

THE HIGHLY ENANTIOSELECTIVE BORANE REDUCTION OF KETONES CATALYZED BY CHIRAL OXAZABOROLIDINE DERIVED FROM STERICALLY CONSTRAINED AMINO ALCOHOLS[#]

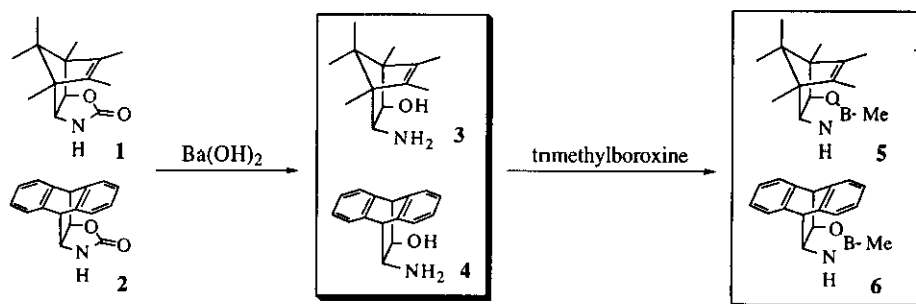
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Abstract - Reagents generated *in situ* from the borane-tetrahydrofuran complex and conformationally rigid and sterically congested amino alcohols (**3**, **4**), as well as oxazaborolidines (**5**, **6**), catalyze the smooth reduction of prochiral ketones to the secondary alcohols with excellent enantiomeric excess.

The development of efficient stereoselective reactions is a challenging subject in organic chemistry. The enantioselective oxazaborolidine-catalyzed reduction of prochiral ketones leading to the formation of chiral secondary alcohols, is a topic of current interest.¹ A number of chiral oxazaborolidines have been reported to be effective catalysts for the asymmetric reduction of ketones, as a result of the pioneering work by Ituno *et al.*² and Corey *et al.*³ Among these, the oxazaborolidines derived from conformationally rigid amino alcohols have shown promise for borane reductions with a high level of enantioselectivity.⁴

Recently we reported the sterically constrained tricyclic 2-oxazolidinones such as **1** and **2** as versatile chiral auxiliaries. These are readily obtained by the cycloaddition of 2-oxazolone to cyclic dienes, such as hexamethylcyclopentadiene⁵ and anthracene.⁶



Scheme 1

[#]Dedicated to the memory of the late Professor Shun-ichi Yamada.

This paper describes the highly enantioselective borane reduction of ketones catalyzed by chiral oxazaborolidines which are conformationally rigid and sterically congested. The *B*-methyloxazaborolidines (**5** and **6**) were readily prepared by the hydrolytic cleavage of the 2-oxazolidinone auxiliaries (**1** and **2**) to the amino alcohols (**3** and **4**), respectively, followed by treatment with trimethylboroxine.⁷

Both oxazaborolidines (**5** and **6**) thus obtained served equally effectively as catalysts for the enantioselective reductions of typical ketones with borane. The results are summarized in Table 1.^{8a} The reaction was carried out by the dropwise addition of ketone to BH₃ solution in THF in the presence of catalytic amounts of oxazaborolidine (**5** or **6**) (0.05 - 0.2 equiv.) at 0 °C and was complete within 5 min. Aromatic ketones, such as acetophenone and α -tetralone, gave the secondary alcohols with 98 % ee. In the reduction of the acyclic methyl ketones, the sterically bulky pinacolone gave excellent enantioselectivity, while 2-hexanone and 2-pentanone were reduced with moderate levels of enantioselectivity, representing still a significant achievement.

Table 1. Borane Reduction of Ketones Catalyzed by Oxazaborolidines^{a)}

$$\begin{array}{ccc}
 \text{R}_\text{L} & & \text{R}_\text{S} \\
 & \diagdown & / \\
 & \text{C} & \\
 & // & \\
 & \text{O} &
 \end{array}
 \xrightarrow[\text{THF, 0 }^\circ\text{C, 5 min}]{\text{oxazaborolidine, BH}_3\cdot\text{THF (1 equiv.)}}
 \begin{array}{ccc}
 \text{R}_\text{L} & & \text{R}_\text{S} \\
 & \diagdown & / \\
 & \text{C} & \\
 & | & \\
 & \text{OH} &
 \end{array}$$

ketone	oxazaborolidine (equiv.)	Yield (%)	% ee
acetophenone	5 (0.1)	84	98 ^{b)}
	5 (0.05)	84	98 ^{b)}
	6 (0.2)	86	97 ^{b)}
α -tetralone	5 (0.1)	100	98 ^{c)}
	6 (0.2)	91	96 ^{c)}
pinacolone	5 (0.1)	68	99 ^{c)}
	6 (0.2)	73	98 ^{c)}
2-hexanone	5 (0.2)	88	64 ^{c)}
2-pentanone	5 (0.2)	75	66 ^{c)}

a). The absolute configuration of the alcohol was assigned by direct comparison of the retention time with that of the authentic sample. Priority : R_L > R_S. b). Determined by HPLC using a Chiralcel OD chiral column. c). Determined by HPLC using a Chiralcel OJ' chiral column. c). Determined by HPLC using a Chiralcel OJ chiral column in the 3,5-dinitrobenzoate form.

