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

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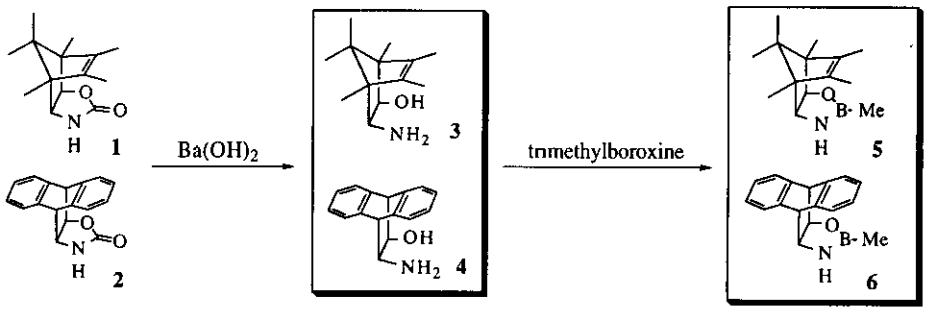
Abstract - Reagents generated *in situ* from the borane-tetrahydrofuran complex and conformationally rigid and sterically congested amino alcohols (**3**, **4**), as well as oxazaborolidines (**5**, **6**), catalyze the smooth reduction of prochiral ketones to the secondary alcohols with excellent enantiomeric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



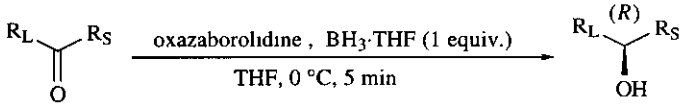
Scheme 1

#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 BH_3 solution in THF in the presence of catalytic amounts of oxazaborolidine (**5** or **6**) (0.05 - 0.2 equiv.) at 0 ℃ 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)]

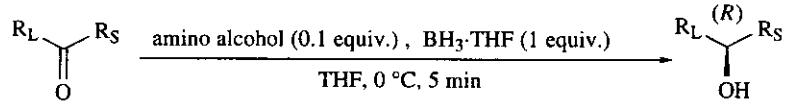


ketone	oxazaborolidine (equiv.)	Yield (%)	% ee
acetophenone	**5** (0.1)	84	98[b)]
	5 (0.05)	84	98[b)]
	6 (0.2)	86	97[b)]
α-tetralone	**5** (0.1)	100	98[c)]
	6 (0.2)	91	96[c)]
pinacolone	**5** (0.1)	68	99[c)]
	6 (0.2)	73	98[c)]
2-hexanone	**5** (0.2)	88	64[c)]
2-pentanone	**5** (0.2)	75	66[c)]

a). The absolute configration 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 BH_3·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.

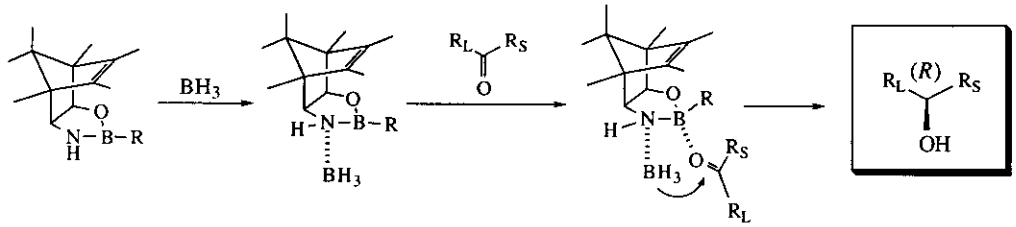
Table 2. Borane Reduction of Ketones Catalyzed by the Aminoalcohol



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 oxazaboloridine-catalyzed reductuion 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.

ACKNOWLEDGEMEMT

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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 : ^{1}H-NMR (500 MHz / $CDCl_3$) 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 : ^{1}H-NMR (500 MHz / $CDCl_3$) 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. **Generaral 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 BH_3·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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