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‘Transmitted’ remote double diastereoselection effects on the asymmetric reduction of β-boronate oxime ethers

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Abstract

Remote asymmetric induction in the reduction of a homochiral β-boronate oxime ether to the corresponding amine failed to provide asymmetric induction with achiral reducing agents, but use of a chiral reducing agent produced extreme double diastereoselection effects which show that remote asymmetry can be ‘transmitted’ by suitable choice of a ‘partner’ molecule.

Establishing correct relationships between remote asymmetric centres, i.e. over a distance of more than three atoms, in conformationally flexible, acyclic systems is a challenging task in organic synthesis. Recently there has been some notable success in tackling this problem,[1] particularly in the remote asymmetric reduction of carbonyl groups.[2–4] However, the application of remote asymmetric induction to C=N double bond reduction is unprecedented in the literature.

Following our success in the directed 1,6-asymmetric reduction of a ketone via homochiral boronate ester **1a** to provide alcohol **3a** in 89% e.e., via active complex **2a**,[3,4] we have been seeking to adopt an analogous methodology for stereoselective C=N double bond reduction. For example, the asymmetric reduction of an imine or oxime ether of type **1b** or **1c**, respectively, may take place via complexes **2b** or **2c** to provide amino alcohol **3b**. Herein we report preliminary results in this area.

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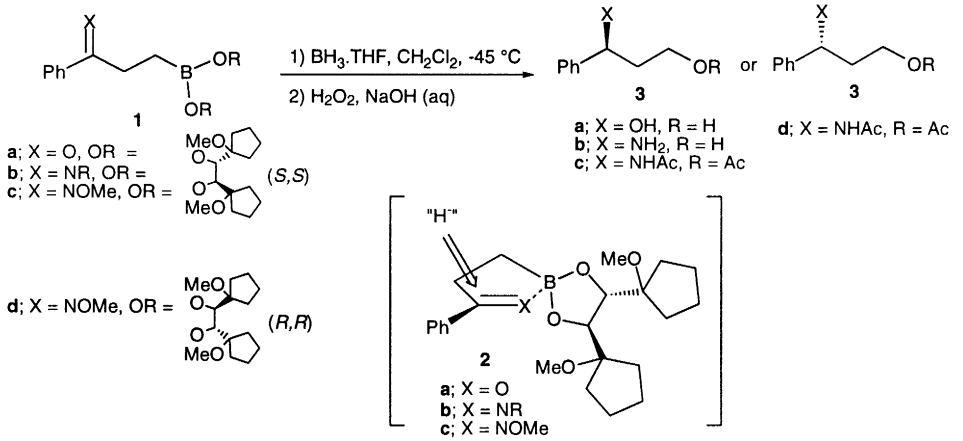
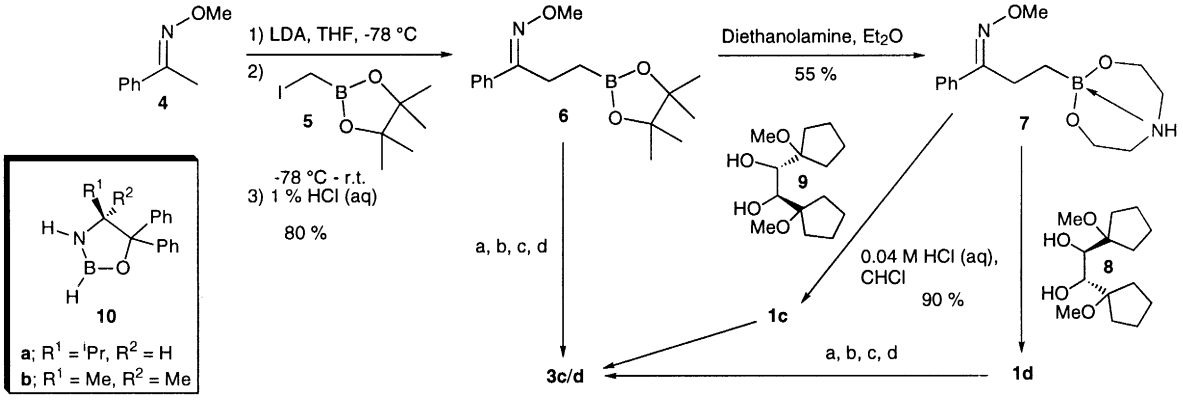


