.37 mmol scale. Reduction was complete after 6 days, yielding acetamide **22c** (0.015 g, 0.054 mmol, 15%) after column chromatography: HPLC (Chiralpak AD, $\lambda = 254$ nm, 0.5 ml min^{-1}, 90% hexane: 10% IPA elution) t_R/min 10.98 (49.5%), 11.89 (50.5%); δ_H (300 MHz; $CDCl_3$) 0.93 [9 H, s, $(CH_3)_3C$], 1.50–1.64 [1 H, m, CH(H)CHN], 2.02 (3 H, s, CH_3C=O), 2.04–2.18 [1 H, m, CH(H)CHN], 3.94–4.02 (1 H, m, CHNH), 4.21–4.29 [1 H, m, CH(H)O], 4.41–4.48 [1 H, m, CH(H)O], 5.25 (1 H, br d, *J* 10.5, NH), 7.41–7.45 (2 H, m, H *meta*), 7.53–7.56 (1 H, m, H *para*), 8.03–8.05 (2 H, m, H *ortho*) (addition of D_2O caused peak at δ 5.25 to disappear); *m*/*z* (FAB) 278 $(M + H)^+$ [Found (HRMS): *m*/*z* 278.1757. $C_{16}H_{23}NO_3$ requires $(M + H)^+$ 278.1756].

(d) Preparation of racemic benzoate 22d. The procedure described above was followed on a 0.18 mmol scale. Reduction was complete after 16 hours, affording acetamide **22d** (0.012 g, 0.036 mmol, 20%) as a white solid: HPLC (Chiralcel OD, $\lambda = 254$ nm, 0.5 ml min^{-1}, 90% hexane: 10% IPA elution) t_R/min 12.83 (45.1%), 13.82 (54.9%); δ_H (300 MHz; $CDCl_3$) 0.87 (3 H, t, *J* 6.8, CH_3CH_2), 1.25–1.59 [14 H, m, $CH_3(CH_2)_7$], 1.75–1.92 [1 H, m, CH(H)CH_2O], 1.97 (3 H, s, CH_3C=O), 1.97–2.12 [1 H, m, CH(H)CH_2O], 4.06–4.17 (1 H, m, CHNH), 4.29–4.47 (2 H, m, CH_2O), 5.33 (1 H, br d, *J* 8.6, NH), 7.41–7.46 (2 H, m, H *meta*), 7.53–7.59 (1 H, m, H *para*), 8.02–8.05 (2 H, m, H *ortho*) (addition of D_2O caused peak at δ 5.33 to disappear); *m*/*z* (FAB) 334 $(M + H)^+$. [Found (HRMS): *m*/*z* 334.2384. $C_{20}H_{31}NO_3$ requires $(M + H)^+$ 334.2382].

General procedure for preparation of *O*-benzoyl derivatives 22 *via* borane reduction of 21 in the presence of oxazaborolidine 13

To a stirred solution of homochiral amino alcohol **14** (0.051 g, 0.20 mmol) in dry THF (0.25 ml) at 0 °C, borane–tetrahydrofuran complex (0.80 ml of a 1.0 M solution in THF, 0.80 mmol) is added dropwise. After 6 hours, oxime ether **21** (0.20 mmol) in

dry THF (0.25 ml) is slowly added and the reaction allowed to warm to room temperature. When reduction is complete, the reaction is quenched at 0 °C with acetic anhydride (0.19 ml, 2.00 mmol), and stirred at room temperature for 1 hour. The THF is removed by rotary evaporation and the residue partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic phases are dried and evaporated yielding the crude acetamide. The acetamide is then dissolved in THF (1 ml) and treated with NaOH (aq.) (1.50 ml of a 2.0 M solution, 3.00 mmol) and H_2O_2 (aq.) (0.20 ml of a 40% w/v solution, 2.35 mmol). After stirring at room temperature for 2 hours the solution is extracted with ethyl acetate (3 × 10 ml). The organic extracts are combined, dried and evaporated, yielding crude alcohol residue. Crude alcohol is dissolved in pyridine (1 ml), treated with benzoyl chloride (0.12 ml, 1.00 mmol) and stirred at room temperature for 2 hours. The resulting solution is partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). Combined organic phases are dried and evaporated yielding crude *O*-benzoylated product **22** which is purified by column chromatography [1 : 4, ethyl acetate–petroleum ether (40–60 °C) as eluent].

