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Rationalising the effect of reducing agent on the oxazaborolidine-mediated asymmetric reduction of *N*-substituted imines

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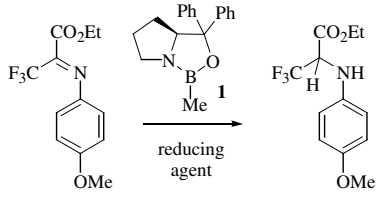
Abstract—Comparing the effect of borane-based reducing agents on the stereochemical outcome of oxazaborolidine-mediated ketone and *N*-substituted imine reduction highlights the potential importance of reducing agent structure on the asymmetric sense of imine reduction.

Chiral oxazaborolidines, typified by (*S*)-methyl-CBS-oxazaborolidine **1** (Corey's reagent), have found wide application in the catalytic asymmetric reduction of ketones.[1,2] They have also been investigated, to a lesser extent, for the reduction of imines,[3] leading to the successful asymmetric synthesis of Metolachlor, a widely used herbicide.[4] Studies by Sakai et al.,[5] in connection with the preparation of fluorinated amino acids, showed that the enantiomer formed on oxazaborolidine-catalysed reduction of imine **2** depended on the borane reducing agent employed (Table 1). On moving from borane–THF to the less reactive catecholborane, the *sense* of the asymmetric reduction changed from *S* to *R*; no explanation was given to account for this observation.

In connection with a medicinal chemistry programme, we had cause to investigate the asymmetric reduction of imines. We were drawn to consider, and rationalise, the impact of the choice of reducing agent on the stereochemical outcome of such reactions; our observations are presented herein.

Table 1. Oxazaborolidine-mediated asymmetric reduction of an imine



2 **3**

Reducing agent	Ester **3**
Borane–THF	42% yield, 28% ee, *S* (see Ref. 6)
Catecholborane	93% yield, 63% ee, *R*

For purposes of comparison, the oxazaborolidine-catalysed reduction of acetophenone **5** and phenyl-(1-phenylethylidene)amine **6** were carried out with Corey's reagent **1** in the presence of either borane–THF or catecholborane.[7] Several differences between ketone and imine reduction were noted (Table 2).

The reduction of ketone **5** with borane–THF in the absence of oxazaborolidine catalyst was sluggish; when catecholborane alone was used, no reduction of **5** was evident. In contrast, the uncatalysed reduction of imine **6** with either of these reducing agents was essentially complete within 10 min. Clearly such an outcome presents problems for asymmetric imine reduction, since

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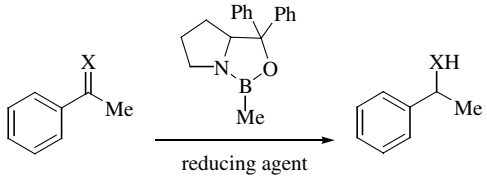
Table 2. Oxazaborolidine-mediated reduction of acetophenone 5 and phenyl-(1-phenylethylidene)amine 6



X = O **5**
X = NPh **6**

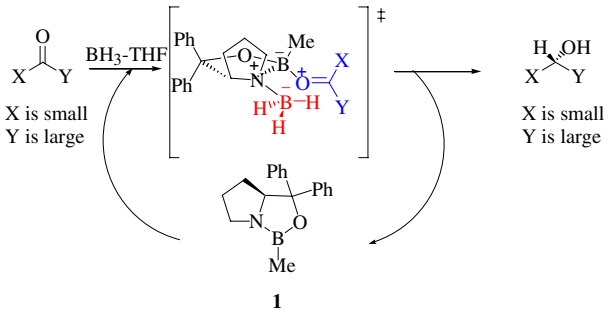
7
8

Substrate	Oxazaborolidine catalyst	Reducing agent	Conversion (%)[a]	ee (%)[a]	Product configuration[b]
Acetophenone **5**	None	Borane–THF	40	0	—
	S	Borane–THF	>99	>99	Alcohol **7** *R*
	None	Catecholborane	0	0	—
	S	Catecholborane	90	80	Alcohol **7** *R*
Phenyl-(1-phenylethylidene)-amine **6**	None	Borane–THF	91	0	—
	S	Borane–THF	69	87	Amine **8** *R*
	None	Catecholborane	87	0	—
	S	Catecholborane	98	47	Amine **8** *S*
	R	Catecholborane	91	49	Amine **8** *R*

[a] Determined by chiral HPLC—see general experimental protocol.[7]
[b] Absolute configurations were confirmed by comparison with literature data.[8]

the competing racemic background reaction may reduce the ee of the amine product, unless the rate of the catalysed reaction is significantly faster than that of its uncatalysed counterpart. With acetophenone **5**, choice of borane reducing agent did not affect the configuration of the product, whereas with imine **6** a change in the absolute configuration of the amine product was evident on changing from borane–THF to catecholborane, in keeping with the observations of Sakai et al.[5] To verify this observation, reduction of imine **6** with catecholborane and (*R*)-methyl-CBS-oxazaborolidine did indeed give rise predominantly to the (*R*)-amine **8**.