(1)

Extremely hydrolytically sensitive imines of type **1b** can be generated in situ from ketone **1a** upon treatment with an amine, for example benzylamine or *p*-methoxybenzylamine, in the presence of molecular sieves. Subsequent reduction with a wide range of borane-derived reducing agents (followed by oxidative boronate cleavage, acetylation and oxidative removal of the *p*-methoxybenzyl moiety) results universally in poor asymmetric induction (<15% e.e.) for the formation of **3c** (after acetylation). The corresponding homochiral β-boronate oxime ether **1c** and its enantiomer **1d** were stable and readily prepared from acetophenone as shown in Scheme 1, via a deprotonation of oxime **4**[5] and alkylation with iodide **5**,[6,7] to provide oxime **6** as a single *E*-stereoisomer. Transesterification via diethanolamine derivative **7** with the appropriate homochiral diols **8**[3] and **9**,[4] yielded the desired β-boronate oxime ethers **1d** and **1c**, respectively.

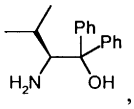
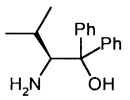
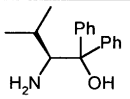
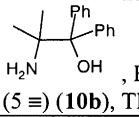


Scheme 1.

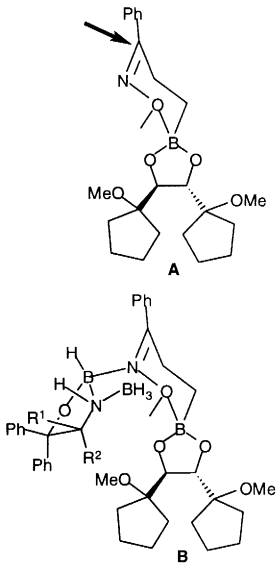
Both homochiral β-boronate oxime ethers **1c** and **1d** were successfully reduced with borane–dimethylsulfide complex and borane–tetrahydrofuran complex. Unfortunately, no asymmetric induction was obtained (Table 1, entries 1–3). In view of the *E*-oxime stereochemistry, it is likely that the formation of a boron–nitrogen chelate **2c** is precluded for substrates **1c** and **1d**. However, application of Itsuno's oxazaborolidine **10a** (prepared in situ from homochiral α,α-diphenyl-β-amino alcohols and borane[8]) produced interesting results. (*S*)-Valine-derived oxazaborolidine **10a** was applied to borane-mediated reductions of achiral β-boronate oxime ether **6** and homochiral systems **1c** and **1d**

(Table 1), followed by quenching with acetic anhydride, oxidative cleavage of the boronate function and final acetylation, to produce the *N*- and *O*-acetyl derivative **3c** and/or **3d**.[*,§]

Table 1
Reductions of β-oxime boronate esters **6**, **1c** and **1d** (see Eq. (1))

Entry	Substrate	Reduction (reagents / conditions)	1-Acetoxy-3-acetylamino-3-phenylpropane*§ 3c/d		
			Yield (%)[a]	E.e. (%)[b]	Absolute config.[b]
1	1d	$BH_3.SMe_2$ (10 ≡), THF, -15 °C – r.t., 16 h	94	0	-
2	1d	BH_3.THF (10 ≡), 0 °C – r.t., 2 d	75	0	-
3	1c	$BH_3.SMe_2$ (10 ≡), THF, -15 °C – r.t., 16 h	73	0	-
4	6	 , BH_3.THF (4 ≡) (**10a**), THF, r.t., 16 h	85	>99	*S*
5	1d	 , BH_3.THF (4 ≡) (**10a**), THF, r.t., 20 h	71	95	*S*
6	1c	 BH_3.THF (4 ≡) (**10a**), THF, r.t., 20 h	74	8	*R*
7	1c	 , BH_3.THF (5 ≡) (**10b**), THF, r.t., 2 d	96	13	*S*
8	1c	Et_3N, BH_3.THF (5 ≡), THF, r.t., 2 d	82	28	*R*

[a]Yields are unoptimised after column chromatography [ethyl acetate : petroleum ether, 1 : 1, as eluant]. [b]E.e.'s and absolute stereochemistries were determined by chiral HPLC.