(a) Preparation of 22a *via* borane reduction of 21a in the presence of oxazaborolidine 13. The general procedure outlined above was followed on a 0.41 mmol scale. Reduction was complete after 48 hours, yielding acetamide **22a** (0.025 g, 0.10 mmol, 24%): HPLC (Chiralcel OJ, $\lambda = 254$ nm, 0.5 ml min^{-1}, 90% hexane: 10% IPA elution) t_R/min 18.29 (63.0%), 20.17 (37.0%); all spectroscopic properties were identical to those reported above.

(b) Preparation of 22b *via* borane reduction of 21b in the presence of oxazaborolidine 13. The general procedure described above was followed on a 0.27 mmol scale. Reduction was complete after 48 hours, affording **22b** (0.016 g, 0.061 mmol, 23%) as a colourless oil: HPLC (Chiralcel OJ, $\lambda = 254$ nm, 1 ml min^{-1}, 95% hexane: 5% IPA elution) t_R/min 17.18 (81.2%), 18.88 (18.8%); all spectroscopic properties were identical to those reported above.

(c) Preparation of 22c *via* borane reduction of 21c in the presence of oxazaborolidine 13. The general procedure outlined above was followed on a 0.37 mmol scale. Reduction was complete after 6 days, furnishing acetamide **22c** (0.010 g, 0.036 mmol, 10%) as a colourless oil: HPLC (Chiralpak AD, $\lambda = 254$ nm, 0.5 ml min^{-1}, 90% hexane: 10% IPA elution) t_R/min 11.00 (73.2%), 11.89 (26.7%); all spectroscopic properties were identical to those reported above.

(d) Preparation of 22d *via* borane reduction of 21d in the presence of oxazaborolidine 13. The general procedure outlined above was followed on a 0.092 mmol scale. Reduction was complete after 16 hours, yielding acetamide **22d** (0.011 g, 0.033 mmol, 36%) as a white solid after chromatography: HPLC (Chiralcel OD, $\lambda = 254$ nm, 0.5 ml min^{-1}, 90% hexane: 10% IPA elution) t_R/min 12.87 (42.0%), 13.83 (58.0%); all spectroscopic properties were identical to those reported above.

Borane reduction of (*R*,*R*)-4 in the presence of oxazaborolidine 13

To a solution of chiral amino alcohol **14** (0.016 g, 0.063 mmol) in dry THF (1 ml) at 0 °C under argon, borane–tetrahydrofuran complex (0.25 ml of a 1.0 M solution, 0.25 mmol) was slowly added. The solution was stirred at 0 °C for 6 hours, then chiral β-boronate oxime ether (*R*,*R*)-**4** (0.027 g, 0.063 mmol) in THF (1 ml) was added dropwise. The reaction allowed to warm to room temperature. After 14 hours, the reaction was quenched with acetic anhydride (0.12 ml, 1.26 mmol) at 0 °C, then allowed to warm to room temperature. After 1 hour the THF was evaporated and the residue partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The organic extracts were combined and dried. Evaporation yielded a colourless oil which was dissolved in THF (1 ml) and treated with NaOH (aq.) (0.50 ml of a 2.0 M solution, 1.00 mmol) and H_2O_2 (aq.) (0.050 ml of a 40% w/v solution, 0.59 mmol) at room temperature for 2 hours. The solution was extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were dried and evaporated. The residue was dissolved in pyridine (1 ml) and acetic anhydride (0.060 ml, 0.63 mmol), was added. This solution was stirred at room temperature for 2 hours then partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic phases were washed with 10% HCl (aq.) (20 ml) and dried. Evaporation yielded acetate (*S*)-**7** (0.011 g, 0.047 mmol, 74%) after purification by column chromatography [1 : 1, ethyl acetate–petroleum ether (40–60 °C) as eluent]: HPLC [Chiralpak AS, SFC, 35 °C, 3000 psi, $\lambda = 218$ nm, 2 ml min^{-1}, 90% CO_2: 10% (IPA + 0.2% Et_2NH) elution] t_R/min 6.20 (2.4%), 8.73 (92.1%); all other spectroscopic and analytical properties were identical to those reported above.