For ketone reduction, the chirality of the oxazaborolidine is responsible for the stereocontrol. Supported by crystallographic data,[9] the proposed mechanism for achieving asymmetric reduction with this system



1

Figure 1. Model to account for asymmetry in oxazaborolidine-mediated ketone reduction.

requires the oxazaborolidine to complex both the ketone and borane in the least sterically demanding arrangement, as outlined in Figure 1.[10]

With imines, the structure of the reducing agent appears to play a role in the stereochemical outcome of the oxazaborolidine-mediated reduction (Table 2). For reaction of phenyl-(1-phenylethylidene)amine **6** with borane–THF, a model analogous to that invoked to explain the asymmetry of ketone reduction (Fig. 1) cannot obviously account for the enantioselectivity observed (i.e., Fig. 2, conformation **A**).[11]

On steric grounds, it seems likely that rotation of both the imine and borane, such that B–H and C=N bonds are aligned, better explains generation of the *R*-amine product **8** (Fig. 2, conformation **B**). Rotation of both reagents therefore gives the same stereochemical outcome as for reduction of the corresponding ketone **5**. However, the analogous complex with catecholborane (Fig. 2, conformation **D**) is untenable for steric reasons, leading to alignment of imine C=N and borane B–H bonds as for ketone reduction (Fig. 2, conformation **C**). This in turn leads to the *S*-amine product **8**, the opposite outcome to that observed when borane–THF is used as the reducing agent.

In summary, in contrast to the corresponding reduction of ketones, choice of reducing agent as well as catalyst chirality can affect the sense of oxazaborolidine-mediated asymmetric reduction of imines. Steric factors provide a rationale for why, in conjunction with methyl-CBS-oxazaborolidine, catecholborane gives rise predominantly to the opposite enantiomer to that formed when borane–THF is employed.

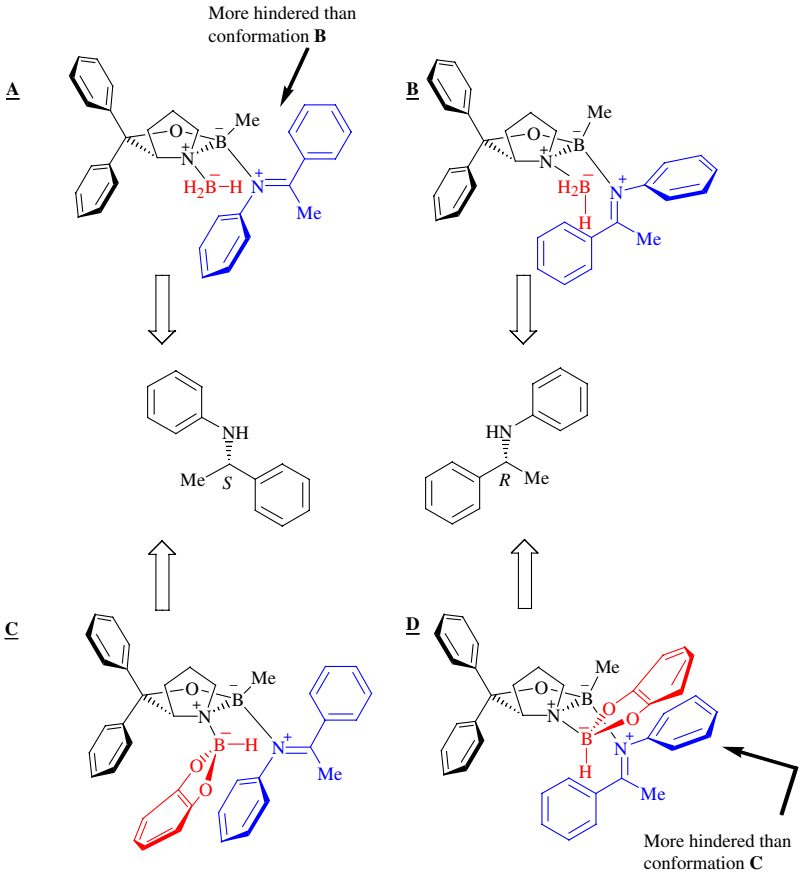


Figure 2. Model to account for asymmetry in oxazaborolidine-mediated imine reduction.[12]

Acknowledgements

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2. For selected recent examples of ketone reductions with immobilised oxazaborolidines see: Price, M. D.; Sui, J. K.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **2002**, *67*, 8086–8089; Schunicht, C.; Biffis, A.; Wulff, G. *Tetrahedron* **2000**, *56*, 1693–1699, and references cited therein.
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6. The low yield of amino-ester **3** is accompanied by formation of the corresponding amino-alcohol (49% yield), albeit of the *R*-configuration (45% ee) (the change in stereochemistry is not accounted for). On moving from borane–THF to the less reactive catecholborane, formation of the amino-alcohol was no longer evident.
7. General procedure for oxazaborolidine-catalysed imine reduction: reduction was achieved by a modification of the procedure described by Cho and Chun.[3b] In THF (1.5 mL), phenyl(1-phenylethylidene)amine **6** (25 mg, 130 μmol), (*S*)-methyl-CBS-oxazaborolidine **1**, (13 μmol, 10 mol %) were stirred under nitrogen for 10 min. Reducing agent (150 μmol) was added and the reaction was stirred at room temperature. Reactions were assessed by HPLC after 1 h (250×4.6 mm Chiralcel OD-H column; 5% ethanol in heptane; 0.5 mL/min; detection at 215/254 nm).
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11. These models are based on the premise that only the *trans* form of the imine is subject to oxazaborolidine-catalysed reduction.
12. The effect of imine structure, including *N*-substitution, on the stereoselectivity of oxazaborolidine-catalysed imine reduction has been noted (see Ref. 3).