Reduction of **6** resulted in formation of the (*S*)-diacetyl derivative **3c** in good yield (after oxidative boronate cleavage and acetylation) and excellent enantioselectivity (e.e. 98%) (Table 1, entry 4), which constitutes an efficient and novel route to enantio-enriched γ-phenyl-γ-amino alcohols (precursors to

* Racemic 1-acetoxy-3-acetylamino-3-phenylpropane **3c**: HPLC [SFC, Chiralpak AS, 35°C, 3000 psi, λ=215 nm, 2 ml min^{-1}, 86% CO_2: 14% (IPA+0.2% Et_2NH) elution] t_R(min) 5.06 (49.7%), 8.01 (50.3%); ν_{max} (KBr)/cm^{-1} ~3300, 1732, 1642, 1548, 1244; δ (^{1}H, $CDCl_3$) 2.00 (3H, s, CH_3C:ON), 2.01 (3H, s, CH_3C:OO), 2.08–2.20 (2H, m, CH_2CHN), 4.01–4.11 (2H, m, CH_2O), 5.08–5.17 (1H, m, CH_2CHN), 5.76 (1H, br, NH), 7.27–7.34 (5H, m, ArH) (addition of D_2O caused peak at δ 5.76 to disappear, and that at δ 5.08–5.17 to collapse to a t, *J* 7.2, δ 5.12); δ (^{13}C, $CDCl_3$) 20.9 (CH_3C:ON), 23.4 (CH_3C:OO), 34.7 (CH_2CHN), 50.7 (CH_2CHN), 61.4 (CH_2O), 126.5, 127.7, 128.8, 141.1 (aromatic C), 169.2 (CH_3C:ON), 171.0 (CH_3C: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].

§ Enantiopure (*S*)-3-amino-3-phenylpropan-1-ol was donated by Chirotech 1-acetoxy-(3*S*)-acetylamino-3-phenylpropane: $[\alpha]_D^{23}$ −72.4 (*c* 0.468, MeOH); HPLC [SFC, Chiralpak AS, 35°C, 3000 psi, λ=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%).

β-amino acids[9]). Reduction of the (4*R*,5*R*)-β-boronate oxime ether **1d** under the same conditions gave a comparable enantiomeric excess (e.e. 95%) to that obtained for **6** (Table 1, entry 5). In contrast however, the reduction of (4*S*,5*S*)-β-boronate oxime ether **1c** afforded (*R*)-diacetyl derivative **3c** (after oxidative boronate cleavage and acetylation) but with only 8% e.e. (Table 1, entry 6) and the opposite sense of absolute asymmetric induction. This result shows that the homochiral boronate functionality in **1c** and **1d** is capable of influencing the C=N double bond reduction by interaction with a suitable partner reducing agent, despite (a) its remoteness, and (b) the disadvantageous *E*-oxime ether geometry.

These results therefore raised the question of whether other achiral reducing agents could also constructively interact with the remote auxiliary and effect efficient asymmetric induction at the C=N bond. A range of other achiral borane–nitrogen reducing systems were examined, two of which are shown in entries 7 and 8 (Table 1). Use of the achiral oxazaborolidine-based system **10b** results in a very slow reduction and low (13%) asymmetric induction (Table 1, entry 7) and this is improved to 28% e.e. by use of triethylamine–borane complex, which is again a slow reaction.

At this moment, it is not clear exactly how **10a** or **10b** and triethylamine–borane interacts with the boronate esters of **1d** and **1c**. It is clear however, that **10a** destructively transmits the boronate ester information through to the oxime of **1c**, resulting in low and reversed asymmetric induction compared to the boronate ester of **1d**. It is also clear that other achiral borane–nitrogen complexes are capable of transmitting the remote asymmetry to the C=N bond. Possible intermediates involved in the reduction process are structures **A** and **B**. Remote asymmetric induction is inherently poor in structure **A** due to the chelation of the boronate ester to the methoxy group, instead of the oxime nitrogen, making the boronate ester too remote. However, triethylamine–borane is seemingly sufficiently hindered that a degree of selectivity does occur for *Si*-face attack. In order to more effectively transmit the asymmetry of the boronate ester to the oxime double bond, another molecule must be involved in the transition state, which seemingly occurs with oxazborolidines **10**, i.e. as shown by an intermediate of type **B**. Further investigations on the exact nature of such transmitted remote asymmetric interactions are underway, together with the application of such methods for the synthesis of β-amino acids.

Acknowledgements

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