Borane reduction of (*S*,*S*)-3 in the presence of oxazaborolidine 13

To a solution of aminoalcohol **14** (0.053 g, 0.21 mmol) in dry THF (2 ml) at 0 °C under Ar, borane–tetrahydrofuran complex (0.84 ml of a 1.0 M solution in THF, 0.84 mmol) was added dropwise. This solution was stirred for 7 hours, then chiral oxime ether (*S*,*S*)-**3** (0.089 g, 0.21 mmol) in THF (1 ml) was added, and the reaction allowed to warm to room temperature. After 14 hours, the solution was cooled in an ice bath and acetic anhydride (0.40 ml, 4.20 mmol) was added. After stirring at room temperature for 2 hours the THF was removed by rotary evaporation. The cloudy residue was partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). Drying and evaporation of the combined organic phases yielded a crude acetamide. The acetamide was dissolved in THF (2 ml) and treated with H_2O_2 (aq.) (0.20 ml of a 40% w/v solution, 2.35 mmol) and NaOH (aq.) (1.50 ml of a 2.0 M solution, 3.00 mmol) at room temperature for 2 hours. A cloudy solution was formed which was extracted with ethyl acetate (3 × 10 ml). The organic phases were combined, dried and evaporated. The residue was dissolved in pyridine (2 ml) and treated with acetic anhydride (0.20 ml, 2.10 mmol). This solution was stirred at room temperature for 2 hours then partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The organic extracts were combined, washed with 10% HCl (aq.) (20 ml) and dried. Evaporation yielded diacetyl derivative **7** (0.037 g, 0.16 mmol, 75%) as a white solid after flash column chromatography [1 : 1, ethyl acetate–petroleum ether (40–60 °C) as eluent]: HPLC [Chiralpak AS, SFC, 35 °C, 3000 psi, $\lambda = 218$ nm, 2 ml min^{-1}, 90% CO_2: 10% (IPA + 0.2% Et_2NH) elution] t_R/min 6.79 (53.7%), 8.96 (46.2%); all spectroscopic and analytical properties were identical to those reported above.

Reduction of (*S*,*S*)-3 with borane in the presence of borane–pyridine complex

To a solution of borane–pyridine complex (5.0 μl, 0.049 mmol) in dry THF (0.25 ml) at 0 °C under Ar, borane–tetrahydrofuran complex (0.19 ml of a 1.0 M in THF, 0.19 mmol) was added dropwise. After 5 hours (*S*,*S*)-**3** (0.020 g, 0.047 mmol) in THF (0.25 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 14 hours. The solution was then cooled in an ice bath and treated with acetic anhydride (0.090 ml, 0.95 mmol). After stirring at room temperature for 1 hour, THF was removed by rotary evaporation and the residue partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The organic extracts were combined, dried and evaporated to yield a crude acetamide as a colourless oil. This oil was treated with NaOH (aq.) (0.50 ml of a 2.0 M solution, 1.00 mmol) and H_2O_2 (aq.) (0.060 ml of a 40% w/v solution, 0.71

mmol) in THF (1 ml) at room temperature for 2 hours. The resulting cloudy solution was extracted with ethyl acetate (3 × 10 ml). The combined organic phases were dried and evaporated affording a cloudy oil which was dissolved in pyridine (1 ml) and treated with acetic anhydride (0.045 ml, 0.48 mmol). After stirring at room temperature for 2 hours, the solution was partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic extracts were washed with 10% HCl (aq.) (20 ml), then dried and evaporated, affording acetate **7** (0.010 g, 0.0425 mmol, 90%) after purification by column chromatography [1 : 1, ethyl acetate–petroleum ether (40–60 °C) as eluent]: HPLC [Chiralpak AS, SFC, 35 °C, 3000 psi, $\lambda = 218$ nm, 2 ml min^{-1}, 90% CO_2: 10% (IPA + 0.2% Et_2NH) elution] t_R/min 6.75 (49.0%), 11.01 (47.6%); all spectroscopic and analytical properties were identical to those reported above.

Reduction of (*S*,*S*)-3 with borane in the presence of borane–triethylamine complex