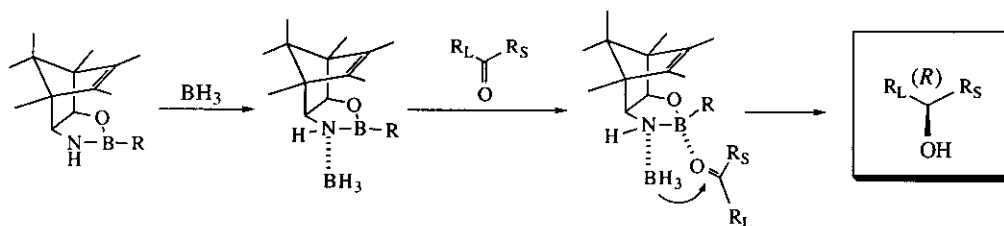
It is also noteworthy that the enantioselective reduction proceeded smoothly when the ketones were directly added to a mixture of sterically rigid amino alcohol (**3** or **4**) (0.1 equiv.) and $\text{BH}_3\cdot\text{THF}$ (1.0 equiv.) in THF at 0 °C within 5 min. This process serves as a practical and convenient procedure for the enantioselective reduction of ketones, as shown in Table 2.^{8b} Hydroxy and amino groups which are conformationally fixed in a *cis* relationship on the amino alcohols may be responsible for the facile generation of active species, which is presumably, a five membered oxazaborolidine.

Table 2. Borane Reduction of Ketones Catalyzed by the Aminoalcohol

$\text{R}_\text{L}-\text{C}(=\text{O})-\text{R}_\text{S} \xrightarrow[\text{THF, 0 } ^\circ\text{C, 5 min}]{\text{amino alcohol (0.1 equiv.), BH}_3\cdot\text{THF (1 equiv.)}} \text{R}_\text{L}-\text{C}(\text{OH})^{\text{(R)}}-\text{R}_\text{S}$			
ketone	amino alcohol	Yield (%)	% ee
acetophenone	3	84	97 ^{a)}
	4	86	97 ^{a)}
α -tetralone	3	88	98 ^{b)}
	4	91	98 ^{b)}
pinacolone	3	75	99 ^{c)}
	4	69	99 ^{c)}

a). Determined by HPLC using a Chiralcel OD chiral column. b) Determined by HPLC using a Chiralcel OJ chiral column. c). Determined by HPLC using a Chiralcel OJ chiral column as the 3,5-dinitrobenzoate.

As shown in Scheme 2, the oxazaborolidine-catalyzed reduction with borane would be predicted to give (*R*)-isomers *via* the transition complexes.⁹



Scheme 2

In summary, conformationally rigid tricyclic oxazaborolidines (**5** and **6**), as well as the reagents prepared *in situ* from borane and sterically constrained amino alcohols (**3** and **4**), serve well as efficient catalysts for the highly enantioselective reductions of aromatic and aliphatic ketones.

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REFERENCE AND NOTES

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7. **Preparation of the oxazaborolidines** : A solution of the amino alcohols (**3**, **4**) and trimethylboroxine (1.1 equiv.) in toluene was stirred at rt for 30 min and the volatile compounds removed azeotropically to afford the oily *B*-methyloxazaborolidines (**5**, **6**).
5 : ¹H-NMR (500 MHz /CDCl₃) δ: 4.56 (d, *J*=7.3 Hz, 1H), 3.67 (d, *J*=7.3 Hz, 1H), 1.66 (br s, 1H), 1.55 (d, *J*= 1.2 Hz, 3H), 1.51 (d, *J*=1.2 Hz, 3H), 1.07 (s, 3H), 0.93 (s, 3H), 0.65 (s, 3H), 0.62 (s, 3H), 0.28 (s, 3H).
6 : ¹H-NMR (500 MHz /CDCl₃) δ: 7.33-7.11 (m, 8H), 4.75 (dd, *J*=7.9, 3.7 Hz, 1H), 4.50 (d, 1H, *J*=3.7 Hz), 4.17 (d, *J*=2.5 Hz), 3.93 (dd, *J*=7.9, 2.5 Hz, 1H), 2.34 (br s, 1H), -0.23 (s, 3H)
8. **General procedure for asymmetric reduction** :
a) A solution of ketone (2.0 mmol) in THF (5 mL) was gradually added to the stirred solution of the *B*-methyloxazaborolidine (0.05-0.1 equiv.) and BH₃·THF complex (2.0 mmol) in THF (20 mL) at 0 °C via a syringe pump over a period of 90 min and the mixture was then acidified with 2 *N* HCl. The usual work-up, followed by chromatographic purification, gave the chiral alcohol.
b) In the above procedure, the amino alcohol was used in the place of the oxazaborolidine.
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