To a solution of triethylamine (6.5 µl, 0.047 mmol) in dry THF (0.25 ml) at 0 °C under argon, borane–tetrahydrofuran complex (0.19 ml of a 1.0 M solution in THF, 0.19 mmol) was slowly added. After 5 hours, the solution was treated with (*S*,*S*)-**3** (0.020 g, 0.047 mmol) in THF (0.25 ml). The reaction was allowed to warm to room temperature overnight, then quenched with acetic anhydride (0.089 ml, 0.94 mmol) at 0 °C. The solution was stirred for a further 1 hour, then THF was evaporated and the residue partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). Drying and evaporation of the combined organic extracts yielded the crude acetamide as a colourless oil. This oil was dissolved in THF (1 ml) and treated with H_2O_2 (aq.) (0.060 ml of a 40% w/v solution, 0.71 mmol) and NaOH (aq.) (0.50 ml of a 2.0 M solution, 1.00 mmol) for 2 hours at room temperature. The resultant solution was extracted with ethyl acetate (3 × 10 ml). The organic phases were dried and evaporated. The residue was treated with acetic anhydride (0.045 ml, 0.48 mmol) in pyridine (1 ml) and stirred at room temperature for 2 hours. The solution was then partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic phases were washed with 10% HCl (aq.) (20 ml), dried and evaporated to yield diacetyl derivative **7** (9 mg, 0.038 mmol, 81%) after purification by flash column chromatography [1 : 1, ethyl acetate–petroleum ether (40–60 °C) as eluent]: HPLC [Chiralpak AS, SFC, 35 °C, 3000 psi, $\lambda = 218$ nm, 2 ml min^{-1}, 90% CO_2: 10% (IPA + 0.2% Et_2NH) elution] t_R/min 6.73 (49.7%), 10.91 (50.3%); all spectroscopic and analytical properties were identical to those reported above.

Reduction of (*S*,*S*)-3 by treatment with one equivalent of borane–triethylamine complex followed by excess borane–tetrahydrofuran complex

To a solution of triethylamine (3.6 µl, 0.026 mmol) in dry THF (0.25 ml) at 0 °C under argon, borane–tetrahydrofuran complex (0.03 ml of a 1.0 M solution in THF, 0.03 mmol) was slowly added. After 5 hours, the solution was treated with (*S*,*S*)-**3** (0.011 g, 0.026 mmol) in THF (0.25 ml). The reaction was allowed to warm to room temperature, and after 20 hours borane–tetrahydrofuran complex (0.08 ml of a 1.0 M solution in THF, 0.08 mmol) was added. After 5 days the reaction was quenched with acetic anhydride (0.20 ml, 2.08 mmol) at 0 °C. The C–B oxidation and acetylation procedure described above was then followed, yielding diacetyl derivative **7** (5 mg, 0.021 mmol, 82%) after purification by flash column chromatography [1 : 1, ethyl acetate–petroleum ether (40–60 °C) as eluent]: HPLC [Chiralpak AS, SFC, 35 °C, 3000 psi, $\lambda = 218$ nm, 2 ml min^{-1}, 90% CO_2: 10% (IPA + 0.2% Et_2NH) elution] t_R/min 6.86 (48.0%), 11.24 (27.0%); all spectroscopic and analytical properties were identical to those reported above.

Reduction of (*S*,*S*)-3 by treatment with one equivalent of borane–triethylamine complex in the presence of 1.5 equivalents of borane–tetrahydrofuran complex

To a solution of triethylamine (7.1 µl, 0.051 mmol) in dry THF (0.10 ml) at 0 °C under argon, borane–tetrahydrofuran complex (0.13 ml of a 1.0 M solution in THF, 0.13 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 4 hours. Oxime ether (*S*,*S*)-**3** (0.022 g, 0.051 mmol) in THF (0.50 ml) was then added. The reaction mixture was stirred at room temperature for 2 days, then borane–tetrahydrofuran complex (0.025 ml of a 1.0 M solution in THF, 0.025 mmol) was added. After 3 days, the reaction was treated with borane–tetrahydrofuran (0.050 ml of a 1.0 M solution in THF, 0.050 mmol), and stirred for a further 24 hours, after which time the reduction was quenched with acetic anhydride (0.050 ml, 0.51 mmol). The C–B oxidation and acetylation procedure described above was then followed, yielding diacetyl derivative **7** (10 mg, 0.042 mmol, 83%) after purification by flash column chromatography [1 : 1, ethyl acetate–petroleum ether (40–60 °C) as eluent]: HPLC [Chiralpak AS, SFC, 35 °C, 3000 psi, $\lambda = 218$ nm, 2 ml min^{-1}, 90% CO_2: 10% (IPA + 0.2% Et_2NH) elution] t_R/min 6.37 (51.7%), 9.70 (48.3%); all spectroscopic and analytical properties were identical to those reported above.

Preparation of 2-amino-2-methyl-1,1-diphenylpropan-1-ol 25

To magnesium turnings (1.42 g, 0.058 mol) and I_2 (1 crystal) in anhydrous diethyl ether (50 ml) under argon, bromobenzene (5.11 ml, 0.049 mol) was added dropwise. The solution was cooled in an ice bath upon initiation of the reaction until addition of bromobenzene was complete. Heating at reflux for 2 hours afforded a dark grey solution which was then cooled in an ice bath. 2-Aminoisobutyric acid (0.40 g, 3.88 mmol) was added portionwise. The solution was allowed to warm to room temperature and heated at reflux for 3 hours. The reaction was then quenched by carefully pouring onto ice (30 ml). Concentrated HCl (aq.) (1 ml) was added and the mixture left to stand at room temperature for 1 hour. The ether layer was separated and the aqueous phase basified to pH 10 with 35% NH_4OH (aq.). The aqueous solution was then extracted with diethyl ether (3 × 20 ml). Drying and evaporation of the combined organic phases afforded **25** (0.213 g, 0.88 mol, 23%) as a white solid: mp 116 °C [lit.[20] 120 °C (from Et_2O)]; IR was as reported in the literature;[20] δ_H (300 MHz; $CDCl_3$) 1.39 [6 H, s, $(CH_3)_2C$], 7.19–7.33 (6 H, m, H *meta*, H *para*), 7.59–7.61 (4 H, m, H *ortho*); δ_C (75.5 MHz; $CDCl_3$) 28.5 (CH_3), 56.7 (CN), 80.7 (CO), 126.4, 127.4, 127.9, 144.9 (C aromatic); *m*/*z* (FAB) 242 $(M + H)^+$ [Found (HRMS): *m*/*z* 242.1545. $C_{16}H_{19}NO$ requires $(M + H)^+$ 242.1545].

Reduction of (*S*,*S*)-3 with borane in the presence of the complex prepared from achiral amino alcohol 25 and borane

To a solution of achiral amino alcohol **25** (0.017 g, 0.070 mmol) in THF (0.50 ml) at 0 °C under argon, borane–tetrahydrofuran complex (0.28 ml of a 1.0 M solution in THF, 0.28 mmol) was slowly added. After 5 hours, oxime ether (*S*,*S*)-**3** (0.030 g, 0.070 mmol) in THF (0.50 ml) was added dropwise, and the solution allowed to warm to room temperature. The reaction was quenched after 14 hours with acetic anhydride (0.13 ml, 1.40 mmol) at 0 °C, then stirred at room temperature for 1 hour. The THF was evaporated and the residue partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The organic extracts were combined and dried. Evaporation yielded crude acetamide which was dissolved in THF (1 ml) and treated with NaOH (aq.) (0.50 ml of a 2.0 M solution, 1.00 mmol) and H_2O_2 (aq.) (0.050 ml of a 40% w/v solution, 0.59 mmol). The solution was stirred for 2 hours at room temperature then extracted with ethyl acetate (3 × 10 ml). The combined organic layers were

dried and evaporated. The residue was dissolved in pyridine (1 ml) and acetic anhydride (0.060 ml, 0.64 mmol) added. The reaction was stirred at room temperature for 2 hours then partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic phases were washed with 10% HCl (aq.) (20 ml), dried and evaporated, furnishing acetamide **7** (0.011 g, 0.047 mmol, 67%) after column chromatography [1 : 1, ethyl acetate–petroleum ether (40–60 °C) as eluent]: HPLC [Chiralpak AS, SFC, 35 °C, 3000 psi, $\lambda = 218$ nm, 2 ml min^{-1}, 90% CO_2: 10% (IPA + 0.2% Et_2NH) elution] t_R/min 6.63 (45.6%), 10.58 (43.6%); all spectroscopic and analytical properties were identical to those reported above.

Reduction of (*S*,*S*)-3 by treatment with one equivalent of the complex prepared from amino alcohol 25 and borane, in the presence of 1.5 equivalents of borane–tetrahydrofuran complex

To a solution of amino alcohol **25** (0.012 g, 0.049 mmol) in THF (0.10 ml) at 0 °C under argon, borane–tetrahydrofuran complex (0.12 ml of a 1.0 M solution in THF, 0.12 mmol) was added. The solution was allowed to warm to room temperature and stirred for 4 hours. Oxime ether (*S*,*S*)-**3** (0.021 g, 0.049 mmol) in THF (0.50 ml) was then added. After 2 days, borane–tetrahydrofuran complex (0.025 ml of a 1.0 M solution in THF, 0.025 mmol) was added and the reaction stirred at room temperature for 3 days. The reaction mixture was then treated with borane–tetrahydrofuran complex (0.050 ml of a 1.0 M solution in THF, 0.050 mmol) and stirred for a further 24 hours. Borane–tetrahydrofuran complex (0.10 ml of a 1.0 M solution in THF, 0.10 mmol) was added and the reaction quenched with acetic anhydride (0.050 ml, 0.51 mmol) after 2 days. The C–B oxidation and acetylation procedure described above was then followed, yielding diacetyl derivative **7** (11 mg, 0.047 mmol, 96%) after purification by flash column chromatography [1 : 1, ethyl acetate–petroleum ether (40–60 °C) as eluent]: HPLC [Chiralpak AS, SFC, 35 °C, 3000 psi, $\lambda = 218$ nm, 2 ml min^{-1}, 90% CO_2: 10% (IPA + 0.2% Et_2NH) elution] t_R/min 6.28 (27.8%), 9.87 (35.8%); all spectroscopic and analytical properties were identical to those reported above.

Reduction of (*R*,*R*)-4 with borane in the presence of complex prepared from ethanolamine and borane

Borane–tetrahydrofuran complex (0.90 ml of a 1.0 M solution in THF, 0.90 mmol) was slowly added to a solution of ethanolamine (5.6 µl, 0.093 mmol) in dry THF (0.30 ml) at 0 °C. After 5 hours, oxime ether (*R*,*R*)-**4** (0.040 g, 0.093 mmol) in THF (0.30 ml) was added dropwise. The reaction was allowed to warm to room temperature, stirred for 14 hours, then quenched with acetic anhydride (0.20 ml, 2.12 mmol) at 0 °C. The solution was stirred at room temperature for 1 hour and the THF evaporated. The residue was partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic extracts were dried and evaporated yielding acetamide. This residue was dissolved in THF (2 ml) and NaOH (aq.) (1.50 ml of a 2.0 M solution, 3.00 mmol) and H_2O_2 (aq.) (0.20 ml of a 40% w/v solution, 2.35 mmol) added. Stirring at room temperature for 2 hours yielded a cloudy solution that was extracted with ethyl acetate (3 × 10 ml). The organic extracts were combined, dried and evaporated. The residue was dissolved in pyridine (2 ml) and acetic anhydride (0.10 ml, 1.06 mmol) was added. The solution was stirred at room temperature for 2 hours then partitioned between dichloromethane and saturated $NaHCO_3$ (aq.). The combined organic extracts were washed with 10% HCl (aq.) (20 ml), dried and evaporated to afford diacetyl derivative **7** (0.015 g, 0.064 mmol, 69%) after flash chromatography [1 : 1, ethyl acetate–petroleum ether (40–60 °C) as eluent]: HPLC [Chiralpak AS, SFC, 35 °C, 3000 psi, $\lambda = 218$ nm, 2 ml min^{-1}, 90% CO_2: 10% (IPA + 0.2% Et_2NH) elution] t_R/min 6.57 (49.9%), 10.46 (50.1%); all spectroscopic and analytical properties were identical to those reported above.

Reduction of (*S*,*S*)-3 by treatment with one equivalent of the complex prepared from ethanolamine and borane, in the presence of 1.5 equivalents of borane–tetrahydrofuran complex

To a solution of ethanolamine (3.2 µl, 0.054 mmol) in THF (0.10 ml) at 0 °C under argon, borane–tetrahydrofuran complex (0.14 ml of a 1.0 M solution in THF, 0.14 mmol) was added. The solution was allowed to warm to room temperature and stirred for 4 hours. Oxime ether (*S*,*S*)-**3** (0.023 g, 0.054 mmol) in THF (0.50 ml) was then added. After 2 days, borane–tetrahydrofuran complex (0.025 ml of a 1.0 M solution in THF, 0.025 mmol) was added and the reaction stirred at room temperature for 3 days. The reaction mixture was then treated with borane–tetrahydrofuran complex (0.050 ml of a 1.0 M solution in THF, 0.050 mmol) and stirred for a further 24 hours. Borane–tetrahydrofuran complex (0.10 ml of a 1.0 M solution in THF, 0.10 mmol) was added and the reaction quenched with acetic anhydride (0.050 ml, 0.51 mmol) after 2 days. The C–B oxidation and acetylation procedure described above was then followed, yielding diacetyl derivative **7** (12 mg, 0.051 mmol, 95%) after purification by flash column chromatography [1 : 1, ethyl acetate–petroleum ether (40–60 °C) as eluent]: HPLC [Chiralpak AS, SFC, 35 °C, 3000 psi, $\lambda = 218$ nm, 2 ml min^{-1}, 90% CO_2: 10% (IPA + 0.2% Et_2NH) elution] t_R/min 6.54 (49.0%), 10.60 (51.0%); all spectroscopic and analytical properties were identical to those reported above.

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